Limited diagnostic accuracy and clinical impact of single-operator peroral cholangioscopy for indeterminate biliary strictures

Authors
Adriaan B. de Vries1, Frans van der Heide1, Rinze W. F. ter Steege2, Jan Jacob Koornstra1, Karel T. Buddingh3, Annette S. H. Gouw4, Rinse K. Weersma1

Institutions
1 Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands
2 Department of Gastroenterology and Hepatology, Martini Ziekenhuis, Groningen, The Netherlands
3 Department of Urology, HagaZiekenhuis, Den Haag, The Netherlands
4 Department of Pathology, University Medical Center Groningen, Groningen, The Netherlands

submitted 10.1.2019
accepted after revision 14.10.2019

ABSTRACT
Background Single-operator peroral cholangioscopy (sPOCS) is considered a valuable diagnostic modality for indeterminate biliary strictures. Nevertheless, studies show large variation in its characteristics and measures of diagnostic accuracy. Our aim was to estimate the diagnostic accuracy of sPOCS visual assessment and targeted biopsies for indeterminate biliary strictures. Additional aims were: estimation of the clinical impact of sPOCS and comparison of diagnostic accuracy with brush cytology.

Methods A retrospective single-center study of adult patients who underwent sPOCS for indeterminate biliary strictures was performed. Diagnostic accuracy was defined as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The clinical impact of sPOCS was assessed by review of medical records, and classified according to its influence on patient management.

Results 80 patients were included, with 40% having primary sclerosing cholangitis (PSC). Prior ERCP was performed in 88%, with removal of a biliary stent prior to sPOCS in 55%. The sensitivity, specificity, PPV, and NPV for sPOCS visual impression and targeted biopsies were 64%, 62%, 41%, and 84%, and 15%, 65%, 75%, and 69%, respectively. The clinical impact of sPOCS was limited; outcome changed management in 17% of patients. Sequential brush cytology sensitivity, specificity, PPV, and NPV were 47%, 95%, 80%, and 83%.

Conclusions The diagnostic accuracy of sPOCS for indeterminate biliary strictures was found to be inferior to brush cytology, with a low impact on patient management. These findings are obtained from a select patient population with a high prevalence of PSC and plastic stents in situ prior to sPOCS.

Introduction
Indeterminate biliary strictures are strictures of the intra- or extrahepatic bile ducts with no mass or lesion detectable on abdominal imaging, and without a clear explanation from the clinical context (e.g. traumatic or iatrogenic causes of biliary strictures, such as recent surgery), in which conventional work-up is non-diagnostic [1,2]. The main goal of diagnostic work-up is to establish or exclude a malignant etiology. Strictures in the context of primary sclerosing cholangitis (PSC) require additional vigilance, as these patients have an increased risk of developing cholangiocarcinoma.

Although several approaches have been proposed, the optimal diagnostic work-up for indeterminate biliary strictures has not been established [2,3]. Conventional imaging consists of computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP), with the aim of establishing vascular and other organ involvement. Diagnosis of an indeterminate stricture relies on tissue sampling, often through brush cy-
tology during endoscopic retrograde cholangiopancreatography (ERCP).

While the specificity of brush cytology is high, it is hampered by a low sensitivity of 45%, resulting in frequent false-negative results [4]. Curative treatment for malignant strictures consists of major surgery or, in selected cases, liver transplantation. Nonetheless, the prognosis of pancreatobiliary malignancy is poor as detection of early stage disease is difficult and a minority of patients present with resectable tumors at the time of diagnosis [5]. These factors can cause a tendency for early surgical treatment in the setting of negative brush cytology to prevent treatment delay. This carries a risk of unnecessary surgical treatment for benign disease, which is estimated to occur in 15% of patients with presumed perihilar cholangiocarcinoma [6] and in 5%–10% with presumed pancreatic cancer [7].

Single-operator peroral cholangioscopy (sPOCS) allows direct visualization of the luminal bile ducts in combination with tissue sampling through targeted biopsies. Several authors have reported sPOCS to be a valuable addition in the diagnostic work-up of indeterminate biliary strictures, finding an improved diagnostic yield over ERCP with brush cytology [8–11]. Although these results are promising, the studies have had a large variation in population size, disease definition, and reported outcome parameters. Furthermore, the impact of sPOCS on patient management is scarcely reported. Insight into these parameters is important to determine the efficacy of a diagnostic modality such as sPOCS, and its place in the diagnostic work-up for indeterminate biliary strictures.

The aim of this study was to estimate the diagnostic accuracy of sPOCS visual assessment and targeted biopsies for indeterminate biliary strictures. In addition, the clinical impact of sPOCS on patient management and comparison with the diagnostic accuracy of brush cytology were evaluated.

Methods

A retrospective single-center open-label cohort study was performed in all patients examined with sPOCS for indeterminate biliary strictures at our tertiary referral center between November 2007 and September 2018. Indeterminate biliary strictures were defined as strictures of the intra- or extrahepatic bile ducts with no mass or lesion detectable on abdominal imaging, in which conventional work-up was non-diagnostic.

Main outcome

The main outcome parameter was the diagnostic accuracy of sPOCS visual assessment and targeted biopsies of indeterminate biliary strictures. The pathology report of the surgical resection specimen was considered the gold standard. Apart from resection specimens, percutaneous biopsies or biopsies taken during exploratory surgery that were positive for malignant disease were also considered the gold standard. Strictures in patients who did not undergo surgical treatment that showed no development of malignant features during 6 months of follow-up were considered benign.

Additional outcomes were: the clinical impact of sPOCS on the management of patients with indeterminate biliary strictures, and a comparison between the diagnostic accuracy of sPOCS and that of standard brush cytology.

Patients

Patients ≥ 18 years who underwent sPOCS for an indeterminate biliary stricture were included. Patients without a diagnosis and with follow-up of less than 6 months after undergoing sPOCS were excluded. The diagnosis of PSC was based on the criteria established in international guidelines [12]. Although strictures developing in PSC cannot strictly be deemed of indeterminate cause, the diagnostic challenge is similar to strictures developing in patients without PSC. In clinical practice, both groups are frequently referred for diagnostic work-up. Therefore, PSC was not seen as an exclusion criterion.

Data collection

Data on the endoscopic procedure, histopathology, and follow-up were gathered retrospectively from the medical records. All CT, MRCP, ERCP, and endoscopic ultrasound (EUS) procedures performed for diagnosis of the indeterminate biliary stricture within 12 months prior to the sPOCS were recorded. In patients with multiple sPOCS procedures, only data from the first successful procedure were recorded.

All patient data were recorded anonymously. Because of the retrospective nature of this study no additional permission from the institutional review board was required.

Cholangioscopy procedure

Procedures were performed with the patient under conscious sedation, general anesthesia, or propofol sedation. ERCP was performed with a side-viewing duodenoscope (Olympus). When present, plastic biliary stents were removed at the start of the procedure. Patients received ceftriaxone prophylaxis before the procedure.

After cannulation and contrast cholangiography, a cholangioscope was inserted via the “mother–baby” technique [13]. All procedures were performed with the image fiber-based SpyGlass and second-generation digital SpyGlass DS cholangioscopy systems (Boston Scientific Netherlands BV, Kerkrade). The SpyGlass DS offers a markedly improved imaging quality in comparison to the first generation and was used from October 2016 onward in our center. The endoscopists (R.W., R.t.S., F.v. d.H.) were not blinded to the patient’s clinical history and previous diagnostic results. A standardized report was used by all endoscopists performing sPOCS, which included structure features, presence of neovascularization, and suspected etiology. Adverse events within 14 days of the procedure were noted.

sPOCS visual impression and targeted biopsies

Previously published visual features were used to distinguish benign from malignant strictures. The presence of irregular, vulnerable, or polypoid tissue were deemed consistent with a malignant etiology [14]. Special attention was paid to the presence of neovascularization as this has been associated with malignant etiology [14, 15]. At the present time, no validated criteria for sPOCS visual assessment exist. The preliminary diag-
nosis based on visual impression was gathered from endoscopy reports and recorded as malignant, benign, or inconclusive.

Targeted biopsies of the strictures were obtained under direct view using a specific biopsy forceps (SpyBite; Boston Scientific Netherlands BV, Kerkrade). The majority of biopsies taken was left to the discretion of the endoscopist performing the procedure. When possible, brush cytology was performed after sPOCS. Biopsies and brush cytology were suspended in Cytolyt (Hologic Inc., Marlborough, Massachusetts, USA).

Histopathological examination
The majority of histopathological analyses were performed by an experienced hepatobiliary pathologist (A.G.). Based on the pathology report, biopsy and brush results were classified as malignant, benign, or inconclusive; the number of biopsies received was also recorded. Reactive changes and atypical cells were considered benign unless the pathologist expressed a strong suspicion of malignancy. Results were deemed inconclusive when the specimen was inadequate for histopathological analysis owing to small size or low tissue yield.

Clinical impact
The impact of sPOCS on patient management was evaluated by review of medical records by the first author (A.B.d.V.), who did not partake in the clinical care of the included patients. The impact of sPOCS was classified into three categories: (1) change in, (2) confirmation of, or (3) no influence on patient management. A change in patient management was defined as the sPOCS (visual impression and/or targeted biopsies) being the sole reason for a change in management, for example finding malignant cells on the sPOCS biopsy when previous tissue sampling had shown benign findings. Confirmation was defined as the sPOCS confirming a previous diagnosis, for example the sPOCS yielding benign findings consistent with previous brush cytology or imaging. No influence was defined as an sPOCS outcome that did not confirm the diagnosis or result in a change in patient management, for example the results of the sPOCS were unclear or the sPOCS was followed by repeated diagnostic modalities because the diagnosis remained unclear. The clinical impact of sPOCS was recorded as unknown when it could not be deduced from medical records.

Statistical analysis
Diagnostic accuracy was defined as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), all of which are reported with a 95 % confidence interval (CI). Sensitivity and specificity were calculated with an intention-to-diagnose analysis, including inconclusive results [16]. In addition, likelihood ratios, post-test probabilities, and number-needed-to-diagnose were calculated, allowing for extensive quantification of diagnostic accuracy [17] (Table 1: see online-only Supplementary material). Statistical analysis was performed with SPSS 23.0 (IBM, Armonk, New York, USA).

Results
Patients
Between November 2007 and September 2018, a total of 185 sPOCS procedures were performed in our center, among these 86 patients underwent sPOCS for the evaluation of an indeterminate biliary stricture. After the exclusion of six patients who did not have a histopathological diagnosis and had not been followed up for at least 6 months, 80 patients were included for analysis. The majority of patients were men and PSC was present in 40 %. A previous ERCP had been performed in 88 % of the patients, with brush cytology being the most common form of tissue sampling prior to sPOCS. A plastic biliary stent was in situ and removed prior to sPOCS in 44 patients (55 %). The characteristics of the included patients are summarized in Table 1.

Outcome
The location of the biliary strictures and their etiology are presented in Table 2. There were 22 patients (28 %) diagnosed with a malignant stricture and four patients (5 %) had a premalignant lesion. A benign stricture was found in 43 patients (54 %), including inflammatory causes and dominant strictures in PSC. Eight patients (10 %) had bile duct stones; no visible stenosis was seen during cholangioscopy in three patients (4 %).

sPOCS procedure details
sPOCS for indeterminate strictures was performed with first-generation SpyGlass (Legacy) cholangioscopy system in 66 patients and the second-generation SpyGlass DS in 14 patients. Cholangioscopy was performed with the patients under con-
Dominant stricture in PSC 20 (25 %)
Mid CBD 14 (18 %)
Premalignant lesion 2
Diffuse/multifocal
No visible stricture during sPOCS
Cholangiocarcinoma 17 (21 %)
Stone
Distal CBD 21 (26 %)
Other malignant lesion 1
Hilar 36 (45 %)
Inflammatory 3
Intrahepatic

Table 2 Stricture location and etiology for the 80 included patients.

<table>
<thead>
<tr>
<th>Stricture characteristics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of indeterminate biliary stricture, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hilare</td>
<td>36 (45 %)</td>
<td></td>
</tr>
<tr>
<td>• Mid CBD</td>
<td>14 (18 %)</td>
<td></td>
</tr>
<tr>
<td>• Distal CBD</td>
<td>21 (26 %)</td>
<td></td>
</tr>
<tr>
<td>• Intrahepatic</td>
<td>3 (4 %)</td>
<td></td>
</tr>
<tr>
<td>• Diffuse/multifocal</td>
<td>6 (7 %)</td>
<td></td>
</tr>
<tr>
<td>Stricture etiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cholangiocarcinoma</td>
<td>17 (21 %)</td>
<td></td>
</tr>
<tr>
<td>• Other malignant lesion 1</td>
<td>5 (6 %)</td>
<td></td>
</tr>
<tr>
<td>• Premalignant lesion 2</td>
<td>4 (5 %)</td>
<td></td>
</tr>
<tr>
<td>• Benign stricture</td>
<td>18 (23 %)</td>
<td></td>
</tr>
<tr>
<td>• Dominant stricture in PSC</td>
<td>20 (25 %)</td>
<td></td>
</tr>
<tr>
<td>• Inflammatory</td>
<td>5 (6 %)</td>
<td></td>
</tr>
<tr>
<td>• Stone</td>
<td>8 (10 %)</td>
<td></td>
</tr>
<tr>
<td>• No visible stricture during sPOCS</td>
<td>3 (4 %)</td>
<td></td>
</tr>
</tbody>
</table>

CBD, common bile duct; PSC, primary sclerosing cholangitis; sPOCS, single-operator peroral cholangioscopy.

1 Metastasis of occult colon carcinoma (n = 1); cholangitis (n = 1); recurrence gallbladder carcinoma (n = 1); suspected cholangiocarcinoma but no definitive pathological diagnosis or resection (n = 2).
2 Intraductal papillary mucinous neoplasm of the bile duct (n = 2); low grade dysplastic adenoma (n = 1); focal high grade dysplasia (n = 1).
3 IgG4-mediated disease (n = 2); chronic inflammation (n = 1); reactive secondary sclerosis (n = 2).

Stricture characteristics:
- Location of indeterminate biliary stricture, n (%): Hilare 36 (45%), Mid CBD 14 (18%), Distal CBD 21 (26%), Intrahepatic 3 (4%), Diffuse/multifocal 6 (7%).
- Stricture etiology, n (%): Cholangiocarcinoma 17 (21%), Other malignant lesion 1 (6%), Premalignant lesion 2 (5%), Benign stricture 18 (23%), Dominant stricture in PSC 20 (25%), Inflammatory 5 (6%), Stone 8 (10%), No visible stricture during sPOCS 3 (4%).

Neovascularization was seen in 28 patients (35%) during sPOCS visual assessment. Of these patients, 20 (71%) had a stent in situ that was removed prior to sPOCS. In the 52 patients without neovascularization, 24 (46%) had a stent in situ prior to sPOCS procedure. In the 22 patients with a malignant biliary stricture, 12 (55%) had signs of neovascularization. In the 58 patients with a benign biliary stricture, 16 (28%) had signs of neovascularization.

sPOCS targeted biopsies
Cholangioscopic targeted biopsies were taken in 57 patients as is shown in Table 3. The number of biopsies was specified in 43 patients, with a median of three biopsies (IQR 2–5) per patient. Targeted biopsies yielded malignant cells in four patients and benign findings in 35 patients. In 18 patients (33%), the biopsies were insufficient for pathological assessment. This resulted in a sensitivity of 15% (95% CI 0%–31%), a specificity of 65% (95% CI 49%–80%), and a PPV and NPV of 75% (95% CI 33%–100%) and 69% (95% CI 53%–84%), respectively. Previous studies [8–11, 14,18–24] that have reported on the diagnostic accuracy of sPOCS targeted biopsies for indeterminate biliary strictures are summarized in Table 4.

Clinical impact of sPOCS
The impact of the sPOCS visual assessment and targeted biopsy result was retrieved by review of medical charts in 77 patients. In 13 patients (17%), the outcome resulted in a change of patient management. In contrast, for 25 patients (32%), the outcome of sPOCS did not influence patient management or confirm a previously established diagnosis, resulting in subsequent diagnostic procedures being performed. In 39 patients (51%), sPOCS resulted in confirmation of the previous findings and the chosen patient management.

Sequential brush cytology
The diagnostic accuracy of brush cytology performed during the ERCP sPOCS procedure is shown in Table 3. Brush cytology was performed in 58 patients. Cytology yielded malignant cells in 10 patients (17%), benign results in 47 patients (81%) and was inconclusive in one patient (2%). The sensitivity was 47% (95% CI 23%–71%) and the specificity was 95% (95% CI 89%–100%). The PPV was 80% (95% CI 55%–100%) and NPV was 83% (95% CI 72%–94%). Two false-positive brush results were seen in patients without PSC but with a plastic stent in situ prior to the sPOCS procedure.

Adverse events
A total of 10 patients (13%) suffered adverse events after the sPOCS procedure. These were mild in six patients (8%) who had self-limiting myalgia and abdominal pain, and serious in three patients (4%), with two episodes of bacterial cholangitis and one of post-ERCP pancreatitis. A further severe complication was seen in one patient who suffered a cardiac arrest during cholangioscopy followed by a stroke. The patient recovered with minimal neurological disability but later died from progressive malignant biliary disease.

Discussion
In this single-center retrospective cohort study, the diagnostic accuracy and clinical impact of sPOCS in a population of 80 patients with indeterminate biliary strictures was evaluated. This
study population represents a difficult-to-diagnose subset of
patients with a high prevalence of PSC and prior stenting. In
22 patients a malignant stricture was diagnosed, resulting in a
disease prevalence of 28%.

An appealing feature of sPOCS is the direct impression of a
biliary stricture it offers, allowing for a visual diagnosis. A pro-
spective multicenter study reported a sensitivity and specificity
of 78 % and 88 %, respectively, for sPOCS visual assessment in 95
patients with indeterminate biliary strictures [8]. Another pro-
spective study in 45 patients showed a sensitivity and specifici-
ty of 83% [18]. The yield of sPOCS visual assessment for inde-
terminate strictures in our cohort was lower, for which we believe the cause to be twofold.

First, a plastic stent was present and removed prior to sPOCS
in 55 % of our patients. In our experience, stents affect the bili-
ary epithelium through friction, and these changes can be mis-
taken for neoplastic changes, hampering visual assessment and
increasing the rate of false-positive diagnosis. This is supported
by our frequent finding of neovascularization in patients with-
out a malignant stricture but with a stent in situ prior to sPOCS.
Both the presence of a stent prior to sPOCS and its effect on vis-
ual assessment is scarcely reported. One study found no visible
effects of stents during sPOCS assessment [19]; however, only
13 % of their patients had a previous stent and the time of re-
moval was not specified.

Second, the prevalence of PSC in comparison to previous
studies is high [18, 19]. In our experience, sPOCS visual assess-
ment is difficult in PSC. This is supported by our comparison of
sPOCS in PSC and non-PSC patients, where we found the lowest
sensitivity and specificity in the former (Table 2). A prospec-
tive study with 47 PSC patients showed similar results and
found that sPOCS visual assessment was insufficient to differ-
entiate between benign and malignant strictures [25]. The dif-
ficulty of visual assessment for indeterminate strictures is illu-
strated in ▶Fig. 1, which shows sPOCS images and cholangio-
grams with different outcomes.

The diagnostic accuracy of sPOCS targeted biopsies in our
study was low, with a high number of inconclusive results. Stud-
ies reporting the sensitivity of sPOCS targeted biopsies in inde-
terminate biliary lesions show a large variation ranging from 48
%–85 %, with an approximate specificity of 90 % [8, 11, 18]. A
comparison of these results is difficult, as the criteria for patho-
logical assessment and the methods for processing targeted
biopsies are poorly reported. In the present study, malignant
cells or atypical cells with a strong suspicion of malignancy
were classified as malignant; atypical cells without specification
were classified as benign. We believe this classification repre-
sents daily practice most accurately, as atypia is insufficient to
establish a malignant diagnosis [26].

The large number of inconclusive results primarily affected
specificity as the number of false-positive biopsies was low. This
is illustrated by the exclusion of inconclusive results, which
increased the sensitivity and specificity of cholangioscopic tar-
targeted biopsies to 21.4 % and 95.6 %, respectively. Although un-

| Table 3 Comparison of single-operator peroral cholangioscopy (sPOCS) visual impression and targeted biopsy, and brush cytology: a vs. the gold-
standard diagnosis; b summary of accuracy measures. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sPOCS visual impression (n = 80)</td>
<td>sPOCS biopsy (n = 57)</td>
<td>Brush cytology (n = 58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>B</td>
<td>I</td>
<td>M</td>
<td>B</td>
<td>I</td>
<td>M</td>
</tr>
<tr>
<td>Gold standard</td>
<td>M</td>
<td>14</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>20</td>
<td>36</td>
<td>2</td>
<td>1</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Sensitivity (95 %CI)</td>
<td>64 % (44 – 84)</td>
<td>15 % (0 – 31)</td>
<td>47 % (23 – 71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity (95 %CI)</td>
<td>62 % (50 – 75)</td>
<td>65 % (49 – 80)</td>
<td>95 % (89 – 100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV (95 %CI)</td>
<td>41 % (25 – 58)</td>
<td>75 % (33 – 100)</td>
<td>80 % (55 – 100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV (95 %CI)</td>
<td>84 % (73 – 95)</td>
<td>69 % (53 – 84)</td>
<td>83 % (72 – 94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>63 %</td>
<td>47 %</td>
<td>81 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR +</td>
<td>1.9</td>
<td>5.5</td>
<td>9.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR -</td>
<td>0.5</td>
<td>0.9</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>3.6</td>
<td>6.6</td>
<td>19.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NND</td>
<td>3.4</td>
<td>8.1</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔPPPTP</td>
<td>14 %</td>
<td>40 %</td>
<td>51 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔNPPTP</td>
<td>12 %</td>
<td>3 %</td>
<td>12 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M, malignant; B, benign; I, inconclusive; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR + , positive likelihood ratio; LR - , negative likelihood ratio; DOR, diagnostic odds ratio; NND, number needed to diagnose; ΔPPPTP, difference between positive post- and pre-test probability; ΔNPPTP, difference between negative post- and pre-test probability.
desirable from a methodologic standpoint, it shows that our results for targeted biopsies are representative, as their specificity is similar to that of brush cytology and previously reported data [4, 20]. A review of targeted biopsy methods and processing did not reveal an explanation for the large number of inconclusive samples. The analysis of second-generation sPOCS did however reveal a trend toward a higher number of biopsies and lower rate of inconclusive samples (Table 3s). This is supported by a previous study, which found less inconclusive results when at least four targeted biopsies were taken [10]. In addition, studies reporting the lowest rates (<6%) of inconclusive samples, took a minimum of four biopsies [18, 19]. The number of biopsies taken in the present study are a likely explanation for the high number of inconclusive samples. Based on these findings we therefore recommend a minimum of four biopsies be taken during sPOCS, ideally with a pathologist on site to examine the yield.

Previous studies have reported sPOCS to be a valuable utility for indeterminate biliary strictures based on sensitivity, specificity, and accuracy [10, 11, 18]. These parameters give insight into test performance but lack information on the clinical impact, which is a scarcely reported outcome for sPOCS. In our cohort, the impact of sPOCS was limited, as the outcome resulted in a change of management in only 17% of the patients. A previous study found that sPOCS altered clinical management in 64% of the patients [8] but, as this was based on the judgement of the attending investigators, a possible overestimation of the impact of sPOCS cannot be excluded.

The cost of sPOCS is estimated to be €4680 ($5482) per patient [27]. As healthcare costs in the Western world continue to rise, the incorporation of a diagnostic modality into the standard of care should be carefully evaluated. Future prospective studies should therefore determine the impact of sPOCS and its cost-effectiveness, in addition to the commonly reported parameters of test validity.

To our knowledge, only one previous study has reported the results of sPOCS and sequential brush cytology for indeterminate biliary strictures [9], with a sensitivity of 5.8% for brush cytology and 76.5% for sPOCS targeted biopsies. The present study found the diagnostic accuracy of brush cytology to be superior to the diagnostic accuracy of sPOCS visual assessment and targeted biopsies. Our results for the diagnostic accuracy of brush cytology were comparable to those found in a systematic review [4], which reported a pooled sensitivity and specificity of 45% and 99% for brush cytology in malignant strictures.

Adverse effects after an ERCP sPOCS procedure were seen in 13% of the patients in our study. The reported rate of adverse events for sPOCS ranges widely, from 2.8% [19] to 21.4% [18], based on differences in definition and registration.

The present study has several limitations that should be taken into account. First, our data has been gathered over an extended period of time, with two generations of sPOCS devices being used. The majority of procedures were performed with first-generation cholangioscopes, which has a reduced image quality compared with the second-generation device, and could have resulted in lower diagnostic accuracy for both visual assess-

<table>
<thead>
<tr>
<th>Author</th>
<th>Design: Pro- vs. retrospective; multi-vs. single center</th>
<th>Patients in study (with PSC)</th>
<th>sPOCS generation</th>
<th>sPOCS visual assessment</th>
<th>sPOCS biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen [8]</td>
<td>Pro; multi</td>
<td>2261 (N/S)</td>
<td>1st</td>
<td>78% 82%</td>
<td>49% 98%</td>
</tr>
<tr>
<td>Ramchandani [14]</td>
<td>Pro; single</td>
<td>36 (2)</td>
<td>1st</td>
<td>95% 79%</td>
<td>82% 82%</td>
</tr>
<tr>
<td>Kalaitzakis [10]</td>
<td>Retro; multi</td>
<td>130 (16)</td>
<td>1st</td>
<td>N/S N/S</td>
<td>77% 100%</td>
</tr>
<tr>
<td>Draganov [9]</td>
<td>Pro; single</td>
<td>26 (Excluded)</td>
<td>1st</td>
<td>N/S N/S</td>
<td>77% 100%</td>
</tr>
<tr>
<td>Hartman [21]</td>
<td>Retro; single</td>
<td>892 (N/S)</td>
<td>1st</td>
<td>88% 86%</td>
<td>57% 100%</td>
</tr>
<tr>
<td>Manta [22]</td>
<td>Pro; single</td>
<td>52 (N/S)</td>
<td>1st</td>
<td>N/S N/S</td>
<td>88% 94%</td>
</tr>
<tr>
<td>Woo [23]</td>
<td>Retro; single</td>
<td>31 (N/S)</td>
<td>1st</td>
<td>100% 90%</td>
<td>64% 100%</td>
</tr>
<tr>
<td>Navaneethan [20]</td>
<td>Retro; multi</td>
<td>44 (8)</td>
<td>2nd</td>
<td>90% 96%</td>
<td>85% 100%</td>
</tr>
<tr>
<td>Kurihara [11]</td>
<td>Pro; multi</td>
<td>89 (3)</td>
<td>1st</td>
<td>95% 93%</td>
<td>65% 89%</td>
</tr>
<tr>
<td>Laleman [18]</td>
<td>Retro; single</td>
<td>45 (14)</td>
<td>1st</td>
<td>83% 83%</td>
<td>85% 100%</td>
</tr>
<tr>
<td>Shah [24]</td>
<td>Retro; multi</td>
<td>74 (6)</td>
<td>2nd</td>
<td>97% 93%</td>
<td>86% 100%</td>
</tr>
<tr>
<td>Robles-Medranda [19]</td>
<td>Pro; single</td>
<td>106 (0)</td>
<td>2nd</td>
<td>96% 92%</td>
<td>83% 98%</td>
</tr>
<tr>
<td>Present paper</td>
<td>Retro; single</td>
<td>80 (32)</td>
<td>Both</td>
<td>64% 62%</td>
<td>15% 65%</td>
</tr>
</tbody>
</table>

PSC, primary sclerosing cholangitis; N/S, not specified.
1 Sensitivity, specificity of sPOCS visual assessment and biopsy was calculated on a subset of 95 patients in whom ERCP impression, sPOCS visual assessment and sPOCS biopsy and a final diagnosis was available.
2 SpyBite biopsies were taken in 29 patients.
3 SpyBite biopsies were taken in 49 patients.
ment and targeted biopsies. It is important to note however that, as can been seen in Table 4, only a small proportion of the previous studies were performed with the second-generation cholangioscopes. The perceived value of sPOCS for indeterminate biliary strictures is therefore largely based on results from studies performed with first-generation cholangioscopes.

A second limitation of our study is that endoscopists and pathologists were not blinded to the results of previous diagnostic tests, which could have influenced their assessment of the visual features and tissue samples. Although methodologically suboptimal, this reflects clinical practice as endoscopists and pathologists are never blinded to previous diagnostic results. Furthermore, we would expect non-blinding to increase the diagnostic accuracy of sPOCS. In contrast, diagnostic accuracy was found to be lower in comparison to previous studies.

Another limitation is the high prevalence of stents prior to the sPOCS procedure, which is a potential confounder that could influence the diagnostic accuracy of sPOCS visual impression, targeted biopsies, and brush cytology. The recent removal of a plastic biliary stent or the procurement of targeted biopsies could result in a higher yield of the subsequently performed brush cytology. The presence of stents prior to sPOCS is inherent in clinical practice as the majority of patients are referred when their initial diagnostic work-up has proved inconclusive and an ERCP and stent placement have already been performed. The present study did not find an increase in the diagnostic accuracy of brush cytology in comparison to previous studies; however, a potential influence of stents or biopsy on the diagnostic yield of brush cytology cannot be excluded and should be evaluated in future studies.

Finally, as our data were collected in a tertiary referral center, there is a risk of selection bias that could have negatively impacted the diagnostic accuracy of sPOCS. In addition, there is a high prevalence of PSC. Both of these limitations are difficult to circumvent as an indeterminate biliary stricture, with or without PSC, is a challenging and complex disease, which re-
quires the advanced modalities and experienced clinicians more often found in specialized centers. Therefore, we believe our study population accurately represents the group of patients encountered in clinical practice for whom diagnostic sPOCS was intended.

In conclusion, we found the diagnostic accuracy of sPOCS for indeterminate biliary strictures to be inferior to brush cytology and to have a low impact on patient management. Our findings are obtained from a select patient population with indeterminate biliary strictures, and with a high prevalence of PSC and plastic stents in situ prior to sPOCS. Based on our results, we advocate the initiation of future prospective studies to further determine the diagnostic accuracy and cost benefit of diagnostic sPOCS, before incorporating this modality as a standard of care for indeterminate biliary strictures.

Acknowledgments

The authors gratefully acknowledge the contributions of Ms. S. Hintzen in her support with data extraction from the endoscopy database and Ms. F. M. Toxopeus for her help with study registration in our local research database.

Competing interests

The authors declare that they have no conflict of interest.

References