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Usefulness of the single-operator cholangioscopy system SpyGlass in biliary disease: a single-center prospective cohort study and aggregated review

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Abstract
Background and study aim Indeterminate biliary strictures and difficult bile duct stones remain clinically arduous and challenging situations. We aimed to evaluate the utility of the single-operator cholangioscopy (SOC)-system SpyGlass in both conditions in a single-center biliopancreatic interventional unit and in perspective of available aggregated literature.
Methods Usefulness of SOC was assessed for the above-mentioned indications by means of the combination of successful procedural completion, clinical success and incidence of procedure-related adverse events in our own prospective cohort from 3/2010 to 7/2014 and all available literature till 6/2015.
Results Our single-center cohort constituted of 84 patients undergoing SpyGlass either for indeterminate strictures ($n = 45$) or difficult stones ($n = 39$). In addition, a comprehensive literature review yielded 851 patients (from 15 series) for either stenosis ($n = 646$, 75.9 %) and difficult stones ($n = 205$, 24.1 %). In our series, overall procedural success amounted to 85.7 % (with 88.9 % for stenosis or 82.1 % for stones) compared to 90.7, 91.5 and 88.3 % in overall literature, respectively. Sensitivity, specificity and accuracy for *visual diagnosis* in our cohort added up to 83.3, 82.9 and 82.9 % compared to 90.8, 90.9 and 90.8 % in the pooled analysis. Respective figures for *SOC-directed biopsies* totaled 85.7, 100 and 95.7 % in our cohort and 72.4, 100 and 84 % overall. Overall procedure-related complications varied between 9.4 and 21.4 %.
Conclusions The SOC-platform SpyGlass can be considered useful in the context of indeterminate biliary strictures and difficult-to-remove biliary stones. In both, SpyGlass-assisted intervention is associated with high procedural success and alters clinical outcome compared to conventional approaches with an acceptable safety profile.

Keywords Indeterminate stricture · Cholangioscopy · Single-operator cholangioscopy · SpyGlass · Indeterminate biliary stenosis · ERCP · Difficult bile duct stone

Direct peroral cholangioscopy was initially introduced in the 1970s but failed to gain widespread acceptance because of complex equipment setup, too fragile or rigid nature of the device, high associated complication rate, lack of a sufficient large working channel or poor image quality [1]. In recent years, interest in this technique got renewed for two reasons.

Firstly, because of unresolved failure to overcome arduous situations, such as *indeterminate biliary strictures* and *difficult bile duct stones,* by conventional endoscopic retrograde cholangiopancreaticography (ERCP) despite progress in its armamentarium [2–4].

Secondly, in 2007, the single-operator per oral cholangioscopy (SOC) system SpyGlass™ (Boston Scientific Corp, Natick, MA, USA) was introduced and announced as a novel platform that could overcome all of the previous mentioned shortcomings [5].

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Traditionally, biliary strictures are classified as "indeterminate" when their nature cannot be determined after basic laboratory work-up, abdominal imaging (using MRI, multi-slice CT and endoscopic ultrasound) and ERCP [3]. Both the value of high-quality cholangiography and tissue sampling techniques, such as brush cytology (sensitivity 45 %), "blind" intraductal forceps biopsy (sensitivity 48.1 %) or a combination of both (sensitivity 59.4 %), have remained far from acceptable in this context [6]. Nonetheless, the stakes remain high since accurate diagnostics form the basis for an appropriate decision in respect of the need for and type of surgery. At present, it is estimated that approximately 15–24 % of patients with an indeterminate stricture undergo surgical resection for suspicion of malignancy but with benign disease at definite pathological examination [7–9].

"Difficult bile duct stones" form the other demanding situation. These are defined as biliary stones for which various difficulties are encountered during conventional attempts at extraction or removal either by difficulties in access (e.g., periampullary diverticula) or—more interesting from the point of cholangioscopy—by primary stone characteristics (size $\geq$ 15 mm, number, impaction, intrahepatic location or the presence above a stricture) [4, 10, 11]. Retained stones are considered to occur in 10–15 % of stone cases imposing alternative options such as intraductal mechanical lithotripsy, a percutaneous approach with electrohydraulic lithotripsy (EHL) or surgery.

In both this diagnostic and therapeutic stalemate, direct visualization of the bile duct by cholangioscopy is considered of added value either by direct macroscopic evaluation of the "indeterminate" stenosis combined with visually targeted biopsies or by assisting in optically guided intraductal fragmentation (via EHL or laser) and clearance of stones.

Since its introduction, several groups have reported on their experience with SpyGlass but most often as single-center experiences and/or with small sample size (ranging between 5 and 226 patients) [5, 12–24]. The aims of this paper are (1) to report on the usefulness of SpyGlass™ in the context of indeterminate stenoses and difficult bile duct stones in a prospective single-center cohort and (2) to review aggregated available literature [5, 12–24] to appraise the clinical value of this technology.

Materials and methods

Study design

This study was designed as a prospective observational cohort study conducted at a single tertiary biliopancreatic interventional European unit with an overall annual volume of over 1000 ERCPs. Institutional review board approval and informed consent were obtained for the purpose of this study.

Patients

Eligibility for study entry related to the need of further evaluation of a biliary stricture of uncertain clinical significance ("indeterminate stricture") or for advanced therapeutic intervention in the case of retained bile duct stones after prior failed conventional attempts to clear the bile duct (see definitions earlier). All consecutive eligible patients in whom the use of the SpyGlass™ platform was considered were registered between March 2010 and July 2014. Patient demographics, specific indication, anatomical target (intrahepatic, common hepatic duct, common bile duct, cystic duct), additional ERC-related procedures at the time of SpyGlass-intervention and probable related adverse events were recorded. Patients were followed up for at least 6 months.

Comparison to available literature and reported series until June 2015 was performed by an extensive PubMed-search using the mesh-terms "SpyGlass," "cholangioscopy," "indeterminate biliary stricture" and/or "difficult bile duct stone" using the same eligibility criteria as for the intended study.

Procedure and description of test system

All interventions were carried out by three experienced therapeutic endoscopists, each with an ERCP-case-volume of over 2500 ERCPs. Prior to the study, each endoscopist performed 5 to 10 SpyGlass-procedures to obtain and build up the necessary skills and technical experience with the platform, which post hoc was felt sufficient.

Except for some cases under conscious sedation (guided by the health status of the patient), 95 % of the procedures were performed under general anesthesia. Before the procedure, patients received antibiotic prophylaxis (levofloxacin) in accordance with institutional protocol or at the discretion of the attending endoscopist. Biliary sphincterotomy, if not yet performed, was carried out just before the SpyGlass examination. In some cases, the pre-existing sphincterotomy was extended or additional balloon dilatation of the papilla was performed if extension of the pre-existing sphincterotomy was deemed unsafe.

Each procedure was performed with an Olympus TJF-160V duodenoscope (Olympus Medical Systems, Tokyo, Japan) along with the SpyGlass Direct Visualization System and accessories (Boston Scientific Corp, Natick, MA, USA). In more detail, the actual cholangioscopy apparatus is conceived as a single-operator device employing a

single-use 10Fr multi-channeled sheath (SpyScope disposable access and delivery catheter) that attaches to the head of the duodenoscope just below the biopsy port and advances through the working channel for insertion into the bile duct. The SpyScope provides four-way steering of the tip and accommodates four channels: two for water irrigation, one for housing of the fiber-optic device (6000-pixel image with 70° field of view) and one for application of accessory devices such as a miniaturized biopsy forceps (SpyBite, single-use, 1.0 mm diameter with 4.1 mm jaw opening at 55°) or the 1.9Fr EHL probe (Northgate Technologies Inc, Elgin, IL, USA).

When a lesion was identified intraductally, the lesion was first characterized visually. The following visual features were considered suspicious for malignancy: prominent vascularization/neo-angiogenesis (e.g., tortuous dilated vessels), villous mucosal projections, irregular mucosal nodularity, mass-forming lesions [13, 21, 25]. Thereafter, if eligible, biopsy specimens (at least 4) were obtained using the SpyBite forceps under SpyGlass cholangioscopic guidance. An experienced pathologist evaluated all samples for adequacy. Depending on the situation, balloon dilatation of the stenosis was performed prior to cholangioscopy in order to accommodate the SpyScope and a stent was inserted following the procedure to ensure biliary drainage.

For EHL, the Northgate Autolith iEHL generator was used in conjunction with the earlier mentioned 1.9Fr single-use probes. Depending on characteristics of the stone (impacted, type of stone) generator, settings were adapted (with a minimum of 10 pulses per second and power output 60). After fragmentation of the stone, stone clearance was followed by auxiliary use of a dormia basket or balloon catheter. If complete clearance was unobtainable, a plastic stent was inserted to secure biliary drainage and the procedure was re-taken later or alternative treatment options were considered.

Outcome and definitions

The main study outcome measure was the usefulness of SpyGlass^{TM} in the context of indeterminate stenoses and difficult bile duct stones. Usefulness was assessed by means of the combination of successful procedural completion, clinical success and incidence of procedure-related adverse events. Definitions are summarized in Table 1.

With regard to capacity of SpyGlass to determine the nature of an indeterminate stenosis, a final diagnosis of bile duct malignancy was considered on the basis of a positive initial SpyGlass-directed biopsy or other definitive tissue sampling methods (such as CT-guided biopsy, intraoperative tissue sampling, surgical specimen or autopsy). With reference to preliminary sensitivity, specificity and accuracy analysis in this context, a provisional final diagnosis of benign etiology was established in patients with ≥6 months uneventful follow-up after the SpyGlass-procedure without evidence of malignancy.

Concordance between visual assessment and SpyBite biopsy diagnosis was also calculated.

Complications were graded according to Cotton et al. [26].

The same above-mentioned criteria were applied to the extensive literature search.

Upon unavailable or unclear data in these reports, corresponding authors were contacted for more information.

Finally, within our own cohort, various factors (demographics, presence of primary sclerosing cholangitis, location of the lesion, diameter of stone) were examined for possible prediction of failure.

Statistics

Descriptive statistics including means, standard error of mean (SEM) and frequencies were calculated. Preliminary sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for visual and biopsy diagnosis. To assess independent variables predicting failure of procedural success, logistic regression analysis was performed. Before entering independent variables in the logistic regression model, multicollinearity was excluded by evaluating correlation matrices between different independent variables and univariate analysis was performed to weigh the different variables.

Statistical analysis was performed using MedCalc software (Ostend, Belgium). $P \leq 0.05$ was considered statistically significant.

Results

Patient demographics and procedural data for the Leuven cohort (Table 2)

Between March 2010 and July 2014, 84 patients underwent SpyGlass-cholangioscopy either for difficult bile stones ($n = 39$) or indeterminate stenoses ($n = 45$). Patient demographics at baseline and procedure data are summarized in Table 2. Primary sclerosing cholangitis was present in 14 patients (16.6 %). The majority of SpyGlass-procedures (67/84, 80 %) intended to target the extra hepatic bile duct. As our unit is a tertiary center, half of the patients were referred for either further work-up of an indeterminate stenosis or either for difficult stones. This also explains the average number of two previous ERCPs prior to SpyGlass-procedure.

Table 1 Outcome definitions

Procedural outcome	
Procedural success	Proportion of SpyGlass-procedures in which diagnostic or therapeutic objective of the procedure was achieved
Diagnostic procedural success	Ability to visualize the stricture and biopsy tissue (if intended)
SpyBite biopsy success	Ability to perform SpyBite forceps biopsy
Adequacy of SpyBite biopsy specimen	Tissue specimen obtained by means of SpyBite considered adequate for histological assessment by a pathologist
Therapeutic procedural success	Ability to visualize and fragment the stone(s) and obtain ductal clearance
Complications	Adverse events observed during and after the procedure
Clinical outcome	
Sensitivity	Ability to identify patients with malignant stenosis
Specificity	Ability to exclude malignancy correctly
Positive predictive value (PPV)	Precision of probability that subjects with a positive diagnostic test truly have the disease
Negative predictive value (NPV)	Probability that subjects with a negative diagnostic test truly do not have the disease
Accuracy	% of correctly diagnosed patients

Table 2 Baseline characteristics of our single-center cohort

Patients (*n*)	84
Age, years [mean ± SEM (range)]	61 ± 2 (18–99)
Male/female [*n* (%)]	38 (45.2)/46 (54.8)
Primary sclerosing cholangitis [*n* (%)]	14 (16.7)
Indication for SpyGlass examination [*n* (%)]	
Indeterminate stricture	45 (46.4)
Difficult bile stones	39 (53.6)
Procedures at time of SpyGlass examination[a] (*n*)	
Sphincterotomy	35
Extension of sphincterotomy	12
Balloon dilatation	22
Stone removal	37
Stent placement	48
Intended region of interest at SpyGlass-procedure [*n* (%)]	
Intrahepatic	17 (20.2)
Hilar	16 (19)
Common bile duct	49 (58.3)
Cystic duct	2 (2.4)
Mean previous ERCPs [*n* (range)]	2 (0–12)
Secondary referral [*n* (%)]	45 (46.4)

[a] A combination of different procedures is possible in one single patient

Procedural outcome and success for the Leuven cohort (Tables 3, 4)

The *overall procedural success* in our cohort amounted to 85.7 % (72/84) with a success rate of 88.9 % (40/45) for indeterminate stenoses and 82.1 % (32/39) for retained stones.

Reasons for procedural failure in our cohort were inability to reach the region of interest ($n = 5$: cystic duct in two patients, intrahepatic localization beyond second generation bile duct branch in three others), incomplete stone fragmentation and/or stone clearance ($n = 4$), unstable position of the SpyScope ($n = 2$) or impossibility to advance the SpyBite ($n = 1$).

If we focus on the *diagnostic* procedures, the ability to merely visualize the region of interest/lesion was possible in 93.3 % (42/45) and biopsy of the lesion with the SpyBite in 24 out of 29 patients (82.8 % SpyBite biopsy success). Biopsy specimens were considered adequate by the pathologist in all but one case (95.8 %, 23/24).

With regard to difficult biliary stones, SpyGlass-assisted therapy led to a *therapeutic procedural success* in 82.1 % (32/39) in our cohort for retained stones of which 81.3 % (26/32) was realized in one procedure.

The corresponding results for both diagnostic and therapeutic intervention in aggregate literature are summarized in Tables 3 and 4 [5, 12–24].

Within our cohort, analysis of various factors (demographic factors, presence of primary sclerosing cholangitis, intended focus of interest, diameter of stone, number of previous ERCPs) was examined for possible prediction of failure. In the stone therapy-group, no factor could be identified in univariate analysis, whereas in the indeterminate stenosis-group "focus of interest" (intra- vs extrahepatic) was withheld ($P = 0.03$; 95 % CI 0.03–0.56) with intrahepatic localization as negative determining factor. No multivariate analysis could be performed.

Clinical outcome and success for the Leuven cohort

Determining the contribution of SpyGlass in the ability to identify patients with malignant stenosis (sensitivity) and/or to exclude malignancy correctly (specificity) defines the impact of direct visualization of the lesion and visual-assisted sampling of the lesion.

Table 3 Overview of overall technical success in our cohort, the aggregated literature and totaled results of SpyGlass-series addressing indeterminate stenosis

Author	Study	Number	Diagnostic procedural success[a]	SPYBITE biopsy success	Adequacy biopsy specimen[b]
Chen [5]	Prospective	22	20/22	20/20	19/20 (95 %)
Draganov [12]	Prospective	44	43/44	36/36	35/36
Ramchandani [13]	Prospective	33	33/33	33/33	27/33
Siddiqui [14]	Retrospective	30	30/30	30/30	30/30
Kalaitzakis [15]	Retrospective	130	117/130	74/94	53/74
Manta [16]	Prospective	52	50/52	43/45	42/43
Nguyen [17]	Prospective	19	18/19	18/18	16/18
Tieu [18]	Retrospective	39	29/39	36/39	29/36
Moura [19]	Prospective	8	7/8	1/1	1/1
Siiki [20]	Prospective	11	11/11	11/11	10/11
Woo [21]	Prospective	32	31/32	19/19	17/19
Chen [22]	Prospective	226	202/226	140/140	122/140
Aggregated literature	9 P/3 R	646	591/646 (91.5 %)	461/486 (94.9 %)	PP 401/461 (87 %)
					ITT 401/486 (82.5 %)
Current series	Prospective	45	40/45	24/29	23/24
Overall	10 P/3 R	691	631/691 (91.3 %)	485/515 (94.2 %)	PP 424/485 (87.4 %)
					ITT 424/515 (82.3 %)

P prospective, *R* retrospective, *PP* per protocol, *ITT* intention to treat

[a] Ability to visualize the indeterminate stricture and obtain biopsy tissue from the target lesion (if intended)

[b] Tissue specimen obtained by means of SpyBite considered adequate for histological assessment by a pathologist

Table 4 Overview of overall technical success in our cohort, the aggregated literature and totaled results of SpyGlass-series addressing difficult bile duct stones

Author	Study	Number	Therapeutic procedural success[a] (%)	In one procedure
Chen [5]	Prospective	5	5/5 (100 %)	2/5
Draganov [12]	Prospective	26	24/26 (92.3 %)	22/24
Kalaitzakis [15]	Retrospective	33	24/33 (72.7 %)	14/24
Fishman [23]	Retrospective	41	37/41 (90.2 %)	37/37
Aljebreen [24]	Retrospective	13	13/13 (100 %)	10/13
Tieu [18]	Retrospective	13	10/13 (76.9 %)	10/10
Moura [19]	Prospective	8	7/8 (87.5 %)	5/7
Chen [22]	Prospective	66	61/66 (92.4 %)	43/61
Aggregated literature	4 P/4 R	205	181/205(88.3 %)	PP 143/181(79 %)
				ITT 143/205(69.8 %)
Current series	Prospective	39	32/39 (82.1 %)	26/32
Overall	5 P/4 R	244	213/244 (87.3 %)	PP 169/213 (79.3 %)
				ITT 169/244 (69.3 %)

P prospective, *R* retrospective, *PP* per protocol, *ITT* intention to treat

[a] Ability to visualize and fragment the stone(s) and obtain ductal clearance

Upon mere macroscopic characterization by means of SpyGlass, the considered indeterminate stenosis could be visually evaluated in 42 patients (cfr. procedural outcome and success). According to predefined suspicious macroscopic features for malignancy (cfr. methods), lesions were visually assessed and classified as "suspected benign" or

"suspected malignant". The diagnosis of malignant disease was subsequently confirmed based on a final histopathological tissue diagnosis, whereas a provisional final diagnosis of benign etiology was retained when histology was negative and/or there was an uneventful follow-up ≥6 months after the SpyGlass-procedure.

Sensitivity, specificity and accuracy for visual diagnosis by SpyGlass in our cohort were 83.3, 82.9 and 82.9 %, respectively. If we review the value of macroscopic features (neo-angiogenesis (e.g., tortuous dilated vessels), villous mucosal projections, irregular mucosal nodularity or mass-forming lesions), neo-angiogenesis appeared the only macroscopic predictor of malignancy (present in 7/42 patients and in 5/7 patients with malignancy, $P = 0.047$; Fig. 1).

The use of SpyBite or obtaining a histological diagnosis to assist in identifying patients with malignant stenosis, to exclude malignancy and to correctly classify diagnosed patients resulted in a sensitivity of 85.7 %, a specificity of 100 % with an overall accuracy of 95.7 %.

The corresponding results for both visual and biopsy diagnosis in aggregate literature are summarized in Table 5 [5, 13, 14, 16–18, 21, 22].

Concordance of visual diagnosis to biopsy diagnosis in our cohort was 74 % (17/23), comparative to 85 % (41/48) in the literature [5, 13].

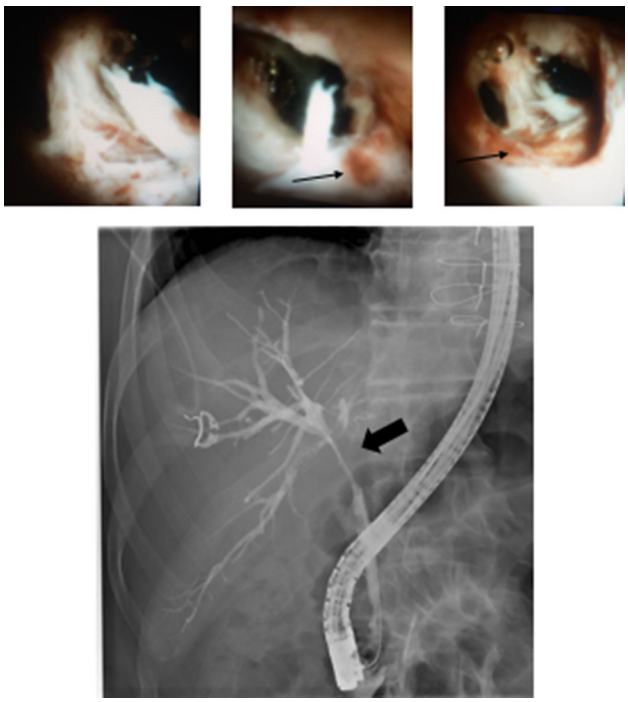

Fig. 1 Indeterminate proximal bile duct stenosis, biopsy proven malignancy: *upper row* cholangioscopy image with neo-angiogenesis typical of malignancy (*small arrow*), *lower row*: cholangiographic image of the stenosis (*thick arrow*)

Procedure-related adverse events for the Leuven cohort (Table 6)

Taking into consideration, all possible adverse events observed during and after the procedure, we encountered 21.4 % complications. In overall reported literature, the reported complications rate amounts to 9.4 % (79/843). The different complications were summarized in Table 6 and compared to existing literature. No mortality or remaining morbidity was reported or observed.

Discussion

Here, we report the usefulness of the SpyGlass-system, as a single-operator cholangioscopy platform, in the specific management of indeterminate stenoses and difficult bile duct stones (Fig. 2). The outcomes obtained from our prospective cohort study were contextualized by comparing to those reported in aggregated literature. "Usefulness" incorporates features with regard to applicability (*procedural success*), yield in diagnostic approach or therapeutic intervention (*clinical outcome*) outweighed by the number and type of *adverse events*.

If we focus first on *procedural success* in our cohort, defined as the ability to either visualize the indeterminate lesion and acquire biopsy tissue (if intended) or either visualize, fragment the stone(s) and obtain ductal clearance, we observed a success rate of 85.7 %. In our practice, the indication for Spyglass was fairly divided between procedures with diagnostic and therapeutic intent with a respective procedural success of 88.9 and 82.1 %. If we compare this to the aggregate literature, reassembling 14 reports with 843 patients in total and series ranging between 11 and 297 patients, the comparable overall, diagnostic and therapeutic success rates amount to 90.7, 91.5 and 88.3 %, respectively [5, 12–24] (Tables 3, 4).

Of interest is that upon review of all reported series individually, overall, diagnostic and therapeutic technical success rates are fairly consistent from the inception of this technology and the first reported experience by Chen and Pleskow [5] providing proof of concept that this technique is generally applicable.

The system allows adequate evaluation of the extrahepatic and proximal intrahepatic biliary tree. The few technical failures that occurred in our cohort relate to deep intrahepatic localization which concern limitations of the platform to overcome steep angulation, decreasing diameter of intrahepatic bile duct branches and rigidity of the device.

Despite the appeal of this single-operator platform, mastery of the Spyglass-system entails a learning curve. However, no group has formally addressed the quality

Table 5 Overview of overall reported clinical diagnostic outcome (including our cohort)

SpyGlass for indeterminate stenosis Sensitivity, specificity and accuracy in all published series							
Visual diagnosis	Final or provisional final diagnosis			Biopsy diagnosis	Final or provisional final diagnosis		
	Malignant	Benign	Total		Malignant	Benign	Total
Malignant	128 TP	15 FP	143	Malignant	113 TP	0 FP	113
Benign	13 FN	149 TN	162	Benign	43 FN	113 TN	156
Total	141	164	305	Total	156	113	269
Sensitivity	90.8 %	95 % CI 84.8–95		Sensitivity	72.4 %	95 % CI 64.7–79.3	
Specificity	90.9 %	95 % CI 85.4–94.8		Specificity	100 %	95 % CI 96.8–100	
PPV	89.5 %	95 % CI 83.3–94.0		PPV	100 %	95 % CI 96.8–100	
NPV	92.0 %	95 % CI 86.7–95.7		NPV	72.4 %	95 % CI 64.7–79	
Accuracy	90.8 %			Accuracy	84 %		
Disease prevalence	46.23 %			Disease prevalence	58 %		

TP true positive, *FP* false positive, *FN* false negative, *TN* true negative

Table 6 Overview of complications encountered in the Leuven cohort in comparison to overall reported

Type of complication	Leuven cohort ($n = 84$)	Overall reported literature ($n = 843$)
Mild pancreatitis	6	12
Cholangitis	5	37
Self-limiting abdominal pain	3	18
Asymptomatic amylasemia	3	1
Hemobilia (after EHL)	1	–
EST-related bleeding	–	2
EST-related perforation	–	2
Radiculopathy	–	1
Sedation-related hypotension/hypothermia	–	6
Overall (%)	18/84 (21.4 %)	79/843 (9.4 %)

assurance of the procedure in terms of this latter and overall training. In our personal experience, it takes about ten procedures to achieve some proficiency in using this system. Technically, the operator needs to learn to both synchronize and sequentially control duodenoscope and cholangioscope movements through a range of positions. This platform therefore is therefore best served by a user with advanced endoscopic skills. Finally, this system imperatively imposes dexterity of the operator given the fact that the operator uses the same hand to maneuver duodenoscope and/or cholangioscopy as well as to load the working channel of the cholangioscope with a biopsy forces or EHL probe.

Focusing next on the impact of SpyGlass on ***clinical outcome*** implies evaluating the ability to classify patients correctly for diagnostic purposes and obtaining ductal clearance for therapeutic interventions.

If we start with diagnostic impact, a distinction needs to be made between *visual assessment* and *intra-ductal tissue acquisition.* Sensitivity, specificity and accuracy of *visual* cholangioscopic assessment of indeterminate stenosis in our series amounted to 83.3, 82.9 and 82.9 %, respectively, which compared to 90.8, 90.9 and 90.8 % for a disease prevalence of 46 % in pooled literature. Since in this context, only eight series were reported with overall 646 patients, and thus underpowered for a robust meta-analysis, we opted to review *all* possible reported series while accepting possible bias (though applicability concerns are low). Interestingly, a recent systematic review, using preset quality criteria despite apparent lack of power, selected six studies and found similar pooled clinical outcome data to ours for visual assessment with a sensitivity of 84.5 % and a specificity of 82.6 % [27].

With respect to SpyGlass-assisted *intra-ductal tissue acquisition*, sensitivity, specificity and accuracy rate in our series were 85.7, 100 and 95.7 %, with pooled equivalents in overall reported literature of 72.4, 100 and 84 % for a disease prevalence of 58 %.

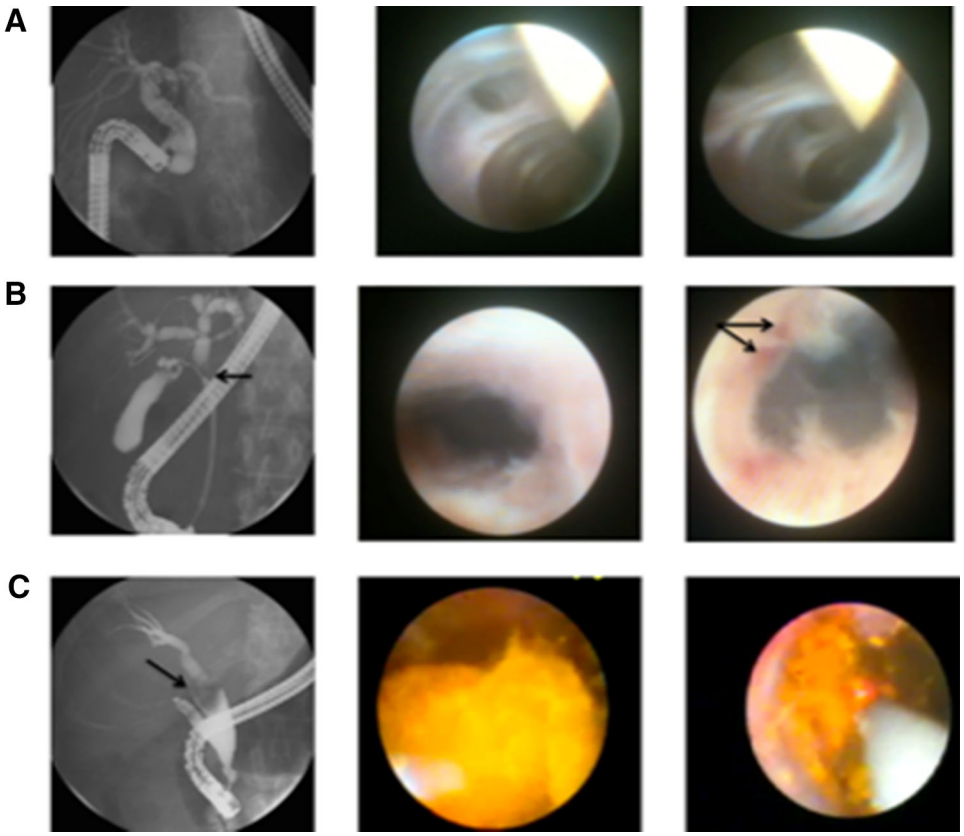

Fig. 2 Combination of cholangiographic and cholangioscopic in normal condition (**A**), indeterminate stenosis (*arrow*) with villous projections and neo-angiogenesis (*double arrow*, **B**) and impacted bile duct stone (*arrow*) subjected to electrohydraulic lithotripsy (**C**)

The higher sensitivity for SpyGlass in visual assessment compared to cholangioscopic biopsies in our pooled unselected analysis can be explained by a "fail-safe" subjective apprehension since mere visual cholangioscopic criteria are highly flawed. In support hereof is the opposite trend in specificity (with more false positives upon visual assessment and none upon histological evaluation), the imperfect concordance of visual to biopsy diagnosis (ranging from 74 % in our series to 85 % overall) and lack of distinct macroscopic features, except for neo-angiogenesis in our and other series [25], or recognition patterns to rule in/out the specific benign/malignant nature of a lesion.

So, in absolute numbers, the overall clinical impact of SpyGlass-assisted visual assessment and guided sampling in our series and the pooled available literature outperforms conventional brushing (45 %), intraductal biopsy (48.1 %) or a combination of both (59.4 %) [6]. However, none of these studies offered a head-to-head comparison to brushing cytology and/or fluoroscopy-guided intraductal biopsies. Only in one paired design cohort study (including 26 patients), Draganov et al. [28] confirmed significantly higher accuracy of SOC-guided biopsies (84.6 %) compared to ERCP-guided cytology brushings (38.5 %) and standard forceps biopsies (53.9 %).

In addition to the lack of comparative data, the evolving role of endoscopic ultrasound (EUS) in an integrated algorithm also remains to be further explored. In a single-center prospective observational study by Nguyen et al. [17], pre-SOC EUS combined with fine-needle aspiration cytology (FNA) provided a correct tissue diagnosis in 58 % of the patients. In the remaining patients without diagnosis, subsequent SOC led to an overall tissue diagnosis of 94 % with a significant reduction in overall cost. To truly address all these voids, a large-sample size multicenter cohort study combining the two-step approach (EUS before SOC) and evaluating conventional sampling techniques (brush and biopsy) versus SOC-guided sampling might provide the answers needed in terms of diagnostic yield and cost-effectiveness.

If we turn to impact on clinical therapeutic outcome in our cohort, SpyGlass-assisted therapy led to ductal clearance in 82.1 % for retained stones with 81.3 % being realized in one procedure. In overall literature, this compares, respectively, to 88.3 and 79 % [14, 15, 18, 21, 22, 25–27]. Given these figures and context (7 out 9 series report on failed mechanic lithotripsy), SOC-assisted therapy represents a highly valuable and less invasive alternative to percutaneous or surgical approaches.

Finally, the last component of usefulness involves *adverse events* related to the SOC-procedure. Addressing all possible adverse events, we noted 21.4 % complications in our series of which 14.2 % clinically relevant. Cumulating all reported events, including our series, revealed 10.5 % overall without reported remaining morbidity or mortality indicating acceptable safety both quantitatively as qualitatively.

Before drawing final conclusions, we need to address some limitations to our analysis, both in general as local. First of all, we cannot vouch for institutional habits in the different reported series nor for different levels of proficiency among different endoscopists. Moreover, our review includes a mix of prospective and retrospective series of different sample size, which cannot preclude a selection bias. This latter also holds true for our series. Lastly, the nature of cohort studies, which imply most of the reported series, per definition lack direct comparison to conventional approaches, and thus preclude robust meta-analysis.

In conclusion, reviewing our series and putting this in perspective of the overall available literature, the SpyGlass-platform can be considered useful in the context of indeterminate biliary strictures and difficult-to-remove biliary stones. In both situations, SpyGlass-assisted intervention is associated with high procedural success, alters clinical outcome in over 80 % of considered insolvable cases with an acceptable safety profile.

Given the recent introduction of an upgraded digitalized version of SpyGlass (SpyDS), usefulness should be re-examined while overcoming above-mentioned methodological pitfalls and considering cost-effectiveness.

Compliance with ethical standards

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