Digital Single-operator Cholangioscopy (DSOC) Improves Interobserver Agreement (IOA) and Accuracy for Evaluation of Indeterminate Biliary Strictures

The Monaco Classification

Amrita Sethi, MD, Amy Tyberg, MD,† Adam Slivka, MD,‡ Douglas G. Adler, MD,§ Amit P. Desai, MD,* Divyesh V. Sejpal, MD,‖ Douglas K. Pleskow, MD,¶ Helga Bertani, MD,# Seng-Ian Gan, MD,** Raj Shah, MD,†† Urban Arnelo, MD,‡‡ Paul R. Tarnasky, MD,§§ Subhas Banerjee, MD,‖‖ Takao Itoi, MD,¶¶ Jong Ho Moon, MD,## Dong Choon Kim, MD,## Monica Gaidhane, MD,† Isaac Raijman, MD,*** Bret T. Peterson, MD,††† Frank G. Gress, MD,‡‡‡ and Michel Kahaleh, MD, AGAF, FACG, FASGE†*

Background: Visual characteristics seen during digital single-operator cholangioscopy (DSOC) have not been validated. The aim of this 2-phase study was to define terminology by consensus for the visual diagnosis of biliary lesions to develop a model for optimization of the diagnostic performance of DSOC.

Materials and Methods: In phase 1 (criteria identification), video-cholangioscopy clips were reviewed by 12 expert biliary endoscopists, who were blinded to the final diagnosis. Visual criteria were consolidated into the following categories: (1) stricture, (2) lesion, (3) mucosal features, (4) papillary projections, (5) ulceration, (6) abnormal vessels, (7) scarring, (8) pronounced pit pattern. During the second phase (validation), 14 expert endoscopists reviewed DSOC (SpyGlass DS, Boston Scientific) clips using the 8 criteria to assess interobserver agreement (IOA) rate.

Results: In phase 1, consensus for visual findings were categorized into 8 criteria titled the "Monaco Classification." The frequency of criteria were: (1) presence of stricture—75%, (2) presence of lesion type—55%, (3) mucosal features—55%, (4) papillary projections—45%, (5) ulceration—42.5%, (6) abnormal vessels—10%, (7) scarring—40%, and (8) pronounced pit pattern—10%. The accuracy on final diagnosis based on visual impression alone was 70%. In phase 2, the IOA rate using Monaco Classification criteria ranged from slight to fair. The presumptive diagnosis IOA was fair ($\kappa = 0.31$, SE = 0.02), and overall diagnostic accuracy was 70%.

Conclusions: The Monaco classification identifies 8 visual criteria for biliary lesions on single-operator digital cholangioscopy. Using the criteria, the IOA and diagnostic accuracy rate of DSOC is improved compared with prior studies.

Key Words: single-operator digital cholangioscopy, cholangioscopy, video cholangioscopy, indeterminate biliary stricture

(*J Clin Gastroenterol* 2020;00:000–000)

Video cholangioscopy provides direct endoscopic visualization of the biliary tree.[1–4] The evaluation of indeterminate biliary lesions has widely been an accepted indication for direct video cholangioscopy.[4–6] Peroral cholangioscopy is conventionally performed using a mother-baby scope system. This system is less convenient, labor intensive, time consuming, and requires 2 expert endoscopists using 2 endoscopic systems.[2,7] These requirements limit the general applicability of this cholangioscopy system and limited performance only to expert referral centers.[2]

A new single-operator cholangioscopy system, SpyGlass direct visualization system (Boston Scientific, Natick, MA), has recently been developed. Technical success rates with improved visual capability have been reported with this system, however there is limited expert consensus on image interpretation.[2,8,9] Recent studies have also demonstrated

Received for publication July 15, 2019; accepted January 3, 2020.

From the *Columbia University Medical Center, New York City; ‖North Shore-LIJ Health System, Manhattan; ‡‡‡Mount Sinai Hospital, NY; †Department of Medicine, Rutgers Robert Wood Johnson Medical School, The State University of New Jersey, Robert Wood Johnson University Hospital, New Brunswick, NJ; ‡University of Pittsburgh Medical Center, Pittsburgh, PA; §University of Utah School of Medicine, Salt Lake City, UT; ¶Beth Israel Deaconess Medical Center, Boston, MA; #Nuovo Ospedale Civile S. Agostino Estense, Modena, Italy; **Virginia Mason Medical Center, Seattle, WA; ††University of Colorado, Denver, CO; ‡‡Karolinska Institutet, Solna, Sweden; §§Methodist Dallas Medical Center, Dallas; ***Greater Houston Gastroenterology, Houston, TX; ‖‖Veteran Affairs/Stanford University, Stanford, CA; ¶¶Tokyo Medical University, Tokyo, Japan; ##Soon Chun Hyang School of Medicine, Chungcheongnam-do, Republic of Korea; and †††Mayo Clinic, Rochester, MN.

A.T.: Consultant for Ninepoint Medical, Endogastric Solutions, Obalon Therapeutics. She is a director of Therapeutic Endocopic Ultrasound society. A.S., D.V.S, R.S., D.K.P.: Consultant for Boston Scientific and Olympus Medical. D.G.A.: Consultant for Boston Scientific. I.R.: Speaker for Boston Scientific, ConMed, Medtronic and GI Supplies. He is on the advisory board of Microtech. And he is a co-owner of EndoRx. P.R.T.: Consultant and speaker for Boston Scientific. T.I.: Speaker for Boston Scientific. M.K. has done consulting work for Boston Scientific, Interscope Med, ERBE, Medrobotic and Abbvie. He has received research grants from Boston Scientific, Emcision, Conmed, Pinnacle, Cook, Gore, Merit, and Olympus. He is the CEO and Founder of Innovative Digestive Health Education & Research Inc., and Therapeutic Endoscopic Ultrasound Society. M. G. has done consulting work for Interscope Med and Capvision. She is the COO of Therapeutic Endoscopic Ultrasound Society and Innovative Digestive Health Education & Research Inc. The remaining authors declare that they have nothing to disclose.

Address correspondence to: Michel Kahaleh, MD, AGAF, FACG, FASGE, Department of Medicine, Rutgers Robert Wood Johnson Medical School, The State University of New Jersey, Robert Wood Johnson University Hospital, 1 RWJ Place, MEB 464, New Brunswick, NJ 08901 (e-mail: mkahaleh@gmail.com).

DOI: 10.1097/MCG.0000000000001321

that single-operator cholangioscopy has a higher diagnostic accuracy and sensitivity than conventional endoscopic retrograde cholangiopancreatography (ERCP) for evaluation of indeterminate biliary lesions.[10,11]

Prior studies have demonstrated that endoscopic visual impression is accurate and valuable in differentiating malignant from benign when assessing ductal lesions, however this accuracy drops when intraductal biopsies are obtained.[5,11,12] These results suggest that there is significant importance in the visual endoscopic impression when assessing ductal lesions. However, recent studies with the single operator direct visualization system have demonstrated poor interobserver agreement (IOA) with 45% accuracy among expert biliary endoscopists.[13] These suggests there is a need for consensus agreement to identify and categorize characteristics of suspicious lesions using digital single-operator cholangioscopy (DSOC).

Therefore, the aim of this 2-phase study was to identify specific features to allow for visual characterization of biliary lesions and then to validate a classification scheme for general applicability of DSOC.

MATERIALS AND METHODS

A 2-phase study was conducted involving 14 experts biliary endoscopists.

All expert biliary endoscopists have performed at least 100 cholangioscopies before this study.

Four international centers contributed a total of 42 peroral cholangioscopy and 21 DSOC (SpyGlass DS, Boston Scientific) clips of at least 20 seconds duration. The duration of the clip was selected during our initial investigator meeting.

Clips were collected from adults >18 who underwent ERCP with indeterminate biliary stricture indications. The clips were chosen based on the quality of the clips, duration, final diagnosis, and presence of either benign or malignant criteria.

The first phase comprised of derivation of the Monaco Classification criteria determining diagnosis for indeterminate biliary strictures. The second phase comprised of validating the criteria, correlating each criterion with malignant and benign features. Accuracy, sensitivity, and specificity were also evaluated.

All patients had biopsy proven cancer and all benign lesions were followed up for at least 6 months before being considered benign.

The study was conducted under an IRB approved registry (NCT02166099).

The study started in January 2016 and ended in December 2018.

First Phase—Derivation of Monaco Classification

A total of 42 peroral cholangioscopy clips were reviewed together by 12 experts biliary endoscopists, who were blinded to the final diagnosis. The team reviewed each clip and identified either benign or malignant criteria. At the end of each clip's review, the characteristics identified in that clip were entered into a database. All reviewers were categorized as experts in the field based on having performed >100 cholangioscopies. Consensus definitions were developed for the visual findings and the criteria were developed.

A consensus diagnosis of malignant versus benign was also determined.

TABLE 1. Revised Criteria Observed in Benign or Malignant Diagnoses Clips

	n/N (%)			
Feature	Overall	Malignant, N = 27	Benign, N = 13	*P*
Ulceration	17/40 (42.5)	15/27 (55.6)	2/13 (15.4)	0.0204
Scar present	16/40 (40.0)	8/27 (29.6)	8/13 (61.5)	0.0857
Papillary projections	18/40 (45.0)	15/27 (55.6)	3/13 (23.1)	0.0896
Lesion	22/40 (55.0)	17/27 (63.0)	5/13 (38.5)	0.1854
Pronounced pit	4/40 (10.0)	2/27 (7.4)	2/13 (15.4)	0.5839
Abnormal vessels	4/40 (10.0)	2/27 (7.4)	2/13 (15.4)	0.5839
Presence of stricture	30/40 (75.0)	21/27 (77.8)	9/13 (69.2)	0.7004
Mucosal features	22/40 (55.0)	15/27 (55.6)	7/13 (53.8)	1.0000

P-value compares malignant rate to benign rate.

Second Phase—Validation of Monaco Classification

Twenty-one deidentified DSOC video clips were sent to 14 interventional endoscopists. They were asked to score the videos based on the presence of the 8 criteria listed above.

The endoscopists then based their final diagnosis of neoplastic or non-neoplastic based on the set of criteria. Fleiss κ scores were calculated for the scoring of each of the criteria and the final diagnosis.

RESULTS

First Phase—Derivation of Monaco Classification

After consensus for visual interpretation definitions were achieved, the following 8 criteria were developed and titled "Monaco Classification":

(1) Presence of stricture, and if stricture was asymmetric or symmetric.
(2) Presence of lesion, and if lesion had a mass greater than one-fourth diameter of the duct, or a nodule (size less than one-fourth diameter of the duct), or had a polypoid appearance.
(3) Mucosal features that were either smooth or granular.
(4) Papillary projections, and whether these projections were fingerlike (long) or short.
(5) Ulceration.
(6) Abnormal vessels.
(7) Scarring, and whether scarring was local or diffuse.
(8) Pronounced pit pattern.

TABLE 2. Frequency of Criteria in Benign or Malignant Clips

	n/N (%)	
No. Criteria Observed	Malignant, N = 27	Benign, N = 13
At least 5 criteria	3/27 (11)	1/13 (8)
At least 4 criteria	11/27 (41)	2/13 (15)
At least 3 criteria	10/27 (37)	4/13 (31)
At least 2 criteria	7/27 (3)	6/13 (46)

TABLE 3. Validation of Monaco Classification—Interobserver Agreement

Variables	κ
Slight IOA	
Ulceration	0.06
White linear bands	0.16
Pronounced pits	0.04
Luminal contents	0.19
Fair IOA	
Presence of stricture	0.34
Presence of a lesion	0.26
Mucosal changes	0.26
Abnormal vessels	0.26
Moderate IOA	
Papillary projections	0.43

IOA indicates interobserver agreement.

Forty peroral cholangioscopy (13 benign, 27 malignant) clips were reviewed and scored utilizing the 8 criteria of the Monaco classification. The frequency of observable criteria were: (1) presence of stricture—75%, (2) presence of lesion type—55%, (3) mucosa features—55%, (4) papillary projections—45%, (5) ulceration—42.5%, (6) abnormal vessels—10%, (7) scarring—40%, and (8) pronounced pit—10% (Tables 1, 2).

Multivariate stepwise logistic regression analysis using model selection showed that the ulceration (odds ratio 10.3, $P = 0.01$) and papillary projections (odds ratio 7.2, $P = 0.02$) criteria were the only 2 features found to be highly associated with the diagnosis of malignancy. Clips showing either ulceration or papillary projections were 10 times and 7 times more likely to be diagnosed as malignant, respectively. Twenty-nine patients had either an ulceration or a papillary projection and of those 29, 24 (82.7%) were diagnosed as malignant.

The accuracy of these experts in determining final diagnosis based on visual interpretation of the new criteria alone was 70%.

Second Phase—Validation of Monaco Classification

Twenty-one DSOC (SpyGlass DS, Boston Scientific) clips were reviewed by 14 interventional endoscopists.

The IOA was slight in scoring for ulceration ($\kappa = 0.06$, SE = 0.02) white linear bands ($\kappa = 0.16$, SE = 0.02), pronounced pits ($\kappa = 0.04$, SE = 0.02), or luminal contents ($\kappa = 0.19$, SE = 0.02). The IOA was fair in scoring for the presence of stricture ($\kappa = 0.34$, SE = 0.02), a lesion ($\kappa = 0.26$, SE = 0.02), mucosal changes ($\kappa = 0.26$, SE = 0.02), or abnormal vessels ($\kappa = 0.26$, SE = 0.02) (Table 3).

The IOA was moderate in scoring for papillary projections ($\kappa = 0.43$, SE = 0.02). The presumptive diagnosis IOA was fair ($\kappa = 0.31$, SE = 0.02).

The overall accuracy with Monaco Classification (8 criteria variables) was 70%, which is 20% higher than the previously published 50% IOA accuracy rate using fiber optic cholangioscopy (Figs. 1A–G).

DISCUSSION

Cholangioscopy has gained significant interest as a complement to ERCP in the evaluation of indeterminate biliary strictures. Direct endoscopic visualization improves the accuracy in classifying biliary strictures as benign or malignant.[13] The accurate classification of biliary strictures has significant implications in selecting surgical treatment options versus conservative, surveillance methods for patients. Studies using the optical cholangioscopy system have demonstrated poor interobserver agreement in the classification of these lesions. The introduction of single-operator digital cholangioscopy has provided superior image acquisition and image quality of biliary pathology as compared with prior single-operator optical cholangioscopy. However, the experience in interpreting these visual findings in

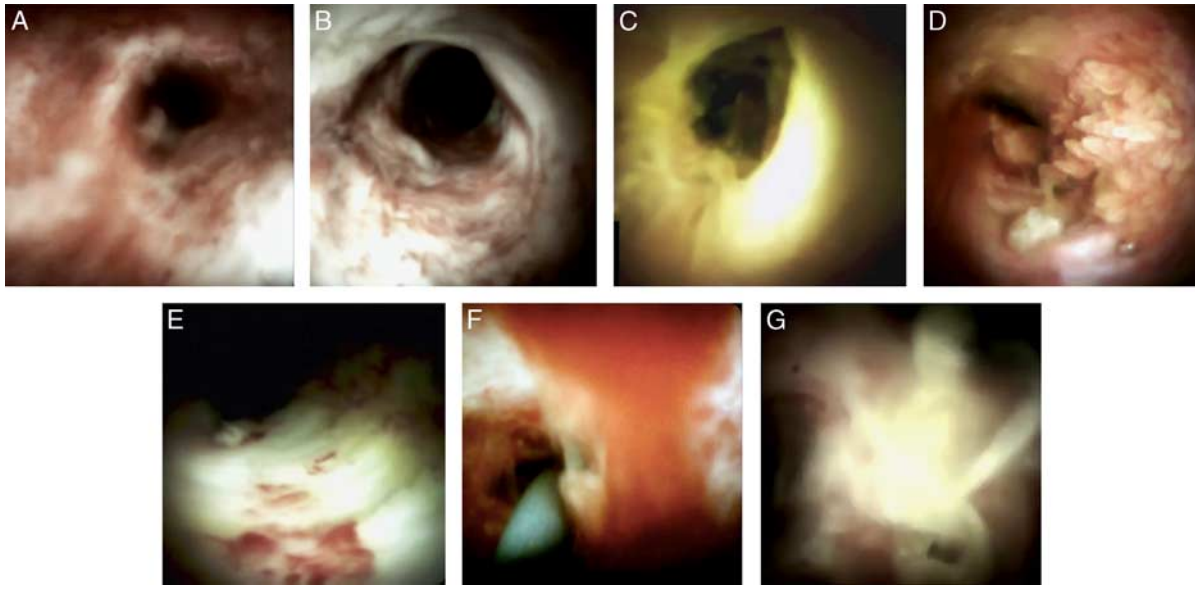

FIGURE 1. A, Digital single-operator cholangioscopy (DSOC) showing biliary stricture. B, DSOC showing abnormal vasculature. C, DSOC showing white linear bands. D, DSOC showing papillary projections. E, DSOC showing ulcerations. F, DSOC showing biliary lesion. G, DSOC showing exudative mucosa.

digital cholangioscopy remains limited, prompting the need to generate visual criteria to differentiate benign from malignant tissue with greater precision.[13]

We performed a retrospective cohort study with derivation and validation cohorts consisting of patients with indeterminate biliary strictures and biliary lesions. The derivation cohort was analyzed by biliary experts to identify suspicious features for malignancy. A separate validation cohort was then evaluated to confirm the accuracy and reproducibility of these features, generating the Monaco Classification for indeterminate biliary strictures and lesions.

Previous studies[14,15] have proposed that dilated or tortuous "tumor vessels," intraductal nodules or papillary projections, ulcerated or infiltrative strictures, and irregular vascular patterns with irregular mucosal surface are suggestive of malignancy. In a prospective clinical cohort study comprising 63 patients, Kim and colleagues[15] found the "tumor vessel" sign to be a predictor of malignancy with a sensitivity of 61% and specificity of 100%. Interestingly, this study showed that ulceration and papillary projections are significant findings suspicious for malignancy. During the revision of the criteria, "pronounced pit pattern" was removed from the classification system. Most papers published on cholangioscopy are not related to the digital single-operator system but offer insight into potential relevant criteria.

A recent paper published by Robles-Medranda et al,[16] introduced also new set of criteria for biliary lesions, assessed by 3 experts and 3 nonexpert cholangioscopists. It demonstrated high reproducibility among observers, for both neoplastic and subtypes categories. However, it was better for experts ($\kappa > 80\%$) than nonexperts ($\kappa = 64.7\%$ to 81.9%).

There are a few limitations to our study. Early in phase 1 of the study, specific parameters were not provided in editing of the clips as to duration, inclusion of specific landmarks, etc. When the criteria were later revised using digital imaging, these parameters were enforced and helped to provide consistency to the quality and contents of the clips.

Although the inclusion of 3 different types of cholangioscopy (video, optical, and digital) may be considered a limitation, we feel that this added to applicability of the Monaco criteria.

Lastly, clinical information was not provided in any phase of this study, which may be considered a limitation as it does not mimic the clinical setting at the time of performing cholangioscopy. However, we considered exclusion of this data a necessity in order to be able to assess the true value of visual findings and the generation of the classification system.

It is important to note that biopsy is still required but believe that the Monaco classification is one more step in the right direction: the establishment of a practical classification facilitating interpretation of intraductal biliary lesions.

In conclusion, the "Monaco classification" is a major step toward digital cholangioscopy interpretation.

Further studies are needed to compare this to other classification systems that have recently been introduced,[16] as well as to determine how to best use the classification system as an adjunctive tool to improve the evaluation of indeterminate biliary strictures and other biliary pathology.

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