EDITORIAL

# Digital single-operator cholangioscopy-guided biopsy for indeterminate biliary strictures: Seeing is believing?

*"The value of experience is not in seeing much, but in seeing wisely."*

–William Osler

The diagnosis and management of biliary strictures still remain a challenge, even in an era of considerable technologic advances regarding our current diagnostic tools.[1] A stricture is considered indeterminate if a diagnosis cannot be made on the basis of clinical information, laboratory results, cross-sectional imaging such as MRCP, and eventually ERCP with tissue acquisition.[1] Physicians confronted with the diagnostic dilemma of an indeterminate biliary stricture must weigh the concern for malignancy against possible benign causes. Although the majority of indeterminate strictures will be malignant, and only 5% to 25% will have a benign cause, the potential morbidity and even mortality related to an unnecessary surgical resection should be taken into consideration.[1,2] Therefore, in many centers, tissue diagnosis is considered a prerequisite to taking a patient to surgery.

Although it is readily available and commonly used, the pooled sensitivity of ERCP-guided brush cytology and analysis of intraductal biopsy specimens for diagnosing an underlying malignancy in a biliary stricture varies between 30% and 60%, with a high positive predictive value but a low negative predictive value.[1] The concept of direct visualization of the biliary duct and targeted biopsy specimens has been explored to increase the diagnostic yield. The first "mother-baby" cholangioscopy systems were cumbersome, required 2 experienced endoscopists, and did not gain widespread acceptance because of procedural difficulties and endoscope fragility.[2] Single-operator cholangioscopy (SOC) with a single-use device was introduced in 2006, thereby overcoming the previous disadvantages. The more recent development is the digital version (DSOC) launched in 2015, which provides high-resolution direct visualization of the bile duct, allowing for targeted tissue acquisition with a dedicated single-use biopsy forceps. Three recent meta-analyses focused on the efficacy of SOC-directed biopsies in differentiating malignant from benign biliary strictures and revealed pooled sensitivity and specificity, respectively, of 60.1% to 71.9% and 98% to 99%.[2-4] Interestingly, SOC visual findings were also assessed and yielded higher sensitivity (84.5%-90%) but lower specificity (82.6%-87%), thus suggesting the possibility of an erroneous diagnosis of malignancy if the diagnosis is based only on the morphologic aspects of the stricture.[3,4]

Gerges et al[5] succeeded in conducting a long-awaited, high-quality, multicenter randomized trial comparing DSOC-directed biopsies with standard ERCP with brush cytology regarding the diagnostic yield in patients with indeterminate biliary strictures. The final study population included 57 patients with indeterminate biliary strictures suspected to be intrinsic (absence of a mass suggesting pancreatic cancer) and located in the proximal part of the common bile duct, based on prior MRCP. Prior ERCP consisted of an exclusion criterion; therefore, none of the included patients had undergone prior intraductal tissue acquisition or biliary stenting, which could have interfered with the morphologic aspects of the stricture. Assessment included visual findings (DSOC vs ERCP cholangiography) and tissue sampling (DSOC-guided biopsies vs ERCP brush cytology). In the DSOC group, an average of 6 biopsy specimens were taken, according to a previous study that concluded that a minimum of 3 DSOC-guided biopsies were necessary to achieve a high diagnostic yield.[6] Final diagnosis was based on surgical specimens or outcome after 6 months of follow-up; on the basis of the above criteria, 36 patients had malignant and 21 benign strictures. The sensitivity of DSOC-guided biopsies was significantly higher than that of ERCP-guided brushing (68.2% vs 21.4%, $P < .01$), whereas other parameters (specificity and overall accuracy) were comparable. Regarding

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visual findings, sensitivity (95.5% vs 66.7%, $P = .02$) and overall accuracy (87.1% vs 65.5%, $P = .05$) were significantly higher in the DSOC group. Adverse events were comparable in both groups. The authors conclude that, compared with standard ERCP-based tissue acquisition, DSOC-guided biopsies provided a higher sensitivity in the histologic diagnosis of indeterminate biliary strictures. Furthermore, DSOC-based visual impressions led to higher diagnostic accuracy and sensitivity compared with conventional ERCP cholangiography; therefore, combining DSOC visual impression with DSOC-guided biopsies provides the highest chance of confirming malignancy in indeterminate biliary strictures.[5]

The above findings further establish the crucial role of DSOC in our repertoire for the management of biliary strictures. Similarly to a previous medical breakthrough, when colonoscopy replaced barium enema for the detection of polyps, it has already been suggested that direct visualization of the mucosa is more efficient than a contrast material–filled image.[7] Nevertheless, despite the existence of suggested criteria for labeling a stricture as malignant (mass, dilatated tortuous vessels, papillary or villous projections, intraductal nodules),[5] we still lack a specific objective validated scoring system to assertively diagnose a biliary stricture as malignant on the basis of visual assessment. Considerable experience is required to be able to correctly interpret DSOC visual findings, and until now, the modalities of the learning curve are still undefined, and interobserver agreement is poor. Indeed, the authors point out that their study findings may not be generalizable because the procedures were performed by expert endoscopists in tertiary referral centers. Additionally, the results of the aforementioned study cannot be extrapolated to patients who have undergone previous ERCP with intraductal brushings or biopsies and eventually biliary stent placement. Indeed, in this case, stent-induced changes can further hinder the correct interpretation of DSOC visual findings.[8] This was illustrated in a recent retrospective study including 80 patients with indeterminate biliary strictures in whom 55% previously undergone biliary stent insertion.[8] The sensitivity and specificity for DSOC visual impression (64% and 62%, respectively) and targeted biopsies (64% and 62%, respectively) were lower than the results reported in the study by Gerges et al.[5] These findings clearly illustrate the limitation in generalizing the findings of the present study in a real-life situation, wherein patients with indeterminate biliary strictures have usually undergone previous ERCP with biliary stenting before being referred for DSOC. Finally, other patient populations with biliary strictures may be more arduous to assess with DSOC, such as patients with primary sclerosing cholangitis (PSC).[8] In the aforementioned retrospective study,[8] patients with PSC represented 40% of the study population. Indeed, comparison of DSOC in PSC and non-PSC patients revealed the lowest sensitivity and specificity in the former.[8]

Cost may represent another obstacle impeding the wide use of DSOC. Despite a recent analysis based on a decision tree model suggesting that DSOC has a better performance than ERCP regarding overall expenditures,[9] true cost-effectiveness studies are lacking. Nevertheless, this would be a challenging endeavor because of differences in healthcare settings regarding reimbursement and true costs of interventions such as surgery.

Finally, parallel to technologic advancement concerning cholangioscopy, impressive progress has been made in deciphering the genomic landscape of neoplasms arising from the biliary tract.[10] Next-generation sequencing combines a high analytic sensitivity with multigene analysis and has been shown to improve the accuracy of pathologic evaluation for both biliary brushing and biopsy specimens, especially in patients with PSC.[10] This test may provide a diagnostic yield that is superior to that of fluorescent in situ hybridization, an assay that detects chromosomal abnormalities in DNA by the use of complementary nuclear hybridizing fluorescent probes and represents the molecular tool with the greatest clinical impact until now.[1]

In conclusion, DSOC is without a doubt a highly performing diagnostic tool, which definitely has its place in the treatment of patients with biliary strictures. Nevertheless, the exact position in the algorithm still needs to be determined, with regard to ERCP and brushings/biopsies, and molecular and genetic analysis of tissue specimens. In any case, we still need to develop a validated reproducible assessment method for visual evaluation during DSOC with determined morphologic criteria and therefore to succeed in "seeing wisely."

## DISCLOSURE

*The author disclosed no financial relationships.*

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*Abbreviations: DSOC, digital single operator cholangioscopy; FISH, fluorescent in situ hybridization; PSC, primary sclerosing cholangitis; SOC, single-operator cholangioscopy.*

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