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Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review

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Abstract

Background and Aims—Evaluation of indeterminate biliary strictures by brush cytology and intraductal biopsies is limited by low sensitivity. The utility of SpyGlass peroral cholangioscopy for diagnosis of malignant biliary strictures and cholangiocarcinoma (CCA), in particular, remains unclear. Our aim was to study the utility of SpyGlass peroral cholangioscopy and targeted biopsy for diagnosis of malignant biliary strictures and CCA.

Methods—In this systematic review, PubMed and Embase databases were reviewed for studies published to October 2014. The main outcomes of interest were sensitivity, specificity, and diagnostic odds ratio (DOR) of SpyGlass cholangioscopy in the diagnosis of malignant biliary strictures.

Results—The search yielded 10 studies involving 456 patients. The pooled sensitivity and specificity of cholangioscopy-guided biopsies in the diagnosis of malignant biliary strictures was 60.1% (95% confidence interval [CI], 54.9%-65.2%) and 98.0% (95% CI, 96.0%-99.0%), respectively. The pooled DOR to detect malignant biliary strictures was 66.4 (95% CI, 32.1-137.5). Four studies included patients who had previous negative imaging and brushings and/or intraductal biopsies. Among these 4 studies, the pooled sensitivity and specificity for diagnosis of malignant biliary strictures was 74.7% (95% CI, 63.3%-84.0%) and 93.3% (95% CI, 85.1%-97.8%), respectively. The pooled DOR was 46.0 (95% CI, 15.4-138.1). Only 1 study directly compared the yield of SpyBite biopsies with standard brushings and biopsies. SpyBite biopsies had a sensitivity of 76.5% compared with brushings (5.8%) and biopsies (29.4%). Six studies specifically reported the role of cholangioscopy with targeted biopsies in the diagnosis of CCA. The pooled sensitivity and specificity to detect CCA was 66.2% (95% CI, 59.7%-72.3%) and 97.0% (95% CI, 94.0%-99.0%), respectively. The pooled DOR to detect CCA was 79.7 (95% CI, 32.7-194.7).

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Conclusions—Our study suggests that SpyGlass cholangioscopy with SpyBite biopsies has moderate sensitivity for the diagnosis of malignant biliary strictures.

Diagnosis of malignancy in a biliary stricture is challenging.^{1,2} When a patient with a biliary stricture is approached, ERCP is used initially.¹ ERCP-based diagnosis of biliary stricture through use of either brush cytology or intraductal biopsies is limited by their poor sensitivity. Hence a significant proportion of strictures remain indeterminate, which has led to development of cholangioscopy-based techniques.³

Per-oral cholangioscopy (POC) can provide endoscopic direct visualization of the biliary system. Single-operator POC (SOPOC) by using the SpyGlass Direct Visualization System (Microvasive Endoscopy; Boston Scientific Corp, Natick, Mass) allows not only optical viewing but also targeted biopsies under direct vision.^{4,5} Previous studies have suggested that the use of SOPOC improves the diagnostic accuracy in approaching indeterminate biliary strictures.^{4,5} No previous study has evaluated the performance of SOPOC and SpyBite (Boston Scientific) biopsies in diagnosis of biliary strictures. The primary aim of this study was to perform a structured systematic review of all eligible studies to evaluate the diagnostic utility of SOPOC for differentiation of malignant from benign biliary strictures. The secondary aim of this study was to evaluate the diagnostic utility of SOPOC for detection of CCA.

METHODS

Literature search

A medical literature search was performed to identify peer-reviewed articles that examined the diagnostic accuracy of POC and/or biopsies to detect malignancy as the etiology of biliary strictures. We systematically searched the PubMed and Embase databases for studies published from January 1980 to October 2014 by using the following search terms: “ERCP cholangioscopy and SpyGlass,” “SpyGlass and strictures,” and “cholangioscopy and SpyGlass” and “cholangioscopy and SpyBite biopsy.” We searched for additional references by cross-checking bibliographies of retrieved full-text articles. Two reviewers (V.L., B.N.) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with the third reviewer (U.N.)

Selection criteria

Only studies involving both cholangioscopy using SpyGlass and SpyBite biopsies in the identification of biliary strictures with availability of data for the construction of 2×2 contingency tables were included. We removed studies with insufficient data and those with a sample size of <10 . The standard criterion for the confirmation of malignancy in the studies was the surgical pathology or autopsy and long-term clinical follow-up. We also determined the usefulness of visual cholangioscopic findings and malignancy. Visual cholangioscopic findings defined a lesion as *definitely malignant* based on the presence of a mass with dilated, tortuous vessels (tumor vessels).

We studied the utility of SpyGlass in indeterminate (benign or inconclusive with strong suspicion for malignancy) strictures. Biliary strictures in which prior brushings and/or biopsy results were negative were categorized as indeterminate (benign or inconclusive with strong suspicion for malignancy) in our study definition.

Index test

The index test was use on SpyGlass and SpyBite biopsy specimens with studies reporting “positive and suspicious for malignancy” in our analysis.

Quality of studies

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) questionnaire was used to evaluate the quality of selected studies.^{6,7}

Statistical analysis

Meta-analysis for the accuracy of SpyGlass visualization and SpyBite biopsies to diagnose malignancy was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. Pooling was performed by using the DerSimonian-Laird method (random effects model). Forest plots were constructed to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the forest plots corresponded to the assigned weight of the study.

The robustness of the meta-analysis to publication bias was assessed by funnel plots and bias indicators, including the Begg-Mazumdar test, and the Harbord-Egger test.^{8,9}

Sensitivity analysis

A sensitivity analysis was conducted for every study to determine undue influence of any particular study. We systematically removed one set of study data and checked the pooled results for the remaining studies to see if there was any significant change in test performance.

Combined weighted sensitivity, specificity, positive likelihood ratio (LR), negative LR, summary receiver operating characteristic curve, and meta regression were determined by use of Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).

RESULTS

Eligible studies and quality assessment

An initial literature search yielded 1333 articles. After excluding irrelevant studies, we reviewed 31 potential studies in detail. Among these, 10 studies (n = 456) met the inclusion criteria and were included in the analysis.^{4,5,10-17} The reported pooled estimates were calculated by the random effect model. Figure 1 shows the flow diagram for studies identified for the systematic review. Table 1 lists the characteristics of various studies included in the meta-analysis.

The quality of the eligible studies as assessed by QUADAS-2 criteria is reported in Figure 2. In most studies, there was a low risk of bias regarding the selection of patients. There were no bias issues or concerns regarding applicability of the selection of patients. There was no risk of bias issues of the index test in any of the studies. In most studies there was a low risk of bias to determine whether an appropriate reference standard was used or its applicability. Ultimately, 10 studies with sufficient data that met our inclusion criteria were included in the final meta-analysis.^{4,5,10-17}

From the studies containing information about the benign and malignant strictures identified through SpyGlass cholangioscopy, 165 (43.2%) were found to have benign etiologies, and 217 (56.8%) had malignant biliary strictures. CCA accounted for 85.3% (N = 185) and pancreatic cancer 9.7% (N = 21) of the malignancies. The rest included gall bladder carcinoma and metastatic cancers.

The indeterminate nature of the strictures was based on previous imaging and/or ERCP findings (defined as previous brush cytology and/or endoscopic biliary biopsy with inconclusive cytology and/or histology or benign cytology and/or histology findings in the presence of a strong suspicion of malignancy). Four studies included patients who all had undergone prior ERCPs with indeterminate (benign or inconclusive with strong suspicion for malignancy) brushing or biopsy pathology results.^{10,12,13,16} Among these 4 studies, the indeterminate nature of the tumors was established based on pathologies from ERCP brushings,^{12,16} ERCP brushings and/or endobiliary biopsy,¹⁰ or ERCP brushing followed by EUS-guided FNA.¹³

SpyGlass cholangioscopic biopsies in all biliary strictures

The pooled sensitivity and specificity for diagnosis of malignant biliary strictures by cholangioscopy-guided biopsies were 60.1% (95% CI, 54.9%-65.2%) and 98.0% (95% CI, 96.0%-99.0%), respectively (Figs. 3 and 4). The pooled positive LR was 21.0 (95% CI, 11.0-40.1) and negative LR was 0.38 (95% CI, 0.29-0.49). The pooled DOR to detect malignant biliary strictures was 66.4 (95% CI, 32.1-137.5).

SpyGlass cholangioscopic biopsies in CCA

Six studies specifically reported the role in the diagnosis of CCA. The pooled sensitivity and specificity were 66.2% (95% CI, 59.7%-72.3%) and 97% (95.0% CI, 94.0%-99.0%), respectively (Figs. 5 and 6). The pooled positive LR was 26.9 (95% CI, 11.7-61.8) and negative LR was 0.37 (95% CI, 0.26-0.52). The pooled DOR to detect CCA was 79.7 (95% CI, 32.7-194.7).

SpyGlass cholangioscopic visual findings in biliary strictures

From the 6 studies that reported the performance of visual cholangioscopic findings in biliary strictures, the pooled sensitivity and specificity were 84.5% (95% CI, 79.2%-88.9%) and 82.6% (95% CI, 77.1%-87.3%), respectively (Figs. 7 and 8). The pooled positive LR was 4.6 (95% CI, 3.5-6.0) and negative LR was 0.11 (95% CI, 0.05-0.29). The pooled DOR to detect CCA was 44.3 (95% CI, 15.3-127.9).

Pooled sensitivities could not be calculated separately for proximal and distal strictures because of lack of data.

SpyGlass cholangioscopic biopsies in all biliary strictures in which prior brushings and/or biopsy results were negative (benign or inconclusive with strong suspicion for malignancy)

Four studies included patients who all had undergone prior ERCPs with indeterminate and/or negative (benign or inconclusive with strong suspicion for malignancy) brushing or biopsy pathology results.^{10,12,13,16} The pooled sensitivity and specificity for diagnosis of malignant biliary strictures by cholangioscopy-guided biopsies in these studies was 74.7% (95% CI, 63.3%-84.0%) and 93.3% (95% CI, 85.1%-97.8%), respectively. The positive LR was 7.9 (95% CI, 3.7-17.1) and negative LR was 0.26 (95% CI, 0.09-0.74). The pooled DOR to detect malignant biliary strictures was 46.0 (95% CI, 15.4-138.1). The pooled sensitivity and specificity for diagnosis of CCA was 67.3% (95% CI, 52.5%-80.1%) and 93.3% (95% CI, 83.1%-98.7%), respectively. The positive LR was 6.7 (95% CI, 2.6-16.9) and negative LR was 0.32 (95% CI, 0.12-0.92). The pooled DOR to detect CCA was 32.1 (95% CI, 8.3-124.4).

Sensitivity analysis

We systematically removed one data set at a time and recalculated the sensitivity and positive LR values for the remaining studies. The largest change occurred when we removed the data set from Nishikawa et al¹⁶ in our meta-analysis of studies with SpyGlass cholangioscopic biopsies in all indeterminate strictures. There was a change in the pooled sensitivity from 60% to 61% (+1.67%), and the corresponding change in negative LR value was from 0.38 to 0.35. These results indicated that no single data set carried enough weight to significantly influence the pooled test performance reported for SpyGlass cholangioscopic biopsies in the diagnosis of indeterminate strictures. Both positive and suspicious pathology were equated in the sensitivity analysis. However, only 3 studies specifically reported the role of positive SpyGlass biopsy in the diagnosis of malignant biliary stricture. Of the remaining 7 studies, 2 studies included suspicious biopsies as malignant,^{14,17} and the remaining 5 studies^{4,5,11,12,16} did not include terminology such as suspicious for cancer in their discussion. The pooled sensitivity and specificity for diagnosis of malignant biliary strictures by cholangioscopy-guided biopsies specifically including positive biopsy results alone was 72.0% (95% CI, 57.0%-84.0%) and 93.0% (95% CI, 82.0%-99.0%), respectively (Supplementary Table 1 and Supplementary Fig. 1, available online at www.giejournal.org).

Publication bias

The Begg-Mazumdar indicator for bias gave a Kendall tau *b* of 0.23; *P*value = .11, and the Egger test, another indicator for publication bias, was -0.15 (95% CI, -0.51 to 0.19; *P* = .42). These tests did not suggest any evidence of publication bias; however, power was low with our small sample size of only 10 studies.

DISCUSSION

Diagnosing malignant etiologies of biliary strictures is a difficult challenge. Cytologic or tissue diagnosis obtained during ERCP by brushing, biopsies, or both is limited by their poor sensitivity.³ Cholangioscopy provides direct visualization of strictures and allows for targeted biopsies, which may help to diagnose or rule out malignancy in indeterminate strictures. In our systematic review, including 10 studies, the pooled sensitivity and specificity for diagnosis of SpyGlass cholangioscopy-guided biopsies in the diagnosis of malignant biliary strictures was 60.1% and 98.0%, respectively. Among the studies specifically reporting the role of SOPOC in CCA diagnosis, the pooled sensitivity and specificity were 66.2% and 97.0%, respectively.

In the 6 studies that reported the visual cholangioscopic impression for diagnosis of biliary strictures, the pooled sensitivity and specificity for detection of malignancy were 84.5% and 82.6%, respectively. For studies in which previous brushings and/or fluoroscopically guided intraductal biopsy results were negative, the pooled sensitivity and specificity for diagnosis of malignant biliary strictures was 74.7% and 93.3%, respectively. This is of particular clinical significance because SpyGlass cholangioscopy aids in the diagnosis of biliary strictures in which brushing and biopsy results were nondiagnostic.

Although the visual impression obtained by SpyGlass cholangioscopy, looking for certain features of cancer, enhances the diagnostic sensitivity (fewer false negatives), diagnosis solely based on visual impression seems to be associated with a loss of specificity (more false positives). This may be due to lax cholangioscopic criteria for labeling a stricture as malignant. Four of the 10 studies^{10,12,13,16} included in our systematic review enrolled patients who had previous indeterminate and/or negative brushing results, and the other studies included patients with indeterminate strictures on previous imaging or cytology. Only 1 study compared the yield of Spy-Bite biopsies with those of standard brushings and intraductal biopsies.¹⁵ SpyBite biopsies had a sensitivity and specificity of 76.5% and 100.0%, respectively, compared with brushings with a sensitivity of 5.8% and biopsies of 29.4%. In our earlier study, the pooled sensitivity and specificity of brushings for the diagnosis of malignant biliary strictures was 45% (95% CI, 45%-50%) and 99% (95% CI, 98%-100%), respectively.⁹ For intraductal biopsies, the pooled sensitivity and specificity were 48.1% (95% CI, 42.8%-53.4%) and 99.2% (95% CI, 97.6%-99.8%), respectively.⁹ A combination of both modalities increased the sensitivity 59.4%, with a specificity of 100%.⁹ This meta-analysis suggests that SpyGlass cholangioscopy visualization with SpyBite biopsy results produces results comparable to those of a combination of standard brushings and biopsies in the diagnosis of malignant biliary strictures. The problem is that only 1 study had compared SpyBite biopsies with standard brushings and biopsies and showed it to be superior. The lack of comparative studies of SpyBite biopsies with the current care of brushings and biopsies in the diagnosis of malignant biliary strictures limits the clinical implications of our observation.

There were a median of 3 to 4 biopsy samples acquired with the SpyBite forceps in the included studies. The small size of the biopsy samples along with only 3 to 4 biopsy samples may have resulted in sensitivity of 66.2% with CCA. In the setting of pancreatic cancer

resulting in indeterminate biliary strictures, the role of cholangioscopy is minimal because EUS with FNA is much more likely to give a diagnosis. This may explain the better sensitivity of cholangioscopy in CCA diagnosis rather than when all patients with indeterminate biliary strictures were included. Also, the studies included in our analysis did not determine the role of SpyGlass cholangioscopy specifically in pancreatic cancer.

We had previously published on the role of brushings, fluorescence in situ hybridization (FISH), and EUS in the diagnosis of malignant biliary strictures.^{18,19} Both brush cytology and intraductal biopsies have a low sensitivity of 44.5% and 49.7%, respectively.³ EUS performs better than these techniques in CCA diagnosis. In a recent meta-analysis, the overall sensitivity of EUS in CCA diagnosis was 66%. However, EUS-guided FNA has a limited role in the diagnosis of hilar strictures (proximal) from CCA because patients get excluded from liver transplantation as per the Mayo Clinic protocol if FNA is performed.²⁰ Given the limitations of these techniques, better diagnostic approaches are required for CCA diagnosis, particularly for those in the proximal location where EUS-guided FNA of the mass cannot be performed.

In this meta-analysis, the pooled DOR, defined as the odds of having a positive result in a patient with true disease compared with a patient who does not have the disease, for cholangioscopically guided targeted biopsy for CCA diagnosis was 79.7. This suggests that SpyGlass biopsies have moderately high diagnostic accuracy for diagnosing CCA. In this study, the pooled positive LR was 26.9 and negative LR was 0.37, highlighting that SpyGlass biopsies are reliable in excluding benign strictures.

There are no direct reported trials of conventional POC and SpyGlass cholangioscopy. Better visualization with direct POC with the availability of large forceps to take biopsies should theoretically increase the yield. It is hoped that future technological updates of SpyGlass will improve the visualization. Also, increasing the number of biopsies may improve its diagnostic utility further in CCA diagnosis. In addition to improvement in SpyGlass technology, it is hoped that development of biomarkers in bile in the future will further improve the sensitivity to diagnose CCA.^{21,22}

This meta-analysis has some limitations. Direct comparative effectiveness data of SpyGlass cholangioscopy in comparison with currently used technology such as brushings and biopsies were lacking in all studies except for one. Only one study directly compared all of the available technology including brushings, intraductal biopsies, and cholangioscopic biopsies for diagnosis. However, 4 studies included patients who had previous evaluation with brushings and/or intraductal biopsies. Also, only 3 studies specifically reported the role of a positive Spyglass biopsy result in the diagnosis of malignant biliary stricture. The other studies either did not distinguish between suspicious or positive findings or failed to comment on it. Also, none of the studies reported the adjunctive role of FISH because it was not routinely performed, at least in large tertiary-care referral centers in clinical practice, until 3 years ago. The drawback with the studies published thus far in SpyGlass cholangioscopy is that they were performed before implementation of FISH in the clinical algorithm for diagnosing CCA. It is important to understand that the tumor board does not allow treatment of CCA based on suspicious cytology alone. Because patients with primary

sclerosing cholangitis were not described in the included studies, our meta-analysis cannot be extrapolated to patients with primary sclerosing cholangitis. Furthermore, these results cannot be applied to direct peroral video cholangioscopy by using ultraslim upper endoscopes because these technologies offer far better image quality compared with the fiber optic image obtained by the currently available SpyGlass system.

The strength of this meta-analysis is that final confirmation was available in all of the studies, and surgical pathology was the confirmatory modality in nearly all cases. In addition, almost all included studies had their pathologists blinded to the clinical information, eliminating observer bias. Bias calculation by using the Egger bias indicator and the Begg-Mazumdar indicator showed no statistically significant publication bias.

To conclude, our study suggests that SpyGlass cholangioscopy with SpyBite biopsies have moderate sensitivity for the diagnosis of malignant biliary strictures. Future trials should develop algorithmic approaches incorporating cholangioscopy targeted biopsies and validate them in diagnosing patients with indeterminate biliary strictures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CCA	cholangiocarcinoma
DOR	diagnostic odds ratio
FISH	fluorescence in situ hybridization
LR	positive likelihood ratio
POC	per-oral cholangioscopy
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SOPC	single-operator POC

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Figure 1.
Flow chart of selected studies.

Figure 2.

The quality of the eligible studies as assessed by QUADAS-2 criteria. *QUADAS*,⁷ Quality Assessment of Diagnostic Accuracy Studies.

Figure 3.

Forest plot of studies reporting the diagnostic role of cholangioscopy-guided biopsies. The pooled sensitivity for diagnosis of malignant biliary strictures by cholangioscopy guided biopsies was 60.1% (95% CI, 54.9%-65.2%). *CI*, confidence interval.

Figure 4.

Forest plot of studies reporting the diagnostic role of cholangioscopy-guided biopsies. The pooled specificity for diagnosis of malignant biliary strictures by cholangioscopy guided biopsies was 98.0% (95% CI, 96.0%-99.0%). *CI*, confidence interval.

Figure 5.

Forest plot of studies reporting the diagnostic role of cholangioscopy-guided biopsies. The pooled sensitivity for the diagnosis of cholangiocarcinoma was 66.2% (95% CI, 59.7%-72.3%). *CI*, confidence interval.

Figure 6.

Forest plot of studies reporting the diagnostic role of cholangioscopy-guided biopsies. The pooled specificity for the diagnosis of cholangiocarcinoma was 97.0% (95% CI, 94.0%-99.0%). *CI*, confidence interval.

Figure 7.

Forest plot of studies reporting the diagnostic role of performance of visual cholangioscopic findings in biliary strictures. The pooled sensitivity for the diagnosis of malignant biliary strictures was 84.5% (95% CI, 79.2%-88.9%). *CI*, confidence interval.

Figure 8.

Forest plot of studies reporting the diagnostic role of performance of visual cholangioscopic findings in biliary strictures. The pooled specificity for the diagnosis of malignant biliary strictures was 82.6% (95% CI, 77.1%-87.3%). *CI*, confidence interval.

TABLE 1

Characteristics of studies including patients with all indeterminate strictures undergoing SpyGlass^{*} biopsies

Author	Patients with biliary strictures undergoing SpyGlass biopsies (no.)	No. of biopsies
Woo et al ¹⁷	19	Mean 3, range 1-6
Nishikawa et al ¹⁶	33	N/A
Draganov et al ¹⁵	26	Minimum 3 bites
Hartman et al ¹⁴	29 (specimens)	Mean 3
Siddiqui et al ¹³	30	Median 5, range 3-7
Manta et al ¹²	52	N/A
Kalaitzakis et al ¹¹	74 (procedures)	Mean 3, range 1-10
Ramchandani et al ¹⁰	33	3-4 biopsies
Chen et al, ⁴	140	Median 3, IQR 3-4
Chen and Pleskow, ⁵	20	112 bites in 20 patients

N/A, not available; IQR, Interquartile range.

* Microvasive Endoscopy; Boston Scientific Corp, Natick, Mass.