Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis

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Background: The most ominous adverse event of primary sclerosing cholangitis (PSC) is development of cholangiocarcinoma (CCA). There is a wide variation in the reported diagnostic yield of bile duct brush cytology in PSC strictures.

Objective: To determine the diagnostic utility of biliary brush cytology for CCA detection in patients with PSC.

Design: Meta-analysis. Systematic search of PubMed, EMBASE, Web of Science, and the Cochrane Library for relevant studies published up to December 2012.

Setting: Meta-analysis of diagnostic parameters.

Patients: A total of 747 patients in studies (both retrospective and prospective) in which histopathologic correlation of CCA was available.

Intervention: Meta-analysis. Construction of 2 × 2 contingency data.

Main Outcome Measurements: Sensitivity, specificity, likelihood ratio, and pooled diagnostic odds ratio.

Results: The search yielded 54 studies of which 11, involving 747 patients, were included in our meta-analysis. The pooled sensitivity and specificity of bile duct brushings for a diagnosis of CCA in patients with PSC were 43% (95% confidence interval [CI], 35%-52%) and 97% (95% CI, 95%-98%), respectively. The pooled diagnostic odds ratio to detect CCA was 20.23 (95% CI, 8.75-46.79). The heterogeneity indices of χ^2 statistics, I^2 measure of inconsistency, and the Cochran Q test were 0.156, 14.4, and 30.5%, respectively. Visual inspection of the funnel plot showed low potential for publication bias.

Limitations: Inclusion of low-quality studies, study heterogeneity.

Conclusion: Our study suggests that bile duct brushing is a simple and highly specific technique for detection of CCA in patients with PSC. However, the modest sensitivity from bile duct brushing precludes its utility as a diagnostic tool for early detection of CCA in patients with PSC. (Gastrointest Endosc 2014;79:783-9.)

(footnotes appear on last page of article)

Primary sclerosing cholangitis (PSC) is a chronic and progressive disease of the biliary tract characterized by obliterative inflammation and progressive fibrosis of intrahepatic and extrahepatic bile ducts that can lead to cirrhosis.[1] PSC confers a markedly increased risk of cholangiocarcinoma (CCA), with a lifetime risk of 10% to 15%.[2,3] It is believed that nearly 10% of patients with PSC undergoing liver transplantation have undiagnosed CCA not detected until the liver is explanted.[4,5] The development of CCA imparts a dismal prognosis for survival and adversely affects the outcome of transplantation. Unfortunately, the occurrence of CCA in PSC is unpredictable, and it is often diagnosed at an advanced stage, precluding curative resection.[5] This underscores the critical importance of a reliable diagnostic tool for early diagnosis of CCA. However, in PSC, the distinction between malignant and inflammatory

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strictures is difficult because the inflammation inherent to this disorder complicates cytologic assessment.

Bile duct brushing is the most common method of tissue sampling in patients with PSC. There is a significant variability in the reported sensitivity and specificity across different studies. To our knowledge, no formal quantitative review of available evidence that comprehensively examines the diagnostic performance of bile duct brushing in PSC has been published. In this study, we performed a structured meta-analysis of all eligible studies to assess the overall diagnostic utility of bile duct brushing in diagnosing CCA in PSC strictures. This meta-analysis and systematic review was written in accordance with the proposal for reporting by Quality of Reporting of Meta-analyses statement.[6]

Take-home Message

- Bile duct brushing is a simple, safe, highly specific technique for detection of cholangiocarcinoma in primary sclerosing cholangitis.
- The results of this meta-analysis suggest that bile duct brushing has moderate sensitivity in detecting cholangiocarcinoma, which precludes its utility as a surveillance tool for early diagnosis of cholangiocarcinoma.

METHODS

Literature search

A comprehensive search of the literature was performed to identify articles that examined the diagnostic accuracy of bile duct brushings in PSC strictures to detect CCA. We systematically searched the PUBMED, MEDLINE, and Cochrane database for studies published until December 2012 by using the search terms "primary sclerosing cholangitis," "PSC," "cholangiocarcinoma," "bile duct brushing," "brush cytology," "biliary tract cytology," and "biliary brush cytology." We searched for additional references by cross-checking bibliographies of retrieved full-text articles. Two reviewers (G.T., 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.).

Study selection criteria

Only studies investigating the use of bile duct brush cytology for detection of CCA in patients with PSC were included. Studies involving malignant biliary strictures were considered only if there was adequate information specifying their yield on PSC strictures. Only studies with data available for the construction of a 2 x 2 contingency table with true-positive, false-negative, false-positive, and true-negative values were included. The criterion standard in all of the studies for cancer was availability of tissue diagnosis of CCA or diagnosis of CCA on long-term follow-up.

The exclusion criteria were (1) studies that did not evaluate PSC strictures with bile duct brushing; (2) studies and/or abstracts with insufficient data; (3) reviews, editorials, or correspondence letters that did not report their own data; and (4) case reports and studies with <10 patients.

Quality of studies

Currently, there is no consensus or criteria to evaluate the quality of studies without a control arm.[7] The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire was used to evaluate the quality of selected studies.[8] Based on this tool, a total of 14 items were appraised, and items were rated as "yes," "no," or "unclear."

Statistical analysis

Meta-analysis for the accuracy of bile duct brushings in PSC strictures to diagnose CCA was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and the diagnostic odds ratio. Pooling was performed by using the Der Simonian-Laird method (random effects model). Forrest 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. Heterogeneity was assessed by using χ^2 statistics, I^2 measure of inconsistency, and the Cochran Q test.

A summary receiver operating characteristic curve was constructed based on the Moses-Shapiro-Littenberg method as a way to summarize the true-positive and false-positive rates from different studies. The proximity of the area under the curve (AUC) to 1 is a well-validated overall representation of the diagnostic accuracy of a test.

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.[9,10]

Sensitivity analysis

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

Combined weighted sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value, 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).