ASGE Guideline on the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology: Summary and Recommendations

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Acronyms:
ASGE American Society for Gastrointestinal Endoscopy; ERCP endoscopic retrograde cholangiopancreatography; EUS endoscopic ultrasound; FNA fine needle aspiration; FISH fluorescence in-situ hybridization; GRADE Grading of Recommendations Assessment, Development and Evaluation; PSC primary sclerosing cholangitis; QALY quality adjusted life years

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This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) using the best available scientific evidence and considering a multitude of variables including, but not limited to, adverse events, patients' values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations which may help standardize patient care, improve patient outcomes, and reduce variability in practice.

We recognize that clinical decision making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgements may, at times, seem contradictory to our guidance due to many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences.

This document is not a rule and should not be construed as establishing a legal standard of care, or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings and/or litigation, as they were not designed for this purpose.

ABSTRACT

This clinical practice guideline from the American Society for Gastrointestinal Endoscopy (ASGE) provides an evidence-based approach for the diagnosis of malignancy in patients with biliary strictures of undetermined etiology. This document was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and addresses the role of fluoroscopic-guided biopsies, brush cytology, cholangioscopy, and endoscopic ultrasound (EUS) in the diagnosis of malignancy in patients with biliary strictures. In the endoscopic work-up of these patients, we suggest the use of fluoroscopic-guided biopsies in addition to brush cytology over brush cytology alone, especially for hilar strictures. Especially for patients with, non-diagnostic sampling we suggest the use of cholangioscopic and EUS-guided biopsies; the former for non-distal and the latter for distal strictures or those with suspected spread to surrounding lymph nodes and other structures.

INTRODUCTION

Cholangiocarcinoma is a rare malignancy with an approximate incidence of 8,000 cases per year in the United States,[1] though it is increasing in frequency.[2, 3] The prognosis of cholangiocarcinoma is poor with an overall 5-year survival rate of about 10%; however, diagnosis at an earlier stage results in a higher likelihood of survival.[1] Therefore, it is important to diagnose malignancy as soon as possible when patients present with biliary strictures.

Patients presenting with a biliary stricture of undetermined etiology often pose a diagnostic challenge. It is estimated that the risk of malignancy in patients with a biliary stricture without an obvious mass on cross-sectional imaging is approximately 55%.[4] Benign etiologies of biliary strictures associated with diseases include primary sclerosing cholangitis (PSC), immunoglobulin G subclass 4 (IgG4) related sclerosing cholangitis, fibrotic strictures, and chronic pancreatitis. The appearance of a benign biliary stricture on cross-sectional imaging often mimic the appearance of a malignant biliary stricture. Thus tissue acquisition is required to distinguish malignant and benign biliary strictures.

Diagnostic modalities for biliary strictures are limited, however, endoscopic approaches are preferred over percutaneous sampling approaches which require an external drain and risk needle track seeding, or surgical approaches. Tissue acquisition in biliary strictures relies heavily on endoscopic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, intraductal biopsies, cholangioscopy, or endoscopic ultrasound (EUS) with fine needle aspiration (FNA) or biopsy (FNB). However, these techniques have limitations, particularly low sensitivity for the diagnosis of malignancy and needle track seeding in the setting of EUS FNA of hilar strictures.[5] The diagnosis of malignancy in biliary strictures often requires multiple procedures resulting in increased cost and patient anxiety as well as delay in diagnosis and potential curative treatment. Therefore, the aim of this guideline is to provide evidence-based recommendations for the endoscopic approach to undetermined biliary strictures.

METHODS

This document was prepared by the Standards of Practice Committee of the ASGE and was conceptualized and conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[6-8] Evidence was presented to a panel of experts representing various stakeholders including a surgical oncologist, medical oncologist, and interventional radiologist. A patient advocate was also included. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies. In developing these recommendations, we took into consideration the certainty of the evidence, benefits and harms of different management options, feasibility, patient values and preferences, resource utilization, cost-effectiveness, and health equity. The final wording of the recommendations, including direction and strength, were approved by all members of the panel and the ASGE governing board. Stronger recommendations are typically stated as "we recommend…" whereas weaker recommendations are indicated by phrases such as "we suggest…".

These guidelines addressed the following three clinical questions using the GRADE format:

1. In patients with undetermined biliary strictures, should ERCP with fluoroscopic-guided biopsies be performed versus ERCP with brush cytology to diagnose malignancy?
2. In patients with undetermined biliary strictures, should ERCP with cholangioscopic-guided biopsies be performed versus ERCP without cholangioscopy to diagnose malignancy?
3. In patients with undetermined biliary strictures, should endoscopic ultrasound (EUS) with fine needle aspiration/biospy (FNA/FNB) be performed versus ERCP with any form of tissue acquisition to diagnose malignancy?

Indeterminate biliary strictures historically have been defined as a stricture in which prior ERCP had inconclusive cytology results. However, this guideline uses the term *undetermined* biliary strictures rather than *indeterminate* biliary strictures as it included studies that had patients undergoing their first ERCP without a prior negative brush cytology. It is important to make this distinction to emphasize the importance of other forms of tissue acquisition that can be used in addition to brush cytology in the initial diagnostic work-up of biliary strictures suspected to have underlying malignancy.

Relevant clinical outcomes included incremental yield, diagnostic test characteristics (sensitivity, specificity, positive predictive value, negative predictive value), technical success, specimen adequacy, and adverse events. Technical success was defined as the percentage of cases where the endoscopist was able to perform the desired tissue sampling, while specimen adequacy was a pathological diagnosis with enough cellular components to make a determination of malignant or benign.

RESULTS/SUMMARY OF RECOMMENDATIONS

Details of our literature searches, data analyses, pooled effect estimates, evidence profiles, forest plots, and panel deliberations for each outcome can be found in the methodology and technical review document. A summary of our final recommendations is listed in **Table 1**.

Question 1: In patients with biliary strictures of undetermined etology, should ERCP with fluoroscopic-guided biopsies be performed in addition to brush cytology versus ERCP with brush cytology alone to diagnose malignancy?

Recommendation 1. In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests the addition of fluoroscopic-guided biopsies with brush cytology to brush cytology alone to diagnose malignancy.

(Conditional recommendation/very low quality of evidence)

Summary of evidence

A de novo systematic review and meta-analysis of 21 observational studies (20 full text, 1 abstract) with a total of 2,726 patients that compared ERCP with fluoroscopic-guided biopsies in combination with brush cytology versus brush cytology alone.[9-29] The incremental yield of intraductal biopsies with brush cytology over brush cytology alone was 20% [95% confidence interval (CI) 9-31%, I^2 54.5%] in diagnosing malignancy.[13, 15, 16, 20, 22, 23, 28] The miss rate of brush cytology alone was 58% (95% CI 46-71%, I^2 79.5%) in diagnosing malignancy while the miss rate of biopsies alone was 41% (95% CI 31-52%, I^2 80.3%).[9, 13, 15, 20, 23, 28, 30] The sensitivity of brush cytology alone was 0.4 (0.37-0.43, I^2 69.5%; p=).[9, 10, 12-20, 25-27, 29, 31] The sensitivity of fluoroscopic-guided biopsies was significantly higher at 0.52 (0.49-0.56, I^2 79.4%; p=0.006) as was the sensitivity of fluoroscopic-guided biopsies in combination with brush cytology at 0.66 (0.63-0.69, I^2 48.4%; p<0.001) [9-13, 15-20, 22, 24-28] compared to brush cytology alone. Subgroup analyses did not reveal a difference in the sensitivity of brushings vs biopsies for proximal/distal strictures and biliary/pancreatic masses.

There was no difference in technical success of brush cytology and fluoroscopic-guided biopsies in the reported studies [odds ratio (OR) 3.27 (95% CI 0.52-20.53), I^2 65%].[9, 15, 16, 18, 20, 21, 24, 27] Nevertheless, the panel acknowledged that intraductal biopsies are technically more difficult to obtain and require more expertise as they often are typically performed without direct endoscopic visualization. Therefore, some studies may not have necessarily attempted intraductal biopsies in all strictures. Based on our analysis, specimen adequacy was higher for brush cytology,[9, 10, 15, 16, 18-21, 24, 26, 28] but this was based on an intention to treat analysis and hence, is likely a reflection of the technical difficulty and failures of fluoroscopic-guided biopsies rather than the specimen quality itself. There was no difference in adverse events between brush cytology and intraductal biopsies [OR 0.53 (95% CI 0.14-2.05), I^2 0%],[15, 16, 19-21, 26, 29] although the overall number of events was low at 2 and 5 patients (out of more than 500 in each group) in the brush cytology and intraductal biopsies groups, respectively. However, the

two severe adverse events of prolonged bleeding and perforation requiring surgical choledochotomy occurred in the fluoroscopic-guided biopsy group.

Our literature search on this topic revealed no significant difference in costs or health equity with intraductal biopsies or brush cytology. A cost utility study showed that biopsies were cost effective based on a willingness to pay threshold of less than $50,000.[32]

Based on the increased incremental yield, lower miss rate, higher sensitivity and overall low adverse event rate, the panel was in favor of adding fluoroscopic-guided biopsies to cytology brushings in the work-up of biliary strictures of undetermined origin. The panel expressed some concerns about the feasibility and safety of intraductal biopsies since this is more technically challenging, is more time consuming, and had more severe adverse events than brushigns alone. Therefore, the panel made a conditional recommendation acknowledging that biopsies should be performed either at tertiary care centers or where there is endoscopic expertise.

Question 2: In patients with a biliary stricture of undetermined etiology, should ERCP with cholangioscopic-guided biopsies be performed versus ERCP without cholangioscopy to diagnose malignancy?

Recommendation 2. In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests the use of cholangioscopic-guided biopsies in:

a) Non-distal biliary strictures where there is a high probability of adequate drainage of the critical liver segment or
b) Previous nondiagnostic ERCP without cholangioscopy and
c) Centers with clinical expertise and easy access to the equipment

Otherwise, the ASGE suggest ERCP with or without cholangioscopy in the diagnosis of malignancy

(Conditional recommendation/very low quality of evidence)

Summary of evidence

A de novo systematic review and meta-analysis identified 13 studies (1 randomized control trial, 12 observational studies)[9, 10, 14, 30, 33-41] with a total of 1,529 patients who underwent ERCP with cholangioscopy and ERCP with other means of tissue acquisition, such as fluoroscopic-guided biopsies, brush cytology, or both. The incremental yield of ERCP with cholangioscopy over ERCP without cholangioscopy was 27% (9-46%, I^2 56.8%) in 4 observational studies[9, 30, 33, 36] and 41% (11-72%) in the only randomized controlled trial evaluating this outcome.[30] The sensitivity of ERCP with cholangioscopy was significantly higher than ERCP without cholangioscopy [0.72 (0.66-0.77), I^2 71.8% vs 0.61 (0.57-0.66), I^2 79.9%, respectively, p=0.001).[9, 10, 14, 30, 33-41] One study reported a higher sensitivity for distal strictures during ERCP with intraductal biopsies (sensitivity 76%) compared to ERCP with cholangioscopic-guided biopsies (sensitivity 50%).[34] No difference in sensitivity was found between ERCP with and without cholangioscopy for proximal bile duct strictures in this study.

There was no difference in technical success[9, 30, 33], specimen adequacy [0.96 (0.23-4), I^2 0%][9, 30, 33, 34], or adverse events [0.58 (0.26-1.26), I^2 0%][30, 35, 38] between ERCP with and without cholangioscopy. The most common adverse event for both groups was acute pancreatitis, the majority of cases being mild episodes. One study reported the additional time needed to do the cholangioscopy portion of the ERCP to be 14 minutes (95% CI 10-20).[9]

As expected, there is a high cost of cholangioscopy. One study quoted an additional $2,637 when cholangioscopy is done during ERCP with stent placement.[42] Furthermore, access to cholangioscopy is limited primarily to tertiary referral centers with experienced operators. However, the use of cholangioscopy has been shown to be cost effective, and decreases the overall number of procedures and costs required to diagnose malignancy.[32] In patients with primary sclerosing cholangitis (PSC), cholangioscopy had an incremental quality-adjusted life years (QALY) gain of 0.22 at an additional cost of $8,562.44.[32] This resulted in a base case incremental cost-effectiveness ratio (ICER) of $39,277.25 which is below the willingness-to-pay threshold of less than $50,000. In this study, cholangioscopy was more cost effective than brush cytology, fluoroscopic-guided biopsies, and flourescence in-situ hybridization (FISH) analysis.

Based on the incremental yield of at least 27% higher sensitivity, no difference in adverse events, and overall cost effectiveness, the panel was in favor of ERCP with cholangioscopy in the diagnostic approach for undetermined biliary strictures. However, with the lack of widespread availability, higher cost, and need for additional training on the technicalities of cholangioscopy, the panel emphasized the importance of cholangioscopy being performed at a tertiary center with expertise in this technique. Furthermore, since cholangioscopy is often difficult and less accurate in the very distal portion of the bile duct due to cholangioscope instability and difficulty passing the mini forceps biopsy, cholangioscopy may not be the optimal approach for distal biliary strictures.

The panel emphasized the importance of adequate proximal biliary segment drainage following cholangioscopy. Since cholangioscopy requires the instillation of water/saline, there is a risk of introducing infection into the proximal biliary tree if it is not drained adequately.[43] Therefore, some experts on the panel expressed preference to not perform cholangioscopy during the initial ERCP but rather wait until the decompression of the proximal ducts is ensured, while others would consider cholangioscopy during the initial session as long as drainage of the proximal ducts appeared feasible.

Although this guideline focused on cholangioscopy-guided biopsies, the panel wanted to also emphasize the importance of interpreting the visualized images during cholangisocopy to help differentiate benign vs malignant strictures. Malignant strictures can appear nodular, papillary or infiltrative.[11060187] Nodular masses have irregular mucosa with severe neovascularization that can obstruct the lumen, while papillary masses have numerous papillary projections and less neovascularization, and infiltrative masses cause luminal narowings without a discrete mass but has more whitish mucosal discoloration and neovascularization. Understanding the distinguishing features of a malignant stricture can assist with targeting the cholangioscopic-guided biospies to potentially increase the diagnostic yield of this technique.

Question 3: In patients with biliary strictures of undetermined etiology, should endoscopic ultrasound (EUS) with fine needle aspiration (FNA) or fine needle biopsy (FNB) be performed versus ERCP with any form of tissue acquisition to diagnose malignancy?

Recommendation # 3: In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests EUS in addition to the ERCP for the diagnosis of malignancy in the presence of:

a) Prior ERCP with nondiagnostic ERCP results
b) Distal biliary stricture, or
c) Presence of lymphadenopathy or metastatic disease on cross-sectional imaging

(Conditional recommendation/very low quality of evidence)

Summary of evidence

A meta-analysis by Chiang et al on the incremental benefit of EUS over ERCP was identified.[44] A systematic review of the topic did not find any additional studies. In this meta-analysis, the incremental benefit of EUS after nondiagnostic ERCP with brush cytology was found to be 15% (95% CI 9-24%, I^2 0%). In 11 studies, the pooled sensitivity of ERCP alone with any method of

tissue acquisition was no different than EUS alone [ERCP sensitivity 0.7 (0.66-0.73), I^2 86.6% vs EUS sensitivity 0.74 (0.71-0.77), I^2 90%, p=0.31].[17, 23, 29, 37, 38, 45-49] However, in 8 studies, the pooled sensitivity of combined EUS + ERCP was significantly higher than ERCP alone [ERCP + EUS sensitivity 0.88 (0.85-0.91), I^2 53.6% vs ERCP alone sensitivity 0.61 (0.57-0.64), I^2 86.4% respectively, p<0.001].[17, 23, 37, 46-50]

On subgroup analyses, EUS had a higher sensitivity than ERCP for distal strictures [0.82 (0.76-0.87) vs 0.62 (0.55-0.69), respectively][17, 45] and pancreatic masses [0.82 (0.78-0.86) vs 0.46 (0.4-0.51), respectively, p<0.0001].[17, 23, 45, 46, 48, 49]

There was no difference in technical success[17, 46-48, 50] or specimen adequacy[17, 48, 49] when comparing ERCP and EUS. EUS had a significantly lower adverse event rate [OR 8.11 (95% CI 2.95-22.29)] with only 3 minor bleeding episodes occurring with EUS with FNA compared to 44 adverse events with ERCP (1 severe pancreatitis, 27 mild pancreatitis, 10 cholangitis, and 6 mild bleeding).[29, 37, 38, 46, 49, 51] According to one study which used historical controls, EUS added an average of 23 minutes (95% CI 14-32 minutes) to the procedure time.[50]

There was a minor cost increase when EUS and ERCP were performed in the same session. Although one study reported the cost of EUS with FNA to be $1,076.25, the panel stressed that the cost is much lower when combined with ERCP than when performed alone.[42] EUS was found to be cost effective in patients with a biliary stricture even without a discrete mass.[52] The panel took into account that EUS is not as widely available throughout the country as compared to ERCP.

With the incremental benefit of EUS, lower adverse event rate, and cost effectiveness, the panel was in favor of performing EUS in patients with a biliary stricture of undetermined etiology. It was clear that EUS is beneficial in the setting of distal biliary strictures and if a pancreatic mass, lymphadenopathy, or metastatic disease is noted within reach of the

echoendoscope on cross-sectional imaging, then EUS should be performed. Some experts on the panel routinely performed EUS combined with ERCP on any biliary stricture, while others were less keen to perform EUS on proximal strictures due to the lower diagnostic yield and additional time involved. It must be emphasized that there is the risk of needle tract seeding during EUS FNA/FNB of hilar cholangiocarcinoma which may exclude patients from undergoing liver transplantation.[5] Therefore if an EUS is performed in the setting of proximal/hilar strictures, the endosonographer should ***not*** perform FNA/FNB of the biliary mass itself.

OTHER CONSIDERATIONS

The panel consider other endoscopic techniques such as intraductal ultrasound (IDUS) and confocal laser endomicroscopy (CLE) which have been studied in patients with biliary strictures. IDUS findings that are suggestive of malignancy include an intraluminal mass with an irregular margin, wall thickness >9 mm, heterogeneous lesion with an uneven mucosal surface, eccentric wall thickening, destruction of the wall layers, and masses that invade the surrounding tissue. [28738976,17451708] IDUS has been shown to increase the sensitivity of diagnosing malignant strictures compared to ERCP alone.[16032489,12196775,12397276] Our previous guidelines consider IDUS is a promising technique in the evaluation of indeterminate biliary strictures.[26147492] Since it is more widely available now, IDUS could potentially be considered to help localize the malignant appearing region for targeted biopsy. One study showed the diagnostic accuracy of IDUS-guided transpapillary biopsy was significant higher than transpapillary biopsy alone (90.8% vs 76.9% respectively, p=0.028).[29409305] However the utility of this techniques needs to be further studied before a recommendation can be made on its wide-spead adopation into clinical practice.

Similaly, CLE uses thin confocal laser probes inserted through the working channel of the duodenoscope (pCLE). A group of endoscopist formed the Miami classification system based on consensus to help differentiate benign vs malignant biliary stricture.[21818734] Malignant biliary strictures included thick dark bands of the collagen fibrils and thickened white bands within the vessels. A limitation of the Miami classification is the low interobserver agreement. Subsequently, the Paris classification further defined the criteria for benign inflammatory strictures including vascular congestion, dark granular patterns with scales, increased inter-glandular space, and thickened reticular structures.[23314855] A meta-analysis had a pooled sensitivity of 90% (95% CI 86.94%, I^2 1.6%) and specificity of 72% (95% CI 65-79%, I^2 0%).[26989684] One systematic review mentioned that its best application may be in that it had a high negative predictive value for malignancy of 94%.[34839621]. Based on thism the panel noted that CLE is difficult master and also expensive. Therefore, its wide-soead adotpation is likely limited in the near future.

FUTURE DIRECTIONS

Our systematic literature review highlighted several areas in need of additional higher quality data to inform the role of endoscopy in the diagnosis of malignancy in biliary strictures of undetermined etiology. Future studies should address the following:

1. Randomized control trials to address the above clinical questions to improve our knowledge on the topic
2. Focus on patients with primary sclerosing cholangitis as the diagnostic algorithm may change in this patient population where FISH analysis plays a higher role

3. Role on technologic developments such as mini over-tubes to facilitate intraductal biopsies, improvements on cholangioscopy platforms and tissue sampling devices, and novel imaging modalities such as confocal laser microscopy to improve the diagnosis of biliary malignancies
4. Role of adjunctive pathologic analyses such as next-gen sequencing, flow cytometry, FISH anaylsis, digital image analysis (DIA), etc in the diagnostic algorithm
5. Diagnostic yield of performing cholangioscopy and/or EUS on consecutive patients who present with biliary strictures (instead of limited to those in whom cholangioscopy is techically successful)
6. Interval of time before next ERCP(s) when nondiagnostic.
7. 6. Utility of AI guided visual interpretation and AI guided sampling during cholangioscopy and EUS for indeterminate biliary strictures.

SUMMARY & CONCLUSIONS

These ASGE guidelines use the best available evidence to make recommendations for the role of endoscopy in the diagnosis of malignancy in patients with biliary stricture of undetermined etiology. If the endoscopic expertise is available, it is suggested that ERCP with fluoroscopic-guided biopsies and brush cytology be performed for any location of the biliary stricture while cholangioscopy and EUS should also be considered, particularly in non-distal and distal biliary strictures, respectively.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years, or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

Table 1. Summary of recommendations

Question	Recommendation	Quality of Evidence	General Concepts
1	In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests the addition of fluoroscopic-guided biopsies with brush cytology to brush cytology alone to diagnose malignancy.	Conditional recommendation, very low quality of evidence	• Review all cross-sectional imaging • Discuss patient in a multidisciplinary board/committee
2	In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests the use of cholangioscopic-guided biopsies in: a) Non-distal biliary strictures where there is a high probability of adequate drainage of the critical liver segment or b) Previous nondiagnostic ERCP without cholangioscopy and c) Centers with clinical expertise and easy access to the equipment Otherwise, the ASGE suggest ERCP with or without cholangioscopy in the diagnosis of malignancy	Conditional recommendation, very low quality of evidence	• Discuss results with dedicated GIU pathologist • Ensure careful alignment and advancement of forceps into the CBD under fluoroscopic guidance
3	In patients with a biliary stricture of undetermined etiology undergoing ERCP, the ASGE suggests EUS in addition to the ERCP for the diagnosis of malignancy in the presence of: a) Prior ERCP with nondiagnostic ERCP results b) Distal biliary stricture , or c) Presence of lymphadenopathy or metastatic disease on cross-sectional imaging	Conditional recommendation, very low quality of evidence	• Upfront EUS should be considered in centers with the ability to do EUS and ERCP in the same session • If EUS is performed in the setting of hilar strictures, it is important for the endoscopist to avoid biopsy of the biliary mass itself

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Acronyms:
ASGE American Society for Gastrointestinal Endoscopy;

ERCP endoscopic retrograde cholangiopancreatography;

EUS endoscopic ultrasound;

FNA fine needle aspiration;

FISH fluorescence in-situ hybridization;

GRADE Grading of Recommendations Assessment, Development and Evaluation;

PSC primary sclerosing cholangitis;

QALY quality adjusted life years