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Number 50

Endoscopic Retrograde Cholangiopancreatography

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Prepared by:
Technology Evaluation Center
Blue Cross and Blue Shield Association
Naomi Aronson, Ph.D.
Program Director
Carole Redding Flamm, M.D., M.P.H.
Project Director

David Mark, M.D., M.P.H.
Frank Lefevre, M.D.
Rhonda L. Bohn, Sc.D., M.P.H.
Beth Finkelstein, Ph.D., M.P.H.
Investigators

Kathleen M. Ziegler, Pharm.D.
Claudia J. Bonnell, B.S.N., M.L.S.
Maurice Carter
Research/Editorial Staff

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

Carolyn Clancy, M.D.
Acting Director
Agency for Healthcare Research and Quality

Robert Graham, M.D.
Director, Center for Practice and
Technology Assessment
Agency for Healthcare Research and Quality

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Structured Abstract

Objectives. Diseases of the pancreas and biliary tree are common in the United States. Prevalence of common bile duct stones is estimated at 6 per 100,000. Incidence of pancreaticobiliary malignancy is approximately 57,400 annually, most with poor prognosis. A variety of diagnostic and therapeutic interventions have been developed to manage these conditions. This systematic review of the evidence on the diagnostic and therapeutic effectiveness of endoscopic retrograde pancreatography (ERCP) addresses four clinical conditions: (1) common bile duct stones; (2) pancreaticobiliary malignancy; (3) pancreatitis; and (4) abdominal pain of possible pancreaticobiliary origin. In addition, the evidence on determinants of complications of ERCP and on the prediction of common bile duct stones are reviewed.

Search Strategy. The PubMed/MEDLINE, BIOSIS, EMBASE, and SCISEARCH databases with a publication date from 1980 through August 13, 2001 were searched for articles indexed to the NLM Medical Subject Heading (MeSH®) "cholangiopancreatography, endoscopic retrograde" and ERCP synonyms and textword combinations. Search was limited to articles on human subjects published in the English language with an online abstract and supplemented by manual searching. Yielded was 5,698 citations.

Selection Criteria. Inclusion was limited to published reports. For diagnostic and therapeutic effectiveness, inclusion was limited to comparative studies prospectively designed or using appropriate retrospective sampling with a prespecified minimum number of subjects. For prediction studies, 100 subjects were required. There were 789 articles retrieved for review, yielding 149 included studies.

Data Collection and Analysis. The protocol was designed prospectively to define: study objectives; search strategy; patient populations; study selection criteria; outcomes; data elements and abstraction; and study quality assessment. One reviewer performed primary data abstraction into evidence tables and a second reviewer checked accuracy. Data synthesis was qualitative.

Main Results.

- Most diagnostic studies were small, did not use common reference standards, and many did not report statistical significance; thus, equivalence and difference among tests cannot be quantified. Qualitative assessment of the available evidence suggests that:

  —Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) provide similar diagnostic performance as ERCP for detecting common bile duct stones or malignant pancreaticobiliary obstruction.

  —Sensitivity of nonsurgical tissue sampling techniques for detecting malignancy is similar or higher for brush cytology versus bile aspiration cytology, similar for fine-needle aspiration (FNA) cytology versus brush cytology, and similar or higher for forceps biopsy versus brush cytology.

- Robust evidence is lacking to compare strategies for treatment of common bile duct stones.

- The absence of any risk factors for common bile duct stones (i.e., clinical jaundice or elevated bilirubin, elevated liver function tests, dilation on ultrasound) is a strong predictor of the absence of stones.

- For palliation of biliary obstruction of malignancy, outcomes of surgical bypass and ERCP stenting are similar, but major complications are greater for surgery and stent replacement occurs with ERCP. Total resource utilization was reported to be lower with metal than plastic stents. Pre-operative stenting has greater overall complications than surgery alone and does not appear to improve surgical outcomes.

- Evidence on treatment of chronic pancreatitis and relapsing or recurrent pancreatitis is sparse.

- Endoscopic sphincterotomy appears to relieve pain in patients with pancreaticobiliary pain, sphincter of Oddi dysfunction, and elevated basal sphincter of Oddi pressure on manometry.

- Factors associated with complications of ERCP were age 60 years or less, suspected sphincter of Oddi dysfunction, precut endoscopic sphincterotomy, difficulty in cannulation, multiple pancreatic contrast injections, and case volume.

Conclusions. Rigorous studies are required in order to reliably quantify the relative performance of diagnostic ERCP compared to alternatives. Comparative studies of alternative diagnostic and treatment strategies for common bile duct stones are urgently needed. Interventions intended to reduce complications of ERCP should incorporate prospectively defined studies to evaluate results.

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Agency for Healthcare Research and Quality

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Endoscopic Retrograde Cholangiopancreatography

Summary

Overview

Diseases of the pancreas and biliary tree are common in the United States. An estimated 6 per 100,000 people are afflicted with common bile duct stones, representing only a small fraction of those with gallstones. There are approximately 57,400 newly diagnosed cases of malignancy of the pancreas, gallbladder, or extrahepatic biliary tract each year, and the prognosis is usually poor. Pancreatitis can occur in an acute, acute recurrent, or chronic pattern, with common etiologic factors including alcohol consumption and choledocholithiasis.

This report is the product of a systematic literature review of the evidence on the diagnostic and therapeutic effectiveness of endoscopic retrograde pancreatography (ERCP) focusing on four clinical conditions: common bile duct stones, pancreaticobiliary malignancy, pancreatitis, and abdominal pain of possible pancreaticobiliary origin. In addition, the evidence describing patient, procedure, or operator determinants of complications of ERCP is systematically reviewed. The evidence on the prediction of common bile duct stones is reviewed as well.

Reporting the Evidence

The clinical topic areas addressed in this evidence report were developed by the planning committee for the National Institutes of Health State-of-the-Science Conference (January 2002) on Endoscopic Retrograde Cholangiopancreatography. For each major topic, there are several key questions that address the most pertinent diagnostic and therapeutic issues.

Topic 1. Patients with known or suspected common bile duct stones

a. What is the diagnostic performance of ERCP in detecting common bile duct stones in comparison to alternatives? Alternatives include endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), or computed tomography cholangiography (CTC).

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical management?

c. What is the diagnostic value of specific risk factors or predictive models for assessing the likelihood of having a common bile duct stone?

Topic 2. Patients with known or suspected pancreaticobiliary malignancy

a. What is the comparative diagnostic performance of ERCP tissue sampling techniques in establishing a tissue biopsy diagnosis of pancreaticobiliary malignancy, and how do these techniques compare to alternative nonsurgical tissue sampling techniques (e.g., endoscopic ultrasound-guided fine-needle aspiration [FNA] or percutaneous FNA)?

b. What is the diagnostic performance of ERCP in diagnosing the presence of malignant pancreaticobiliary obstruction in comparison to other imaging alternatives (e.g., EUS or MRCP)?

c. What are the outcomes of treatment using ERCP strategies to treat malignant pancreaticobiliary obstruction compared to using surgical or interventional radiology treatment?

Topic 3. Patients with pancreatitis

a. What is the diagnostic performance of ERCP in detecting underlying causes or complications of pancreatitis that are amenable to treatment in comparison to alternatives (e.g., EUS or MRCP)?

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy?

Topic 4. Patients with abdominal pain of possible pancreaticobiliary origin

a. What is the diagnostic performance of ERCP with sphincter of Oddi manometry in identifying a pancreaticobiliary origin of pain in comparison to alternatives (e.g., biliary scintigraphy, EUS, or MRCP)?

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy?

Topic 5. What patient, procedure, or operator factors are determinants of complications of ERCP?

Methodology

The protocol for this review was designed prospectively to define study objectives, search strategy, patient populations of interest, study selection criteria, outcomes of interest, data elements to be abstracted and methods for abstraction, and methods for study quality assessment.

One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer checked accuracy of the evidence tables. Disagreements were resolved between the two reviewers, or if necessary, in consultation with the Evidence-based Practice Center Director or members of the Technical Advisory Group.

Search Strategy for the Identification of Articles

The National Library of Medicine (NLM) staff conducted a comprehensive literature search for journal articles on ERCP from the PubMed®/MEDLINE®, BIOSIS, EMBASE, and SciSearch® databases with a publication date from 1980 through August 13, 2001. Articles which had been indexed to the NLM Medical Subject Heading (MeSH®) "cholangiopancreatography, endoscopic retrograde" as well as those containing the following list of ERCP synonyms and textword combinations were retrieved:

Endoscopic retrograde cholangiopancreatogr?

Endoscopic retrograde cholangio-pancreatogr?

Endoscopic retrograde pancreatocholangiogr?

Endoscopic retrograde pancreato-cholangiogr?

ERCP

ERCPs

Endoscopic retrograde cholangiogr?

ERC and endoscop?

ERC and cholangiogr?

Endoscopic cholangiogr?

Endoscopic retrograde pancreatogr?

ERP and endoscop?

ERP and pancreatogr?

Endoscopic pancreatogr?

Endoscopic cholangiopancreatogr?

Endoscopic cholangio-pancreatogr?

ECP and endosc?

ECP and cholangiogr?

Endoscopic pancreatocholangiogr?

Endoscopic pancreato-cholangiogr?

EPC and endoscop?

EPC and pancreatogr?

The "?" is a truncation symbol used to permit retrieval for variant word endings, as cholangiopancreatography, cholangiopancreatographic, etc.

Excluded from the search results were articles that:

- Were written in a foreign language.
- Did not have abstracts as a part of the online record in any of the databases searched.
- Did not include human subjects.
- Contained reports of only a single case.

The literature search for Topic 1c on prediction of common bile duct stones and for additional studies selected by the secondary selection criteria for Topics 3 and 4 used a streamlined search process to identify key articles addressing the clinical issue of interest. Reference lists from these articles were reviewed, focused MEDLINE searches were performed, and related articles were identified.

The Technical Advisory Group and peer reviewers for this project were asked to inform the project team of any studies relevant to the key questions addressed in this evidence report that were not retrieved by either of the search strategies.

Search Results

The online searches of the PubMed, EMBASE, BIOSIS, and SciSearch databases in conjunction with additional citations identified through manual searching yielded a total of 5,698 titles and abstracts for review. Based on review of abstracts, 789 articles were selected for review in full text.

Approximately 117 of these articles were excluded as review articles. Primary and secondary selection criteria were applied to articles identified as potential clinical trial reports. This process yielded a total of 149 included studies for the review of evidence.

Study Selection Criteria

Primary Selection Criteria

The selection criteria for all topics in this report were:

1. Full-length report in peer-reviewed medical journals.
2. Published in English.
3. Reported outcomes relevant to this systematic review.
4. Where there were multiple reports of a single study, only the report judged to be most recent and complete, based on number of included patients and length of followup, was included. If additional relevant outcomes were included in the duplicate reports, these data were abstracted and added to the data from the primary report with citation to the supplementary articles.
5. Prospective in design, or if retrospective, enrolled consecutive patients or used appropriate sampling methods (e.g., case-control sampling method).

In order to keep readers informed of ongoing studies, studies published only in abstract form since 1999 and judged to be important are noted in this systematic review; but data were not abstracted into the evidence tables.

Studies of diagnostic performance met the following additional selection criteria:

1. Compared ERCP and at least one of the relevant diagnostic alternatives or compared two ERCP alternatives.
2. Subjected at least 90 percent of participants to both ERCP and the relevant diagnostic alternative.
3. Addressed a relevant patient population.
4. Included at least 25 subjects.
5. Reported sufficient information to be able to calculate 2x2 contingency tables of diagnostic performance.

Studies of therapeutic outcomes met the following additional selection criteria:

1. Compared ERCP strategies with at least one of the relevant therapeutic alternatives.
2. Addressed a relevant patient population.
3. Included at least 25 subjects in each treatment group being analyzed separately.
4. Reported on at least one relevant outcome measure.
5. Were a contemporaneous comparison studies. If not contemporaneous, the populations and treatment settings were comparable.

Studies of predictors of ERCP complications met the following additional selection criteria:

1. Included a multivariable analysis of the relationship between patient, procedure, or operator factors and ERCP complications.
2. Enrolled at least 100 patients if a cohort study, or at least 25 cases if a case-control study.
3. Addressed potential confounding variables in either the selection of subjects or analysis.

Studies on the prediction of common bile duct stones met the following additional selection criteria:

1. Reported the association of either (a) specific risk factors of interest and the presence of a common bile duct stone (specific risk factors of interest were jaundice, liver function test results, and ultrasound finding of a dilated common bile duct), or (b) a prediction rule or model predicting likelihood of having a common bile duct stone and the presence of a common bile duct stone.
2. Enrolled at least 100 patients.
3. Reported sufficient information to be able to calculate 2x2 contingency tables of diagnostic performance in the prediction of presence or absence of a common bile duct stone.

Secondary Selection Criteria

There was a paucity of literature that met the primary selection criteria for questions on ERCP treatment of chronic pancreatitis (Topic 3b) and ERCP treatment of chronic abdominal pain of possible pancreaticobiliary origin (Topic 4b). In order to examine these questions, the original study selection criteria were relaxed for these topics to include:

1. Randomized controlled trials or otherwise concurrently controlled studies of an ERCP intervention compared to a relevant therapeutic alternative, regardless of sample size for pancreatitis.
2. Single arm pre-post-intervention studies which selected a well-defined population with a predictable natural history ascertained by baseline evaluation over 3 months. These studies must also have used an appropriate well-designed outcome measure over at least 6 months of followup.

Outcomes of Interest

For diagnostic performance studies, the outcomes of interest were test performance characteristics (i.e., sensitivity, specificity) in diagnosing clinically relevant findings.

For therapeutic outcome studies, the primary outcomes of interest include:

1. Measures of technical success (e.g., removal of stone, relief of obstruction, cyst drainage, need for repeat procedure or placement of stent).
2. Measures of clinical success (e.g., survival, quality of life, performance scores, relief of jaundice, relief of infection, symptom scores, or pain scores).
3. Resource utilization (e.g., hospitalization, perioperative care, return to work, intensity of post-procedure care).
4. Procedure-related morbidity (e.g., stent-related problems, cholangitis, sepsis, sedation-related outcomes, bleeding, perforation, pancreatitis, long-term effects of sphincterotomy, mortality).

For studies of factors predicting ERCP complications, the primary outcomes of interest were measures of relative risk or predictive value associated with patient, procedure, or operator factors.

Study Quality Assessment

The approach to assessing the quality of evidence used domains commonly recognized as important in the literature on study quality. Quality criteria were developed for each of the three types of studies included in this systematic review: studies of therapeutic effectiveness; studies of diagnostic performance; and multivariable regressions analysis. For many topics addressed in this evidence review, studies meeting the most rigorous standards of quality do not exist. Thus, the main purpose of quality assessment in this systematic review is to discriminate between the better and lesser quality studies in the available evidence base.

For studies of therapeutic efficacy, the approach to quality assessment was adapted from that of the U.S. Public Health Preventive Services Task Force. Study quality domains of interest were: initial assembly of comparable groups (includes adequacy of randomization and controls for confounders); maintenance of comparable groups (includes attrition, crossovers, adherence, contamination); comparable performance of interventions; comparable measurements (unbiased, reliable, and valid); and appropriate analysis of outcomes (includes intent-to-treat analysis). A study was rated as "Good" if it clearly met all quality parameters. A study was rated "Fair" if it reasonably met these parameters and had no fatal flaw. A study was rated "Poor" if it was fatally flawed on one or more parameters (e.g, if comparable groups were not assembled or maintained or outcome measures were invalid or not applied equally among groups).

For studies of diagnostic performance, criteria for assessing study quality were developed using key references in the field of study quality assessment. The selection criteria used for this systematic review eliminated poor quality studies from inclusion. Study quality domains of interest to discriminate between good and fair quality studies were: enrollment of representative subjects (includes appropriate spectrum of patients, unbiased enrollment, complete enrollment of eligible patients, accounting for all eligible subjects); ERCP interpreted independently of diagnostic alternative; and diagnostic alternative interpreted independently from ERCP. As relevant, issues of suitability and interpretation of reference standards are addressed qualitatively in the discussion of each question.

For multivariable logistic regression analysis studies, the quality domains of interest were the degree of over-fitting present in the multivariable models, the nature of statistical reporting, and the use of procedures to establish internal validity. Degree of over-fitting was assessed using the ratio of the number of endpoints divided by the number of candidate variables in the model and was classified as satisfactory (ratio $\geq$10) to severe (ratio <4).

Findings

Topic 1. Patients with known or suspected common bile duct stones

Diagnostic performance of ERCP compared to alternatives:

- The search and selection process yielded 10 studies on MRCP (total n=834), 9 studies on EUS (total n=601), and 6 studies with 7 sets of findings on CTC (total n=266), but reference standards were not consistent among studies.
- Individual studies were relatively small and unlikely to have adequate power to detect a statistically significant difference; and no studies reported tests of statistical significance. Thus, it is not possible to determine with confidence whether the diagnostic performance is similar or poorer than ERCP or to accurately quantify any difference.
- The evidence comparing EUS to ERCP employs a reference standard that permits inferences regarding comparative performance. The evidence suggests that EUS is similar to ERCP in detecting common bile duct stones.
- MRCP has a degree of concordance with ERCP that results in sensitivities and specificities greater than 90 percent in most studies. Concordance of CTC with

ERCP appears to be lower, with sensitivities as low as 80 percent in some studies.

- The role of alternative tests in the management of patients with suspected common bile duct stones cannot be determined strictly by diagnostic performance. The costs and risks of the tests, and the costs and risks of actions based on test results, along with the pretest probability of stones must all be considered to determine the optimal management strategy.

ERCP treatment strategies compared to surgical or medical management:

- In order to evaluate ERCP treatment strategies, studies must account for patients through the diagnostic and treatment process, including additional procedures needed when initial treatment fails, and total morbidity of the alternative strategies. Overall, the literature is very thin and spread out over many different comparisons of interest, preventing strong conclusions about any specific comparison of treatment strategies.
- The limited evidence available suggests that: laparoscopic common bile duct exploration may be better than ERCP strategies to manage cholecystectomy patients with the least resource use; definitive surgery with cholecystectomy prevents long term complications at acceptable short-term morbidity when compared to sphincterotomy alone in high-risk surgical patients with suspected common bile duct stones; and endoscopic treatment of acute cholangitis reduces short-term mortality when compared to emergency surgery.
- Limited evidence suggests that the following techniques have similar stone removal rates and short-term complications: intracorporeal and extracorporeal lithotripsy methods for removing large common bile duct stones; balloon dilation and sphincterotomy; and needle-knife fistulotomy and needle-knife precut papillotomy.

Diagnostic value of specific risk factors or predictive models for assessing the likelihood of having a common bile duct stone:

- The probability of a common duct stone is one important factor in determining diagnostic and treatment strategies. When preoperative probability is high, ERCP may be preferred. When probability is low, expectant management is preferred. Additional diagnostic tests may be used to discriminate among patients in the middle range of probability. The exact probability cutoffs depend on the risks and benefits of the diagnostic and treatment alternatives. The risk factor or prediction model with the best receiver-operating characteristics (ROC) would make the best decision rule if the cutoff threshold were set correctly.
- Thirteen studies (total n=7,409) reported multiple findings of sensitivities and specificities of a single or combination of risk factors to predict the presence of common bile duct stones. The single risk factors most commonly assessed were: clinical jaundice or elevated bilirubin, liver function tests, and ultrasound findings of a dilated common bile duct. All have significant associations with the presence of common duct stones, but none have both high sensitivity and specificity. Of the four studies testing prediction rules based on combinations of risk factors, only one study was a validation of an independently developed prediction rule. Multivariable prediction rules appear to have superior ROCs compared to individual risk factors.
- The absence of any risk factors for stones (or a discriminant function indicating absence of stones) is a very strong predictor of the absence of stones. Absence of any risk factor produces probabilities of stones that are in the same range as a negative ERCP exam in a patient with risk factors for stones (0 percent to 17 percent).

Topic 2. Patients with known or suspected pancreaticobiliary malignancy

Diagnostic performance of ERCP tissue sampling techniques in establishing a tissue biopsy diagnosis of pancreaticobiliary malignancy in comparison to each other and compared to alternative nonsurgical tissue sampling techniques:

- Twelve studies comparing at least two tissue sampling techniques were identified in this systematic review. The available studies are limited by small size and do not consistently compare techniques in the same group of patients. Most studies do not report statistical tests, so it is not possible to determine with confidence whether reported differences in sensitivity are significantly different. While available evidence is suggestive, larger studies are needed to draw conclusions on relative performance of tissue sampling techniques.
- The available evidence suggests that sensitivity for detecting malignancy is similar or higher for brush cytology vs. bile aspiration cytology, similar for fine-needle aspiration (FNA) cytology vs. brush cytology, and similar or higher for forceps biopsy vs. brush cytology. Using combinations of two or more sampling techniques may increase overall sensitivity. No comparative studies evaluated whether incremental

improvement could also be achieved by repeated sampling using the same technique.

- In the absence of comparative studies of endoscopic ultrasound (EUS)-FNA and ERCP-FNA, indirect comparison of single-arm studies was attempted. Results from 10 studies including at least 400 subjects with pancreatic mass suggest a range of sensitivity in detecting pancreatic malignancy of 60-94 percent with a specificity of 100 percent. Two studies of ERCP-FNA including 164 subjects with various pancreatobiliary tumors reported sensitivities ranging from 25 percent to 62 percent. While sensitivity reported in these studies appears to be lower than that for EUS-FNA, such a comparison is not valid due to differences in study populations, cytology techniques, and study settings.

Diagnostic performance of ERCP compared to alternatives in detecting malignant pancreaticobiliary obstruction:

- The available evidence directly comparing ERCP with either MRCP or EUS is modest in size and of varying methodologic quality. The evidence comparing ERCP with MRCP is some what stronger than that comparing ERCP with EUS.
- Individual studies do not demonstrate statistically significant differences in diagnostic performance for ERCP vs. MRCP or for ERCP vs. EUS for characterizing malignant strictures. In sum, the available studies suggest that both MRCP and EUS provide similar diagnostic performance as ERCP in detecting pancreaticobiliary malignant obstruction.

Treatment outcomes using ERCP strategies to treat malignant pancreaticobiliary obstruction compared to using surgical or interventional radiology treatment:

- Five studies compared endoscopic stent drainage with surgical bypass for palliation of malignant obstructive jaundice, and a randomized controlled trial of 204 patients provided the most robust evidence. There were no significant differences in overall survival, relief of jaundice, technical success, total hospitalization days, or perioperative mortality. Major complications were more frequent in the surgery group (11 percent vs. 29 percent, p=0.02); and stent replacement was required in 37 percent of patients treated with ERCP stents.
- Two randomized controlled trials (total n=206) and one nonrandomized trial (n=165) compared metal to plastic stents placed by ERCP for palliation of biliary obstruction due to malignancy. Both types of stents offer initial relief of jaundice and the available evidence does not conclusively show any difference in perioperative adverse events. Overall patient survival is not significantly different when stent occlusions are treated with stent exchange as needed. Total resource utilization including need for repeat ERCP, total hospital days, and costs was reported to be lower with metal stents compared with plastic stents.
- Six studies (total n=782), addressed preoperative stenting compared to no stenting prior to surgery for malignant pancreaticobiliary obstruction. The available evidence is of poor methodologic quality and fails to demonstrate that preoperative stenting improves health outcomes. Few studies report overall complications including both those related to the preoperative stent and the surgery, and these suggest that when complications of preoperative endoscopic stenting are considered along with the perioperative complications of surgery, preoperative stenting is associated with more complications. Preoperative stenting does appear to significantly improve elevated bilirubin and liver function tests, but the available evidence does not suggest that surgical outcomes are improved as a result.

Topic 3. Patients with pancreatitis

Diagnostic performance of ERCP compared to alternatives to detect underlying causes or complications of pancreatitis that are amenable to treatment:

- Three studies (total n=190) were found which met selection criteria. Each study addresses a different potential cause or complication of pancreatitis amenable to treatment. The available evidence is insufficient to compare ERCP and other diagnostic modalities for the identification of treatable causes or complications of pancreatitis.

Treatment outcomes of ERCP strategies compared to surgical or medical therapy:

- For treatment of acute pancreatitis, three randomized controlled trials (total n=554) compared early ERCP to delayed or selective ERCP. The available evidence suggests that early ERCP reduces complications in patient populations with acute pancreatitis and signs and symptoms suggesting biliary obstruction. In patients with low likelihood of biliary obstruction, delayed or selective ERCP permits many patients to avoid the procedure, and may result in lower complication rates. In addition, one retrospective associational study of a Veterans Administration database of patients with acute pancreatitis (n=2,075) suggests that outcomes of ERCP treatment are similar to those of surgery.
- For ERCP treatment in patients with acute recurrent or chronic pancreatitis, study selection criteria were relaxed as described above. Although the available evidence is

sparse and largely uncontrolled, it suggests that ERCP treatment reduces emergency room visits and hospitalization in patients with pancreas divisum and acute recurrent pancreatitis. Evidence on ERCP drainage of pseudocysts is also sparse and poorly controlled, but suggests that pain relief with ERCP is similar to results of surgery.

Topic 4. Patients with abdominal pain of possible pancreaticobiliary origin

Diagnostic performance of ERCP with sphincter of Oddi manometry compared with alternatives to identify a pancreaticobiliary origin of pain:

- The available evidence is not sufficient to permit conclusions on the diagnostic performance of biliary scintigraphy for sphincter of Oddi dysfunction. The body of evidence consists of three studies that included only 54 patients with sphincter of Oddi dysfunction; results of these studies cannot be synthesized due to differences in populations and methodology. There was substantial variability in the reported performance characteristics of biliary scintigraphy.

Treatment outcomes of ERCP strategies compared to surgical or medical therapy:

- Two randomized controlled trials (total n=128) show that endoscopic sphincterotomy relieves pain in patients with pancreaticobiliary pain, sphincter of Oddi dysfunction, and elevated basal sphincter of Oddi pressure on manometry (greater than 40mm Hg). The results of five single arm studies (total n=183) corroborate these data and suggest that patients with a dilated common bile duct and/or delayed contrast emptying may also benefit from endoscopic sphincterotomy.
- There is insufficient evidence to determine whether endoscopic sphincterotomy improves outcomes in patients with normal manometry findings. For this group, the small studies included in this review do not report significant improvements in pain with endoscopic sphincterotomy.

Topic 5. What patient, procedure, or operator factors are determinants of complications of ERCP?

- Thirteen studies reported on multivariable logistic regression analyses of factors associated with complications of ERCP. The four largest studies each included more than 1,800 patients, and the total number of complications observed in these studies ranged from 98 to 229. Overall, the methodologic quality of the available analyses is limited by over-fitting, i.e., testing an excessive number of factors relative to the number of complications observed. Consequently, this literature is exploratory in nature. Reported magnitudes of association are not reliable, significant independent variables may have been overlooked, and some significant associations may be misleading. Moreover, the existing studies do not use common, standardized definitions for the complications and factors of interest. Thus, caution should be used in drawing inferences for clinical practice from these studies.
- Patient, procedure, and operator factors were identified that were found to be significantly associated with complications in several of the more robust studies. Younger age (using various cut-offs, but generally 60 years or less) was significantly associated with total complications and with pancreatitis; as was suspected sphincter of Oddi dysfunction. Precut endoscopic sphincterotomy was the procedure-related factor most commonly associated with total complications or pancreatitis; a significant association with difficulty in cannulation was also reported, but less frequently. Multiple pancreatic contrast injections were associated with pancreatitis. For hemorrhage, the clearest association was patient factors related to coagulopathy. Case volume was the only operator-related factor found to be significantly associated with complications. These studies used various cut-offs to define lower volume centers: one or fewer procedures per endoscopist per week; fewer than 40 endoscopic sphincterotomies per endoscopist per year; and fewer than 150 procedures per year.

Future Research

Recommendations for future research include the following:

- Rigorous studies are required in order to reliably quantify the relative performance of diagnostic ERCP compared to alternatives. Existing studies do not consistently use common reference standards and frequently do not report tests of statistical significance. Thus, assumptions about equivalence or difference among alternative diagnostic technologies are not supported by robust empirical evidence.
- Comparative studies of alternative diagnostic and treatment strategies are urgently needed. It is imperative to use a comprehensive approach to outcomes assessment, taking into account the total burden of morbidity and resource utilization.
- Evidence on treatment of chronic pancreatitis and relapsing or recurrent pancreatitis is sparse. Rigorously designed controlled trials are needed to assess the outcomes of treatment for this debilitating condition.

- Risk factors for complications of diagnostic and therapeutic ERCP have been explored using multivariable model analysis. Such analyses generate hypotheses for reducing complications, but cannot demonstrate cause and effect. Thus, interventions intended to reduce complications should incorporate prospectively defined studies to evaluate the results.

Availability of Full Report

The full evidence report from which this summary was derived was prepared for AHRQ by the Technology Evaluation Center, an Evidence-based Practice Center, under contract number 290-97-001-5. It is expected to be available in early 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requestors should ask for *Evidence Report/Technology Assessment No. 50, Endoscopic Retrograde Cholangiopancreatography*. Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

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Chapter 1. Introduction

This systematic review of the literature primarily addresses the diagnostic and therapeutic efficacy of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic intervention in comparison with available alternative diagnostic or therapeutic techniques in specifically defined clinical settings. This section will outline the clinical scope of this review, highlight the relevant epidemiology and public health impact of the relevant pancreaticobiliary diseases, describe briefly ERCP and the available alternative techniques, and provide an overview of the major topics and key questions guiding this systematic review.

Scope of Systematic Review

The National Institutes of Health Office of Medical Applications of Research (OMAR) is convening a State-of-the-Science conference in January 2002 to discuss the role of endoscopic retrograde pancreatography (ERCP) in diagnosing and treating 4 specific pancreaticobiliary conditions: common bile duct stones, pancreaticobiliary malignancy, pancreatitis, and abdominal pain of suspected pancreaticobiliary origin. In addition, the conference will discuss risk factors relating to complications of ERCP.

Epidemiology and Public Health Impact of Pancreaticobiliary Disease

Diseases of the pancreas and biliary tree are common in the United States population with various anatomic or acquired conditions resulting in a variety of obstructive, inflammatory, neoplastic, or functional conditions. An estimated 6 per 100,000 people are afflicted with common bile duct stones, representing only a small fraction of those with gallstones (WebMD/Lycos, 1999). Malignancy of the pancreas, gallbladder, or extrahepatic biliary tract represents approximately 57,400 newly diagnosed cases in the United States each year (Greenlee, Hill-Harmon, Murray, et al., 2001), and the associated prognosis is usually poor. Pancreatitis can occur in an acute, acute recurrent, or chronic pattern and may be associated with a variety of causes, with common etiologic factors including alcohol consumption and choledocholithiasis (Greenberger, Toskes, and Isselbacher, 1994).

In patients with persistent abdominal pain of suspected pancreaticobiliary origin, where no structural abnormality has been identified, functional disorders including sphincter of Oddi dysfunction may be present. Finally, complications of ERCP, such as pancreatitis, hemorrhage, infection, or intestinal rupture, occur in approximately 8% of patients undergoing ERCP depending on the case mix of diagnostic and therapeutic ERCP (Cotton, Lehman, Vennes, et al., 1991). Improving the understanding of risk factors for ERCP-related complications may improve patient selection or lead to improved methods of preventing complications in those at highest risk.

Endoscopic Retrograde Pancreatography (ERCP)

Patients with suspected pancreaticobiliary pathology require diagnostic assessment of the pancreaticobiliary tract to establish the correct diagnosis. Diagnostic assessment frequently

includes imaging to detect the presence of dilation or narrowing of the ducts and to determine the cause of such morphologic changes.

Endoscopic retrograde pancreatography was first introduced for diagnostic evaluation of the pancreatic and biliary tree in the late 1960s. Using an endoscope inserted orally into the duodenum, a catheter can be placed into the biliary and/or pancreatic ducts for direct injection of radiographic contrast to provide X-ray images of the pancreaticobiliary ducts. Direct cholangiopancreatography can also be accomplished via a percutaneous transhepatic insertion of a needle or catheter with injection of radiographic contrast.

Noninvasive or less-invasive alternatives for imaging the pancreaticobiliary tree have been developed using magnetic resonance imaging, so-called magnetic resonance cholangiopancreatography (MRCP), ultrasound through an orally placed endoscope, so-called endoscopic ultrasonography (EUS), computed X-ray tomography often using specific biliary contrast agents, so-called computed tomography cholangiography (CTC), and nuclear medicine imaging with radiotracers specific to the biliary system, so-called biliary scintigraphy.

The endoscope used for ERCP can also be used selectively place catheters into the pancreaticobiliary ducts to obtain samples of pancreaticobiliary fluid or to deploy specialized tissue sampling devices (e.g., brush, fine-needle aspiration, forceps) to obtain cellular material for cytologic or histologic assessment. Alternative techniques for obtaining tissue samples for diagnosis include surgical biopsy, percutaneous fine-needle aspiration using imaging guidance, or endoscopic ultrasound guided fine-needle aspiration (EUS-FNA).

Once an accurate diagnosis has been established, surgical and nonsurgical treatment alternatives are frequently available. The ERCP scope permits access to the biliary tree to deliver endoscopic therapeutic interventions. Such interventions frequently include sphincterotomy of the sphincter of Oddi, which involves using an electrocautery device to cut and enlarge the opening of the pancreaticobiliary tract into the duodenum. Additional devices such as balloon catheters and specially designed wire baskets may be used to facilitate removal of duct stones, and specialized catheter insertion systems permit endoscopic placement of a variety of stents into the biliary or pancreatic ducts.

Key Questions for this Systematic Review

In preparation for the NIH State-of-the-Science conference on ERCP, an evidence-based assessment of the ERCP literature was commissioned through a partnership agreement with the Agency for Healthcare Research and Quality Evidence-based Practice Center program. This report outlines 5 major topics selected for discussion at the NIH OMAR ERCP State-of-the-Science conference. For each major topic, several key questions have been designed to specifically address the most pertinent diagnostic and therapeutic issues.

Topic 1: In patients with known or suspected common bile duct stones,

a. What is the diagnostic performance of ERCP in detecting common bile duct stones in comparison to alternatives (e.g., EUS, MRCP, or CTC)? *(Section 1: Diagnostic Performance of ERCP in Detecting Common Bile Duct Stones – Comparison to Alternatives)*

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical management? *(Section 2: Outcomes of Treatment Using ERCP for Common Bile Duct Stones – Comparison of Strategies Using ERCP, Surgery, or Medical Management)*

c. What is the diagnostic value of individual risk factors or predictive models for assessing the likelihood of having a common bile duct stone? *(Section 3: Diagnostic Value of Individual Risk Factors or Predictive Models for Assessing the Likelihood of Having a Common Bile Duct Stone)*

Topic 2: In patients with known or suspected pancreaticobiliary malignancy,

a. What is the diagnostic performance of ERCP tissue sampling techniques, in establishing a tissue biopsy diagnosis of pancreaticobiliary malignancy in comparison to each other or alternative nonsurgical tissue sampling techniques (e.g., endoscopic ultrasound-guided fine-needle aspiration (FNA) or percutaneous FNA)? *(Section 1: Diagnostic Performance of Nonsurgical Tissue Sampling Techniques in Pancreaticobiliary Malignancy – Comparison of Strategies Using ERCP, EUS, or Percutaneous Approach)*

b. What is the diagnostic performance of ERCP, in diagnosing the presence of malignant pancreaticobiliary obstruction in comparison to other imaging alternatives (e.g., EUS or MRCP)? *(Section 2: Diagnostic Performance of ERCP in Pancreaticobiliary Malignant Obstruction – Comparison To Alternatives)*

c. What are the outcomes of treatment using ERCP strategies to treat malignant pancreaticobiliary obstruction compared to using surgical or interventional radiology treatment? *(Section 3: Outcomes of Treatment Using ERCP for Palliation of Pancreaticobiliary Malignancy – Comparison of Strategies Using ERCP, Surgery, or Interventional Radiology; A. Comparison of ERCP stent versus Surgical Bypass; B. Comparison of Metal vs. Plastic stents During ERCP; C. Additional Comparisons of ERCP Strategies)*

(Section 4: Outcomes of Treatment Using Preoperative ERCP Drainage for Relief of Malignant Obstructive Jaundice)

Topic 3: In patients with pancreatitis,

a. What is the diagnostic performance of ERCP in detecting underlying causes or complications of pancreatitis that are amenable to treatment in comparison to alternatives (e.g., EUS or MRCP)? *(Section 1: Diagnostic Performance of ERCP in Detecting Underlying Causes or Complications of Pancreatitis Amenable to Treatment – Comparison to Alternatives)*

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy? *(Section 2: Outcomes of Treatment Using ERCP for Pancreatitis – Comparison of Strategies Using ERCP, Surgery, or Medical Management)*

Topic 4: In patients with abdominal pain of possible pancreaticobiliary origin ,

a. What is the diagnostic performance of ERCP with sphincter of Oddi manometry in identifying a pancreaticobiliary origin of pain in comparison to alternatives (e.g., biliary scintigraphy, EUS, or MRCP)? *(Section 1: Diagnostic Performance of ERCP Manometry in Evaluation of Abdominal Pain of Possible Pancreaticobiliary Origin – Comparison To Alternatives)*

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy? *(Section 2: Outcomes of Treatment Using ERCP for Abdominal Pain of Possible Pancreaticobiliary Origin)*

Topic 5: What patient, procedure, or provider factors are determinants of adverse events of ERCP?

(Section 1: Multivariable Analyses)
(Section 2: Randomized, Controlled Comparison Trials)

Chapter 2. Methodology

This report is the product of a systematic literature review of the evidence on the diagnostic and therapeutic effectiveness of endoscopic retrograde cholangiopancreatography (ERCP) with a specific focus on four clinical conditions: (1) common bile duct stones; (2) pancreaticobiliary malignancy; (3) pancreatitis; and (4) abdominal pain of possible pancreaticobiliary origin. In addition, the evidence describing patient, procedure, or operator determinants of complications of ERCP is systematically reviewed. Also reviewed is the evidence on the prediction of common bile duct stones.

The protocol for this review was designed prospectively as much as possible to define: study objectives; search strategy; patient populations of interest; study selection criteria; outcomes of interest; data elements to be abstracted and methods for abstraction; and methods for study quality assessment.

The key questions guiding the scope of this report have been outlines in the Introduction. This chapter of the report describes the search strategies used to find articles, the criteria and methods for selecting eligible articles, the methods for data abstraction, the methods for quality assessment, and finally, the peer review and technical assistance received during the project.

Search Strategy for the Identification of Articles

The National Library of Medicine (NLM) conducted a comprehensive literature search for journal articles on ERCP from the PubMed/MEDLINE, BIOSIS, EMBASE, and SCISEARCH databases with a publication date from 1980 forward until the final search date of August 13, 2001. Articles which had been indexed to the NLM Medical Subject Heading (MeSH®) "cholangiopancreatography, endoscopic retrograde" as well as those containing the following list of ERCP synonyms and textword combinations were retrieved:

Endoscopic retrograde cholangiopancreatogr?
Endoscopic retrograde cholangio-pancreatogr?
Endoscopic retrograde pancreatocholangiogr?
Endoscopic retrograde pancreato-cholangiogr?
ERCP
ERCPs
Endoscopic retrograde cholangiogr?
ERC and endoscop?
ERC and cholangiogr?
Endoscopic cholangiogr?
Endoscopic retrograde pancreatogr?
ERP and endoscop?
ERP and pancreatogr?
Endoscopic pancreatogr?
Endoscopic cholangiopancreatogr?
Endoscopic cholangio-pancreatogr?

ECP and endosc?
ECP and cholangiogr?
Endoscopic pancreatocholangiogr?
Endoscopic pancreato-cholangiogr?
EPC and endoscop?
EPC and pancreatogr?

Textwords are words appearing in the titles, abstracts, and subject term lists of the online record of the articles.

The "?" is a truncation symbol used to permit retrieval for variant word endings, as cholangiopancreatography, cholangiopancreatographic, etc.

Excluded from the search results were articles that:

- were written in a foreign language
- did not have abstracts as a part of the online record in any of the databases searched
- did not include human subjects
- contained reports of only a single case

Citations without abstracts were not reviewed, as citations that have no abstracts have little or no yield in producing articles eligible for inclusion in the evidence report.

There was not a method developed to systematically identify studies published in abstract form only. However, if an abstract of potential importance was identified, it was included it if it was published in 1999 or after, with the reason that abstracts published before 1999 should have been published in full manuscript form by now.

Secondary Search Strategy

The literature search for the supplemental question (Topic 1c), for the indirect comparison of single arm studies of for ERCP-guided fine needle aspiration (FNA) and EUS-guided FNA for Topic 2, and for additional studies selected by the secondary selection criteria for Topics 3 and 4, did not follow the same search process. The literature review process for these supplemental questions was based on a focused identification and selection of key articles addressing the clinical issue of interest. Reference lists from these articles, were then reviewed, focused MEDLINE searches were performed, and related articles identified. It was thought that this approach led to retrieval of the important studies addressing the questions of interest.

The Technical Advisory Group and individuals and individuals providing peer review also were asked to inform the project team of any studies relevant to the key questions addressed in this evidence report that were not retrieved by either of the search strategies.

Search Results

The online searches of the PubMed, EMBASE, BIOSIS, and SciSEARCH databases in conjunction with additional citations identified through manual searching yielded a total of 5,698 titles and abstracts for review. During application of Phase I of the selection process, 789 articles were selected for review in full text. Approximately 117 of these articles were identified as review articles. Primary and secondary selection criteria were applied to articles identified as potential clinical trial reports. This process yielded a total of 149 included studies for the review of evidence. Citations for the excluded articles and the reason(s) for exclusion are listed in Appendix A.

Study Selection Criteria

Primary Selection Criteria

The criteria which applied to all topic areas in this report were:

1. Full-length report in peer-reviewed medical journals.
2. Published in the English language.
3. Study reported outcomes relevant to this systematic review.
4. Where there were multiple reports of a single study, only the report judged to be most recent and complete, based on number of included patients and length of follow-up, was included. If additional relevant outcomes were included in the duplicate reports, these data were abstracted and added to the data from the primary report with citation to the supplementary articles.
5. Was prospective in design, or if retrospective, enrolled consecutive patients or with appropriate sampling methods (i.e. case-control sampling method).

For diagnostic performance topic areas, studies were included if the study:

1. Compared ERCP and at least one of the relevant diagnostic alternatives or compared two ERCP alternatives. Relevant diagnostic alternatives included endoscopic ultrasound, MRCP, intraoperative cholangiography, or other diagnostic tests as advised by the TAG. Studies reporting only non-breath hold MRCP imaging techniques were not included in this review as these do not represent the current state-of-the-art MRCP techniques.
2. Subjected all participants to both ERCP and the relevant diagnostic alternative;
3. Addressed a relevant patient population;
4. Included at least 25 subjects;
5. Reported sufficient information to be able to calculate 2x2 contingency tables of diagnostic performance.

For therapeutic outcome topic areas, studies were included if they:

1. Compared ERCP strategies with at least one of the relevant therapeutic alternatives. Relevant therapeutic alternatives included surgical methods to remove common ducts stones,

surgical methods of bypassing malignant biliary obstructions, and surgical and medical methods of treating pancreatitis and pancreatitis-associated conditions.
2. Addressed a relevant patient population;
3. Included at least 25 subjects in each treatment group being analyzed separately; however, this criterion was relaxed to require 25 subjects in the trial for pancreaticobiliary malignancy and abdominal pain of possible pancreaticobiliary origin.
4. Reported on at least one relevant outcome measure;
5. Was a contemporaneous comparison study or if it was a noncontemporaneous study, the populations and treatment setting were comparable;

For Part V, a study was included if it:

1. Included an analysis of the relationship between patient, procedure, or operator factors and ERCP complications;
2. Enrolled at least 100 patients if a cohort study, or at least 25 cases if a case-control study;
3. Addressed potential confounding variables in either the selection of subjects or analysis.

For Part I, Section 3, a study was included if it:

1. Reported the association of individual risk factors of interest and the presence of a common bile duct stone. Based on a consensus from the TAG, these individual risk factors were jaundice, liver function test results, and an ultrasound finding of a dilated common bile duct.
2. Reported the association of a prediction rule or model predicting likelihood of having a common bile duct stone and the presence of a common bile duct stone;
3. Enrolled at least 100 patients;
4. Reported sufficient information to be able to calculate 2x2 contingency tables of diagnostic performance in the prediction of presence or absence of a common bile duct stone.

Secondary Selection Criteria

Due to a paucity of literature which met the primary selection criteria for Part III, Section 2 and Part IV, Section 2, additional selection criteria were created so that these questions could be examined. There was a lack of literature which provided comparative data on the value of ERCP treatment for these conditions. Thus studies were included from the primary search strategy and sought out using the secondary search strategy if the study was:

1. a randomized controlled trial or otherwise concurrently controlled study of an ERCP intervention compared to a relevant therapeutic alternative, regardless of sample size;
2. a single arm observational study (subject serves as own control) of ERCP intervention in treatment of chronic pancreatitis or chronic abdominal pain of possible pancreaticobiliary origin with a minimum size of 25 subjects; where the studies selected a well-defined population with a predictable natural history absent intervention based on thorough baseline evaluation; and where the study used an appropriate well-designed outcome measure. Baseline evaluation had to be obtained over a sufficient time period (approx. 3 months) and follow-up data needed be obtained over at least 6 months. Studies reporting exploration of subgroup differences in observed results were also included.

3. A single arm observational study of an ERCP intervention on pancreas divisum, subject to the above conditions in #2, but regardless of sample size.

In addition, there was an absence of direct comparative data for ERCP-guided fine needle aspiration (FNA) and EUS-guided FNA. Thus, an indirect comparison of single-arm studies was attempted. Studies of EUS-FNA that included at least 25 subjects for the evaluation of suspected pancreaticobiliary malignancy were identified and included.

Outcomes of Interest

For diagnostic performance studies, the outcomes of interest include:
Test performance characteristics (sensitivity, specificity) as well as predictive values in diagnosing clinically relevant findings.

For therapeutic outcome studies, the primary outcomes of interest include:
1. Measures of technical success (e.g., removal of stone, relief of obstruction, cyst drainage, need for repeat procedure or placement of stent)
2. Measures of clinical success (e.g., survival, quality of life, performance scores, relief of jaundice, relief of infection, symptom scores, or pain scores)
3. Resource utilization (e.g., hospitalization, perioperative care, return to work, intensity of post-procedure care)
4. Procedure-related morbidity (e.g., stent-related problems, cholangitis, sepsis, sedation-related outcomes, bleeding, perforation, pancreatitis, long-term effects of sphincterotomy, mortality)

For Part V:

Measures of relative risk or predictive value associated with patient, procedure, or operator factors associated with ERCP complications.

For Part I, Section III:

Test performance characteristics (sensitivity, specificity) and predictive values in predicting the presence or absence of common bile duct stone(s).

Methods of the Review

Article Selection

Selection of articles was a two-stage process. All abstracts retrieved by the two search strategies were reviewed. First, titles and abstracts were reviewed using the primary and secondary study selection criteria. A single reviewer marked each citation as either: (1) eligible for review as full-text articles; (2) ineligible for full-text review; or (3) uncertain. Studies were excluded at this stage only if information revealed in the abstract showed that the study did not meet selection criteria. A second reviewer reviewed all citations marked as uncertain by the first reviewer, and a consensus decision was reached.

Using the primary and secondary study selection criteria, a single reviewer then reviewed the full-text article and determined whether selection criteria were met. The reviewer marked each full-text article as either (1) included in systematic review; (2) excluded from systematic review; or (3) uncertain. A second reviewer reviewed all articles marked as uncertain by the first reviewer, and a consensus decision was reached.

Records of the results of this evaluation were kept for each full-text paper retrieved including the reason for exclusion of each excluded study. Any disagreement about the inclusion or exclusion of a particular article was resolved by consultation with the Program Director or one or more members of the Technical Advisory Group.

Data Abstraction

Prior to the start of data abstraction, data elements were defined for abstraction from each selected article in consultation with the Technical Advisory Group. However, since some of the therapeutic key questions were not fully defined before articles were selected, many elements had to be defined based on the articles that ultimately met selection criteria. These data elements were abstracted from the articles that met final selection criteria. The data elements addressed:

1. Critical features of the study design (for example, patient inclusion/exclusion criteria, controlled or uncontrolled studies, randomized or non-randomized trials, number of subjects, or blinding, reference standard for diagnostic studies);
2. Treatment protocols;
3. The specified key outcomes.

For key questions assessing diagnosis, sensitivity, specificity, positive and negative predictive values, and prevalence of condition were all abstracted, including statistical analysis when available. Studies were grouped for presentation by categories according to diagnostic test, reference standard, clinically relevant patient subgroup, or other category of interest. For key questions assessing therapy, all outcomes that corresponded to the outcome categories that were specified in the protocol were abstracted, and studies were grouped by treatment alternative, clinically relevant patient subgroup, or other category of interest. Templates for evidence tables were then created in Microsoft Word.

Due to the anticipated heterogeneity in reported outcome measures, data were not abstracted into an electronic database. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer performed accuracy checks on the evidence tables. Disagreements were resolved between the two reviewers, or if necessary, consultation with the Program Director or relevant members of the Technical Advisory Group. If small differences occurred in quantitative estimates of data from published figures, the values abstracted independently by the two reviewers were averaged.

Quality Assessment

In consultation with the AHRQ Task Order Officer and Technical Advisory Group, a general approach to grading evidence on therapeutic studies developed by the U.S. Preventive Services Task Force (provided by Dr. Mark Helfand) was applied. Criteria for assessment of study quality for diagnostic tests were developed using the following as resources: Irwig, Tosteson, Gatsonis, et al. (1994) and the Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests (1996). Criteria for assessment of study quality for cross sectional analyses with multivariable regression analysis were developed with reference to Concato, Feinstein, Holford, et al. (1993).

The issues about reference standards are complex in this particular topic, and quality assessment did not take this into account. Instead, these issues are discussed in the "Review of Evidence" for each section (as applicable).

Quality criteria for therapeutic studies:

1. Initial assembly of comparable groups
   -for randomized controlled trials: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
   -for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
2. Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
3. Comparable performance of and clear definition of interventions with equivalent attention and quality of care
4. Comparable measurements: unbiased, reliable, and valid (i.e. masking of treatment assignments)
5. Appropriate analysis of outcomes. Intent-to-treat analysis for randomized, controlled trials, consideration of confounding variables in nonrandomized studies. All important outcomes considered

Summary ratings of therapeutic studies based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for randomized controlled trials, intention to treat analysis is used.

Fair: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for randomized controlled trials.

Poor: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups; and key confounders are given little or no attention. For randomized controlled trials, intention to treat analysis is lacking.

Quality criteria for diagnostic accuracy studies:

1. Enrollment of representative subjects. Appropriate spectrum of patients, unbiased enrollment, few eligible patients not enrolled, appropriate accounting of all potentially eligible subjects.
2. ERCP interpreted independently of diagnostic alternative.
3. Diagnostic alternative interpreted independently of ERCP.

Issues regarding the suitability and interpretation of different reference standards were not abstracted as quality measures but are discussed in each section of the report as needed. Study selection criteria required use of a reference standard in order to construct a 2 X 2 contingency table for diagnostic performance operating characteristics.

Summary ratings of diagnostic accuracy studies based on above criteria:

Good: Excellent documentation of prospective enrollment, identification and accounting of eligible and enrolled patients, few exclusions. Both ERCP and diagnostic alternative interpreted without knowledge of other test.

Fair: Had fair enrollment of patients, not too many exclusions, interprets reference standard independent of diagnostic test; and a good spectrum of patients, though reported details may have been incomplete.

Poor: Studies that had fatal flaws (e.g., Uses inappropriate reference standard; diagnostic test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients) were not eligible for inclusion in this systematic review. Thus, no included studies were assigned a Poor rating.

Quality Ratings for Multivariable Logistic Regression Analysis Studies

The most relevant criteria that provided discrimination of quality differences between studies were the degree of overfitting present in the multivariable models, the nature of statistical reporting, and the use of procedures to establish internal validity. Degree of overfitting was assessed using the ratio of the number of endpoints divided by the number of candidate variables in the model. Studies were classified as: Satisfactory, ratio $\geq$ 10; Mild, ratio = 7 to <10; Moderate, ratio = 4 to <7; Severe, ratio <4. The nature of statistical reporting was considered satisfactory when the study reported both magnitude of effect estimates as well as associated confidence intervals or p-value for statistically significant findings. If either of these elements was not reported, studies were considered unsatisfactory. The degree of internal validity was

evaluated by the use of procedures (e.g., test-validation split samples or bootstrapping) to guard against overfitting the model and spurious results.

Summary ratings of multivariable logistic regression analysis studies based on above criteria:

Good: Studies use procedures to guard against overfitting the model and spurious results; degree of overfitting is not severe for at least one analysis, and statistical reporting is satisfactory.

Fair: degree of overfitting is not severe for at least one analysis, and statistical reporting is satisfactory, but no use of procedures to guard against overfitting the model and spurious results.

Fair Minus: severe degree of overfitting for all analyses

Technical Assistance and Peer Review

The development of the evidence report was subject to extensive expert review including input from the Technical Advisory Group (TAG), the panel of designated peer reviewers, and the Medical Advisory Panel of the Technology Evaluation Center of the Blue Cross and Blue Shield Association.

The Technical Advisory Group (TAG) included the panel chairperson for the NIH State-of-the-Science conference, Sidney Cohen, MD, who is a gastroenterologist and Professor of Medicine at Jefferson Medical College, and two gastroenterologists with expertise in ERCP, Glen Eisen, MD, MPH, Associate Professor of Medicine/Gastroenterology at Vanderbilt University Medical Center, and Michael Kimmey, MD, Professor of Medicine, Division of Gastroenterology, University of Washington. TAG members provided on-going guidance and review on all phases of this project including review of the draft report.

The draft report was also reviewed by a panel of external peer reviewers that included experts in gastroenterology, surgery, radiology, and oncology. Comments were elicited from external peer reviewers using a structured comment form, compiled, and submitted with description of disposition of comments to the Agency for Healthcare Research and Quality. (Appendix B lists the members of the Technical Advisory Group and external expert reviewers).

In addition, two sections of the draft report were reviewed by the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) Medical Advisory Panel (MAP). This interdisciplinary panel comprises experts in technology assessment methods and clinical research, and also includes managed care physicians from Blue Cross and Blue Shield and Kaiser Permanente health plans.

Chapter 3. Results and Conclusions, Part I: Common Bile Duct Stones

This chapter reviews evidence on the following questions:

In patients with known or suspected common bile duct stones,

a. What is the diagnostic performance of ERCP in detecting common bile duct stones in comparison to alternatives (e.g., EUS, MRCP, or CTC)? (*Part I, Section 1: Diagnostic Performance of ERCP in Detecting Common Bile Duct Stones – Comparison to Alternatives*)

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical management? (*Part I, Section 2: Outcomes of Treatment Using ERCP for Common Bile Duct Stones – Comparison of Strategies Using ERCP, Surgery, or Medical Management*)

c. What is the diagnostic value of individual risk factors or predictive models for assessing the likelihood of having a common bile duct stone? (*Part I, Section 3: Diagnostic Value of Individual Risk Factors or Predictive Models for Assessing the Likelihood of Having a Common Bile Duct Stone*)

Part I, Section 1: Diagnostic Performance of ERCP In Detecting Common Bile Duct Stones—Comparison With Alternatives

Introduction

The literature review identified three techniques that could be used as alternatives for diagnostic ERCP in the diagnosis of common bile duct stones: magnetic resonance cholangiography (MRCP), endoscopic ultrasound (EUS), and computed tomography cholangiography (CTC, with and without oral or intravenous biliary contrast). This section of the review only assesses diagnostic performance, and does not consider costs, availability, or adverse effects.

All included studies enrolled patients who underwent both the diagnostic test under consideration and ERCP. However, the choice of reference standard varied between studies and needs to be taken into account when interpreting the test characteristics calculated in each study, particularly if the goal is to determine which test is superior. Although ERCP had traditionally been considered the most accurate test for diagnosis of common bile duct stones, the test can produce both false-negative and false-positive results. The studies reviewed here generally used one of three different types of reference standards.

Ideally, ERCP and the alternative diagnostic test are both compared to a perfect reference standard such as actual examination of the common bile duct, producing unbiased estimates of test characteristics for both tests. Such a reference standard would not be ethical in most circumstances. Short of that, there may be selective confirmation of positive ERCP or other

tests, producing slightly biased estimates of test characteristics that are upwardly biased. However, the relative performance of ERCP to the alternative diagnostic test can be examined.

If ERCP is used as the reference standard, then the comparator test can only be worse. In such a case, the analysis can not determine which test is superior, but only the degree of concordance between the two tests.

Finally, a few studies (Neitlich, Topazian, Smith et al., 1997; Jimenez Cuenca, del Olmo Martinez, Perez Homs et al., 2001; Sugiyama, Atomi, and Hachiya, 1998) used ERCP images *and* sphincterotomy findings as the reference standard. This does not really allow an evaluation of the comparison between ERCP and the diagnostic test of interest, because the unreported diagnostic errors of ERCP images are "corrected" by the sphincterotomy findings. The performance of diagnostic ERCP cannot be evaluated in such studies unless the interpretation of the diagnostic ERCP is reported separately.

Given that the expected difference in diagnostic performance between ERCP and the diagnostic alternatives reported here are relatively small and the number of cases with the outcome of interest is generally small, these studies may have very limited power to detect statistically significant differences in test performance. None of the studies actually calculated any statistical significance values. Thus, it is not possible to determine with confidence whether the diagnostic performance of the alternative is similar or poorer than ERCP or to accurately quantitate any difference.

Evidence Base

The search and selection process yielded 10 studies on MRCP (total n=834), 9 studies on EUS (total n=601), and 6 studies with 7 sets of findings on CTC (total n=266). In addition to these studies reporting diagnostic performance specific to common duct stones, 2 studies on MRCP which reported only on overall detection of obstructive abnormalities (total n=121) are also presented here. Study quality assessment is outlined in Table 1.

Review of Evidence: MRCP Performance

Ten studies studying a total of 834 patients were selected which examined the performance of MRCP compared to ERCP for the diagnosis of common bile duct stones (Table 2). Nine of the studies used ERCP as the reference standard, and thus measure the concordance of the two techniques rather than the relative performance. Only one study (Sugiyama, Atomi, and Hachiya, 1998) confirmed positive tests and allowed a comparison between the two tests. All the studies were rated as good quality with the exception of Guibaud, Bret, Reinhold, et al. (1995) and Sugiyama, Atomi, and Hachiya (1998).

Seven of the 9 studies which use ERCP as a reference standard show high concordance between the two tests with both sensitivity and specificity being greater than 90 percent. Two studies showed lesser degrees of concordance (Guibaud, Bret, Reinhold, et al., [1995], sensitivity 81 percent specificity 98 percent, and Stiris, Tennoe, Aadland et al. [2000], sensitivity 88 percent and specificity 94 percent).

Table 1. Quality Assessment

Study Author, Year	Patient Enrollment	Diagnostic performance of ERCP determined without knowledge of other test results	Diagnostic Performance of other test(s) determined without knowledge of ERCP results	Summary Evaluation
MRCP				
Demartines, Eisner, Schnabel et al., 2000	Prospective (n=70) Uncertain enrollment of consecutive patients	Yes	Yes	Good
Guibaud, Bret, Reinhold, et al., 1995	Prospective (n=126) Some exclusions because of no ERCP confirmation	Uncertain	Yes	Fair
Holzknecht, Gauger, Sackmann et al., 1998	Prospective (n=61) 61 of 66 eligible patients enrolled, all exclusions accounted for	Yes	Yes	Good
Lomas, Bearcroft, and Gimson 1999	Prospective (n=69) Consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good
Soto, Barish, Alvarez et al., 2000	Prospective (n=49) Consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good
Stiris, Tennoe, Aadland et al., 2000	Prospective (n=50) Consecutive patients enrolled	Yes	Yes	Good
Varghese, Farrell, Courtney et al., 1999	Prospective (n=100) Consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good
Sugiyama, Atomi, and Hachiya 1998	Prospective (n=97) Nonconsecutive enrollment, but stated to be arbitrary without known selection bias	Uncertain	Yes	Fair
Varghese, Liddell, Farrell et al., 2000	Prospective (n=191) 191 of out 256 consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good

Table 1. Quality Assessment (cont'd)

Study Author, Year	Patient Enrollment	Diagnostic performance of ERCP determined without knowledge of other test results	Diagnostic Performance of other test(s) determined without knowledge of ERCP results	Summary Evaluation
MRCP (cont'd)				
Burtin, Palazzo, Canard et al., 1997	Prospective (n=68) Consecutive patients enrolled	Yes	Yes	Fair—unorthodox reporting of data, uncertain of data
Endoscopic Ultrasound				
Canto, Chak, Stellato et al., 1998	Prospective (n=64) 64 out of 70 consecutive patients enrolled, 6 refusals	Yes	Yes	Good
Dancygier and Nattermann 1994	Prospective (n=41) Unstated whether consecutive	Uncertain	Yes	Fair
Norton and Alderson 1997	Prospective (n=46) Unstated whether consecutive	Yes	Yes	Fair
Prat, Amouyal, Amouyal et al., 1996	Prospective (n=119) Consecutive patients recruited, exclusions and refusals accounted for	Yes	Yes	Good
Sugiyama and Atomi 1997	Prospective (n=142) Consecutive patients enrolled	Uncertain	Yes	Fair
Sugiyama and Atomi 1998	Prospective (n=35) Consecutive patients enrolled	Uncertain	Uncertain	Fair
Chak, Hawes, Cooper et al., 1999	Prospective (n=36) Consecutive patients enrolled	Yes	Yes	Good

Table 1. Quality Assessment (cont'd)

Study Author, Year	**Patient Enrollment**	**Diagnostic performance of ERCP determined without knowledge of other test results**	**Diagnostic Performance of other test(s) determined without knowledge of ERCP results**	**Summary Evaluation**
CTC				
Ishikawa, Tagami, Toyota et al., 2000	Prospective (n=45) Unstated whether enrollment truly consecutive, not full accounting of exclusions	Uncertain	Uncertain	Fair
Polkowski, Palucki, Regula et al., 1999	Prospective (n=52) Full accounting of enrolled and excluded consecutive patients	Uncertain	Yes	Fair
Soto, Velez, and Guzman 1999	Prospective (n=29) Uncertain consecutive enrollment	Yes	Uncertain	Fair
Jimenez Cuenca, del Olmo Martinez, Perez Homs et al., 2001	Prospective (n=40) 40 of 60 consecutive patients enrolled, 20 excluded due to scheduling	Yes	Yes	Good
Neitlich, Topazian, Smith et al., 1997	Prospective (n=51) 51 of 96 consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good
Soto, Alvarez, Munera et al., 2000	Prospective (n=51) 51 of 56 eligible consecutive patients enrolled, all exclusions accounted for	Yes	Yes	Good

Table 2. Studies of MRCP, choledocholithiasis outcome, ERCP used as reference standard for all studies except Sugiyama, Atomi and Hachiya (1998)

Study	N	Population	Diagnostic test	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Comments
Demartines, Eisner, Schnabel et al., 2000	40	Patients with suspected CBD stones referred for ERCP	MRCP	48	100	90	90	100	
Guibaud, Bret, Reinhold, et al., 1995	126	Patients with suspected CBD obstruction referred for ERCP	MRCP	25	81	98	93	94	10 patients with other methods for gold standard
Holzknecht, Gauger, Sackmann et al., 1998	61	Patients referred for ERCP	MRCP (on-site reading) MRCP (off-site independent reading)	21	92 85	96 93	86 79	98 96	
Lomas, Bearcroft, and Gimson 1999	69	Patients with suspected CBD stones or stricture referred for ERCP	MRCP	13	100	97	100	97	
Soto, Alvarez, Munera et al. 2000	51	Patients with suspected CBD stones referred for ERCP	MRCP	51	96	100	100	96	1 false-negative ERCP considered positive after stone found at sphincterotomy
Soto, Barish, Alvarez et al., 2000	49	Patients with suspected CBD stones referred for ERCP	MRCP fast Spin Echo Reviewer 1 Reviewer 2 Single Section half-Fourier RARE Reviewer 1 Reviewer 2 Multisection half-Fourier RARE Reviewer 1 Reviewer 2	49	 96 92 100 92 92 96	 96 100 96 96 92 92	 96 100 96 96 92 92	 96 93 100 92 92 96	
Stiris, Tennoe, Aadland et al., 2000	50	Patients with suspected CBD stones referred for ERCP	MRCP	68	88	94	97	81	

Table 2. Studies of MRCP, choledocholithiasis outcome, ERCP used as reference standard for all studies except Sugiyama, Atomi and Hachiya (1998) (cont'd)

Study	N	Population	Diagnostic test	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Comments
Varghese, Farrell, Courtney et al. 1999	100	Patients with CBD obstruction referred for ERCP	MRCP	30	93	99	97	97	12 patients with gold standard of IOC or PTC included in analyses
Varghese, Liddell, Farrell et al., 2000	191	Patients with CBD obstruction referred for ERCP	MRCP	18	91	98	91	98	5 patients with gold standard of IOC or PTC included in analyses
ERCP findings confirmed									
Sugiyama, Atomi, and Hachiya 1998	97	Patients with suspected CBD stones referred for ERCP	MRCP ERCP (ERCP findings confirmed)	35	91 100	100 100	100 100	95 100	Positive ERCP confirmed by sphincterotomy, negative ERCP not confirmed

Sugiyama, Atomi, and Hachiya (1998) did the only study that confirms positive ERCP tests and allows a comparison between the two tests. In that study of 97 patients, ERCP had 100 percent sensitivity, and MRCP had 91 percent sensitivity. Specificity for both tests was 100 percent. This was the only study that analyzed sensitivity by subgroups of stone diameter. Sensitivity was 100 percent for stone diameters from 11–27 mm, 89 percent for stone diameter from 6–10 mm, and 71 percent for stone diameter between 3–5 mm.

Two studies reporting on a total number of patients of 121 had a mixed category of outcomes that included common duct stones (Table 3). In the study by Adamek, Albert, Weitz et al. (1998), the abnormalities included benign and malignant strictures, cholangiocarcinoma and choledochal cyst in addition to common duct stones. MRCP had a sensitivity and specificity for detecting any abnormality of 89 percent and 92 percent, whereas ERCP had a sensitivity of 91 percent and 92 percent.

In the study by Holzknecht, Gauger, Sackmann et al. (1998), the abnormalities detected included common bile duct dilatation and stenosis, in addition to common duct stones. Only the concordance with ERCP was evaluated. According to an image interpretation performed on-site, the sensitivity was 91 percent and the specificity was 80 percent. An off-site interpretation showed similar results.

In conclusion, most of the evidence on MRCP allows only conclusions as to whether MRCP and ERCP are concordant, rather than which test is superior. Most studies show fairly good concordance, with sensitivities and specificities both higher than 90 percent. Evidence limited to one study may indicate that ERCP is slightly better than MRCP.

Review of Evidence: Endoscopic Ultrasound Performance

There are 9 studies (total n=601) reporting on the capability of endoscopic ultrasound to diagnose common duct stones compared to ERCP (Table 4).. In all the studies except 1 (Sugiyama and Atomi, 1998), positive tests of either method were confirmed with sphincterotomy, allowing for inferences regarding comparative performance. The study by Prat, Amouyal, Amouyal et al. (1996) stands out in this regard by subjecting all patients to sphincterotomy and endoscopic exploration, and thus is the only study in this whole section examining common bile duct stones with a truly independent reference standard. Chak, Hawes, Cooper et al. (1999) and Canto, Chak, Stellato et al. (1998) were also rated as “good” quality studies.

Given the small differences in performance noted in most of the studies, none of the studies is likely to detect statistically significant differences in test performance. In three of the studies, the sensitivity of EUS was higher than ERCP (Prat, Amouyal, Amouyal et al., 1996, Norton and Alderson 1997; Burtin, Palazzo, Canard et al., 1997). In three studies, the sensitivity of ERCP was higher than EUS (Canto, Chak, Stellato et al., 1998; Dancygier and Nattermann 1994, Sugiyama and Atomi, 1997) and in the two other studies the sensitivities were within 1 percent (Polkowski, Palucki, Regula et al., 1999; Chak, Hawes, Cooper et al., 1999). The specificities were very close in all studies except Chak, Hawes, Cooper et al. (EUS 100 percent, ERCP 87 percent).

Table 3. Studies of MRCP, mixed outcome including CBD stones, stratified by reference standard

Study	N	Population	Diagnostic test	outcome	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Comments
ERCP findings confirmed										
Adamek, Albert, Weitz et al., 1998	60	Referrals for ERCP with suspected CBD obstruction	MRCP ERCP	Any abnormality	78	89 91	92 92	98 98	71 75	Uncertain method of ascertaining reference standard
ERCP used as reference standard										
Holzknecht, Gauger, Sackmann et al., 1998	61	Patients referred for ERCP	MRCP (on-site reading) MRCP (off-site reading)	Any abnormality	75	91 94	80 80	93 94	75 80	

Table 4. Studies comparing ERCP to endoscopic ultrasonography, ERCP findings confirmed except for one study (Sugiyama and Atomi, 1998)

Study	**N**	**Population**	**Diagnostic test**	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	**Comments**
Prat, Amouyal, Amouyal et al., 1996	119	High suspicion of CBD stones, sphincterotomy candidates	EUS ERCP	66	94 90	98 100	99 100	89 84	Sphincterotomy and endoscopic exploration on all patients. Numbers differ from published report due to rounding errors in published report
Burtin, Palazzo, Canard et al., 1997	68	Patients with suspected CBD obstruction referred for ERCP	EUS ERCP	50	97 91	97 97	97 97	97 92	Unorthodox presentation of data in report, test characteristics calculated from text descriptions, technical failures counted as neg tests
Canto, Chak, Stellato et al., 1998	64	Patients with suspected CBD stones referred for ERCP	EUS ERCP	31	84 95	98 98	94 no report	93 no report	Actual numbers not reported, all values quoted from study. Positive ERCP confirmed with stone extraction, negatives with 12 mo clinical follow up
Norton and Alderson 1997	46	Patients with suspected CBD stones referred for ERCP	EUS ERCP	52	88 79	96 92	95 90	89 83	Positive ERCP and EUS confirmed by sphincterotomy, no confirmation of negative ERCP and EUS
Dancygier and Nattermann 1994	41	Patients with obstructive jaundice, referred for ERCP	EUS ERCP	39	94 100	100 100	100 100	96 100	Positive ERCP confirmed by sphincterotomy, no apparent confirmation of negative ERCP
Polkowski, Palucki, Regula et al., 1999	50	Patients referred for ERCP for suspected CBD stones	EUS ERCP	68	91 91	100 100	100 100	84 84	Positive ERCP confirmed by sphincterotomy, selective confirmation of negative ERCP
Sugiyama and Atomi 1997	142	Patients referred for ERCP for suspected CBD stones	EUS ERCP	36	96 100	100 100	100 100	98 100	Positive ERCP confirmed by sphincterotomy, no apparent confirmation of negative ERCP

Table 4. Studies comparing ERCP to endoscopic ultrasonography, ERCP findings confirmed except for one study (Sugiyama and Atomi, 1998) (cont'd)

Study	**N**	**Population**	**Diagnostic test**	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	**Comments**
Chak, Hawes, Cooper et al., 1999	36	Patients with suspected acute biliary pancreatitis	EUS ERCP	33	91 92	100 87	100 79	95 94	Positives for either test confirmed with sphincterotomy, negatives not confirmed
ERCP + sphincterotomy as ref standard									
Sugiyama and Atomi 1998	35	Patients with suspected acute biliary pancreatitis	EUS	43	100	100	100	100	ERCP reference standard, but positive ERCP confirmed with stone removal

Although most of the studies are small, within the limits of the evidence available, it appears that EUS is similar to ERCP in the detection of common bile duct stones.

Review of Evidence: CTC Performance

Seven sets of findings report the diagnostic characteristics of CTC compared to ERCP for the diagnosis of common bile duct stones (Table 5). The studies varied considerably in the reference standard used. Three studies used ERCP as a reference standard, 2 studies used an independent reference standard, and 2 studies used ERCP and sphincterotomy findings as a reference standard. Three variations of CTC were used—no biliary contrast (3 studies, total n=142) , intravenous biliary contrast (2 studies, total n=95) and oral contrast (2 studies, total n=80). This results in a body of literature in which, at most, 2 studies share the same CT technique and reference standard. The studies by Jimenez Cuenca, del Olmo Martinez, Perez Homs et al. (2001), Neitlich, Topazian, Smith et al. (1997), and Soto, Alvarez, Munera et al. (2000) were rated as "good" quality.

Three sets of findings from 2 studies, all from the same principal author (Soto, Velez, Guzman et al., 1999 and Soto, Alvarez, Munera et al., 2000), used ERCP images as the reference standard. Soto, Alvarez, Munera et al. (2000, n=51), which used no biliary contrast, showed poor concordance with ERCP (sensitivity 65 percent and 84 percent specificity). The other two sets of findings (Soto, Velez, Guzman et al., 1999, n=29 and Soto, Alvarez, Munera et al., 2000, n=51), found higher concordance with ERCP when using oral biliary contrast (sensitivities and specificities both greater than 90 percent).

Two studies (Ishikawa, Tagami, Toyota et al., 2000, n=45 and Polkowski, Palucki, Regula et al., 1999, n=50) examined CTC with IV biliary contrast, and both studies used methods where ERCP findings were confirmed. In both studies ERCP was more sensitive and specific than CTC (Ishikawa, Tagami, Toyota et al., 2000, ERCP 100 percent sensitivity, 100 percent specificity, CTC 71 percent sensitivity, 95 percent specificity; Polkowski, Palucki, Regula et al., 1999, ERCP 91 percent sensitivity, 100 percent specificity, CTC 85 percent sensitivity, 88 percent specificity).

Finally, the two studies that use ERCP sphincterotomy results as the reference standard (Jimenez Cuenca, del Olmo Martinez, Perez Homs et al., 2001, n=40 and Neitlich, Topazian, Smith et al., 1997, n=51) showed sensitivities of 80 percent and 88 percent, respectively, and specificities of 100 percent and 97 percent. A direct comparison to ERCP cannot be done with these data, but these sensitivities are lower than generally has been shown for ERCP.

In conclusion, most studies show a fair concordance with ERCP diagnosis of common bile duct stones, but in studies which allow a determination of which test is superior ERCP seems to have better sensitivity and specificity. However, no estimate of the magnitude of this superiority can be made from this evidence.

Table 5. Studies comparing CTC to ERCP, stratified by reference standard and presence and by type of contrast

Study	N	Population	Diagnostic test	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Comments
ERCP used as reference standard (No biliary contrast)									
Soto, Alvarez, Munera et al., 2000	51	Patients referred for ERCP for suspected CBD stones	CTC	51	65	84	81	70	
ERCP used as reference standard (Oral biliary contrast)									
Soto, Alvarez, Munera et al., 2000	51	Patients referred for ERCP for suspected CBD stones	CTC with oral biliary contrast	51	92	92	92	92	
Soto, Velez, Guzman et al. 1999	29	Patients referred for ERCP for suspected CBD stones	CTC with oral biliary contrast Observer 1 Observer 2	48	 93 86	 100 100	 100 100	 94 88	
ERCP findings confirmed (independent reference standard) *IV biliary contrast*									
Ishikawa, Tagami, Toyota et al., 2000	45	Laparoscopic patients undergoing routine preoperative ERCP	CTC with IV biliary contrast ERCP	16	71 100	95 100	71 100	95 100	Positive ERCP apparently confirmed during cholecystectomy, negative ERCP unlikely to be confirmed
Polkowski, Palucki, Regula et al., 1999	50	Patients referred for ERCP for suspected CBD stones	CTC with IV biliary contrast ERCP	68	85 91	88 100	94 100	74 84	Positive ERCP confirmed by sphincterotomy, selective confirmation of negative ERCP

Table 5. Studies comparing CTC to ERCP, stratified by reference standard and presence and by type of contrast

Study	N	Population	Diagnostic test	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Comments
No biliary contrast, ERCP + sphincterotomy findings used as reference standard									
Jimenez Cuenca, del Olmo Martinez, Perez Homs et al., 2001	40	Patients referred for ERCP for suspected CBD stones	CTC	50	80	100	100	83	ERCP reference standard based on image and/or sphincterotomy findings, not only images
Neitlich, Topazian, Smith et al., 1997	51	Patients referred for ERCP for suspected CBD stones	CTC	33	88	97	94	94	ERCP reference standard based on image and/or sphincterotomy findings, not only images

Conclusion

The evidence about the relative performance of EUS compared to ERCP is the strongest, because most of the studies used reference standards which allowed inferences regarding comparative performance. With some studies showing EUS is better, and other studies showing ERCP is better, and no remarkable outlying results, the weight of the evidence suggest that EUS is similar to ERCP in detecting common bile duct stones.

MRCP has a concordance with ERCP that results in sensitivities and specificities greater than 90 percent in most studies when using ERCP as a reference standard. Along with evidence limited to one study regarding comparative performance of MRCP and ERCP, MRCP may be slightly worse than ERCP in detecting common bile duct stones.

CTC also has reasonable concordance with ERCP, but the range of sensitivities and specificities is lower, with sensitivities dipping down to the 80 percent level in some studies. Again with evidence limited to only 2 small studies on the relative performance of CTC to ERCP, it appears that CTC is not as good as ERCP in detecting common bile duct stones.

Although some tests may not perform quite as well as ERCP, the role of these tests in the management of patients with suspected common bile duct stones cannot be determined strictly by an examination of their test characteristics. The costs and risks of the tests, and the costs and risks of actions based on their results, along with the pretest probability of stone needs to be taken into account to determine the optimal strategy that most efficiently treats patients with suspected common duct stones.

Part I, Section 2: Outcomes of Treatment Using ERCP for Common Bile Duct Stones—Comparison of Strategies Using ERCP, Surgery, or Medical Management

Introduction

ERCP can both provide diagnosis and treatment of common bile duct stones in one session in a less-invasive manner than an open surgical procedure. Commonly performed in conjunction with cholecystectomy, it could be performed before or after or, rarely, during surgery. However, there are risks from the procedure and it may not be successful at removing the common bile duct stones. Common bile duct exploration was the traditional surgical treatment to remove stones. This used to be performed with an open surgical incision. Then laparoscopic cholecystectomy became a common operation, and in order to avoid an open incision, ERCP was used in the diagnosis and removal of common duct stones. Recently, laparoscopic methods of exploring the common bile duct and removing stones have evolved, making for even more varied potential treatment options.

In order to appropriately evaluate ERCP treatment strategies, studies must properly account for the patients throughout the diagnostic and treatment process, including additional procedures needed for failed initial procedures. Alternatively, studies can assess outcomes through identical stages of the diagnostic or treatment process. Complication rates in and of themselves may not be fair measures of outcomes between treatment strategies if the baseline morbidity of procedures (e.g., open common bile duct exploration versus ERCP common duct stone extraction) are very different. Ideally, a measure of morbidity that could fairly assess both the quantity of procedures and total morbidity endured during each procedure would be a fair comparison between treatment strategies.

Evidence Base

For the purposes of this evidence review, the literature remaining after selection criteria were applied was very thin and spread out over many different research questions. Generally, there was only one or at most, two, studies on a specific comparison of interest. Study quality assessment is outlined in Table 6.

Review of Evidence: ERCP with Laparoscopic Cholecystectomy to Remove Common Bile Duct Stones

Three randomized controlled trials enrolling a total of 289 patients compared alternative strategies for removal of common bile duct stones in patients undergoing laparoscopic cholecystectomy (Tables 7–9). Although all 3 trials were judged to be of good quality, the evidence is limited because there is only a single study addressing each comparison of interest. Each trial reported on a different comparison, with respect to both the procedures compared and the patient population selected.

Table 6. Quality Assessment

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Cuschieri, Lezoche, Morino et al., 1999	RCT (n=300) Good comparability — computerized randomization — comparable characteristics	31 patients not treated according to random allocation, reported separately	Adequate for comparison	Adequate outcome measures used.	Those treated to assigned treatment reported as principal findings. Patients not treated by assigned treatment reported separately.	good
Rhodes, Sussman, Cohen et al., 1998	RCT (n=80) Uncertain comparability — randomization technique unknown — limited data on comparability	All patients retained for analysis	Adequate for comparison	Outcomes were not assessed blindly Uncertain how morbidity rates determined	All retained patients analyzed	Good
Chang, Lo, Stabile et al., 2000	RCT (n=59) Good comparability — sealed envelope randomization — comparable characteristics	All patients retained for analysis	Adequate for comparison	Outcomes were not assessed blindly Definition of morbidity not provided	All retained patients analyzed	Good

Table 6. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Targarona, Ayuso, Bordas et al., 1996	RCT (n=98) Good comparability — stratified randomization with sealed envelopes — patient characteristics comparable	2 out of 100 patients excluded because of incorrect randomization	Adequate for comparison	Outcomes were not assessed blindly Short-term morbidity rates do not capture difference in invasiveness between treatments	All patients retained for short-term outcomes analysis 89/93 surviving patients retained for long term outcomes analysis	Good
Trias, Targarona, Ros et al., 1997	Prospective study with historical control group (n=110) Good comparability Patient characteristics comparable	All patients prospectively identified as eligible enrolled	Surgical arm may include endoscopic sphincterotomy, more intensive treatment	Outcomes were not assessed blindly Short-term morbidity rates do not capture difference in invasiveness between treatments	All patients retained for short-term outcomes analysis 99/105 surviving patients retained for long term outcomes analysis	Fair
Hammarstom, Holmin, Stridbeck et al., 1995	RCT (n=80) Good comparability — random numbers — patient characteristics comparable	All potential patients accounted for, few refusals	Adequate for comparison	Outcomes not systematically defined or enumerated	Adequate follow up	Poor, most results could not be tabulated

Table 6. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Lai, Mok, Tan et al., 1992	RCT (n=82) Good comparability — randomized by consecutive envelopes — patient characteristics comparable	82 of 96 patients with severe acute cholangitis enrolled	Adequate for comparison	Outcomes were not assessed blindly Complication rates do not capture difference in invasiveness between treatments	All patients retained for analysis	Good
Leese, Neoptolemos, Baker et al., 1986	Retrospective observational study (n=82) Not very comparable Patients undergoing ERCP older, greater numbers of risk factors	Not applicable-retrospective study	Adequate for comparison	Outcomes were not assessed blindly	Analysis does not take into account difference in risk factors	Poor

Table 6. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Adamek, Maier, Jakobs et al., 1996	Retrospective observational study (n=145) Fair comparability Patients comparable on all measured characteristics	Not applicable-retrospective study	Adequate for comparison	Outcomes were not assessed blindly	Simple unadjusted comparisons	Fair/poor
Neuhaus, Zillinger, Born et al., 1998	RCT (n=60) Good comparability — randomization technique unknown — patients comparable on all measured characteristics	All patients retained for analysis	Adequate for comparison	Outcomes were not assessed blindly	All patients retained for analysis	Good
Bergman, Rauws, Fockens et al., 1997	RCT (n=202) Good comparability — blinded computer-generated randomization — patients comparable on all measured characteristics	16 out of 218 excluded after randomization because of ineligibility	Adequate for comparison	Outcomes were not assessed blindly	All patients retained for analysis	Good

Table 6. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Ochi, Mukawa, Kiyosawa et al., 1999	RCT (n=110) Good comparability — randomization not described — patients comparable on all measured characteristics	All patients retained for analysis	Adequate for comparison	Outcomes were not assessed blindly	All patients retained for short-term outcome analysis 105/110 patients retained for long-term outcome analysis	Good
Mavrogiannis, Liatsos, Romanos et al., 1999	RCT (n=153) Good comparability – randomization by sealed envelopes – Baseline characteristics similar for age, gender, presence of GB and gallstones	No cross-overs, drop outs reported.	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention to treat analysis used.	Good
Chopra, Peters, O'Toole et al., 1996	RCT (n=86) Good comparability — Randomization by sealed envelopes — patients comparable on all measured characteristics	All patients retained for analysis	Adequate for comparison	Outcomes not blindly assessed Adequate for comparison	All patients analyzed for short term outcomes, 82/86 followed for long term outcomes	good

Table 7. Preoperative versus Postoperative ERCP in Cholecystectomy: Randomized Trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Chang, Lo, Stabile et al., 2000	59	59 patients with mild to moderate gallstone pancreatitis, undergoing cholecystectomy after acute pancreatitis Mandatory preoperative ERCP (n=30) vs. selective postoperative ERCP (n=29) based on IOC findings	Stone Removal, successful ERCP/ERCP with stones: Preop ERCP: 12/12, 100% Postop ERCP: 7/7 , 100%		Morbidity rates (not defined) Preop ERCP: 10% Postop ERCP: 10%	n.s.	Hospital stay: mean, median days Preop ERCP: 11.7,9.5 Post op ERCP: 9.0 , 8 ICU days: mean, median Preop ERCP: 1.7, 1 Post op ERCP: 1.9 ,1 Total Costs: Preop ERCP: $10,210 Postop ERCP: $8,586	 .04 n.s. .049

Table 8. Preoperative ERCP versus Intraoperative cholangiogram and laparoscopic common bile duct exploration in patients undergoing laparoscopic cholecystectomy in patients with suspected common bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Cuschieri, Lezoche, Morino et al., 1999	269	Patients with suspected CBD stones needing cholecystectomy Preoperative ERCP (n=136) versus IOC and laparoscopic CBD exploration (n=133) as initial strategies for removing stones	Stone clearance: Preop ERCP: 84% IOC, LCBDE: 84%	n.s.	Conversion to open cholecystectomy: Preop ERCP: 6% IOC, LCBDE: 13% Overall morbidity: Preop ERCP: 12.8% IOC, LCBDE: 15.8% Mortality: Preop ERCP: 1.5% IOC, LCBDE: 0.75%	.08 n.s. n.s.	Hospital stay, mean days: Preop ERCP: 9 IOC, LCBDE: 6	<.05

Table 9. Postoperative ERCP versus laparoscopic exploration of common bile duct in patients with common duct stones found on intraoperative cholangiography, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Rhodes, Sussman, Cohen et al., 1998	80	80 patients with CBD stones found on cholangiography during cholecystectomy Laparoscopic CBD exploration (LCBDE) (n=40) versus postoperative ERCP (n=40)	Initial clearance of CBD stones: LCBDE: 75% Postop ERCP: 75% Final clearance of CBD stones: LCBDE: 100% Postop ERCP: 93%	n.s. n.s.	Overall Morbidity: LCBDE: 18% Postop ERCP: 15%	n.s.	Hospital stay, median days: LCBDE: 1 Postop ERCP: 3.5	<.01

Overall, both arms in each of these 3 studies reported similar rates of stone clearance and morbidity, although morbidity was not well defined in two of these trials (Chang, Lo, Stabile et al., 2000; Rhodes, Sussman, Cohen et al., 1998). Thus, the main outcome of interest is relative resource utilization for each pair of alternative strategies for stone removal.

Mandatory Preoperative ERCP versus Selective Postoperative ERCP

Chang, Lo, Stabile et al. (2000) randomized 59 patients undergoing cholecystectomy during recovery from acute gallstone pancreatitis. Selective postoperative ERCP was based on findings from intraoperative cholangiogram. Resource utilization was lower in the selective postoperative ERCP group as measured by mean total hospital stay (9.0 vs. 11.7 days, p=0.04), and total costs ($8,586 vs. $10,210, p=0.049)

Preoperative ERCP versus intraoperative cholangiogram and laparoscopic common bile duct exploration (LCBDE)

Cuschieri, Lezoche, Morino et al. (1999) randomized 300 patients undergoing laparoscopic cholecystectomy who had suspected common bile duct stones. In one treatment arm, preoperative ERCP was performed, and sphincterotomy and stone removal was attempted if stones were detected. In the other treatment arm, LCBDE was performed if stones were detected on intraoperative cholangiogram. Mean hospital stay was reduced in the LCBDE treatment group (6 versus 9 days, $p<0.05$).

LCBDE versus Postoperative ERCP

Rhodes, Sussman, Cohen et al. (1998) randomized 80 patients with common bile duct stones found on intraoperative cholangiography during laparoscopic cholecystectomy. The hospital stay was reduced in the LCBDE group (median days, 1 vs. 3.5, $p<0.01$)

Summary

There is insufficient evidence determine whether there is an optimal strategy for common bile duct stone removal in patients undergoing cholecystectomy. The available evidence suggests that resource utilization is lower when:

(1) selective postoperative ERCP is performed, as compared to routine ERCP prior to cholecystectomy; and
(2) when laparoscopic common bile duct exploration is performed during laparoscopic cholecystectomy, as compared to adjunctive pre- or postoperative ERCP.

However, since success and complications of ERCP and laparoscopic cholecystectomy with LCBDE may be operator dependent, findings may not be generalizable across clinical settings. The availability of expertise in LCBDE may be limited at present.

Review of Evidence: ERCP Sphincterotomy alone versus Definitive Surgery for suspected common duct stones

Patients at High Surgical Risk

One randomized, controlled trial (Targarona, Ayuso, Bordas et al., 1996) and an observational study derived from the Targarona trial (Trias, Targarona, Ros et al., 1997) addressed whether removal of common duct stones with endoscopic sphincterotomy alone has lower morbidity and mortality than approaches which also remove the gall bladder during initial treatment (Table 10 and Table 11). The population of interest is patients at high surgical risk if subjected to cholecystectomy. For patients at high surgical risk, there may be advantages to a nonsurgical approach for removing common duct stones during acute symptomatic episodes. However, there may be differences in long term outcome if the gall bladder is not removed. Study quality was judged to be "Good" for the Targarona, Ayuso, Bordas et al. (1996) trial, and "Fair" for the Trias, Targarona, Ros et al. (1997) study.

The Targarona and Trias studies included high-risk surgical candidates based on age, cardiac risk, and pulmonary disease. The technique used in the Targarona, Ayuso, Bordas et al. (1996) study may not be representative of current surgical practice as the investigators performed open cholecystectomy for the definitive surgery arm; only the observational study by Trias, Targarona, Ros et al. (1997) used laparoscopic cholecystectomy.

Targarona, Ayuso, Bordas et al. (1996; n=98) found that both groups had similar short-term treatment failure, mortality, and morbidity, but initial postoperative length of stay favored endoscopic sphincterotomy alone (5 versus 11 days, $p<0.001$). However, over the longer term, the cholecystectomy patients had fewer biliary complications (6 percent versus 21 percent, $p=0.04$) and fewer readmissions (4 percent versus 23 percent, $p<0.01$). Eventually,15 percent of patients in the sphincterotomy group underwent cholecystectomy.

Trias and colleagues performed laparoscopic cholecystectomy with preoperative ERCP as needed in 60 high-risk patients, and compared outcomes the to endoscopic sphincterotomy arm of the Targarona, Ayuso, Bordas et al. (1996) trial. Short-term and long-term results were similar to the Targarona trial, but initial hospital length of stay no longer favored the endoscopic sphincterotomy group when compared to laparoscopic, rather than open, cholecystectomy.

Patients Not at High Surgical Risk

One randomized controlled trial by Hammarstrom, Holmin, Stridbeck et al. (1995) enrolled 80 patients with intact gallbladders diagnosed with common bile duct stones on ERCP (Table 12). Patients either received sphincterotomy alone or open cholecystectomy and common bile duct exploration. Patients were followed for 5 years.

The study does not coherently define and compare outcomes between treatment groups for the most part; rather, various post-procedure events are unsystematically enumerated, making it difficult to tabulate any overall sense of outcomes. Total hospital stay (short term and follow up

stays) was compared between the groups and was not statistically significantly different (median stay, 13 days sphincterotomy, 16 days surgery, p=ns). Of patients who received sphincterotomy, 13 were subsequently treated with cholecystectomy, 4 urgently because of acute cholecystitis. The authors also noted that the death rate from non-biliary related causes was higher in the endoscopic sphincterotomy group (30 percent vs. 10 percent, p=0.02). The authors conclude that the two alternatives are equally effective in the long term, but that due to the difference in heart disease mortality surgery might be the better option.

Summary

The very limited available evidence shows that definitive treatment prevents long term recurrence of biliary symptoms, hospitalization, and need for further treatment. In high-risk patients as defined in these studies, definitive treatment can be performed with acceptable short term morbidity and equivalent mortality as sphincterotomy alone. Not all patients develop recurrent problems, so the choice of definitive treatment versus sphincterotomy alone involves the weighing of short term morbidity of treatment, be it sphincterotomy alone, open or laparoscopic surgery, against the probability of recurrent biliary symptoms.

Table 10. Endoscopic sphincterotomy alone versus open cholecystectomy in high risk surgical patients as primary treatment for common bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Targarona, Ayuso, Bordas et al., 1996	98	Surgical high risk patients presenting with symptoms consistent with CBD stones Endoscopic sphincterotomy only (n=50) versus open cholecystectomy and CBD exploration if necessary (n=48)	Initial failure of treatment: ES: 12% Surgery: 6% Immediate mortality: ES: 6% Surgery: 4%	0.3 .5	Immediate morbidity: ES: 16% Surgery: 23% LONG TERM Biliary complications: ES (n=46): 21% Surgery(n=43): 6% Readmissions: ES: 23% Surgery: 4% Cholecystectomy: ES: 15% Surgery: 0% Need for sphincterotomy: ES: 2% Surgery: 4%	0.4 .04 .01 .01 .9	Post-treatment length of stay, mean days: ES: 5 Surgery: 11	 .001

Table 11. Endoscopic sphincterotomy alone versus laparoscopic cholecystectomy (with or without preoperative ERCP) in high risk surgical patients as primary treatment for common bile duct stones, observational studies

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Trias, Targarona, Ros et al., 1997	110	Surgical high risk patients presenting with symptoms consistent with CBD stones Endoscopic sphincterotomy only (n=50) versus laparoscopic cholecystectomy and with preoperative ERCP if necessary (n=60)	Initial failure of treatment: ES: 12% Surgery: 11% Immediate mortality: ES: 6% Surgery: 3%	n.s. 0.5	Immediate morbidity: ES: 16% Surgery: 18% LONG TERM Biliary complications: ES (n=46): 21% Surgery(n=53): 4% P Readmissions: ES: 23% Surgery: 2% P Need for reoperation: ES: 15% Surgery: 2%	n.s. <.04 <.01 <.01	Post-treatment length of stay, mean days: ES: 5 Surgery: 4.4	n.s.

Table 12. Endoscopic sphincterotomy alone versus open cholecystectomy and CBD exploration in non-high risk surgical patients as primary treatment for common bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Hammarstrom, Holman, Stridbeck et al., 1995	80	Patients presenting with CBD stones on ERCP with intact gall bladder Endoscopic sphincterotomy only (n=39) versus open cholecystectomy and CBD exploration if necessary (n=41)	Biliary outcomes not coherently tabulated		Biliary complications not coherently tabulated Deaths from non-biliary related disease ES: 30% Surgery: 10% 13 patients in ES group required cholecystectomy on follow up	0.02	Total hospitalization days, median ES: 13 Surgery: 16	NS

Review of Evidence: ERCP versus surgery for patients with acute cholangitis

Two studies compared of ERCP treatment to open surgery for patients with acute cholangitis due to common bile duct stones (Table 13 and Table 14). Lai, Mok, Tan et al. (1992) randomized 82 patients diagnosed with common bile duct stones by ERCP to endoscopic nasobiliary drainage or open common bile duct exploration. This study is from Hong Kong, where oriental cholangiohepatitis is a common cause of common duct stones, and may not generalize to populations with a different spectrum of disease. Leese, Neoptolemos, Baker et al. (1986) conducted a retrospective review of 43 patients treated with endoscopic sphincterotomy to 28 contemporaneous patients undergoing surgical decompression for relief of cholangitis.

The Leese, Neoptolemos, Baker et al. (1986) study was judged to be of poor quality due to imbalance of patient characteristics between groups.

Acute severe cholangitis is a condition of very high mortality, thus the important outcome is to reduce the acute mortality rate. Both studies show that short-term mortality from acute cholangitis is lower in the ERCP-treated group compared to open surgery. Lai, Mok, Tan et al. (1992) reported lower hospital mortality (10 percent versus 32 percent, $p<0.05$) in the group treated with endoscopic nasobiliary drainage. Despite prognostic factors favoring the open surgery group, Leese, Neoptolemos, Baker et al. (1986) found that mortality at 30 days was lower in the endoscopic sphincterotomy group (5 percent versus 21 percent, $p<0.02$).

Review of Evidence: Endoscopic lithotripsy vs. extracorporeal shock wave lithotripsy (ESWL) in stones not removable with standard endoscopic techniques

Two studies compared endoscopic lithotripsy techniques to extracorporeal shock wave lithotripsy (ESWL) in removing common bile duct stones that cannot be removed with standard endoscopic techniques (which includes mechanical lithotripsy) (Neuhaus, Zillinger, Born et al., 1998 and Adamek, Maier, Jakobs et al., 1996; Table 15 and Table 16). In these studies, successful removal of stones is the important outcome.

Neuhaus, Zillinger, Born et al. (1998) randomized 60 patients to ESWL or intracorporeal laser lithotripsy. Adamek, Maier, Jakobs et al. (1996) performed an observational comparison between ESWL (n=79) and intracorporeal electrohydraulic lithotripsy (n=46).

Neuhaus, Zillinger, Born et al. (1998), found that intracorporeal laser lithotripsy was more successful than ESWL in clearing the bile duct of stones (97 percent versus 73 percent, $p<0.05$). Adamek, Maier, Jakobs et al. (1996) found no significant difference between ESWL and electrohydrolic lithotripsy.

Table 13. Endoscopic drainage for treatment of acute cholangitis due to common bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Lai, Mok, Tan et al., 1992	82	82 patients with acute severe cholangitis due to CBD stones diagnosed with diagnostic ERCP Nasobiliary drainage placed by ERCP (n=41) versus open CBD exploration (n=41)	Hospital mortality rate: ERCP: 10% Surgery: 32%	<.03	Overall complication rate: ERCP: 34% Surgery: 66%	>.05		

Table 14. Sphincterotomy for treatment of acute cholangitis due to common bile duct stones, observational studies

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Leese, Neoptolemos, Baker et al., 1986	71	Retrospective review of patients with acute cholangitis due to CBD stones Early sphincterotomy (n=43) versus early surgery (n=28)	30 day mortality ERCP: 5% Surgery: 21%	<.02	Total % of patients with complications: ERCP: 28% Surgery: 57%	N/A	Hospital stay, median days: ERCP: 20 Surgery 23	n.s.

Patients receiving ERCP had greater baseline medical risk factors than patients having surgery (2 vs. 1, P<.05)

Table 15. Intracorporeal vs. extracorporeal lithotripsy for common bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Neuhaus, Zillinger, Born et al. 1998	60	Patients with stones not removable with ERCP techniques due to impacted stones or inaccessable bile duct. 33 patients with endoscope access, 27 patients with percutaneous access Extracorporeal shock wave lithotripsy (ESWL) (n=30) versus intracorporeal laser lithotripsy (ILL) (n=30)	Bile duct clearance: ESWL: 73% ILL: 97%	<.05	Not formally enumerated, appeared to be mild		Treatment sessions needed, mean: ESWL: 3.0 ILL: 1.2 Duration of treatment, mean days: ESWL: 3.9 ILL: 0.9	<.001 <.001

Table 16. Intracorporeal vs. extracorporeal lithotripsy for common bile duct stones, observational studies

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Adamek, Maier, Jakobs et al., 1996	125	Patients with stones not removeable with ERCP techniques due to large stone size, impaction, biliary stricture, inaccessable bile duct Extracorporeal shock wave lithotripsy (ESWL) (n=79) versus intracorporeal electrohydraulic lithotripsy (EHL) (n=46)	Fragmentation of stones: ESWL: 97% EHL: 93% Bile duct clearance: ESWL: 79% EHL: 74%	n.s. n.s.	Not formally compared between treatments		Treatment sessions needed, mean: ESWL: 2.0 EHL: 1.1 Hospital stay, mean days: ESWL: 13 EHL: 11	 N/A N/A

Characteristics of patients, stone size, number of stones, stone location not statistically significantly different between treatment groups.

Review of Evidence: Endoscopic balloon dilation versus endoscopic sphincterotomy

Two randomized controlled trials (Bergman, Rauws, Fockens et al., 1997 and Ochi, Mukawa, Kiyosawa et al., 1999) compared endoscopic balloon dilation to endoscopic sphincterotomy for removal of common bile duct stones in a total of 312 patients (Table 17). Study quality was judged as "Good" for both trials.

Concern about possible long term effects of sphincterotomy on biliary function, plus concern about hemorrhage induced by sphincterotomy have led to consideration of dilation of the biliary sphincter as an alternative method to remove common bile duct stones. Dilation would potentially preserve the function of the biliary sphincter. However, concern has been raised that pancreatitis may occur more often as a complication after balloon dilation.

However, neither study assesses long term outcomes, so the only outcomes that can be assessed are success in removing common bile duct stones and early complications. Both studies found that although balloon dilation ultimately produces equivalent stone removal rates (Bergman, Rauws, Fockens et al., 1997, balloon 89 percent success, sphincterotomy 91 percent success; Ochi, Mukawa, Kiyosawa et al., 1999, balloon 93 percent success, sphincterotomy 98 percent). Some patients in the balloon treatment arm must either cross over or be subject to additional procedures such as mechanical lithotripsy to compensate for the lower initial success rate. Early complications and follow-up complications were not statistically significantly different in the Bergman, Rauws, Fockens et al. (1997) study. In the Ochi, Mukawa, Kiyosawa et al. (1999) study, early complications were not statistically different. Late complications were reported (balloon 4 percent, sphincterotomy 15 percent), but statistical significance tests were not reported.

DiSario, Freeman, Bjorkman et al., (1998) also completed a randomized controlled trial comparing balloon dilation to sphincterotomy, but this trial had only been reported in abstract form in 1998. The results of this study are summarized here because it is commonly cited in reviews and the findings on post-procedure pancreatitis are striking. In this randomized controlled trial of 240 patients, stone clearance was achieved in 99 percent of patients. However, morbidity occurred in 15 percent of balloon dilation patients and 4 percent of sphincterotomy patients ($p=0.014$) Most of the morbidity in the dilation group was due to moderate or severe pancreatitis which occurred in 4 patients and resulted in 2 deaths.

Review of Evidence: Needle-knife fistulotomy versus needle-knife precut papillotomy for the treatment of common bile duct stones in patients with difficult cannulations

Mavrogiannis, Liatsos, Romanos et al. (1999) performed a randomized, controlled trial ($n=153$) comparing two precutting techniques for cannulating the common bile duct when difficulty is encountered when trying to cannulate the common bile duct. (Table 18). Needle-knife fistulotomy (NKF) has been proposed as a safer method of precutting than traditional needle-

Table 17. Endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bile duct stones, randomized trials

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Bergman, Rauws, Fockens et al., 1997	202	Patients referred for ERCP for removal of CBD stones, stones visualized Balloon dilation and stone removal versus sphincterotomy and stone removal	Stone removal in one session: Balloon: 89% Sphincterotomy: 91% *9 patients in Balloon group required sphincterotomy to remove stones	n.s.	Early complications: Balloon: 17% Sphincterotomy: 24% Follow-up complications: Balloon: 18% Sphincterotomy: 23%	n.s. n.s.		
Ochi, Mukawa, Kiyosawa et al., 1999	110	Patients referred for ERCP for removal of CBD stones, stones visualized, < 15 mm and less than 10 stones Balloon dilation and stone removal versus sphincterotomy and stone removal	Stone removal, final: Balloon: 93% Sphincterotomy: 98% Stone removal after initial procedure (before lithotripsy): Balloon: 78% Sphincterotomy: 94%	.36 .02	Early complications: Balloon: 2% Sphincterotomy: 6% Late complications: Balloon: 4% Sphincterotomy: 15%	n.s. n/a		

Table 18. Needle-knife fistulotomy versus needle-knife precut papillotomy for the treatment of common bile duct stones

Study	N	Population and Interventions	Outcomes	P	Adverse effects, complications	P	Resource utilization	P
Mavrogiannis, Liatsos, Romanos et al., 1999	153	Consecutive patients who required treatment of suspected choledocholithiasis who had difficulty achieving selective CBD cannulation were randomized to either needle-knife fistulotomy (NKF, n=74) or needle-knife precut papillotomy (NKPP, n=79). All patients had biochemical cholestasis and one or more of the following: biliary pain, bile duct cannulation, and gallbladder stones.	Cannulation success rates (overall): NKF=90.5% NKPP=88.6% Successful stone extraction without lithotripsy NKF (40/48) = 83% NKPP (45/46) =98% Overall stone extraction NKF =100% NKPP =100%	n.s. .05 n.s.	Comp (%): NKF NKPP Bleeding 6.75 5.06 Perforation 2.7 2.53 Cholangitis 1.35 0 Pancreatitis 0 7.59 Total 10.81 15.18 Hyperamylasemia 2.7 17.72 Death 0 1.26	 n.s. n.s. n.s .05 n.s. .01 n.s.		

knife precut papillotomy (NKPP), with the potential disadvantage of a smaller opening into the bile duct which may prevent successful stone removal.

Overall success in cannulating the common bile duct (after second attempts) was equivalent between the two techniques (NKF 91 percent, NKPP 89 percent, p=n.s.) Stone removal without use of lithotripsy was greater for NKPP than for NKF (98 percent versus 83 percent), but final stone removal rates were 100 percent for both groups. Overall complications were not statistically significantly different (NKF 11 percent, NKPP 15 percent, p=n.s.), but NKPP had a greater pancreatitis rate (7.6 percent versus 0 percent, $p<0.05$) and a higher rate of hyperamylasemia (17.7 percent versus 2.7 percent, $p<0.01$). Both methods appear to be similar in the management of patients with common bile duct stones.

Review of Evidence: Endoscopic biliary endoprosthesis versus endoscopic sphincterotomy and stone extraction for common bile duct stones in high risk patients

One randomized study (Chopra, Peters, O'Toole, et al., 1996) compared biliary endoprosthesis placement to conventional endoscopic sphincterotomy and stone extraction for patients with common duct stones who were at high risk because of old age or serious debilitating disease. It was theorized that placement of the endoprosthesis might successfully prevent biliary complications with lower short term morbidity than endoscopic sphincterotomy.

Early complications arising within 72 hours after the procedure were 3/43 in the endoprosthesis group and 7/43 in the endoscopic sphincterotomy group (p=0.18). Among the 82 patients followed long term for a median of 16 to 20 months, 9 patients in the endoprosthesis group had 11 episodes of cholangitis, and 6 patients in the endoscopic sphincterotomy group developed cholangitis. Overall, a higher proportion of the sphincterotomy group (86 percent) remained free of biliary complications at 20 months than the endoprosthesis group (64%, p=0.03). Thus although endoprosthesis placement is as effective and safe as sphincterotomy over the short term, complications and cholangitis are higher over the long term.

Conclusion

Overall, a very thin literature spread out over many different comparisons of interest prevents strong conclusions about any specific treatment comparison. Keeping in mind this thin literature base, the available evidence suggests that:

- Laparoscopic common bile duct exploration may be better than ERCP strategies to manage cholecystectomy patients with the least resource use.

- Definitive surgery prevents long term complications at acceptable short-term morbidity when compared to sphincterotomy alone in high-risk surgical patients.

- Endoscopic treatment of acute cholangitis reduces short-term mortality when compared to emergency surgery.

- Limited evidence suggests that intracorporeal and extracorporeal lithotripsy methods show similar outcomes in removing large common bile duct stones.

- Limited evidence suggests similar stone removal rates and short-term complications when comparing balloon dilation and sphincterotomy.

- Limited evidence suggests similar stone removal rates and complications when comparing needle-knife fistulotomy to needle-knife precut papillotomy.

- Limited evidence suggests that endoscopic sphincterotomy and duct stone clearance is more effective than biliary endoprosthetic placement for prevention of long term complications in patients considered to be high surgical risks.

Part I, Section 3: Diagnostic Value of Individual Risk Factors or Predictive Models for Assessing the Likelihood of Having a Common Bile Duct Stone

Introduction

In trying to determine optimum diagnostic and treatment strategies, many investigators have analyzed individual risk factors and combinations of risk factors that may predict the presence or absence of common bile duct stones. With information about the probability of a common bile duct stone, it may be possible to design a diagnostic and treatment strategy that minimizes patient morbidity and/or minimizes medical resource utilization.

The data reviewed here cannot be directly translated into optimum diagnostic and treatment strategies because there are many possible strategies, given the variety of methods possible to diagnose common bile duct stones (ERCP, MRCP, endoscopic ultrasound, intraoperative cholangiogram) and treat them (preoperative ERCP, laparoscopic common bile duct exploration, postoperative ERCP, expectant management).

However, a few simple principles surface. From the perspective of the individual patient, the probability of a common duct stone is the key factor in determining which approach may be best. If the preoperative probability of a common bile duct stone is high enough, ERCP tends to become efficient and effective because both diagnosis and therapy can be carried out in a single procedure in one setting. If the preoperative probability of a common duct stone is low enough, then it may be possible to avoid any diagnostic procedure to diagnose common duct stones and rely on expectant postoperative management with ERCP to manage any stones that were missed. In the middle range of probability, use of diagnostic tests such as EUS, MRCP, or intraoperative cholangiogram may be efficient methods to treat patients.

All the risk factors or decision rules evaluated in this section have potentially variable cutoff thresholds, so that sensitivity or specificity can be manipulated with the expected trade-offs to produce a particular positive or negative predictive value. However, at a particular cutoff point that produces the desired predictive value, a superior risk factor or decision rule will have higher sensitivities and specificities than other decision rules, and thus better performance in discriminating between those patients who do and do not have stones.

For example, suppose that a probability of stone of 60 percent or greater makes preoperative ERCP the optimum strategy for that particular patient. For example, risk factor A at a particular cutoff produces a positive predictive value of 60 percent, and risk factor B at a particular cutoff point also produces a positive predictive value of 60 percent in the same population. However, risk factor A only identifies 40 percent of the patients with stones at that cutoff (40 percent sensitive), and risk factor B identifies 80 percent of the patients with stones at that cutoff (80 percent sensitivity). Thus, using risk factor B, 80 percent of the patients with stones can be managed by a strategy which requires a 60 percent probability of stone to be optimal.

In sum, then, given that the particular cutoff threshold can be varied to meet desired criteria, then the exact sensitivity and specificity calculated in any single study is not important. The critical factor differentiating any of these risk factors or decision rules is the capability to have both the highest sensitivity and specificity, or in the parlance of diagnostic decision-making, the best receiver-operator characteristic (ROC). Then the cutoff point can be defined that produces the sensitivities and specificities that result in the desired positive predictive value. The studies reviewed here did not in general calculate ROC curves. A risk factor or decision rule with both high sensitivity and specificity would have the best ROC.

Evidence Base

A total of 13 studies with a total of 7,409 patients contributed to the findings reported here. Most studies reported on several of the individual risk factors, some reported on individual risk factors and a multivariate risk prediction model.

Review of Evidence: Univariate Risk Factors for Common Bile Duct Stones

The single risk factors commonly examined in studies included clinical jaundice or elevated bilirubin, liver function tests, and ultrasound findings of a dilated common bile duct. Studies varied in the definitions and cutoff thresholds for the various tests

Five studies (total n=2,661) reported on clinical jaundice as a risk factor (Table 19). Positive predictive values ranged from 29 percent to 86 percent, sensitivity from 24 percent to 56 percent, and specificity from 87 percent to 99 percent. Clinical jaundice does not have an exact threshold cutoff value, nor is the reliability of measurement certain. In general, though, sensitivities are low, specificities are higher, and in the situation of a low prevalence condition such as common bile duct stones, the high specificity drives the predictive values to be high.

Six studies (total n=2369) reported on bilirubin levels. At varying cutoff levels, positive predictive values ranged from 42 percent to 95 percent, sensitivity from 31 percent to 56 percent, and specificity from 48 percent to 99 percent. In general, sensitivities were low, specificities higher, and the resulting positive predictive values are reasonably high.

Eight studies (total n=3,551) reported on various liver function tests (Table 20). Some studies examined more than 1 cutoff level. There was a broad range of predictive values, sensitivities and specificities for all the different liver function tests examined. In general, the trade off between sensitivity and specificity can be noted in all the studies. The studies with cutoff values that produce high specificity tend to have low sensitivity, but this type of cutoff produces the highest positive predictive values.

Ten studies (total n=4,321) reported on the finding of a dilated common bile duct seen on ultrasound (Table 21). The threshold for a dilated duct varied from 5 to 10 mm, and was undefined in a few studies. Predictive values ranged from 28 percent to 91 percent, sensitivities from 28 percent to 94 percent, and specificities from 72 percent to 98 percent. Studies with high sensitivity tend to have low specificity, and vice versa.

Table 19. Jaundice or elevated bilirubin as a risk factor for CBD stone

Study	Population	% prevalence of stone in population	n	Rule tested	Predictive Value	Sensitivity	Specificity	Comments
Alponat, Kum, Rajnakova et al., 1997	Patients with risk factors for CBD stones having ERCP	32	192	jaundice	67	56	87	
Barkun, Barkun, Fried et al., 1994	Patients undergoing lap cholecystectomy who had ERCP	48	139	bilirubin>1.8	57	48	48	
Bergamaschi, Tuech, Braconier et al., 1999	Patients undergoing lap cholecystectomy	15	990	jaundice	76	24	99	
Hauer-Jensen, Karesen, Nygaard et al., 1985	Patients undergoing cholecystectomy	12	319	jaundice bilirubin>1.5	29 42	26 45	91 91	
Kim, Kim, Lee et al., 1997a	Patients undergoing lap cholecystectomy	17	561	jaundice bilirubin >2	52 53	36 41	93 92	
Koo and Traverso 1996	Patients undergoing lap cholecystectomy	12	420	bilirubin>1.2	47	31	93	
Menezes, Marson, Debeaux et al. 2000	Patients undergoing lap cholecystectomy	33	233	bilirubin>nl bilirubin>2xnl	95 92	48 31	98 99	
Santucci, Natalini, Sarpi et al., 1996	Patients undergoing lap cholecystectomy	9	697	bilirubin>3	83	56	82	
Trondsen, Edwin, Reiertsen et al., 1995	Patients undergoing lap cholecystectomy	38	599	jaundice	86	46	95	

Table 20. Elevated liver function tests as a risk factor for CBD stone

Study	Population	% prevalence of stone in population	n	Rule tested	Predictive Value	Sensitivity	Specificity	Comments
Alponat, Kum, Rajnakova et al., 1997	Patients with risk factors for CBD stones having ERCP	32	192	Any LFT>2xnl AST > 2xnl ALT > 2xnl Alk phos >2xnl GGT > 2xnl LDH > 2xnl	37 41 40 43 35 38	84 89 87 84 87 68	33 40 38 46 22 46	Numbers for any LFT do not make sense, cannot be less sensitive
Barkun, Barkun, Fried et al., 1994	Patients undergoing lap cholecystectomy who had ERCP	48	139	AST>120 Alk phos>300	49 53	81 79	25 35	
Bergamaschi, Tuech, Braconier et al., 1999	Patients undergoing lap cholecystectomy	15	990	Alk phos >400 and GGT>200	87	58	99	
Hauer-Jensen, Karesen, Nygaard et al., 1985	Patients undergoing cholecystectomy	12	319	Alk phos>250	37	58	87	
Kim, Kim, Lee et al., 1997a	Patients undergoing lap cholecystectomy	17	561	SGOT>50 SGPT>50 Alk phos>160	43 39 50	65 67 75	82 79 85	
Koo and Traverso 1996	Patients undergoing lap cholecystectomy	12	420	SGOT>44 Alk phos>140	48 48	40 31	94 93	
Menezes, Marson, Debeaux et al. 2000	Patients undergoing lap cholecystectomy	33	233	SGOT>nl SGOT>2xnl Alkphos>nl Alkphos>2xnl	88 93 77 97	47 35 66 44	97 99 90 99	
Santucci, Natalini, Sarpi et al., 1996	Patients undergoing lap cholecystectomy	9	697	ALT> 40 AST> 40 GGT>150 Alk phos>300	88 76 75 94	94 78 80 72	79 78 76 90	Cutoffs established by ROC analysis, maximize sensitivity and specificity

Table 21. Dilated CBD as a risk factor for CBD stone

Study	Population	% prevalence of stone in population	n	Rule tested	Predictive Value	Sensitivity	Specificity	Comments
Alponat, Kum, Rajnakova et al., 1997	Patients with risk factors for CBD stones having ERCP	32	192	Dilated CBD with stone on ultrasound Dilated CBD without stone on ultrasound	72 36	42 31	92 74	
Barkun, Barkun, Fried et al., 1994	Patients undergoing lap cholecystectomy who had ERCP	48	139	Dilated CBD, subjective	64	53	73	
Bergamaschi, Tuech, Braconier et al., 1999	Patients undergoing lap cholecystectomy	15	990	CBD > 8mm	75	28	98	
Hauer-Jensen, Karesen, Nygaard et al., 1985	Patients undergoing cholecystectomy	12	319	CBD >10 mm	34	63	92	
Kim, Kim, Lee et al., 1997a	Patients undergoing lap cholecystectomy	17	561	CBD > 10 mm	61	94	88	
Koo and Traverso 1996	Patients undergoing lap cholecystectomy	12	420	CBD> 5mm + 1 mm per decade over age 50	28	22	92	
Menezes, Marson, Debeaux et al. 2000	Patients undergoing lap cholecystectomy	33	233	CBD dilated (not defined)	91	51	97	
Santucci, Natalini, Sarpi et al., 1996	Patients undergoing lap cholecystectomy	9	697	CBD> 8 mm	74	59	72	

Table 21. Dilated CBD as a risk factor for CBD stone (cont'd)

Study	Population	% prevalence of stone in population	n	Rule tested	Predictive Value	Sensitivity	Specificity	Comments
Trondsen, Edwin, Reiertsen et al., 1998	Patients undergoing lap cholecystectomy	15	171	CBD > 6 mm	35	64	79	
Trondsen, Edwin, Reiertsen et al., 1995	Patients undergoing lap cholecystectomy	38	599	CBD dilated (not defined)	85	31	96	

In sum, although all the previously mentioned single risk factors for common duct stones have significant associations with the presence of stones, none of them have outstanding ROC characteristics. The presence of any of these factors certainly increases the probability of the presence of a common bile duct stone, possibly high enough to change clinical decision-making. However, changing the cutoff value to increase the positive predictive value (by increasing the specificity) usually results in poor sensitivity.

Review of Evidence: Multivariable Predictors for Common Bile Duct Stones

Four studies (total n=1,461) examined the use of multiple risk factors for prediction of the presence of common bile duct stones (Table 22). Many studies that simply used the criterion of "any one risk factor" as a prediction rule were not included in this evidence review, as such a criterion has been used for many years to select patients for ERCP and has a known poor specificity and low positive predictive value.

The four studies varied in the analytic technique used to develop the prediction rule. Hawasli, Lloyd, Pozios et al. (1993) did not use any quantitative technique but defined combinations of risk factors to classify patients at high risk of stones. Menezes, Marson, Debeaux et al. (2000) developed a logistic model based on age, sex, jaundice, presence of cholangitis, liver function tests, and ultrasound examination of the common bile duct. Trondsen, Edwin, Reiertsen et al. (1995) used a discriminant analysis technique based on age, bilirubin, alanine aminotransferase, and gamma glutamyltransferase. In Trondsen, Edwin, Reiertsen et al. (1998), a new rule was not developed, but the previously developed discriminant analysis rule was prospectively validated in a new population of patients.

Thus, except for Trondsen, Edwin, Reiertsen et al. (1998), the findings of the three other studies should be viewed as optimistic estimates of stone prediction, since the performance of the rules was only evaluated on the set of patients used to develop the rule.

All the studies produced decision rules in which both the sensitivity and specificity were greater than 80 percent. However, these findings should be viewed cautiously, since there has been no independent validation. The prospective validation study by Trondsen, Edwin, Reiertsen et al. (1998) is a particularly strong finding, since the rule was derived from an independent population—the sensitivity was 94 percent and the specificity was 88 percent in an independent set of patients. The discriminant function cutoff could be varied to increase sensitivity at the expense of specificity or vice-versa, but since both are high the actual discriminative capability of the rule compared to individual risk factors was far superior.

In conclusion, multivariable modeling of risk factors for prediction of common duct stones shows promise as a method of triage for determining appropriate treatments, given that they appear to have superior discriminatory power. These prediction models have yet to be integrated into clinical decision models to determine optimal cutoffs.

Table 22. Decision rules for prediction of stones

Study	population	% prevalence of stone in population	n	Rule tested	Predictive value	Sensitivity	Specificity	Comments
Hawasli, Lloyd, Pozios et al., 1993	Patients undergoing lap cholecystectomy	4	459	High suspicion combination	75	83	99	
Menezes, Marson, Debeaux et al. 2000	Patients undergoing lap cholecystectomy	15	211	Score>= 2 Score>=3 Based on logistic regress	56 67	86 82	66 80	
Trondsen, Edwin, Reiertsen et al., 1995	Patients undergoing lap cholecystectomy	38	599	Discriminant function	91	95	94	Rule applied to same data used to develop function
Trondsen, Edwin, Reiertsen et al., 1998	Patients undergoing lap cholecystectomy	17	192	Discriminant function	60	94	88	Same 2 by 2 data as Trondsen, Edwin, Reiertsen et al., 1995, above

Review of Evidence: Absence of Any Risk Factor as A Predictor of Common Bile Duct Stone Absence

Seven studies (total n=599) examined the prediction of absence of common duct stones (Table 23). Usually, the absence of any of the known risk factors (all the individual factors reviewed previously) was used as the indicator. Trondsen, Edwin, Reiertsen et al. (1995) and Trondsen, Edwin, Reiertsen et al. (1998) reviewed previously, are also included here because the discriminant function used to predict stones can also be used to predict the absence of stone.

If the prevalence of stone is low enough in some patients, then some clinicians might avoid use of any diagnostic test to diagnose common duct stones. Such a case would be very compelling if the probability of stone is in the same range or lower as it is in the case of a negative ERCP examination. Although ERCP is selectively performed on patients with higher risk of common duct stones, if physicians are willing to believe a negative ERCP, they should be willing to believe a prediction rule if the probabilities of stones are equally low.

The seven studies reported a probability of common duct stones in those predicted not to have stones between a range of 0.25 percent to 7 percent. In all studies, a reasonable sensitivity for stone-free patients was shown, from 60 percent to 98 percent, and reasonable specificity, 60 percent to 96 percent. Thus, the decision rules all can identify more than half of the patients that do not have stones.

The strongest finding is Trondsen, Edwin, Reiertsen et al. (1998), in which the same discriminant function which identifies stones can rule out stones with both high sensitivity (88 percent) and specificity (94 percent). This study is also a validation study of an independently developed discriminant function, which further increases its validity.

These probabilities of stones compare quite favorably to the probabilities of stones in patients having a negative ERCP. If the probability is calculated, using the equation "1-NPV" and some of the reported NPVs of the ERCP studies in the section of this report comparing ERCP to EUS, a range of stone probabilities is calculated from 0 percent to 17 percent.

In conclusion, the absence of any risk factors for stones (or a discriminant function indicating absence of stone) is a very strong predictor of the absence of stones, producing probabilities of stones that are in the same range as a negative ERCP exam in a patient with risk factors for stones.

Conclusions

The probability of a common duct stone is the key factor to determining diagnostic and treatment strategies. When preoperative probability of a common bile duct stone is high enough, ERCP may be preferred because diagnosis and therapy can be carried out in a single procedure. If the preoperative probability of a common duct stone is low enough, then expectant management may be preferred in order to avoid unnecessary procedures. In the middle range of probability, use of diagnostic tests such as EUS, MRCP, or intraoperative cholangiogram may be used to further discriminate patients with high or low probability of common bile duct stones.

Table 23. Rules ruling out stones, absence of stone is the outcome

Study	population	% prevalence of stones in population	n	Rule tested	Prevalence of stone in those ruled out by rule (1 – PPV)	Sensitivity--% of stone-free patients detected by rule	Specificity--% of patients with stones ruled out by rule	Comments
Carroll, Phillips, Rosenthal et al., 1996	Patients undergoing lap cholecystectomy	15	100	Normal LFTs, CBD, past history	4	61	87	
Hawasli, Lloyd, and Cacucci 2000	Patients undergoing lap cholecystectomy	5	2834	Normal LFTs, CBD, past history	0.25	89	96	Hawasli, Lloyd, Pozios et al. 1993 results of this same question included in these data
Khaira, Ridings, and Gompertz 1999	Patients undergoing lap cholecystectomy	5	154	Normal LFTs, CBD, past history	1	60	88	
Koo and Traverso 1996	Patients undergoing lap cholecystectomy	12	420	Normal LFTs, US, past history	7	78	60	
Santucci, Natalini, Sarpi et al., 1996	Patients undergoing lap cholecystectomy	9	697	Normal LFTs, US, past history	1.4	98	86	Clinical followup to detect stones in patients with no indications
Trondsen, Edwin, Reiertsen et al., 1998	Patients undergoing lap cholecystectomy	17	192	Discriminant function value negative	1.4	88	94	Rule applied to validation set of patients
Trondsen, Edwin, Reiertsen et al., 1995	Patients undergoing lap cholecystectomy	38	599	Discriminant function value negative	3	94	95	Rule applied to same data used to develop function

Thirteen studies with a total patient population of 7,409 patients that reported multiple findings of sensitivities and specificities of a single or combination of risk factors to predict the presence of common bile duct stones were reviewed.

The single risk factors most commonly assessed were clinical jaundice or elevated bilirubin, liver function tests, and ultrasound findings of a dilated common bile duct. All have significant associations with the presence of common duct stones, but none have both high sensitivity and specificity.

Four studies tested prediction rules based on combinations of risk factors for the presence of stones. All the studies produced decision rules in which both the sensitivity and specificity were greater than 80 percent. These findings must be viewed cautiously, since only one study was a validation of an independently developed prediction rule. Presently, multivariable modeling of risk factors for prediction of common duct stones is a promising approach.

The absence of any risk factors for stones (or a discriminant function indicating absence of stone) is a very strong predictor of the absence of stones, producing probabilities of stones that are in the same range as a negative ERCP exam in a patient with risk factors for stones (0 percent to 17 percent).

Results and Conclusions, Part II: Pancreaticobiliary Malignancy

This chapter reviews evidence on the following questions:

In patients with known or suspected pancreaticobiliary malignancy,

a. What is the diagnostic performance of ERCP tissue sampling techniques, in establishing a tissue biopsy diagnosis of pancreaticobiliary malignancy in comparison to each other or alternative nonsurgical tissue sampling techniques (e.g., endoscopic ultrasound-guided fine-needle aspiration (FNA) or percutaneous FNA)? *(Section 1: Diagnostic Performance of Nonsurgical Tissue Sampling Techniques in Pancreaticobiliary Malignancy – Comparison of Strategies Using ERCP, EUS, or Percutaneous Approach)*

b. What is the diagnostic performance of ERCP, in diagnosing the presence of malignant pancreaticobiliary obstruction in comparison to other imaging alternatives (e.g., EUS or MRCP)? *(Section 2: Diagnostic Performance of ERCP in Pancreaticobiliary Malignant Obstruction – Comparison To Alternatives)*

c. What are the outcomes of treatment using ERCP strategies to treat malignant pancreaticobiliary obstruction compared to using surgical or interventional radiology treatment? *(Section 3: Outcomes of Treatment Using ERCP for Palliation of Pancreaticobiliary Malignancy – Comparison of Strategies Using ERCP, Surgery, or Interventional Radiology; A. Comparison of ERCP stent versus Surgical Bypass; B. Comparison of Metal vs. Plastic stents During ERCP; C. Additional Comparisons of ERCP Strategies)*

(Section 4: Outcomes of Treatment Using Preoperative ERCP Drainage for Relief of Malignant Obstructive Jaundice)

Part II, Section 1: Diagnostic Performance of Nonsurgical Tissue Sampling Techniques in Pancreaticobiliary Malignancy—Comparison of Strategies Using ERCP, EUS, or Percutaneous Approach

Introduction

When a malignant cause is suspected for biliary obstruction, preoperative tissue confirmation of malignancy may be helpful in guiding management decisions. Nonsurgical tissue sampling methods include endoscopic and percutaneous approaches. Cytologic assessment can be performed on endoscopically acquired specimens such as aspirated biliary or pancreatic fluid, wire brushing specimens, or fine-needle aspiration (FNA) specimens. FNA specimens can be obtained during ERCP, EUS, or through a percutaneous approach using imaging guidance. Endoscopic tissue biopsy can be performed during ERCP with a forceps device.

The goal of tissue sampling techniques is to provide sufficient cellular material to make an accurate pathologic diagnosis. Theoretically, increasing the numbers of samples and/or the types of samples might yield more cellular tissue for assessment and might improve diagnostic accuracy, but the extent to which combinations of different sampling techniques increase the diagnostic accuracy is still being investigated (Lee and Leung 1998).

It is outside the scope of this systematic review to determine whether biliary versus pancreatic location of sampling is related to differences in diagnostic performance of sampling techniques. A recent review summarized the diagnostic sensitivity of brush cytology for detection of pancreatic cancer (Lee and Leung 1998). In a total sample of 362 patients who had pancreatic cancer, brush cytology samples diagnosed 55% of cases with a range among studies of 0–85%. When the subset of 190 brush cytology samples taken from the pancreatic duct was analyzed separately, 66% of pancreatic cancers were detected. The few studies using blinded readings reported a lower range of sensitivity (0–40%).

Cytology findings may be interpreted as definite malignancy or may be reported according to the degree of atypia. The sensitivity and specificity of cytology will be dependent on where the criterion is set for calling the test positive. Using a strict criterion where only definite malignancy is counted as positive will achieve the highest specificity, but the associated sensitivity will usually be the lowest. Likewise, considering any degree of atypia as a positive test will increase the test's sensitivity, but the specificity will generally be reduced.

This systematic review selected studies comparing the diagnostic performance of at least 2 of the available nonsurgical tissue sampling techniques in patients with pancreaticobiliary malignancy. Comparative studies including at least one ERCP tissue sampling technique compared to an alternative technique were the primary focus defined prospectively in the systematic review protocol. None of the studies identified with this set of selection criteria included any comparison of ERCP tissue techniques and EUS sampling techniques. Upon discussion of this result with the Technical Advisory Group, a supplementary request was made to review single arm studies reporting the diagnostic performance of endoscopic ultrasound (EUS) fine-needle aspiration (FNA). Studies included in this secondary analysis were not selected using a formalized systematic review, but were identified by manually searching for recent reports on EUS-FNA and carefully reviewing prior articles referenced in these studies to identify additional studies.

Evidence Base

Twelve studies comparing at least two tissue sampling techniques were identified in this systematic review. Quality ratings are displayed in Table 24. Five of these studies were rated as "Good" quality, signifying the use of blinded interpretation of test results. Only three studies include over 100 patients, and six studies include less than 50 subjects.

There is considerable variation in reported estimates of sensitivity for each tissue sampling technique, and comparison of results for the same technique across studies may be limited due to differences in populations with regard to distribution of tumor types as well as differences in tissue sampling technique and interpretation methods. To minimize this problem, this analysis

Table 24. Quality Assessment

Study Author, Year	**Patient Enrollment**	**Diagnostic performance of ERCP determined without knowledge of other test results**	**Diagnostic Performance of other test(s) determined without knowledge of ERCP results**	**Summary Evaluation**
Jaiwala, Fogel, Sherman et al., 2000	(n=133 pts) Prospective Study Enrollment of subjects stated to be selected and nonconsecutive and reasons for exclusion were stated.	No	No	**Fair**
Kurzawinski, Deery, Dooley et al., 1993	(n=46 pts) Prospective study of 37 of 46 consecutive pts w/ biliary tract stricture had ERCP and 9 had PTC cytology. Reasons for exclusions provided.	No	No	**Fair**
de Peralta-Venturina, Wong, Purslow et al., 1996	(n=74 pts; 104 spec) Retrospective review of all eligible cytology specimens during 1990 to mid 1994 in pts with verified diangosis.	Yes	Yes	**Good**
Foutch et al. 1991	(n=30 pts; 78 specimens) Prospective study 30 consecutive patients with bile duct stricture	Yes	Yes	**Good**
Mansfield et al. 1997	(n=43 pts; 54 procedures) Prospective study All pts with biliary stricture suspicious for malignancy	Yes	Yes	**Good**

Table 24. Quality Assessment (cont'd)

Study Author, Year	Patient Enrollment	Diagnostic performance of ERCP determined without knowledge of other test results	Diagnostic Performance of other test(s) determined without knowledge of ERCP results	Summary Evaluation
Sugiyama, Atomi, Wada et al., 1996	(n= 43 pts) Prospective study 52 Consecutive pts with stricture (n=48) or filling defect (n=4) Papillary lesions excluded. Analysis includes 43 pts with all 3 techniques	No	No	**Fair**
Howell, Beveridge, Bosco et al., 1992	?Prospective 31 consecutive patients with malignant appearing strictures	No	No	**Fair**
Ferrari, Lichtenstein, Slivka et al., 1994	(n=74) Retrospective study of all pts who had ERCP with brush cytology of biliary or pancreatic duct stricture	No	No	**Fair**
Ponchon, Gagnon, Berger et al., 1995	(n=193) Prospective study Enrolled subjects meeting entry criteria. Complete explanation of enrollment process provided.	Yes	Yes	**Good**
Schoefl, Haefner, Wrba et al., 1997	119 consecutive pts (133 samples) ?retrospective	No	No	**Fair**

Table 24. Quality Assessment (cont'd)

Study Author, Year	Patient Enrollment	Diagnostic performance of ERCP determined without knowledge of other test results	Diagnostic Performance of other test(s) determined without knowledge of ERCP results	Summary Evaluation
Pugliese, Antonelli, Vincenti et al., 1997	(n=52) Prospective enrollment of consecutive biliary strictures at ERCP Excluded strictures associated with bile duct stones, periampullary tumors, or postop stricture	Yes	Yes	**Good**
Gmelin and Weiss 1981	(n=32) 32 proven malignant or benign tumors in papillary region out of 36 consecutive cases.	Uncertain	Uncertain	**Fair**

will focus primarily on within-study comparisons of the relative sensitivity of alternative sampling techniques. However, this problem is not completely avoided because the selected comparative studies frequently reported diagnostic performance for individual sampling techniques being compared on a different number of patients and thus slight differences in the population characteristics may be present.

Given that the expected difference in diagnostic performance between tissue sampling techniques and the diagnostic alternatives reported here are frequently relatively small and the number of cases with the outcome of interest is generally small, these studies may have limited power to detect statistically significant differences in test performance. Only 4 of 12 studies (Jaiwala, Fogel, Sherman et al., 2000; Sugiyama, Atomi, Wada et al., 1996; Ponchon, Gagnon, Berger et al., 1995; Kurzawinski, Deery, Dooley et al., 1993) actually reported any statistical comparisons, and all of these only reported chi square comparisons of sensitivity.

The specificity estimates for cytology techniques reported in these studies were generally close to 100%, though Jaiwala, Fogel, Sherman et al. (2000; n=133) found that specificity fell to 90% when any atypia was considered equivalent to malignancy.

The nonsurgical tissue sampling techniques being evaluated in these studies are measured against a reference standard incorporating the best available information from surgical findings, surgical or nonsurgical pathology, autopsy, imaging follow-up, and clinical follow-up.

Review of Evidence: Diagnostic Performance

Bile Aspiration Cytology Compared to Brush Cytology

Five studies (total n=approximately 178), including 3 with "Good" quality, (Kurzawinski, Deery, Dooley et al., 1993; de Peralta-Venturina, Wong, Purslow et al., 1996; Foutch et al. 1991; Mansfield et al. 1997; Sugiyama, Atomi, Wada et al., 1996) provided comparisons between bile cytology and brush cytology for biliary strictures (Table 25 and Table 26). In each comparison, brush cytology provided higher sensitivity than bile aspirate cytology, although only one study reported a statistical assessment. The absolute increase in sensitivity ranged from 16 to 50%. Reported range of bile cytology sensitivity was 6–50% and that for brush cytology was 33–100%.

Two studies reported comparative data for tissue sampling using an ERC approach versus a percutaneous transhepatic cholangiographic (PTC) approach. de Peralta-Venturina, Wong, Purslow et al. (1996) noted lower sensitivity with PTC compared with ERC, 43 versus 100%. Kurzawinski, Deery, Dooley et al. (1993) observed similar sensitivity for brush cytology techniques using either approach and possibly lower sensitivity for bile aspirates with PTC.

In sum, the available studies are relatively small and most are limited by lack of statistical analysis but do provide suggestive evidence that brush cytology is more sensitive than bile aspiration cytology.

Table 25. Comparisons of Bile Cytology and Brush Cytology

Study	N Pts	N Spec	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Quality Rating and Comments
Kurzawinski, Deery, Dooley et al., 1993	37 31	37 31	ERCP-Bile cytology ERCP-Brush cytology	81 77	33[a] 71[b]	100 100	100 100	26 50		**Fair** p< 0.05 a vs. b p< 0.01 c vs. d
	9 15	9 15	PTC-Bile cytology PTC-Brush cytology	?	0[c] 67[d]	n.r. n.r.				
de Peralta-Venturina, Wong, Purslow et al., 1996	74	13 61	Bile cytology Brush cytology[10]	? ?	50 100	100 95	100 95	40 100	69 98	**Good**
		55 19	ERCP PTC	? ?	100 43	95 100	96 100	100 57	98 79	Stratified results for bile vs. brushing not reported by ERCP vs. PTC technique

Table 26. Comparisons of Bile Cytology, Brush Cytology, and Other Technique

Study	N Pt	N Sp	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Quality Rating and Comments
Foutch et al. 1991	30	31	Bile cytology	58	6	100	100	43		**Good**
		31	Brush cytology[1]	58	33	100	100	52		
		16	Stent cytology	69	36	100	100	42		
Mansfield et al. 1997	43	54	Bile cytology	96	12	100	100	4	44	**Good**
		54	Brush cytology[2]	96	42	100	100	6	96	Clearly malignant or
		19	Soehendra stent retriever screw head	?	25	?	?	?	70	suspicious cytology = (+)
		19	Stent	?	37	?	?	?	84	
		54	Combined	?	54	100	100	8		
Sugiyama, Atomi, Wada et al., 1996[3]	43	43	Bile cytology	72	32[a]	100	100	36	100	**Fair**
	43	43	Brush cytology[4]	72	48[b]	100	100	43	88	$p<0.01$, a vs c; $p<0.05$, b vs.
	43	43	Forceps biopsy	72	81[c]	100	100	67	87	c; p = n.r., a vs b

[1] Milrose Lab, 230 cm, 2.5-mm diameter
[2] Combocath, Microvasive, Boston Scientific
[3] Specifically excluded patients with papillary tumor.
[4] BC-23Q cytology brush (outer diameter, 1.8 mm, Olympus, Tokyo, Japan)

Brush Cytology Compared to FNA Cytology

Three studies (total n=approximately 193), all rated "Fair" (Jaiwala, Fogel, Sherman et al., 2000; Howell, Beveridge, Bosco et al., 1992; Ferrari, Lichtenstein, Slivka et al., 1994) compare brush cytology with FNA cytology (Table 27 and Table 28). The first two studies use ERCP to obtain both the FNA specimen and the brush cytology specimens while Ferrari, Lichtenstein, Slivka et al. (1994) compares ERCP brush cytology with percutaneous CT-guided FNA. The largest study, (Jaiwala, Fogel, Sherman et al., 2000, n=133) reports similar sensitivity for FNA and for brush cytology and the combination of both techniques increased overall sensitivity by about 9%. This difference was not statistically significant in 2 of 3 comparisons and was found significant ($p<0.05$) only when high-grade atypia was considered equivalent to malignancy.

The study by Howell, Beveridge, Bosco et al. (1992, n=31) notes a higher sensitivity for FNA than for brush cytology (62% vs. 8%) but the combination of both techniques only yielded a slight increase to 65% sensitivity. Ferrari, Lichtenstein, Slivka et al. (1994, n=29 with FNA and 70 for brush cytology) found percutaneous CT-guided FNA to be more sensitive than brush cytology (91% versus 56%) but the large difference in sample sizes makes direct comparison limited. Furthermore, the small size and lack of statistical analysis of these two studies limits the interpretation of these findings.

Among these studies, the findings of Jaiwala, Fogel, Sherman et al. (2000) provide the more reliable information and suggest that brush cytology and ERCP-FNA may be similar in sensitivity. When used together, the available evidence does not demonstrate a statistically significant increase in sensitivity.

Forceps Biopsy Sampling Compared to Brush Cytology

Six studies (total n=approximately 437), including the 3 largest studies and 3 "Good" quality studies, compared forceps biopsy sampling to brush cytology (Tables 25–28). Gmelin and Weiss (1981) exclusively studied papillary tumors and found an increase in sensitivity of about 30% using forceps biopsy over brush cytology (86% versus 55%), but statistical analysis was not reported. Sugiyama, Atomi, Wada et al. (1996) specifically excluded papillary tumors and also found a large increase in sensitivity with forceps biopsy, 81% versus 48%, $p<0.05$. The remaining studies (Jaiwala, Fogel, Sherman et al., 2000; Ponchon, Gagnon, Berger et al., 1995; Schoefl, Haefner, Wrba et al., 1997; Pugliese, Antonelli, Vincenti et al., 1997) included a mixture of pancreaticobiliary malignancies. These studies reported generally similar sensitivity with forceps biopsy compared with brush cytology, though one study (Jaiwala, Fogel, Sherman et al., 2000) noted statistically significant increases for forceps biopsy over brush cytology when atypia was not interpreted as malignancy).

In addition, each of these studies reports that the combination of forceps biopsy and brush cytology increases the sensitivity in detecting malignancy between 5-20%. Jaiwala, Fogel, Sherman et al. (2000) and Ponchon, Gagnon, Berger et al. (1995) both reported the increase in sensitivity for the combination of forceps biopsy plus brush cytology compared to forceps biopsy alone to be statistically significant ($p<0.05$).

Table 27. Comparisons of Brush Cytology and Biopsy Technique

Study	N Pt	N Sp	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Quality Rating and Comments
Howell, Beveridge, Bosco et al., 1992	31		Brush cytology FNA – ERCP Combined	84 84 84	8 62 65	100 100 100	100 100 100	17 33 36		**Fair**
Ferrari, Lichtenstein, Slivka et al., 1994	 70 51 19 29		Brush cytology – Overall – Biliary – Pancreatic FNA – percutaneous	 76 ?	 56 54 64 91	 100 100 100 75	 100 100 100 95	 51 45 67 60	 93	**Fair**
Ponchon, Gagnon, Berger et al., 1995	233	193 118 105	Brush cytology Forceps biopsy[5] Combination	66 69 70	35[a] 43[b] 63[c]	97 97 97	96 97 98	66 69 70	90 57	**Good** p= n.s. for a vs b p<0.001 for a vs c p<0.05 for b vs. c
Schoefl, Haefner, Wrba et al., 1997	59 106 48	65 119 51	Brush cytology[6] Forceps biopsy[7] Combination	?	47 65 70	100 100 100	100 100 100	62 69 71		**Fair**
Pugliese, Antonelli, Vincenti et al., 1997	52	52	Brush cytology[8] Forceps biopsy[9] Combination	69 69 69	53 53 61	100 100 100	100 100 100	48 48 53		**Good** Uncertain cytology was considered negative.
Gmelin and Weiss 1981	32	32 26 26	Papillary tumors Brush cytology Forceps biopsy	 85 81	 18 71 55 86	 100 100 100 100	 100 100 100 100	 18 45 29 63		**Fair** Suspicious cells considered negative Suspicious cells considered positive

[5] Either Biomed 31010 (Paris, France: 175 cm length, 2mm diameter, round and fenestrated jaw with 2mm diameter, flexible tip, no needle) or Olympus prototype (Scop Medecine; 180cm length, 2.2mm diameter, round and fenestrated jaw with 2mm diameter, teflon sheath, no needle)
[6] Endo-Flex 42 22E-A
[7] Olympus FB-19N for about 60% and FB26N for about 30% and FB-39Q for about 10%
[8] Olympus mod. BC-19Q or Wilson-Cook Medical Inc., Winston-Salem, NC, Mod. GBC-200-3-3.5
[9] Olympus FB-19K or FB-39Q

Table 28. Comparison of Brush Cytology, FNA cytology, and Forceps biopsy in biliary strictures

Study	N Pts	N Spec	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Quality Rating and Comments
Jaiwala, Fogel, Sherman et al., 2000	133	133	Brush cytology[10]	78	48[a]	90	94	33	n.r.	**Fair**
			FNA cytology[11]		38[b]	97	98	30	n.r.	Any atypia on cytology was considered equivalent to cancer.
			Forceps biopsy[12 or 13]		54[c]	76	89	31	n.r.	
			Brush + FNA		57[d]	86	94	36	n.r.	
			Brush + Biopsy		71[e]	69	89	40	n.r.	P<0.05 for: a vs. e, f, g;
			Biopsy + FNA		64[f]	72	89	36	n.r.	b vs. c, d, e, f, g; c vs. e, f, g;
			Brush+Biopsy+FNA		77[g]	66	89	44	n.r.	d vs. e, g; f vs. g
			Brush cytology		30[a]	100	100	28		
			FNA cytology		30[b]	100	100	28		Only high-grade atypia considered equivalent to cancer.
			Forceps biopsy		43[c]	90	94	31		
			Brush + FNA		39[d]	100	100	32		
			Brush + Biopsy		55[e]	90	95	36		P<0.05 for: a vs. c, d, e, f, g;
			Biopsy + FNA		53[f]	90	95	35		b vs. c, d, e, f, g; c vs. e, f, g;
			Brush+Biopsy+FNA		62[g]	90	96	39		d vs. e, f, g
			Brush cytology		26[a]	100	100	27		
			FNA cytology		25[b]	100	100	27		All atypia on cytology considered negative.
			Forceps biopsy		37[c]	100	100	31		
			Brush + FNA		34[d]	100	100	30		P<0.05 for: a vs. c, e, f, g; b
			Brush + Biopsy		48[e]	100	100	35		vs. c, e, f, g; c vs. e, d, f; d
			Biopsy + FNA		46[f]	100	100	34		vs. e, f, g.
			Brush+Biopsy+FNA		52[g]	100	100	37		

[10] Geenan brush system (Wilson-Cook Medical, Inc. Winston-Salem, N.C.)
[11] Howell needle system (Wilson-Cook)
[12] Malleable forceps (Olympus America, Inc., Melville, N.Y.)
[13] Standard colonoscopic pinch forceps (Ballard Medical Products, Draper, Utah)

In sum, the available evidence suggests that forceps biopsy provides similar, or higher, sensitivity compared to brush cytology, and both tests used in combination may slightly increase sensitivity over that achieved with either technique alone.

Combination of Three Sampling Techniques

Jaiwala, Fogel, Sherman et al. (2000; n=133) also reports on the combination of brush cytology, FNA cytology, and forceps biopsy (Table 28). This study reports increases in overall sensitivity for detecting pancreaticobiliary malignancy as more sampling techniques are added together. The size of incremental the gains in sensitivity and statistically significance associated with adding the third sampling technique vary depending on the criteria used to interpret positive results on cytology. The largest gains are observed when forceps biopsy is being added as the third procedure (approximately 18–23% higher sensitivity, $p<0.05$), but smaller gains are still noted when one of the cytology techniques is added as the third procedure (approximately 4–13%).

Comparison of ERCP-FNA with EUS-FNA

In the absence of comparative studies directly comparing EUS-FNA and ERCP-FNA, an indirect comparison of single arm studies was attempted. Ten articles were identified, including one large multicenter report (Wiersema, Vilmann, Giovannini et al., 1997), three reports from Indiana University (Gress, Gottlieb, Sherman et al., 2001; Gress, Hawes, Savides et al., 1997; Wiersema, Kochman, Cramer et al., 1994), one report from Massachusetts General Hospital (Brandwein, Farrell, Centano et al., 2001), two reports from University of South Carolina (Williams, Sahai, Aabakken et al., 1999; Bhutani, Hawes, Baron et al., 1997), two reports from University of California (Chang, Nguyen, Erickson et al., 1997; Chang, Katz, Durbin et al., 1994), and one report from University of Pennsylvania (Bentz, Kochman, Faigel et al., 1998) (Table 29). Overlap of patient populations and data from separate reports from the same institution is difficult to assess due to limitations in reported detail. An attempt was made to minimize duplicate reporting of subjects. Earlier reports of studies from the same institution that were later published with more subjects have omitted from Table 29. However, some duplication of results likely remains between the multicenter report and separate reports from contributing institutions. The two reports by Gress et al. (Gress, Gottlieb, Sherman et al., 2001 and Gress, Hawes, Savides et al., 1997) address differently selected, but probably overlapping patient groups; however, both are included as they address slightly different questions.

All of these studies reported results separately for diagnosis of pancreatic mass. Additional results on lymph node evaluation and intestinal lesions were not relevant to this review. Despite uncertainties over the exact number of subjects included among the reports detailed in Table 29, the available studies include at least 400 subjects with pancreatic mass and report a range of sensitivity in detecting pancreatic malignancy of 60-94% with a specificity of 100%. Brandwein, Farrell, Centano et al. (2001; n=93) reported results separately for cystic versus solid pancreatic masses and found slightly lower sensitivity for cystic lesions, 50% versus 60%.

Table 29. Supplemental Analysis: Single Arm Studies Reporting Diagnostic Operating Characteristics of EUS-FNA in Pancreatic Mass

Study	N Enr	N Res	Diagnostic test Population setting	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Comments
Wiersema, Vilmann, Giovannini et al., 1997 Multicenter – Including Indiana University and University of California	124	124	EUS-FNA Subgroup with pancreatic mass	74	89	100	100	76	97	**Prospective** 4 inadequate specimens excluded. Results in article are unclear regarding 5 cases of suspicious or atypical cytology.
Gress, Gottlieb, Sherman et al., 2001[14] Indiana University	102	94	EUS-FNA Suspected pancreatic ca after negative CT-FNA or ERCP cytology	64	88	100	100	92		**Prospective** 8 inconclusive or nondiagnostic results excluded
Gress, Hawes, Savides et al., 1997[14] Indiana University	121	121	EUS-FNA Pancreatic mass	42	80	100	100	88		**Prospective**
Brandwein, Farrell, Centano et al., 2001 Massachusetts General Hospital	96	93	EUS-FNA Suspected pancreatic ca underwent surgery	85 23 58	60 50 60	100 100 100	100 100 100	29 60 60		**Retrospective** Solid lesions (n=43) Cystic Lesions (n=26) Dilated duct (n=24)
Williams, Sahai, Aabakken et al., 1999 University of South Carolina	144	144	EUS-FNA All EUS-FNA referrals to single center	85	72 73 70	100 100 100	100 100 100	38 34 45		**Retrospective** All pancreatic masses Pancreatic mass $\geq$ 3 cm Pancreatic mass < 3 cm
Bentz, Kochman, Faigel et al., 1998 University of Pennsylvania	45	38	EUS-FNA Pancreatic mass	82	94	100	100	78	84	**Prospective**

[14] Both studies by Gress et al. are reported from the same institution, but patient selection criteria differ with the 2001 report choosing only the subset with persistently high clinical suspicion of pancreatic cancer following otherwise negative workup. The earlier study provides more generally selected patients.

Table 29. Supplemental Analysis: Single Arm Studies Reporting Diagnostic Operating Characteristics of EUS-FNA in Pancreatic Mass (cont'd)

Study	N Enr	N Res	Diagnostic test Population setting	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adequate Specimens (%)	Comments
Chang, Nguyen, Erickson et al., 1997 University of California	44 pts 47 les	44	EUS-FNA Pancreatic mass	70	92	100	100	75	95	**Retrospective**

The sensitivity estimates for ERCP-FNA derived from the two studies identified in the systematic review (Jaiwala, Fogel, Sherman et al., 2000, n=133; Howell, Beveridge, Bosco et al. (1992, n=31) were obtained in subjects with a mixture of pancreaticobiliary malignancy and included subjects with pancreatic cancer, ampullary tumors, cholangiocarcinoma, and metastases. While the reported range of sensitivity of 25-62% for ERCP-FNA appears to be lower than that reported for EUS-FNA, direct comparisons do not seem appropriate due to differences in the case mix of tumors between studies. Further limitations secondary to relatively small numbers of subjects in ERCP-FNA studies and potential differences in cytology techniques and interpretations between studies preclude direct comparison of these estimated ranges of sensitivity.

Summary

There is a modest body of evidence directly comparing the diagnostic performance of nonsurgical tissue sampling techniques for the evaluation of suspected pancreaticobiliary malignancy. The available studies are limited by small size and do not consistently compare techniques in the same group of patients. Most studies do not report statistical tests, so it is not possible to determine with confidence whether reported differences in sensitivity are significantly different. While available evidence is suggestive, larger studies are needed to draw conclusions on relative performance of tissue sampling techniques.

The available evidence suggests that sensitivity for detecting malignancy is similar or higher for brush cytology versus bile aspiration cytology, similar for FNA cytology versus brush cytology, and similar or higher for forceps biopsy versus brush cytology. Using combinations of two or more sampling techniques may increase the overall sensitivity. No comparative studies evaluated whether incremental improvement could also be achieved by repeated sampling using the same technique.

In the absence of comparative studies of EUS-FNA and ERCP-FNA, indirect comparison of single arm-studies was attempted. Results from 10 studies including at least 400 subjects with pancreatic mass suggest a range of sensitivity in detecting pancreatic malignancy of 60-94% with a specificity of 100%. Two studies of ERCP-FNA including 164 subjects with various pancreatobiliary tumors reported of sensitivities ranging from 25% to 62%. While sensitivity in reported in these studies appears to be lower than that for EUS-FNA, such a comparison is not valid due to differences in study populations, cytology techniques, and study settings.

Part II, Section 2: Diagnostic Performance of ERCP In Pancreaticobiliary Malignant Obstruction—Comparison To Alternatives

Introduction

The evaluation of suspected malignant obstructive jaundice includes imaging evaluation to determine if there is an anatomic narrowing or stricture of the biliary or pancreatic ducts. If a stricture is identified, the appearance and location of the stricture are characterized to determine the likelihood of malignancy and to guide subsequent treatment decisions.

Images of the pancreaticobiliary system can be obtained using a variety of techniques. Direct cholangiopancreatography performed via an ERCP approach is the subject of this systematic review, and the primary diagnostic alternatives to ERCP are magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), computed tomography cholangiography (CTC), and percutaneous transhepatic cholangiography (PTC). Both ERCP and PTC are minimally invasive procedures involving injection of contrast directly into the biliary tree. EUS involves endoscopy, but does not directly invade the biliary system. MRCP and CTC are both noninvasive procedures, though oral or intravenous biliary contrast agents may be used to enhance CTC while MRCP does not require the administration of a contrast agent to visualize the biliary tree.

This systematic review selected studies that directly compared the diagnostic performance of ERCP with at least one of the primary alternative diagnostic tests. Given that the expected difference in diagnostic performance between tissue sampling techniques and the diagnostic alternatives reported here are relatively small and the number of cases with the outcome of interest is generally small, these studies may have very limited power to detect statistically significant differences in test performance.

Evidence Base

ERCP vs. MRCP

Eight studies (total n=538) were identified that compared ERCP with MRCP and that used current MRCP technique. Five studies utilized an independent reference standard consisting of best available information derived from surgery, biopsy, imaging, and clinical follow-up to establish the final diagnosis, thus providing comparative data for ERCP and MRCP. The remaining three studies considered ERCP to be the reference standard against which MRCP was measured, yielding concordance of findings of MRCP with ERCP. Four studies were rated "Good" quality, signifying use of blinded interpretation of tests (Table 30). Four of these studies included over 100 subjects and the smallest study contained 46 subjects.

Table 30. Quality Assessment

Study **Author, Year**	**Patient Enrollment**	**Diagnostic performance of ERCP determined without knowledge of other test results**	**Diagnostic Performance of other test(s) determined without knowledge of ERCP results**	**Summary Evaluation**
MRCP Studies				
Varghese, Farrell, Courtney et al., 1999	Prospective (n=100) Complete explanation provided of 113 consecutive enrolled and 13 excluded subjects	Yes	Yes	**Good**
Adamek, Albert, Weitz et al., 1998	Prospective (n=60) 60 of 86 pts w/ suspected biliary obstruction Reasons for exclusions fully explained	Yes	Yes	**Good**
Arslan, Geitung, Viktil et al., 2000	Retrospective (n=135) 135 of 153 consecutive patients had diagnostic MRCP and ERCP Results reported in 78 patients with diagnostic quality MRCP and ERCP among of 85 patients with obstruction	Uncertain	Uncertain	**Fair**
Lee, Lee, Kim et al., 1997	? Retrospective (n=46) Complete explanation of 71 consecutive eligible patients and 25 exclusions	Yes	No	**Fair** MRCP results seem to factor into the reference standard determination
Holzknecht, Gauger, Sackmann et al., 1998	Prospective (n=61) Complete explanation provided of 66 consecutive enrolled patients and 5 excluded subjects	Yes	Yes	**Good**
Lomas, Bearcroft, and Gimson 1999	Prospective (n=69) Complete explanation provided of 76 enrolled and 7 excluded subjects	Yes	Uncertain	**Fair**

Table 30. Quality Assessment (cont'd)

Study Author, Year	Patient Enrollment	Diagnostic performance of ERCP determined without knowledge of other test results	Diagnostic Performance of other test(s) determined without knowledge of ERCP results	Summary Evaluation
MRCP Studies (cont'd)				
Adamek, Albert, Breer et al., 2000	Prospective (n=124) 124 of 141 pts w/ suspected pancreatic malignancy Reasons for exclusion fully explained	Yes	Yes	**Good**
Guibaud, Bret, Reinhold et al., 1995	Prospective (n=126) Some exclusions because of no ERCP confirmation	Uncertain	Yes	**Fair**
EUS Studies				
Kaneko, Nakao, Inoue et al., 2001	Prospective (n=27) Consecutive patients with no reported exclusions	No	No	**Fair**
Glasbrenner, Schwarz, Pauls et al., 2000	Prospective (n=95) Consecutive patients referred for surgical resection of pancreatic mass	Yes	Yes	**Good**
Rosch, Schusdziarra, Born et al., 2000	Retrospective (n=184) Full explanation of 18 exclusions provided but selection based on having all 3 diagnostic tests creates a potential bias.	Yes	Yes	**Fair**
Cellier, Cuillerier, Palazzo et al., 1998	Retrospective (n=47) Consecutive patients with partial explanations for 17 excluded patients.	Uncertain	Yes	**Fair**
Burtin. Palazzo, Canard et al., 1997	Prospective (n=68) Consecutive patients enrolled	Yes	Yes	**Fair**—unorthodox reporting of data, uncertain of data
Dancygier and Nattermann 1994	Prospective (n=41) Unstated whether consecutive	Uncertain	Yes	**Fair**
Snady, Cooperman, Siegel et al., 1992	Retrospective (n=60) Methods not well described other than pts were "diagnostically problematic"	No	No	**Fair**

ERCP vs. EUS

Seven studies (total n=466) were identified that compared ERCP with EUS. Six of these employed an independent reference standard consisting of best available information derived from surgery, biopsy, imaging, and clinical follow-up to establish the final diagnosis, and therefore reported data for both EUS and ERCP. Only one study was rated "Good" (Glasbrenner, Schwarz, Pauls et al., 2000, n=90–91) (Table 30). Three studies addressed populations with obstructive jaundice, two studies addressed populations with suspected pancreatic cancer, and two studies addressed patients with either known or suspected intraductal papillary mucinous tumors of the pancreas.

Review of Evidence: Diagnostic Performance

Presence of Malignant Stricture/Lesion

ERCP vs. MRCP. Five studies including a total of 379 patients reported on diagnostic performance of MRCP in identifying and characterizing a malignant stricture (Table 31). In the two studies where ERCP was the reference standard (Guibaud, Bret, Reinhold et al., 1995; n=126; Lomas, Bearcroft, and Gimson 1999, n=69; both rated "Fair"), MRCP showed 86% and 92% sensitivity and 98 and 100% specificity. These data suggest good concordance between MRCP and ERCP results.

The three studies comparing MRCP and ERCP with an independent reference standard report slight differences in estimates of sensitivity and specificity, but none of these differences is statistically significant. The one study rated "Good" quality (Adamek, Albert, Weitz et al., 1998, n=60), reported slightly lower sensitivity (81% vs. 93%) and higher specificity (100% vs. 94%) for MRCP compared with ERCP, but both tests were considered equivalent. The largest study (Arslan, Geitung, Viktil et al., 2000, n=78) found similar sensitivity (86% vs. 89%) and reports lower specificity (82% vs. 94%) for MRCP, but 95% confidence intervals overlap significantly. Finally, Lee et al. (1998; n=46) reports higher sensitivity (81% vs. 71%) and similar specificity (92% vs. 92%) for MRCP, but overall accuracy was not statistically different.

ERCP vs. EUS. Three studies, all rated "Fair" quality and including a total of 129 patients with obstructive jaundice, reported on the diagnostic performance of EUS in identifying the presence of a malignant lesion/stricture (Table 32). One study (Burtin. Palazzo, Canard et al., 1997, n=34) reported similar diagnostic performance for ERCP and EUS, with both tests achieving 89% sensitivity and similar specificity (96% for EUS and 92% for ERCP). Dancygier and Nattermann (1994, n=41) reported complete concordance between EUS and ERCP. One study (Snady, Cooperman, Siegel et al., 1992, n=54–60) compared EUS with the combination of ERCP plus CT and reports both higher sensitivity and specificity for EUS, 85% vs. 75% sensitivity, and 80% vs. 65% specificity, respectively, but these differences were not statistically significant.

In summary, individual studies were relatively small and did not identify significant differences in diagnostic performance between ERCP and either MRCP or EUS. These data permit

Table 31. Comparison of MRCP and ERCP

Study	N Pt	N Res	Diag test	Outcome	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adeq Studies (%)	Comments
Independent Reference Standard[15]											
Adamek, Albert, Weitz et al., 1998	86	60	MRCP ERCP	Presence of malignant stricture	45 45	81 93	100 94	100 93	87 94	97 79	**Good, prospective** p=n.r., but "equivalent"
Arslan, Geitung, Viktil et al., 2000	153	78	MRCP ERCP	Presence of malignant stricture		86 (74-94) 89 (77-96)	82 (67-93) 94 (82-99)			98.7 90	**Fair, retrospective** Kappa = 0.82
Lee, Lee, Kim et al., 1997 [16]	71	46	MRCP ERCP	Presence of malignant stricture	46 46	81 71	92 92	89 88	85 79	98 n.r.	**Fair, ?retrospective** McNemar p>0.05
Adamek, Albert, Breer et al., 2000	141	124	MRCP ERCP	Presence of pancreatic cancer	30 30	84 70	97 94	91 84	93 88	n.r. n.r.	**Good, prospective** McNemar p=0.059
Varghese, Farrell, Courtney et al., 1999[17]	113 113	100 98 100 98	MRCP ERCP MRCP ERCP	Presence of stricture Level of stricture	28 28 28 28	100 100 100 100	100 100 100 100	100 100 100 100	100 100 100 100	97 89 97 89	**Good, prospective** No statistical analysis

[15] Independent reference standards relied on best available information from surgery, biopsy, cytology, imaging, and clinical follow-up.
[16] Reference standard also took into consideration MRCP and ERCP results as well as surgery
[17] MRCP provided additional information over ERCP regarding cause of stricture in one case of 1.5 cm periampullary adenocarcinoma

Table 31. Comparison of MRCP and ERCP (cont'd)

Study	N Pt	N Res	Diag test	Outcome	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adeq Studies (%)	Comments
ERCP Reference Standard											
Guibaud, Bret, Reinhold et al., 1995	126	126	MRCP	Presence of malignant stricture	11	86 (67-100)	98 (96-100)	86	97	99	**Fair, prospective**
Lomas, Bearcroft, and Gimson 1999	76	69	MRCP	Presence of malignant stricture	17	92	100	100	98	97	**Fair, prospective** Kappa = 0.88
	76	69		Presence of stricture	29	100	98 (94-100)	95 (85-100)	100	97	
	76	69		Level of stricture	n.r.	100	100	100	100		
Holzknecht, Gauger, Sackmann et al., 1998	66	61	MRCP[18]	Presence of stricture	59	89	84	89	84		**Good, prospective** No statistical analysis

[18] This study performed MRCP using only "snapshot" techniques (RARE and half-Fourier RARE) in the coronal and angles sagittal planes. It is unclear whether axial images were routinely obtained.

Table 32. Comparison of EUS and ERCP

Study	N Pt	N Res	Diag test	Outcome	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adeq Stud (%)	Comments
Population with obstructive jaundice											
Independent Reference Standard											
Burtin. Palazzo, Canard et al., 1997	34	34	EUS ERCP	Presence of malignant lesion	36 36	89 89	96 92	89 80	96 96	97 97	**Fair, prospective** data not clearly reported p=n.s., diagnostic accuracy
Snady, Cooperman, Siegel et al., 1992	60	60 54	EUS ERCP+CT	Presence of malignant lesion	67 67	85 75	80 65	89 81	73 57		**Fair, retrospective** p=n.s.
ERCP Reference Standard											
Dancygier and Nattermann 1994	41	41	EUS	Presence of malignant lesion	100	100	100	100	100		**Fair, prospective** No statistical analysis
	41	41	EUS	Level of stricture	100	100	100	100	100		
Population with suspected pancreatic disease											
Independent Reference Standard											
Glasbrenner, Schwarz, Pauls et al., 2000	95	90 91 90	EUS ERCP Combo	Presence of pancreatic cancer	54 53 53	78 81 92	93 88 86	93 89 88	78 80 90		**Good, prospective** p=n.s. for all comparisons
Rosch, Schusdziarra, Born et al., 2000	184	184 184	EUS ERCP Clinical	Presence of pancreatic cancer vs. chronic pancreatitis	42	86 81 81	87 85 85				**Fair, retrospective** p=n.s. p=n.s.
	184	184 184	EUS ERCP Clinical	Presence of pancreatic cancer vs. inflammatory tumor	42	86 81 81	72 61 72				
Population with IPMT											
Independent Reference Standard[19]											
Kaneko, Nakao, Inoue et al., 2001	27	27 27	EUS ERP	Presence of mural nodules[20]	81 81	59 50	100 100	100 100	36 31		**Fair, prospective** p=n.s.
Cellier, Cuillerier, Palazzo et al., 1998	47	21 29	EUS ERCP	Presence of invasive tumor[21]	43 31	78 55	75 90	70 71	82 82		**Fair, retrospective** No statistical analysis

[19] Reference standard consists of surgical specimen histology and/or pancreatography
[20] Population of patients with suspected intraductal papillary mucinous tumors of the pancreas
[21] population of patients with histologically proven diagnosis of intraductal papillary mucinous tumors of the pancreas

preliminary conclusions that MRCP and EUS provide similar diagnostic assessment as ERCP for detection of malignant pancreaticobiliary obstruction.

Diagnosis of Pancreatic Cancer

MRCP vs. ERCP. Diagnostic performance for demonstrating pancreatic cancer in 37 of 124 was reported by Adamek, Albert, Breer et al. (2000; Table 31). This study compares MRCP and ERCP and reported slightly higher sensitivity (84% vs. 70%) and similar specificity (97% vs. 94%) for MRCP and ERCP, respectively, but these differences did not reach statistical significance (McNemar p=0.059). This study was rated "Good" for quality.

EUS vs. ERCP. Diagnostic performance for pancreatic cancer was reported in two studies specifically addressing populations with suspected pancreatic disease (Table 32). Rosch, Schusdziarra, Born et al. (2000) retrospectively evaluated 184 patients who had ERCP, EUS, and CT and compared the diagnostic performance of clinical assessment with the various imaging tests. This study finds similar performance for clinical assessment, ERCP, or EUS in distinguishing pancreatic cancer from chronic pancreatitis and in distinguishing pancreatic cancer from inflammatory tumor. Interpretation of Rosch, Schusdziarra, Born et al. (2000) is somewhat limited by the retrospective selection of patients on the basis of having all three imaging tests, which might bias the study toward cases where findings were inconclusive. Glasbrenner, Schwarz, Pauls et al. (2000; n=95) noted ERCP and EUS to have similar sensitivity (81% vs. 78%, respectively) and specificity (88% vs. 93%, respectively), and the combination of the two tests yielded 92% sensitivity and 86% specificity, but these differences were not statistically significant.

Summary. In summary, there is little evidence directly comparing ERCP with either MRCP or EUS in diagnosing pancreatic cancer. The available evidence does not demonstrate statistically significant differences between ERCP and either MRCP or EUS.

Presence of Stricture

ERCP vs. MRCP. Three studies reported diagnostic performance in demonstrating the presence of stricture (either benign or malignant) (Table 31). One of the two studies rated as "Good" independently verified results and found 100% sensitivity and 100% specificity for both MRCP and ERCP (Varghese, Farrell, Courtney et al., 1999, n=98–100). The other (Holzknecht, Gauger, Sackmann et al., 1998, n=61) used ERCP as reference standard and reported 89% sensitivity and 85% specificity for MRCP relative to ERCP, though this study utilized only projection ("snapshot") MRCP techniques without additional multislice techniques which may limit its comparability. One additional study (Lomas, Bearcroft, and Gimson 1999, n=69) rated as "Fair" quality because of uncertainties with regard to complete blinding of interpretation, noted 100% concordance for MRCP with ERCP.

ERCP vs. EUS. No studies reported this specific analysis.

Summary. In summary, the evidence specifically evaluating MRCP in relation to ERCP for detecting strictures is sparse and suggests similar results for MRCP and ERCP in identifying the

presence of a stricture. However, these studies do not report full statistical analysis. The relative performance of EUS and ERCP in this setting has not been reported.

Level of Stricture

ERCP vs. MRCP. One study comparing ERCP and MRCP (Varghese, Farrell, Courtney et al., 1999, n=98-100, "Good") specifically reported 100% sensitivity and specificity for both MRCP and ERCP in defining the level of the stricture (Table 31). Lomas, Bearcroft, and Gimson (1999, n=69, "Fair") also reported complete concordance for MRCP with ERCP in defining the level of malignant strictures.

ERCP vs. EUS. Only one study comparing ERCP and EUS (Dancygier and Nattermann 1994, n=41, "Fair") specifically reported sensitivity and specificity in defining the level of the stricture (Table 32). This study reports 100% sensitivity and specificity for both ERCP and EUS.

Summary. In summary, there is little evidence specifically reporting the diagnostic accuracy of MRCP or EUS relative to ERCP in defining the level of stricture, but the available studies suggest that all three tests provide highly accurate localization of pancreaticobiliary stricture.

Evaluation of Suspected Intraductal Papillary Mucinous Tumors (IPMT) of the Pancreas

ERCP vs. MRCP. No studies reported this specific analysis

ERCP vs. EUS. Two studies evaluated EUS in comparison with endoscopic retrograde pancreatography (ERP) in patients with either known or suspected IPMT of the pancreas (Table 32). Kaneko, Nakao, Inoue et al. (2001; n=27, "Fair") found that EUS and ERP were similarly sensitive (59% vs. 50%, respectively) in detecting mural nodules while both tests were 100% specific for this finding. Cellier, Cuillerier, Palazzo et al. (1998; n=47, "Fair") compared ERCP and EUS in defining the presence of invasive tumor and reported EUS to be more sensitive (78% vs. 55%) and less specific (75% vs. 90%), but no statistical analysis was reported.

These two small studies, reporting estimates of diagnostic performance relating to different diagnostic endpoints, suggest that EUS may provide a similar information to ERCP in patients with known or suspected intraductal papillary mucinous tumors of the pancreas, but confirmation of these findings would be helpful.

Conclusions

The body of evidence directly comparing ERCP with either MRCP or EUS is modest in size and of varying methodological quality. The evidence comparing ERCP with MRCP is slightly stronger than that comparing ERCP with EUS both in terms of number of subjects and study quality. The available studies do not demonstrate statistically significant differences in diagnostic performance for ERCP versus MRCP or for ERCP versus EUS for characterizing malignant strictures. In sum, the available studies suggest that either MRCP or EUS provides similar diagnostic performance as ERCP in detecting pancreaticobiliary malignant obstruction.

Part II, Section 3: Outcomes of Treatment Using ERCP and Endoscopic Sphincterotomy and Endoscopic Stent for Palliation of Pancreaticobiliary Malignancy—Comparison of Strategies Using ERCP, Surgery, or Interventional Radiology

Introduction

Biliary obstruction is a frequent presenting feature of pancreaticobiliary malignancy. Unfortunately, patients with pancreaticobiliary malignancy are usually incurable at the time of diagnosis (Conio, Demarquay, De Luca et al., 2001; England and Martin 1996). Whether surgical resection for attempted cure is feasible or not, management of biliary obstruction is desirable to palliate the morbidity of jaundice. Endoscopic stent drainage has been proposed as an alternative to biliary-enteric bypass surgery to palliate malignant biliary obstruction. In addition, alternative approaches to biliary stenting have been compared with particular interest to determining optimal stent material, design, and placement strategies.

Part II, Section 3A. Comparison of ERCP Stent Versus Surgical Bypass

Body of Evidence

Five studies compared results of surgical bypass with endoscopic stent drainage for palliation of malignant obstructive jaundice. Quality assessments are described in Table 33. Results of these studies are detailed in the "Evidence Tables" section and summarized in Tables 34–37. Three randomized, controlled trials were identified comparing surgical biliary bypass with endoscopic biliary stent placement. Two of these (Smith, Dowsett, Russell et al., 1994, n=204; Andersen, Sorensen, Kruse et al., 1989, n=50) were rated as "Good" quality, and Shepherd, Royal, Ross et al. (1988, n=52) was rated as "Fair"). Two retrospective comparisons (Raikar, Melin, Ress et al., 1996, n=66; Leung, Emergy, Cotton et al., 1983, n=98) were both rated as "Poor."

Review of Evidence: Treatment Outcomes

All studies reported that there was no significant difference in overall patient survival between the ERCP and the surgery groups (Table 35). Two randomized controlled trials reported both treatments to have high rates for relief of jaundice but no statistically significant difference. A third study reported on quality of life, as measured by mean percentage of survival time with normal activity or limited activity with no aid; there were no significant differences.

Review of Evidence: Adverse Outcomes

There were no significant differences in perioperative mortality (Table 36). The randomized controlled trial by Smith, Dowsett, Russell et al. (1994) was designed to show a 5–20% decrease in 30-day mortality at 95% power with 115 patients entered into each arm. Accrual was stopped at 204 patients when interim analysis indicated that additional accrual would not change the outcome. While this trial did not show a statistically significant difference in perioperative (30-

Table 33. Quality Assessment

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Smith, Dowsett, Russell et al., 1994	RCT (n=204) Good comparability – Randomization by computer minimization on age, bilirubin, albumin, urea, and Hb conc. – Patient characteristics not significantly different	Surgery: (n=103) 2 excluded due to benign disease 7 did not get surgery (2 technical failures, 1 elected crossover, 3 deteriorated clinically and got stents, 1 deteriorated and got no further rx) Stent: (n=101) 1 excluded due to benign disease 5 did not get stents (1 elected crossover, 3 technical failures got surgery, 1 technical failure got no further rx)	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention-to-treat analysis used	**Good**
Andersen, Sorensen, Kruse et al., 1989	RCT (n=50) Good comparability – Sealed envelopes – Patient characteristics not significantly different	Surgery: n=25 6 did not undergo surgery (2 wanted crossed over, 1 found inoperable at surgery, 2 psychological compromise, 1 surgeon not available) Endoprosthesis: n=25 None	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention-to-treat analysis used Results also analyzed by treatment received and findings were consistent.	**Good**

Table 33. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Shepherd, Royal, Ross et al., 1988	RCT (n=52) Fair comparability – Randomization method not specified – Patient characteristics mostly comparable	Surgical: n=27 4 total: 2 withdrawn (1 died pre-op and 1 had attempted curative surgery). 2 technical failures crossed over to endoprosthesis. Endoprosthesis: n=25 6 total: 1 had benign biopsies but later found to have cancer at surgery; 4 failed and crossed-over to surgery; 1 failed both stent and surgery	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Does not clearly state method of analysis	**Fair**

Table 33. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Raikar, Melin, Ress et al., 1996	Retrospective series (n=66) Fair to Poor comparability Baseline patient characteristics show no SSD but differences in performance status distribution noted with ERCP subjects having relatively higher percentages of good and poor PS while surgery had relatively higher midrange PS.	All subjects included in analysis	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Univariate analysis does not account for important confounders	**Poor**
Leung, Emergy, Cotton et al., 1983	Retrospective series (n=98) Poor comparability Baseline patient characteristics show differences in age and lesion location.	All subjects included in analysis	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Univariate analysis does not account for important confounders	**Poor**

Table 34. Overview of studies and reported outcomes

Study	Population	Procedure	N ERCP Surg (treated)	Outcome Measures Reported									Study Quality
				Total Hospital Days	Initial Hospital Days	Readmissions	Need for Add'l Procedure	Survival	Jaundice Relief	Quality of Life	Perioperative Mortality	Perioperative Morbidity	
Randomized Controlled Trials													
Smith, Dowsett, Russell et al., 1994	Malignant distal CBD obstruction and jaundice Mean age 70	10 Fr stents[22] vs. Bypass Surgery	101 (100) 103 (101)	X			**X**	**X**		**X**	**X**	**X**	Good
Andersen, Sorensen, Kruse et al., 1989	Malignant distal CBD obstruction and jaundice Age>60y	7-10 Fr stents vs. Bypass Surgery	25 (19) 25 (30)	**X**			**X**	**X**		**X**	**X**	**X**	Good
Shepherd, Royal, Ross et al., 1988	Malignant distal CBD obstruction Mean age 73	10 Fr stents vs. Bypass Surgery	27 (23) 25	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	Fair

[22] 19 of 101 stent patients required combined ERCP and percutaneous transhepatic approach to place stent

Table 34. Overview of studies and reported outcomes (cont'd)

Study	Population	Procedure	N ERCP Surg (treated)	Outcome Measures Reported									Study Quality
				Total Hospital Days	Initial Hospital Days	Readmissions	Need for Add'l Procedure	Survival	Jaundice Relief	Quality of Life	Perioperative Mortality	Perioperative Morbidity	
Retrospective Studies													
Raikar, Melin, Ress et al., 1996	Unresectable pancreatic carcinoma	10-12 Fr stents vs. Bypass Surgery	34 32			**X**	**X**	**X**			**X**	**X**	Poor
Leung, Emergy, Cotton et al., 1983	Malignant obstructive jaundice (CBD location not specific)	8-10 Fr stents vs. Bypass Surgery	64 34			**X**	**X**	**X**			**X**		Poor

Table 35. Treatment Outcomes

Study	Study arm N Enrolled/ (treated or results)	Survival (median) (*mean) (**Life Table Analysis)	P	Relief of Jaundice	p	Quality of Life	p
Randomized Controlled Trials							
Smith, Dowsett, Russell et al., 1994	ERCP[23] 101 (100)	21 weeks	ns	97%	ns		
	Surgery 103 (101)	26 weeks		98%			
Andersen, Sorensen, Kruse et al., 1989	ERCP 25 (19)	**84 days (3-498)[24]	ns			57% survival time mean normal activity or limited, no aid	ns
	Surgery 25 (30)	**100 days (10-642)				51% survival time mean normal activity or limited, no aid	
Shepherd, Royal, Ross et al., 1988	ERCP 27 (23)	**152 days (39-411)	ns	91%	nr		
	Surgery 25	**125 days (52-354)		92%			

[23] Stent placement was attempted first with ERCP approach. In 19 patients a combined transhepatic-endoscopic approach was required when initial ERCP failed.
[24] No significant difference when analyzed by treatment received.

Table 35. Treatment Outcomes (cont'd)

Study	Study arm N Enrolled/ (treated or results)	Survival (median) (*mean) (**Life Table Analysis)	P	Relief of Jaundice	p	Quality of Life	p
Retrospective Studies							
Raikar, Melin, Ress et al., 1996	ERCP 34	*9.7 months (10d-35)	0.13				
	Surgery 32	*7.3 month (7d-29)					
Leung, Emergy, Cotton et al., 1983	ERCP 64	6 mos. approximate	Ns				
	Surgery 34	6 mos. approximate					

Table 36. Adverse Outcomes

Study	Study arm N Enrolled/ (treated or results)	Perioperative Mortality	P	Perioperative Complications	p
Randomized Controlled Trials					
Andersen, Sorensen, Kruse et al., 1989	ERCP 25 (19)	5 (20%)	Nr	36% (total severe infection)	Ns
	Surgery 25 (30)	6 (24%)		20% (total severe infection)	
Shepherd, Royal, Ross et al., 1988	ERCP 27 (23)	2 (9)%	Ns	7 procedure-related complication events	Ns
	Surgery 25	5 (20%)		14 procedure-related complication events	
Smith, Dowsett, Russell et al., 1994	ERCP[25] 101 (100)	8%[26]	Ns	11% major complications	0.02
	Surgery 103 (101)2 (n)	15%		29% major complications	
Retrospective Studies					
Leung, Emergy, Cotton et al., 1983	ERCP 64	1 (3%)	Nr	21%	ns
	Surgery 34	1 (4%)		33%	
Raikar, Melin, Ress et al., 1996	ERCP 34	10 (16%)	Nr		
	Surgery 32	3 (9%)			

[25] Stent placement was attempted first with ERCP approach. In 19 patients a combined transhepatic-endoscopic approach was required when initial ERCP failed.
[26] Procedure related mortality was significantly higher in the surgery group (14% vs. 3% , p=0.006). Also of note, 3 deaths in the surgical group were in patients who did not undergo surgery.

Table 37. Resource Utilization Outcomes

Study	Study arm N Enrolled/ (Treated or Results)	Total Hospital Days median[27] (range)	p	Initial Hospital Days (median) (*mean)	p	Readmission to Hospital N (%)	p	Need for Additional Procedure	p
Randomized Controlled Trials									
Smith, Dowsett, Russell et al., 1994	ERCP[28] 101 (100)	19 (4-59)	ns					Recurrent obstructive jaundice requiring stent replacement in 36 (36%) Late gastric outlet obstruction requiring gastric bypass in 10 (10%)	ns ns
	Surgery 103 (101)	26 (8-85)						Recurrent obstructive jaundice in 2 (2%). One required stent. Late gastric outlet obstruction requiring gastric bypass in 5 (5%)	
Andersen, Sorensen, Kruse et al., 1989	ERCP 25 (19)	26 (3-210)	ns[29]					1 (4%) early failure requiring surgical bypass.	nr
	Surgery 25 (30)	27 (10-202)						3 (12%) early failure requiring stent placement.	
Shepherd, Royal, Ross et al.,1988	ERCP 27 (23)	8 [30] (2-30)	<0.01	5 (2-16)	<0.002	10 (43%)	nr	Gastric outlet obstruction developed in 2 (9%)	nr
	Surgery 25	13 (8-49)		13 (8-49)		3 (12%)		Gastric outlet obstruction developed in 1 (4%)	

[27] Results generally reported as median. Results reported as mean are demarcated by an asterisk (*)
[28] Stent placement was attempted first with ERCP approach. In 19 patients a combined transhepatic-endoscopic approach was required when initial ERCP failed.
[29] Comparison of hospital stay was not statistically significant when analyzed by treatment received.
[30] Calculated only in patients who were alive 30 days post-op.

Table 37. Resource Utilization Outcomes (cont'd)

Study	Study arm N Enrolled/ (Treated or Results)	Total Hospital Days median[31] (range)	p	Initial Hospital Days (median) (*mean)	p	Readmission to Hospital N (%)	p	Need for Additional Procedure	p
Retrospective Studies									
Raikar, Melin, Ress et al., 1996	ERCP 34	$17,738	.05	7*	<0.001	12 (35%)	nr	Average of 1.7 stent replacements per patient One patient developed gastric outlet obstruction requiring surgical gastric bypass.	nr nr
	Surgery 32	$25,101		14*		8 (25%)		Two patients required stent placement for recurrent jaundice. No report of surgical patients developing gastric outlet obstruction.	
Leung, Emergy, Cotton et al., 1983	ERCP 64			14* (4-30)	Nr	8 (13%)[32]	nr	Recurrent jaundice developed in 3 (5%) Gastric outlet obstruction developed in 2 (3%)	nr nr
	Surgery 34			30* (14-79)		3 (9%)		Recurrent jaundice developed in 1 (3%) Gastric outlet obstruction developed in 2 (6%)	

[31] Results generally reported as median. Results reported as mean are demarcated by an asterisk (*)
[32] Local complications included cholangitis, recurrent jaundice, duodenal obstruction, or chest wall metastasis

day) mortality, intent-to-treat analysis showed significantly greater procedure-related mortality in the surgery arm (14% vs. 3%, p=0.006). Smith, Dowsett, Russell et al., (1994) also found that major complications were significantly greater in the surgery group than in the ERCP group (29% vs. 11%, p=0.02). Andersen, Sorensen, Kruse et al. (1989) reported severe infections in 36% of ERCP patients compared to 20% of surgical patients, but the difference was not statistically significant. Shepherd, Royal, Ross et al. (1988) found twice the rate of complications in the surgical group, but again this was not statistically significant.

Review of Evidence: Resource Utilization

The two randomized controlled trials rated as good quality found no significant difference in total days of hospitalization, including the largest of trials in this group of studies (Smith, Dowsett, Russell et al., 1994, n=203) (Table 37). Three studies report on initial hospitalization; including 1 randomized controlled trial (Shepherd, Royal, Ross et al., 1988, n=52). All show fewer days of initial hospitalization with ERCP, and 2 report that the difference is statistically significant. Readmissions were more common with ERCP, but tests of statistical significance were not reported. The randomized controlled trial by Shepherd, Royal, Ross et al. (1988) reports significantly fewer initial and total hospitalization days with ERCP, despite a readmission rate twice that of surgery. However, this randomized controlled trial was judged of lesser quality ("fair"), largely due to lack of clarity in the method of analysis.

Stent replacement was reported in the Smith, Dowsett, Russell et al., (1994) study as necessary in 37% of patients, all but 1 case due to recurrence of obstructive jaundice. Raikar, Melin, Ress et al. (1996) reported an average of 1.7 stent replacements per patient.

Summary

The most robust evidence is provided in the randomized controlled trial by Smith, Dowsett, Russell et al. (1994). There were no significant differences in overall survival, relief of jaundice, technical success, total hospitalization days or perioperative mortality. Major complications were more frequent in the surgery group (11% vs. 29%, p=0.02), presumably reflecting the more invasive nature of surgical versus endoscopic treatment. Stent replacement was required in 37% of ERCP patients.

Part II, Section 3B. Comparison of Metal vs. Plastic Stents During ERCP

Evidence Base

Three studies were identified comparing endoscopically placed metal or plastic stents for palliation of biliary obstruction due to malignancy. Quality ratings are described in Table 38. Results are detailed in the "Evidence Tables" chapter and summarized in Tables 39–42. Two randomized, controlled trials (total n=206) were identified. Davids, Groen, Rauws et al. (1992, n=105, "Fair" quality) compared metal versus plastic stents. Prat, Chapat, Ducot et al. (1998, n=101, "Fair" quality) randomized patients into 3 arms (either metal stents, plastic stents with exchange as needed for stent dysfunction, or plastic stents with routine exchange every 3 months). In addition, Schmassmann, Von Gunten, Knuchel et al. (1996, n=165, "Poor" quality) retrospectively compared results with metal versus plastic stents.

Review of Evidence: Treatment Outcomes

Metal stents showed statistically significantly longer patency rates compared with plastic stents in all three studies (Table 40). Two of the studies reported that median duration of patency with metal stents was twice as long as plastic stents (9.1–10 months versus 4–4.2 months, $p<0.006$), but one of the randomized trials showed a smaller benefit for metal stents (4.8 months versus 3.2 months, $p<0.05$).

The two randomized studies reported no significant difference in overall survival for patients treated with metal or plastic stents, with median survival ranging from 4.5–5.8 months. In contrast, the retrospective study found slightly longer median survival in the metal stent group (6.5 months versus 4 months, $p<0.05$), but related this observation to increased mortality in 18% of subjects (predominantly plastic stent group) who did not receive treatment for stent dysfunction.

All studies reported both treatments to have high rates for relief of jaundice with no statistically significant differences reported.

Review of Evidence: Adverse Outcomes

Two studies (Prat, Chapat, Ducot et al., 1998; Schmassmann, Von Gunten, Knuchel et al., 1996) reported no significant difference in perioperative mortality (Table 41). The randomized, controlled trial by Davids, Groen, Rauws et al. (1992) noted a higher perioperative mortality rate in the metal stent group (14% vs. 4%, $p=0.047$), but the causes of death in 6 of 7 cases were completely unrelated to biliary pathology. No significant differences were noted in complications in the two randomized studies and the retrospective study did not specifically report complications other than perioperative mortality.

Table 38. Study Quality Assessment

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Davids, Groen, Rauws et al., 1992	RCT (n=105) Good comparability - Randomization by computer generated random number - patient characteristics well-balanced	115 initially randomized and 105 included in analysis 10 patients excluded. 5 due to prior history of malignancy in past 10 years and 5 due to selection for surgical therapy. None lost to follow-up	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not clearly stated.	Fair
Prat, Chapat, Ducot et al., 1998	RCT (n=101) Good comparability - Randomization by blocks of six and stratified for gender and investigation center - patient characteristics well-balanced	4 of 105 excluded Three for failed endoprosthesis insertion and one for not complying with required quarterly stent changes for group 2 Four lost to follow-up (3 moved away and 1 no follow-up information)	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not clearly stated	Fair

Table 38. Study Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Schmassmann, Von Gunten, Knuchel et al., 1996	Retrospective study (n=165) Fair comparability Baseline patient characteristics similar for age, gender, bilirubin, type of tumor and stage, location of stricture, or associated procedures	All subjects included in analysis	Adequate for comparison 87% of metal stent and 100% of plastic stent patients had sphincterotomy	Adequate outcome measures used. Outcomes were not assessed blindly.	Univariate analysis does not account for confounders	Poor

Table 39. Overview of studies and reported outcomes

Study	Population	Procedure	N (treated) Metal Plastic	Outcome Measures Reported									STUDY QUALITY
				Total Hospital Days	Initial Hospital Days	Cost Utilization	Need for Add'l Procedure	Survival	Jaundice Relief	Stent Patency	Periop Mortality	Periop Morbidity	
Randomized Controlled Trials													
Davids, Groen, Rauws et al., 1992	Patients with irresectable distal bile-duct malignancy Pancreatic ca = 93 Papillary ca = 12	Metal stent[33] Straight 10 Fr polyethylene stent[34]	49 56				X	X	X	X	X	X	Fair
Prat, Chapat, Ducot et al., 1998	Patients with malignant CBD strictures Not involving hilum Pancreatic ca = 65 Cholangioca = 21 Ampullary ca = 3 Metastatic = 12	Metal stent Polyethylene 11.5 Fr stent[35] w/ routine exchange Polyethylene 11.5 Fr stent w/ as needed exchange	34 33 34	X		X	X	X	X		X	X	Fair
Retrospective Studies													
Schmassmann, Von Gunten, Knuchel et al., 1996	Consecutive patients with unresectable malignant biliary obstruction	Metal stent Straight 12 Fr or 10 Fr polyethylene stent[36]	95 70				X	X	X	X	X		Poor

[33] Metal stents were of the Wallstent type (Schneider, Switzerland (Davids et al.; Schmassmann et al.)) or (Schneider-Howmedical, Lyons, France (Prat et al.)).
[34] Polyethylene stents were made by PBN Medicals (Stenlose, Denmark)
[35] Polyethylene stents were made by Wilson-Cook (Winston-Salen, N.C.)
[36] Polyethylene stents 12 Fr were made by Olympus (Volketswil, Switzerland) and 10 Fr Huibregtse (Cook, Nottwil, Switzerland)

Table 40. Treatment Outcomes

Study	Study arm N Enrolled/ (treated or results)	Survival (median)	P	Relief of Jaundice N (%)	p	First Stent Patency (median)	p
Randomized Controlled Trials							
Davids, Groen, Rauws et al., 1992	Metal 49	5.8 months[37]	0.45	47/49 (96%)	n.r.	9.1 months	0.006
	Plastic 56	4.9 months		53/56 (95%)		4.2 months	
Prat, Chapat, Ducot et al., 1998	Metal 34	4.5 months	n.s.	48h Decrease in bilirubin: 41%	n.s.	4.8 months	<0.05
	Plastic-routine 33	5.6 months		34.3%		Not reported separately	
	Plastic-as needed 34	4.8 months		35.4%		3.2 months	
Retrospective Studies							
Schmassmann, Von Gunten, Knuchel et al. 1996	**Metal 95**	6.5 months[38]	<0.05	95%	n.s.	10 months[39]	<0.001
	Plastic 70	4 months		88%		4 months	

[37] Data were converted to months from reported days by dividing by 30.
[38] When 29 subjects (8 metal stent, 21 plastic stent) who died related to untreated stent dysfunction were excluded from the analysis, the remaining 136 subjects had similar survival between the two groups.
[39] Subgroup analysis did not show any significant difference between different locations (common bile duct vs. hilar or intrahepatic stricture) but numbers were small in the hilar and intrahepatic subgroups.

Table 41. Adverse Outcomes

Study	Study arm N Enrolled/ (treated or results)	Perioperative Mortality	P	Complications	p
Randomized Controlled Trials					
Davids, Groen, Rauws et al., 1992	Metal 49	7 (14%)[40]	0.047	6 (12%)[41]	n.r.
	Plastic 56	2 (4%)[42]		6 (11%)	
Prat, Chapat, Ducot et al., 1998	Metal 34	Overall rate was 3.9% No significant difference between groups		Overall rate was 11.9% No significant difference between groups	
	Plastic-routine 33				
	Plastic-as needed 34				
Retrospective Studies					
Schmassmann, Von Gunten, Knuchel et al. 1996	Metal 95	2%	n.s.		
	Plastic 70	3%			

[40] Causes of death were sepsis after recurrent cholangitis (1); cardiac failure (2); cachexia (4).
[41] Complications in Davids et al. were measured in 7 days after procedure.
[42] Causes of death were cachexia (2).

Table 42. Resource Utilization Outcomes

Study	Study arm N Enrolled/ (Treated or Results)	Total Hospital Days median (range)	p	Resource Utilization Costs	p	Need for Additional Procedure	p
Randomized Controlled Trials							
Davids, Groen, Rauws et al., 1992	Metal 49					1.3 per person	n.r.
	Plastic 56					1.8 per person	
Prat, Chapat, Ducot et al., 1998	Metal 34	5.5 ± 1.4*	*0.01 others n.s.	Mean costs (95% CI) $4643 (4207-5079)	n.r.	1.2 ± 0.4 per patient	0.01 ANOVA
	Plastic-routine 33	10.6 ± 1.7*		$6770 (5394-8146)		2.5 ± 1.9 per patient	
	Plastic-as needed 34	7.4 ± 1.5		$5547 (4082-7013)		1.7 ± 1.3 per patient	
Retrospective Studies							
Schmassmann, Von Gunten, Knuchel et al., 1996	Metal 95					1.2 per patient	<0.005
	Plastic 70					1.58 per patient	

Review of Evidence: Resource Utilization Outcomes

All studies examined the relative utilization of ERCP procedures and found patients receiving metal stents to require the fewest ERCP procedures (Table 42). Patients receiving metal stents required 1.2–1.3 ERCP procedures on average and those receiving plastic stents and undergoing stent exchange only when needed required 1.58–1.8 ERCP procedures. The study by Prat, Chapat, Ducot et al. (1998) examined the strategy of routine plastic stent exchange every 3 months which necessitated an average of 2.5 ERCP procedures per patient. The differences in ERCP utilization between metal and plastic stents were reported to be statistically significant in two studies and a statistical comparison was not reported in the third study.

Prat, Chapat, Ducot et al. (1998) also examined utilization of total hospital days and found the metal stent group averaged 5.5 days while the plastic stent groups required 7.4 to 10.6 days on average, depending on whether "as needed" or routine stent exchange was used, respectively. The difference between metal stents and routinely exchanged plastic stents was statistically significant (5.5 ± 1.4 versus 10.6 ± 1.7, $p=0.01$) while the differences between metal stents and plastic stents exchanged as needed were not statistically significant.

Prat, Chapat, Ducot et al. (1998) also reported lower average total costs for the metal stent group than costs associated with either of the plastic stent strategies, but statistical analysis was not reported for these results.

Summary

Three studies including a total of 371 subjects provide consistent evidence that metal stents remain patent longer than plastic stents. Both types of stents offer initial relief of jaundice and the available evidence does not conclusively show any difference in perioperative adverse events. Overall patient survival is not significantly different when stent occlusions are treated with stent exchange as needed. Total resource utilization including need for repeat ERCP, total hospital days, and costs was reported to be lower with metal stents compared with plastic stents.

Part II, Section 3C. Additional Comparisons of ERCP Strategies

Evidence Base

The ERCP literature systematically reviewed for this report also included nine studies comparing various alternative ERCP treatment techniques. The comparisons reported in these studies were sufficiently dissimilar from the studies reviewed in preceding sections on palliative treatments of pancreaticobiliary malignancy that they are briefly summarized separately in this section. The quality assessments of these studies are detailed in Table 43 and the results of these studies are in Tables 44–46.

Review of Evidence: Stent Material and Design

Four studies, including two randomized controlled trials (one quality rated as "Good" and one as "Fair") and two nonrandomized studies (both rated "Poor" quality) compared different features of endoscopically placed stents for palliation of pancreaticobiliary malignancy (Tables 44–46.).

van Berkel, Boland, Redekop et al. (1998, n=84, "Fair") randomized patients to receive stents made of Teflon™ versus stents made of polyethylene and found no significant differences in efficacy or complications (Table 44). Median stent patency duration was 83 days for Teflon™ stents and 80 days for polyethylene stents (p=0.93).

Pedersen (1993, n=89, "Poor") and Speer, Cotton, MacRae et al. (1988, n=79, "Poor") both compared outcomes using different caliber stents, but neither of these studies uses a randomized, controlled design (Table 45). Speer, Cotton, MacRae et al. (1988) found significantly longer median stent patency for 10Fr stents compared with 8Fr stents (32 weeks vs. 12 weeks, $p<0.001$). Complications reported included a lower rate of cholangitis with 10 Fr stents (5% vs. 34%, $p<0.05$), and similar rates of local perforation and stent migration. However, the 8Fr stents had pigtail-shaped ends compared with straight-shaped 10Fr catheters, a potential confounding factor in interpreting this study. Pedersen (1993) did not reveal a statistically significant difference in stent patency comparing 10Fr and 7 Fr, and did not show significant differences in total complication rates. However, this study also suffered from baseline differences in age, with younger patients receiving 7 Fr stents, increasing concerns over interpretation of findings.

Sung, Chung, Tsui et al. (1994, n=70, "Good") randomized patients to receive 10Fr stents with or without sideholes (Table 46). No statistically significant differences were noted in stent patency and reported complications appeared similar, although statistical analysis was not reported.

None of these studies provides a sufficient basis for a conclusion regarding the relative efficacy the stent features being compared.

Table 43. Quality Assessment

Study Author, Year Record Number	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
van Berkel, Boland, Redekop et al., 1998	RCT (n=84) Good comparability - Randomization by computer generated numbers in sealed envelopes - Patient characteristics similar	97 consecutive patients enrolled. 13 excluded for protocol violations (11 had surgical resection, 1 had PTH drainage, 1 refused treatment). Details about which treatment arm patients were assigned to were not provided. None lost to follow-up.	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not stated but all 84 included in analysis.	**Fair**
Pedersen 1993	Prospective study (n=89) Fair comparability Differences in age noted with younger 7Fr group. No SSD in stenosis location, gender, or type of cancer.	All subjects included in analysis	Adequate for comparison. Adjunctive sphincterotomy was performed equally in 7Fr and 10Fr groups.	Adequate outcome measures used. Outcomes were not assessed blindly.	Univariate analysis does not account for important confounders	**Poor**
Speer, Cotton, MacRae et al., 1988	Retrospective study (n=79) Fair comparability Baseline patient characteristics similar for age and site of obstruction.	All subjects included in analysis	Limitations for comparison 8 Fr stents had pigtails whereas 10Fr stents were straight	Adequate outcome measures used. Outcomes were not assessed blindly.	Univariate analysis does not account for important confounders	**Poor**

Table 43. Quality Assessment (cont'd)

Study Author, Year Record Number	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Sung, Chung, Tsui et al., 1994	RCT (n=70) Good comparability - Sealed envelopes - Patient characteristics show no SSD	SH: (n=35) NSH: (n=35) 3 subjects dropped out before 4 week f/u and were excluded from analysis	Adequate for comparison	Adequate outcome measures used. Patient and follow-up physician were blinded to type of stent placed.	Method of analysis not reported but no crossover reported.	**Good**
Speer, Cotton, Russell et al., 1987	RCT (n=75) Good comparability - Computer generated random numbers and stratified by referring center - Patient characteristics similar for age, ASA[43] grade, duration of jaundice, bilirubin, albumin, creatinine, and Hb, but ERCP group had more proximal obstructions, more unrelated medical problems, and more elevated WBC. No statistical results reported.	ERCP: (n=39) No dropouts 4 failures Percutaneous: (n=36) No dropouts 8 failures	Percutaneous stents were initially 6Fr and exchanged 2-3 days later to 12 Fr while endoscopic stents were 10 Fr in size	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention-to-treat analysis used. Results were also analyzed taking into account relevant confounders that were not balanced.	**Good**

[43] American Society of Anesthesiology's performance status classification

Table 43. Quality Assessment (cont'd)

Study Author, Year Record Number	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Pedersen, Lassen, De Muckadell et al., 1998	RCT (n=34) Good comparability - Randomization by computer generated numbers and sealed numbered envelopes - Baseline characteristics similar for age, type of cancer, and no SSD for gender	<u>Stent above SO (n=22)</u> 22 randomized - 5 technical failures crossed over. Final n=17. No other dropouts. <u>Stent across SO (n=19)</u> 19 randomized - 2 withdrawn for curative surgery. Final n=17. No other dropouts.	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis primarily based on treatment received. Results for one outcome reported using intention-to-treat.	**Fair**
DePalma, Galloro, Iovino et al., 2001	RCT (n=157) Good comparability - Randomization by sealed opaque envelopes - Baseline characteristics similar	<u>Unilateral stent (n=79)</u> No dropouts <u>Bilateral stent (n=78)</u> No dropouts	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention to treat used.	**Good**
Chang, Kortan, and Haber 1998	Retrospective study (n=141) Baseline patient characteristics were comparable for age, gender, and tumor type	All subjects included in analysis	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Analysis made some attempts to stratify results by Bismuth type, but did not fully consider possible confounders.	**Fair**

Table 43. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Deviere, Baize, de Toeuf et al., 1988	Retrospective study (n=70) Baseline patient characteristics were not reported other than stricture type	All subjects included in analysis	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Analysis made some attempts to stratify results by Bismuth type, but did not fully consider possible confounders.	**Poor**

Table 44. Comparison of Plastic versus Teflon™ stents

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
van Berkel, Boland, Redekop et al., 1998	84	Patients with distal malignant biliary stricture. No previous drainage procedure. Pancreas ca = 76 Papilla ca = 1 Bile duct ca = 5 Metastasis = 2 42 Teflon™ stents 42 polyethylene stents (Amsterdam-type) All stents 10Fr and 9cm Baseline characteristics comparable.	Median survival (days) Teflon™ 165 Poly 140 p=0.6 Successful biliary drainage Teflon™ 90% Poly 92% Median stent patency (days) Teflon™ 83 Poly 80 p=0.93 No significant differences found in: Mean weight gain for 26 removed stents	<u>Perioperative mortality</u> Teflon™ 14% Poly 14% Early procedure-related complications Teflon™ 4 (10%) Poly 4 (10%) Late complications Stent dysfunc / Repeat ERCP / # ERCP Teflon™ 28 / 24 / 79 Poly 29 / 25 / 75	Univariate analysis of factors associated with reduced stent patency was reported. Previous failure of cannulation (p=0.03) Previous CBD contrast injection without papillotomy (p=0.004) Previous papillotomy (p=0.08) Gender, age>75, jaundice> 14 days, bilirubin > 300 μmol/L not significant factors.

Table 45. Comparison of different caliber stents

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Prospective observational studies					
Pedersen 1993	89	Pts with malignant biliary strictures 31 Single 7 Fr (S7) 45 Single 10 Fr (S10) 13 Double 7Fr (D7) 85% of all patients also had sphincterotomy, evenly distributed between 7 and 10 Fr. 7 Fr stent chosen when no large bore ERCP scope available. Baseline patient characteristics were different for age (7Fr group younger than 10Fr group). No SSD in stenosis location, gender, or type of cancer.	Median Stent Patency (days) Median, 25%-75% range S7 67 (20-336) S10 144 (39-237) D7 110 (62-145) Total 110 (33-237) P=0.11, comparing 7Fr vs. 10Fr	<u>Mortality (2-week)</u> S7 (n=31) 4 (13%) S10 (n=45) 4 (9%) D7 (n=13) 2 (15%) p=0.84 Total Early Complications S7 (n=31) 13% S10 (n=45) 22.1% D7 (n=13) 23.1% p=n.s. <u>Fever</u> S7 (n=31) 9.7% S10 (n=45) 17.7% D7 (n=13) 23.1% p=n.r. Bleeding S7 (n=31) 6.5% S10 (n=45) 4.4% D7 (n=13) 0% p=n.r. <u>Perforation</u> S7 (n=31) 3.2% S10 (n=45) 0% D7 (n=13) 0% p=n.r.	

Table 45. Comparison of different caliber stents (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Retrospective studies					
Speer, Cotton, MacRae et al., 1988	79	All patients receiving stent palliation for malignant obstructive jaundice 28 8Fr pigtail stents 51 10Fr straight stents Baseline patient characteristics similar for age and site of obstruction.	Median Stent Patency (weeks) 8 Fr 12 10 Fr 32 p<0.001 Patency advantage of 10Fr stents primarily in first month.	Early complications (2 week) Cholangitis 8 Fr (n=28) 13 (34%) 10 Fr (n=51) 3 (5%) p<0.01 (text) Local perforation 8 Fr (n=28) 2 (5%) 10 Fr (n=51) 4 (5%) p=n.s. Stent migration 8 Fr (n=28) 3 (8%) 10 Fr (n=51) 2 (3%) p=n.s. Late complications Need for stent replacement 8 Fr 12 (43%) 10 Fr 13 (25%) p=n.r.	

Table 46. Comparison of stents with or without sideholes

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
Sung, Chung, Tsui et al., 1994	70	Most pts (93%) had malignant obstruction SH= side-hole stent (n=35) NSH = no side-hole (n=35) 10Fr stents Patient characteristics show no SSD for age, gender, diagnosis, location of stent, prior stent	Biochemical improvement at 4 weeks SH (n=35) 95% NSH (n=32) 78% p>0.1 All stent patency (weeks), median (range) SH (n=35) 7.8 (2.6-28) NSH (n=32) 7.9 (0.6-28) p>0.1 Initial stent patency (weeks), median (range) SH (n=35) 9.5 (6.3-28) NSH (n=32) 8.0 (0.6-28) p>0.1 Second stent patency (weeks), median (range) SH (n=35) 6.6 (2.6-19.9) NSH (n=32) 5.6 (0.9-23.3) p>0.1	<u>Mortality</u> SH (n=35) 8 (23%) NSH (n=32) 8 (25%) p=n.r. <u>Fever</u> SH (n=35) 82% NSH (n=32) 83% p=n.r.	

Review of Evidence: Comparisons of Stent Placement

Five studies including three RCT (two quality rated as "Good" and one as "Fair") and two retrospective studies (one "Fair" and one "Poor" quality) looked at issues of stent placement (Tables 47–49).

Speer, Cotton, Russell et al. (1987, n=75, "Good") randomized patients to undergo percutaneous transhepatic placement of 12 Fr stents or endoscopic placement of 10 Fr stents (Table 47). This trial was terminated early when a prespecified statistical criterion was reached, specifically increased perioperative mortality was observed in subjects randomized to percutaneous stent insertion, 33% vs. 15%, p=0.016. Early complications also favored endoscopic over percutaneous placement (19% vs. 67%, p=n.r.). Patient survival and stent patency results did not demonstrate statistically significant differences.

Pedersen, Lassen, De Muckadell et al. (1998, n=34, "Fair") randomized patients to have 10Fr stents placed with the inferior tip above the sphincter of Oddi or across the sphincter of Oddi (Table 48). Stents placed across the sphincter of Oddi were less likely to become dislocated (12% vs. 53%, p=0.026). Otherwise, no statistically significant differences were observed between the two groups with regard to patient survival, stent patency, procedure-related mortality, or complications.

Three studies compared results of unilateral versus bilateral stent placement in patients with biliary obstruction secondary to hilar malignancy (Table 49). DePalma, Galloro, Iovino et al. (2001, n=157, "Good") provides the best evidence derived from a randomized controlled trial. This study finds no statistically significant differences in overall patient survival, perioperative mortality, procedure-related mortality, or late complications between those randomized to receive a unilateral versus bilateral stent. Moreover, the significant results reported favored unilateral stent placement over bilateral stents. Those randomized to receive bilateral stents had significantly lower rates of successful drainage (73% versus 81%, p=0.049), significantly more early complications (26.9% versus 18.9%, p=0.026), and significantly higher rates of cholangitis (16.6% versus 8.8%, p=0.013).

The two earlier retrospective studies, Chang, Kortan, and Haber (1998, n=141, "Fair") and Deviere, Baize, de Toeuf et al. (1988, n=70, "Poor") both examined patients who all had hilar malignancy and compared outcomes for those receiving unilateral or bilateral stents. Chang, Kortan, and Haber (1998) further considered subgroups who had different combinations of having received unilateral versus bilateral diagnostic biliary opacification and unilateral versus bilateral stent drainage. Deviere, Baize, de Toeuf et al. (1988) restricted analysis only to deceased patients. The results of these studies are complex with primary findings reported to be longer median patient survival in patients receiving bilateral drainage procedures, and higher perioperative mortality and increased rate of acute cholangitis among the subgroup which had unilateral stent placement in Deviere, Baize, de Toeuf et al. (1988) and the subgroup with unilateral drainage but bilateral diagnostic opacification performed in Chang, Kortan, and Haber (1998). However, the reported analyses do not fully account for various possible confounding influences and in light of findings of the randomized controlled trial, these retrospective findings are likely related to unmeasured differences in the groups being compared.

Table 47. Comparison of Percutaneous versus Endoscopic Stent Insertion

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
Speer, Cotton, Russell et al., 1987	75	Malignant biliary obstruction, unresectable Stents: 39 ERCP 10 Fr 36 Percutaneous 12 Fr Patient characteristics similar for age, ASA[44] grade, duration of jaundice, bilirubin, albumin, creatinine, and Hb, but ERCP group had more proximal obstructions, more unrelated medical problems, and more elevated WBC. No statistical results reported.	**Survival** (days), median (range) Hilar / Low bile duct / Total ERCP 65 (8-623) / 160 (14-598) / 119 (9-623) PTH 24 (2-351) / 94 (4-391) / 88 (2-391) p=0.35 **Stent patency** (days) No significant difference in median time to blockage, p=0.16 **Failed Insertion** ERCP (n=37) 4 PTH (n=33) 8 **Successful Insertion but No Drainage** ERCP (n=37) 3 PTH (n=33) 5 **Relief of Jaundice** ERCP (n=37) 30 (81%) PTH (n=33) 20 (61%) p=0.017 **Initial Hospitalization** (days) (for those surviving at least 30 days) ERCP 11 (2-49) PTH 17 (3-24) p=0.4	<u>Early complications</u> ERCP (n=37) 7 (19%) PTH (n=33) 22 (67%) <u>Perioperative Mortality</u> ERCP 6 (15%) PTH 12 (33%) p=0.016 And Cox regression analysis confirmed that ERCP had significantly lower 30-day mortality (p=0.008). Cox proportional hazards model was performed. Predictors of 30-day mortality were ASA grade of 3 or more (p=0.002), randomization to PTH (p=0.008), WBC > 10 $x10^9$ cells/l (p=0.018), hilar obstruction (p=0.01), and age 69-76 y (p=0.016). Predictors of decreased overall survival were WBC > 10 $x10^9$ cells/l (p=0.01) and hilar obstruction (p=0.05)	This trial was originally planned to enroll 200 patients. After the 1st of 3 planned interim data analyses, the trial was halted based on prospectively defined statistical criteria.

[44] American Society of Anesthesiology's performance status classification

Table 48. Comparison of stent placement above versus across sphincter of Oddi

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trial					
Pedersen, Lassen, De Muckadell et al., 1998	34	Pts with unresectable CBD biliary obstruction 17 placed above SO 17 placed across SO 10 Fr straight stents Baseline characteristics Similar for age, type of cancer, and no SSD for gender	<u>Patient survival (days)</u> Median (25%-75% range) Above SO (n=17) 144 (82-347) Across SO (n=17) 46 (35-155) p=n.s. Median stent patency (days) Median (25%-75% range) Above SO (n=17) 110 (61-320) Across SO (n=17) 126 (89-175) p=n.s. Intent-to-treat analysis: <u>Median stent patency (days)</u> Above SO (n=17) 99 (53-320) Across SO (n=17) 126 (89-175) p=n.s. <u>Stent Function</u> \# w/ Stent Dysfunction / Time to dysfunction Above SO 10 / 82 (31-185) Across SO 5 / 89 (13-150) p=n.s.	<u>Mortality (2 weeks)</u> Above SO (n=17) 2 (12%) Across SO (n=17) 1 (12%) p=n.s. <u>Early complications (1 week)</u> Above SO (n=17) 2 (12%) Across SO (n=17) 4 (24%) p=n.s. <u>Dislocation of stent</u> Above SO (n=17) 9 (53%) Across SO (n=17) 2 (12%) p=0.026	

Table 49. Comparison of unilateral versus bilateral drainage in hilar malignancy

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
DePalma, Galloro, Iovino et al., 2001	157	Pts w/ hilar obstruction due to cholangio-carcinoma, gallbladder cancer, or lymph node metastasis Type I (n=49) Type II (n=56) Type III (n=52) Randomized to unilateral (group A) or bilateral (Group B) stents	Median Survival (days) A 140 (21-612) B 142 (24-498) p=0.48 Technical Success Drainage Success A 88.6 % 81% B 76.9 % 73% p= 0.041 0.049	Perioperative Mortality A 11.3% B 14.1% p=0.638 Procedure-related Mortality A 2.5% B 3.8% p=0.681 Early complications A 18.9% B 26.9% p=0.026 Cholangitis A 8.8% B 16.6% p=0.013 Late complications A 39.7% B 39.1% p=0.735	

Table 49. Comparison of unilateral versus bilateral drainage in hilar malignancy (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Retrospective Studies					
Chang, Kortan, and Haber 1998	141	Pts w/ bifurcation tumors Bismuth Type: Type I (n=43) Type II (n=58) Type III (n=40) Types II and III were divided into 3 groups: N=32 A= one lobe of liver opacified with contrast and 1 side drained N=29 B = both lobes liver opacified and both drained N=37 C = both lobes liver opacified and one drained Single stents (n=104) 11 – 7 Fr; 40 – 10 Fr 53 – 11.5 Fr 3 – metal stents Double ERCP stents (n=15) 21 – 7 Fr; 7 – 10 Fr 2 – 11.5 Fr 18 technical failures drained percutaneously Among those with double drains, 15 ERCP only, 3 PTH only, and 11 ERCP and PTH	Median survival (days) I 160 A 145 B 225 C 46 p<0.001 Comparing single drains (groups A + C) versus double drains (group B), double drains had significantly better survival p<0.0001	<u>Perioperative Mortality</u> I 2 (5%) A 0 B 1 (3%) C 11 (30%) p<0.01 <u>Early complications</u> Acute cholangitis I 2 (5%) A 2 (6%) B 0 C 12 (32%) p<0.01 Stent migration I 1 (2%) A 0 B 0 C 1 (3%) p=n.s. Pancreatitis I 0 A 0 B 1 (3%) C 1 (3%) p=n.s. <u>Total early complications</u> I 3 (7%) A 2 (6%) B 1 (3%) C 14 (38%) p=n.s. <u>Late complications</u> Need for stent replacement I 19 (44%) A 16 (50%) B 12 (41%) C 2 (5%) p=n.r.	This is a study comparing unilateral versus bilateral drainage of bifurcation tumors

Table 49. Comparison of unilateral versus bilateral drainage in hilar malignancy (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Retrospective Studies (cont'd)					
Deviere, Baize, de Toeuf et al., 1988	70	Deceased pts with hilar tumors and biliary obstruction Type I stricture (n=20) 1 stent (Gr I-1) Type II or III (n=50) 24 w/ 1 stent (Gr II/III-1) 24 w/ 2 stent (Gr II/III-2) 2 w/ failed (Gr II/III-0)	Mean Survival (days) Median[45] Gr I-1 156 (6-570) 156 Gr II/III-1 119[a] (2-760) 162 Gr II/III-2 176[a] (4-660) 198 Gr II/III-0 16 (6-26) [a] = p<0.01	<u>Perioperative Mortality</u> Gr I-1 0% Gr II/III-1 29% Gr II/III-2 8% Gr II/III-0 100%	

[45] Median survival after exclusion of patients who died within 30 days

Summary

Several additional comparative studies addressing variations in stent design and stent placement were identified in this systematic review. Since each research comparison has only one or no randomized controlled trial available, the results of these studies support only preliminary conclusions regarding the relative efficacy of these alternative approaches to stent palliation of pancreaticobiliary malignancy.

Part II, Section 4: Outcomes of Treatment Using Preoperative ERCP Drainage for Relief of Malignant Obstructive Jaundice

Introduction

Biliary obstruction results in a variety of biochemical and physiological disturbances such as elevated bilirubin and other liver function tests, as well as impaired hepatic and renal function with associated coagulation problems. In patients who are scheduled for potentially curative surgery, it has been postulated that using a course of preoperative biliary drainage to alleviate biliary obstruction may result in reduced surgical morbidity and mortality.

Evidence Base

Six studies addressed preoperative stenting compared to no stenting prior to surgery for malignant obstruction. Quality assessments are described in Table 50. Results are displayed in detail in the "Evidence Tables" chapter and summarized in Tables 51 and 52. The four nonrandomized series (Sewnath, Birjmohun, Rauws et al., 2001, n=290; Karsten, Allema, Reinders et al., 1996, n=241; ten Hoopen-Neumann, Gerhards, van Gulik et al., 1998, n=52; Heslin, Brooks, Hochwald et al., 1998, n=74) were judged to be of poor quality, largely due to lack of between-group comparability of patients or performance of intervention; and the randomized controlled trial by Lygidakis, van der Heyde, Lubbers et al. (1987, n=38) suffered from inappropriate use of statistical tests. Accompanying letters to the editor suggest that the conclusions as stated in the Lygidakis, van der Heyde, Lubbers et al. (1987) paper are not substantiated by the reported data. The randomized controlled trial by Lai, Mok, Fan et al. (1994, n=87) was judged to be of "Fair" quality, but is limited by insufficient sample size, which is the reason the trial was terminated by the investigators after initial analysis. Outcomes reported in these studies are largely limited to laboratory values and perioperative mortality and morbidity and postoperative hospital stay.

Review of Evidence: Treatment Outcomes

One randomized trial (Lygidakis, van der Heyde, Lubbers et al., 1987) and two nonrandomized comparisons reported on hospital days (Table 52). Lygidakis, van der Heyde, Lubbers et al. (1987) reported that preoperative ERCP group had higher initial hospital days (7 vs. 3.7) and lower total hospital days (23 vs. 26.7) than the no stent group, respectively. Tests of statistical significance were not reported. Heslin, Brooks, Hochwald et al. (1998, n=74) found patients receiving preoperative stents had slightly longer postoperative hospital stay (median of 11 versus 10 days, p=0.04) but Sewnath, Birjmohun, Rauws et al. (2001, n=290) reported slightly shorter postoperative stays in the stented groups that did not reach statistical significance (median of 13-15 days versus 16 days, p=0.09).

Lai, Mok, Fan et al. (1994) reported on technical success of preoperative stenting, which was 87%.

Table 50. Quality Assessment

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Lygidakis, van der Heyde, Lubbers et al., 1987	RCT (n=38) Patient characteristics similar. Method of randomization not specified	All subjects included in analysis	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	All subjects enrolled were included in analysis. Inappropriate statistical tests used[46]	**Poor**
Lai, Mok, Fan et al., 1994	RCT (n=87) Fair comparability – Randomization: Consecutive numbered envelopes – Patient characteristics showed no SSD but early surgery w/o stent group tended to be higher risk with more medical problems	Preop Stent: (n=43) 6 technical failures crossed over 2 refused surgery after successful stent placement. No Stent: (n=44) No changes reported.	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention-to-treat analysis used in most comparisons. This trial was terminated because interim analysis showed that planned sample size was inadequate.	Fair

[46] Soreide O and Eide GE, Letter to the Editor: Preoperative Biliary Drainage. Acta Chir Scand 156:251-252 1990.

Table 50. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Prospective Studies						
Sewnath, Birjmohun, Rauws et al., 2001 Same series as Karsten, Allema, Reinders et al., 1996, but subjects accrued June 1992 – Dec 2000	Prospective series (n=290) Excluded 21 patients who had external biliary drainage Fair comparability of baseline patient characteristics Patients without preop drainage were usually not jaundiced	All subjects included in analysis	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Analysis did compare preop drainage and no drainage for primary outcomes. Additional analysis by subgroups based on degree of preop jaundice	**Poor**

Table 50. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Retrospective Studies						
Karsten, Allema, Reinders et al., 1996 Subjects accrued Oct 1983 – June 1992	Retrospective series (n=241) Patients without preop drainage were usually not jaundiced; patients with jaundice assigned to ERCP Fair comparability of other baseline patient characteristics	All subjects included in analysis except for bile culture results obtained only in 195/241 (81%).	Adequate for comparison ERCP group received stent only if papillotomy alone was insufficient	Adequate outcome measures used. Outcomes were not assessed blindly.	Comparison of pre-op ERCP vs. immediate surgery outcomes lacking for most outcomes	**Poor**

Table 50. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Retrospective Studies (cont'd)						
Heslin, Brooks, Hochwald et al., 1998	Retrospective series (n=74) Patients undergoing pancreaticoduodenectomy Slight imbalances in baseline patient characteristics such as gender and presence of positive nodes	All subjects included in analysis	Adequate for comparison	Adequate outcome measures used. Complications were assessed by an independent physician.	Analysis considered important outcomes. Secondary multivariable analysis did consider potential confounding factors. However, multivariable model may include too many candidate variables making it susceptible to overfitting.	**Poor**
ten Hoopen-Neumann, Gerhards, van Gulik et al., 1998	Retrospective series (n=52) Fair comparability Baseline patient characteristics showed no SSD for age, gender, tumor classification, type of surgery	All subjects included in analysis	No stent group included ERCP technical failures Post-operative radiation therapy performed in 37% of stent patients vs. 27% of immediate surgery patients.	Adequate outcome measures used. Outcomes were not assessed blindly.	Analysis did qualitatively identify possible confounding factors such as radiation therapy.	**Poor**

Table 51. Overview of studies and outcomes reported

Study	Population	Procedure	N Stent No Stent	Outcome Measures Reported						STUDY QUALITY
				Hospital Days	Laboratory Values	Technical Success	Perioperative Mortality	Perioperative Complications	Implantation Metastases	
Randomized Controlled Trials										
Lygidakis, van der Heyde, Lubbers et al., 1987	Patient with resectable pancreatic head carcinoma	preop ERCP placed stent vs. no pre-op stent	19 19	**X**	**X**		**X**	**X**		**Poor**
Lai, Mok, Fan et al., 1994	Malignant obstructive jaundice	preop ERCP placed stent vs. no pre-op stent	43 44		**X**	**X**	**X**	**X**		**Fair**
Prospective Studies										
Sewnath, Birjmohun, Rauws et al., 2001 Same series as Karsten, Allema, Reinders et al., 1996, but subjects accrued June 1992 – Dec 2000	Patients with presumed resectable tumor in pancreatic head region	232 had preop drainage - 192 stent+papillotomy - 27 papillotomy alone - 13 required percutaneous combined drainage procedure 58 with no drainage were - 25 had dx ERCP only - 24 not jaundiced - 9 failed drainage and got immediate surgery	232 58	**X**	**X**		**X**	**X**		**Poor**

Table 51. Overview of studies and outcomes reported (cont'd)

Study	Population	Procedure	N Stent No Stent	Outcome Measures Reported						STUDY QUALITY
				Hospital Days	Laboratory Values	Technical Success	Perioperative Mortality	Perioperative Complications	Implantation Metastases	
Retrospective Studies										
Karsten, Allema, Reinders et al., 1996 Subjects accrued Oct 1983 – June 1992	Patients with presumed resectable tumor in pancreatic head region	184 had preop drainage - 149 stent + papillotomy when papillotomy alone not sufficient - 25 papillotomy alone - 10 external drainage when ERCP stent not possible 57 with no drainage were not jaundiced (n=33) or had immediate operation planned (n=24)	149 57		**X**			**X**		**Poor**
Heslin, Brooks, Hochwald et al., 1998	Patients undergoing pancreaticoduodenectomy	39 had preop drainage 35 had no drainage preop	39 35	**X**	**X**		**X**	**X**		**Poor**
ten Hoopen-Neumann, Gerhards, van Gulik et al., 1998	Patients with Klatskin tumor with planned resection	41 of 52 had preop stent Main reasons for no stent were technical failure or lack of proximal congestion of bile	41 11		**X**				**X**	**Poor**

Table 52. Treatment Outcomes and Adverse Outcomes

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Periop Mortality	p	Periop Complications	p	Implantation Metastases	p
Randomized Controlled Trials													
Lygidakis, van der Heyde, Lubbers et al., 1987	ERCP 19	Preop: 7 Total: 23 (Days for group/n)	**nr**	Significant reduction in Serum bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT after stent Significant increase in white blood cell count after stent Hct, creatinine, albumin, and clotting parameters unchanged	<.002 <.001			0 (0%)		3 (16%)	[47]		
	No stent 19	Preop: 3.7 Total: 26.7 (Days for group/n)		No significant change in laboratory values between baseline and preoperative testing				2 (11%) (1 sepsis; 1 aneurysm)		14 (74%)[48]			

[47] Inappropriate statistical tests reported raising concerns over appropriateness of conclusions reported.

[48] This study has a high baseline rate of cholangitis in the no stent group, which may contribute to the higher rate of complications in this group. Perioperative blood loss (800+/-100 vs/ 1800+/-200 ml.) and operative time (5+/- 2 vs. 7+/-2 h) were greater in the no stent group. Tests of statistical significance were not reported for these outcomes.

Table 52. Treatment Outcomes and Adverse Outcomes (cont'd)

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Periop Mortality	p	Periop Complications		p	Implantation Metastases	p
Randomized Controlled Trials (cont'd)														
Lai, Mok, Fan et al., 1994	Stent 43			Serum bilirubin, alkaline phosphatase, ALT/SGPT but not AST/SGOT significantly lower than no stent group Hb, Hct, BUN, creatinine, albumin no different. WBC not reported.	<0.05	86%		6 (14%)	**ns**	Post-op:	16 (39)%	**ns**		
										Total[49]	23 (56%)			
	No Stent 44							6 (14%)		Post-op	18 (41%)			
										Total	18 (41%)			

[49] In addition, 7 of the 23 patients had complications from both procedures (preoperative stenting and surgery.)

Table 52. Treatment Outcomes and Adverse Outcomes (cont'd)

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Perioperative Mortality	p	Perioperative Complications	p	Implantation Metastases	p
Prospective Studies													
Sewnath, Birjmohun, Rauws et al., 2001 Same series as Karsten, Allema, Reinders et al., 1996, but subjects accrued June 1992 – Dec 2000	Pre-op Drain (n=232) 177 relieved of jaundice 32 with moderate jaundice 23 with severe jaundice	 13 (6-167) 15 (12-39) 15 (10-70)	0.09	Median decrease in bilirubin 82%* 57% 37%* * p<0.01				1.3%	n.r.	50%	0.69		
	No drainage 58	16 (8-222)		None reported				0%		55%			

Table 52. Treatment Outcomes and Adverse Outcomes (cont'd)

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Perioperative Mortality	p	Perioperative Complications	p	Implantation Metastases	p
Retrospective Studies													
Karsten, Allema, Reinders et al., 1996 Subjects accrued Oct 1983 – June 1992	Pre-op Drain (n=184) 149 stent+papillotomy 25 papillotomy alone 10 external drainage			Median decrease in bilirubin 82% 74% 50%	nr					Infectious Complication[50] Stent 49/149 (33%) Papillotomy 11/25 (44%) External drain 6/10 (60%)	nr		
	No drainage 57			None reported						No drainage 18/57 (32%)			

[50] The relationship between use of pre-operative drainage and postoperative complications was not significant when analyzed by preoperative bilirubin level.

Table 52. Treatment Outcomes and Adverse Outcomes (cont'd)

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Perioperative Mortality	p	Perioperative Complications	p	Implantation Metastases	p
Retrospective Studies (cont'd)													
Heslin, Brooks, Hochwald et al., 1998	Stent 39	11	0.04	Serum bilirubin, AST/SGOT significantly lower than no stent group. Albumin and alkaline phosphatase trended lower. BUN, creatinine, albumin, WBC no different.				2.6%	0.34	23 (59%)	0.04		
	No stent 35	10						0		12 (34%)			

Table 52. Treatment Outcomes and Adverse Outcomes (cont'd)

Study	Study arm N	Hospital Days	p	Laboratory Values	p	Technical Success	p	Perioperative Mortality	p	Perioperative Complications	p	Implantation Metastases	p
Retrospective Studies (cont'd)													
ten Hoopen-Neumann, Gerhards, van Gulik et al., 1998	Stent 41			Bilirubin, mean (range) 117 (12-511)	0.008							8/41 (20%)[51]	0.18
	No stent 11			235 (14-412)								0	

[51] At 1 year, 4 of 8 patients with implantation metastases did not receive any postoperative radiation therapy. Overall, 37% of stented patients and 27% of non-stented patients did not receive radiotherapy (p=not reported)

Comparison of changes in laboratory values before and after placement of a preoperative stent consistently showed a reduction in serum bilirubin and liver function tests. One study showed a significant increase in white blood cell count in the preoperative stent group after stenting. These changes were significantly different from the pattern of laboratory values seen in the "no stent" group that went immediately to surgery. No significant changes were noted in hemoglobin, hematocrit, creatinine, blood urea nitrogen, albumin or coagulation profiles.

Review of Evidence: Adverse Outcomes

The available data shows no apparent differences in perioperative mortality (Table 52). Lygidakis, van der Heyde, Lubbers et al. (1987) reported no deaths in the stent group and 2 (11%) in the "no stent" group; and Lai, Mok, Fan et al. (1994) reported 14% mortality for both groups. However, the sample sizes (n=34 and n=87, respectively) in these randomized controlled trials are likely too small to make a meaningful comparison. A larger but nonrandomized comparative study (Sewnath, Birjmohun, Rauws et al., 2001, n=290) and a smaller retrospective comparison (Heslin, Brooks, Hochwald et al., 1998, n=74) also reported no statistically significant differences in mortality.

Only Lai, Mok, Fan et al. (1994) reported on total complications, including complications from preoperative endoscopic stenting plus those from surgery. Total complications were greater in the preoperative stent group (56% vs. 41%), but results were not statistically significant. Of patients in the preoperative stent group who had complications, 30% had complications from both preoperative endoscopic stenting and from surgery. Sewnath, Birjmohun, Rauws et al. (2001) reported no significant difference in postoperative complications (50% for stented versus 55% without stent, p=0.69) but also reported that 6% of those receiving preoperative stenting experienced a stent-related complication. Lygidakis, van der Heyde, Lubbers et al. (1987), Karsten, Allema, Reinders et al. (1996), and Heslin, Brooks, Hochwald et al. (1998) reported only postoperative complications. The nonrandomized comparison by Heslin, Brooks, Hochwald et al. (1998) reported higher complications in the stent group (59% versus 34%, p=0.04), and the study by Karsten, Allema, Reinders et al. (1996) reported the same rate of infective complications (39%) in no drainage group as in the preoperative ERCP papillotomy plus stent group.

The retrospective series by ten Hoopen-Neumann, Gerhards, van Gulik et al. (1998) reports that implantation metastases (i.e., metastases presumed to be attributable to an invasive procedure) occurred in 20% of patients with preoperative stent and none in patient without stent, but the difference was not statistically significant. Moreover, this study did not control for whether patients received postoperative radiation therapy.

Summary

The evidence available is limited by poor methodological quality and fails to demonstrate that preoperative stenting improves health outcomes. Five of the six studies were judged to be of poor quality and the sixth, a randomized controlled trial judged to be of fair quality, is limited by insufficient sample size. Few studies report overall complications including both those related to the preoperative stent and the surgery, and these suggest that when complications of preoperative

endoscopic stenting are considered along with the perioperative complications of surgery, pre-operative stenting is associated with more complications. The other studies did not report on total complications, and thus fail to account for the morbidity associated with undergoing two procedures rather than one. Preoperative stenting does appear to significantly improve elevated bilirubin and liver function tests, but the available evidence does not suggest that surgical outcomes are improved as a result.

Results and Conclusions, Part III: Pancreatitis

This chapter reviews evidence on the following questions:

In patients with pancreatitis,

a. What is the diagnostic performance of ERCP in detecting underlying causes or complications of pancreatitis that are amenable to treatment in comparison to alternatives (e.g., EUS or MRCP)? *(Section 1: Diagnostic Performance of ERCP in Detecting Underlying Causes or Complications of Pancreatitis Amenable to Treatment – Comparison to Alternatives)*

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy? *(Section 2: Outcomes of Treatment Using ERCP for Pancreatitis – Comparison of Strategies Using ERCP, Surgery, or Medical Management)*

Part III, Section 1: Diagnostic Performance of ERCP in Detecting Underlying Causes or Complications of Pancreatitis Amenable to Treatment—Comparison to Alternatives

Introduction

In this section, evidence was sought to find studies that compared the diagnostic performance of ERCP and another diagnostic modality to diagnose treatable causes or complications of pancreatitis. Studies that demonstrate the utility of a single diagnostic modality in detecting treatable conditions did not meet selection criteria; only studies comparing ERCP with an alternative method were included. Studies whose aim was to diagnose or characterize chronic pancreatitis itself by two diagnostic modalities also did not meet selection criteria. Common duct stones can cause pancreatitis, but these studies were included in the review of studies evaluating diagnosis of common duct stones (*see* "ERCP Evidence Report Results and Conclusions, Part I: Common Bile Duct Stones").

Evidence Base

Only 3 studies were found that met selection criteria. Study quality is outlined in Table 53.

Review of Evidence

Duvnjak, Rotkvic, Vucelic et al. (1991, n=43, "Fair to Poor"; Table 54) compared ERCP to percutaneous cystopancreatography with measurement of pseudocyst amylase concentration to detect whether the pseudocyst communicates with the pancreatic duct. Knowledge of such a communication would help determine appropriate treatment for the pseudocyst. Although

Table 53. Quality Assessment

Study Author, Year	**Patient Enrollment**	**Diagnostic performance of ERCP determined without knowledge of other test results**	**Diagnostic Performance of other test(s) determined without knowledge of ERCP results**	**Summary Evaluation**
Duvnjak, Rotkvic, Vucelic et al., 1991	Prospective (n=43) States that patients were "randomly" selected, but otherwise not stated	Uncertain	Percutaneous pancreatography- Uncertain Amylase concentration- uncertain if 64 WU cutoff determined prospectively or post-hoc	Fair to poor
Bret, Reinhold, Taourel et al., 1996	Prospective (n=108) Most patients prospectively recruited, uncertain number with referral bias	Yes	Yes	Good
Takehara, Ichijo, Tooyama et al., 1994	Prospective (n=39) Not stated whether consecutive	Yes	Yes	Fair, small sample size

Table 54. Percutaneous pseudocystogram or percutaneous amylase measurement versus ERCP to diagnose communication between pseudocyst and pancreatic duct

Study	N	Population	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comments
Duvnjak, Rotkvic, Vucelic et al., 1991	43	Patients with persistent pseudocysts >25 cm area on cross-section image	Percutaneous cystogram Amylase> 64 WU	51% communication	59 100	100 90	100 92	70 100	ERCP was the reference standard

cystopancreatography alone has poor sensitivity compared to ERCP, measurement of the amylase concentration showed that amylase concentration greater than 64 WU had a sensitivity of 100 percent and a specificity of 90 percent compared to ERCP. It is not stated whether the 64 WU cutoff was prospectively defined. These results require further prospective validation.

Bret, Reinhold, Taourel et al. (1996, n=108, "Good"; Table 55) compared ERCP to MRCP for the diagnosis of pancreas divisum. Out of 108 undergoing both ERCP and MRCP, pancreas divisum was demonstrated by both techniques in 6 patients with complete concordance. The clinical significance of this finding is uncertain, as it is not reported or known whether the demonstration of the pancreas divisum alone determined the etiology or treatment of the clinical problem.

Takehara, Ichijo, Tooyama et al. (1994, n=39, "Fair"; Table 56) compared ERCP to MRCP to examine morphology of the pancreatic ducts in 39 patients with chronic pancreatitis. Ductal narrowing is potentially treatable with surgery or endoscopy, although evidence supporting effectiveness is lacking. In the area of the pancreas with the highest prevalence of stenosis, MRCP had only fair sensitivity, 57 percent, and fair specificity, 73 percent. The prevalence of lesions in other parts of the pancreas is too low to make any conclusions comparing MRCP to ERCP.

Conclusion

In sum, there is an inadequate literature base to compare ERCP and other diagnostic modalities for the identification of treatable complications of pancreatitis.

Table 55. MRCP versus ERCP to diagnose pancreas divisum

Study	N	Population	Diagnostic test	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comments
Bret, Reinhold, Taourel et al., 1996	108	Patients referred for ERCP for pancreatic disease	MRCP	6	100	100	100	100	ERCP was the reference standard

Table 56. MRCP versus ERCP to diagnose pancreatic duct stenoses and filling defects in patients with pancreatitis

Study	N	Population	Outcome studied	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Comments
Takehara, Ichijo, Tooyama et al., 1994	39	Patients with chronic pancreatitis	Stenosis head:	18	100	81	36	100	ERCP reference standard for all comparisons.
			Stenosis body:	31	57	73	31	89	
			Stenosis Tail:	6	50	91	25	97	2 sets of data presented in paper, each observer compared with ERCP, only 1 set abstracted
			Filling defect head:	5	100	100	100	100	
			Filling defect body:	6	100	100	100	100	
			Filling defect Tail:	5	50	94	33	97	

Part III, Section 2: Outcomes of Treatment Using ERCP for Pancreatitis—Comparison of Strategies Using ERCP, Surgery, or Medical Management

Introduction

This chapter reviews the evidence on ERCP for the treatment of pancreatitis. Pancreatitis encompasses a number of distinct entities with differing etiologies, clinical expression, and treatment options. Each will be addressed separately to the extent allowed by the available literature. Also, there are a number of different endoscopic techniques employed for varying clinical situations. For the purposes of this chapter, "ERCP" will refer to the spectrum of interventional endoscopic techniques that are employed in the treatment of pancreatitis.

Evidence Base

Pancreatitis was classified as "acute," "acute recurring," and "chronic," and evidence was sought to address a total of 9 separate indications within these classifications (Table 57). However, evidence meeting study selection criteria for this systematic review was available for only 4 of 9 indications of interest. These are: acute biliary pancreatitis; pancreas divisum; idiopathic recurrent pancreatitis, and pancreatic pseudocyst. Table 58 shows the quality and type of available evidence on pancreatitis together with the number of studies that met our inclusion criteria for each indication.. A more detailed account of the reason(s) for each of the excluded studies can be found in Table 59.

For acute pancreatitis, comparative studies are included that evaluate ERCP in the treatment of acute biliary pancreatitis. For acute recurrent pancreatitis (ARP) and chronic pancreatitis, there is a notable lack of comparative and/or prospective studies. To address the paucity of evidence on the indications, study selection criteria were relaxed to include retrospective, single arm studies that met a minimum threshold for reporting outcome measurements. Chronic pain, one of the most important outcome measures in chronic pancreatitis, is a subjective outcome that is prone to bias, especially when assessed in the absence of a comparison group. Therefore, retrospective single arm studies of acute relapsing and chronic pancreatitis were restricted to those that reported quantifiable pre and post measurements of pain and/or other similar outcomes such as analgesic use or hospitalization rates.

Review of Evidence: Acute Pancreatitis

Three randomized controlled trials compared early ERCP to delayed or selective ERCP. One associational study of a Veterans Administration database compared ERCP to surgery (Aiyer, Burdick, Sonnenberg et al., 1999).

Early ERCP Vs. Delayed or Selective ERCP for Acute Biliary Pancreatitis

There are three randomized controlled trials included in this review that compare early ERCP vs. delayed or selective ERCP for acute biliary pancreatitis. Two of these three trials were rated as "Good" (Fan, Lai, Mok et al., 1993; Folsch, Nitsche, Ludtke et al., 1997) by the quality

Table 57. ERCP in the treatment of pancreatitis: Overview of the literature by indication and study type

		Comparative studies			Single arm studies		
Indication	**Status**	**RCT**	**Prospective non-randomized**	**Retrospective**	**Prospective**	**Retrospective**	**Total**
Acute Pancreatitis							
Acute biliary pancreatitis	Reviewed	3	--	2	1	2	8
	Included	3	--	1	--	--	4
Acute non-biliary pancreatitis	Reviewed	--	--	--	--	--	--
	Included	--	--	--	--	--	--
Acute recurrent pancreatitis							
Pancreas divisum	Reviewed	1	--	--	--	7	8
	Included	1	--	--	--	2	3
Sphincter of Oddi dysfunction	Reviewed	--	--	--	--	--	--
	Included	--	--	--	--	--	--
Idiopathic ARP	Reviewed	1	1	--	1	1	4
	Included	1	0	--	--	--	1
Chronic pancreatitis							
Drainage of pseudocyst	Reviewed	--	--	1	1	3	5
	Included	--	--	1	1	1	3
Pancreatic duct stones (ERCP plus ESWL)	Reviewed	--	--	--	--	9	9
	Included	--	--	--	--	--	--
Pancreatic duct stricture (ERCP plus stenting)	Reviewed	--	--	--	--	11	11
	Included	--	--	--	--	--	--
Other chronic pancreatitis	Reviewed	--	--	--	--	6	6
	Included	--	--	--	--	--	--
Total	Reviewed	5	1	3	3	39	51
	Included	5	1	2	1	3	11

Table 58. Quality Assessment

Study, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized controlled trials						
Neoptolemos, Carr-Locke, London et al., 1988	No • Randomization process not well described • Some baseline group differences present	No	Yes	Yes	Yes Intent-to-treat analysis not performed, but exclusions <10% overall and ratio less than 2:1 between arms	FAIR Does not meet all quality indicators, but does not contain any fatal flaws
Fan, Lai, Mok et al., 1993	Yes (?) • Randomization process not well-described • groups appear balanced	Yes	Yes Adequate for comparison	Yes	Yes Intent-to-treat analysis not performed, but exclusions <10% overall and ratio less than 2:1 between arms	GOOD Meets all quality indicators
Folsch, Nitsche, Ludtke et al., 1997	Yes	Yes	Yes	Yes	Yes	GOOD Meets all quality indicators
Lans, Geenen, Johanson et al., 1992	Yes (?) • Randomization by 'card selection', ? adequate • Small numbers make prone to selection bias • Comparability of groups not demonstrated	Yes (?) No dropouts	Yes	No • Pt reported outcomes, no blinding to treatment • No blinded outcome assessment	Yes	FAIR Does not meet all quality indicators, but does not contain any fatal flaws

Table 58. Quality Assessment (cont'd)

Study, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized controlled trials (cont'd)						
Jacob, Geenen, Catalano et al., 2001	Yes (?) • Randomization process not described • Small numbers make prone to selection bias • Comparability of groups not demonstrated	Yes (?) No dropouts	Yes	No • Pt reported outcomes, no blinding to treatment • No blinded outcome assessment	Yes	FAIR Does not meet all quality indicators, but does not contain any fatal flaws
Non-randomized, retrospective comparative studies						
Aiyer, Burdick, Sonnenberg et al., 1999	No • Database study, no randomized treatment assignment • Highly prone to selection bias • Comparability of groups not demonstrated	No	No Cannot control for unequal intensity of treatment	Yes	Yes	POOR Lack of comparability of groups is a fatal flaw
Froeschle, Meyer-Pannwitt, Brueckner et al., 1993	No • No randomized treatment assignment • Highly prone to selection bias • Comparability of groups not demonstrated • Located 76% of treated patients	No	No Cannot control for unequal intensity of treatment	Yes	No Statistical analysis not described or reported	POOR Lack of comparability of groups is a fatal flaw

Table 59. excluded articles

Study/yr.	Study description	Reason for exclusion
Acute pancreatitis		
Rosseland and Solhaug 1984	Retrospective comparative clinical series Compared early ERCP with delayed ERCP (historical controls) in acute biliary pancreatitis	No objective pre and post measurements
Uomo, Galloro, Rabitti et al., 1991	Prospective clinical series 50 patients with acute biliary pancreatitis treated with early ERCP	No comparison group
al Karawi, el Shiekh Mohamed, al Shahri et al. 1993 1062	Retrospective clinical series 35 patients with acute biliary pancreatitis treated with ERCP and EX at one institution	No comparison group
Chronic pancreatitis (not otherwise specified)		
Ell, Rabenstein, Schneider 1998	Retrospective clinical series 118 patients with chronic pancreatitis treated with guidewire versus needle-knife pancreatic sphincterotomy	Only short term complications reported Techniques not randomized, needle knife used if guidewire failed
Kim, Myung, Kim et al., 1998	Clinical trial 60 patients with chronic pancreatitis, treated with dual sphincterotomy vs. pancreatic sphincterotomy only	Only short term complications reported Only outcomes on small (n<25) subgroups reported
Kozarek and Terrance 1994	Retrospective clinical series 56 patients with chronic pancreatitis who were treated with ERCP and pancreatic duct sphincterotomy.	NR study question Primarily evaluated complications of stenting
Treacy and Worthley 1996	Retrospective (?) clinical series 9 patients with chronic pancreatitis treated with stents over a 3yr period at one institution	<25 patients
Guelrud, Mujica, Jaen et al., 1994	Retrospective clinical series 51 children and adolescents with acute recurrent pancreatitis over an 8-year period at one institution. 18 patients treated endoscopically	No objective pre and post measurements <25 patients (therapeutic)
Festen, Severijnen, vd Staak et al., 1991	Case reports of two children with chronic relapsing pancreatitis evaluated and treated with ERCP	<25 patients
Fuji, Amano, Ohmura et al., 1989	Retrospective clinical series 21 patients with chronic pancreatitis from one institution, treated with ERCP and endoscopic sphincterotomy	No objective pre and post measurements <25 patients
Bornman, Marks, Girdwood et al., 1980	Retrospective clinical series 52 patients with calcific pancreatitis who underwent ERCP	NR study question Evaluated the association of obstruction and pain in this population

Table 59. excluded articles (cont'd)

Study/yr.	Study description	Reason for exclusion
Stent treatment in chronic pancreatitis with stricture		
Grimm, Meyer, Nam et al., 1989	Retrospective clinical series 70 patients with obstructive chronic pancreatitis treated with ERCP with or without ESWL	No objective pre and post measurements
Ashby and Lo 1995	Retrospective, clinical series 21 patients with chronic pancreatitis and stricture, treated with ERCP and stent at one institution	<25 patients
Binmoeller, Jue, Seifert et al., 1995	Retrospective, clinical series 93 patients with chronic pancreatitis and stricture, treated with endoscopic stent at one institution over a 9-year period	No objective pre and post measurements
Smits, Badiga, Rauws et al., 1995	Retrospective clinical series. 51 patients with chronic pancreatitis and stricture of pancreatic duct, treated with ERCP over an 11-year period at one institution	No objective pre and post measurements
Cremer, Deviere, Delhaye et al., 1991	Retrospective clinical series. 76 patients with severe chronic pancreatitis and stricture, treated with endoscopic stent at one institution over a 4-year period.	No objective pre and post measurements
Kozarek, Patterson, Ball et al., 1989	Retrospective clinical series. 17 patients with chronic pancreatitis treated endoscopically with either stents or drains	Mixture of stents and drains for different indications
McCarthy, Geenen, and Hogan 1988	Retrospective clinical series. 35 patients with benign pancreatic disease and suspected obstruction treated with endoscopic stent	No objective pre and post measurements Mixed population (CP, pancreas divisum, unexplained pain)
Ponchon, Gagnon, Berger et al., 1995	Retrospective clinical series 23 patients with chronic pancreatitis, pain and MPD stricture treated with ERCP stenting	No objective pre and post measurements <25 patients
Smith and Sherman 1996	Retrospective clinical series 61 patients treated with pancreatic stenting at one institution	NR study question Primarily evaluated complications of stenting
Sherman, Hawes, Savides, et al., 1996	Retrospective clinical series 61 patients with stent treatment who had long term follow-up after stent removal	NR study question Primarily evaluated complications of stenting
Vitale, Reed, Nguyen, et al., 2000	Retrospective clinical series 25 patients with chronic pancreatitis and CBD stricture, treated with ERCP stent	No objective pre and post measurements

Table 59. Excluded articles (cont'd)

Study/yr.	Study description	Reason for exclusion
Endoscopic treatment of pancreatic pseudocysts		
Kolars, Allen, Ansel, et al., 1989	Retrospective clinical series 51 patients with pseudocyst, treated either with surgery alone, ERCP alone, or ERCP followed by surgery	No relevant outcome data No objective pre and post measurements
Ahearne, Baillie, Cotton, et al., 1992	Retrospective clinical series 102 patients with pseudocysts, treated according to algorithm at one institution. Most patients (69/102) received surgical drainage	NR study question Did not evaluate outcomes of ERCP treatment
Endoscopic treatment of pancreatic duct stones		
Smits, Rauws, Tytgat, et al. 1996	Retrospective clinical series. 53 patients with chronic pancreatitis and pancreatic stones treated with ERCP from one institution over a 9-year period	No objective pre and post measurements
Dumonceau, Deviere, Le Moine, et al., 1996	Retrospective clinical series 70 patients with chronic pancreatitis and pancreatic stones, treated with ERCP at one institution over a 15-year period	No objective pre and post measurements
Kozarek, Ball, Patterson, et al., 1992	Retrospective clinical series. 12 patients with chronic pancreatitis and pancreatic duct stones treated with ERCP at one institution	No objective pre and post measurements <25 patients
Sherman, Lehman, Hawes, et al., 1991	Retrospective clinical series. 32 patients with chronic pancreatitis and pancreatic stones treated with ERCP at two institutions	No objective pre and post measurements
Ponsky and Duppler 1987	Case report Description of technique and response to therapy by patient	<25 patients No objective pre and post measurements
ERCP plus lithotripsy for pancreatic stones		
Ohara and Oshino 1996	Retrospective clinical series 32 patients with chronic pancreatitis and pancreatic duct stones, treated with ERCP and lithotripsy at one institution over a 4-year period	No objective pre and post measurements
Schreiber, Gurakuqi, Pristautz, et al., 1996	Retrospective clinical series. 10 patients with pancreatic stones and chronic pancreatitis treated with ERCP and lithotripsy over a 2-year period from a single institution	No objective pre and post measurements <25 patients
Schneider and May 1994	Retrospective clinical series 50 patients with chronic pancreatitis and pancreatic stones treated with ERCP and lithotripsy at one institution	No objective pre and post measurements
Delhaye, Vandermeeren, Baize, et al., 1992	Retrospective clinical series 123 patients referred for chronic pancreatitis who were treated with ERCP and lithotripsy at one institution over a 2-year period	No objective pre and post measurements

Table 59. excluded articles (cont'd)

Study/yr.	Study description	Reason for exclusion
Pancreas divisum		
Satterfield, McCarthy, Geenen, et al., 1988	Retrospective clinical series 82 patients with pancreas divisum seen at 2 institutions over a 4-year period Descriptive analysis of multiple subgroups	Outcomes not reported for all patients Reported outcome data on only 10/33 patients with pancreatitis
Chevillotte, Sahel, Pietri, et al., 1984 (French with English abstract)	Retrospective clinical series Descriptive analysis of 63 cases of pancreas divisum, from a series of 2800 ERCP procedures over a 6-year period at one institution	No objective pre and post measurements
Warshaw, Richter, and Schapiro, 1983	Retrospective clinical series 40 patients with pancreas divisum and recurrent pancreatitis or refractory pain, treated endoscopically over an 8-year period at one institution	No objective pre and post measurements
Keith, Shapero, and Sabil, 1982	Retrospective case series 5 patients with chronic or recurrent acute pancreatitis and pancreas divisum treated with ERCP and sphincterotomy, from 480 patients seen with pancreatitis at one institution over a 5 year period.	No objective pre and post measurements
Other studies		
Guelrud, Morera, Rodriguez, et al., 1999	Retrospective clinical series 128 children with pancreatobiliary disease who underwent ERCP at one institution over a 14-year period	NR study question (evaluated prevalence of sphincter of Oddi dysfunction in children with recurrent pancreatitis) Mixed population of patients with pancreatobiliary pathology
Hammarstrom, Stridbeck, and Ihse, 1997	Retrospective clinical series 28 patients who received ERCP treatment for benign pancreatic disease, from 319 patients who underwent ERCP at one institution for suspected pancreatic disease over a 13-year period	Mixed population of patients with benign pancreatic disease No objective pre and post measurements
He, Zheng, Zhang, et al., 2000	Retrospective clinical series 56 patients with congenital choledochal cysts, 39 evaluated and treated with ERCP	No objective pre and post measurements
Kozarek and Traverso 1996	Review and expert opinion	No primary data
Mori, Nagakawa, Ohta, et al., 1991	Retrospective clinical series 48 patients with anomalous union of pancreatic ducts, identified over an 11-year period at one institution	NR study question Evaluated prevalence of pancreatitis in patients with anomalous union of the ductal system
Malfertheiner and Buchler 1991	Review	No primary data

Table 59. excluded articles (cont'd)

Study/yr.	Study description	Reason for exclusion
Other studies (cont'd)		
Venu, Geenen, Hogan, et al., 1989	Retrospective clinical series 116 patients with idiopathic recurrent pancreatitis referred for ERCP at one institution	NR study question (yield study) Evaluated diagnostic yield of ERCP in this population
Ammann, Akovbiantz, Larglader, et al., 1984	Prospective cohort study 163 patients with chronic pancreatitis at two hospitals over a 19-year period.	NR study question Evaluated natural history of chronic pancreatitis
Himal 1999	Retrospective clinical series 55 patients with mild biliary pancreatitis. Evaluated ERCP preoperatively prior to cholecystectomy	NR study question
Testoni, Caporuscio, Bagnolo, et al., 2000	Prospective (?) clinical series 40 patients with idiopathic recurrent pancreatitis. Evaluated yield of ERCP for etiology and follow-up after treatment. Microlithiasis (n=11), sphincter of Oddi dysfunction (n=14), pancreas divisum (n=3), no etiology (n=12)	<25 patients for any one category

assessment, the third was rated as "Fair" (Neoptolemos, Carr-Locke, London et al., 1988). Among the three randomized controlled trials, there are differences in the patient eligibility criteria, severity of pancreatitis and application of ERCP intervention that are important to interpretation of the results (Table 60, Table 61). With respect to patient population: Neoptolemos, Carr-Locke, London et al. (1988, n=121) is restricted to patients with acute biliary pancreatitis; Fan, Lai, Mok et al. (1993, n=195) includes patients with non-biliary pancreatitis; and Folsch, Nitsche, Ludtke et al. (1997, n=238) excluded patients with signs of obstructive jaundice, and the remaining population largely represented patients with mild pancreatitis. Thus, the likelihood that pancreatitis was associated with ongoing biliary obstruction was highest in the Neoptolemos, Carr-Locke, London et al. (1988) study; lower in the Fan, Lai, Mok et al. (1993) study because patients with nonbiliary causes of pancreatitis were included; and lowest in the Folsch, Nitsche, Ludtke et al. (1997) study, which excluded patients with obvious obstruction.

In all three studies, patients were classified with mild or severe pancreatitis based on commonly used scales. These scales use readily available clinical information to predict prognosis in acute pancreatitis, but are not specifically meant to select patients for ERCP or to identify patients with biliary obstruction. Given the sophistication of contemporary imaging techniques, such classification systems may be of less clinical significance in predicting which patients are likely to benefit from ERCP treatment.

In these studies, ERCP was performed in 20–28 percent of patients in the delayed or selective groups. This represents a substantial minority of patients in the control group that actually underwent ERCP; but is a much lower percentage compared to the early ERCP groups, where almost all patients had the procedure.

Treatment Outcomes. No study reported statistically significant differences in mortality between groups (Table 62). Neoptolemos, Carr-Locke, London et al. (1988) and Fan, Lai, Mok et al. (1993) found numerically greater mortality in the delayed or selective ERCP group, but only for patients with severe pancreatitis. Consistent with these data, in a study population with milder disease, Folsch, Nitsche, Ludtke et al. (1997) found numerically greater mortality in the early ERCP group. This trial was terminated prematurely as the question of interest was whether early ERCP might lead to reduced mortality in the study population.

The lack of benefit for early ERCP in Folsch, Nitsche, Ludtke et al. (1997) is seen in conjunction with the exclusion of patients with ongoing biliary obstruction. This implies that the potential mortality benefit of ERCP is limited to patients with obstruction. Additionally, the overall magnitude of benefit among theses studies appears to be related to the likelihood of biliary obstruction in the population. Neoptolemos, Carr-Locke, London et al. (1988), which reports the greatest benefit, also has the highest likelihood of obstruction in their population, while the study with the least benefit, Folsch, Nitsche, Ludtke et al. (1997), has a population with the lowest likelihood of obstruction. The population in the Fan, Lai, Mok et al. (1993) study had a higher likelihood of obstruction compared to Folsch, Nitsche, Ludtke et al. (1997). Neoptolemos, Carr-Locke, London et al. (1988), reported a degree of benefit intermediate between those studies.

For total complications, Neoptolemos, Carr-Locke, London et al. (1988) reported a statistically significant reduction for the early ERCP group. Fan, Lai, Mok et al. (1993) and Folsch, Nitsche, Ludtke et al. (1997) reported no significant difference in total complication rates. However, Fan,

Lai, Mok et al. (1993) observed half as many total complications with early ERCP (22 of 41 patients vs. 44 of 40) among the subgroup of patients with severe pancreatitis, but did not report statistical significance. In a subgroup analysis of patients with severe pancreatitis and documented common bile duct stone, Fan, Lai, Mok et al. (1993) reported a significantly lower rate of total complications for early ERCP group (3/19 vs. 10/16, p=0.005). In a study population presenting mainly with mild pancreatitis, Folsch, Nitsche, Ludtke et al. (1997) reported a significantly greater respiratory failure (15/126 vs. 5/112, p=0.03) with early ERCP.

In summary, the interpretation of this group of studies is that early ERCP reduces complications in patient populations with acute pancreatitis and biliary obstruction. In studies that report benefit for patients with severe pancreatitis, but not mild pancreatitis, this finding likely represents the correlation of biliary obstruction with more severe disease. In patients with low likelihood of biliary obstruction, a clinical approach that includes delayed or selective ERCP may result in lower complications, and permits many patients to avoid the procedure.

Previous meta-analysis. Sharma and Howden (1999), pooled four randomized controlled trials of early vs. delayed or selective ERCP for acute biliary pancreatitis, three of which are the studies discussed here. The fourth randomized controlled trial, Nowak, Nowakowska-Dulawa, Marek et al. (1995), has been published only in abstract form. This meta-analysis is flawed because it combines studies that have different patient populations and interventions. Also, these studies report subgroup analyses suggesting that aggregate outcomes may be misleading when applied to subsets of patients that are stratified on the severity of pancreatitis or the likelihood of biliary obstruction.

The authors computed summary estimates for total mortality and complications, and reported the relative risk reduction associated with the early ERCP strategy. For overall mortality, the combined relative risk reduction associated with early ERCP was 42.9 percent. For total complications, there was a 34.6 percent relative risk reduction associated with early ERCP. These summary results are driven largely by the results of Neoptolemos, Carr-Locke, London et al. (1988) and Nowak, Nowakowska-Dulawa, Marek et al. (1995), neither of which allowed selective early ERCP in the control group for clinical indications. The authors did not perform sensitivity analyses or stratified analysis of the data.

The authors concluded that all patients with acute biliary pancreatitis should undergo early ERCP. Given the differences in the methodology of these studies and the lack of rigor in the meta-analysis, this conclusion is not supported by a critical analysis of the data.

ERCP vs. Surgery for Acute Pancreatitis

There was a single study that met the inclusion criteria for this comparison (Table 63, Table 64). This study (Aiyer, Burdick, Sonnenberg et al., 1999) was a retrospective comparison of outcomes for patients with biliary pancreatitis that were treated initially either by ERCP or surgery, using the United States Veterans Administration computerized database. Investigators identified all hospitalizations in the VA database that had simultaneous diagnoses of pancreatitis and cholelithiasis. Outcomes for 650 patients treated initially with ERCP were compared with 1,425 patients treated initially with surgery.

This study was assigned a quality rating of "Poor" by quality assessment. The major methodologic limitation of this study is that the two groups being compared are likely to differ substantially on a variety of clinical factors. Limited information contained in the database on severity of illness indicated that the patients in ERCP group were older and had higher baseline Charlsson score as compared to patients initially treated with surgery. Also, a higher percentage of patients in the ERCP group had cholangitis, choledocholithiasis, and pancreatic cysts.

Outcomes for the two groups were generally similar or favorable towards ERCP, despite the fact that the ERCP group appeared to be more severely ill. Mortality was 4 percent for the surgery group and 2 percent for the ERCP group (p=0.08), while the rate of total complications was identical for the two groups at 2 percent.

Conclusions

Early ERCP Vs. Delayed or Selective ERCP for Acute Biliary Pancreatitis

Evidence from three randomized controlled trials suggests that early ERCP reduces complications in patient populations with acute pancreatitis and signs and symptoms suggesting biliary obstruction. In patients with low likelihood of biliary obstruction, delayed or selective ERCP permits many patients to avoid the procedure, and may result in lower complications.

ERCP vs. Surgery for Acute Pancreatitis

A single retrospective study suggests that outcomes from ERCP are at least as good as those from surgery. This study reported comparable outcomes for the two groups despite evidence for a higher severity of illness in ERCP group. However, this is a retrospective database study and confidence in the conclusions is limited by a number of methodologic factors, especially the potential for imbalances among the groups that are compared. Also, given the limited clinical information available, this study cannot ascertain the best strategy to employ given particular patient characteristics and/or clinical presentation.

Review of Evidence: Acute Recurrent Pancreatitis

Four studies, two randomized controlled trials and two single-arm retrospective series, met the inclusion criteria for this category. The main outcomes reported in these studies were pain, episodes of recurrent pancreatitis and/or hospitalization (Table 65).

Acute, Recurrent Pancreatitis Associated with Pancreas Divisum

Three studies, one randomized controlled trial (Lans, Geenen, Johanson et al., 1992) and two retrospective single-arm studies (Lehman, Sherman, Nisi et al., 1993; Kozarek, Ball, Patterson et al., 1995), reporting on a total of 110 patients, evaluated ERCP treatment for acute, recurrent pancreatitis associated with pancreas divisum. Lans, Geenen, Johanson et al. (1992) was a randomized controlled trial in 19 patients with pancreas divisum and recurrent acute pancreatitis. All patients received diagnostic ERCP, and patients who were amenable to stenting were randomized to stent or no stent. Patients were followed for a mean of approximately 30 months for the outcomes of recurrent pancreatitis, emergency room visits/hospitalizations, and clinical improvement. The quality of this study was rated "Fair." Confidence in the results of this study

is limited by its small size, lack of blinding, and lack of comparison with alternatives. Quality ratings were not applied to the two retrospective single studies, which are prone to confounding by the placebo effect, natural history of the disease, and a potentially large number of clinical factors.

The small randomized controlled trial by Lans, Geenen, Johanson et al. (1992, n=19) and the two retrospective single-arm studies (n=91) reported that ERCP treatment with stent or sphincterotomy decreased recurrent episodes of pancreatitis, and reduced pain as measured on visual analog scales. None of these studies met the threshold study selection criteria initially set for this systematic review. Although the body of evidence is sparse and largely uncontrolled, the observation that hospitalizations and emergency room visits were significantly reduced is consistent for both the single randomized controlled trial and the less rigorous single arm studies.

Idiopathic Acute, Recurrent Pancreatitis

A single, small, randomized controlled trial (Jacob, Geenen, Catalano et al., 2001, n=34) in patients with idiopathic acute, recurrent pancreatitis reported that ERCP plus stenting reduces episodes of recurrent acute pancreatitis as compared to diagnostic ERCP alone. However, the percent of patients with persistent pain was no less in the ERCP plus stent group as compared to the diagnostic ERCP group. Thus, this trial provides evidence that ERCP treatment reduces subsequent episodes of pancreatitis in idiopathic recurrent acute pancreatitis, similar to the results seen in patients with pancreas divisum. However, this single small, unblinded trial is insufficient to determine whether ERCP treatment reduces pain in patients who present with idiopathic acute recurrent pancreatitis.

Review of Evidence: Chronic Pancreatitis

The three studies (n=187) included in this review evaluate ERCP drainage of pancreatic pseudocysts (Table 66). There are a number of different endoscopic approaches for drainage of pseudocysts. The available studies generally report aggregate outcomes and are not adequately robust to compare outcomes among different approaches to drainage. Thus, this review will not attempt to differentiate among variations of endoscopic drainage. Only one of these studies is prospective (Barthet, Sahel, Bodiou-Bertei et al., 1995), and none provides robust information on prospective, long-term outcomes from these procedures.

One of the three studies met the threshold study selection criteria initially set for this systematic review (Froeschle, Meyer-Pannwitt, Brueckner et al., 1993). Results of this retrospective comparative study initial suggest that ERCP drainage results in a similar rate of pain relief as compared with surgery, with equivalent or lower mortality. Two additional single arm series that met the relaxed selection criteria suggest that regression of pseudocysts occurs in a majority of cases following ERCP drainage, in the range of 70–86 percent (Libera, Siqueira, Morais et al., 2000; Barthet, Sahel, Bodiou-Bertei et al., 1995). Pain relief after ERCP drainage was reported in the comparative study and in one case series, with approximately half of patients reporting complete pain relief following the procedure. The uncontrolled trial by Libera, Siqueira, Morais et al. (2000) also reported a significant improvement in pain scores following ERCP drainage.

Using a 0–3 pain scale, the mean pain score was reduced from 2.48 pre-treatment to 0.28 post-treatment ($p<0.001$).

Conclusions

For treatment of acute pancreatitis, 3 randomized controlled trials (total n=554) compared early ERCP to delayed or selective ERCP. The available evidence suggests that early ERCP reduces complications in patient populations with acute pancreatitis and signs and symptoms suggesting biliary obstruction. In patients with low likelihood of biliary obstruction, delayed or selective ERCP permits many patients to avoid the procedure, and may result in lower complications. In addition, one retrospective associational study of a Veterans Administration database of patient with acute pancreatitis (n=2,075) suggests that outcomes of ERCP treatment are similar to those of surgery.

For ERCP treatment in patients with acute recurrent or chronic pancreatitis, study selection criteria were relaxed as described above in order to address this question. Although the available evidence is sparse and largely uncontrolled, it suggests that ERCP treatment reduces emergency room visits and hospitalization in patients with pancreas divisum and acute recurrent pancreatitis. Evidence on ERCP drainage of pseudocysts is also sparse and poorly controlled, but suggests that pain relief with ERCP is similar to results of surgery.

Table 60. Comparison of population and intervention in RCTs of ERCP for acute biliary pancreatitis

	Patient population	Early ERCP	Delayed/selective ERCP	Severity Pancreatitis	
				mild	severe
Neoptolemos, Carr-Locke, London et al., 1988	• Patients hospitalized with acute biliary pancreatitis • No other cause for pancreatitis	ERCP ± ES within 72 hours of admission for all patients	No patient received ERCP within first five days. Selective ERCP performed in 23% of control patients after day five for clinical indications (not specified).	56%	44%
Fan, Lai, Mok et al., 1993	• Patients hospitalized with acute pancreatitis (all causes) • No prior work-up for biliary stones • Pancreatitis not induced by ERCP	ERCP ± ES within 24 hours of admission for all patients	Selective ERCP performed in 28% of control patients for rising fever, leukocytosis or tachycardia; increasing jaundice or bilirubin; shock	58%	42%
Folsch, Nitsche, Ludtke et al., 1997	• Patients hospitalized with acute pancreatitis • No signs of obstructive jaundice • No other potential causes of pancreatitis	ERCP ± ES within 72 hours of onset of symptoms in all patients	Selective ERCP performed in 20% of control patients for signs of obstructive jaundice	78%	22%

Table 61. Early ERCP for treatment of acute biliary pancreatitis – study characteristics

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Early ERCP vs. delayed/selective ERCP					
Neoptolemos, Carr-Locke, London et al., 1988	131 pts with suspected acute biliary pancreatitis, drawn from 223 consecutive pts admitted with acute pancreatitis Exclusions: 1) age less than 18yrs, 2) chronic alcoholism or acute alcohol intake, 3) pregnancy, and 4) identifiable secondary cause for pancreatitis.	Single center RCT Patients randomized to immediate ERCP or conventional management. Patients followed until discharged from hospital. All ERCP procedures performed by one "highly skilled" endoscopist.	Immediate ERCP – ERCP +/- ES within 72hrs of hospitalization. Control – Conventional management for first five days. Patients in conventional management group offered ERCP + ES after 5 days if clinically indicated.	Mortality Local complications (pseudocysts, ascites, duodenal obstruction) Systemic complications (respiratory failure, cardiovascular failure, stroke, DIC, renal failure)	No patients in control group got ERCP until at least day 5.
Fan, Lai, Mok et al., 1993	195 pts with acute biliary pancreatitis, selected from 206 consecutive patients with acute pancreatitis Exclusions: 1) prior workup for biliary stones 2) iatrogenic pancreatitis	Single center RCT Patients randomized to immediate ERCP or selective ERCP. Patients followed until discharge from hospital.	Immediate ERCP – ERCP +/- ES within 24hrs of hospitalization. Control – Selective ERCP for: rising fever, leukocytosis, or tachycardia; increasing jaundice or bilirubin; shock. All control patients had elective ERCP after acute attack resolved if selective ERCP not performed.	Mortality Local complications (pseudocysts, abscess, phlegmon, bleeding) Systemic complications (respiratory failure, cardiovascular failure, sepsis, DIC, renal failure, GI bleeding)	ERCP performed selectively in 27/98 (28%) control patients. Study included patients with etiologies for pancreatitis other than biliary stones. 64% of patients in study had documented biliary stones.
Folsch, Nitsche, Ludtke et al., 1997	238 adult patients with suspected acute biliary pancreatitis, selected from 339 consecutive patients Exclusions: 1) Indications for early ERCP (bilirubin >5, temp >39°), 2) age <18yrs, 3) pregnancy, 4) inability to perform ERCP within 72hrs of onset of symptoms.	Multi-center RCT, 22 clinical centers Patients randomized to immediate ERCP or selective ERCP. Patients followed for three months	Immediate ERCP – ERCP +/- ES within 72hrs of onset of symptoms. Control – Conventional management. ERCP performed for persistent biliary colic, temp >39°, or increased bilirubin. After 3 weeks, ERCP could be performed in any patient if indicated.	Mortality Local complications (pseudocysts, ascites, duodenal obstruction) Systemic complications (respiratory failure, cardiovascular failure, stroke, DIC, renal failure)	ERCP performed selectively in 22/112 (20%) of patients. Study terminated early due to inability to shoe a benefit in the early ERCP group.

Table 62. Early ERCP for treatment of acute biliary pancreatitis – outcomes

Study/yr.	Severity	Mortality		P value	Complications								
					Overall		P value	Systemic		P value	Local		P value
		Early[1]	D/S[2]		Early[1]	D/S[2]		Early[1]	D/S[2]		Early[1]	D/S[2]	
Early ERCP vs. delayed/selective ERCP													
Neoptolemos, Carr-Locke, London et al., 1988	Overall (n=121)	1.7% (1/59)	8.1% (5/62)	0.23	17% (10/59)	34% (17/62)	0.03	7% (4/59)	19% (12/62)	0.08	12% (7/59)	24% (15/62)	0.08
	Mild (n=68)	0% (0/34)	0% (0/34)	NS	12% (4/34)	12% (4/34)	NS	2.9% (1/34)	0% (0/34)	NR	12% (4/34)	12% (4/34)	NS
	Severe (n=53)	4% (1/25)	18% (5/28)	NR	24% (6/25)	61% (17/28)	<0.01	12% (3/25)	43% (12/28)	NR	12% (3/25)	39% (11/28)	NR
Fan, Lai, Mok et al., 1993	Overall (n=195)	5.2% (5/97)	9.2% (9/98)	0.40	18% (17/97)	29% (28/98)	NR	10% (10/97)	14% (14/98)	NS	10% (10/97)	12% (12/98)	NS
	Mild (n=114)	0% (0/56)	0% (0/58)	NS	8 total/ 56 pts	6 total/ 58 pts		1 total/ 56 pts	5 total/ 58 pts		7 total/ 56 pts	1 total/ 58 pts	
	Severe (n=81)	12% (5/41)	23% (9/40)	NR	22 total/ 41 pts	44 total 40 pts		16 total/ 41 pts	33 total/ 40 pts		6 total/ 41 pts	11 total/ 40 pts	
Folsch, Nitsche, Ludtke et al., 1997	Overall (n=238)	11% (14/126)	6.3% (7/112)	0.10	46% (58/126)	51% (57/112)	NS	91 total/ 126 pts	89 total/ 112 pts		25% (31/126)	25% (28/112)	
	Mild (n=160)												
	Severe (n=46)												

[1] Early ERCP group
[2] Delayed and/or selective ERCP group

Table 63. ERCP vs. surgery for treatment of acute biliary pancreatitis – study characteristics

Study	Population	Study design	Interventions(s)	Outcomes	Comments
ERCP vs. surgery					
Aiyer, Burdick, Sonnenberg et al., 1999	2075 pts with acute biliary pancreatitis from VA system, 650 treated with endoscopy and 1425 treated with surgery.	Retrospective analysis of VA database, comparing outcomes and complications of endoscopy versus surgery	ERCP – Received ERCP as initial intervention during hospitalization for acute biliary pancreatitis Surgery – Had cholecystectomy and/or other biliary/pancreatic surgery as initial intervention during hospitalization for acute biliary pancreatitis	Mortality Local complications (pseudocysts) Systemic complications (respiratory failure, sepsis, GI bleed, DIC, renal failure, hypocalcemia) Complications from therapy (hemorrhage, laceration/puncture of viscus organ)	

Table 64. ERCP vs. surgery for treatment of acute biliary pancreatitis – outcomes

Study/yr.	Populations/Severity	Mortality	P value	Complications (overall)	P value
ERCP vs. surgery					
Aiyer, Burdick, Sonnenberg et al., 1999	ERCP: (n=650) average SOI by Charlsson score 0.9 Surgery: (n=1425) average SOI by Charlsson score 0.8	2% (15/650) 4% (56/1425)	0.08	2% (14/650) 2% (33/1425)	0.94

*32 patients had undefined severity level

Table 65. ERCP for treatment of acute recurrent pancreatitis

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Acute recurrent pancreatitis associated with pancreas divisum					
Lans, Geenen, Johanson et al., 1992	19 patients with pancreas divisum and recurrent acute pancreatitis at one institution over a 5yr period Exclusions: other potential causes of pancreatitis; prior pancreatic resection or sphincterotomy	Randomized controlled trial ERCP alone vs. ERCP plus stent. F/U every 4 mos. in both groups Mean F/U 28.6 mos. for stent group, 31.5 mos. for controls	Stent placement in dorsal pancreatic duct. Stent replaced every 4 mos. in stent group. Stents removed after one year	1) Number of hospitalizations ER visits Stent (n=10) 0 Control (n=9) 7 p<0.05 2) Number of episodes acute pancreatitis Stent (n=10) 1 Control (n=9) 7 p<0.05 3) Number of pts with subjective improvement on visual analogue scale Stent (n=10) 9 Control (n=9) 1 p<0.05	
Kozarek, Ball, Patterson et al., 1995	39 pts with pancreas divisum and chronic pancreatitis (CP) (n=19), acute relapsing pancreatitis (ARP) (n=15), or chronic abdominal pain (CAP) (n=5)	Retrospective (?) single arm case series	ERCP treatment determined at time of treatment: Stent 13 pts Sphincterotomy 4 pts Stent + Sphinct 22 pts	1) Pain (0-10 scale) Pre / Post / p value* CP 9.4 / 4.8 / <0.001 Pain 8.3 / 7.3 ARP NR / NR * pre vs. post 2) number of episodes pancreatitis/year Pre / Post / p value* CP 2.0 / 1.6 / 0.025 Pain NR / NR ARP 2.1 / 0.3 / 0.016 * pre vs. post	

Table 65. ERCP for treatment of acute recurrent pancreatitis (cont'd)

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Acute recurrent pancreatitis associated with pancreas divisum (cont'd)					
Lehman, Sherman, Nisi et al., 1993	52 previously untreated pts with pancreas divisum and chronic pancreatitis (CP) (n=11), acute recurrent pancreatitis (ARP) (n=17), or disabling pancreatic pain (Pain) (n=24)	Retrospective (?) single arm case series	ERCP plus sphincterotomy of minor papilla	1) Pain (0-10 scale) Pre / Post / p value* CP 9.5 ± 0.3 / 6.6 ± 1.3 / NS Pain 8.4 ± 0.2 / 6.6 ± 0.8 / 0.02 ARP 9.1 ± 0.3 / 2.1 ± 0.8** / <0.001 * pre vs. post ** significantly greater change in symptom score as compared to CP (p=0.007) and pain (p<0.001) 2) number of hospital days/month Pre / Post / p value* CP 1.7 ± 0.3 / 1.5 ± 0.5 / NS Pain 1.4 ± 0.4 / 1.0 ± 0.2 / NS ARP 1.6 ± 0.4 / 0.1 ± 0.1** / <0.001 * pre vs. post ** significantly greater change in hospital days as compared to CP (p<0.05) and pain (p=0.003)	

Table 65. ERCP for treatment of acute recurrent pancreatitis (cont'd)

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Idiopathic acute recurrent pancreatitis					
Jacob, Geenen, Catalano et al., 2001	34 patients with idiopathic acute recurrent pancreatitis randomized to ERCP alone or ERCP plus stenting of pancreatic duct	Prospective, randomized, non-blinded clinical trial	ERCP alone: diagnostic ERCP and pancreatogram at baseline and every 3 mos. for 9 mos. Mean follow-up 35 mos. ERCP plus stent: ERCP plus stenting of pancreatic duct, stent changed every 3 mos. for 9 mos.. Mean follow-up 33 mos.	Recurrent episodes of pancreatitis: P value ERCP alone 53% (8/15) ERCP plus stent 11% (2/19) <0.02 Persistence of pain*: P value ERCP alone 40% (6/15) ERCP plus stent 32% (6/19) NS *Presence of pancreatic type pain of at least moderate intensity (4 or greater on 0-10 scale) post-treatment	

Table 66. ERCP for treatment of chronic pancreatitis

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Endoscopic drainage of pseudocysts					
Libera, Siqueira, Morais et al., 2000	30 pts referred for drainage of pseudocysts. Inclusion: 1) Pseudo-cyst >4cm for at least 6 weeks with persistent abdominal pain, 2) progressive increase in size, 3) complications from pseudocyst	Retrospective (?) single arm case series	ERCP drainage performed in one of four ways: 1) transpapillary 2) cyst-gastrostomy 3) cyst-duodenoscopy 4) combined procedure Drainage performed with or without stent, as clinically indicated Treatments were repeated, or alternate drainage attempted, if clinically indicated.	**1) Abdominal pain (0-3 scale):** Pre: 2.48 ± 0.51; Post: 0.28 ± 0.64; p value: <0.001 Complete pain relief in 17/30 pts (57%) 2) Regression of pseudocyst on CT: 21/30 (70%) pts had regression. 21/25 (84%) pts with successful procedure had regression 3) Complications: 6 complications among 37 procedures (16.2%) 2 stent migration 1 duodenal perforation 1 bleeding 1 pancreatitis 1 pneumoperitoneum	
Barthet, Sahel, Bodiou-Bertei et al., 1995	30 pts with pancreatic pseudocyst amenable to drainage by ERCP. Exclusions: none	Prospective single arm clinical series	Transpapillary ERCP performed in all cases. Serial US and/or CT at 4 mo. intervals. F/U ERCP performed if cyst no longer present on imaging	Early resolution of pseudocyst: 26/30 (87%) Recurrence of pseudocyst: 3/26 (12%) Complications: 4/30 (13%)	7/30 patients needed surgical intervention, 3 for failure of pseudocyst to resolve and 4 for recurrence

Table 66. ERCP for treatment of chronic pancreatitis (cont'd)

Study	Population	Study design	Interventions(s)	Outcomes	Comments
Endoscopic drainage of pseudocysts (cont'd)					
Froeschle, Meyer-Pannwitt, Brueckner et al., 1993	127 pts treated for pancreatic pseudocysts from one hospital. 35% treated surgically, 29% endoscopically, 6% percutaneously	Retrospective comparative analysis of outcomes and complications among the three approaches used	Surgery (n=44) Endoscopy (n=37) Percutaneous (n=7) Combined procedure (n=26) No procedure (n=13) F/U performed a mean of 33 mos. after intervention 30/127 (23.6%) lost to F/U.	1) Mortality Post-op / F/U / p value Surgery 6.8% 13.6% NR Endoscopy 0 2.7% NR Combined 0 15.4% NR 2) Percent of patients free of pain at F/U p value Surgery 50% (16/32) NR Endoscopy 52% (16/31) NR Combined 54% (10/18) NR	

Results and Conclusions, Part IV: Abdominal Pain Of Possible Pancreaticobiliary Origin

This chapter reviews evidence on the following questions:

In patients with abdominal pain of possible pancreaticobiliary origin ,

a. What is the diagnostic performance of ERCP with sphincter of Oddi manometry in identifying a pancreaticobiliary origin of pain in comparison to alternatives (e.g., biliary scintigraphy, EUS, or MRCP)? *(Section 1: Diagnostic Performance of ERCP Manometry in Evaluation of Abdominal Pain of Possible Pancreaticobiliary Origin—Comparison To Alternatives)*

b. What are the outcomes of treatment using ERCP strategies compared to using surgical or medical therapy? *(Section 2: Outcomes of Treatment Using ERCP for Abdominal Pain of Possible Pancreaticobiliary Origin)*

Part IV, Section 1: Diagnostic Performance of ERCP Manometry In Evaluation of Abdominal Pain of Possible Pancreaticobiliary Origin—Comparison With Alternatives

Evidence Base

Three studies comparing biliary scintigraphy with ERCP with or without manometry for the diagnosis of sphincter of Oddi dysfunction met the inclusion criteria for this chapter. There were a total of 136 patients enrolled in these studies, 54 of whom had sphincter of Oddi dysfunction. Quality assessment of these studies is available in Table 67. The study characteristics and diagnostic performance of biliary scintigraphy in these studies are summarized in Table 68.

Review of Evidence

There are notable differences in the study objectives, populations, diagnostic criteria for biliary scintigraphy, and reference standards that limit the ability to synthesize results from these studies. The earliest study (Kloiber, AuCoin, Hershfield et al., 1988) evaluated the ability of biliary scintigraphy to diagnose obstruction of the biliary tree postcholecystectomy. In this study, not all patients with obstruction had sphincter of Oddi dysfunction. Sostre, Kalloo, Spiegler et al. (1992) compared a number of different biliary scintigraphy diagnostic criteria for sphincter of Oddi dysfunction in a consecutive sample of postcholecystectomy patients, with the intent of determining the optimal criterion for diagnosing sphincter of Oddi dysfunction. The most recent study, Peng, Lai, Tsay et al. (1994), attempted to define the performance characteristics of biliary scintigraphy in a group of patients with suspected sphincter of Oddi

Table 67. Quality Assessment

Study Author, Year	**Patient Enrollment**	**Diagnostic performance of ERCP determined without knowledge of other test results**	**Diagnostic Performance of other test(s) determined without knowledge of ERCP results**	**Summary Evaluation**
Peng, Lai, Tsay et al., 1994	Retrospective study Partial description provided of method of enrollment of 60 patients.	No	No	**Fair**
Sostre, Kalloo, Spiegler et al., 1992	Prospective study 26 consecutive patients	Yes	Yes	**Good**
Kloiber, AuCoin, Hershfield et al., 1988	Retrospective study (?) Partial description provided of method of enrollment of 50 consecutive patients	No	No	**Fair**

Table 68. Study Details

Study	Pt population N enrolled	N evaluable	Diagnostic Test criterion	Prev (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Adeq Studies (%)	Comments
ERCP + Manometry Reference Standard										
Peng, Lai, Tsay et al., 1994	34 pts with: • Postcholecystectomy • RUQ symptoms • Normal LFT's • No other pathology on UGI, US, ERCP 26 control pts: • Postcholecystectomy • Asymptomatic • Normal LFT's	26	Quantitative scintigraphy Time activity curve Common bile duct dynamics	62 62	69 69	80 90	85 92	62 64	n.r. n.r.	
Sostre, Kalloo, Spiegler et al., 1992	26 consecutive postcholecystectomy patients, some with biliary pain, some with non-biliary pain and some with no symptoms	26	Quantitative scintigraphy Liver peak Biliary visualization Biliary prominence Bowel visualization CBD emptying CBD-to-Liver ratio Final scintigraphic score	 46 46 46 46 46 46 46	 83 50 100 92 100 100 100	 79 100 79 71 93 86 100	 77 100 80 73 92 86 100	 85 70 100 91 100 100 100	n.r.	This study administered CCK routinely to all patients before scintigraphy. 12/26 pts thought to have SOD
ERCP Reference Standard										
Kloiber, AuCoin, Hershfield et al., 1988	50 consecutive pts with • Postcholecystectomy • RUQ pain	50	Quantitative scintigraphy Time to peak bile duct activity	18	93	64	n.r.	n.r.	n.r.	Scintigraphy was used to assess presence of obstruction in post-choly syndrome. 9/50 pts thought to have SOD

dysfunction and a control group of asymptomatic postcholecystectomy patients. Other differences in the study populations, diagnostic criteria, and reference standards for biliary scintigraphy are summarized in Table 68.

The reported performance characteristics varied among these studies. The sensitivity of biliary scintigraphy for diagnosing sphincter of Oddi dysfunction ranged from 50–100 percent. The specificity ranged from 64–100 percent. The positive predictive value ranged from 73–100 percent and the negative predictive value ranged from 62–100 percent. Confidence intervals were not reported around the point estimates for these values in any of the studies. While it is likely that differences in study methodology and populations are related to the variability in reported outcomes, it cannot be determined which variables are associated with variability in outcomes.

Conclusions

The evidence is not sufficient to permit conclusions on the diagnostic performance of biliary scintigraphy for sphincter of Oddi dysfunction. The body of evidence consists of three studies that included only 54 patients with sphincter of Oddi dysfunction; results of these studies cannot be synthesized due to differences in populations and methodology. There was substantial variability in the reported performance characteristics of biliary scintigraphy.

Part IV, Section 2: Outcomes Of Treatment Using ERCP For Abdominal Pain of Possible Pancreaticobiliary Origin

Introduction

Patients with abdominal pain showing a typical biliary or pancreatic pattern who have undergone diagnostic evaluation excluding a pancreaticobiliary anatomic or structural cause for the pain may have what is termed "sphincter of Oddi dysfunction." This diagnostic category of functional abdominal pain encompasses both sphincter of Oddi stenosis and sphincter of Oddi dyskinesia. In sphincter of Oddi stenosis, there is persistent narrowing in the region of the sphincter of Oddi with abnormal pancreaticobiliary manometry findings of elevated basal pressure and abnormality of phasic contraction patterns. In sphincter of Oddi dyskinesia, there is intermittent functional obstruction in the sphincter of Oddi, and, like sphincter of Oddi stenosis, basal sphincter of Oddi pressures may be elevated at manometry, but in sphincter of Oddi dyskinesia abnormal manometry pressures may be temporarily reversible following administration of a smooth muscle relaxant (Tzovaras and Rowlands, 1998).

Classification systems for biliary type pain have been proposed with one frequently cited system derived by Hogan and Geenen (1998). In this system, patients are classified into Types I, II, and III, depending on the number of features present. Type I biliary patients have all features present including: typical biliary type pain, elevated alanine transaminase (ALT) and aspartate transaminase (AST) on two separate occasions, dilated common bile duct on ultrasound or ERCP, and delayed biliary drainage. Type II biliary patients have biliary type pain and only one or two of the additional features required for Type I. Finally, Type III patients have biliary type pain but none of the accompanying features. The prevalence of sphincter of Oddi dysfunction is generally highest for Type I biliary patients and decreases among Type II and Type III biliary patients. Additional modifications of this classification system have been made reflecting the limited role of delayed biliary drainage as a criterion (personal communication, Elta G.).

Pancreatic type sphincter of Oddi dysfunction has been classified into three types by Sherman, Troiano, Hawes, et al., 1991). In this system, Type I patients demonstrate recurrent pancreatitis and/or typical pancreatic-type pain, elevated amylase and/or lipase, dilated pancreatic duct, and prolonged drainage of pancreatic duct. Type II pancreatic type patients have typical pancreatic-type pain and one or two of the additional features listed for Type I patients. Type III pancreatic type patients have typical pancreatic type pain but none of the accompanying features.

Evidence Base

This systematic review selected studies reporting results of endoscopic treatment with sphincterotomy in patients with abdominal pain of suspected pancreaticobiliary origin (e.g., suspected sphincter of Oddi dysfunction). Studies comparing outcomes of ERCP sphincterotomy with alternative treatment strategies were included.

There were 7 studies that met the selection criteria for this question. Quality ratings are described in Table 69 and results of these studies are detailed in Tables 70 and 71. Two of these studies were prospective randomized, controlled trials (Geenen, Hogan, Dodds et al., 1989; Toouli, Robert-Thomson, Kellow et al., 2000) and met the study selection criteria as originally defined. Because of the paucity of evidence found using the original selection criteria, criteria were relaxed to include single arm studies that reported quantifiable pre- and post-outcome measures, or that compared outcomes among relevant clinical subgroups. Four studies were identified that met these modified selection criteria. One was a prospective single-arm study that evaluated consecutive patients treated with endoscopic sphincterotomy and used quantifiable pre- and post-outcome measures. Three additional articles were retrospective single-arm studies in which outcomes were compared among different clinical subgroups of patients. These studies evaluated the relative success of treatment in relation to specific clinical factors.

Finally, an eighth study, a randomized controlled trial (Jamidar, Sherman, and Hawes, 1992) was only available in abstract form and has not been submitted for publication (personal communication, Sherman S, August 2001). This abstract was not included in the review of evidence.

Review of Evidence: Randomized Controlled Trials

There were 2 double-blind randomized, controlled trials reporting on a total of 126 patients, comparing endoscopic sphincterotomy with a sham procedure (Table 70). Both of the published randomized, controlled trials were rated as "Good" by quality assessment. Strengths of these randomized, controlled trials include double blinding, the use of a sham procedure in the control group, and independent blinded assessment of outcomes. For both studies, the primary outcome was improvement in abdominal pain. Geenen, Hogan, Dodds et al. (1989) compared outcomes between groups at 1 year and Toouli, Robert-Thomson, Kellow et al. (2000) compared outcomes at 2 years. Geenen, Hogan, Dodds, et al. (1989) also reports the number of patients in each group who have persistent objective abnormalities (increased liver enzymes, dilatation of common bile duct, delayed contrast drainage) following treatment.

In the Geenen, Hogan, Dodds, et al. (1989) study, there was a significantly greater improvement in pain scores for the overall endoscopic sphincterotomy group as compared to control (65 percent vs. 30 percent with good/fair improvement, $p<0.01$). In Toouli, Robert-Thomson, Kellow et al. (2000), more patients in the endoscopic sphincterotomy group had improvement in pain scores than in the sham endoscopic sphincterotomy group (62 percent vs. 43 percent), however, statistical significance was not reported for the overall group comparison.

Both studies evaluated subgroups of patients with and without an elevated sphincter of Oddi pressure, defined as greater than 40mmHg. In patients with an elevated pressure, both studies report a statistically significant benefit for the endoscopic sphincterotomy group. Geenen, Hogan, Dodds, et al. (1989) reported that 91 percent (10/11) patients in the endoscopic sphincterotomy group had good or fair improvement in pain scores, compared with 25 percent (3/12) in the sham group. Similarly, Toouli, Robert-Thomson, Kellow et al. (2000) reported that 85 percent of patients in the endoscopic sphincterotomy group with elevated pressure had

Table 69. Quality Assessment in studies comparing endoscopic treatment in patients with abdominal pain of suspected pancreaticobiliary origin

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Geenen, Hogan, Dodds, et al., 1989	RCT (n=47) Unknown comparability - Randomization by sealed opaque envelopes - patient characteristics not reported	All subjects included in one-year outcome analysis Four-year follow-up only in 40 of 47. All 7 had normal SO pressure (5 ES; 2 sham). Four lost to f/u and 3 dropped out.	Adequate for comparison.	Double-blinded assessment for 1-year outcomes. Outcome measurement instruments for pain not well described.	Method of first-year outcomes analysis not stated but equivalent to intention-to-treat because all subjects enrolled were included in analysis. Four-year analysis equivalent to treatment received because sham cross-overs were analyzed with ES group.	Good
Toouli, Robert-Thomson, Kellow et al., 2000	RCT (n=81) Comparability - randomized by draw of cards - patient characteristics not reported	One lost to follow-up and 1 dropout due to pancreatitis x 2.	Adequate for comparison.	Double-blinded assessment for two-year outcomes. Outcome measurement instruments for pain not well described.	Does not clearly state method of analysis	Good

Table 70. Randomized Controlled Trials

Study	N	Study Group	Improved Pain Scores	P	Mean Symptom Score	P	Objective Abnormalities[1]	P	Complications	P
Geenen, Hogan, Dodds, et al., 1989[2] Group II Biliary patients			One-Year:				Baseline 1-year			
		Overall:	Good/fair improvement						1 Hemorrhage	
	23	ES	15/23 (65%)	<0.01			37 6	n.r.	1 Perforation	
	24	Sham	7/17 (30%)				49 30		2 Pancreatitis	
		SOM >40 mmHg[3]			Baseline 1-year					
			10/11 (91%)		10 1.8		21 1			
		ES	3/12 (25%)	<0.005	10 6.7	n.r.	30 22	n.r.		
	11	Sham								
	12									
		SOM <40 mmHg[3]								
			5/12 (42%)		10 5.7		16 5			
	12	ES	4/12 (33%)	n.r.	10 6.3	n.r.	19 8	n.r.		
	12	Sham								
			Four-Year:							
		Overall:	Good/fair improvement							
	30	ES[3]	21/30 (70%)	n.r.						
	10	Sham	4/10 (40%)							
		SOM >40 mmHg								
	18		17/18 (94%)							
	5	ES	2/5 (40%)	<0.005						
		Sham								

[1] Summary score of presence of abnormal liver function tests, enlarged common bile duct (>12 mm), delayed drainage of contrast/bile (>45 minutes).
[2] Common bile duct dilatation (≥12mm), abnormal liver function tests, or delayed drainage of contrast/bile (>45 minutes) were not statistically significant predictors of treatment response after ES; however, sample size was small limiting statistical power to detect a difference.
[3] At 1-year, 17 sham subjects were considered treatment failures and were offered cross-over treatment with ES. 7 of 9 sham subjects w/ SO pressure > 40 mm Hg crossed over to ES. After 3 years follow-up, 7 of 7 (100%) were virtually symptom free. Five of 8 sham subjects w/ SO pressure <40 mmHG crossed over to ES. After 3 years follow-up, 2 of 5 (40%) showed Good or Fair improvement in pain scores.

Table 70. Randomized Controlled Trials (cont'd)

Study	N	Study Group	Improved Pain Scores	P	Mean Symptom Score	P	Objective Abnormalities[4]	P	Complications	P
Toouli, Robert-Thomson, Kellow et al., 2000(n=79)	13 13	SOM >40mmHg ES Sham	2-year 11 (85%) 5 (38%)	0.041					7 Mild pancreatitis 1 Perforation	
	11 10	SO Dyskinesia ES Sham	4 (36%) 5 (50%)	0.67						
	13 19	Normal SOM ES Sham	8 (62%) 8 (42%)	0.473						

[4] Summary score of presence of abnormal liver function tests, enlarged common bile duct (>12 mm), delayed drainage of contrast/bile (>45 minutes).

Table 71. Single-arm studies of results of endoscopic sphincterotomy for abdominal pain of suspected pancreaticobiliary origin

Study	N1	N2	Study Group	Improved Pain Scores	P	Objective Abnormalities[5]	P	Complications	P
Brand, Wiese, Thonke, et al., 2001		29	29 consecutive patients with: abd pain of suspected pancreatobiliary origin. Elevated liver enzymes No other pathology on diagnostic ERCP	Pre-treatment: median pain score 8 (0-10) Post-treatment: 26/28 (93%) pts pain-free at 12wks (1 pt lost to f/u)	n.r.	Normalization of liver enzymes post-treatment: 22/29 (76%)		procedure induced pancreatitis in 1/29 pts (3%)	
Wehrmann, Wiemer, Lembcke, et al., 1996	108	33	33 of 108 consecutive pts w/ unexplained abdominal pain referred for workup 35 type II SOD - 20 got ES 29 type III SOD - 13 got ES ES performed only in those with SO pressure > 40mmHg	Mean pain score (0-10) Pre-treatment Type II: 7.2+/-1.4 Type III: 6.8+/-1.3 Post-treatment 4-6 weeks Type II: 2.3+/-2.6 Type III: 3.7+/-2.6 Post-treatment Median f/u 2.5 y Type II: 2.5+/-2.8 Type III: 5.1+/-2.0 Type II SOD 12/20 (60%) improved Type III SOD 1/13 (8%) improved	n.s. <0.01 <0.01	Bile duct dilatation (>9mm) Type II SOD Pre ES = 5 pts Post ES = 2 pts Type III SOD No significant changes	n.s.	Pancreatitis 15% No perforation	

[5] Summary score of presence of abnormal liver function tests, enlarged common bile duct (>12 mm), delayed drainage of contrast/bile (>45 minutes).

Table 71. Single-arm studies of results of endoscopic sphincterotomy for abdominal pain of suspected pancreaticobiliary origin (cont'd)

Study	N1	N2	Study Group	Improved Pain Scores	P	Objective Abnormalities[6]	P	Complications	P
Botoman, Kozarek, Novell, et al., 1994[7]		 19 16	SO Pressure >40 mm Hg Type II Type III	Mean f/u 3.1 y 13/19 (68%) 9/16 (56%)	 n.s.				
Choudhry, Ruffolo, Jamidar, et al., 1993		35	SO Pressure >40mmHg	**1 Month** 43% pain-free 34% good 0% fair 23% no response **During follow-up** 56% of responders stayed well 44% relapsed					
		  1 18 16	SO Pressure >40mmHg Type I Type II Type III	 0% 38% 56%	 >0.05				

[6] Summary score of presence of abnormal liver function tests, enlarged common bile duct (>12 mm), delayed drainage of contrast/bile (>45 minutes).
[7] Common bile duct dilatation (≥12mm) and presence of cholecystectomy were not statistically significant predictors of treatment response after ES; however, sample size was small limiting statistical power to detect a difference.

Table 71. Single-arm studies of results of endoscopic sphincterotomy for abdominal pain of suspected pancreaticobiliary origin (cont'd)

Study	N1	N2	Study Group	Improved Pain Scores	P	Objective Abnormalities[8]	P	Complications	P
Thatcher, Sivak, Tedesco, et al., 1987[9]	34 17	31 15	Group 1[10] Group 2	Pain-free at 3-months n=N2 27/31 (87%) 10/15 (67%)	n.r.			N=N1 4 perforations 2 pancreatitis 2 hemorrhage	
			Group 1 Group 2	Pain free at 12-months 25/31 (81%) 7/15 (47%)	n.r.				
			Group 1 Group 2	Pain free at Last evaluation Mean f/u=12.5 m 24/31 (77%) Mean f/u=20.3 m 7/15 (47%)	0.05				

[8] Summary score of presence of abnormal liver function tests, enlarged common bile duct (>12 mm), delayed drainage of contrast/bile (>45 minutes).
[9] Stastistically significant associations were noted between satisfactory response to ES and dilated CBD (p=0.02), delayed drainage of contrast (p=0.04), and combination of both of these (p=0.01). No significant association was seen for abnormal manometry or abnormal biochemical parameters.
[10] Group 1 (roughly similar to Type II) had "a dilated bile duct and a clinical history compatible with sphincter dysfunction. These patients had evidence of bile duct obstruction which was defined as either a dilated common bile duct (CBD) at ERCP or CT scan (greater than 12 mm in diameter) and/or delayed drainage of contrast material (greater than 45 min in the absence of a gallbladder)." Group 2 (roughly similar to Type III) "did not have CBD dilation or delayed contrast drainage at ERCP. The sphincter of Oddi dysfunction was based on a typical history combined with abnormal sphincter of Oddi manometry."

improvement in pain, as compared with 38 percent in the sham group ($p<0.04$). In patients without an elevated sphincter of Oddi pressure, both studies reported that the improvement in pain scores was not statistically significant for the endoscopic sphincterotomy group as compared to the sham group.

Geenen, Hogan, Dodds et al. (1989) reported the number of patients with objective abnormalities post treatment. At 1 year, objective abnormalities were found in 16 percent of patients in the endoscopic sphincterotomy group and 61 percent of patients in the sham group. Statistical tests were not reported for this comparison. This study also allowed crossover from sham to endoscopic sphincterotomy after one year and continued to follow patients for up to four years. After four years, the improvement in pain scores was maintained for the endoscopic sphincterotomy group. The patients who crossed over from sham to endoscopic sphincterotomy had similar outcomes as the initial endoscopic sphincterotomy group.

Review of Evidence: Nonrandomized Controlled Trials

Five nonrandomized studies reported outcomes of endoscopic sphincterotomy in patients with abdominal pain of suspected pancreaticobiliary origin (Table 71). Brand, Wiese, Thonke, et al. (2001) was a prospective single-arm study that reported quantifiable pre and post values for pain. This study treated 29 consecutive patients with biliary-type pain, increased liver enzymes, and no evidence of other pancreatobiliary pathology with ERCP and endoscopic sphincterotomy. At 12 weeks post-treatment, 26 of the remaining 28 patients available for follow-up were pain-free, and all 26 patients remained pain-free after a median follow-up of 19 months. Wehrmann, Wiemer, Lembcke, et al. (1996) prospectively compared the results after endoscopic sphincterotomy in 20 patients with Type II SOD and 13 patients with Type III SOD. After a median of 2.5 years follow-up, 60 percent of the Type II SOD patients and only 8 percent of the Type III SOD patients maintained symptomatic relief.

The 3 retrospective single-arm studies compare outcomes among subgroups of patients who underwent ERCP and endoscopic sphincterotomy (Botoman, Kozarek, Novell, et al., 1994; Choudhry, Ruffolo, Jamidar, et al., 1993; Thatcher, Sivak, Tedesco, et al., 1987). In particular, these studies explore the relationship between improvement in pain following endoscopic sphincterotomy, baseline sphincter of Oddi pressure, and/or the presence of a dilated common bile duct. Because of the retrospective, uncontrolled nature of these studies, they do not provide strong data on the absolute improvement seen following treatment with endoscopic sphincterotomy. However, comparison of outcomes among clinical subgroups in these studies may provide useful information regarding the relative success of this treatment in different patient groups.

Among all patients treated with endoscopic sphincterotomy, these studies report good/fair improvement in over 60 percent. The presence of baseline sphincter of Oddi pressure greater than 40 mm Hg, a dilated common bile duct and/or delayed common bile duct emptying appear to be associated with slightly higher success rates after endoscopic sphincterotomy. However, confidence in this conclusion is limited by the small numbers of patients in the subgroup analyses, and the lack of tests of statistical significance in some cases.

Conclusions

The randomized controlled trials by Geenen, Hogan, Dodds et al. (1989) and Toouli, Robert-Thomson, Kellow et al. (2000) provide strong and consistent evidence that endoscopic sphincterotomy provides effective relief of pain in patients with pancreaticobiliary pain, sphincter of Oddi dysfunction, and elevated basal sphincter of Oddi pressure on manometry (greater than 40 mm Hg). The results of the nonrandomized studies corroborate these data and suggest that patients with a dilated common bile duct and/or delayed contrast emptying may also benefit from endoscopic sphincterotomy.

There is insufficient evidence to determine whether endoscopic sphincterotomy improves outcomes in patients with normal manometry findings. For this group, the small studies included in this review do not report significant improvements in pain for the endoscopic sphincterotomy group.

ERCP Evidence Review Results and Conclusions, Part V: Patient, Procedure or Operator Determinants of ERCP Complications

This chapter reviews evidence on the following questions:

What patient, procedure, or provider factors are determinants of adverse events of ERCP?

(Section 1: Multivariable Analyses)

(Section 2: Randomized, Controlled Comparison Trials)

Part V, Section 1: Multivariable Analyses

Body of Evidence

Thirteen studies reported on multivariable logistic regression analyses of factors associated with complications of ERCP (Table 72; see also "Evidence Tables" chapter). The four largest studies each included more than 1,800 patients, and the total number of complications observed in these studies ranged from 98 to 229 (Loperfido, Angelini, Benedetti, et al., 1998; Freeman, DiSario, Nelson, et al., 2001; Freeman, Nelson, Sherman, et al., 1996; Masci, Toti, Mariani, et al., 2001). The remaining 9 studies ranged from 100 to 535 patients, and the number of complications observed ranged from 10–34. Seven studies reported on therapeutic ERCP, 5 studies combined therapeutic and diagnostic ERCP, and one study reported on diagnostic ERCP.

Total complications were analyzed in seven studies. The specific complications most commonly analyzed separately were pancreatitis (7 studies) and hemorrhage (4 studies). The number of cases of pancreatitis observed ranged from 17 to 131; and cases of hemorrhage ranged from 10 to 48. Other complications analyzed separately in these studies include cholangitis, septicemia, and retroperitoneal perforation, with number of cases observed ranging from 10 to 34.

This systematic review addresses the relationship of patient, procedure, and operator factors to complications. The 13 included studies assessed numerous factors suspected to be related to the likelihood of complications. The various measures used in the literature were classified into categories. There are 12 categories for patient factors, 13 for procedure factors; and 4 categories for operator factors. Independent variables reported to be statistically significant risk factors for complications are listed for each study along with an estimate of the magnitude of the effect when available (i.e., odds ratio and confidence interval). Independent variables that were considered in the study but not found to be significantly associated with complications are denoted by an "X" under the appropriate category for that factor.

Table 72. Overview Table

Study	N Pts	Pop	Patient Factors	Procedure Factors	Operator Factors	Outcomes Analyzed
Fair Quality						
Masci, Toti, Mariani, et al., 2001	2444	M	X	X		Total complications (121) Pancreatitis (44) Hemorrhage (30)
Freeman, DiSario, Nelson, et al., 2001	1963	M	X	X	X	Pancreatitis (131)
Freeman, Nelson, Sherman, et al., 1996	2347	T (ES)	X	X	X	Total complications (229) Pancreatitis (127) Hemorrhage (48)
Fair Minus Quality						
Rabenstein, Schneider, Bulling, et al., 2000	438	T (ES)	X	X	X	Total complications (33) Pancreatitis (19)
Loperfido, Angelini, Benedetti, et al., 1998	1827	T[1]	X	X	X	Total complications (98) Pancreatitis (29) Hemorrhage (21) Cholangitis (21) Retroperitoneal perforation (12)
Mehta, Pavone, Barkun, et al., 1998	535	M	X	X		Pancreatitis (34)
Neoptolemos, Shaw, and Carr-Locke, 1989	190	T (ES)	X			Total complications (32)
Motte, Deviere, Dumonceau, et al., 1991	105	T (ST)	X	X		Septicemia (34)
Tzovaras, Shukla, Kow, et al., 2000	372	M	X	X		Total complications (21)
Lai, Lo, Choi, et al., 1989	323	D	X			Acute cholangitis (21)
Boender, Nix, de Ridder, et al., 1994	242	T (ES)	X	X		Total complications (34)
Nelson and Freeman, 1994	189	T (ES)	X	X		Hemorrhage (10)
Maldonado, Brady, Mamel, et al., 1999	100	M[2]	X	X		Pancreatitis (17)

[1] Loperfido included a broad population of both diagnostic and therapeutic ERCP. However, multivariate analysis of risk factors was reported only for therapeutic subpopulation.
[2] Maldonado was restricted to a specific population with suspected sphincter of Oddi dysfunction who were undergoing sphincter of Oddi manometry

Study Quality

The number of events observed is the primary determinant of the power of a study to detect a significant association between a factor and an outcome of interest. When multivariable analysis is performed, the number of events also constrains the number of potential relationships that can be appropriately tested. A commonly accepted benchmark is a minimum of 10 outcome events per independent variable tested. A larger number of variables relative to events can lead to unstable results, spurious findings of significance, and unreliable estimates of the magnitude of the association. Extremely wide confidence intervals are a hallmark of such "overfitted" models. Another problem is that when multiple variables are incorporated in a model, some may be highly correlated. As a result, some independently significant factors can be obscured. Concato, Feinstein, and Holford (1993) offer an overview of the methodologic deficiencies that are common in multivariable analyses published in the medical literature.

Overall, the multivariable analyses included in this systematic review demonstrated overfitting, i.e., testing an excessive number of factors relative to the number of complications observed. Consequently, this literature is exploratory in nature. Candidate variables included in the analyses are often likely to be closely related to each other (potentially leading to collinearity) resulting in potentially spurious results from multivariable analysis including all variables. Instances where multiple factors identified to be highly associated with complications on univariate analysis disappear entirely from the multivariable models raises concern over the stability of the findings. Reported magnitudes of association are not reliable, significant independent variables may have been overlooked, and some significant associations may be misleading. Moreover, the existing studies do not use common, standardized definitions for the complications and factors of interest. Thus, caution should be used in drawing inferences for clinical practice from these studies.

This body of literature was overall rated as "Fair" (Table 73). The associations found in these analyses are hypothesis generating, but not predictive. The three studies with notably larger numbers of cases of complications (121–229 vs. 10–98) were designated as "Fair" quality for purposes of this review (Freeman, DiSario, Nelson, et al., 2001; Freeman, Nelson, Sherman, et al., 1996; Masci, Toti, Mariani, et al., 2001) while the remaining 10 studies were rated "Fair Minus." The results of the three "Fair" studies are slightly more robust, despite some degree of overfitting. The study by Loperfido, Angelini, Benedetti, et al. (1998) had 98 cases, but was classified as "Fair Minus" because confidence intervals were not reported and problems with missing data were noted.

This review focuses on factors that were found to be significant either in the more robust studies or in several studies. Also, factors are noted that were found to be not significant in all analyses. Rarely was a factor found to be significant in all studies in which it was analyzed; which is not surprising given the characteristics of the available studies. Extremely wide confidence intervals also are noted, which may suggest a spurious association.

Table 73. Quality Assessment

Study	N	No. candidate variables	Total complications	Pancreatitis	Hemorrhage	Cholangitis	Retroperitoneal perforation	Septicemia	Ratio of group size/# variables	Degree of Overfitting	Statistical reporting	Internal validity	Overall Quality Rating
Masci, Toti, Mariani, et al., 2001	2444	16	121	44	30	--	--	--	7.6 – 1.9	Mild to Severe	S	No	Fair
Freeman, DiSario, Nelson, et al., 2001	1963	32	--	131	--	--	--	--	4.1	Moderate	S	No	Fair
Freeman, Nelson, Sherman, et al., 1996	2347	22	229	127	48	--	--	--	10.4 - 2.2	Satisfactory to Severe	S	No	Fair
Rabenstein, Schneider, Bulling, et al., 2000	438	26	33	19	--	--	--	--	1.3 - 0.7	Severe	S	No	Fair Minus
Loperfido, Angelini, Benedetti, et al., 1998	1827	13	98	29	21	21	12	--	7.5 - 0.9	Mild to Severe	U	No	Fair Minus
Mehta, Pavone, Barkun, et al., 1998	535	9	--	34	--	--	--	--	3.7	Severe	U	No	Fair Minus
Neoptolemos, Shaw, and Carr-Locke, 1989	190	19	32	--	--	--	--	--	1.7	Severe	U	No	Fair Minus
Motte, Deviere, Dumonceau, et al., 1991	105	13	--	--	--	--	--	34	2.6	Severe	U	No	Fair Minus
Tzovaras, Shukla, Kow, et al., 2000	372	16	21	--	--	--	--	--	1.3	Severe	S	No	Fair Minus
Lai, Lo, Choi, et al., 1989	323	9	--	--	--	21	--	--	2.3	Severe	S	No	Fair Minus

Table 73. Quality Assessment (cont'd)

Study	N	No. candidate variables	Total complications	Pancreatitis	Hemorrhage	Cholangitis	Retroperitoneal perforation	Septicemia	Ratio of group size/# variables	Degree of Overfitting	Statistical reporting	Internal validity	Overall Quality Rating
Boender, Nix, de Ridder, et al., 1994	242	9	34	--	--	--	--	--	3.7	Severe	S	No	Fair Minus
Nelson and Freeman, 1994	189	7	--	--	10	--	--	--	0.14	Severe	S	No	Fair Minus
Maldonado, Brady, Mamel, et al., 1999	100	9	--	17	--	--	--	--	1.9	Severe	U	No	Fair Minus

Explanation of categorization:
Degree of Overfitting assessed using the ratio of number of endpoints over number of candidate variables: Satisfactory, ratio $\geq$ 10; Mild, ratio – 7 to 10; Moderate, ratio 4-7; Severe, ratio <4.
Statistical reporting: S=satisfactory, reported both magnitude of effect estimates as well as associated confidence intervals or p-value for statistically significant findings; U = unsatisfactory, did not report both magnitude of effect estimate and statistical significance information for statistically significant findings.
Internal validity: Yes = the study used procedures (e.g., test-validation split samples or bootstrapping) to guard against overfitting the model and spurious results; No = the study did not utilize such procedures

Quality Rating:
Good = use of procedures to guard against overfitting the model and spurious results, degree of overfitting not severe for at least one analysis, and satisfactory statistical reporting
Fair = degree of overfitting not severe for at least one analysis, satisfactory statistical reporting, but no use of procedures to guard against overfitting the model and spurious results.
Fair Minus = Severe degree of overfitting

Review of Evidence: Patient Factors

All 13 studies reported on patient factors associated with complications. These various factors were classified into 12 categories: age, gender, common bile duct size/diameter, cholangitis, anatomic variation, coagulopathy, laboratory values, comorbidities, indication for ERCP procedure, previous gastrectomy, history of jaundice, and history of allergy to contrast media.

Total Complications

Seven studies reported on total complications **(**Table 74**)**. Two factors were found to be significant in a study rated as "Fair" and in one additional study. These were age equal to or less than 60 years (Masci, Toti, Mariani, et al., 2001; Rabenstein, Schneider, Bulling, et al., 2000) and suspected sphincter of Oddi dysfunction (Freeman, Nelson, Sherman, et al., 1996; Tzovaras, Shukla, Kow, et al., 2000).

Jaundice of malignancy was significant in the study by Tzovaras, Shukla, Kow, et al. (2000) and elevated serum bilirubin in Neoptolemos, Shaw, and Carr-Locke (1989). Factors found to be significant in a single study rated as "Fair Minus" were: pancreas divisum, coagulopathy, pancreatic obstruction (Rabenstein, Schneider, Bulling, et al., 2000), and juxtapapillary diverticulum (Boender, Nix, de Ridder, et al., 1994). However, confidence intervals were extremely wide for pancreas divisum (1.56–36.6) and coagulopathy (1.95–48.1).

The following factors were analyzed, but were not found to be significant for total complications in any study: gender (6 studies); common bile duct size/diameter (4 studies); cholangitis (2 studies); previous gastrectomy (3 studies);

Pancreatitis

Seven studies reported on patient factors associated with pancreatitis (Table 75). Younger age was significant in four studies, two rated as "Fair" quality. Each of the four studies used a different age cut-off: 70 years in Loperfido, Angelini, Benedetti, et al. (1998); 60 years in Masci, Toti, Mariani, et al. (2001); 59 years in Mehta, Pavone, Barkun, et al., (1998); and 30 years vs. 70 years in Freeman, Nelson, Sherman, et al. (1996). Suspected sphincter of Oddi dysfunction was significant in two studies, both rated "Fair" (Freeman, Nelson, Sherman, et al., 1996; Freeman, DiSario, Nelson, et al., 2001). Note that the two studies by Freeman and co-workers included different patient populations.

Factors found to be significant in a single study rated "Fair" (Freeman, DiSario, Nelson, et al., 2001) were: normal bilirubin, female gender, absence of chronic pancreatitis, and history of post-ERCP pancreatitis.

Factors found to be significant in a single study rated as "Fair Minus" were: absence of a common bile duct stone at ERCP (Mehta, Pavone, Barkun, et al., 1998); and pancreas divisum, but with an extremely wide (1.91-34.79) confidence interval (Rabenstein, Schneider, Bulling, et

Table 74. Relationship between Patient Factors and Total Complications[3]

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[4]	Coagulopathy[5]	Laboratory values	Other[6] Comorbidities	Indication for ERCP proc[7]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 121	Age ≤60 years OR=1.53 (1.06-2.2)	X	X		X Stone size Papilla features GB stones				X			
Freeman, Nelson, Sherman, et al., 1996	2347 229	X	X	X	X	X	X		Cirrhosis OR=2.93 (1.48-5.90)	Susp. SOD OR=2.9 (1.70-4.94) All pts had ES	X		
Fair Minus Quality													
Rabenstein, Schneider, Bulling, et al., 2000	438 33	Age ≤60 years OR=2.9 (1.33-6.21)	X			Pancreas divisium OR=7.6 (1.56-36.6)	Coagulopathy OR=9.7 (1.95-48.10)		X	Pancreatic obstruction OR=0.07 (0.01-0.59) All pts had ES	X		

[3] Independent variables reported to be statistically significant risk factors for complications are listed for each study along with an estimate of the magnitude of the effect when available (i.e., odds ratio and confidence interval). Independent variables that were considered in the study but not found to be significantly associated with complications are denoted by an "X" under the appropriate category for that factor

[4] Summary of pancreas divisum, juxtapapillary diverticulum, acinarization

[5] Summary of related factors – anticoagulation, coagulopathy, PT time, ASA/NSAID use, bleeding

[6] "Comorbidities" includes reports of cirrhosis diabetes, anemia, hemodialysis etc.

[7] Summary of related factors - Pancreatitis or Obstruction, sphincter of Oddi dysfunction, indication of than bile duct stone

Table 74. Relationship between Patient Factors and Total Complications (cont'd)

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[8]	Coagulopathy[9]	Laboratory values	Other[10] Comorbidities	Indication for ERCP proc[11]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 98	X	X	X		X					X	X	
Neoptolemos, Shaw, and Carr-Locke, 1989	190 32	X	X		X		X	elevated bilirubin elevated serum albumin	X	X All pts had ES			
Tzovaras, Shukla, Kow, et al., 2000	372 21	X	X							Suspected SOD OR=8.57 (2.59-28.43); Malignant jaundice OR=4.76 (1.46-15.58)			

[8] Summary of pancreas divisum, juxtapapillary diverticulum, acinarization
[9] Summary of related factors – anticoagulation, coagulopathy, PT time, ASA/NSAID use, bleeding
[10] "Comorbidities" includes reports of cirrhosis diabetes, anemia, hemodialysis etc.
[11] Summary of related factors - Pancreatitis or Obstruction, sphincter of Oddi dysfunction, indication of than bile duct stone

Table 74. Relationship between Patient Factors and Total Complications (cont'd)

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[12]	Coagulopathy[13]	Laboratory values	Other[14] Comorbidities	Indication for ERCP proc[15]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Boender, Nix, de Ridder, et al., 1994	242 34	X		X		JPD Outside OR=3.1 (p=.072) Lower rim OR=4.3 (p=.015) Inside OR=9.4 (p=.002) Presence of GB NS				All pts had ES			

[12] Summary of pancreas divisum, juxtapapillary diverticulum, acinarization
[13] Summary of related factors – anticoagulation, coagulopathy, PT time, ASA/NSAID use, bleeding
[14] "Comorbidities" includes reports of cirrhosis diabetes, anemia, hemodialysis etc.
[15] Summary of related factors - Pancreatitis or Obstruction, sphincter of Oddi dysfunction, indication of than bile duct stone

Table 75. Relationship between Patient Factors and Pancreatitis

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 44	Age ≤60y OR=2.11 (1.16-3.8)	X	X		X				X			
Freeman, DiSario, Nelson, et al., 2001	1963 131	X	Female OR=2.51 (1.49-4.24)	X		X		Normal bilirubin OR=1.89 (1.22-2.93)	Absence of CP OR=1.87 (1.00-3.48) Hx post-ERCP pancreatitis OR=5.35 (2.97-9.66)	Susp. SOD OR=2.6 (1.59-4.26)			
Freeman, Nelson, Sherman, et al., 1996	2347 127	Age 30 vs. Age 70y OR=2.14 (1.41-3.25)	X	X	X	X	X		X	Susp. SOD OR=5.01 (2.73-9.22)	X		
Fair Minus Quality													
Rabenstein, Schneider, Bulling, et al., 2000	438 19	X	X			Pancreas divisium OR=8.2 (1.91-34.79)	X		X	X	X		

Table 75. Relationship between Patient Factors and Pancreatitis (cont'd)

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 29	Age <70 OR=1.11 n.r.	X	Nondilated duct OR=2.85 n.r.		X						X	
Mehta, Pavone, Barkun, et al., 1998	535 34	Age <59 years (p=0.04)	X	X		Absence of a CBD stone at ERCP (p=0.004)		X	X History of pancrea-titis	X Pre-lap choly			
Maldonado, Brady, Mamel, et al., 1999	100 17	X	X							X			

al., 2000). Loperfido, Angelini, Benedetti, et al. (1998) found non-dilated duct to be significant, but did not report the confidence interval.

Previous gastrectomy was analyzed in two studies, but was not significant.

Hemorrhage

Four studies reported on patient factors associated with hemorrhage (Table 76). Coagulopathy was significant in a study rated as "Fair" (Freeman, Nelson, Sherman, et al., 1996), prothrombin time and hemodialysis (Nelson and Freeman, 1994) were significant in one additional study. Factors found to be significant in a single study rated as "Fair" were: cholangitis (Freeman, Nelson, Sherman, et al., 1996), and obstructed papilla of Vater orifice (Masci, Toti, Mariani, et al., 2001).

Factors that were not significant in any analysis were: age (3 studies), gender (3 studies); common bile duct size/diameter (4 studies); indications for ERCP (3 studies); previous gastrectomy (2 studies); and history of jaundice (1 study).

Cholangitis

Two studies, both rated as "Fair Minus" quality, reported on patient factors associated with cholangitis (Table 77). Loperfido, Angelini, Benedetti, et al. (1998) reported that jaundice had a significant association with cholangitis. Lai, Lo, Choi, et al. (1989) reported significant associations for fever greater than 37.5 degrees Celsius within prior 72 hours; malignant obstruction; and serum AST of 70 IU or less.

The study by Loperfido, Angelini, Benedetti, et al. (1998) also included age, gender, common bile duct size and diameter, anatomic features, and previous gastrectomy in the analysis, but none were significant.

Septicemia and Retroperitoneal Perforation

Septicemia (Table 78) and retroperitoneal perforation (Table 79) were each addressed in a single study of "Fair Minus" quality.

Motte, Deviere, Dumonceau, et al. (1991) reported that prior cholangitis and elevated white blood count were significant factors for septicemia, but did not report p-values. Age, gender, anatomic variation, other comorbidities, and history of jaundice were not significant in this analysis.

Loperfido, Angelini, Benedetti, et al. (1998) reported that previous gastrectomy was a significant factor for retroperitoneal perforation, but did not report confidence intervals. Age, gender, common bile duct size/diameter; anatomic variation, and history of jaundice were not significant in this analysis.

Table 76. Relationship between Patient Factors and Hemorrhage

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 30	X	X	X		Obstructed orifice of papilla of Vater OR=2.57 (1.69-6.17)				X			
Freeman, Nelson, Sherman, et al., 1996	2347 48	X	X	X	OR=2.59 (1.38-4.86)	X	OR=3.32 (1.54-7.18)		X	X	X		
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 21	X	X	X		X					X	X	
Nelson and Freeman, 1994	189 10			X			Prothrombin time 2x > control OR=12.1 (1.8-90.9)		Hemodialysis OR=16.4 (2.9-93.1)	X All pts had ES			

Table 77. Relationship between Patient Factors and Cholangitis

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 21	X	X	X		X					X	OR=4.14	
Lai, Lo, Choi, et al., 1989	323 21							Subgroup analysis excluding 43 febrile patients Serum AST ≤70IU (discriminant coefficient= 2.09, p<0.04)	Fever (>37.5° C) within 72 hours prior to examination (discriminant coefficient= 2.73, p<0.0001)	Pathologic nature of the obstructive lesion, malignant vs. benign (discriminant coefficient= 1.75, p<0.002)			

Table 78. Relationship between Patient Factors and Septicemia

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Motte, Deviere, Dumonceau, et al., 1991	105 34	**X**	**X**		Prior Cholangitis (F=7.1)	X		WBC count (F=6.6) Alk Phos n.s.	**X**			**X**	

Table 79. Relationship between Patient Factors and Retroperitoneal Perforation

Study	N Pts Cx	Age	Gender	CBD Size\Diameter	Cholangitis	Anatomic variation/ features[1]	Coagulopathy[2]	Laboratory values	Other[3] Comorbidities	Indication for ERCP proc[4]	Previous Gastrectomy	Hx Jaundice	Hx Contrast Allergy
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 12	X	X	X		X					OR=11.7 n.r.	X	

Relationship of Total and Specific Complications

Pancreatitis and hemorrhage together comprise the majority of total complications in the three studies that report all 3 outcomes (Masci, Toti, Mariani, et al., 2001; Freeman, Nelson, Sherman, et al., 1996; Loperfido, Angelini, Benedetti, et al., 1998). Pancreatitis was 36 percent, 55 percent, and 30 percent, respectively in these studies; and hemorrhage was 25 percent, 21 percent and 21 percent.

In the study by Masci, Toti, Mariani, et al. (2001), younger age was a significant factor for both pancreatitis and total complications. There was no other overlap between risk factors for total complications and pancreatitis or hemorrhage.

In Freeman, Nelson, Sherman, et al. (1996), suspected sphincter of Oddi dysfunction was a significant factor for both pancreatitis and total complications. There was no other overlap between total complications and pancreatitis or hemorrhage. In contrast to Masci, Toti, Mariani, et al. (2001), younger age was significant only for pancreatitis, not for total complications.

Loperfido, Angelini, Benedetti, et al. (1998) found no significant relationships between patient factors and overall complications.

The inconsistencies noted here might suggest that analysis of patient factors related to specific complications may be more informative than total complications. Analysis of total complications may not be sufficiently sensitive. This suggests that large studies with adequate numbers of cases of the specific complications of interest will be more useful in identifying patient-related factors that might be used to improve clinical outcomes.

Review of Evidence: Procedure Factors

Eleven studies reported on patient factors associated with complications. The various measures were classified into 13 categories: papillotomy/endoscopic sphincterotomy; pre-cut endoscopic sphincterotomy; biliary drainage; failed procedure; length of endoscopic sphincterotomy; bleeding during endoscopic sphincterotomy; combination with other procedures; difficulty of cannulation; pancreatic opacification; post-procedure care; intramural injection; sphincter of Oddi manometry; emergency procedure.

Total Complications

Six studies reported on procedure factors associated with total complications (Table 80). Precut endoscopic sphincterotomy was significant in all four studies that tested for this association; including two studies rated as “Fair” (Masci, Toti, Mariani, et al., 2001; Freeman, Nelson, Sherman, et al., 1996). Freeman, Nelson, Sherman, et al. (1996) also found two additional significant factors, combined percutaneous-endoscopic procedures and difficulty in cannulation. Masci, Toti, Mariani, et al. (2001) found that failed stone removal, another indicator of a difficult procedure, was a significant factor for total complications.

Table 80. Relationship between Procedure Factors and Total Complications

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 121		OR=1.70 (1.10-2.68)	X	No stone removal OR=2.52 (1.44-4.53)					X			
Freeman, Nelson, Sherman, et al., 1996	2347 229	All pts had ES	OR=3.61 (1.78-7.34)		X		X	Comb. percut.-endo. proc. OR=3.40 (1.04-11.13)	OR=3.05 (1.83-5.08)				X
Fair Minus Quality													
Rabenstein, Schneider, Bulling, et al., 2000	438 33	All pts had ES			X								X
Loperfido, Angelini, Benedetti, et al., 1998	1827 98		OR=1.73							X			X
Tzovaras, Shukla, Kow, et al., 2000	372 21				Previous failed ERCP OR=4.66 (1-21.80)			Need for PTC OR=10.3 (2.30-45.83)				X	X
Boender, Nix, de Ridder, et al., 1994	242 34	All pts had ES	OR=4.9 p=0.001	X	Failed biliary drainage OR=34.8 p=0.007	X							

Failed biliary drainage was significant in the study by Boender, Nix, de Ridder, et al. (1994). Tzovaras, Shukla, Kow, et al. (2000) reported two significant factors: previous failed ERCP (CI=1–21.8) and need for percutaneous procedure (CI=2.3–45.8); but confidence intervals were extremely wide for both factors.

Factors not significant were: emergency procedure (4 studies); pancreatic opacification (2 studies); and bleeding during endoscopic sphincterotomy (1 study).

Pancreatitis

Seven studies reported on procedure factors associated with pancreatitis (Table 81). Precut endoscopic sphincterotomy was significant in two studies rated as "Fair" (Masci, Toti, Mariani, et al., 2001; Freeman, Nelson, Sherman, et al., 1996); as was difficulty in cannulation and multiple pancreatic contrast injections (Freeman, Nelson, Sherman, et al., 1996 and Freeman, DiSario, Nelson, et al., 2001). Multiple pancreatic contrast injections was also a significant risk factor in Loperfido, Angelini, Benedetti, et al. (1998); and in Mehta, Pavone, Barkun, et al. (1998) for the subgroup of patients that did not undergo endoscopic sphincterotomy.

Masci, Toti, Mariani, et al. (2001) also reported that failed stone removal was a significant factor; and Freeman, DiSario, Nelson, et al. (2001) found that pancreatic sphincterotomy and balloon biliary sphincter dilatation were also significant factors.

Maldonado, Brady, Mamel, et al. (1999) identified performing a complete ERCP procedure in addition to sphincter of Oddi manometry as a significant risk factor for pancreatitis among patients who all underwent sphincter of Oddi manometry.

Factors not significant were: emergency procedure (3 studies); biliary drainage (1 study); and bleeding during endoscopic sphincterotomy (1 study).

Hemorrhage

Four studies reported on procedure factors associated with hemorrhage (Table 82). Bleeding during endoscopic sphincterotomy was significant in two studies, one of which was rated as "Fair" (Freeman, Nelson, Sherman, et al., 1996; Nelson and Freeman, 1994). Precut endoscopic sphincterotomy (Masci, Toti, Mariani, et al., 2001) and anticoagulation less than 3 days after procedure (Freeman, Nelson, Sherman, et al., 1996) were significant in a single study rated "Fair."

Factors not significant were: pancreatic opacification (3 studies) emergency procedure (2 studies); combined with other procedures (2 studies); biliary drainage (1 study); failed procedure (1 study); endoscopic sphincterotomy length (1 study); and difficulty of cannulation (1 study).

Cholangitis, Septicemia and Retroperitoneal Perforation

Cholangitis (Table 83), septicemia (Table 84) and retroperitoneal perforation (Table 85) were each addressed in a single study of "Fair Minus" quality.

Table 81. Relationship between Procedure Factors and Pancreatitis

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 44		OR=2.8 (1.38-5.84)	X	No stone removal OR=3.35 (1.33-9.1)					X			
Freeman, DiSario, Nelson, et al., 2001	1963 131	Pancreatic ES OR=3.07 (1.64-5.75)	X		X			Biliary Balloon Sphincter Dilation OR=4.51 (1.51-13.46)	Moderate to Difficult OR=3.41 (2.13-5.47)	>1 pancreatic contrast injection OR=2.72 (1.43-5.17)		X	
Freeman, Nelson, Sherman, et al., 1996	2347 127	All pts had ES	OR=4.34 (1.73-10.88)		X		X	X	OR=2.4 (1.07-5.36)	OR=1.35 (1.04-1.75)			X
Fair Minus Quality													
Rabenstein, Schneider, Bulling, et al., 2000	438 19	All pts had ES			X								X
Loperfido, Angelini, Benedetti, et al., 1998	1827 29		X							OR=2.84 n.r.			X

Table 81. Relationship between Procedure Factors and Pancreatitis (cont'd)

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Minus Quality													
Mehta, Pavone, Barkun, et al., 1998	535 34	X						X		Subgroup with ES n.s. Subgroup without ES p=0.05			
Maldonado, Brady, Mamel, et al., 1999	100 17	X ES no added risk						X	Length of procedure			X ERCP was risk factor but not SOM	

Table 82. Relationship between Procedure Factors and Hemorrhage

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Quality													
Masci, Toti, Mariani, et al., 2001	2444 30		OR=2.45 (1.6-5.39)	X	X					X			
Freeman, Nelson, Sherman, et al., 1996	2347 48	All pts had ES	X		X		OR=1.74 (1.15-2.65)	X	X	X	Anticoag <3d after procedure OR=5.11 (1.57-16.68)		X
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 21		X							X			X
Nelson and Freeman, 1994	189 10	All pts had ES				X	OR=13.7 (2.2-87.3)						

Table 83. Relationship between Procedure Factors and Cholangitis

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 21		X							X			X

Table 84. Relationship between Procedure Factors and Septicemia

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Postprocedure Care	Sphincter Manometry	Emergency procedure
Fair Minus Quality													
Motte, Deviere, Dumonceau, et al., 1991	105 34			Incomplete Drainage (F=319.2)				X					

Table 85. Relationship between Procedure Factors and Retroperitoneal Perforation

Study	N Pts Cx	Standard Papillotomy/ ES	Precut ES	Biliary drainage	Failed Procedure	ES length	Bleeding during ES	Combined with other procedures	Difficulty of cannulation	Pancreatic opacification	Intramural Injection	Sphincter Manometry	Emergency procedure
Fair Minus Quality													
Loperfido, Angelini, Benedetti, et al., 1998	1827 12		OR=7.19 n.r.							X	OR=6.86		X

Loperfido, Angelini, Benedetti, et al. (1998) analyzed precut endoscopic sphincterotomy, pancreatic opacification; and emergency procedure; but none of these factors were significant for cholangitis.

Motte, Deviere, Dumonceau, et al. (1991) reported that incomplete biliary drainage was a significant factor for septicemia, but did not report p-values. Combination with another procedure was not significant in this analysis.

Loperfido, Angelini, Benedetti, et al. (1998) reported that precut endoscopic sphincterotomy and intramural injection were significant factors for retroperitoneal perforation, but did not report confidence intervals. Pancreatic opacification and emergency procedure were not significant in this analysis.

Relationship of Total and Specific Complications

Pancreatitis and hemorrhage together comprise the majority of total complications in the three studies that report all three outcomes (Masci, Toti, Mariani, et al., 2001; Freeman, Nelson, Sherman, et al., 1996; Loperfido, Angelini, Benedetti, et al., 1998).

Masci, Toti, Mariani, et al. (2001) found the precut endoscopic sphincterotomy was a significant factor for total complications, pancreatitis and hemorrhage. Failed stone removal was a significant factor for total complications and pancreatitis, but not for hemorrhage. There was no other overlap between total complications and pancreatitis or hemorrhage.

Freeman, Nelson, Sherman, et al. (1996) found that precut endoscopic sphincterotomy and difficulty in cannulation were significant factors for total complications and pancreatitis. There was no other overlap between total complications and pancreatitis or hemorrhage.

Loperfido, Angelini, Benedetti, et al. (1998) found no overlap between total complications and pancreatitis or hemorrhage.

This suggests that procedure factors may be more generalizable across total and specific complications than is the case with patient factors.

Review of Evidence: Operator Factors

Operator factors were analyzed in four studies (Freeman, DiSario, Nelson, et al., 2001; Freeman, Nelson, Sherman, et al., 1996; Loperfido, Angelini, Benedetti, et al., 1998; Rabenstein, Schneider, Bulling, et al., 2000); two of which were rated as “Fair” quality (Table 86). Case volume was analyzed in all four studies; participation of a trainee in three studies; university affiliated center in one study and center size in one study. Only case volume was a significant factor for complications in any of these analyses. Importantly, cut-off points for classification as a low-volume operator varied significantly across studies. Freeman, Nelson, Sherman, et al. (1996) used a cut-off of centers with 1 or fewer procedures per endoscopist per week; Loperfido, Angelini, Benedetti, et al. (1998) defined lower volume centers as those with fewer than 200 procedures per year.

Table 86. Relationship between Operator Factors and Total Complications

Study	N Pts Cx	Case volume	Participation of a trainee	University affiliated center	Center size
Fair Quality					
Freeman, Nelson, Sherman, et al., 1996	2347 229	X[16]	X	X	
Fair Minus Quality					
Rabenstein, Schneider, Bulling, et al., 2000	438 33	X	X		
Loperfido, Angelini, Benedetti, et al., 1998	1827 98	Centers which performed <200 ERCPs per year OR=2.93			X

[16] Case volume was not independently significant in the primary multivariate analysis of total complications conducted by Freeman 1996, probably because of the close relationship with intraoperative technique. In a multivariable model that was based solely on data available prior to the procedure, lower case volume (average <1 case/week per endoscopist vs > 1 case) was independently associated with higher complications (OR 1.43, CI=1.07-1.89).

Table 87. Relationship between Operator Factors and Hemorrhage

Study	N Pts Cx	Case volume	Participation of a trainee	University affiliated center	Center size
Fair Quality					
Freeman, Nelson, Sherman, et al., 1996	2347 48	Endoscopist volume ≤1/week OR=2.17 (1.12-4.17)	X	X	
Fair Minus Quality					
Loperfido, Angelini, Benedetti, et al., 1998	1827 21	Centers which performed <200 ERCPs per year OR=2.98			X

Case volume was not independently significant in the primary multivariate analysis of total complications conducted by Freeman, Nelson, Sherman, et al. (1996), probably because of the close relationship with intraoperative technique. In a multivariable model that was based solely on data available prior to the procedure, lower case volume (average less than 1 case/week per endoscopist vs more than one 1 case) was independently associated with higher complications (OR 1.43, CI=1.07–1.89). This suggests that endoscopist skill in avoiding specific procedural technique is the basis for the association between case volume and complications.

Lower volume of ERCP procedures was associated with hemorrhage in two studies (Freeman, Nelson, Sherman, et al., 1996 and Loperfido, Angelini, Benedetti, et al., 1998) (Table 87). Rabenstein, Schneider, Bulling, et al. (2000) was the only study to find a significant association between lower case volume and pancreatitis (Table 88). The cut off used was fewer than 40 endoscopic sphincterotomies per endoscopist per year. Loperfido, Angelini, Benedetti, et al., (1998) also explored the relationship between case volume and cholangitis or retroperitoneal perforation (Tables 89 and 90) and reported an odds ratio of 4.22 for cholangitis and no association with retroperitoneal perforation.

Conclusion

- Thirteen studies reported on multivariable logistic regression analyses of factors associated with complications of ERCP. The four largest studies each included more than 1,800 patients, and the total number of complications observed in these studies ranged from 98 to 229. Overall, the methodologic quality of the available analyses is limited by overfitting, i.e., testing an excessive number of factors relative to the number of complications observed. Consequently, this literature is exploratory in nature. Reported magnitudes of association are not reliable, significant independent variables may have been overlooked, and some significant associations may be misleading. Moreover, the existing studies do not use common, standardized definitions for the complications and factors of interest. Thus, caution should be used in drawing inferences for clinical practice from these studies.

- Patient, procedure and operator factors were identified that were found to be significantly associated with complications in several of the more robust studies. Younger age (using various cut-offs, but generally 60 years or less) was significantly associated with total complications and with pancreatitis; as was suspected sphincter of Oddi dysfunction. Precut endoscopic sphincterotomy was the procedure-related factor most commonly associated with total complications or pancreatitis; a significant association with difficulty in cannulation was also reported, but less frequently. Multiple pancreatic contrast injections was associated with pancreatitis. For hemorrhage, the clearest association was patient factors related to coagulopathy. Case volume was the only operator-related factor found to be significantly associated with complications. These studies used various cut-offs to define lower volume centers: 1 or fewer procedures per endoscopist per week; fewer than 40 endoscopic sphincterotomies per endoscopist per year; and fewer than 200 procedures per year.

Table 88. Relationship between Operator Factors and Pancreatitis

Study	N Pts Cx	Case volume	Participation of a trainee	University affiliated center	Center size
Fair Quality					
Freeman, DiSario, Nelson, et al., 2001	1963 131	X	X		
Freeman, Nelson, Sherman, et al., 1996	2347 127	X	X	X	
Fair Minus Quality					
Rabenstein, Schneider, Bulling, et al., 2000	438 19	Endoscopist ES case load <40/year OR=3.8 (1.44-10.00)	X		
Loperfido, Angelini, Benedetti, et al., 1998	1827 29	X			X

Table 89. Relationship between Operator Factors and Cholangitis

Study	N Pts Cx	Case volume	Participation of a trainee	University affiliated center	Center size
Fair Minus Quality					
Loperfido, Angelini, Benedetti, et al., 1998	1827 21	Centers which performed <200 ERCPs per year OR=4.22			X

Table 90. Relationship between Operator Factors and Retroperitoneal Perforation

Study	N Pts Cx	Case volume	Participation of a trainee	University affiliated center	Center size
Fair Minus Quality					
Loperfido, Angelini, Benedetti, et al., 1998	1827 12	X			X

Part V, Section 2: Randomized, Controlled Comparison Trials

Introduction

This section summarizes the available randomized, controlled trials that compare technical variations in performing the ERCP procedure and compare associated complication rates. Quality ratings for these studies are available in Table 91. In addition, some of these studies provide comparative information on technical success of the procedure. Based on discussion with this project's Technical Advisory Group, studies evaluating the use of pharmacologic agents or different contrast agents in preventing ERCP-induced pancreatitis were specifically excluded from this systematic review as the volume of this literature could not be incorporated within the scope of this project.

Review of Evidence

Sphincterotome versus Standard Catheter to Achieve Selective Common Bile Duct Cannulation

Two randomized controlled trials (total n=147) compared standard catheterization versus techniques using sphincterotomes to achieve higher success rates in selectively cannulating the common bile duct (Table 92). Cortas, Mehta, Abraham, et al. (1999) randomized 47 patients to standard catheter versus either a standard or wire-guided sphincterotome, and was rated a "Good" quality study. Fifteen attempts were made to cannulate the common bile duct with the randomly assigned catheter, after which patients crossed over. In the initial attempt, the sphincterotome was more successful than the standard catheter in achieving cannulation (97 percent vs. 67 percent, p=0.009). After cross overs, the techniques were equivalent (standard catheter 94 percent sphincterotome 97 percent, p=n.s.), but successful cannulation was achieved in the sphincterotome group with fewer attempts (12.4 vs. 2.8, p<0.001) and in less time (13.5 vs. 3.1 minutes, p<0.001). Pancreatitis occurred in 5.6 percent of standard catheter group, and 10.3 percent of the sphincterotome group, but numbers are too small to assess statistical significance.

Schwacha, Allgaier, Deibert, et al. (2000) randomized 100 patients to standard catheter versus sphincterotome and was rated "Fair." If the randomly assigned technique was unsuccessful patients underwent attempts with a tapered cannula, crossing over to the other treatment arm, and then needle knife sphincterotomy. In the initial attempts, the sphincterotome was more successful than the standard catheter (84 percent vs. 62 percent, p=0.023). Eventually, cannulation was equally successful in both groups (91 percent for both). Complications were not statistically different between the two groups.

Based on limited evidence, techniques using a sphincterotome appear to have greater success in selective cannulation of the common bile duct than standard catheter, but no definite conclusion can be made regarding the effect of this variation on complications.

Table 91. Quality Assessment

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Schwacha, Allgaier, Deibert, et al., 2000	RCT (n=100) Good comparability - Randomization not described - Patient characteristics similar	Standard catheter (n=50): 19 crossed over to GS Guidewire Sphincterotome (n=50): 8 crossed over to SC	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not clearly stated to be intention to treat Complications reported only in those with primary success	Fair
Cortas, Mehta, Abraham, et al., 1999	RCT (n=47) Good comparability - Randomization method not fully described - Patient characteristics not reported	Standard catheter (n=18) 6 crossed over Sphincterotome (n=29)	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Intention to treat analysis was used.	Good
Elta, Barnett, Wille, et al., 1998	RCT (n=170) Good comparability - Randomization by even or odd calendar date - Patient characteristics similar for age, gender, reason for ES	Pure cut (n=86) 8 crossed over to BC Blended current (n=84) No crossover reported	Adequate for comparison.	Adequate outcome measures used. Outcomes reported to be assessed blindly.	Method of analysis not clearly stated to be intention to treat	Fair

Table 91. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Kohler, Maier, Benz et al., 1998	RCT (n=100) Good comparability – Randomization method not fully described – Patient characteristics similar for age, gender, and indication for sphincterotomy	Conventional Current (n=50) No dropouts or exclusion Controlled Current (n=50) No dropouts or exclusion	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not clearly stated but equivalent to intent to treat	Good
Siegel, Veerappan, and Tucker, 1994	RCT (n=100) Fair comparability – Randomization method not fully described – Baseline characteristics similar for biliary diagnosis and reason for ES	Monopolar (n=50) 3 crossed over to BP Bipolar (n=50) 5 crossed over to MP	Adequate for comparison	Adequate outcome measures used. Complication outcomes were reportedly assessed blindly.	Method of analysis not clearly reported.	Fair

Table 91. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Kim, Lee, Lee, et al., 1997	RCT (n=45) Fair comparability – Randomization technique not specified – Baseline characteristics similar for age, gender, type of Billroth II anastomosis	No crossovers or exclusions from analysis reported	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	Method of analysis not stated.	Fair
Bergman, Rauws, Fockens, et al., 1997	RCT (n=202) Good comparability – blinded computer-generated randomization – patients comparable on all measured characteristics	16 out of 218 excluded after randomization because of ineligibility	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly.	All patients retained for analysis	Good

Table 91. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Tarnasky, Palesch, Cunningham et al., 1998	RCT (n=80) Fair comparability – Randomization method not reported – Baseline characteristics were similar except for two areas: biliary cannulation more difficult in No stent group (p=0.03) and longer mean time to repeat pancreatic access in the No stent group (p=0.04)	Stent (n=41) No Stent (n=39) No crossovers or loss to follow-up reported	Adequate for comparison.	Adequate outcome measures used. Outcomes were not assessed blindly.	Analysis not stated to be intention to treat but equivalent because all subjects included in analysis. Analysis did include multivariate adjustment to account for baseline differences.	Good

Table 91. Quality Assessment (cont'd)

Study Author, Year	Comparable Initial Groups?	Comparable Groups Maintained?	Comparable Performance of Intervention?	Comparable Measurement of Outcomes?	Appropriate Analysis	Summary Evaluation
Randomized Controlled Trials						
Smithline, Silverman, Rogers, et al., 1993	RCT (n=98) Fair comparability – Randomization method not reported – Patient characteristics similar for age, gender, clinical history of pancreatitis, suspected SOD, abnormal SOM	Stent (n=48) 5 technical failures excluded 8 who required pre-cut were assigned out of sequence to stent placement No Stent (n=50) No dropouts or exclusions. No crossovers reported.	Adequate for comparison	Adequate outcome measures used. Outcomes were not assessed blindly	Method of analysis not stated.	Fair
Ochi, Mukawa, Kiyosawa, et al., 1999	RCT (n=110) Good comparability – randomization not described – patients comparable on all measured characteristics	All patients retained for analysis	Adequate for comparison	Outcomes were not assessed blindly	All patients retained for short-term outcome analysis 105/110 patients retained for long-term outcome analysis	Good

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods

Article	N	Population and Interventions	Complications/Outcomes
Schwacha, Allgaier, Deibert, et al., 2000 Research Issue: Techniques to achieve selective CBD cannulation Standard catheter vs. sphincterotome	100	100 consecutive patients randomized to a group undergoing CBD and PD cannulation using and SC with a metallic tip or a GS without guidewire. Exclusion criteria: ERCP within 1 week before randomization Emergency ERCP Previous therapeutic ERCP Previous surgery of the upper GI tract Indications*: SC GS Choledocholithiasis 9 13 Pancreato-biliary Malignancy 11 9 Acute pancreatitis 6 4 Chronic pancreatitis 5 3 Cholestasis of unknown origin 13 13 PSC 2 3 Cholangitis 0 2 Tumor of papilla 1 1 Others 3 2 * No statistical difference between groups	**Initial Success rates (4 to 5 attempts with assigned technique)** Standard catheter (SC) =62% Guidewire sphincterotome (GS)=84% P=0.023 Final Success rates (crossovers, needle-knife attempted on failures) Standard catheter (SC)=91% Guidewire sphincterotome (GS)=91% Complications (%)** SC GS None 65 69 n.s. Clinical pancreatitis 10 5 n.s Biochemical pancreatitis 10 12 n.s. Intramural injection 3 5 n.s Other, not relevant 12 9 n.s. ** Among patients for whom ERCP was primarily successful (SC n=31; GS n=42)

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Cortas, Mehta, Abraham, et al., 1999 Research Issue: Techniques to achieve selective CBD cannulation Standard catheter vs. sphincterotome	47	Consecutive patients undergoing ERCP with the intent to selectively cannulate the CBD. Patients randomized to cannulation of the CBD with either a standard catheter (n=18) or a sphincterome (standard or guidewire) (n=29). There were 6 crossovers from SC to SS after initial attempt (15 tries) Exclusion criteria: Patients who had undergone a previous therapeutic ERCP, selective cannulation was not sought as first intention, or a gastroduodenal anatomic anomaly was present. Indication (N): Suspected CBD stones=41 Pancreatico-biliary malignancies=4 Bile leak=2	Initial CBD cannulation success (%, 95% CI): Standard catheter=67% (41-87) Sphincterotome=97% (82-100) p=0.009 After crossovers, Final selective CBD cannulation (%, 95% CI): Standard catheter=94% (73-99) Sphincterotome=97% (82-100) P= n.s. Complications: Pancreatitis (%, CI):* SC=5.6 (0.1-27) SS/WS=10.3 (2.2-27.4) *Numbers too small to assess statistical significance

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Elta, Barnett, Wille, et al., 1998 Research Issue: Techniques of ES Pure cute vs. blended current	170	170 consecutive patients undergoing biliary endoscopic sphincterotomy between November 1994 and June 1995 were randomized to either blended or pure cut current. Patients undergoing sphincterotomy on even calendar dates received blended current, whereas patients receiving sphincterotomy on odd calendar dates received pure cut* Indication: Pure Blended Choledocholithiasis 55 56 SOD 18 18 Stent placement 9 6 Miscellaneous 4 4 Total 86 84 * The study was stopped after interim analysis showed a lower pancreatitis rate in the pure cut group.	Complications (N): Pure Blended Mild pancreatitis* 3 7 Moderate pancreatitis* 0 2 Severe pancreatitis* 0 1 Bleeding 1 1 Cholangitis 0 1 Total 4 12 *Patients with SOD (n=36) actually had a higher rate of pancreatitis (17% vs. 28%), but not significantly different due to low numbers. Difference in the proportion of patients who developed pancreatitis (including SOD patients) was statistically significant ($p<0.05$). When SOD patients were excluded, the difference in the rate of pancreatitis was still statistically different ($p=0.018$).

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Siegel, Veerappan, and Tucker, 1994 Research Issue: Techniques of ES Monopolar vs. Bipolar device using blended current for both	100	Consecutive patients requiring ERCP and sphincterotomy at one institution were randomly assigned to either standard monopolar electrocautery current (n=50) or the bipolar system (n=50).* Indication: Monopolar Bipolar CBD stones 21 23 Pancreatitis 7 6 Pancreatic CA 7 6 SOD 11 6 CBD stricture 3 7 Ampullary CA 1 0 Biliary fistula 0 2 Total 50 50 *5 patients assigned to the bipolar group were switched to monopolar group due to difficulties in the insertion of the sphincterome. 3 patients assigned to the monopolar group were crossed over to the bipolar group. The first 50 patients in each group in whom sphincterotomy was performed were included in the study.	Complications (N): MP BP Pancreatitis 6 0 p<0.047 Bleeding 1 0 n.s. Cholangitis 4 3 n.s. Perforation 0 0 n.s. Death 1 0 n.s.

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Kim, Lee, Lee, et al., 1997 Research Issue: Techniques to achieve ERCP and ES in Billroth II patients Forward vs. Side viewing scope	45	Patients s/p Billroth II gastrectomy who required ERCP with sphincterotomy. Patients were randomized to either a forward-viewing (FV) endoscope (n=23) or a side-viewing (SV) endoscope (n=22). Exclusion criteria: Cases of Roux-en Y surgery	Successful cannulation of the papulla*(%): FV= 20 of 23 (87%) SV= 15 of 22 (68%) p= n.s. Successful endoscopic sphincterotomy (%): FV= 10 of 12 (83%) SV= 8 of 10 (80%) p= n.s. Complications advancing endoscope (%): FV=0 of 23 (0%) SV= 4 of 22 (18%) p<0.05 * Among the causes of failure to cannulate the papulla, jejunal perforation occurred in 0 patients in the FV group and 4 patients in the SV group. Complications of endoscopic needle-knife sphincterotomy FV n=12 SV n=10 Pancreatitis 1 2 n.s. Retroperitoneal perforation 0 1 n.s.

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Bergman, Rauws, Fockens, et al., 1997 Research Issue: Techniques to remove CBD stone Balloon dilation vs. ES	202	Consecutive patients referred for ERCP because of symptoms of CBD stones. Patients meeting inclusion and exclusion criteria were randomized to either endoscopic sphincterotomy (n=101) or endoscopic balloon dilation (n=101). Eligibility criteria: Over age 18 years BDS visualized at ERCP Deep cannulation of the BD achieved without sphincterotomy Exclusion criteria: Signs of acute cholangitis Acute pancreatitis Acute cholecystitis History of previous sphincterotomy Choledochoduodenal fistula Hemostatic disorders Intrahepatic stone disease Hemolytic anemia Concomitant pancreatic or biliary malignant disorders Coexisting bile leakage or choledochoduodenal fistula Previous participation in this study Life expectancy of less than 1 month	Complete stone removal in one endoscopic session (%): EBD=89 EST=91 n.s. Early Complications (N): EBD EST Pancreatits 7 7 Fever 4 5 Bleeding 0 4 Perforation 2 1 Pain in right upper abdomen 0 4 Slow resolution of jaundice 2 1 Bile leakage 1 1 Cardiopulmonary 1 1 Total 17 24 n.s. (continued next page)

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Bergman, Rauws, Fockens, et al., 1997 (cont'd) Research Issue: Techniques to remove CBD stone Balloon dilation vs. ES	202	(see previous page)	**Complications during follow-up (N):** Recurrence of symptoms 14 14 Stones on repeat ERCP 8 7 No stones on repeat ERCP 6 5 No repeat ERCP done 0 2 Acute cholecystitis* 1 7 Symptomatic cholecystolithiasis 2 1 Liver abscess 0 1 Abnormal liver function at follow-up 1 0 Total 18 23 n.s. * Statistically significantly lower in the EBD group Logistic regression analysis of treatment allocation, stone size, stone number, gender, periampullary diverticulum, and Billroth II gastrectomy on successful stone removal identified stone size (p=0.0008), and stone number (p=0.0216) as the only significant predictors of this outcome. Further subgroup analyses were undertaken (not reported in this table).

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Ochi, Mukawa, Kiyosawa, et al., 1999 Research Issue: Techniques to remove CBD stone Balloon dilation vs. ES	110	Patients with bile duct stones up to 15 mm in diameter and less than 10 in number as indicated by ERCP were randomly treated with either endoscopic papillary dilation (n=55) or endoscopic sphincterotomy (n=55). Exclusion criteria: Recurrent stones following previous procedures Intrahepatic stone disease Acute cholangitis Cholecystitis Pancreatitis Pancreatic or biliary malignant disorders	Successful bile duct clearance (%): EPD=92.7 EST=98.1 n.s. Successful bile duct clearance achieved in the initial procedure (%): EPD=78.4 EST=94.4 p=0.02 Early complications (total)(%) (EPD n=51, EST n=54): EPD=2.0 EST=5.6 n.s. Specific complications (N) EPD EST Progression of jaundice 1 0 Perforation 0 2 Late complications (total/eligible for follow-up)(N): EPD=2/51 EST=8/54 n.s. Specific complications (N) EPD EST Recurrence of BDS 2 3 n.s. Acute cholangitis 2 2 n.s. Acute cholecystitis 1/30 5/27 n.s. Acute cholecystitis in patients with gallbladder stones in situ 1/22 5/17 p<0.03

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Tarnasky, Palesch, Cunningham et al., 1998 Research Issue: Pancreatic stenting to reduce pancreatitis after ES	80	Consecutive adult patients scheduled for ERCP with SOD manometry, for evaluation of unexplained pancreatobiliary pain or pancreatitis, were randomized to either pancreatic duct stents (n=41) or no stents (n=39). Exclusions: Pancreatic SOM results normal SOM failure or not attempted Severe chronic pancreatitis Pancreas divisum Prior gastric surgery PSH No sphincterotomy Both biliary and pancreatic sphincterotomy Precut sphincterotomy required to achieve biliary access Preference of physician or patient not to participate Failure to gain repeat pancreatic access after biliary sphincterotomy Indications (%): Stent No Stent Pancreatobiliary pain (gallbladder out) 51 72 Pancreatobiliary pain (gallbladder in) 20 5 Prior acute pancreatitis 29 23	**Complications:** **Incidence of post-ERCP pancreatitis (%):** Stent=2 No Stent=26 p=0.003 RR of post-ERCP pancreatitis after biliary sphincerotomy in the no stent group=10.5, 95% CI=1.4-78.3 Logistic regression analysis controlling for differences in baseline data (difficulty of biliary cannulation and time to repeat pancreatic access) resulted in an AOR=14.4, 95% CI=1.7-125.0 for the risk of post-ERCP pancreatitis among patients in the no stent group.

Table 92. Randomized Clinical Trials Comparing Different ERCP Methods (cont'd)

Article	N	Population and Interventions	Complications/Outcomes
Smithline, Silverman, Rogers, et al., 1993 Research Issue: Pancreatic stenting to reduce pancreatitis after ES	98	High risk patients (those with SOD or CBD <10 mm and patients requiring pre-cut biliary ES) were randomized to receive a main pancreatic duct stent or no stent following biliary sphincterotomy. Exclusions: Patients with pancreatic divisum, pancreatobiliary tumors, or those undergoing pancreatic septotomy	<u>Complications:</u> Incidence of pancreatitis (%): MPD Stent=14 No Stent=18 n.s. * Severity of pancreatitis (%): Mild MPD Stent=13 No Stent=12 n.s. Moderate MPD Stent=0 No Stent=6 n.s. Severe MPD Stent=0 No Stent=6 n.s. Other suspected risk factors for pancreatitis were examined including acinarization, precut ES, and history of pancreatitis. None of these risk factors were found to be independent risk factors of pancreatitis in high-risk patients. * Pancreatitis developed in 2 of 5 patients in whom stent placement failed

Variations in Electric Current Used in Sphincterotomy to Reduce Post-ERCP Complications

Three randomized clinical trials (all rated "Fair" quality) compared variations of the electric current used in performing sphincterotomy as methods to reduce post-procedure complications such as hemorrhage or pancreatitis.

Elta, Barnett, Wille, et al. (1998) randomized 170 patients to either blended or pure cut current when undergoing sphincterotomy. Blended current combines intermittent high voltage pulses with continuous low voltage current, whereas pure cut current is simply continuous low voltage current. Total complications were significantly lower in the pure cut group (5 percent vs. 14 percent, $p<0.05$).

Kohler, Maier, Benz et al. (1998) randomized 100 patients to either conventional high-frequency blended current or a newly developed high-frequency system with automatically controlled cutting mode (Endocut). Mild bleeding during sphincterotomy was significantly reduced (4 percent compared to 26 percent, $p=0.002$), but no significant difference was observed in moderate/severe bleeding or mild pancreatitis, which both occurred very infrequently.

Siegel Veerappan, and Tucker (1994) randomized 100 patients to receive either a bipolar or monopolar electric current device when undergoing sphincterotomy. Pancreatitis occurred in 6 patients receiving monopolar electrocautery and 1 patients receiving bipolar electrocautery ($p<0.05$). Other complications were very uncommon and numbers were too small to make conclusions about statistical significance.

Forward-Viewing Endoscope versus Side-Viewing Endoscope to Achieve Successful Cannulation and Sphincterotomy in Patients with Billroth II Gastrectomy

Kim, Lee, Lee, et al. (1997) randomized 45 patients with Billroth II gastrectomy who required ERCP and sphincterotomy to have the procedure done with either a forward-viewing (FV) endoscope or side-viewing (SV) duodenoscope. Successful cannulation occurred in 87 percent of FV group and 68 percent of SV group (p=n.s.) Successful sphincterotomy was not statistically different (FV 83 percent, SV 80 percent). Jejunal perforation occurred in 4 patients using the SV duodenoscope and 0 patients using the FV endoscope ($p<0.05$). Use of the FV endoscope may cause fewer perforations than the SV duodenoscope.

Pancreatic Stenting to Reducing Pancreatitis after Sphincterotomy

Two small randomized controlled trials examined whether placing pancreatic stents after sphincterotomy reduces the incidence of post-ERCP pancreatitis among certain patients considered to be at high risk for such a complication.

Smithline, Silverman, Rogers, et al. (1993) randomized 98 patients using an alternate assignment scheme and was rated Fair quality. The patients included those with abnormal SOD manometry, clinical suspicion of SOD, a common bile duct <=10 mm or patients requiring a pre-cut sphincterotomy. Some patients requiring a pre-cut sphincterotomy were assigned a stent out of

the randomization scheme. The results are analyzed only among those who received intended treatment, as patients with failed stent placement (5 patients) are analyzed separately. The no-stent group had an 18 percent rate of pancreatitis, the stent group had a 14 percent rate of pancreatitis (p=n.s.) If appropriately analyzed by intent-to-treat, the pancreatitis rates would be even more similar.

Tarnasky, Palesch, Cunningham et al. (1998) randomized 80 patients to receive stents or no stent and was rated "Good" quality. The selection criteria appear to be more selective than the study by Smithline, Silverman, Rogers, et al. (1993), as only patients with confirmed abnormal sphincter of Oddi manometry and pancreatic sphincter hypertension were included. The incidence of post-ERCP pancreatitis in the stent group was 2 percent, and in the no stent group was 26 percent (p=0.003). After correction for some baseline differences between study groups, the risk of post-ERCP pancreatitis was still highly associated with lack of stent placement (odds ratio 14.4, p=0.002).

An important distinction between the two studies is the selection criteria. Smithline, Silverman, Rogers, et al. (1993) included several types of patients that are thought to be at risk of post-ERCP pancreatitis, Tarnasky, Palesch, Cunningham et al. (1998) included only patients with both confirmed abnormal sphincter of Oddi manometry and pancreatic sphincter hypertension. About three-fourths of the patients in the Smithline, Silverman, Rogers, et al. (1993) study had abnormal sphincter of Oddi manometry, and among those, pancreatic sphincter pressure was not assessed. Thus the results may not be inconsistent, even though the same intervention is assessed using identical outcome measures.

In conclusion, evidence limited to only one trial shows some evidence of efficacy of pancreatic stent placement in preventing post-ERCP pancreatitis, but only among patients with confirmed sphincter of Oddi manometry and concurrent pancreatic sphincter hypertension.

Chapter 4. Future Research

- **Rigorous studies are required in order to reliably quantify the relative performance of diagnostic ERCP compared to alternatives. Existing studies do not consistently use common reference standards and frequently do not report tests of statistical significance. Thus assumptions about equivalence or difference among alternative diagnostic technologies are not supported by robust empirical evidence.**

The selection criteria for diagnostic studies included in this review eliminated lesser quality studies. Thus, included studies were relatively free of referral and verification biases; and blinded interpretation of ERCP and the comparison technology was commonly performed. Nonetheless, the available literature on diagnostic performance suffers from two notable deficiencies. The first is failure to consistently use an adequate reference standard for comparative studies; technologies known to have good performance characteristics should be agreed upon for use as common reference standards. Valid comparisons between diagnostic alternatives cannot be made in the absence adequate reference standards. The second is the failure to provide for adequate statistical power or to report tests of statistical significance. Based on the available literature, is not possible to make confident determinations about the equivalence or magnitude of difference in performance among alternative diagnostic technologies.

- **Comparative studies of alternative diagnostic and treatment strategies are urgently needed. It is imperative to use a comprehensive approach to outcomes assessment, taking into account the total burden of morbidity and resource utilization.**

ERCP differs from its diagnostic alternatives in that a treatment intervention can be performed at the same time also and that ERCP generally has higher complication rates. The decision to use ERCP rather than an alternative should not be based solely on diagnostic test characteristics. Comprehensive measures of patient outcomes that take into account short-term morbidity, as well as cure, are needed. In some settings, most obviously laparoscopic cholecystectomy, the ultimate clinical outcomes are likely to be similar regardless of diagnostic and treatment strategy. Strategies should be evaluated based on comprehensive measures of resource utilization and measures of the total burden of morbidity that incorporate all relevant short-term and long-term effects on health. Studies are needed that compare diagnostic and treatment strategies using rigorous observational or experimental designs.

- **Evidence on treatment of chronic pancreatitis or recurrent pancreatitis is sparse. Rigorously designed controlled trials are needed to assess the outcomes of treatment for this debilitating condition.**

Prospectively designed comparative studies have been performed in many of the clinical setting addressed by this systematic review, although methodological weaknesses frequently limited the quality of the available evidence. However, in the area of treatment for chronic or recurrent pancreatitis and abdominal pain, studies comparing treatment alternatives were practically nonexistent, leaving only case series and before-after studies of varying quality. Based on this deficiency in the current literature, evaluation of treatments for chronic or recurrent pancreatitis

is a priority topic for future research. As new topics are prioritized for future research, careful attention must be paid to study design so that the appropriate clinical questions are addressed in a rigorous fashion.

- **Risk factors for complications of diagnostic and therapeutic ERCP have been explored using multivariable model analysis. Such analyses generate hypotheses for reducing complications, but cannot demonstrate cause and effect. Thus, interventions intended to reduce complications should incorporate prospectively defined studies to evaluate the results.**

The multivariable analyses predicting patient, procedure, or operator risk factors for ERCP complications included in this report suffer from methodological weaknesses that give rise to unstable and potentially misleading results. Younger patient age, suspected sphincter of Oddi dysfunction, use of precut sphincterotomy, and lower operator case volume have been repeatedly associated with increased ERCP complication rates. These findings should be used in setting hypotheses for future research. Intervention programs modifying these identified risk factors to reduce complication rates should incorporate prospectively defined studies to confirm whether the interventions actually reduce complications and improve outcomes.

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Part II, Section 3: Outcomes Of Treatment Using ERCP For Palliation of Pancreaticobiliary Malignancy – Comparison Of Strategies Using ERCP, Surgery, Or Interventional Radiology; A. Comparison of ERCP stent versus surgical bypass

Palliation of malignant biliary obstruction: ERCP endoprosthesis compared with surgical bypass
A. Prospective Randomized Controlled Trials

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Andersen, Sorensen, Kruse et al., 1989	50	50 pts with extrahepatic low biliary obstruction and jaundice Age>60y Pancreatic = 43 Biliary = 7 Both 7Fr and 10Fr stents were used in this study, predominantly 7Fr	**Survival (days),** median (range) Intent-to-treat ERCP (n=25): 84 (3-498) Surgery (n=25): 100 (10-642) Life-table analysis = n.s. Treatment received ERCP (n=30): 81 (3-564) Surgery (n=19): 108 (20-642) Life-table analysis = n.s. **Treatment failures** ERCP: 1 pt failed and treated with surgery Surgery: 3 patients failed at 13-53 days postop and treated successfully with ERCP (no statistical comparison reported) **Hospitalization (days),** median (range)[1] ERCP (n=25): 26 (3-210) Surgery (n=25): 27 (10-202) p=n.s. **Quality of life ratings, % survival time** mean (range): ERCP / Surgery Normal activity 21 (0-86) / 20 (0-91) Limited activity, No aid 36 (0-95) / 31 (0-80) Limited Activity, Aid needed 8 (0-100) / 14 (0-100) Bedridden 19 (0-100) / 18 (0-100) Massive aid needed 16 (0-100) / 17 (0-100) p = n.s.	**Perioperative death (≤ 30 days)** ERCP = 5 (20%) Surgery = 6 (24%) p=n.r. **Complications[2]** Cholangitis (%) ERCP = 28 Surgery = 16 p=n.r. Abscess (%) ERCP = 8 Surgery = 4 p=n.r. Total Severe Infection (%) ERCP = 36 Surgery = 20 p= n.s.	

[1] Comparison of hospital stay was not statistically significantly different when analyzed by treatment received.
[2] Comparison of infectious complication rates by treatment received was ERCP = 30% and surgery = 20%, which was not statistically significant

Palliation of malignant biliary obstruction: ERCP endoprosthesis compared with surgical bypass
A. Prospective Randomized Controlled Trials (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Shepherd, Royal, Ross et al., 1988	52	Pts w/ malignant distal CBD obstruction Randomized: ERCP stent (n=27) Surgical bypass (n=25) Results: ERCP stent (n=23) Surgical bypass (n=25) Baseline characteristics mostly comparable 10 Fr ERCP stents used	**Overall Survival (days),** median (range) ERCP 152 (39-411) Surgery 125 (52-354) Life table analysis=n.s. **Initial Hospitalization (days)**[3], median (range) ERCP (n=23) 5 (2-16) Surgery (n=25) 13 (8-49) p<0.002 **Readmission to Hospital** N (%) ERCP (n=23) 10 (43%) Surgery (n=25) 3 (12%) p=n.r. **Total Hospital stay (days),** median (range) ERCP 8 (2-30) Surgery 13 (8-49) p<0.01 **Relief of jaundice** ERCP (n=23) 21 (91%) Surgery (n=25) 23 (92%) p=n.r.	**Perioperative mortality** ERCP (n=23) 2 (9%) Surgery (n=25) 5 (20%) p=n.s. **Procedural complications, events** ERCP (n=23) 7 Surgery (n=25) 14 p=n.s. **Development of duodenal stenosis** ERCP 2 (9%) Surgery 1 (4%) p=n.r.	

[3] Calculated only in patients who were alive at 30 days postop

Palliation of malignant biliary obstruction: ERCP endoprosthesis compared with surgical bypass
A. Prospective Randomized Controlled Trials (cont'd)

Smith, Dowsett, Russell et al., 1994	204	Pts with probable malignant low bile duct obstruction ERCP[4] (n=101) Surgery (n=103) 10 Fr stents Baseline characteristics comparable	**Survival** (weeks), median ERCP (n=99) 21 Surgery (n=100) 26 p=n.s. **Technical Success** ERCP (n=100) 95 (95%) Surgery (n=101) 94 (94%) p=n.s. **Therapeutic success**[5] ERCP 92% Surgery 92% p=n.s. **Total Hospitalization** (days), median (range) ERCP (n=100) 19 (4-59) Surgery (n=101) 26 (8-85) p=n.s. **Recurrent obstructive jaundice** ERCP (n=100) 36 Surgery (n=101) 2 p=n.s.	**Perioperative Mortality** ERCP (n=100) 8% Surgery (n=101) 15% p=n.s. **Procedure-related Mortality** ERCP (n=100) 3 (3%) Surgery (n=101) 14 (14%) P=0.006 **Major Complications** ERCP (n=100) 11 (11%) Surgery (n=101) 29 (29%) p=0.02 **Minor Complications** ERCP (n=100) 18% Surgery (n=101) 29% p=n.s. **Late Gastric Bypass** ERCP (n=100) 10 Surgery (n=101) 5 p=n.s.	

[4] Stent placement was attempted first with ERCP approach. In 19 patients, a combined percutaneous transhepatic-endoscopic approach was required when initial ERCP failed.
[5] Defined as "a fall in serum bilirubin of at least 20% within 5 days in patients who had a successful procedure (in most patients confirmatory ultrasound evidence of biliary decompression was also obtained". Note data in study Table 3 does not agree with text.

Palliation of malignant biliary obstruction: ERCP endoprosthesis compared with surgical bypass

B. Retrospective studies

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Raikar, Melin, Ress et al., 1996	66	All pts had pancreatic carcinoma 34 ERCP stent 32 surgical bypass **Baseline Characteristics** No significant differences ERCP Surgery Age 72 (44-100) 69 (43-85) Mean PS 0.8 0.9 PS 0,1 79% 59% PS 2 9% 34% PS 3 12% 6% 10-12 Fr stents	**Survival (months),** mean (range) ERCP 9.7 (10d-35) Surgery 7.3 (7d-29) p=0.13 **Hospitalization (days), mean** ERCP 7 Surgery 14 p<0.001 **Rehospitalization (pts)** ERCP 12 Surgery 8 **Initial + Subsequent Costs** ERCP 17,738 Surgery 25,101 p<0.05	**Perioperative mortality** ERCP 1 (2.9%) Surgery 1 (3.5%) **Perioperative morbidity** ERCP 21% Surgery 33% p=n.s.	

Palliation of malignant biliary obstruction: ERCP endoprosthesis compared with surgical bypass

B. Retrospective studies

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Leung, Emergy, Cotton et al., 1983	98	Pts w/ malignant obstructive jaundice 64 ERCP stent 34 Surgical bypass **Baseline Characteristics** Statistical comparisons not reported ERCP Surgery Age 68 (35-91) 60 (25-73) Age>70y 44% 9% Location: Hilum/CHD 30% 3% CBD 14% 6% Pancreatic head 55% 85% Papilla 1.5% 6% 8-10 Fr stents	**Survival (months)** ERCP and Surgery both had median survival approximately 6 months. Not significantly different. **Technical Success** ERCP 89% Surgery 100% p=n.r. **Initial Hospitalization** (days), mean ERCP 14 (4-30) Surgery 30 (14-79) p=n.r.	**Perioperative Mortality** ERCP 10 (16%)[6] Surgery 3 (9%)[7] **Readmission for local complication**[8] ERCP 8 (13%) Surgery 3 (9%)	

[6] Causes of death include 4 metastases, 1 renal failure, 3 cholangitis, 1 pneumonia, 1 strangulated hernia

[7] Causes of death include 1 arterial thrombosis and 2 unknown.

[8] Local complications included cholangitis, recurrent jaundice, duodenal obstruction, or chest wall metastasis.

Part II, Section 3B. Studies comparing metal versus plastic stents to relieve biliary obstruction due to pancreaticobiliary malignancy

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
Davids, Groen, Rauws et al., 1992	105	Patients with irresectable distal bile-duct malignancy Pancreatic ca = 93 Papillary ca = 12 49 metal stent 56 straight polyethylene (poly) stent Baseline Characteristics Well-balanced	**Overall median survival (days)** Metal 175 Poly 147 p=0.45 **Median Patency of 1st stent (days)** Metal 273 Poly 126 p=0.006 **Occlusion rate for secondary poly stents** [9] Metal 0/14 (0%) Poly 11/23 (48%)[10] p=0.002 **Successful initial drainage** Metal 47/49 (96%)[11] Poly 53/56 (95%)[12] **Resource utilization** **Need for additional ERCP** Metal 64 Poly 102 p=n.r. Initial placement of a metal stent in 100 patients would prevent 50 ERCP procedures	**Perioperative mortality** Metal 7 (14%)[13] Poly 2 (4%)[14] p=0.047 **Early complications**[15] (7 days) Metal 6 (12%) Poly 6 (11%)	In the metal-stent group only, univariate analysis showed association between decreased stent patency and jaundice > 14 days before stent (p=0.01) as well as bilirubin > 300 μmol/L (p=0.03)

[9] All second stents implanted for occlusion were polyethylene stents
[10] Six patients required a 3rd stent after a median of 109 days. Three and two patients required and 4th or 5th stent, respectively.
[11] In 1 patient jaundice eventually subsided. The other patient died 11 days after stent placement, and autopsy revealed proximal kinking of the stent.
[12] Jaundice slowly subsided in all 3 patients.
[13] Causes of death were sepsis after recurrent cholangitis (1); cardiac failure (2); cachexia (4).
[14] Causes of death were cachexia (2).
[15] The incidence of mild cholangitis was similar between groups (6 metal; 5 poly). One poly stent patient developed cholecystitis.

Part II, Section 3B. Studies comparing metal versus plastic stents to relieve biliary obstruction due to pancreaticobiliary malignancy (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
Prat, Chapat, Ducot et al., 1998	101	Patients with malignant CBD strictures Not involving hilum Pancreatic ca = 65 Cholangioca = 21 Ampullary ca = 3 Metastatic = 12 Group 1 (n=33) 11.5Fr polyethylene stent, exchanged for dysfunction Group 2 (n=34) 11.5Fr polyethylene stent, exchanged every 3 months Group 3 (n=34) Self-expanding metal stent Baseline characteristics comparable	**Median survival (months)** Group 1 4.8 Group 2 5.6 Group 3 4.5 p=n.s. **Stent Patency or Median symptom-free survival[16] (months)** Group 1 3.2* Group 2 not reported* Group 3 4.8* * $p < 0.05$ comparing Group 1 with combined Groups 2 and 3. No significant difference between Group 2 and 3. **Bilirubin level reduction in 48 hours** Group 1 35.4% Group 2 34.3% Group 3 41% p=n.s. **Total Hospitalization (days)** Group 1 7.4 ± 1.5 Group 2 10.6 ± 1.7 $p_{2,3} = 0.01$ Group 3 5.5 ± 1.4 $p_{1,2}$ and $p_{1,3}$ = n.s. **Resource utilization** Total ERCP / ERCP per patient Group 1 57* / 1.7 ± 1.3 Group 2 85* / 2.5 ± 1.9 Group 3 40 / 1.2 ± 0.4 * $p_{1,2} = 0.05$ p=0.01, ANOVA	No significant difference in complications seen between groups. Overall procedure-related morbidity = 11.9% and mortality = 3.9%. **Proportion of mortality related to jaundice or sepsis** Group 1 11.5% Group 2 14.8% Group 3 7.4% p=n.s.	

[16] This was primary endpoint and defined as timespan between insertion of first stent and the first episode of stent dysfunction

Part II, Section 3B. Studies comparing metal versus plastic stents to relieve biliary obstruction due to pancreaticobiliary malignancy (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Randomized Controlled Trials					
Prat, Chapat, Ducot et al., 1998 (cont'd)	101		**Mean costs per patient (95% CI)** <u>Overall observed costs</u> Group 1 5547 (4082-7013) Group 2 6770 (5394-8146) Group 3 4643 (4207-5079) Overall cost advantage for group 3, p=n.r. <u>For pt surviving < 3months</u> Group 1 3715 Group 3 4246 (15% more than Group 1) <u>For pt surviving < 6 months</u> Group 1 4533 Group 2 4887 (8% more than Group 1 Group 3 4544 (same as group 1)		

Part II, Section 3B. Studies comparing metal versus plastic stents to relieve biliary obstruction due to pancreaticobiliary malignancy (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Retrospective Study					
Schmassmann, Von Gunten, Knuchel et al., 1996	165	Consec pts w/ irresect-able malignant biliary obstruction Initial stent placed: 95 metal stents ('92-93) 70 plastic stent ('90-91) Stent occlusion rx w/ plastic stent placement. Plastic stents were 14% 10 Fr and 86% 12 Fr Baseline characteristics were comparable for age, gender, bilirubin, type of tumor and stage, location of stricture, or associated procedures. 87% of metal stent and 100% of plastic stent patients had sphincterotomy.	**Median survival (months)**[17] Metal 6.5 Plastic 4 p<0.05 **Relief of jaundice after 3-5 weeks** Metal 95% Plastic 88% p = n.s. **Median patency of 1st stent (months)**[18] Metal 10 Plastic 4 p<0.001 **Median patency of 2nd stent, all plastic** (months) Metal initial 8 Plastic initial 3 p<0.05 **Resource utilization** Mean ERCP per patient Metal 1.2 Plastic 1.58 p<0.005 Thus, initial placement of metal stents in 100 patients would save 38 ERCP procedures.	**Perioperative Mortality** Metal 2% Plastic 3% p=n.s.	

[17] When 29 subjects (8 metal stent, 21 plastic stent) who died related to untreated stent dysfunction were excluded from the analysis, the remaining 136 subjects had similar survival between the two groups.

[18] Subgroup analysis did not show any significant difference between different locations (common bile duct vs. hilar or intrahepatic stricture) but numbers were small in the hilar and intrahepatic subgroups.

Part II, Section 4. Management of jaundice before surgical resection of pancreaticobiliary malignancy: Preoperative stent versus immediate surgery
A. Randomized Controlled Trials

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Lygidakis, van der Heyde, Lubbers et al., 1987	38	38 pts with resectable pancreatic head carcinoma Group A = 19 preop ERCP placed stent Group B = 19 w/o stent	**Laboratory values** Baseline: A / B; Preoperative: A / B WBC ** 9.3 / 8.2 / 14.6 / 9.1 Bilirubin * 18.4 / 19.2 / 11.5 / 20.1 Alk Phos* 895 / 689 / 498 / 697 AST/SGOT* 104 / 141 / 75 / 149 ALT/SGPT* 152 / 181 / 129 / 195 PT 3 / 3 / 3 / 3 Platelets 170 / 179 / 275 / 199 Clot time 75 / 76 / 65 / 71 * = significant reduction for Group A, p<0.002 ** = significant increase for Group A, p<0.001 Baseline / Postoperative Bile cult (+) 10 / 9 / 6 / 12 Blood cult (+) 4 / 5 / 1 / 6 Biliary pressure[19] -- / -- / 8 / 25 p<0.001 when all 3 correlated and combined No difference noted for hematocrit, creatinine, or albumin **Hospitalization (total days for group)** Preop / Postop / Combined Stent 135 / 304 / 439 No Stent 70 / 437 / 507 p=n.r.	**Perioperative Mortality** Stent = 0 No stent = 2 p=n.s. (1 sepsis, 1 aneurysm) **Perioperative morbidity** Stent = 3 No Stent = 14 p<0.005 **Peroperative Blood Loss** Stent = 800 ± 100 ml No Stent = 1800 ± 200 ml p = n.r. **Operative time** Stent = 5 ± 2 h No Stent = 7 ± 2 h p = n.r.	This study has been noted to have a high baseline rate of cholangitis in the no stent group. Leaving the Group B patients with clear signs of infection undrained preoperatively probably accounts for the higher rate of complications in this group.

[19] Mean cm H_20

Part II, Section 4. Management of jaundice before surgical resection of pancreaticobiliary malignancy: Preoperative stent versus immediate surgery
A. Randomized Controlled Trials (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Lai, Mok, Fan et al., 1994	87	Malignant obstructive jaundice Group A = preop stent, n=43 Group B = no preop stent, n=44	**Technical Success of preop stent =** 37 (86%) **Laboratory values** Baseline A B / Preoperative A B Bilirubin * 266 209 151 264 Alk Phos* 498 376 338 555 ALT/SGOT 122 132 77 114 AST/SGPT* 156 216 80 163 * = p<0.05 for preoperative comparison between groups No significant differences were noted between groups for Hb, Hct, BUN, creatinine, or albumin	**Hospital Mortality** (not specified to be 30-day) Stent (n=43) 6 (14%) No Stent (n=44) 6 (14%) p=n.s. **Postoperative Complications** Stent (n=41) 16 (39%) No Stent (n=44) 18 (41%) P<0.9 **Total Complications** Stent (n=41) 23 (56%) No Stent (n=44) 18 (41%) P<0.17 Level of obstruction had no statistically significant effect on morbidity and mortality	"Analysis of the available data [at the planned interim data analysis] showed that the estimated sample size was inadequate. As the hospital mortality of the two treatment groups were close, inclusion of the remaining patients as planned would have added no further information and the trial was therefore terminated."

Part II, Section 4. Management of jaundice before surgical resection of pancreaticobiliary malignancy: Preoperative stent versus immediate surgery
B. Retrospective Studies

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Sewnath, Birjmohun, Rauws et al., 2001 Same series as Karsten, Allema, Reinders et al., 1996 but subjects accrued June 1992 – Dec 2000	290	Patients with presumed resectable tumor in pancreatic head region 232 had preop drainage - 192 stent+papillotomy - 27 papillotomy alone - 13 required percutaneous combined drainage procedure 58 with no drainage were - 25 had dx ERCP only - 24 not jaundiced - 9 failed drainage and got immediate surgery Subgroups for analysis by preoperative bilirubin level Grp I (<40μmol/L) Grp II (40-100μmol/L) Grp III (>100 μmol/L)	**Degree of Preoperative Jaundice in Preop Drainage Patients** Preoperative bilirubin level (μmol/L) — Degree of Jaundice 177 (76%) <40 — none 32 (14%) 40-100 — moderate 23 (10%) >100 — severe **At least 50% reduction in bilirubin by bilirubin group** Grp I 87% Grp II 81% Grp III 78% **Postoperative Hospital Stay** median days(range) Grp I 13 (6-167) Grp II 15 (12-39) Grp III 15 (10-70) No drain 16 (8-222) p=0.09	**Drainage procedure-related complications** 14/232 (6%) had complication 4 duodenal perforation 4 pancreatitis 6 bleeding **Cholangitis** 27 (12%) patients and 21 (9%) needed stent replacement **Post-drainage morbidity** 77 (33%) developed recurrent jaundice from stent dysfunction **Postoperative Complication** Preop drain 50% No drainage 55% p=0.69 **Incidence of anastomotic leakage after surgery** Preop drain 14% No drainage 7% p=0.19 **Mortality** Preop drain 3/232 (1.3%) No drainage 0/58 p=n.r.	

Part II, Section 4. Management of jaundice before surgical resection of pancreaticobiliary malignancy: Preoperative stent versus immediate surgery
B. Retrospective Studies (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Karsten, Allema, Reinders et al., 1996	241	Patients with presumed resectable tumor in pancreatic head region 184 had preop drainage - 149 stent + papillotomy - 25 papillotomy alone - 10 external drainage when ERCP stent not possible 57 with no drainage were not jaundiced (n=33) or had immediate operation planned (n=24) 10 Fr Stents were placed only if papillotomy did not provide adequate drainage Baseline characteristics No significant differences between 4 groups in age, year of operation, tumor type, type of operation, *method of preoperative drainage* (??)	**Median reduction in bilirubin concentration** ERCP stent 82% ERCP papillotomy 74% External drainage 50% p=0.0036 **Bile Cultures (+)** (n=195) ERCP stent = 94% ERCP papillotomy = 59%, p=0.001 External drainage = 62%, p=0.01 No drainage = 34%, p=0.000001 Agreement between bile and other infection cultures in 48% (40/84)	**Cholangitis** ERCP stent = 51 episodes and 43 (29%) needed stent replacement Information on other groups not reported. **Postoperative Complication**[20] **Bilirubin vs. Use of preop drainage** Bili Conc μmol/L — Preop drainage — No Drain — p 0-40 61/118(52)* 20/34 (58) 0.6 40-100 21/38 (60) 1/1 (100) 1.0 > 100 20/28 (71)* 14/22 (63) 0.8 Total 102/184 (56) 35/57 (61) 0.4 * p=0.09 **Infective Complication** Stent 49/149 (33%) Papillotomy 11/25 (44%) External drain 6/10 (60%) No drainage 18/57 (32%) Total 84/241 (35%) p=n.r.	

[20] Authors conclude that preoperative biliary drainage did not reduce postoperative morbidity irrespective of the mode of biliary drainage applied.

An alternative conclusion, since the selection process favored preop drainage for jaundiced patients and no preop drainage for non-jaundiced patients, the observation that postoperative complication rates were similar regardless for those drained and not drained could suggest that the selective use of preoperative drainage reduces the complication rate to the level expected in those who do not require drainage.

Part II, Section 4. Management of jaundice before surgical resection of pancreaticobiliary malignancy: Preoperative stent versus immediate surgery
B. Retrospective Studies (cont'd)

Study	N	Population and Interventions	Outcomes	Adverse Events	Comments
Heslin, Brooks, Hochwald et al., 1998	74	Patients undergoing pancreaticoduodenectomy who were part of a separate RCT	**Postop Hospital Days** (median) Stent 11 No Stent 10 p=0.04 **Preop Laboratory Values** Serum bilirubin, AST/SGOT significantly lower than no stent group. Albumin and alkaline phosphatase trended lower but not statistically significant. BUN, creatinine, albumin, WBC no different.	**Perioperative Mortality** Stent 1 (2.6%) No Stent 0 (0%) p=0.34 **Perioperative Complications** Stent 23 (59%) No Stent 12 (34%) p=0.04	
ten Hoopen-Neumann, Gerhards, van Gulik et al., 1998	52	Patients with Klatskin tumor with planned resection 41 of 52 had preop stent Main reasons for no stent were technical failure or lack of proximal congestion of bile Baseline characteristics similar for gender and age, w/ slight differences in classification of hilar tumor between groups	**Total serum bilirubin**[21], mean (range) Stent 117 (12-511) No Stent 235 (14-412) p=0.008	**Occurrence of Implantation Metastasis, 1 yr** Stent = 8/41 (20%) No stent = 0 p = 0.18 4 of 8 patients with implantation metastases did not receive any postoperative radiation therapy. Overall, 37% of stented patients and 27% of non-stented patients did not receive radiotherapy (p=not reported)	

[21] Serum bilirubin levels reported in μmol/L (micromol/L)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Quality					
Freeman, DiSario, Nelson, et al., 2001 Prospective, observational study	1,963 consecutive ERCPs in 11 U.S. centers during study periods ranging from 6 months to 3 years from December 1995 to December 1998. Simple endoscopic stent removals without attempted cannulation were excluded. Indication (%): Diagnostic=18.0 Manometry plus diagnostic=4.9 Therapeutic=77.1	Patient and procedure-related data were prospectively recorded by the endoscopist on a data collection sheet at the time of ERCP. 30-day follow-up was performed by a research assistant and was obtained by clinic or telephone interview with the patient, and by chart review. Risk factors were first evaluated by univariate analysis. Significant predictors on univariate analysis were then included in a forward stepwise multiple logistic regression model.	**Patient-related factors** Age Chronic pancreatitis Distal CBD diameter Gender History of acute pancreatitis of any etiology History of post-ERCP pancreatitis Pancreas divisum Presence of definite CBD stone Previous sphincterotomy Prior cholecystectomy Prior failed ERCP Recurrent abdominal pain Serum bilirubin Suspected SOD **Procedure factors:** >1 pancreatic contrast injection >1 pancreatic deep wire pass/cannulation Acinarization of pancreas Cholangiogram Pancreatogram Biliary sphincter balloon dilation for stone Biliary sphincterotomy Intramural contrast injection Minor papilla cannulation Moderate or difficult cannulation Pancreatic duct tissue sampling Pancreatic sphincterotomy Pancreatic stent placement Pancreatic stricture dilation Precut papillotomy SOD manometry **Provider factors:** Endoscopist performing >2 ERCP/week Training fellow involved	<u>Main Endpoint:</u> Pancreatitis (N=131)	No significant differences in the risk of pancreatitis between diagnostic and therapeutic ERCP. <u>Adjusted OR (95% CI) (Post-ERCP pancreatitis, n=131):</u> History of post-ERCP pancreatitis=5.35 (2.97-9.66) Biliary balloon sphincter dilation=4.51 (1.51-13.46) Moderate to difficult cannulation=3.41 (2.13-5.47) Pancreatic sphincterotomy=3.07 (1.64-5.75) <u>≥</u>1 pancreatic contrast injections=2.72 (1.43-5.17) Suspected SOD=2.60 (1.59-4.26) Female gender=2.51 (1.49-4.24) Normal serum bilirubin=1.89 (1.22-2.93) Absence of chronic pancreatitis=1.87 (1.00-3.48) <u>Cumulative adjusted OR associated with multiple risk factors:</u> Female=2.5 Female+normal bilirubin=4.8 Female+normal bilirubin+SOD=12.4 Female+normal bilirubin+difficult cannulation=16.2 Female+normal bilirubin+SOD+difficult cannulation=42.1

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Quality (cont'd)					
Masci, Toti, Mariani, et al., 2001 Prospective, observational study	2444 consecutive diagnostic or therapeutic ERCPs performed on 2103 patients from June 1997 to December 1998 in 9 endoscopic units in Italy. Mean age=64.6±15.7 years Gender=55.5% female Indication for ERCP/ES (%): Choledocholithiasis (including pancreatitis due to gallstones)=62.6 Placement of biliary stent for malignant obstruction=17.5 Treatment of SOD=7.3 Miscellaneous=2.5	Data was collected at the time of ERCP/ES and before hospital discharge. 150 variables including demographic details, referral pattern, clinical condition, medical history, results of blood tests, sedation, techinical procedures, and endoscopic and radiologic findings were collected. For each potential risk factor univariate analysis was conducted. Only factors significant in the univariate analysis were included in the Multivariable logistic regression analysis.	Patient factors: Age Characteristics of orifice of papilla Characteristics of papilla Clinical history Diameter of common bile duct Gender Indication for ERCP/ES Previous dilation of the papilla Stone size Stones in gallbladder Procedure factors: Biliary or pancreatic opacification Contrast medium Placement of nasobiliary drainage Placement of stent Sphincterotomy technique Stone removal	Main endpoint: Any complication[22] (n=121 pts) Including: Pancreatitis (n=44 proc) Hemorrhage (n=30 proc)	Adjusted OR (All complications, n=121) Age (≤ 60 years)=1.53 (95% CI=1.06-2.20) Sphincterotomy technique (precut vs. other)=1.70 (95% CI=1.10-2.68) Stone removal (no vs. yes)=2.52 (95% CI=1.44-4.53) Adjusted OR (Pancreatitis, n=44) Age (≤ 60 years)=2.11 (95% CI=1.16-3.80) Sphincterotomy technique (precut vs. other)=2.80 (95% CI=1.38-5.84) Stone removal (no vs. yes)=3.35 (95% CI=1.33-9.10) Adjusted OR (Hemorrhage, n=30) Sphincterotomy technique (precut vs. other)=2.45 (95% CI=1.60-5.39) Orifice of papilla of Vater (obstructed vs. other)=2.57 (95% CI=1.69-6.17)

[22] Complications of diagnostic or therapeutic ERCP defined as any adverse event requiring more than one night of hospitalization. Included Pancreatitis, Hemorrhage, Cholecystitis, Cholangitis, Perforation during ES, Perforaton during endoscope, Basket trapping, Cardiopulmonary events, Drug side effects, Deaths

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Quality (cont'd)					
Freeman, Nelson, Sherman, et al., 1996 Prospective, observational Study	2420 consecutive patients undergoing biliary sphincterotomy in 16 institutions in the U.S. and Canada from 1992 to 1994. 73 (3.0%) of patients were lost to follow-up and excluded from the analysis, leaving 2347 patients. Indication for sphincterotomy (%): Stone in CBD =68.2 Placement of biliary stent for malignant obstruction-13.2 Suspected SOD=11.6 Placement of a stent or dilation of benign strictures=4.2 Miscellaneous conditions=7.8 More than one indication for sphincterotomy was recorded for 5.0% of patients.	All sphincterotomies performed in an attempt to establish access to the bile duct were included. Patients in whom attempts at biliary cannulation without sphincterotomy failed and those who underwent pancreatic sphincterotomy were excluded. Data was collected at the time of the procedure, before discharge, and approximately 30 days after sphincterotomy. Patients were interviewed and charts were reviewed by means of a standardized questionnaire. Univariate analysis and simple logistic regression analysis were used to assess potentially relevant risk factors. Significant predictors were then included in a forward, stepwise logistic regression analysis to identify the most important risk factors for pancreatitis, hemorrhage, and overall complications. Patients for whom relevant data was missing were excluded from analysis.	<u>Patient factors:</u> Age Cholangitis Cirrhosis Coagulopathy before procedure Distal bile duct diameter Gender Indication other than BDS Number of coexisting illnesses Periampular diverticulum Sphincter of Oddi dysfunction Bilroth II gastrectomy <u>Procedure factors:</u> Acinarization of pancreas Bleeding during procedure Combined percutaneous-endoscopic procedure Dificulty of cannulation Emergency procedure Failed biliary access or drainage Number of pancreatic contrast injections Precut sphincterotomy <u>Provider factors:</u> Case volume University affiliated center Participation of a trainee	<u>Main Outcome:</u> All complications within 30 days <u>Including:</u> Pancreatitis Hemorrhage	<u>Adjusted OR (All complications, N=229 pts)</u> Difficulty of cannulation=3.05 (95% CI=1.83-5.08) Precut sphincterotomy=3.61(95% CI=1.78-7.34) Combined percutaneous-endoscopic procedure= 3.40 (95% CI=1.04-11.13) Suspected SOD=2.90 (95% CI=1.70-4.94) Cirrhosis=2.93 (95% CI=1.48-5.90) <u>Adjusted OR (Pancreatitis, N=127 pts)</u> Suspected Sphincter of Oddi dysfunction =5.01 (95% CI=2.73-9.22) Younger age=2.14 (95% CI=1.41-3.25) Precut sphincterotomy =4.34 (95% CI=1.73-10.88) Difficulty of cannulation =2.40 (95% CI=1.07-5.36) Number of pancreatic contrast injections =1.35 (95% CI=1.04-1.75) <u>Adjusted OR (Hemorrhage, N=48 pts)</u> Coagulopathy before procedure=3.32 (95% CI=1.54-7.18) Anticoagulation within 3 days of procedure=5.11 (95% CI=1.57-16.68) Cholangitis before procedure=2.59 (95% CI=1.38-4.86) Mean case volume of endoscopist - $\leq$1/week=2.17 (95% CI=1.12-4.17) Bleeding during procedure=1.74 (95% CI=1.15-2.65)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Rabenstein, Schneider, Bulling, et al., 2000 Prospective, observational study	438 consecutive endoscopic sphincterotomies performed from September 1994 through December 1996. Mean age=61.3±16.4 years Gender=55.5% males Indication for sphincterotomy (%): CBD stones=37.7 Malignancies=23.3 Chronic pancreatitis= 21.9 Other=17.1	Patients were followed up using physical exams and blood samples at 4, 24, and 48 hours after ES. Clinical observations were recorded throughout the patient's hospital stay. After 30 days family physicians were contacted by phone or mail to monitor any later occurrence of complications. Inclusion criteria for the Multivariable logistic regression model were a univariate p-value of <0.1. Variables with a p-value >0.05 in the last step of the Multivariable model were excluded via variable selection. Only variables with a p-value <0.05 were included in the final model. Due to the low number of events, Multivariable analysis of hemorrhage was not conducted.	Patient factors: Age Anemia Coagulopathy Diabetes mellitus Gender NSAID treatment Intensive-care patient Pancreas divisum Pancreatic obstruction Previous gastrectomy Previous jaundice Previous post-ERCP pancreatitis Laparoscopic cholecystectomy Procedure factors: Anticoagulation Conventional cholecystectomy Emergency ES ES frequency Failed procedure Nasobiliary tube NKP involvement Pancreatic cannulation Pancreatic contrast Size of sphincterotomy Sphincterotomy procedures Operator factors: ES caseload Participation of trainee	Main Outcome: All complications Including: Acute pancreatitis Hemorrhage Cholangitis Technical	Adjusted OR (All complications, N=33) Age ≤60 years=2.9 (95% CI=1.33-6.21) Coagulopathy=9.7 (95% CI=1.95-48.10) Pancreas divisum=7.6 (95% CI=1.56-36.6) Pancreatic obstruction=0.07 (95% CI=0.01-0.59) AOR (Pancreatitis, N=19) Pancreas divisum=8.2 (95% CI=1.91-34.79) Endoscopist ES case load <40/year=3.8 (95% CI=1.44-10.00)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Loperfido, Angelini, Benedetti, et al., 1998 Prospective, observational study	1827 Therapeutic ERCP drawn from 3,356 ERCPs carried out in 2,769 patients from 9 endoscopy centers in Italy during the period from February 1992 to January 1994. Every unit that participated included all patients who underwent ERCP, on an intention-to-treat basis. ERCP was performed by a single operator or team of no more than 3 endoscopists. Large centers performed more than 200 endoscopies/year (3 centers). Median age=66 years (range=7-93 years) Gender=45.5% male ERCP performed on an urgent basis in 9.5% of cases.	Data was collected at the time of ERCP, before discharge, and in cases of readmission, within 30 days. The attending physician's record and medical records were reviewed. Univariate and Multivariable analyses were conducted. A forward stepwise regression analysis was performed for the Multivariable analysis of complications.	<u>Patient factors:</u> Age Bile duct size Gender Jaundice Papillary diverticulum Billroth II gastrectomy <u>Procedure factors:</u> Emergency ERCP Intramural injection of contrast agents Pancreatic opacification Precut ES Pure vs. blended cut Repeat ERCP <u>Provider Factors:</u> Center size Small center, <150 ERCP/yr	<u>Main Outcome:</u> All complications <u>Including:</u> Pancreatitis Hemorrhage Cholangitis Retroperitoneal perforation	<u>Adjusted OR (Therapeutic ERCP, overall complications, N=98)</u> Small center=2.93 Precut=1.73 <u>Adjusted OR (Pancreatitis, N=29)</u> Age < 70 year=1.11 Pancreatic duct opacification=2.84 Nondilated duct=2.85 <u>Adjusted OR (Hemorrhage, n=21)</u> Small center=2.98 <u>Adjusted OR (Cholangitis, n=21)</u> Small center=4.22 Jaundice=4.14 <u>Adjusted OR (Retroperitoneal Perforation, n=12)</u> Billroth II procedure=11.70 Precut=7.19 Intramural injection=6.86

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Mehta, Pavone, Barkun, et al., 1998 Retrospective study (? Prospective database)	535 patients who underwent ERCP for suspected common bile duct stones over a five- year period in one university. 45 with complications and 490 randomly selected from 1194 uncomplicated cases. A single endoscopist carried out the majority of ERCPs. Mean age=56.6 ±18.5 years (range=17-91 years, median=59 years) Gender=38% male Sphincterotomy=47 %	Data were obtained by fellows and attending staff from an ongoing endoscopic database. Complementary information was collected from hospital charts, endoscopc reports, abdominal ultrasound, and ERCP films. Univariate and Multivariable analyses were conducted. The ability of a single clinical variable to predict the occurrence of a complication was assessed in this fashion. Multivariable logistic regression models were then constructed to evaluate the clinical and laboratory predictors. Predictors of complications were studied amongst all patients, as well as in subgroups of patients undergoing and not undergoing endoscopic sphincterotomy.	Patient factors: Age Amylase level CBD diameter CBD stones found at ERCP Gender History of pancreatitis Prelaparoscopic cholecystectomy Procedure factors: Pancreatic channel opacification Sphincterotomy	Main endpoint: Pancreatitis (n= 34)	*Subgroup undergoing endoscopic sphincterotomy:* Risk factors for pancreatitis: Age < 59 years (p=0.04) Absence of a CBD stone at ERCP (p=0.004) Subgroup NOT undergoing endoscopic sphincterotomy: Risk factors for pancreatitis: Pancreatic channel opacification (p=0.05)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Neoptolemos, Shaw, and Carr-Locke, 1989 Retrospective study (part prospective)	190 patients who had ES were drawn from 439 consecutive patients who underwent operative exploration of the CBD and/or ES for CBD stones form 1981 to 1985. ES was the only intended procedure for 132 and in 58 cases it was followed by surgery as part of deliberate treatment.	Clinical and hematologic/ biochemical variables were captured at the time of admission. Medical risk factors were also recorded. Univariate analysis and Multivariable analysis was performed. Multivariable stepwise logistic regression analysis was used to identify independently significant factors for use in predicting complications.	<u>Patient factors:</u> Age Gender Jaundice Temperature Acute cholangitis Acute pancreatitis Medical risk factors Hemoglobin Hematocrit White blood cell count Urea Creatinine Total proteins Albumin Alkaline phosphatase Glutamyl transpeptidase Alanine transaminase Bilirubin Preoperative ES	<u>Main Outcome:</u> All complications <u>Including:</u> Acute pancreatitis (N=3) Hemorrhage (N=5) Acute cholangitis (N=15) Septicemia (N=4) empyema of gallbladder (N=2) Gastric erosions (N=2) Cardiac failure (N=2) Perforation (N=1) Death (N=11)	<u>Significant independent risk factors for post-ERCP complications (N=32):</u> Elevated bilirubin Elevated serum albumin.

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Tzovaras, Shukla, Kow, et al., 2000 Prospective, observational study	372 patients who had an ERCP performed between January 1, 1997 and December 31, 1997. Median age=66 years (range=13-95 years) Gender=42.2% male Indications (N): **Urgent (N=75)** Cholangitis=47 Acute biliary pancreatitis=21 Post-surgery complications=7 **Elective (N=297)** Choledocholithiasis =120 Malignant jaundice=52 Benign stricture/injury=51 Suspected SOD=40 Miscellaneous=34	Using a standardized form, data was collected during the procedure, and following discharge from the hospital at least once 4-6 weeks after the procedure at the outpatient clinic. Mortality and morbidity were defined as 30-day or in-hospital stay. Potential relevant risk factors were assessed separately with risk ratios and confidence intervals calculated for each variable. Significant predictors on univariate analysis were then included in a stepwise multiple regression analysis.	<u>Patient factors:</u> Age Previously failed ERCP Choledocholithiasis Gender Malignant jaundice <u>Procedure factors:</u> Sphincterotomy Stent manipulation Suspected SOD Therapeutic ERCP Urgent ERCP Balloon clearance Balloon dilation Basket clearance Manometry Need for PTC Needle-knife sphincterotomy	<u>Main Endpoint:</u> All Complications (N=21) <u>Including:</u> Death (N=5) Pancreatitis (N=5) Hemorrhage (N=1) Cholangitis (N=7) Perforation (N=2) Aspiration (N=1)	<u>Adjusted OR (95% CI) (All complications)</u> Need for PTC=10.27 (2.30-45.83) Suspected SOD=8.57 (2.59-28.43) Malignant jaundice=4.76 (1.46-15.58) Previously failed ERCP=4.66 (1-21.80)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Motte, Deviere, Dumonceau, et al., 1991 Retrospective study (case-control)	105 total patients: 34 cases of septicemia (documented by positive blood culture) after ERCP stent placement and 71 selected controls (no documented bacteremia, infectious complication, or post-ERCP fever) drawn from 313 remaining patients who had ERCP stent placement. Mean age (+SD: Septicemia=69±11 No Septicemia=68±14 Gender (% male): Septicemia=56 No Septicemia=48	Patient charts reviewed for the following data: age, gender, underlying conditions, previous endoscopic procedures, cholangitis before endoscopic biliary therapy, antibiotic treatment administered before the procedure, type of biliary drainage, radiologic-endoscopic diagnosis, laboratory values, and microbiologic data Discriminant analysis performed with septicemia as the dependent variable and the clinical and biological data prior to the procedure as independent variables. A second analysis was performed including the clinical data following the endoscopic procedure. A discrimant analysis was also conducted of patients with *P. aeruginosa* (exogenous source) compared with patients with *E. coli* septicemia (endogenous source) to predict the microorganism involved .	Variables included in the primary analysis (variables preceding the procedure): Patient factors: Age Gender Associated Diseases Previous manipulations of the biliary tract Antibiotic therapy Prior Cholangitis Status as a preferred patient White blood cell counts Serum levels of bilirubin Alkaline phosphatase Level of stricture (CBD or hilum) Variables included in the second analysis (additional variables following the procedure): Procedure factors: Use of combined percutaneous and endoscopic drainage Quality of drainage (complete or incomplete)	Septicemia (n=34)	Prediction of septicemia including variables preceding the procedure: Prior Cholangitis (F=7.1)* White blood cell count (F=6.6)* * A linear combination of these variables failed to predict the outcome in 50% of cases. Prediction of septicemia including additional variables following the procedure: Quality of drainage incomplete (F=319.2)** **91% of cases identified. No other variable entered into this analysis. For the prediction of Pseudomonas aeruginosa septicemia including pre-procedure variables: Referral from another center (F=6.3)*** ***Age and antibiotic therapy were also selected resulting in the correct classification of 67% of cases. For the prediction of Pseudomonas aeruginosa septicemia including post-procedure variables: Referral (F=6.3) Combined percutaneous-endoscopic drainage (F=5.2) Diagnosis of hilum or CBD stricture (F=4.4)**** **** With the addition of age, these variables correctly classified 83% of cases.

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Lai, Lo, Choi, et al., 1989 Retrospective, cohort study	323 patients who underwent diagnostic ERCP at one institution from January 1984 to July 1987. All patients had biliary obstruction on endoscopic cholangiograms. The majority of patients (54%) had previous attacks of acute cholangitis.	Clinical records and cholangiograms were reviewed to identify risk factors for acute cholangitis. Univariate and stepwise logistic regression were used to identify significant risk factors for acute cholangitis.	<u>Patient factors:</u> Type of obstruction Type of lesion Total bilirubin Alkaline phosphatase Alanine transaminase (ALT) Asparatate transaminase (AST) Glutamyl transpeptidase White blood count Fever	<u>Main Outcome:</u> Acute cholangitis (n=21)	Acute Cholangitis, n=21: <u>Results of stepwise logistic regression:</u> Pathologic nature of the obstructive lesion, malignant vs. benign (discriminant coefficient=1.75, $p<0.002$) Fever (>37.5° C) within 72 hours prior to examination (discriminant coefficient=2.73, $p<0.0001$) ***<u>Subgroup analysis excluding the 43 febrile patients (n=280):</u>*** Nature of the biliary obstruction (discriminant coefficient=2.12, $p<0.01$) Serum AST $\leq$70 IU (discriminant coefficient=2.09, $p<0.04$)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Boender, Nix, de Ridder, et al., 1994 Prospective, observational study	242 consecutive patients who underwent ERCP sphincterotomy for CBD stones. No previous gastric surgery, papillotomy, or other pancreatobiliary diseases such as cholangitis, pancreatitis, or parenchymal liver disease. Mean age=70 years (range=32-97 years) Gender=35.5% male Average duration of symptoms=9 months (8 days-10 years)	Endoscopic findings, therapeutic procedures, and acute complications of sphincterotomy were recorded during ERCP or within 5 days. In addition, 3 months after ERCP, a questionnaire was sent to the patient's general practitioner and referring specialist to ascertain the patient' clinical condition and remaining complaints and complications. Risk factors statistically analyzed using univariate and Multivariable logistic regression.	<u>Patient factors:</u> Age CBD size Location and presence of JPD Presence and position of diverticulum Presence of GB <u>Procedure factors:</u> Papillotomy procedure (Standard vs. precut ES) Drainage procedure Size of papillotomy Failed procedure	<u>Main Outcome:</u> All complications combined (N=34) <u>Including:</u> Pancreatitis Bleeding Cholangitis Retroperitoneal leakage	<u>Adjusted OR (All complications)</u> Precut vs,. standard papillotomy=4.9, p=0.001 Failed endoscopic biliary drainage vs. successful biliary drainage=34.8, p=0.007 Failed therapeutic precut vs. successful=5.9, p=0.098 Failed diagnostic precut vs successful=0.28, p=0.321 Location of papilla in relation to JPD -Outside vs. without=3.1, p=0.072 -Lower rim vs. without=4.3, p=0.015 -Inside vs. without=9.4, p=0.002.

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Nelson and Freeman, 1994 Retrospective study	189 patients (191 sphincterotomies) undergoing endoscopic biliary sphincterotomy form July 1987 to July 1991 at one institution. All sphincterotomies were performed by one of two gastroenterologists. Charts were unavailable for 4 patients and they were excluded from the analysis. Mean patient age=66±19 years Gender=57% male Indication for sphincterotomy (%): Choledocholithiasis = 38.2 Cholangitis=26.7 Tumor/stricture=13.6 Gallstone pancreatitis=8.4 SOD/papillary stenosis=8.9 Bile leak=2.1 Other=2.1	Data was recorded at the time of initial or follow-up endoscopy and charts were reviewed for laboratory. clinical parameters, medication use, type and outcome of interventions, and mortality. Relative risks with Fisher's Exact Test were used for univariate analysis of risk factors. Multiple logistic regression analysis with forward stepwise selection was then conducted.	<u>Patient factors:</u> Aspirin/NSAID use CBD diameter Hemodialysis Prothrombin time Sphincter of Oddi dysfunction <u>Procedure factors:</u> Bleeding at ES ES length	<u>Main Outcome:</u> Hemorrhage (n=10)	<u>Adjusted OR (Hemorrhage, n=10)</u> Hemodialysis=16.4 (95% CI=2.9-93.1) Prothrombin time 2s > control=12.1 (95% CI=1.8-90.9) Bleeding seen at ES=13.7 (95% CI=2.2-87.3)

Part V, Section 1: Multivariable Analyses

Article/Study Design	Study Population	Data Acquisition Methods/ Analysis	Risk Factors Assessed	Outcomes Assessed	Results
Fair Minus Quality					
Maldonado, Brady, Mamel, et al., 1999 Retrospective study	Records of 100 consecutive patients referred for suspected SOD and who underwent sphincter of Oddi manometry 1992–1996 at two university-affiliated hospitals reviewed. Group 1= patients who only had SOM (54%) Group II= patients who had SOM and ERCP with or without sphincterotomy (46%). Groups I and II further subdivided (A and B) into normal SOM and abnormal SOM (Group IA=79.6%, Group IB=20.4%, Group IIA=23.9%, Group IIB=76.1%). Mean age=47+14.2 years (range=23-83 years) Gender=9% male SOD biliary type II=37 patients SOD biliary type III=58 SOD pancreatic type II=1 patient SOD pancreatic type III=4 patients	Patient and procedure data recorded from the medical records. Univariate and Multivariable analyses were performed. Multiple regression analysis was used to determine the independent predictors of pancreatitis.	<u>Patient factors:</u> Age Clinical type of sphincter of Oddi dysfunction Gender <u>Procedure factors:</u> Doses of medication Duct cannulated ERCP with or without sphincterotomy performed during the same session Length of procedure Sphincter of Oddi pressures	<u>Main Outcome:</u> Pancreatitis	# pts w/ pancreatitis Grp I - SOM only (n=54) (A) 43 normal SOM 4 (B) 11 abnormal SOM 1 Grp II – SOM and ERCP (n=46) (A) 11 normal SOM 3 (B) 33 abnormal SOM got ES 9 2 abnormal SOM but no ES Multiple regression analysis, including all potential predictors revealed: Only ERCP had an independent association with the development of pancreatitis. Endoscopic sphincterotomy (ES) added no additional risk for pancreatitis beyond that associated with ERCP.

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Appendix A. All Retrieved, Excluded Publications

The following reference list shows all publications that were retrieved for review and then not included in the final group of studies for evidence review. The possible reasons for exclusion are listed in the table. Abbreviations denoting the reason for exclusion are printed within each citation (following).

AND	Not prospective in Design OR does Not have consecutively enrolled patients in a retrospective design OR is a single-arm study.
ANMJ	Not a full length report in a peer-reviewed Medical Journal
ANNQ	Content does not address one of the key questions
AN25	Study is not clearly only diagnostic or therapeutic but is excluded for having less than 25 subjects
R	REVIEW=Article presents no original data
DCOM	No comparison between an eligible diagnostic alternative and ERCP for KQ1-4 Diagnostic.
DPOP	No relevant patient population
DN25	Fewer than 25 subjects.
DN50	Fewer than 50 subjects (KQ1 stones only).
DNSI	Not Sufficient Information in study to calculate 2X2 contingency tables
DNCC	Diagnostic populations are not comparable
TCOM	No comparison between an eligible therapeutic alternative and ERCP for KQ1-4 Therapeutic.
TPOP	No relevant patient population
TN25	Fewer than 25 subjects in each treatment group analyzed separately
TNRO	No Relevant Outcome measure reported
TNCC	Not a Contemporaneous Comparison Study, OR Not comparable populations or treatment settings in a noncontemporaneous study.
TNFU	No follow-up in required # of months.
TNRS	ERCP outcomes not reported separately
NOBJ	No objective pre and post measurement of outcomes in a single arm observational study
NBH	MRCP technique used only non-breath hold technique
5NA	No analysis of relationship between patient, procedure, or provider covariates, and outcome after ERCP.
5N100	Fewer than 100 patients enrolled in cohort study
5N25	Fewer than 25 cases in case-controlled study.
5NCV	Does not address potential confounding variables in subject selection or analysis
NOMVA	No multivariate analysis reported
6NCPR	No Clinical Prediction Rule or model predicting likelihood of a relevant pancreaticobiliary condition requiring intervention.
X6	Duplicative and noncontributory information for prediction of common bile duct stones. This section was not a systematic review
6N100	Fewer than 100 patients enrolled.

Excluded Studies

Aabakken L, Karesen R, Serck-Hanssen A, and Osnes M. Transpapillary biopsies and brush cytology from the common bile duct. Endoscopy 86 18(2):49-51. **Exclusion Code(s):** DN25

Abdul Ghani AK. Selective per-operative cholangiography and scoring method for selection. Bangladesh Medical Research Council Bulletin 89 15(2):81-9. **Exclusion Code(s):** X6

Acosta JM, Ronzano GD, and Pellegrini CA. Ampullary obstruction monitoring in acute gallstone pancreatitis: a safe, accurate, and reliable method to detect pancreatic ductal obstruction. American Journal of Gastroenterology 2000 95(1):122-7. Comment in: Am J Gastroenterol. 2000 Jan;95(1):2-3. **Exclusion Code(s):** ANNQ

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Adams DB and Anderson MC. Changing concepts in the surgical management of pancreatic pseudocysts. American Surgeon 92 58(3):173-80. **Exclusion Code(s):** AND

Adams DB and Srinivasan A. Failure of percutaneous catheter drainage of pancreatic pseudocyst. American Surgeon 2000 66(3):256-61. **Exclusion Code(s):** TN25

Adams DB, Tarnasky PR, Hawes RH, Cunningham JT, Brooker C, Brothers TE, and Cotton PB. Outcome after laparoscopic cholecystectomy for chronic acalculous cholecystitis. American Surgeon 98 64(1):1-5; discussion 5-6. **Exclusion Code(s):** TCOM

Adzick NS, Shamberger RC, Winter HS, and Hendren WH. Surgical treatment of pancreas divisum causing pancreatitis in children. Journal of Pediatric Surgery 89 24(1):54-8; discussion 58. **Exclusion Code(s):** DCOM, DN25, TCOM

Agenant DM, Bartelsman JF, and Tijtgat GN. Endoscopic retrograde cholangiopancreaticographic aspects of choledocholithiasis and its sequelae. Radiologia Clinica 78 47(6):397-411. **Exclusion Code(s):** DPOP, TCOM,ANNQ

Ahearne PM, Baillie JM, Cotton PB, Baker ME, Meyers WC, and Pappas TN. An endoscopic retrograde cholangiopancreatography (ERCP)-based algorithm for the management of pancreatic pseudocysts. American Journal of Surgery 92 163(1):111-5; discussion 115-6. **Exclusion Code(s):** TCOM TNRO ANNQ

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Wang CH, Mo LR, Lin RC, Kuo JY, and Chang KK. Rapid diagnosis of choledocholithiasis using biochemical tests in patients undergoing laparoscopic cholecystectomy. Hepato-Gastroenterology 2001 48(39):619-21. **Exclusion Code(s):** 6NCPR

Warshaw AL, Richter JM, and Schapiro RH. The cause and treatment of pancreatitis associated with pancreas divisum. Annals of Surgery 83 198(4):443-52. **Exclusion Code(s):** TNRO

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Wehrmann T, Schmitt TH, Arndt A, Lembcke B, Caspary WF, and Seifert H. Endoscopic injection of botulinum toxin in patients with recurrent acute pancreatitis due to pancreatic sphincter of Oddi dysfunction. Alimentary Pharmacology and Therapeutics (Aliment. Pharmacol. Ther.) 2000 14(11):1469-1477. **Exclusion Code(s):** TN25

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Yamakawa T, Sakai S, Mu ZB, and Pineres G. Laparoscopic management of common bile duct stones. Journal of Hepato-Biliary-Pancreatic Surgery 2000 7(1):9-14. **Exclusion Code(s):** AND

Yamashita Y, Abe Y, Tang Y, Urata J, Sumi S, and Takahashi M. In vitro and clinical studies of image acquisition in breath-hold MR cholangiopancreatography: single-shot projection technique versus multislice technique. AJR. American Journal of Roentgenology 97 168(6):1449-54. **Exclusion Code(s):** ANNQ

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Zoepf T, Zoepf DS, Arnold JC, Benz C, and Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: Analysis of 350 patients. Gastrointestinal Endoscopy 2001 54(1):56-61. **Exclusion Code(s):** 5NA

Appendix B. Technical Advisory Group (TAG) Members and Affiliations

Sidney Cohen, M.D.
NIH State-of-the-Science Conference Panel Chair
Professor of Medicine
Director, Research Programs
Division of Gastroenterology and Hepatology
Jefferson Medical College

Glenn M. Eisen, M.D., M.P.H.
Associate Professor of Medicine/Gastroenterology
Vanderbilt University Medical Center

Michael B. Kimmey, M.D.
Professor of Medicine
Assistant Chief of Clinical Affairs
Division of Gastroenterology
University of Washington

External Expert Peer Reviewers

Gastroenterologists

Mimi Canto, M.D.
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
Johns Hopkins University School of Medicine

Grace Elta, M.D.
Professor of Medicine
University of Michigan

David Weinberg, M.D., M.Sc.
Associate Professor of Medicine
Jefferson Medical College

Surgeons

Theodore Pappas, M.D., M.S.
Professor of Surgery
Duke University

Michael Sarr, M.D.
Professor of Surgery
Mayo Clinic

Radiologists

Barbara McNeil, M.D., Ph.D.
Professor of Radiology
Harvard Medical School

Oncologists

Al B. Benson III, M.D.
Professor or Medicine
Division of Hematology Oncology
Northwestern University

Alan P. Venook, M.D.
Associate Professor of Medicine
Division of Hematology and Oncology
Department of Medicine, Cancer Research
University of California San Francisco

Appendix C. Abbreviations

Adeq	adequate
AHRQ	Agency for Healthcare Research and Quality
Alk phos	alkaline phosphatase
ALT	alanine transaminase (see also SGPT)
ARP	acute, recurrent pancreatitis
ASA	American Society of Anesthesiology
ASA/NSAID	aspirin/nonsteroidal anti-inflammatory drugs
AST	aspartate transaminase (see also SGOT)
BCBSA	Blue Cross Blue Shield Association
Bili	bilirubin
BUN	blood urea nitrogen
ca, CA	cancer, carcinoma
CAP	chronic abdominal pain
CBD	common bile duct
CCK	cholecystokinin
CHD	common hepatic duct
cont'd	continued
CP	chronic pancreatitis
CT	computed tomography
CTC	computed tomography cholangiography
cx	control
D	diagnostic
D/S	delayed/selective
Diag	diagnostic
DIC	disseminated intravascular coagulation
dx	diagnosis, diagnostic
EHL	electrohydraulic lithotripsy
EPC	Evidence-based Practice Center
ER	emergency room
ERCP	endoscopic retrograde cholangiopancreatography
ES	endoscopic sphincterotomy
ESWL	extracorporeal shock wave lithotripsy
EUS	endoscopic ultrasound
F/U, f/u	follow-up
FNA	fine-needle aspiration
Fr	French
FV	forward-viewing
GGT	gamma glutamyltransferase
GI	gastrointestinal
Gr	grade
h, hr(s)	hour(s)
HASTE	half-Fourier acquisition single-shot turbo spin echo (a.k.a., "half-Fourier RARE")
Hb	hemoglobin
Hb conc	hemoglobin concentration
Hct	hematocrit

ILL	intracorporeal laser lithotripsy
IOC	intraoperative cholangiogram
IPMT	intraductal papillary mucinous tumor
IU	international units
IV	intravenous
lap	laparoscopic
LCBDE	laparoscopic common bile duct exploration
les	lesion
LFTs	liver function tests
M	manometry
MAP	Medical Advisory Panel
MeSH®	Medical Subject Headings®
mo, mos.	month(s)
MRCP	magnetic resonance cholangiography
n	number
n.r.	not reported
n.s., NS	not significant
N/A	not applicable
neg	negative
NIH	National Institutes of Health
NKF	needle-knife fistulotomy
NKPP	needle-knife precut papillotomy
nl	normal
NPV	negative predictive value
OMAR	Office of Medical Applications of Research
OR	odds ratio
pos	positive
postop	postoperative
PPV	positive predictive value
preop	preoperative
prev	prevalence
PS	performance status
pt, pts	patients
PTC	percutaneous transhepatic cholangiographic
PTH	percutaneous transhepatic
RARE	rapid acquisition with relaxation enhancement
RCT	randomized controlled trial
ROC	receiver-operating characteristic
RUQ	right upper quadrant
sens	sensitivity
SGOT	serum glutamic oxaloacetic transaminase (see also AST)
SGPT	serum glutamic pyruvic transaminase (see also ALT)
SO	sphincter of Oddi
SOD	sphincter of Oddi dysfunction
SOI	severity of illness
SOM	sphincter of Oddi manometry
spec	specificity
SSD	statistically significant difference
Stud	study
susp	suspected
SV	side-viewing

T	therapeutic
TAG	Technical Advisory Group
TEC	Technology Evaluation Center
tx	treatment
UGI	upper GI
US	ultrasound
VA	Veterans Administration
WBC	white blood count
yr, yr.	year(s)