Initial Cholecystectomy vs Sequential Common Duct Endoscopic Assessment and Subsequent Cholecystectomy for Suspected Gallstone Migration: A Randomized Clinical Trial

Pouya Iranmanesh, MD; Jean-Louis Frossard, MD; Béatrice Mugnier-Konrad; Philippe Morel, MD; Pietro Majno, MD; Thai Nguyen-Tang, MD; Thierry Berney, MD; Gilles Mentha, MD; Christian Toso, MD, PhD

**IMPORTANT** The optimal management of treatment for patients at intermediate risk of a common duct stone (including increased liver function tests but bilirubin <4 mg/dL and no cholangitis) is a matter of debate. Many stones migrate spontaneously into the duodenum, making preoperative common duct investigations unnecessary.

**OBJECTIVE** To compare strategies of cholecystectomy first vs a sequential endoscopic common duct assessment and cholecystectomy for the management of patients with an intermediate risk of a common duct stone. The main objective was to reduce the length of stay and the secondary objectives were to reduce the number of common duct investigations, morbidity, and costs.

**DESIGN, SETTING, AND PARTICIPANTS** Intervventional, randomized clinical trial with 2 parallel groups performed between June 2011 and February 2013, with a patient follow-up of 6 months. The trial comprised a random sample of 100 adult patients admitted to Geneva University Hospital, Geneva, Switzerland, for acute gallstone-related conditions with an intermediate risk of a common duct stone. Fifty patients were randomized to each group.

**INTERVENTIONS** Cholecystectomy first with intraoperative cholangiogram for the study group and endoscopic common duct assessment and clearance followed by cholecystectomy for the control group.

**MAIN OUTCOMES AND MEASURES** Length of initial hospital stay (primary end point), number of common duct investigations and morbidity and mortality within 6 months after initial admission, and quality of life at 1 and 6 months after discharge (EQ-5D-5L [EuroQol Group, 5-level] questionnaire).

**RESULTS** Patients who underwent cholecystectomy as a first step had a significantly shorter length of hospital stay (median, 5 days [interquartile range (IQR), 1-8] vs median, 8 days [IQR, 6-12]; P < .001), with fewer common duct investigations (25 vs 71; P < .001), no significant difference in morbidity or quality of life.

**CONCLUSIONS AND RELEVANCE** Among patients at intermediate risk of a common duct stone, initial cholecystectomy compared with sequential common duct endoscopy assessment and subsequent surgery resulted in a shorter length of stay without increased morbidity. If these findings are confirmed, initial cholecystectomy with intraoperative cholangiogram may be a preferred approach.

**TRIAL REGISTRATION** Clinicaltrials.gov Identifier: NCT01492790.

JAMA. 2014;312(2):137-144. doi:10.1001/jama.2014.7587
ight-upper-quadrant pain and elevated liver function tests (LFTs) raise the suspicion of a stone migration into the common duct. Since many stones migrate spontaneously into the duodenum, it is not known if magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), or intraoperative cholangiogram (IOC) with intraoperative common duct exploration is the best initial strategy for treating common duct stones. The optimal management of treatment for these patients is therefore a matter of debate.

In 2010, the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal and Endoscopic Surgeons published common guidelines regarding the management of cases of suspected choledocholithiasis based on the likelihood of having a common duct stone. A laparoscopic cholecystectomy was proposed for low-risk patients and a preoperative ERCP was proposed for high-risk patients. For intermediate-risk patients (5%-50% risk), namely those with increased LFTs, age older than 55 years, biliary pancreatitis (excluding bilirubin level >4 mg/dL, clinical ascending cholangitis, visible common duct stone on ultrasound, and patients with both common duct diameter >6 mm and bilirubin levels 1.8-4.0 mg/dL), or any combination of the 3 aforementioned variables, no specific guideline for the initial approach was provided. Preoperative common duct investigations reduce the need for postoperative ERCP, but may result in a number of unnecessary procedures due to the spontaneous migration of common duct stones into the duodenum. Conversely, a strategy of cholecystectomy first can lead to the discovery of a retained common duct stone during surgery.

The objective of the present randomized clinical trial was to compare the management strategies of cholecystectomy-first vs sequential common duct endoscopic investigation and cholecystectomy, for patients at intermediate risk of a common duct stone. The hypotheses were that a cholecystectomy-first strategy would decrease the length of stay, the number of common duct investigations, and morbidity and mortality with similar postoperative quality of life.

### Methods

#### Trial Design and Interventions
The study was an interventional, randomized clinical trial with 2 parallel groups, conducted at Geneva University Hospital, Geneva, Switzerland.

Patients who were randomized to the cholecystectomy first study group underwent primary emergency laparoscopic cholecystectomy (performed within 48 hours from hospital admission) with IOC. In case of a detected common duct stone, defined as a lack of contrast filling on multiple images, absence of duodenal passage of contrast media, or both combined, an ERCP was performed either intraoperatively or postoperatively, depending on gastroenterologist availability. Patients who were randomized to the classical treatment control group underwent a common duct exploration by EUS followed, if required, by ERCP, and subsequently by a laparoscopic cholecystectomy with IOC. EUS was chosen because it has been documented as being more accurate than MRCP, especially for stones measuring less than 6 mm. Because MRCP is better tolerated in the postoperative setting, it was mandatory when the IOC was not feasible. The overall management algorithm is shown in Figure 1. Intraoperative cholangiography was performed by a surgeon via insertion of a transcystic catheter and injection of contrast media under fluoroscopic guidance. EUS was performed, with the patient under light sedation, by a gastroenterologist using an Olympus echoendoscope (GFUM160). ERCP was performed, with the patient under general anesthesia, by a gastroenterologist using an Olympus endoscope (TFJ180V). Incision in the sphincter of Oddi during ERCP was made using a Cook sphincterotome (D.A.S.H.), whereas extraction of stones was performed using a conventional balloon catheter under fluoroscopic guidance. Clearance of the common duct was assessed after balloon removal by direct opacification.

#### Sample Size and Inclusion and Exclusion Criteria
The sample size calculation was based on a retrospective study comparing the 2 strategies and demonstrating a decreased length of stay from 11.8 to 9.1 days with a cholecystectomy first management. In order to detect a similar reduction in the length of hospital stay of 3 days with a standard deviation of 5 days, when requiring a 2-sided α = .05 and a statistical power of 0.8, a sample size of 45 patients was necessary in each group. When taking into account a potential drop-out rate of 10%, 50 patients were included in each group (n = 100). A period of 24 months was anticipated to complete enrollment.

Only patients aged 16 years or older were eligible for the study. All presented in the emergency department with a clinical suspicion of choledocholithiasis (defined by sudden abdominal pain in the right upper quadrant, epigastric region, or both), associated with elevated LFTs and the presence of a gallstone on an ultrasound performed by a certified radiologist. To avoid randomizing patients with 1 isolated increased LFT (as might occur in regular alcohol consumers with only abnormal γ-glutamyl transpeptidase levels), a minimal threshold for LFTs was set with alanine aminotransferase, aspartate aminotransferase, or both values twice the normal range in association with at least 1 other modified LFT. Patients were included with or without the presence of an associated acute cholecystitis, defined by clinical criteria (fever, presence of Murphy sign) and ultrasound (gallbladder wall thickness >4 mm, striated gallbladder wall, perivesicular fluid).

Exclusion criteria were severe sepsis and septic shock (eg, from acute ascending cholangitis), pancreatitis (defined by lipase value at least 3 times >normal and a minimal Balthazar score of B on computed tomography), radiologically proven common duct stone, bilirubinemia of greater than 4 mg/dL, existence of an alternative differential diagnosis (eg, acute hepatitis), medical conditions precluding surgery, previous history of cholecystectomy, modified anatomy interfering with endoscopic assessments (eg, Roux-en-Y gastric bypass), con-
Randomization and Blinding
The randomization sequence was created using random.org statistical software (Randomness and Integrity Services) with a 1:1 allocation using blocks of 10 without stratification. This randomization process was chosen to optimize the balance between the 2 groups in terms of size and characteristics. The software generated true random numbers by analyzing atmospheric noise with radio receivers.

The allocation was performed within 12 hours of hospital admission by physicians blinded for the allocation sequence, using sequentially numbered, opaque and sealed envelopes placed in a single central location. The corresponding envelope was opened only after the eligible participant had signed an informed consent form explaining all modalities of the trial. The investigator who created the allocation sequence (P.I.) did not participate at any point in the assessment and enrollment of patients but ensured the integrity of the randomization process.

Although it was impossible to conceal the group to which patients were randomized from patients and surgeons, data collection and analysis was performed blindly.

Collected Data, Outcomes, and Follow-up
Collected data included demographic characteristics (sex, age, body mass index, and American Society of Anesthesiologists score), presence or absence of associated acute cholecystitis as defined previously, detailed LFTs (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin), lipase values on admission, and ultrasonographic common duct diameter measurement. The outcomes were length of primary hospital stay (primary outcome), number of EUS, ERCPs and MRCPs performed after randomization, presence or absence of a common duct stone on IOC, number of failed cholangiograms, operating time, number of patients with choledocholithiasis, number of laparotomy conversions, and number of readmissions. Morbidity and mortality were assessed by collecting surgical and medical complications according to the Clavien-Dindo classification. For the length of hospital stay, the following discharge criteria were used: availability of a support person at the time of discharge, absence of fever (Ts ≤37.8°C), absence of leukocytosis (neutrophils ≤12 000/μL), absence of symptoms (no nausea, no vomiting), presence of bowel movements, ability to ambulate independently, and pain rated at 2 or less on the visual analog scale.

Patients evaluated their quality of life at 1 and 6 months after discharge by completing the EQ-5D-5L questionnaire (full questionnaire available under http://www.euroqol.org /eq-5d-products/eq-5d-5l.html), used with the agreement of the EuroQol Group. Five individual items (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) were rated (1, indicating no problems to 5, extreme problems). These items were recalculated into a single figure, the Comprehensive Index Score (0, indicating extremely poor quality of life to 1, optimal quality of life), using the provided EQ-5D-5L calculator. Patients evaluated their overall quality of life on a visual analog scale (0, indicating the worst to 100, the best imaginable level of health).

Statistical Analysis
The statistical analysis was performed twice independently, by both the clinical epidemiology department, which performed it blindly, and the lead author (P.I.). All analyses of primary and secondary outcomes were executed on an intention-to-treat basis by including the results of all patients according to their allocated treatment group using PASW software (IBM Corporation). For the quality-of-life analysis, multiple imputation was used (PASW software) to compensate missing data (eTable in the Supplement). The level of the quality-of-life items (mobility, self-care, usual...
activities, pain and discomfort, and anxiety and depression) were modeled using an ordinal logistic regression model. Patient sex, age, length of stay, and presence of associated cholecystitis were included in the model since these characteristics could potentially affect the quality of life. The imputation was performed separately in both groups. One hundred datasets were imputed. The association between groups and the quality-of-life items were tested from the imputed datasets using an ordinal logistic regression model. A similar approach was performed for the comparison of the visual analogue scale and the comprehensive index of quality of life. Because the index and the score on the visual analogue scale were continuous variables, missing data were imputed using a linear regression model and the medi-ans were compared using quantile regression. Mann-Whitney and Fisher exact tests were used to compare groups. Two-sided P values of less than .05 were considered statistically significant.

**Trial Registration and Quality Considerations**

The study was approved by our local ethics committee and subsequently registered on Clinicaltrials.gov with the registration number NCT01492790. The reporting of the trial was based on CONSORT 2010 recommendations.

**Results**

**Recruitment and Flow Diagram**

Between June 2011 and February 2013, 151 patients were assessed for eligibility. Fifty-one patients did not meet the inclusion requirements (Figure 2) and 100 patients were randomized, 50 in each group. The randomization process was fully complied with and there was no crossover between groups. In the study group, 47 of 50 patients (94%) received the allocated intervention (initial cholecystectomy with IOC). Three patients did not undergo the allocated procedure because of contraindications to anesthesia (New York Heart Association grade IV [severe heart disease], pneumonia, and postadmission biliary pancreatitis). In the control group, 48 of 50 patients (96%) received the allocated intervention (common duct investigations followed by cholecystectomy). The 2 remaining patients underwent EUS but had other diagnoses explaining their abnormal LFTs (acute hepatitis and mononucleosis) and did not undergo cholecystectomy. Twelve patients (24%) in the study group and 10 patients (20%) in the control group did not answer the EQ-5D-5L questionnaires. The results of all patients (N = 100) were analyzed except the quality-of-life assessment (secondary end point), with 38 patients analyzed in the study group and 40 in the control group due to missing data linked to losses to follow-up. There were no discrepancies between the analyses performed by the primary investigator (P.I.) and the clinical epidemiology department.

**Demographic Data**

Both groups were comparable in terms of age, ratio of women to men, body mass index, and ASA score. The number of patients with acute cholecystitis, LFT profiles, lipase values, and common duct diameter were also similar (Table 1).

**Outcomes**

Patients in the study group had a significantly shorter median (interquartile range [IQR]) length of hospital stay (5 days...
The total number of EUS, MRCPs, and ERCPs performed in the study group was smaller (25 vs 71; $P < .001$), with mainly a lower number of EUS (10 vs 54; $P < .001$). The median number of EUS, MRCPs, and ERCPs per patient was 0 (0-1) for the study group vs 1 (1-2) for the control group ($P < .001$) (Table 1). All patients in the control group (100%, 50 of 50) had at least 1 common duct investigation performed exclusive of the IOC vs 40% (20 of 50) in the study group. Both groups had similar conversion rates to laparotomy, median operation times, and number of failed IOCs. There was no statistically significant difference between groups in the time interval between admission and first procedure (cholecystectomy for the study group and preoperative EUS for the control group; Table 2). For the control group, the median time interval between preoperative EUS and cholecystectomy was 1.5 (1-3) days. The median time interval between cholecystectomy and postoperative ERCP was 2 (1.5-2.5) days.

Overall, 21 patients (21%) had a common duct stone, 11 (22%) in the study group (common duct stone found on IOC in 10 patients and on postoperative ERCP in 1) and 10 (20%) in the control group (common duct stone found on preoperative EUS in 8 patients and on IOC in 2). There was no statistically significant difference between patients with or without a common duct stone in terms of LFTs, lipase values, and common duct diameter. Common duct clearance by ERCP was successful in all patients.

### Table 1. Demographic Data, Liver Function Tests, and Common Duct Diameter for All Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Cholecystectomy First)</th>
<th>Control (Sequential Treatment)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 50)</td>
<td>(n = 50)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>Length of stay, median (IQR), d</td>
<td>$&lt;.001^b$</td>
</tr>
<tr>
<td>Common duct investigations, No.</td>
<td>Common duct investigations, No.</td>
<td>$&lt;.001^d$</td>
</tr>
<tr>
<td>Overall</td>
<td>Overall</td>
<td>$&lt;.001^d$</td>
</tr>
<tr>
<td>MRCP</td>
<td>MRCP</td>
<td>$&lt;.001^d$</td>
</tr>
<tr>
<td>EUS</td>
<td>EUS</td>
<td>$&lt;.001^d$</td>
</tr>
<tr>
<td>ERCP</td>
<td>ERCP</td>
<td>$.71^d$</td>
</tr>
<tr>
<td>Same-session EUS and ERCP</td>
<td>Same-session EUS and ERCP</td>
<td>$.99^d$</td>
</tr>
<tr>
<td>Patients with confirmed common duct stone</td>
<td>Patients with confirmed common duct stone</td>
<td>$.81^d$</td>
</tr>
<tr>
<td>Failed ERCP</td>
<td>Failed ERCP</td>
<td>$.99^d$</td>
</tr>
<tr>
<td>Surgical common duct exploration</td>
<td>Surgical common duct exploration</td>
<td>$.99^d$</td>
</tr>
<tr>
<td>Conversion to laparotomy, No.</td>
<td>Conversion to laparotomy, No.</td>
<td>$.56^d$</td>
</tr>
<tr>
<td>Operating time, median (IQR), min</td>
<td>Operating time, median (IQR), min</td>
<td>$.18^d$</td>
</tr>
<tr>
<td>Failed intraoperative cholangiogram</td>
<td>Failed intraoperative cholangiogram</td>
<td>$.12^d$</td>
</tr>
<tr>
<td>Reoperations</td>
<td>Reoperations</td>
<td>$.24^d$</td>
</tr>
<tr>
<td>Readmissions</td>
<td>Readmissions</td>
<td>$.98^d$</td>
</tr>
<tr>
<td>Interval between admission and first procedure, median (IQR), d</td>
<td>Interval between admission and first procedure, median (IQR), d</td>
<td>$.44^d$</td>
</tr>
</tbody>
</table>

### Table 2. Outcomes for All Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Study</th>
<th>Control</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%): Study</td>
<td>No. (%): Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>Length of stay, median (IQR), d</td>
<td>$.99^d$</td>
<td></td>
</tr>
<tr>
<td>Common duct investigations, No.</td>
<td>Common duct investigations, No.</td>
<td>$.81^d$</td>
<td></td>
</tr>
<tr>
<td>Failed ERCP</td>
<td>Failed ERCP</td>
<td>$.99^d$</td>
<td></td>
</tr>
<tr>
<td>Surgical common duct exploration</td>
<td>Surgical common duct exploration</td>
<td>$.99^d$</td>
<td></td>
</tr>
<tr>
<td>Conversion to laparotomy, No.</td>
<td>Conversion to laparotomy, No.</td>
<td>$.56^d$</td>
<td></td>
</tr>
<tr>
<td>Operating time, median (IQR), min</td>
<td>Operating time, median (IQR), min</td>
<td>$.18^d$</td>
<td></td>
</tr>
<tr>
<td>Failed intraoperative cholangiogram</td>
<td>Failed intraoperative cholangiogram</td>
<td>$.12^d$</td>
<td></td>
</tr>
<tr>
<td>Reoperations</td>
<td>Reoperations</td>
<td>$.24^d$</td>
<td></td>
</tr>
<tr>
<td>Readmissions</td>
<td>Readmissions</td>
<td>$.98^d$</td>
<td></td>
</tr>
<tr>
<td>Interval between admission and first procedure, median (IQR), d</td>
<td>Interval between admission and first procedure, median (IQR), d</td>
<td>$.44^d$</td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviations
- ASA: American Society of Anesthesiologists
- BMI: body mass index
- IQR: interquartile range
- IOC: intraoperative cholangiogram
- LFT: liver function test
- MRI: magnetic resonance imaging
- ERCP: endoscopic retrograde cholangiopancreatography
- EUS: endoscopic ultrasound
- SI conversion factor: to convert bilirubin to μmol/L, multiply values by 17.1.

$a$ Data are reported as No. (%) unless otherwise indicated.

$b$ Mann-Whitney test.

$c$ Fisher exact test.

$d$ Including same-session EUS and ERCP.

$e$ Conversion factor: to convert bilirubin to μmol/L, multiply values by 17.1.

$f$ For the study group, this indicates the time between admission and cholecystectomy; for the control group, this is the time between admission and preoperative EUS.
In the control group, all 8 patients with common duct stones found on preoperative EUS underwent successful preoperative ERCPs. Among them, 1 patient needed 2 consecutive preoperative ERCPs and 1 presented an interval migration after the preoperative ERCP with an IOC showing common duct stones that were cleared by a second ERCP (during the operation). Two patients had common duct stones found on IOC despite a normal preoperative EUS; common duct clearance was achieved by normal saline flushing during IOC in 1 case and by postoperative ERCP in the second case.

In the study group, 10 patients had a postoperative ERCP and 1 patient had an intraoperative ERCP. In 1 patient, common duct stones were missed on IOC and were removed with an ERCP performed a few days later, motivated by the persistence of elevated LFTs.

Complications
Overall, complications were observed in 4 of 50 patients (8%) in the study group and 7 of 50 patients (14%) in the control group (P = .53). When considering only severe complications (Clavien-Dindo grades III and IV), 2 of 50 patients in the study group (4%) vs 4 of 50 patients in the control group (8%) (P = .68). There were no deaths (grade V). Complications are detailed in Table 3.

Quality-of-Life Assessment
The detailed scores of the EQ-5D-5L assessments are shown in the eTable (Supplement). There was no statistically significant difference between groups in any of the parameters.

Discussion
This randomized clinical trial demonstrates that initial cholecystectomy with IOC for patients at intermediate risk of a common duct stone results in shorter lengths of stay and fewer common duct investigations, with no increased morbidity and a maintained postoperative quality of life.

Overall, 60% of patients (30 of 50) in the study group did not need any common duct investigation after the IOC. Thus, many intermediate-risk patients undergo unnecessary preoperative common duct procedures. Both groups had similar ERCP rates, showing that a cholecystectomy-first strategy limits invasive endoscopic procedures to patients with retained common duct stones only. The common duct clearance rate by ERCP was 100% in this study, but the rate is based on 21 patients only and may come closer to the estimates reported in previous studies (92%–97%) with larger cohorts of patients.14,15

Of note, 1- and 6-month follow-ups showed excellent quality of life and no statistically significant difference between groups.

Although a thorough cost analysis was beyond the scope of the present study, the significantly shorter length of hospital stay and fewer common duct investigations in the study group, coupled with the similar complication rates between the 2 groups, predicts substantial savings when using a cholecystectomy-first strategy.

The optimal management sequence for patients with suspected choledocholithiasis is not known. Some surgeons are choosing to perform routine preoperative common duct assessments and others selecting a cholecystectomy-first approach with selective postoperative ERCP. Rural US hospitals with limited access to endoscopy mostly use a cholecystectomy-first approach, whereas, urban hospitals usually pursue an investigation-first approach. Both result in similar outcomes.36 ERCP ductal clearance rates are similar prior to and after cholecystectomy, ranging between 80% to 97%.14,17,18 In this study, most ERCPs were performed after surgery in the study group. Performance of intraoperative ERCPs would have theoretically further decreased the length of hospital stay.19,20 However, intraoperative ERCP remains challenging in terms of logistics and its routine use is not necessary as demonstrated by the present study.

A number of recent reports advocate for a single-stage approach with the use of intraoperative common duct exploration. The main advantages are shorter length of stay, fewer an-
Surgical Options for Suspected Gallstone Migration

Original Investigation Research

duct exploration vs 2-stage strategies in terms of outcomes.22,28 Mentha, Toso.

Author Affiliations: ARTICLE INFORMATION

ARTICLE INFORMATION

Other

1Deceased. Author Affiliations: Division of Digestive Surgery, Department of Surgery, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland (Iranmanesh, Mugnier-Konrad, Morel, Majno, Berney, Mentha, Toso); Division of Transplant Surgery, Department of Surgery, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland (Iranmanesh, Mugnier-Konrad, Morel, Majno, Berney, Mentha, Toso); Hepato-Pancreato-Biliary Centre, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland (Iranmanesh, Frossard, Morel, Majno, Nguyen-Tang, Berney, Mentha, Toso); Division of Gastroenterology and Hepatology, Department of Medical Specialties, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland (Frossard, Nguyen-Tang).

Author Contributions: Drs Iranmanesh and Toso had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Iranmanesh, Frossard, Morel, Nguyen-Tang, Berney, Mentha, Toso. Acquisition, analysis, or interpretation of data: Iranmanesh, Frossard, Mugnier-Konrad, Majno, Toso. Drafting of the manuscript: Iranmanesh, Frossard. Critical revision of the manuscript for important intellectual content: Iranmanesh, Frossard, Mugnier-Konrad, Morel, Majno, Nguyen-Tang, Berney, Mentha, Toso. Statistical analysis: Iranmanesh.

Obtained funding: Toso. Administrative, technical, or material support: Iranmanesh, Mugnier-Konrad, Majno, Nguyen-Tang, Berney, Mentha. Study supervision: Iranmanesh, Frossard, Morel, Majno, Berney, Mentha, Toso.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Toso reports receipt of salary support from the Swiss National Science Foundation (PP00P3 139021). This grant was not given specifically for the present study and was not used for its conduct. The other authors report no disclosures.

Additional Contributions: We thank Christophe Combescure, PhD, Clinical Research Center, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland, for the methodological support and the independent and blind statistical analyses. Dr Combescure did not receive compensation in association with his contribution to this article.

Additional Information: Professor Gilles Mentha, MD, passed away unexpectedly on May 25, 2014, after bringing key input into the study. He was a world-renowned hepatobiliary and transplant surgeon, and professor of surgery at the Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland. The coauthors pay tribute to his humane personality, clinical expertise, scientific excellence, and numerous endeavors in the field of liver surgery and transplantation. He was an example and a mentor. He will be greatly missed.

REFERENCES


8. Costi R, Mazzeo A, Tartamella F, Manceau C, Vacher B, Valverde A. Cholecystocholedocholithiasis: a case-control study comparing the short-


