# Study title

Subtotal cholecystectomy for complicated acute cholecystitis: a multicenter prospective observational study

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# Participating sites:

- 1. LAC+USC Medical Center (coordinating center)
- 2. Additional sites will be added upon the site's local IRB approval

# **Background and significance**

Subtotal cholecystectomy (defined as a surgical procedure in which more than the top half of the gallbladder being removed) provides a viable alternative to the proverbial "difficult" gallbladder. Despite the recent increase in surgical preference for this technique as a means of avoiding common bile duct or major vascular injury when severe inflammation or unfavorable anatomy are encountered intraoperatively, few studies have observed the establishment of subtotal cholecystectomy as an increasingly common and safe surgical practice. Additionally, different techniques have been described within the subtotal cholecystectomy operation; namely reconstituting and fenestrating subtypes. Despite this, little remains known about the impact of these differing techniques for the management of the difficult cholecystectomy on short-term and long-term patient outcomes. Specifically, a large, prospective, multi-center U.S. trial comparing outcomes of subtotal cholecystectomy (and its subtypes) to that of the standard, total cholecystectomy has not been done.

# **Existing Literature**

The first reported subtotal cholecystectomy occurred in 1955. Additional case reports and studies have been carried out, further defining this terminology as a method of avoiding misidentification injuries of the biliary system or portal vasculature when critical view of safety cannot be safely achieved. Recent data supports the safety of this decision, showing equivalent morbidity rates to total cholecystectomy in a large metanalysis of 1,231 patients. Importantly, only 4 of the 30 included studies were prospective in nature, allowing definition variability and inconsistent reporting of outcomes. Additional reporting shows variable data regarding effect on hospital LOS, need for secondary intervention (including ERCP, percutaneous drainage, or completion cholecystectomy), infectious complications, biliary or major vascular injury, and mortality. Some small series suggest that while subtotal cholecystectomy is associated with a decreased rate of bile duct injury and a lower conversion to open operation, this comes at the cost of increasing bile leak and recurrent biliary complications. Furthermore, the relatively recent distinction between fenestrating and reconstituting subtypes of subtotal cholecystectomy remain ill defined in many of these studies, and outcomes between the two modalities remain variable across the literature. There is an obvious need for a head-to-head, prospective comparison between these subtypes to determine the safety and efficacy of the chosen intervention.

# Study Aim

The primary aim of the study is to determine the safety and efficacy of subtotal cholecystectomy for treatment of complicated cholecystitis. Additionally, evaluation of the effect of fenestrating vs reconstituting subtypes will be carried out; further elucidating any significant difference the chosen technique has on patient outcomes.

# Hypothesis

We believe that subtotal cholecystectomy is a safe alternative to total cholecystectomy when the complicated gallbladder is encountered, resulting in decreased or equivalent risk of bile duct injury, major vascular injury, postoperative hemorrhage, infectious complications and mortality. Additionally, we hope to further elucidate the expected outcomes of the varying subtypes of subtotal cholecystectomy in order to determine the safest approach, assuring the lowest need for secondary intervention, recurrent biliary disease, or need for completion cholecystectomy.

# Methods

A multicenter, prospective, observational study of cholecystectomy patients will be performed at participating centers, including both total and subtotal cholecystectomy patients.

# Inclusion criteria

- Patients ≥ 18 years of age
- Preoperative definitive diagnosis of acute cholecystitis (Tokyo guideline: appendix 1)

### **Exclusion criteria**

- Pregnant patients
- Preoperative diagnosis other than acute cholecystitis
  - o Symptomatic cholelithiasis
  - o Gallstone pancreatitis
  - o Choledocholithiasis
  - Malignant/benign tumor
  - o Others

- Prior history of subtotal cholecystectomy
- Percutaneous cholecystostomy tube in place

Data to be collected will include patient demographics, comorbidities, presenting signs and symptoms, laboratory values, imaging findings, diagnosis, intraoperative grading (AAST acute cholecystitis grading: **appendix 2**), and operative technique. Measured outcomes will be divided into both short- and long-term, including hospital length of stay, postoperative hemorrhage, bile leak, bile duct injury, need for secondary intervention, infectious complications, recurrent biliary infection, and need for completion cholecystectomy if not performed at index operation. REDCap will be used for data collection, and information shared from participating institutions will be deidentified and assigned a patient study number to protect patient privacy.

## Data Points

- Demographics
  - o Age
  - o Sex
  - Comorbidities
  - Weight/Height/BMI
  - Prior abdominal surgery
- Preoperative indicators
  - Preoperative AAST grade (appendix 2)
  - Duration of symptoms (days)
  - Length of admission prior to operation
  - Prior gallbladder-related diagnosis
    - Acute cholecystitis
    - Symptomatic cholelithiasis
    - Choledocholithiasis
    - Gallstone pancreatitis
    - Others
  - Fever (y/n)
  - Tachycardia (y/n)
  - Murphy's sign (y/n)
  - WBC / AST / ALT / AP / bilirubin / lactate
  - ERCP / MRCP
  - o U/S
    - Gallbladder wall thickness (mm)
      - Measured distance
    - Pericholecystic fluid
    - Presence of gallstones
    - Presence of sludge
    - Common bile duct diameter (mm)

- Operative
  - Lapacoscopic
  - Laparoscopic converted to open
  - o Open
  - Total cholecystectomy (y/n)
  - Subtotal cholecystectomy technique (Appendix 3)
    - Fenestrating
    - Reconstituting
  - Drain placement
  - Intraoperative AAST grade (appendix 1)
  - Duration of procedure (min)
- Outcomes
  - Short-term outcomes
    - Hospital LOS (days)
    - ICU LOS (days)
    - Postoperative hemorrhage (clinical signs of active hemorrhage such as bloody output from drain, acute anemia: Hgb>2g/dL AND requiring transfusion of PRBC or reoperation)
    - Bile leak (drain output, radiographic findings: ERCP, HIDA, surgical findings)
    - Bile duct injury (intraoperative, radiographic diagnosis)
    - Retained stone (Radiographic findings)
    - Secondary intervention
      - ERCP
      - Percutaneous drainage of abscess/fluid collections including biloma
    - Infectious complications (appendix 4)
      - Superficial incisional surgical site infection
      - Deep incisional surgical site infection
      - Organ/space surgical site infection
    - In-hospital mortality
  - Long-term outcomes (6 months following discharge)
    - Recurrent biliary infections
      - Acute cholecystitis (Tokyo guideline: **appendix 1**)
      - Acute cholangitis (Tokyo guideline: appendix 5)
    - Repeat intervention
      - ERCP
      - Percutaneous drainage
    - Need for completion cholecystectomy
      - Indications

### Data collection and statistical analysis

Standard data will be collected for each patient enrolled in the study. Our institution (LAC+USC medical center) is a coordinating center for this multi-institutional study. All data from a coordinating center and other participating centers will be collected through REDCap, on-line data entry and managing system. All data will be collected and entered in REDCap only by the research personnel. Paper data collection sheet can be used only for reviewing the list of variables. All participating centers will be conducting the study. For statistical analysis, patient identifiers will be coded and kept in password-protected computers. All data, the results of statistical analysis will be kept for 3 years.

Primary and secondary outcomes will be examined using univariate and multivariate analysis. We will report the mean values for parametric continuous variables and median values for non-parametric data. In univariate analyses, we will use Student-t test or Mann-Whitney test for continuous variables and chi-square test or Fisher's exact test for categorical variables as appropriate. Subsequently, multiple logistic regression models will be created for each outcome adjusting for clinically significant potential confounders. We will report odds ratios (ORs) and 95% confidence intervals (CIs) for all variables.

### **Consent procedures**

This is a prospective observational study. Waiver of informed consent is requested. No intervention will be performed and no change in patient management will occur as a result of this study being conducted.

### References

Brumbhatt TS, Martin MJ. Subtotal cholecystectomy as an effective and safe option for complicated Cholecystitis: A 2018 EAST Master Class Video Presentation. 2018 EAST Surgical Video. J Trauma. 2018;85(1):235-238.

Van Dijk AH, Donkervoort SC, Lameris W et al. Short- and long-term outcomes after reconstituting and fenestrating subtotal cholecystectomy. J Am Coll Surg. 2017;225(3):371-379.

Lidsky ME, Speicher PJ, Ezekian B et al. Subtotal cholecystectomy for the hostile gallbladder: failure to control the cystic duct results in significant morbidity. HPB (Oxford). 2017;19(6):547-556.

Sanders G et al. Gallstones. BMJ. 2007;335(7614):295-99

Salky BA, Edye MB et al. The difficult cholecystectomy: problems related to concominant diseases. Semin Laparosc Surg. 1998;5(2):107-114

Lee et al. Gallbladder damage control: compromised procedure for compromised patients. Surg Endosc. 2012;26(10):2779-83

https://www.sages.org/safe-cholecystectomy-program/

Madding GF. Subtotal cholecystectomy in acute cholecystitis. Am J Surg. 1955;89(3):604-07

Bornman PC, Terblanche J. Subtotal cholecystectomy: for the difficult gallbladder in portal hypertension and cholecystitis. Surgery. 1985;98(1):1-6.

Strasberg et al. Subtotal Cholecystectomy—"Fenestrating" vs "Reconstituting" Subtypes and the Prevention of Bile Duct Injury: Definition of the Optimal Procedure in Difficult Operative Conditions. J Am Coll Surg. 2016;222(1):89-96.

Elshaer M, Gravante G, Thomas K et al. Subtotal Cholecystectomy for "Difficult Gallbladders" Systematic Review and Meta-analysis. JAMA Surg. 2015;150(2):159-168

# Appendix 1

Table 1 TG18/TG13 diagnostic criteria for acute cholecystitis

A. Local signs of inflammation etc.

(1) Murphy's sign, (2) RUQ mass/pain/tenderness

B. Systemic signs of inflammation etc.

(1) Fever, (2) elevated CRP, (3) elevated WBC count

C. Imaging findings

Imaging findings characteristic of acute cholecystitis

Suspected diagnosis: one item in A + one item in B

Definite diagnosis: one item in A + one item in B + C

# Appendix 2

AAST Grade	Description	Clinical Criteria	Imaging Criteria (CT/US/HIDA findings)	Operative Criteria	Pathologic Criteria
I	Acute cholecystitis	Right upper quadrant (RUQ) or epigastric pain; Murphy's Sign; leukocytosis	Wall thickening; distention; gallstones or sludge; pericholecystic fluid; non-visualization of gallbladder (GB) on hepatobiliary iminodiacetic acid (HIDA) scan	Inflammatory changes localized to GB; wall thickening; distention; gallstones	Acute inflammatory changes in the GB wall without necrosis or pus
п	GB empyema or gangrenous cholecystitis or emphysematous cholecystitis	RUQ or epigastric pain; Murphy's Sign; leukocytosis	Above, plus air in GB lumen, wall or in the biliary tree; focal mucosal defects without frank perforation	Distended GB with pus or hydrops; necrosis or gangrene of wall; not perforated	Above, plus pus in the GB lumen; necrosis of GB wall; intramural abscess; epithelial sloughing; no perforation
ш	GB perforation with local contamination	Localized peritonitis in RUQ	HIDA with focal transmural defect, extraluminal fluid collection or radiotracer but limited to RUQ	Perforated GB wall (non-iatrogenic) with bile outside the GB but limited to RUQ	Necrosis with perforation of the GB wall (non-iatrogenic)
IV	GB perforation with perichole- cystic abscess or gastrointestinal fistula	Localized peritonitis at multiple locations; abdominal distention with symptoms of bowel obstruction	Abscess in RUQ outside GB; bilio-enteric fistula; gallstone ileus	Pericholecystic abscess; bilio-enteric fistula; gallstone ileus	Necrosis with perforation of the GB wall (non-iatrogenic)
V	GB perforation with generalized peritonitis	Above, with generalized peritonitis	Free intra-peritoneal bile	Above, plus generalized peritonitis	Necrosis with perforation of the GB wall (non-iatrogenic)

# Appendix 3



A: fenestrated technique, B: reconstituting technique

# Appendix 4



#### Table 1. Summary of CDC definition of SSI.

#### Superficial Incisional SSI

- Infection occurs within 30 days after the operation;
- · infection involves only the skin or subcutaneous tissue; and
- · at least 1 of the following:
  - o purulent drainage (culture documentation not required);
  - o organisms isolated from fluid/tissue of superficial incision;
  - o at least 1 sign of inflammation (eg, pain or tenderness, induration, erythema, local warmth of the wound);
  - o wound is deliberately opened by the surgeon; or
- o surgeon or attending physician declares the wound infected.

#### A wound is not considered a superficial site infection if there is:

- o a stitch abscess present;
- o infection of episiotomy or circumcision site;
- o infection of a burn wound; or
- o incisional SSI that extends into the fascia or muscle.

#### Deep Incisional SSI

- Infection occurs within 30 days of operation or within 1 year if an implant is present;
- · infection involves deep soft tissues (eg, fascia and/or muscle) of the incision; and
- · at least 1 of the following:
  - o purulent drainage from the deep incision but without organ/space involvement;
  - o fascial dehiscence or fascia is deliberately separated by the surgeon due to signs of inflammation;
  - deep abscess is identified by direct examination, during reoperation, by histopathology, or by radiologic examination; or
  - o surgeon or attending declares deep incisional infection is present.

#### Organ/Space SSI

- Infection occurs within 30 days of operation or within 1 year if an implant is present;
- · infection involves anatomic structures not opened or manipulated by the operation; and
- at least 1 of the following:
  - o purulent drainage from a drain placed by a stab wound into the organ/space;
  - o organisms isolated from organ/space by aseptic culturing technique;
  - identification of abscess in the organ/space by direct examination, during reoperation, or by histopathological or radiological examination; or
  - o diagnosis of organ/space SSI by surgeon or attending physician.

Adapted from<sup>16</sup> Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol*. 1992;13(10):606-608.

#### Appendix 5

 Table 2 TG18/TG13 diagnostic criteria for acute cholangitis [4]

A. Systemic inflammation
A-1. Fever and/or shaking chills
A-2. Laboratory data: evidence of inflammatory response
B. Cholestasis
B-1. Jaundice
B-2. Laboratory data: abnormal liver function tests
C. Imaging
C-1. Biliary dilatation
C-2. Evidence of the etiology on imaging (stricture, stone, stent etc.)
Suspected diagnosis: one item in A + one item in either B or C
Definite diagnosis: one item in A, one item in B and one item in C

Note:

A-2: Abnormal white blood cell counts, increase of serum Creactive protein levels, and other changes indicating inflammation B-2: Increased serum ALP, r-GTP (GGT), AST, and ALT levels Other factors which are helpful in diagnosis of acute cholangitis include abdominal pain (right upper quadrant or upper abdominal) and a history of biliary disease such as gallstones, previous biliary procedures, and placement of a biliary stent.

In acute hepatitis, marked systematic inflammatory response is observed infrequently. Virological and serological tests are required when differential diagnosis is difficult.

### Thresholds:

A-1	Fever		BT >38°C
A-2	Evidence of inflammatory response	WBC count (×1,000/µL) CRP (mg/dL)	<4 or >10 ≥1
<b>B-1</b>	Jaundice		T-Bil ≥2 (mg/dL)
B-2	Abnormal liver function tests	ALP (IU) γGTP (IU) AST (IU) ALT (IU)	$>1.5 \times \text{STD}^{\text{a}}$