ChOlanGiography performed selectively versus routinely during cholecystectomy: A NAtional register-based randomized Controlled trial (the COGNAC trial)

1. Introduction and background:

Stones in the gallbladder are common [1] and cholecystectomy for symptomatic gallstone disease is one of the most common surgical procedures worldwide. Moreover, the stones may migrate through the cystic duct into the common bile duct where they can be asymptomatic or cause biliary obstruction, cholangitis, pancreatitis, or secondary biliary cirrhosis in patients who have had the stones for a long time. Since neither the prevalence nor the natural course of common bile duct stones is known the potential benefit of active diagnosis and treatment of them, is yet to be decided.
There are several techniques available for extraction of CBDS, all being associated with a risk of complications such as iatrogenic cholangitis, pancreatitis or bleeding. Endoscopic Retrograde Cholangiopancreatography (ERCP) is the most commonly used method with reported rates of complications in about 10-15% of the procedures [2] ranging in severity from mild to lethal. The mortality in acute pancreatitis is is 1.6 per 100 000 person-years (ref Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, Petrov MS. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016 Sep;1(1):45-55.).
Whether IOC should be performed routinely during cholecystectomy is controversial [3-5]. Apart from diagnosing common bile duct stones, IOC may reduce the risk for intraoperative bile duct injuries (BDI). Severe BDI occur in about three to five per thousand cholecystectomies [5]. A BDI may have a devastating impact on patients' long-term health [6]. Randomized trials evaluating IOC effect on BDI have been attempted, but they have been severely underpowered due to the low incidence of BDI. Larger, population- and quality register-based studies have addressed the issue, most of them concluding that IOC may prevent, or at least down-stage the severity of, BDI [5].
At most centers worlwide, IOC is only performed selectively, i.e. either when there are preoperative clinical or laboratory signs of CBDS, or when the biliary anatomy is unclear to the surgeon intraoperatively. In Sweden, however, based on the assumption that IOC might reduce the risk of severe BDI, this routine is recommended in national guidelines and usually adhered to in clinical practice (ref GallRiks). However, data from the Netherlands and other countries, where a selective IOC policy is adhered to, indicate a lower need for biliary interventions, especially ERCP and consequently, less iatrogenic morbidity due to such interventions.

Research idea

Whether routine IOC reduces the risk of morbidity related to undetected common bile duct stones and BDI or, on the contrary, causes overdiagnosis and overtreatment of common bile duct stones that would have passed spontaneously if left undetected, to an extent that increases overall morbidity, compared to the selective use of IOC, remains an unanswered question. In addition to exploring this, the study also aims at assessing whether IOC reduces the risk for BDI in routine gallstone surgery.

2. Hypothesis:

3. Study objectives:

Primary objective:

The primary objective of this trial is to compare the overall absence of morbidity, measured as *textbook outcome*, in patients undergoing cholecystectomy with randomisation to either the control intervention, routine intraoperative cholangiography (IOC), or the experimental intervention, selective IOC. Reasons for selectively performing IOC are at the discretion of the operating surgeon, but would mainly be, 1. Uncertainty regarding the biliary anatomy, 2. Suspicion of common bile duct stones (CBDS).

Secondary objectives:

Secondary objectives are assessment of complications related to interventions aimed at CBDS extraction, or to CBDS undetected/left in place during cholecystectomy, iatrogenic bile duct injuries, health-related quality of life and health economy.

4. Schedule

Patient population

All patients undergoing cholecystectomy for gallstone disease, or gallstone associated complications, at centers reporting to the Swedish Registry for Gallstone Surgery and ERCPs (GallRiks) comprise the source population for this trial.

Stratification

Admission

- Electively planned cholecystectomy
- Emergency admission cholecystectomy

- Center

5. Study design

5.1 The study is designed as a two-armed register-based phase III, randomized, open label multicenter, clinical trial.

5.2 All patients undergoing cholecystectomy for gallstone disease, or gallstone associated complications, at centers reporting to the Swedish Registry for Gallstone Surgery and ERCPs (GallRiks) comprise the source population for this trial.

5.3 Patients that fulfill all inclusion criteria and none of the exclusion criteria will be asked for participation and on acceptance and receival of the written informed consent randomized to either of the two interventions.

5.4 Randomisation will be performed on the day of surgery, but before the first skin incision of the cholecystectomy.

5.5 Included patients will be followed up for a minimum of two years after the cholecystectomy and analyses will be performed mainly according to the intention-to-treat principle.

6. Eligibility criteria

Inclusion criteria

1. Patients undergoing elective or emergency cholecystectomy.
2. Open or laparoscopic access both permitted.
3. Patients with any type of manifestation of gallstone disease.
4. Cholecystectomy is the main surgical procedure.

Exclusion criteria

1. Age < 18 years
2. Preoperative suspicion of cancer of the biliary tract, liver or pancreas.
3. Preoperative suspicion of biliary obstruction providing an indication for an intraoperative cholangiogram
4. Cognitive dysfunction or language problem potentially interfering with the possibility to reach fully informed consent.

7. Stratification and randomization

7.1 Prior to randomization, patients will be stratified by:
   a. Elective/emergency cholecystectomy
   b. Study centre

7.2 Randomization will be carried out by a randomization software module within the GallRiks registry platform

8. Follow-up

8.1 Patients enrolled in the trial will be followed for a minimum of one year after randomisation.
8.2 Electronic Case record forms (CRFs) will be completed at defined points in time during follow-up.
8.3 A centralized trial data follow-up team will complete CRFs.
8.4 Data monitoring will be perfomed in accordance with good clinical practise principles.

9. Health-related quality of life assessment

10. Definitions of outcomes

10.1 Primary outcome

The incidence of textbook outcome will be compared between the intervention arms.

A 'textbook outcome' is obtained when the three following criteria are met within 6 months after surgery:

1. No prolonged hospital stay (max 3 days postoperative following cholecystectomy).
2. No intraoperative or postoperative Clavien-Dindo grade 3a or higher complications (including mortality) of cholecystectomy or associated interventions.
3. No readmissions for abdominal pathology (e.g. recurrent pancreatitis).

10.2 Secondary outcomes

Secondary outcomes include:

- The textbook outcome at 30-day follow-up.
- All the individual components of the textbook outcome, specifically gallstone related complications requiring readmission (i.e. recurrent pancreatitis, cholangitis, obstructive choledocholithiasis), complications of bile duct clearance (i.e. bleeding, perforation of a hollow viscus, respiratory insufficiency, post-ERCP pancreatitis).
- Clinically relevant post-cholecystectomy complications (Clavien-Dindo grade 3a or higher).
- Thirty day and one year mortality.
- Health-related quality of life.

11. Statistical methodology

1. **Sample size**

In a previous study based on data from GallRiks [Referens M Möller, JAMA Surg], the prevalence of incidentally detected common bile duct stones found at perioperative cholangiography in patients undergoing laparoscopic cholecystectomy without preoperative suspicion of CBDS was 1685/38864 (4.3%). Of these, three fourths (3.3%) were extracted intraoperatively. Based on the assumption that the natural course of these CBDS would have necessitated a postoperative ERCP to remove half of them within a year, a total of 1096 procedures in each arm where the decision to perform intraoperative cholangiography is determined by the protocol and not intraoperative findings would be required to reach 80% chance of detecting a statistically significant difference in the number of interventions aimed at extracting CBDS between the groups at the $p<0.05$ level. Since intraoperative circumstances are expected to necessitate intraoperative cholangiography in 30% of the selective intraoperative cholangiography group, a total of 1566 in each arm is required to give a sufficient sample to answer the primary hypothesis based on to the protocol analysis. In order to compensate for drop-outs, we aim on a total sample of 3200 patients.

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2. **Analysis plan**

3. **Interim analyses, monitoring and stopping rules**

14. Quality assurance and monitoring

Quality assurance and monitoring will be done according to GCP rules.:

a. Intervention according to randomization will be closely monitored.

b. Follow-up, complications, reinterventions,length of stay deaths and cause of deaths will be closely monitored.

c. Data reporting and management.
Case Record Forms (CRFs) should be kept as originals at each study centre until termination of trial, however copies of CRFs should be sent on a continuous basis to the central study centre in Stockholm.

d. All operative procedures and related postoperative courses are concomitantly recorded in the Swedish Quality Assurance Register (GallRiks).

15. Time plan

16. Publication

Authors of the publications are those who actively participate in processing of the study protocol, recruiting patients, compiling the results and writing the article/articles. However, all participating centers will be named in a special appendix, and contacts identified. First the steering committee determines who will be actively participating in the analyses of data and writing of manuscripts of all scientific reports addressing the primary and secondary end-points, defined in the protocol from this study. The steering committee decides who will be the 1st author of respective publications as well as the co-authors regarding publications referred to above. Co-authorship will be offered any institution where $\geq$ 30 patients have been enrolled.

17. Ethical aspects

The investigator will ensure that this study is conducted in full conformance with principles of the ”Declaration of Helsinki” (as amended in Tokyo, Venice and Hong-Kong), or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

18. Study coordination

A steering committee is established which represents all participating institutions. Provided that one centre is unable to enroll patients to the level which motivates a position in the committee the continuation and representation of that centre in the committee will be decided upon at these regular meetings. The committee will take decisions with simple majority as the basic principle in case a consensus based decision cannot be taken. The committee will meet at least once yearly after which a study report will be distributed to each participating center. If individual trialists or centres are interested in specific subanalyses or specific subgroup studies, the committee has to be addressed through a formal application and the committee will give approval with delineation of the details of the conduct of the study as well as the publication principles. The committee will be competent to make decisions provided that half of the delegates are present or have given their written approval. If a delegate will not answer this his/her will shall be interpreted in favour of the opinion of the majority of the present members of the committee.

Steering committee: One representative from each participating institution: ***Safety and Data Monitoring Committee:***

19. Investigators

Principal investigator:

Site investigators at participating sites:

20. References

21. List of appendices

22. Appendix A – ECOG performance status scale

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

23. Appendix B –Appendix B Clavien-Dindo classification of complications after surgery

1=Complication without need for specific treatment,
2= Complication treated pharmacologically, blood transfusion etc.,
3a=Intervention without generel anesthesia,
3b=Intervention in general anesthesia,
4a=ICU care because of single organ dysfunction,
4b=ICU care because of multiple organ dysfunction,
5=Death due to a complication that occurred within 30 days

24. Appendix C – Endoscopic documentation protocol

All endoscopies should be performed with a flexible 9-10 mm instrument. The following data should be collected:

A. Length of tumour (or fibrosis in case of complete response)
    a. Proximal limit (cm from the incisors)
    b. Distal limit (cm from the incisors)
B. Maximum circumferential extension of protrusion into the esophageal lumen
    a. 0
    b. <1/3
    c. 1/3-2/3
    d. 2/3-3/3
C. Stenosis
    a. No resistance when passing the tumour
    b. Resistance when passing the tumour
    c. Not possible to pass the tumour
D. Stiffness during inflation-exuflation
    a. Normal
    b. Moderate stiffness
    c. Completely stiff
E. At least 3 biopsies
F. Which brand and model of endoscope that was used
G. Photo documentation (optional)

25. Appendix D – Ogilvie Dysphagia Score[1]

Ogilivie score is determened by physician or clinical dietitian

Grad	**Symptomes**	**Proposed definition of dysphagia score (Malene Slott &Sissi Stove Lorentzen**
0	Normal, eats anything	*Swallowing function is normal, normal food intake*
1	Eats mostly normally but avoids some foods	*Prefers soft foods. Avoids some foods such as some meats (pork chops), apples, must toast bread or prefers crisp breads, must intake fluids with foods, use dressing or sauces in order to swallow*
2	Eats pureed foods only	*Purees foods before intake with a fork or blender, etc.*
3	Drinks liquids only	*Only intake of liquids also yoghurt or ice cream*
4	No swallowing foods at all	*Is unable to swallow liquids*

[1] **(Ogilvie et al, Gut 1982), Mellow & Pinkas 1984/1985)**

26. Appendix E – Nutrition study (optional)

a. Flow chart of nutritional assessments:

	1) Baseline	**2) 1-10 days post-CRT**	**3) Before surgery 4-6 weeks**	**4) Before surgery 10-12 weeks**	**5) Follow up visits**
Weight	•	•	•	•	•
Height	•				
Waist circumference	•	•	•	•	•
Grip strength	•	•	•	•	•
Bia impedance	•		• **(arm A only)**	•	
PG-SGA	•	•	•	•	•
24 hrs recall (food intake)	•	•	•	•	•
Ogilivie Dysphagia score	•	•	•	•	•

Guidelines for nutritional measurement procedures:

a. Weight

Weight measured on a seca 285 Wireless measuring station
for weight and height to the nearest 0.1 kg. Weight is measured with light clothes and without shoes.

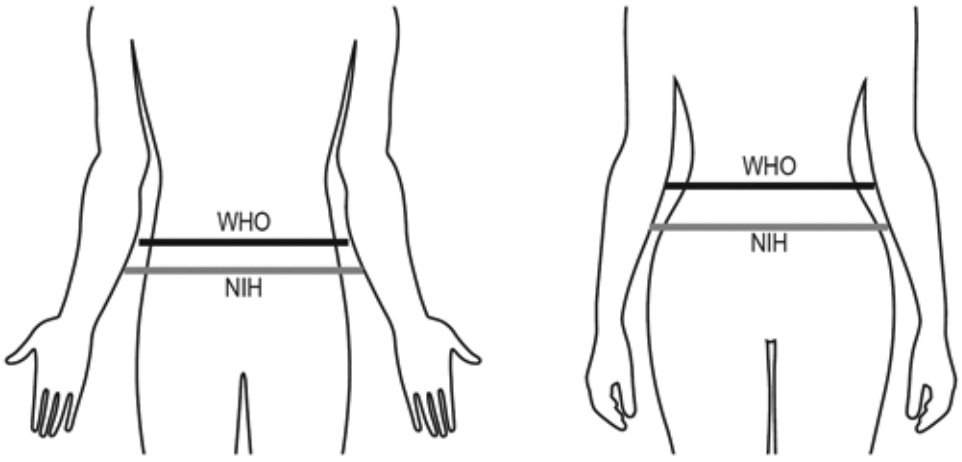
b. Height

As measured by measured on a seca 285 Wireless measuring station

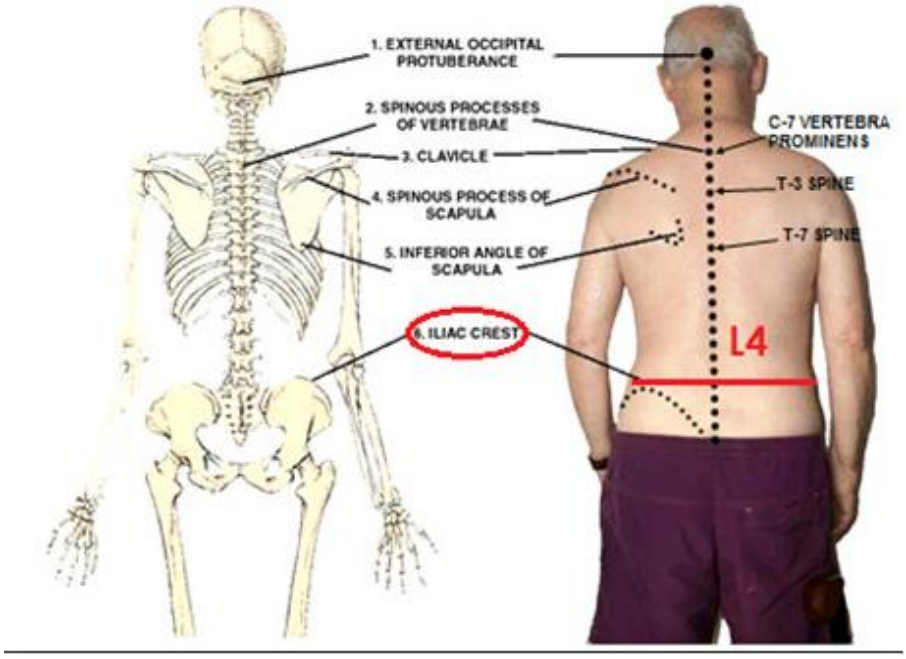
c. Waist circumference

The waist circumference was measured at the preoperative clinical evaluation by the study nutritionist. The WHO measurement is used : midway between the iliac crest and bottom of the lowest ribcage, using a non stretchable measuring tape, see figures below:

Waist circumference measurement sites for men and women based on World Health Organization (WHO) and National Institutes of Health (NIH) protocols



Note: Following the WHO protocol, the measure is taken midway between the highest point of the iliac crest and the bottom of the ribcage. Following the NIH protocol, the measure is taken at the highest point of the iliac crest.



d. BMI

BMI is the height/weight index. The BMI is calculated by the following equation:
weight (kg) /height2(m)

e. Gripstrength

A hydraulic hand dynamometer2 is used for the test. The scale (kg) displays isometric grip force from 0-90 kg. The standard guidelines, as recommended by the American Society of Hand Therapists are used as follows:

The non dominant hand is to be measured. Subjects are to be seated upright against the back of a chair without armrests, with feet placed flat on the floor. Shoulder are adducted and neutrally rotated, elbow are flexed and the forearm is in a neutral position with wrist slightly extended. The subject is instructed to perform a maximal isometric contraction. The best of the six grip strength measurements is used in statistical analyses so as to encourage the subjects to get as high a score as possible.

(1) Sit the participant comfortably in a standard chair with legs, back support and fixed arms. Use the same chair for every measurement.

(2) Ask them to rest their forearms on the arms of the chair with their wrist just over the end of

[2] Isometric hand grip strength kilogram/pounds correlates with musclemass, nutrition status, goldstandard: Jamar, Dexter and Baseline dynamometers

the arm of the chair—wrist in a neutral position, thumb facing upwards.

(3) Demonstrate how to use the Jamar handgrip dynamometer to show that gripping very tightly registers the best score.

(4) Start with the right hand.

(5) Position the hand so that the thumb is round one side of the handle and the four fingers are around the other side. The instrument should feel comfortable in the hand. Alter the position of the handle if necessary.

(6) The observer should rest the base of the dynamometer on the palm of their hand as the subject holds the dynamometer. The aim of this is to support the weight of the dynamometer (to negate the effect of gravity on peak strength), but care should be taken not to restrict its movement.

(7) Encourage the participant to squeeze as long and as tightly as possible or until the needle stops rising. Once the needle stops rising the participant can be instructed to stop squeezing.

(8) Read grip strength in kilograms from the outside dial and record the result to the nearest 1 kg on the data entry form.

(9) Repeat measurement in the left hand.

(10) Do two further measurements for each hand alternating sides to give three readings in total for each side.

(11) The best of the six grip strength measurements is used in statistical analyses so as to encourage the subjects to get as high a score as possible.

(12) Also record hand dominance, i.e. right, left or ambidextrous (people who can genuinely write with both hands).

Equipment: Model J00105 JAMAR Hydraulic Hand Dynamometer.

f. BIA Impedance 3 (Maltron)

The measurements for phase angel and body mass are to be performed with Maltron as follows:

1. Position of subject.

The subject is laid in supine position on a non-conductive surface (gym mats), with legs and arms abducted to 45º, without using jewelry or metal objects. Arms not touching the body.

[3] Bioelectrical impedance analysis (BIA)(measures bodycomposition and phaseangel (Norman K 2013)(non invasive method)

2. Placement of electrodes.

The two sensing electrodes were attached to the right side of the wrist and ankle. The two current electrodes were attached to the right dorsum of hand and foot.

3. Fasting /exercise before measurement.

In order to assure the accuracy of the measurements, the following is recommended: 4 hours of absolute fasting; not perform vigorous exercise 12 hours before; not drink alcohol 48 hours before; and urinate at least 30 minutes before testing.

g. CT (Including L3)- lean/ fat bodymass) – Slice O'matic software

1. Each patient's record is for recent CT images taken within 30 d of BMI assessment.

2. CT – at L3 level. Two consecutive CT images that extend from L3 in the inferior direction are to be assessed with the use of Slice-O-Matic software4 V4.2 (Tomovision, Montreal, Canada). To calculate tissue crosssectional area (cm2), the surfaces of the respective tissues in each slice are computed automatically by summing the given tissue's pixels and multiplying by the pixel surface area.

h. Patient-Generated Subjective Global Assessment (PG-SGA) [5]

1. The patient is required to complete the first part of the instrument, which includes anthropometric measurements, food intake, symptoms and functional capacity.

2. The remaining sections (diagnosis, metabolic demand, physical examination and nutritional status) are completed by a health professional.

All patients receive the first part of the PG-SGA in the waiting room and are required to fill the instrument before consultation with health professionals

[4] Slice O Matic software directly deteremines CT image analysis total L3 skeletal muscle. This value is linearly related to whole-body muscle mass. The unit of expression of L3 skeletal muscle index is cm2 /m2 . Estimates of whole-body tissue mass is to be generated from the raw data of muscle area (cm2) with the use of the regression equation .

[5] Ottery FD: (1996) Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition 12(1 suppl):S15-S19, 1996.
Persson C1, Sjödén PO, Glimelius B , 1999, The Swedish version of the patient-generated subjective global assessment of nutritional status: gastrointestinal vs urological cancers.
Clin Nutr. 1999 Apr;18(2):71-7.

i. 24 hrs recall (food and energy intake)

Two trained dietitians will perform all interviews.

Participants will be asked to recall food and beverage intakes during the previous 24 hours (midnight to midnight), starting with the first food/beverage consumed on waking.

Portion sizes for foods and fluids will be estimated by the patient and described in household measures as number of units consumed (e.g. cups, glasses, spoons, number of slices, pieces, decilitres).

Tables of portion sizes will be used to translate household measures to weightssupplemented by a photographic booklet with portion sizes[6] . EI will be calculated using the Dietist NET PRO http://www.kostdata.se/nb/dietist-net) and reportin absolute amounts (kcal) and per kg BW. The Norwegian food composition tables and Danish and Swedish food composition tables are used for calculations.

[6] Mål, vekt og porsjonsstørrelser for matvarer, Utgitt: 02/2015 Utgitt av: Mattilsynet, Universitetet i Oslo og Helsedirektoratet