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Benefits and risks of using laparoscopic ultrasonography versus intraoperative cholangiography during laparoscopic cholecystectomy for gallstone disease

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Benefits and risks of using laparoscopic ultrasonography versus intraoperative cholangiography during laparoscopic cholecystectomy for gallstone disease

[Nytta och risker med laparoskopiskt ultraljud jämfört med kolangiografi under laparoskopisk kolecystektomi för gallstenssjukdom]

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1. Abstract

Background

Laparoscopic cholecystectomy is a main treatment alternative in gallstone disease. For visualisation of the biliary tract anatomy and identification of retained gallstones during surgery, intraoperative cholangiography (IOC) is used routinely in Sweden. Laparoscopic ultrasonography (LUS) is a less invasive procedure for these purposes; access to the biliary tract for injection of contrast medium is normally not needed. Furthermore, LUS, as opposed to IOC, does not include radiation.

Question at issue

In patients undergoing laparoscopic cholecystectomy for gallstone disease, how does the use of LUS compare to the use of IOC regarding the risk of mortality, bile duct injury, retained gallstone, conversion to open cholecystectomy, procedural failure, surgical complications, other complications, and operation time?

Methods

Two authors performed searches (December 15th 2022) in PubMed, Embase, the Cochrane Library, Medline, and Web of Sciences, with a search update in PubMed performed on October 5th 2023. They independently assessed the abstracts, and selected, in consensus, full-text articles to be sent to the other authors, who then decided in consensus on inclusion. The included studies were critically appraised, and data were extracted. Studies without major risk of bias formed the basis for the conclusions. Meta-analyses were performed when applicable using random effects models. Certainty of evidence was assessed according to GRADE.

Results

Sixteen non-randomised studies and two case series fulfilled the predetermined inclusion criteria.

Mortality, bile duct injury, retained gallstone: Two before/after studies (594 versus 807 patients) formed the basis for the conclusions regarding mortality (LUS: 0 events versus IOC: 0 events), bile duct injury (1 versus 0 events), retained gallstone (2 versus 2 events). The studies had very serious imprecision and some uncertainty regarding directness (one single surgeon). ***Conclusion:*** It is uncertain whether there is any difference in mortality/bile duct injury/retained gallstone using LUS compared with IOC for intraoperative imaging during laparoscopic cholecystectomy (GRADE ⊕○○○).

Conversion to open cholecystectomy: The two studies above reported 6/594 versus 21/807 events, resulting in a pooled risk ratio of 0.38 (0.15 to 0.95; I2=0%). There was some uncertainty regarding directness. ***Conclusion:*** LUS may be associated with fewer conversions to open surgery compared with IOC (GRADE ⊕⊕○○).

Procedural failure: The two studies above as well as seven studies with intra-individual comparisons reported 275/2,504 versus 287/2,699 procedural failures, resulting in a pooled risk ratio of 1.12 (95% confidence interval: 0.70 to 1.78; I2=83%). Procedural failures were mainly visualisation failures for LUS, including failures to demonstrate the entire common bile duct, and application failures for IOC, due to, for instance, unsuccessful cannulation or iodine allergy. There was serious inconsistency, two studies favouring LUS and two favouring IOC, combined with uncertain precision. ***Conclusion:*** It is uncertain whether there is any difference in procedural failure using LUS compared with IOC (GRADE ⊕○○○).

Surgical/other complications: No major bile duct injuries were reported in two case series (2,113 patients).

Operation time (including imaging time): No studies reported this outcome. Mean imaging time, a subset of the outcome, was reported in 12 studies, ranging between 4.8 and 10.2 minutes for LUS and between 10.9 and 17.9 minutes for IOC. Pooled results showed a mean difference of -7.8 minutes favouring LUS (95% confidence interval: -9.3 to -6.3).
Conclusion: LUS is probably associated with shorter imaging time compared with IOC (GRADE ⊕⊕⊕◯).

Costs

The present evidence synthesis does not allow conclusions regarding important outcomes for the comparison of LUS versus IOC, i.e., if one imaging technique is better than the other or if both have similar consequences for the patient. This makes cost analyses highly hypothetical. Assuming that effectiveness and safety are at least similar for the two techniques, use of LUS may reduce costs if the probably of shorter imaging time for LUS could be translated to an overall shorter operation time. The potential of fewer conversions to open cholecystectomy with LUS was not considered. Assuming that 2,200 laparoscopic cholecystectomies are performed yearly in Region Västra Götaland, all using IOC for intraoperative imaging, the total annual costs could be estimated at 78.5 MSEK, the operation time accounting for 92.5% of the costs. From a long-term perspective, using LUS instead of IOC in 25% to 75% of the laparoscopic cholecystectomies could be expected to result in annual regional cost savings ranging from 1.0 to 7.3 MSEK, with costs saved in several sensitivity analyses. Short-term budget impact in Region Västra Götaland, that is, initial costs for investments in devices and training, could be expected to range between 11.1 and 15.4 MSEK over the first year.

Ethical considerations

It is an ethical problem to take into use in clinical routine a method where the benefit-risk balance compared to the routine technique is largely unknown. As current evidence base does not indicate evident patient risks, however, there are no ethical obstacles for further research on LUS. As IOC is contraindicated in patients with iodine allergy and avoided in pregnancy due to the exposure to radiation, unequal access to visualisation of the biliary tract during laparoscopic cholecystectomy could be considered an ethical issue if LUS is not available. Although a potential introduction of LUS may imply long-term cost savings associated with the probably shorter imaging time, the cost-effectiveness of LUS will remain very uncertain as long as no conclusions can be drawn regarding the effectiveness and safety of this imaging technique compared with IOC. A potential introduction of LUS would imply initial costs due to the required investments and training, and, hence, budgetary displacement effects may occur during the first year.

Conclusion

For the comparison LUS versus IOC to visualise the biliary tract during laparoscopic cholecystectomy, this HTA shows that no conclusions can be drawn regarding the critical and important outcomes mortality, bile duct injury, retained gallstone, and procedural failure (all very low certainty of evidence). LUS may be associated with fewer conversions to open cholecystectomy (low certainty evidence) and is probably associated with a shorter imaging time (moderate certainty evidence), but data are lacking regarding potential effects on the entire operation time. Given the sparsity of evidence combined with promising results, further well-designed studies are considered highly warranted.

2. Populärvetenskaplig sammanfattning – Plain language summary in Swedish

Fråga

Gör det någon skillnad avseende effekt och säkerhet om man använder ultraljud eller röntgen för att kartlägga gallgångarna vid laparoskopisk kirurgi (titthålsoperation) för att ta bort gallblåsan vid gallstenssjukdom?

Konklusion

Denna systematiska översikt av befintliga vetenskapliga studier i fältet visar att det inte går att dra någon slutsats avseende viktiga mått för effekt och säkerhet vid jämförelse mellan ultraljud och röntgen, men det är möjligt att man något mer sällan behöver övergå till öppen kirurgi (att operera öppet via ett snitt i buken) om ultraljud används. Det saknas data avseende om den totala operationstiden påverkas, men det är troligt att kartläggningen av gallgångarna, efter en inlärningsperiod, går snabbare om man använder ultraljud istället för röntgen under operationen. Det mycket begränsade vetenskapliga underlaget i kombination med lovande resultat innebär att det finns ett stort behov av välgjorda studier.

Bakgrund

För en patient som har besvär med gallsten är det vanligt att göra laparoskopisk kirurgi där gallblåsan tas bort. För att under operationen kartlägga hur gallgångarna ser ut och för att utesluta att det finns någon gallsten i gallgångarna görs vanligen en röntgenundersökning under operationen. Kontrastmedel sprutas då in för att gallgångarna ska synas på röntgen. Ett alternativ till röntgenundersökning är att använda ultraljud för att visualisera gallgångarna. Om man använder ultraljud behöver inget kontrastmedel sprutas in och ingen röntgenstrålning användas. Av de kirurger som idag opererar gallsten är det dock bara ett fåtal som är upplärda på ultraljudstekniken.

Metod

Med hjälp av etablerade metoder identifierade vi de vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågan. Vi granskade de enskilda studierna, summerade ihop deras resultat och bedömde hur säkra vi kunde vara på det sammanlagda resultatet.

Resultat

Denna rapport baseras på 16 studier där ultraljud jämförts med röntgen vid laparoskopisk kirurgi för att ta bort gallblåsan vid gallstenssjukdom. I två av studierna jämfördes operationsresultatet för patienter vars gallvägar under operationen undersökts med ultraljud eller röntgen. Dessa studier var för små för att visa eventuella skillnader mellan metoderna vad gäller risken att dö, få en gallvägsskada eller att gallstenar finns kvar i gallgångarna efter operation – detta är mycket ovanliga komplikationer. Om ultraljud användes visade studierna att det är möjligt att kirurgen något mer sällan behöver övergå till öppen kirurgi, även om enbart laparoskopisk kirurgi var planerat från början. När det gäller hur väl ultraljud respektive röntgen fungerar för kartläggning av gallgångarna, samt hur lång tid respektive metod tar, kunde även resultat från studier där både ultraljud och röntgen använts på samma patient användas. Avseende hur väl de båda metoderna fungerar visade studierna motstridiga resultat – några visade att det var vanligare att ultraljud fungerade bäst och några att det tvärtom var vanligare att röntgen fungerade bäst. Det vanligaste problemet med ultraljud var att man inte kunde se alla delar av den djupa gallgången. För röntgen var det vanligaste problemet att undersökningen inte gick att genomföra på grund av att gallgången inte kunde kanyleras eller att patienten var allergisk mot kontrastmedlet. Utifrån befintliga studier är det därför osäkert om båda metoderna är likvärdiga när det gäller nytta och risker för patienten eller om någon av metoderna är bättre än den andra. Däremot visade studierna att det i genomsnitt går nästan 8 minuter snabbare med ultraljuds- jämfört med röntgenundersökning för kartläggning av gallgångarna. Inga studier redovisade om detta förkortade den totala operationstiden. Inga studier hade heller analyserat eventuella långtidseffekter av den strålning som är förknippad med röntgenundersökningen.

Kostnader

Tillgängliga studier medger inga slutsatser vad gäller viktiga mått på effekt och säkerhet för ultraljud jämfört med röntgen. Kostnadsberäkningar blir därför hypotetiska. Vid antagande om att metoderna är likvärdiga ur nytta- och risksynpunkt, och att den totala operationstiden när LUS används minskar på motsvarande sätt som den troligen kortare undersökningstiden, uppskattas de totala kostnaderna på sikt kunna bli lägre. I Västra Götalandsregionen skulle besparingarna utifrån ett långtidsperspektiv kunna uppgå till mellan 1 och 7 miljoner kronor varje år, under förutsättning att den insparade operationstiden kan användas till ytterligare operationer. Den lägre siffran utgår från att 25% av gallstensoperationerna skulle göras med ultraljud istället för röntgen. Den högre siffran utgår från att andelen med ultraljud skulle vara 75%. Att använda ultraljud i ökad omfattning vid laparoskopisk kirurgi för gallstenssjukdom innebär initiala kostnader för inköp av apparatur och arbetstid för att opererande läkare ska lära sig tekniken. Investeringskostnaderna uppskattas uppgå till mellan 11 och 15 miljoner kronor under det första året.

Etiska överväganden

Det är ett etiskt problem att i rutinsjukvård införa en metod där nytta/risk-balansen för patienterna jämfört med nuvarande metod till stor del är okänd. Eftersom nuvarande mycket begränsade underlag inte visar ökade patientrisker finns emellertid inga etiska hinder mot fortsatt forskning. Patienter som är gravida eller allergiska mot jod kan inte genomgå röntgenundersökningen. Ur ett etiskt perspektiv, att alla ska behandlas lika, kan det därför vara problematiskt om enbart röntgen finns tillgängligt. Även om introduktion av ultraljud för att kartlägga gallgångarna vid laparoskopisk galloperation på sikt kan förväntas ge kostnadsbesparingar, är kostnadseffektiviteten i jämförelse med röntgenundersökning osäker eftersom patienteffekter och -säkerhet till stor del är oklart. Ur ett budgetperspektiv kan undanträngningseffekter inte uteslutas under det första året, det vill säga att annan sjukvård kan behöva prioriteras ner när utrustningen köps in och de gallstensopererande läkarna lär sig ultraljudstekniken.

The HTA report was approved by the regional board for quality assurance of activity-based HTA. The English abstract is a concise summary of the HTA. The Swedish summary is written in plain language.

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3. Summary of findings

Outcomes	**Studies, all non-randomised (comparison, patients)**	**I *vs* C**		**Certainty of evidence GRADE**
		Relative	**Absolute**	
Mortality	2 before/after studies (594 *vs.* 807 patients)		0 *vs* 0 events	⊕○○○[1]
Bile duct injury	2 before/after studies (594 *vs.* 807 patients)		1 *vs* 0 events	⊕○○○[1]
Retained gallstone	2 before/after studies (594 *vs.* 807 patients)		2 *vs* 2 events	⊕○○○[1]
Conversion to open cholecystectomy	2 before/after studies (594 *vs.* 807 patients)	RR: 0.38 (95% CI: 0.15 to 0.95)*	6 *vs* 21 events RD: -0.02 (95% CI: -0.03 to -0.002)*	⊕⊕○○[2]
Procedural failure	2 before/after studies (594 *vs.* 807 patients) 7 cross-sectional studies (inter/intra-individual comparisons; 3,184 patients)	RR: 1.12 (95% CI: 0.70 to 1.78)	275/2,504 *vs* 287/2,699 events RD: 0.01 (95% CI: -0.04 to 0.055)	⊕○○○[3]
Operation time /Imaging time	No studies /2 before/after studies (1,401 patients) 10 cross-sectional studies (inter/intra-individual comparisons; 3,854 patients)	-	- /Mean difference: -7.8 minutes (95% CI: -6.3 to -9.3) Duration (range): 4.8–10.2 *vs*10.9–17.9 minutes	- ⊕⊕⊕○[4]

[1]Very serious imprecision, uncertain directness (single-surgeon studies)
[2]Uncertain directness (single-surgeon studies) and uncertain precision but not enough to downgrade
[3]Very serious inconsistency
[4]Large magnitude of effect (upgrade)
*P<0.05
C = comparison (intraoperative cholangiography), I = intervention (laparoscopic ultrasonography)

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕○	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕○○	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕○○○	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

C = comparison
CI = confidence interval
ERCP = endoscopic retrograde cholangiopancreatography
I = intervention
IOC = intraoperative cholangiography
LUS = laparoscopic ultrasonography
O = outcome
P = patients
RD = risk difference
RR = risk ratio

5. Background

Disease/disorder of interest and its degree of severity

Gallstone disease is a major health problem worldwide. Although most people with this disease remain asymptomatic, there may be severe consequences. Presentation varies from none or only mild discomfort, to cholecystitis, cholangitis, jaundice, pancreatitis, and sepsis. Treatment depends on presentation and alternatives include open, laparoscopic, or endoscopic surgery. Complications to surgery, in turn, carry a risk of permanent illness and premature death. In summary, gallstone disease, and its complications, is a condition with a moderate/high degree of severity.

Prevalence and incidence

The median prevalence and incidence of gallstone disease in Europe ranges from 5.9 to 21.9% and 0.34 to 0.97%, respectively (Aerts et al., 2003). In an Italian population-based study, including 29,739 participants 30–69 years of age, gallstones were found in the gallbladder in 10.5% of the women and 6.5% of the men using ultrasonography for detection (Attili et al., 1995). In addition, 8.4% of included women and 3.0% of included men had previously undergone cholecystectomy (Attili et al., 1995). At 10-year follow up of the same patient group with gallstones confirmed by ultrasound, 73% had no symptoms, 12% had mild symptoms, and 15% had severe symptoms (Festi et al., 2010). In the United States, an increase in the prevalence of gallstone disease has been reported, from 7.4% in 1988-1994 to 13.9% in 2017-2020 (Unalp-Arida et al., 2023). According to the Swedish National Register for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks), the mean annual cholecystectomy rate between 1998 and 2013 was 157/100,000 inhabitants (Noel et al., 2016) and in 2022, 14,984 cholecystectomies were performed in Sweden. Among the latter, 709 (4.7%) were open cholecystectomies.

Gallstones may pass from the gallbladder into the deeper biliary ducts (Figure 1). Sometimes stones may even pass further into the intestine resulting in mild to severe symptoms. Residual stones in the biliary ducts postoperatively are associated with an increased risk for developing jaundice, pancreatitis, and sepsis.

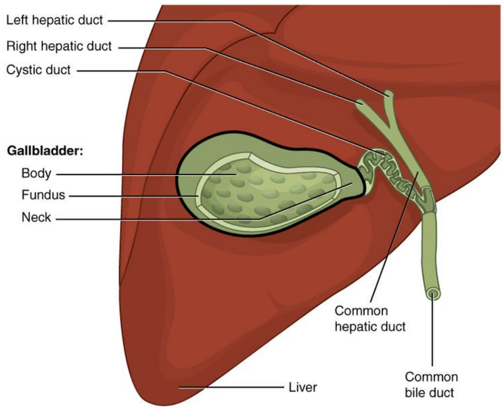

Figure 1 Anatomy of the gallbladder and the biliary ducts
(Wikimedia, commons; Creative Commons Attribution 3.0 Unported)

Damage to the biliary tract, ranging from a small injury of a bile duct wall to total transection, is a dreaded complication in cholecystectomy. Bile duct injuries occur at a frequency of about 0.5% (Rystedt et al., 2021). Small injuries can, if discovered early, usually be managed without much impact on the patient. Major injuries, on the other hand, may require extensive repeated surgery to restore the bile passage. Furthermore, long-term bile duct injury-related mortality has been reported to range between 1.8% and 4.6%, and such injuries may also contribute to impaired quality of life (Schreuder et al., 2020).

Present treatment

In symptomatic gallstone disease, the accepted treatment is to remove the gallbladder, nowadays preferably by laparoscopic cholecystectomy. In Sweden, intraoperative cholangiography (IOC) is routinely performed during cholecystectomy to verify biliary anatomy and to ensure that there are no residual stones in the biliary tract. IOC is also useful for intraoperative discovery of bile duct injuries.

Internationally, however, there is an ongoing dispute regarding the routine versus selective intraoperative visualisation of the biliary tract during cholecystectomy. In a meta-analysis based on eight non-randomised studies including about 2 million patients, selective IOC was associated with increased odds for bile duct injury (Rystedt et al., 2021). Conversely, another meta-analysis, based on 14 randomised and non-randomised studies including 440,659 patients, did not find statistically significant differences between routine or selective IOC regarding bile duct injuries, choledocholithiasis detection, or missed gallstones in laparoscopic cholecystectomies (Hall et al., 2023). Using GallRiks data, the odds for a complication in patients with common bile duct stones were lower when intraoperative measures were taken to clear the bile ducts (Möller et al., 2014).

Normal pathway through the healthcare system and current wait time for medical assessment/treatment

Gallstone disease is often diagnosed in primary health care and patients are referred to the surgical outpatient clinic for elective surgery. In case of complicated gallstone disease, like cholecystitis, jaundice, or pancreatitis, the patient often presents at the emergency department.

If a patient has been admitted due to complicated gallstone disease, all hospitals in Sweden aim to perform a cholecystectomy during the first emergency hospital stay. In reality, however, only a minor part undergo cholecystectomy during that stay due to lack of operation resources. Instead, many patients will be planned for elective surgery when, for example, the cholecystitis has declined.

Most elective surgery for gallstone disease is performed in a day-care setting. A laparoscopic cholecystectomy usually lasts for 83 to 89 minutes, and a surgeon often performs three to four procedures per surgery day (Enochsson et al., 2013). Waiting time for elective surgery varies in the Swedish health care regions. The aim by law is a maximum of 3-month waiting time for the visit to the outpatient clinic and another maximum of 3-month waiting time until surgery is performed. The Covid-19 pandemic has resulted in longer waiting times, in some regions amounting to years.

Number of patients per year who undergo current treatment regimen

According to GallRiks, IOC, or an attempt to IOC, was made in 86.4% of all cholecystectomies, i.e., both open and laparoscopic procedures (Rystedt et al., 2016). Internationally, a selective approach is instead advocated, reportedly based on disadvantages such as IOC being time-consuming; implying a risk of allergic reactions to contrast medium; exposing patient, surgeon, and personnel to radiation; as well as a significant failure rate (Jamal et al., 2016). The increased radiation associated with routine use of IOC in Sweden, compared with selective IOC, has been estimated to result in one extra case of cancer every second year in Sweden, based on 13,000 cholecystectomies performed per year (SBU, 2018).

Present recommendations from medical societies or health authorities

In Sweden today, IOC is a routine procedure during surgery for gallstone disease or gallstone complications such as acute or chronic inflammation of the gallbladder. This practice is supported by a systematic literature review in which routine IOC was estimated to prevent seven bile duct injuries every year compared with selective IOC based on approximately 13,000 cholecystectomies performed yearly in Sweden (SBU, 2018).

6. Health technology at issue: Intraoperative laparoscopic ultrasound

Compared with IOC, laparoscopic ultrasonography (LUS) is a less invasive procedure for visualisation of the bile ducts; access to the biliary tract or injection of contrast medium is normally not needed. Meta-analyses show that the sensitivity and the specificity for the detection of gallstones in the biliary tract by LUS is comparable with that of IOC (Aziz et al., 2014, Jamal et al., 2016). In addition, LUS has the advantage of giving an overview of adjacent anatomical structures, for instance, the cystic and hepatic arteries. In severe cholecystitis, this may be of particular value (Deziel et al., 2022). Other advantages of LUS include that visualisation can easily be repeated throughout the procedure and it does not involve ionising radiation. The latter also implies that LUS can be safely used in pregnant women as well as in patients with iodine/contrast allergy. The disadvantage of LUS, as with all forms of ultrasound examinations, is that it is user dependent. In the literature, the learning curve is poorly investigated, but it has been suggested that 10 to 40 LUS procedures, combined with IOC, could be required (Falcone et al., 1999, Machi et al., 1999, Röthlin et al., 1996b). Some studies have pointed out that bile duct visualisation may be particularly difficult in the distal intrapancreatic part, an aspect that can be simplified by infusion of sodium chloride in the cystic bile duct. Whereas routine IOC is a well-established method in Sweden, a resistance to change visualisation method could be expected among surgeons as the learning process may require increased operation time.

7. Focused question

In patients undergoing laparoscopic cholecystectomy for gallstone disease, how does the use of intraoperative laparoscopic ultrasonography compare to the use of intraoperative cholangiography regarding the risk of mortality, bile duct injury, retained gallstone, conversion to open cholecystectomy, procedural failure, surgical complications, other complications, and operation time (with time for diagnostic method reported separately)?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P Patients undergoing intraoperative imaging of the biliary tree during laparoscopic cholecystectomy because of gallstone disease

I Intraoperative laparoscopic ultrasonography

C Intraoperative cholangiography

O Critical for decision-making

- Mortality
- Bile duct injury

Important for decision-making

- Retained gallstone
- Conversion to open cholecystectomy
- Procedural failure
- Surgical complications
- Other complications (including radiation-induced cancer)
- Operation time (with imaging time reported separately)

Restricted to:

- Randomised controlled trials
- Non-randomised controlled trials (≥100 patients in each comparison group)
- Case series (for complications; ≥500 patients)
- Studies written in English, Swedish, Danish or Norwegian

We did not involve a patient representative in the PICO definition.

8. Methods

Systematic literature search (Appendix 1)

Two authors (J.G., T.S.) performed systematic searches in PubMed, Embase, the Cochrane Library and Web of Science (December 15th 2022), with a search update in PubMed (October 5th 2023). The websites of SBU and Folkehelseinstituttet were visited. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1.

Two authors (J.G., T.S.) independently screened titles and abstracts to exclude publications that clearly did not meet the PICO criteria. All abstracts were screened using the Rayyan tool (Ouzzani et al., 2016). Discrepancies were resolved in consensus. For the remaining publications, the full texts were retrieved and were independently assessed by at least two authors, after which consensus discussions were performed with all authors to decide on inclusion or exclusion according to PICO. For articles excluded in consensus, after full-text reading, reasons for exclusion are presented in Appendix 3.

The HTA was registered with PROSPERO prior to data extraction (CRD42023404758).

Critical appraisal and certainty of evidence

For included studies, data on design and methodology were extracted, as well as data regarding participant characteristics and outcomes reported (Appendix 2). Number of events or measures of effect were also extracted. Data were independently extracted by two authors, with discrepancies resolved in consensus. The outcome procedural failure was defined as the opposite to procedural success, i.e., (i) that the imaging technique could not be applied, or (ii) that the biliary tree could not be visualised from confluence of the hepatic ducts to the pancreatic ampulla. Conversions to open surgery were not included in the analysis of procedural failure.

At least two authors independently appraised the included studies using checklists used by HTA-centrum, Sahlgrenska University Hospital, modified from checklists developed by the Swedish Agency for Health Technology Assessment and Assessment of Social Services. Consensus discussions were then performed to decide on the domains directness, study limitations (risk of bias), and precision, in the categories + (plus; no or minor problems), ? (some problems), and – (minus; major problems). The assessments were performed at the outcome level. The assessments regarding directness and study quality (risk of bias) are summarised in Appendix 5.

Meta-analyses

If two or more studies provided poolable data regarding the outcomes at issue, random effects meta-analyses were performed using Revman (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analyses based on studies without major risk of bias were the basis for the conclusions. Regarding the outcome procedural failure, studies were required to report both feasibility and visualisation numbers. If not, they were considered to have major study limitations and were not included in the meta-analysis. Studies with between-group and intra-individual comparisons were considered adequate to pool regarding the outcomes procedural failure and operation time including imaging time.

Certainty of evidence

The certainty of evidence was assessed according to GRADE (Atkins et al., 2004), with reasons for downgrading described. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 9).

Ongoing research

A search in Clinicaltrials.gov was performed on March 20th 2023, using the search terms (cholecystectomy OR cholecystectomies) AND ((laparoscopic OR laparoscopy) AND (ultrasound OR ultrasonography) OR LUS)).

9. Results

Search results and study selection (Appendix 1)

After removal of duplicates, the literature search identified 2,575 articles (Appendix 1). Two authors excluded 2,529 publications at the abstract level, and another 18 after full-text reading. The remaining 28 articles were sent to all authors for inclusion/exclusion according to PICO, and 18 articles were finally included in the HTA (Appendix 2). The 28 excluded articles are reported with reasons for exclusion in Appendix 3. The search update in PubMed resulted in 68 search hits; 64 were excluded at the abstract level and 4 after full-text reading.

Included studies

The PICO of this HTA was fulfilled in 16 non-randomised studies with inter-individual (n=4) as well as intra-individual comparisons (n=12), and two case series. The studies were performed in the United States (n=11), France (n=2), Switzerland (n=2), Germany (n=1), Belgium (n=1), and China (n=1). In eight studies, one single surgeon performed the LUS. One study included seven LUS performing surgeons, and two studies included three and five sites, respectively. In the remaining seven studies, the number of LUS performing surgeons was not reported. LUS experience was reported in six studies, with five to 100 previous procedures required.

Results per outcome

<u>Outcomes, critical for decision-making</u>

Mortality (Appendix 4.1)

Mortality was reported in two before/after studies including 594 versus 807 patients in the intervention and comparison groups, respectively, and no events. Both studies had a follow-up of one month, and did not have major problems regarding risk of bias.

In the GRADE process, we downgraded two steps because of very serious imprecision; the studies contained no events. There was also some uncertainty regarding directness as LUS is user-dependent and underlying evidence was restricted to single surgeon studies.

> *<u>Conclusion:</u>* It is uncertain whether there is any difference in mortality using LUS compared with IOC for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease (GRADE ⊕○○○).

Bile duct injury (Appendix 4.2)

Bile duct injuries were reported in four studies with inter-individual comparisons. Two before/after studies did not have major risk of bias and included 594 versus 807 patients in the intervention and comparison groups, respectively, with a total of 1 versus 0 events.

In the GRADE process, we downgraded two steps because of very serious imprecision; the studies contained a total of one event. There was also some uncertainty regarding directness as LUS is user-dependent and underlying evidence was restricted to single surgeon studies.

> *<u>Conclusion:</u>* It is uncertain whether there is any difference in the incidence of bile duct injury using LUS compared with IOC for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease. (GRADE ⊕○○○).

Outcomes, important for decision-making

Retained gallstone (Appendix 4.3)

Retained gallstone was reported in three studies with inter-individual comparisons. Two before/after studies did not have major risk of bias and included 594 versus 807 patients in the intervention and comparison groups, respectively, with a total of 2 versus 2 events.

In the GRADE process, we downgraded two steps because of very serious imprecision; the studies contained a total of four event. There was also some uncertainty regarding directness as LUS is user-dependent and underlying evidence was restricted to single surgeon studies.

> *Conclusion:* It is uncertain whether there is any difference in the incidence of retained gallstones using LUS compared with IOC for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease (GRADE ⊕○○○).

Conversion to open cholecystectomy (Appendix 4.4)

Conversion to open cholecystectomy was reported in two before/after studies, both without major risk of bias. In all, 6 versus 21 events were reported in the intervention (n=594) and control (n=807) groups, resulting in a pooled risk ratio of 0.38 (95% CI: 0.15 to 0.95; Figure 2), and a pooled risk difference of -1.6 (95% CI: -3.0 to -0.2) percentage points.

	LUS		IOC			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Wu 1998	2	200	10	407	36.2%	0.41 [0.09, 1.84]	1998
Halpin 2002	4	394	11	400	63.8%	0.37 [0.12, 1.15]	2002
Total (95% CI)		**594**		**807**	**100.0%**	**0.38 [0.15, 0.95]**	
Total events	6		21				

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

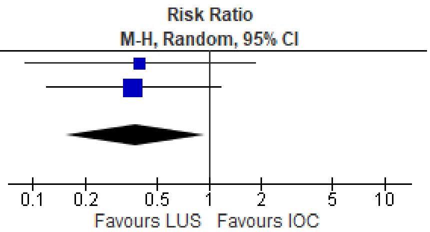

Figure 2 Forest plot and meta-analysis of studies without major risk of bias providing results regarding conversion to open cholecystectomy.

In the GRADE process, there was some uncertainty regarding directness as LUS is user-dependent and underlying evidence was restricted to single surgeon studies. Furthermore, there was uncertain precision as the confidence interval was wide. As GRADE starts at low certainty of evidence for non-randomised studies, we did not consider these aspects sufficient for further downgrading.

> *Conclusion:* Intraoperative LUS may be associated with fewer conversions to open surgery, compared with IOC, for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease (GRADE ⊕⊕○○).

Procedural failure (Appendix 4.5)

Procedural failure was reported in 15 studies, four of which including inter-individual comparisons and eleven providing intra-individual comparisons only. In nine studies without major risk of bias (3,184 unique patients), 275 versus 287 events were reported in the intervention (n=2,504) and control (n=2,699) groups, resulting in a pooled risk ratio of 1.12 (95% CI: 0.70 to 1.78; Figure 3), and a pooled risk difference of 1 (95% CI: -4 to 5) percentage points. Six studies reported application and visualisation failures separately. For LUS overall, the distribution between application and visualisation failures was 35% and 65%, respectively. Visualisation failures for LUS included for instance failures to demonstrate parts of the common bile duct. For IOC, the distribution was the opposite; 69% were application failures and 31% visualisation failures. Application failures for IOC included for instance unsuccessful cannulation or iodine allergy.

Study or Subgroup	LUS Events	LUS Total	IOC Events	IOC Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Barteau 1995	14	125	2	125	6.1%	7.00 [1.62, 30.16]	1995
Stiegmann 1995	24	202	15	201	12.3%	1.59 [0.86, 2.94]	1995
Birth 1998	79	518	46	518	14.4%	1.72 [1.22, 2.42]	1998
Wu 1998	14	198	16	393	11.6%	1.74 [0.87, 3.49]	1998
Catheline 1999	78	600	137	600	15.0%	0.57 [0.44, 0.73]	1999
Machi 1999	5	100	8	100	8.5%	0.63 [0.21, 1.84]	1999
Halpin 2002	47	390	38	388	14.0%	1.23 [0.82, 1.84]	2002
Tranter 2003	3	135	14	135	7.5%	0.21 [0.06, 0.73]	2003
Perry 2008	11	236	11	239	10.6%	1.01 [0.45, 2.29]	2008
Total (95% CI)		**2504**		**2699**	**100.0%**	**1.12 [0.70, 1.78]**	
Total events	275		287				

Heterogeneity: Tau² = 0.36; Chi² = 47.68, df = 8 (P < 0.00001); I² = 83%

Test for overall effect: Z = 0.46 (P = 0.64)

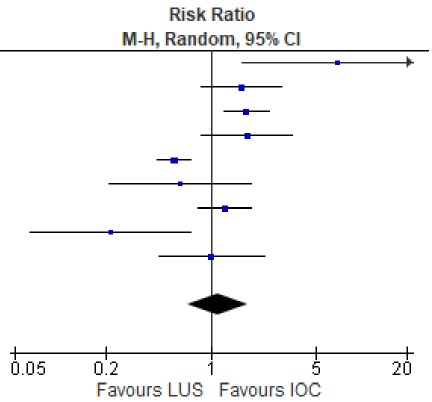

Figure 3 Forest plot and meta-analysis of studies without major risk of bias providing results regarding procedural failure.

In the GRADE process, we downgraded two steps because of very serious inconsistency; four studies showed statistically significant results, two of which favouring LUS and two IOC. Furthermore, two of these studies explicitly included more than one surgeon (Birth et al., 1998, Catheline et al., 1999), also with statistically significant results in opposite directions.

> _Conclusion:_ It is uncertain whether there is any difference in procedural failure using LUS compared with IOC for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease (GRADE ⊕○○○).

Surgical/other complications (Appendix 4.6)

Two case series, including 2,113 patients undergoing LUS, reported no major bile duct or vascular injury. One of them, including 1,381 patients, reported a total of three cases of minor bile leaks, secondary to a liver bed injury. No other complications were reported. Radiation-induced cancer was not reported in any study.

Operation time (with imaging time reported separately) (Appendix 4.7)

No studies provided results regarding operation time.

Imaging time was reported in 12 studies, two of which made between-groups comparisons and ten intra-individual comparisons. No studies were assessed to have major risk of bias regarding this outcome.

In all, the studies included 3,854 patients. Mean imaging time for LUS ranged between 4.8 to 10.2 minutes, whereas mean imaging time for IOC ranged between 10.9 and 17.9 minutes. A meta-analysis, including studies that provided mean values, as well as standard deviation or standard error of the mean, revealed a pooled mean difference of -7.8 minutes (95% CI: -6.3 to -9.3) (Figure 4).

Study or Subgroup	LUS Mean [Minutes]	LUS SD [Minutes]	LUS Total	IOC Mean [Minutes]	IOC SD [Minutes]	IOC Total	Weight	Mean Difference IV, Random, 95% CI	Year
Stiegmann 1995	7	3.3	178	13.4	5.7	186	10.2%	-6.40 [-7.35, -5.45]	1995
Barteau 1995	6.6	3.3	122	10.9	6.7	123	9.8%	-4.30 [-5.62, -2.98]	1995
Röthlin 1996b Cohort I	5.4	2.4	100	16.4	7.4	93	9.5%	-11.00 [-12.58, -9.42]	1996
Röthlin 1996b Cohort II	4.5	1.7	100	13.5	4.5	90	10.1%	-9.00 [-9.99, -8.01]	1996
Röthlin 1996a	4.8	1.9	158	14.1	4.1	146	10.3%	-9.30 [-10.03, -8.57]	1996
Thompson 1998	6.6	3.1	140	10.9	7.1	140	9.8%	-4.30 [-5.58, -3.02]	1998
Wu 1998	5.3	2.6	172	15.1	7.8	381	10.2%	-9.80 [-10.67, -8.93]	1998
Machi 1999	8.2	3.5	95	15.9	6.8	92	9.5%	-7.70 [-9.26, -6.14]	1999
Halpin 2002	5.1	1.9	380	16	9.7	374	10.1%	-10.90 [-11.90, -9.90]	2002
Li 2009	8.5	1.9	109	13.8	3.7	94	10.3%	-5.30 [-6.13, -4.47]	2009
Total (95% CI)			**1554**			**1719**	**100.0%**	**-7.80 [-9.31, -6.30]**	

Heterogeneity: $Tau^2 = 5.57$; $Chi^2 = 192.43$, $df = 9$ ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 10.15$ ($P < 0.00001$)

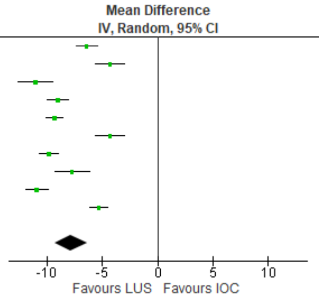

Figure 4 Forest plot and meta-analysis of studies without major risk of bias providing poolable results regarding imaging time.

In the GRADE process regarding imaging time, a subset of the outcome operation time, there was no indirectness or inconsistency; all studies reported statistically significant reductions, between four and eleven minutes, and several surgeons/sites were involved in some studies. We upgraded one step because of a large magnitude of effect; dichotomisation of imaging time, e.g.</≥10 minutes, would likely result in a risk ratio <0.5/>2 favouring LUS, i.e., the limit for upgrading according to Atkins et al. (2004).

Conclusion: No studies provide information regarding the entire operation time using LUS versus IOC for intraoperative imaging of the biliary tree in patients undergoing laparoscopic cholecystectomy because of gallstone disease. Intraoperative LUS is probably associated with shorter imaging time compared with IOC (GRADE ⊕⊕⊕○).

10. Organisational aspects

Time frame for the putative introduction of the new health technology

To perform LUS, ultrasound equipment is required. In some cases, when ultrasound equipment is already available, a designated laparoscopic probe may suffice. With equipment at hand, introduction can start.

Present use of the technology in other hospitals in Region Västra Götaland

In Region Västra Götaland, LUS is used regularly in Frölunda Specialist Hospital but not in any other hospital in the region. In Frölunda Specialist Hospital, LUS has been used since 2009. Up till now, approximately 1,200 LUS investigations have been performed by five surgeons without any injury of common bile duct, and hands-on LUS courses are offered regularly.

Consequences of the new health technology for personnel

With IOC, operating and assisting personnel are exposed to radiation and have to manage a fluoroscope, a quite bulky equipment. With LUS, no exposure to radiation is at hand, and no bulky equipment. An obstacle for LUS, however, is that the surgeon has to learn a visualising technique with which they may not be acquainted. As mentioned in the background section, experience of 10-40 surgeries may be required to achieve a sufficient level (Falcone et al., 1999, Machi et al., 1999, Röthlin et al., 1996b).

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Utilisation of LUS instead of IOC could be an alternative for both elective and acute laparoscopic cholecystectomies. Thus, the procedure may be relevant for approximately 2,200 surgeries per year in Region Västra Götaland.

11. Economic aspects

The present evidence synthesis does not allow conclusions regarding important outcomes for the comparison of LUS versus IOC, i.e., if one imaging technique is better than the other or if both have similar consequences for the patient. This makes cost analyses highly hypothetical. In the calculations below, we have assumed that effectiveness and safety are at least similar for the two techniques, and that the probably shorter imaging time for LUS can be translated to a shorter operation time. The potential of fewer conversions to open cholecystectomy with LUS has not been considered.

Assuming that 2,200 laparoscopic cholecystectomies are performed by 70 surgeons in 15 hospitals in Region Västra Götaland, all using IOC for intraoperative imaging, the total annual costs could be estimated at 78.5 MSEK, the operation time accounting for 92.5% of the costs (Table 1). From a long-term perspective and assuming that a shortened imaging time of 7.8 minutes would result in a corresponding shortened operation time and that the saved time could be used for other surgeries, yearly cost savings in the region using LUS instead of IOC in 25%, 50%, and 75% of the surgeries could be estimated at 1.0 MSEK, 3.9 MSEK, and 7.3 MSEK, respectively. A sensitivity analysis, applying the 95% CI of the saved time for intraoperative imaging (6.3–9.3 minutes/operation) and assuming that 75% of the laparoscopic cholecystectomies were performed using LUS, resulted in annual long-term cost savings ranging from 6.4 to 8.2 MSEK. In another sensitivity analysis, assuming that merely 25% of the saved time could be used for additional laparoscopic cholecystectomies or other surgeries, the annual long-term costs would be increased by 937 kSEK (25% LUS) or 18 kSEK, or be reduced by 1.4 MSEK (75% LUS).

Table 1 Estimated annual costs[a] (kSEK) for laparoscopic cholecystectomy in Region Västra Götaland by the proportion of operations using LUS instead of IOC, with an assumed reduced imaging time of 7.8 minutes per operation.

Cost component	**Proportion of laparoscopic cholecystectomies using LUS instead of IOC**							
	0% (n=0)		**25% (n=550)**		**50% (n=1,100)**		**75% (n=1,650)**	
	IOC	**LUS**	**IOC**	**LUS**	**IOC**	**LUS**	**IOC**	**LUS**
Device	2,814	0	2,110	1,829	1,407	1,829	703	1,372
Service Agreement	2,400	0	1,800	0	1,200	0	600	0
Reusable equipment	162	0	122	0	81	0	41	0
Training	0	0	-	27	0	27	0	27
Operation consumables	552	0	414	170	276	340	138	510
Cost of operation time	72,607	0	54,455	16,579	36,303	33,157	18,152	49,736
Total costs	**78,535**	**0**	**58,901**	**18,604**	**39,267**	**35,353**	**19,634**	**51,644**
Costs/operation	**36**		**35**		**34**		**32**	
Saved costs	**Ref**		**1,029**		**3,915**		**7,257**	

[a]Calculations based on the annuitization technique (Drummond et al. 2015) and the following assumptions:

- Regarding LUS devices, an ultrasonographic machine has to be purchased in half of the units (n=8), and all 16 units need 2 probes. One ultrasonographic machine is estimated at 1.3 MSEK, and a 20% reduced price is estimated for machines 2–7. One probe is estimated at 100 kSEK.
- 25% of the costs for the IOC device is attributed to laparoscopic cholecystectomies.
- Devices for IOC and LUS have a lifetime of 10 years and a probe has a lifetime of 2 years.
- 25% of the costs for the IOC service agreement is attributed to laparoscopic cholecystectomies.
- IOC reusable equipment includes radiation shields and lead aprons, with a lifetime of 10 and 5 years, respectively.
- Training requires an additional 0.5-hour working time for 20 laparoscopic cholecystectomies, i.e. 10 hours per surgeon.

- Lifetime of training is 25 years as the surgeon gets this training once a lifetime.
- Operation consumables include sterile dressings, catheters, three-way taps, and contrast medium.
- Costs per work hour for the surgeon is 676 SEK (including social security costs).
- Discounting rate for annuitizing capital items is 3%.

A potential introduction of LUS would imply initial costs due to additional equipment purchases (without investment discounts) as well as the entire learning costs for surgeons to learn the LUS technique. With the assumption that these costs would occur during one year, initial budget impact was estimated; using LUS instead of IOC in 25%, 50%, and 75% of the surgeries, the first year of LUS would require 15.4, 13.3, and 11.1 MSEK in Region Västra Götaland (Table 2).

Table 2 Budget impact the first year of LUS (kSEK) (for assumptions, see Table 1).

Cost components	**Proportion of laparoscopic cholecystectomies using LUS instead of IOC**		
	25% (n=550)	**50% (n=1,100)**	**75% (n=1,650)**
Device incl probe	17,100	17,100	17,100
Saved service agreement (75%)	-600	-1,200	-1,800
Training	473	473	473
Operation consumables	32	64	96
Cost of operation time	-1,573	-3,146	-4,719
Total	**15,432**	**13,291**	**11,149**

12. Ethical aspects

It is an ethical problem to take into use in clinical routine a method where the benefit-risk balance compared to the routine technique is largely unknown. As current evidence base does not indicate evident patient risks, however, there are no ethical obstacles for further research on LUS.

From the perspective of equality, access to IOC and not LUS may be problematic for some patient groups. Indeed, IOC implies radiation and should be avoided in pregnancy, and iodine allergy may likewise constitute a contraindication for IOC. Consequently, access to visualisation of the biliary tract during laparoscopic cholecystectomy may not be available for all patient groups if LUS is not an available alternative.

Although a potential introduction of LUS may imply long-term cost savings associated with the probably shorter imaging time, the cost-effectiveness of LUS will remain uncertain as long as no conclusions can be drawn regarding the effectiveness and safety of this imaging technique compared with IOC. A potential introduction of LUS would imply initial costs due to the required investments and training, and, hence, budgetary displacement effects may occur during the first year.

13. Discussion

Summary of main results

For the comparison LUS versus IOC to visualise the biliary tract during laparoscopic cholecystectomy, this HTA shows that no conclusions can be drawn regarding the critical and important outcomes mortality, bile duct injury, retained gallstone, and procedural failure. At present, we therefore do not know whether one imaging technique is better than the other or if both have similar consequences for the patient. As studies with inter-individual comparisons and without major risk of bias were restricted to two non-randomised studies including 1,405 patients, combined with the rareness of these events, our results may not be unexpected. Furthermore, comparable sensitivity and specificity for detection of gallstones or debris in the extrahepatic biliary tract has been reported (Jamal et al 2016, Hall et al 2023).

The results suggest that fewer conversions to open cholecystectomy may occur for LUS compared with IOC. It may be speculated that an underlying factor for this result could be that LUS allows visualisation of adjacent anatomical structures, a fact that may be particularly important in the presence of severe inflammation which, in turn, may render a higher rate of conversion to open surgery in the laparoscopic setting.

Regarding the outcome procedural failure, it is uncertain whether there are any differences between LUS and IOC. Although there were 15 non-randomised studies, nine of which without major risk of bias and the meta-analysis suggesting no statistically significant difference, a main issue was the very serious inconsistency; two of the studies favoured LUS (Catheline et al., 1999, Tranter et al., 2003) and two favoured IOC (Barteau et al., 1995, Birth et al., 1998). The wide range in results regarding procedural failure for both LUS and IOC may reflect the intrinsic difficulties associated with each procedure. LUS, with procedural failures ranging from 2% to 15%, has the limitation of being user dependent and may also require interpretation in parallel to the performance. The latter could be resolved by the storage of moving sequences, an aspect also worth consideration from the perspective of the Patient Data Act (2008:355). Nevertheless, the ampulla may be the most challenging area for visualisation with LUS, and some studies have facilitated interpretation by simultaneous infusion of sodium chloride into the bile ducts (Thompson et al., 1998, Hashimoto et al., 2010,) or into the right upper quadrant (Barteau et al., 1995, Stiegmann et al., 1995, Röthlin et al., 1996a, Wu et al., 1998, Falcone et al., 1999, Halpin et al., 2002, Tranter et al., 2003, Perry et al., 2008, Hublet et al., 2009, Luo et al., 2018, Deziel et al., 2022).

The ultrasonography technique has evolved over time. For instance, a higher sonographic frequency can be applied to facilitate interpretation. However, although the forest plot of studies that reported procedural failures may visually suggest a correlation between year of study and result, there was no obvious corresponding correlation with MHz applied. Indeed, most studies reporting this technical detail used 7.5 MHz (Stiegmann et al., 1995, Birth et al., 1998, Wu et al., 1998, Halpin et al., 2002, Tranter et al., 2003, and Hublet et al., 2009) and no study used more than 10 MHz, compared with the routine in Frölunda Specialist Hospital where 12 MHz is used for visualisation of the biliary tree. For IOC, it can be speculated that the wide range of procedural failures, 1.6% to 23%, may reflect the difference between routine and selective use; IOC performed in selective cases may be associated with less experience and more visualisation challenges like, for instance, inflammation. In the literature, it has been argued that using LUS repeatedly during dissection, for visualisation of the biliary tract as well as the adjacent anatomical structures, could be particularly helpful during arduous surgery, for instance in case of acute or chronic cholecystitis, to avoid conversion to open cholecystectomy (Dili et al., 2017). Our findings regarding conversion rates may be of interest in this context, although the overall certainty of evidence was very low.

Regarding complications, two case series including a total of 2,113 patients undergoing LUS reported no cases of major bile duct or vascular injury. In one of them, three cases of minor bile leaks, secondary to a liver bed injury, were reported. Such minor leaks are often associated with the surgical dissection and appear in a part of the surgical field that is not primarily visualised by IOC or LUS. Furthermore, the dissection of the gallbladder from the liver bed is most often performed after IOC or LUS has been performed, and may thus appear independently from the visualisation procedure.

Operation time, the preferred time-related outcome from an overall perspective including both the imaging procedure *per se* and the surgery, was not reported in any of the included studies. For imaging time, however, an evidence synthesis of 12 cross-sectional studies, all without major risk of bias regarding this outcome, shows that LUS is probably associated with shorter imaging time compared with IOC. On average, 7.8 minutes are saved per visualisation procedure. In high-volume centres, such a procedure-related consequence corresponding to 9% of the 83- to 89-minute surgery time (Enochsson et al 2013), can be relevant, in particular if IOC is performed routinely and if the operation room can be used for other purposes or an additional laparoscopic cholecystectomy. If imaging is only used in selective cases, on the other hand, provided that LUS expertise is available, the limited time required may lower the threshold for bile duct visualisation avoiding bile duct injuries or residual bile duct stones.

Overall completeness and applicability of evidence

Although this HTA included 16 non-randomised studies, only four included between-groups comparisons and only two of these, including 1,405 patients were without major risk of bias. This evidence base can be considered very restricted, in particular regarding rare patient events such as deaths, bile duct injuries, and retained gallstones. In addition, LUS was performed by a single surgeon in these studies, an aspect that may be of importance for the generalisability of the results.

Implications for research

Although only very low certainty evidence was available for most outcomes, the lower conversion rate for LUS in the meta-analyses, combined with potentially no difference in procedural failure, can be worth further investigation. Furthermore, knowledge of other potential patient-relevant effects of using LUS instead of IOC, such as mortality, bile duct injuries, and surgical/other complications, is needed. In particular, randomised studies would be useful; no study with such a design was identified in this HTA. For rare events, register-based studies, for instance using GallRiks, could be considered. In future studies, the total operation time also needs to be recorded and analysed.

14. Future perspectives

Scientific knowledge gaps

Given that there was only very low certainty evidence regarding the critical outcomes mortality and bile duct injury as well as the important outcome retained gallstone, there are evident knowledge gaps regarding patient-relevant outcomes using LUS or IOC for visualisation of the biliary tract during laparoscopic cholecystectomy. Furthermore, additional research may be worthwhile as low certainty evidence favoured LUS regarding conversion to open cholecystectomy. Two case series of limited size focused on surgical complications but did not include other complications. No study investigated potential long-term effect like radiation-induced cancer.

Knowledge gaps also include the risk of procedural failure. Furthermore, although the imaging time was found to probably be shorter with LUS compared with IOC, no study reported comparisons of the entire operation time which is the main question at issue from an operating theatre utilisation perspective.

Ongoing research

The search in Clinicaltrials.gov resulted in 100 records, none of which fulfilled our PICO.

15. Participants in the project

The question was nominated by:

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Participating healthcare professionals

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Participants from HTA-centrum

Lennart Jivegård, MD, consultant vascular surgeon; PhD, associate professor
Jahangir Khan, professor of health economics
Susanna M Wallerstedt, MD, consultant physician specialised in clinical pharmacology; PhD, professor

Participants from the Medical Library

Joss Gustavsson, librarian
Therese Svanberg, HTA librarian

External reviewers

Michael Breimer, MD, senior surgeon; PhD, professor
Anne Haglund Olmarker, MD, senior radiologist
Björn Lindkvist, MD, senior gastroenterologist; PhD, associate professor

Declaration of interests

The authors report that they have no conflicts of interest related to the content of this HTA.

Project time

The HTA was accomplished during the period of 12-07-23 – 10-01-24.
Literature searches were made on December 15th 2022, PubMed update October 5th, 2023.

Appendix 1: PICO, study selection, search strategies, and references

Question at issue:
In patients undergoing laparoscopic cholecystectomy for gallstone disease, how does the use of intraoperative laparoscopic ultrasonography compare to the use of intraoperative cholangiography regarding the risk of mortality, bile duct injury, retained gallstone, conversion to open cholecystectomy, procedural failure, surgical complications, other complications, and operation time (with time for diagnostic method reported separately)?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Patients undergoing intraoperative imaging of the biliary tree during laparoscopic cholecystectomy because of gallstone disease
I	Intraoperative laparoscopic ultrasonography
C	Intraoperative cholangiography
O	Critical for decision-making • Mortality • Bile duct injury Important for decision-making • Retained gallstone • Conversion to open cholecystectomy • Procedural failure • Surgical complications • Other complications (including radiation-induced cancer) • Operation time (with imaging time reported separately)

Eligibility criteria

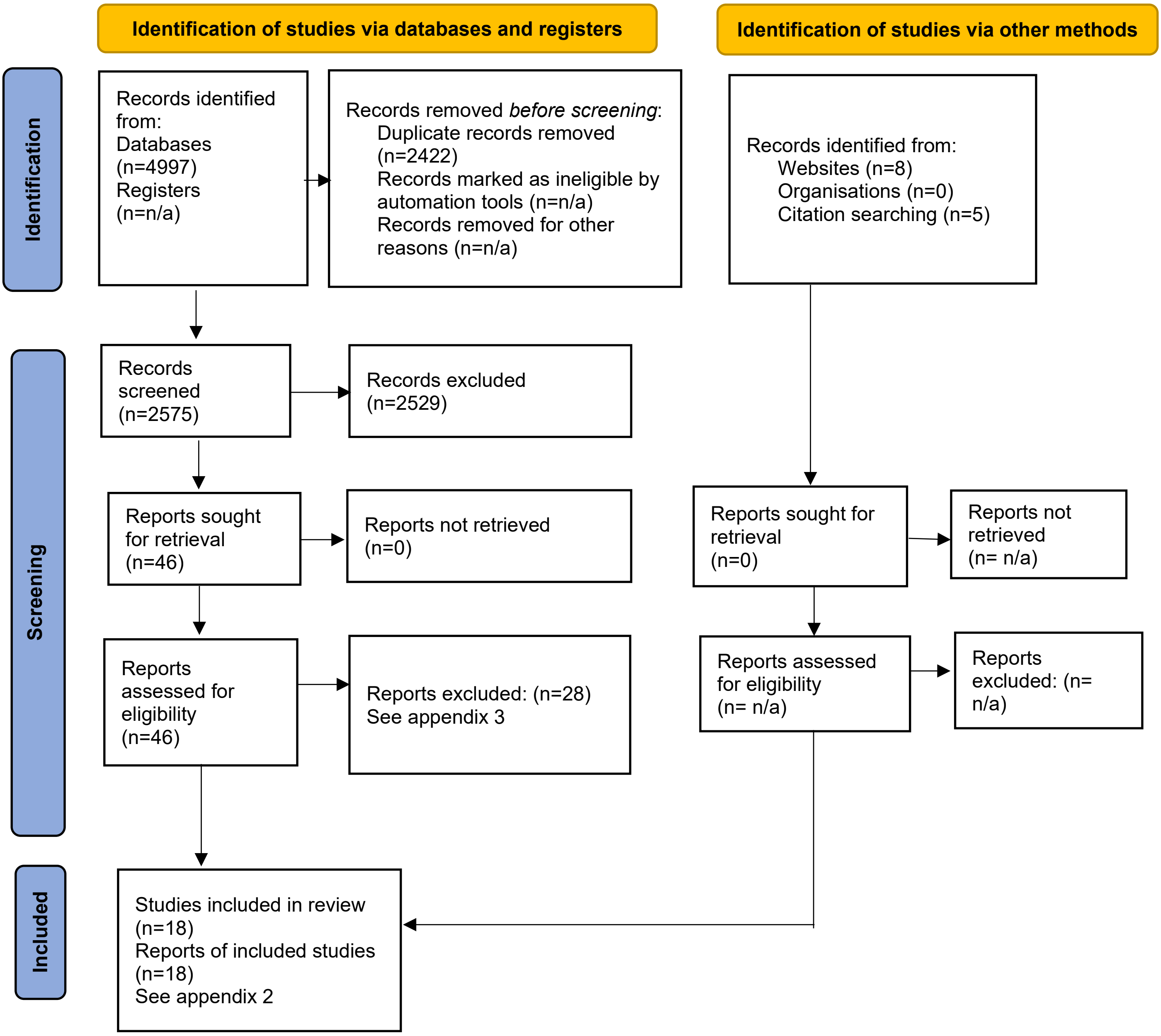
Study design:
Randomised controlled trials
Non-randomised controlled studies (≥100 patients in each comparison group)
Case series (for complications; ≥500 patients)

Language:
English, Swedish, Norwegian, Danish

Publication date:
No restrictions

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page MJ et al, 2021

Search strategies

Database: PubMed
Date: 15 dec 2022
No. of results: 1,702

Search	Query	Items found
#20	**Search: #12 NOT #15 Filters: Danish, English, Norwegian, Swedish**	**1,702**
#16	Search: #12 NOT #15	2,027
#15	Search: #13 OR #14	5,468,262
#14	Search: animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR rodent[ti] OR rodents[ti] OR dog[ti] OR dogs[ti] OR cat[ti] OR cats[ti] OR koalas[ti] OR hamster[ti] OR hamsters[ti] OR rabbit[ti] OR rabbits[ti] OR swine[ti] OR pigs[ti] OR murine[ti] OR porcine[ti] OR horses[ti] or horse[ti]	2,118,272
#13	Search: animals[mh] NOT (animals[mh] AND humans[mh])	5,072,156
#12	Search: #10 NOT #11	2,044
#11	Search: block[ti]	56,748
#10	Search: #3 AND #6 AND #9	2,142
#9	Search: #7 OR #8	517,953
#8	Search: ultrasound[tiab] OR ultrasonography[tiab]	381,085
#7	Search: "Ultrasonography"[Mesh:NoExp] OR "Ultrasonography, Doppler"[Mesh]	271,989
#6	Search: #4 OR #5	166,138
#5	Search: laparoscop*[tiab]	148,083
#4	Search: "Laparoscopy"[Mesh]	114,158
#3	Search: #1 OR #2	45,964
#2	Search: cholecystectom*[tiab]	32,803
#1	Search: "Cholecystectomy"[Mesh] OR "Gallbladder/surgery"[Mesh] OR "Gallstones/surgery"[Mesh]	34,742

Database: Embase 1974 to 2022 December 14 (Ovid)
Date: 15 dec 2022
No. of results: 1,448

#	Searches	Results
1	exp *cholecystectomy/	23117
2	exp *gallbladder/su [Surgery]	307
3	exp *gallstone/su [Surgery]	2542
4	cholecystectom$.ab,kf,ti.	45907
5	1 or 2 or 3 or 4	49673
6	exp *laparoscopy/	85571
7	laparoscop$.ab,kf,ti.	240214
8	6 or 7	245354
9	*echography/ or exp doppler ultrasonography/ or peroperative echography/	145625
10	(ultrasound or ultrasonography).ab,kf,ti.	585040
11	9 or 10	649970
12	5 and 8 and 11	2811

13	block.ti.	60641
14	12 not 13	2678
15	animal/ not (animal/ and human/)	1169955
16	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or koalas or hamster or hamsters or rabbit or rabbits or swine or pigs or murine or porcine or horses or horse).ti.	2257999
17	15 or 16	3144808
18	14 not 17	2664
19	limit 18 to (embase or medline)	1743
20	limit 19 to (danish or english or norwegian or swedish)	1448

Database: The Cochrane Library
Date: 15 dec 2022
No of results: 100 ref
Cochrane Reviews (1)
Other Reviews (0)
Trials (99)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)
Cochrane Groups (0)

ID	Search name:	Hits
#1	MeSH descriptor: [Cholecystectomy] explode all trees	2059
#2	MeSH descriptor: [Gallbladder] explode all trees and with qualifier(s): [surgery - SU]	35
#3	MeSH descriptor: [Gallstones] explode all trees and with qualifier(s): [surgery - SU]	194
#4	(cholecystectom*):ti,ab,kw (Word variations have been searched)	6283
#5	#1 OR #2 OR #3 OR #4	6355
#6	MeSH descriptor: [Laparoscopy] explode all trees	6594
#7	(laparoscop*):ti,ab,kw (Word variations have been searched)	24492
#8	#6 OR #7	24613
#9	MeSH descriptor: [Ultrasonography] this term only	5140
#10	MeSH descriptor: [Ultrasonography, Doppler] explode all trees	2965
#11	(ultrasonography OR ultrasound):ti,ab,kw (Word variations have been searched)	47838
#12	#9 OR #10 OR #11	48868
#13	#5 AND #8 AND #12	404
#14	(block):ti (Word variations have been searched)	17766
#15	#13 NOT #14	201
#16	(clinicaltrials OR trialsearch):so	442149
#17	#15 NOT #16	121
#18	(conference proceeding):pt	214308
#19	#17 NOT #18	100

Database: **Web of Science Core Collection**
Date: 15 dec 2022
No. of results: 1,747

#	Search query	Results
1	cholecystectom* (Topic)	33528
2	laparoscop* (Topic)	170412
3	ultrasound OR ultrasonography (Topic)	492872
4	#3 AND #2 AND #1	2033
5	TI=(block)	198616
6	#4 NOT #5	1900
7	TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or koalas or hamster or hamsters or rabbit or rabbits or swine or pigs or murine or porcine or horses or horse)	2708340
8	#6 NOT #7	1878
9	**#6 NOT #7 and English (Languages)**	**1747**

The web-sites of Statens beredning för medicinsk och social utvärdering (SBU), Folkehelseinstituttet and Swedish regional HTA-agencies were also visited in March 2023.
Nothing directly answering the question at issue was found.

Sökkällor	Sökord/ Browsa	Antal träffar	Antal relevanta träffar
SBU www.sbu.se	Gallsten Ultraljud Kolecystektomi	8 totalt på alla tre ord	0
Folkehelseinstituttet www.fhi.se	Browsat kategori Metodevurdering		0
CAMTÖ https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/	Browsat		0
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat		0
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat		0
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat		0
Medicinska rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/ovrig-halso--och-sjukvard/medicinska-radet/	Browsat		0

Reference lists
A comprehensive review of reference lists brought 5 new records.

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Project: Laparoscopic ultrasonography
Appendix 2 Included articles

First author Year Country	**Study design**	**Patients (n)**	**Indication for cholecystectomy**	**Age, years**	**Female sex (%)**	**Intervention (LUS)** **1. Performing physicians (n)** **2. LUS experience** **3. LUS frequency**	**Outcome variables**
Barteau 1995 USA	Cross-sectional (intra-individual comparison)	125	All indications	mean±SEM: 54.6±1.4	73%	1. NR 2. NR 3. 7.0/10 MHz	Procedural failure Imaging time
Birth 1998 Germany	Cross-sectional (intra-individual comparison)	518	Elective cholecystitis	mean (range): 51.7 (15–88)	75%	1. NR 2. NR 3. 7.5 MHz	Procedural failure Imaging time
Catheline 1999 France	Cross-sectional (intra-individual comparison)	600	All indications	mean (range): 54 (21–94)	72%	1. 7 2. 5 previous procedures required 3. 5/6.5/7.5 MHz	Procedural failure Imaging time
Catheline 2002 France	Cross-sectional (intra-individual comparison)	900	All indications	mean (range): 52 (18–95)	71%	1. NR 2. NR 3. NR	Procedural failure Imaging time
Deziel 2022 USA	Case series	732	All indications	NR	NR	1. 1 2. NR 3. 5/7.5/10 MHz	Surgical complications
Halpin 2002 USA	Before/after	I: 394 C: 400	All indications	mean±SEM: I: 48.1±0.7 C: 48.8±0.8	I: 78% C: 75%	1. 1 2. Transition period: first 100 LUS excluded 3. 7.5 MHz	Mortality Bile duct injury Retained gallstone Conversion to open cholecystectomy Procedural failure Imaging time
Hublet 2009 Belgium	Cross-sectional (inter-individual comparison)	I: 269 C: 695	All indications	NR	NR	1. 1 2. NR 3. 7.5 MHz	Bile duct injury Retained gallstone Procedural failure

Project: Laparoscopic ultrasonography
Appendix 2 Included articles

First author Year Country	Study design	Patients (n)	Indication for cholecystectomy	Age, years	Female sex (%)	<u>Intervention (LUS)</u> 1. Performing physicians (n) 2. LUS experience 3. LUS frequency	Outcome variables
Li 2009 China	Cross-sectional (intra-individual comparison)	103	Score system to include those who might have occult choledocholithiasis, and to exclude those who were preferred to undergo ERCP before laparoscopic cholecystectomy	mean (range): 48.7 (25–85)	63%	1. NR 2. NR 3. NR	Procedural failure Imaging time
Machi 1999 USA	Cross-sectional (intra-individual comparison)	100	All indications	mean: 55.9 (SD/SEM/range NR)	71%	1. NR 2. NR 3. 5/7/8 MHz	Procedural failure Imaging time
Machi 2009 USA	Case series	1381	All indications, without conversion to open	NR	69.2%	1. NR, 5 centres 2. “surgeons experienced with the performance of LUS” 3. 5–10 MHz	Surgical complications
Perry 2008 USA	Cross-sectional (inter/intra-individual comparisons)	I: 236 C: 239 (partly overlapping; 104 had both)	Cholelithiasis	NR	NR	1. 1 2. NR 3. 5–10 MHz	Bile duct injury Procedural failure
Röthlin 1996a (Intra...) Switzerland	Cross-sectional (intra-individual comparison)	158	All indications	mean (range): 52 (19–80)	63%	1. NR 2. NR 3. 5.5/5–7.5 MHz	Procedural failure Imaging time
Röthlin 1996b (Laparo...) Switzerland	Cross-sectional (intra-individual comparison)	200 Cohort I: 100 Cohort II: 100	All indications	mean (range): Cohort I: 52.0 (19–80) Cohort II: 49.8 (17–81)	Cohort I:60% Cohort II: 73%	1. 1 2. 30 LUS performed prior to this study 3. 5.5/5–7.5 MHz	Procedural failure Imaging time

Project: Laparoscopic ultrasonography
Appendix 2 Included articles

First author Year Country	**Study design**	**Patients (n)**	**Indication for cholecystectomy**	**Age, years**	**Female sex (%)**	**Intervention (LUS)** **1. Performing physicians (n)** **2. LUS experience** **3. LUS frequency**	**Outcome variables**
Siperstein 1999 USA	Cross-sectional (intra-individual comparison)	300	All indications	NR	NR	1. NR 2. NR 3. NR	Procedural failure
Stiegmann 1995 USA	Cross-sectional (intra-individual comparison)	209	Elective or semi-elective laparoscopic cholecystectomy	mean: 46 (SD/range NR)	78%	1. NR, 3 sites 2. ≥20 LUS 3. 7.5 MHz	Procedural failure Imaging time
Thompson 1998 USA	Cross-sectional (intra-individual comparison)	140	All indications	mean (range): 54.9 (22–93)	71%	1. 1 2. NR 3. 7 MHz	Imaging time
Tranter 2003 USA	Cross-sectional (intra-individual comparison)	135	All indications	mean: 53 (SD/range NR)	77%	1. 1 2. 80 LUS performed prior to this study 3. 7.5 MHz	Procedural failure
Wu 1998 USA	Before/after	I: 200 C: 407	All indications	mean±SEM: I: 49±1 C: 49±1	I: 74% C: 74%	1. 1 2. NR 3. 7.5 MHz	Mortality Bile duct injury Retained gallstone Conversion to open cholecystectomy Procedural failure Imaging time

C = comparison, ERCP = endoscopic retrograde cholangiopancreatography, I = intervention, LUS = laparoscopic ultrasonography, NA = not applicable, NR = not reported

Project: Laparoscopic ultrasonography
Appendix 3 Excluded articles

Author Year	**Reason for exclusion**
Antal 1994	No comparison of I and C: too few patients for case series
Aziz 2014	Wrong design: meta-analysis
Bezzi 1998	Too few patients for comparison and for case series
Biffl 2001	Too few patients for comparison and for case series
Bush 2022	C: Too few patients (n=80)
Catheline 1998	Same patients as Catheline 1999
Chandra 2017	I/C missing: descriptive analysis of saline sono-cholanriography
Dili 2017	Wrong design: systematic review
Fisher 2022	Wrong design: systematic review
Hashimoto 2010	Wrong C: ultrasonography-guided IOC
Jakimowicz 1991	No comparison of I and C: too few patients for case series
Jakimowicz 1993	No comparison of I and C: too few patients for case series
Jamal 2016	Wrong design: systematic review
Madsen 1995	Wrong publication type/study design: descriptive analysis of technique/instruments
Merhar 1998	Too few patients for comparison and for case series
Mosnier 1992	Wrong P: cholecystectomy, not laparoscopic
Noble 2011	Wrong I: choledochoscopy before LUS
Olsen 1999	Too few patients for comparison and for case series
Paolucci 1995	Wrong publication type/study design: descriptive analysis of technique/instruments
Pereira 2020	Wrong I: no laparoscopic ultrasonography
Piccolboni 2008	No comparison of I and C: too few patients for case series
Santambrogio 1997	No comparison of I and C: too few patients for case series
Shabanzadeh 2022	Wrong design: guidelines
Smulders 1995	Wrong publication type/study design: descriptive analysis of technique/instruments
Sun 2016	Wrong design: health economics
van de Graaf 2018	Wrong design: systematic review
Wu 1998	Too few patients for comparison and for case series
Zha 2010	I/C missing: descriptive analysis of 13,000 laparoscopic cholecystectomies

C = comparison, I = intervention, P = Population, I; Intervention, LUS = laparoscopic ultrasonography, IOC = intraoperative cholangiography

Project: Laparoscopic ultrasonography
Appendix 4.1
Outcome variable: Mortality

*	+	No or minor problems
	?	Some problems
	-	Major problems

Author Year Country	**Study design**	**Patients**	**Withdrawals - dropouts**	**Results**		**Comments**	**Directhness ***	**Study limitations ***	**Precision ***
				Intervention (LUS)	**Comparison (IOC)**				
Halpin 2002 USA	Before/after	I: 394 C: 400	I: 14 C:26	0/380	0/374	Single surgeon Follow-up: 1 month	?	?	-
Wu 1998 USA	Before/after	I: 200 C: 407	I: 28 C: 26	0/172	0/381	Single surgeon Follow-up: 1 month	?	?/+	-

LUS = laparoscopic ultrasonography, NR = not reported, IOC = intraoperative cholangiography

Project: Laparoscopic ultrasonography
Appendix 4.2
Outcome variable: Bile duct injury

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	**Study design**	**Patients**	**Withdrawals - dropouts**	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
				Intervention (LUS)	**Comparison (IOC)**				
Halpin 2002 USA	Before/after	I: 394 C: 400	I: 14 C:26	1/380	0/374	Single surgeon Description of event: Biloma from a hepatic bed leak and cholangitis and sepsis from a biliary stent occlusion, recovered	?	?	-
Hublet 2009 Belgium	Cross-sectional (inter-individual comparison)	I: 271 C: 730	NR	0/271	5/730	Single surgeon Two wounds during dissection before IOC, one wound because of thermic injury, one wound following a lateral stenosis by a cystic clip, one late stenosis at 6-month follow-up	?	-	-
Perry 2008 USA	Cross-sectional (inter/intra-individual comparisons)	I: 236 C: 239 (partly overlapping; 104 had both)	I: 104 C: 104	0/132	0/135	Single surgeon	?	-	-
Wu 1998 USA	Before/after	I: 200 C: 407	I: 28 C: 26	0/172	0/381	Single surgeon	?	?/+	-

LUS = laparoscopic ultrasonography, NR = not reported, IOC = intraoperative cholangiography

Project: Laparoscopic ultrasonography
Appendix 4.3
Outcome variable: Retained gallstone

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directhness *	Study limitations *	Precision *
				Intervention (LUS)	Comparison (IOC)				
Halpin 2002 USA	Before/after	I: 394 C: 400	I: 14 C:26	1/380	1/374	Single surgeon Description of event: I: LUS incompletely visualized duct and IOC unsuccessful, stone treated with ERCP. C: Stone treated with postoperative ERCP	?	?	-
Hublet 2009 Belgium	Cross-sectional (inter-individual comparison)	I: 271 C: 730	NR	0/271	1/730	Single surgeon IOC false negative in one case: “CBD migration during the follow-up”	?	-	-
Wu 1998 USA	Before/after	I: 200 C: 407	I: 28 C: 26	1/172	1/381	Single surgeon I: Readmitted for presumed retained CBD stone, resolved spontaneously C: Retained CBD stone despite normal IOC, successfully treated with ERCP	?	?/+	-

CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography, LUS = laparoscopic ultrasonography, NR = not reported, IOC = intraoperative cholangiography

Project: Laparoscopic ultrasonography
Appendix 4.4
Outcome variable: Conversion to open cholecystectomy

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directhness *	Study limitations *	Precision *
				Intervention (LUS)	Comparison (IOC)				
Halpin 2002 USA	Before/after	I: 394 C: 400	NA	4/394 (1%)	11/400 (3%)	Single surgeon I: Converted due to severe inflammation, frozen abdomen, unclear anatomy, and gallbladder cancer. C: Converted due to adhesions or severe inflammation.	?	?	-
Wu 1998 USA	Before/after	I: 200 C: 407	I:26	2/200 (1%)	10/407 (2%)	Single surgeon I: Converted due to adhesions or severe inflammation. C: Converted due to adhesions or severe inflammation.	?	?/+	-

LUS = laparoscopic ultrasonography, NA = not applicable, IOC = intraoperative cholangiography

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results: Intervention (LUS)	Results: Comparison (IOC)	Comments	Directness *	Study limitations *	Precision *
Barteau 1995 USA	Cross-sectional (intra-individual)	125	0	14/125 Application failure: - unavailability of equipment (n=3) Visualisation failure: - unable to demonstrate intrapancreatic portion of CBD (n=11)	2/125 Application failure: - pregnancy (n=1) - lithotomy position for subsequent laparoscopic sigmoid colectomy (n=1) Visualisation failure: 0	Number of surgeons NR LUS typically failed in the presence of pancreatitis	?	?	?
Birth 1998 Germany	Cross-sectional (intra-individual)	518	0	79[1]/518 Application failure: - adhesions in the upper right abdomen preventing correct positioning (n=1) - defective probe (n=1) Visualisation failure: - unable to demonstrate intraligamental CBD (n=3) - unable to demonstrate periampullary portion of CBD (n=77)	46[1]/518 Application failure: - unsuccessful cannulation of very thin cystic duct (n=25) - short cystic duct (n=4) - cystic duct transection (n=1) - cystic duct perforation (n=1) - iodine allergy (n=4) - thyroid hyperfunction (n=6) Visualisation failure: - unable to demonstrate intraligamental CBD (n=5) - unable to demonstrate periampullary portion of CBD (n=2)	Number of surgeons NR	?	+	+
Catheline 1999 France	Cross-sectional (intra-individual)	600	0	78[1]/600 Application failure: 0	127[1]/600 Application failure: - limited light or the presence of cystic duct valves (n=36) - inflamed uncatheterisable cystic duct (n=50)	Number of surgeons: 7 Old IOC technology: failure because of limited light	?	?	+

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results: Intervention (LUS)	Results: Comparison (IOC)	Comments	Directness *	Study limitations *	Precision *
				Visualisation failure: - unable to demonstrate distal 1/3 of CBD (n=0) - unable to demonstrate distal 1/3 of CBD (n=78)	- iodine allergy (n=16) Visualisation failure: - unable to demonstrate distal 1/3 of CBD (n=20) - unable to demonstrate distal 1/3 of CBD (n=25)				
Catheline 2002 France	Cross-sectional (intra-individual)	900	0	0+?/900 Application failure: 0 Visualisation failure: NR	138+?/900 Application failure: - narrow lumen or cystic duct valves (n=49) - excessively inflamed cystic duct (n=70) - iodine allergy (n=19) Visualisation NR	Number of surgeons NR	+	-	+
Halpin 2002 USA	Before/after	I: 394 C: 400	I: 4 C: 12	47/390 Application failure: - unavailability of equipment (n=3) - technical problems (n=3) - IOC performed (n=1) - obesity (n=1) - could not insert probe (n=1) - probe contaminated (n=1) - equipment failure (n=1) Visualisation failure: - unable to demonstrate middle/distal CBD (n=36)	38/388 Application failure: - equipment failure (n=1) - technical problems (n=1) - LUS performed (n=4) - obesity (n=3) - pregnancy (n=1) - poor medical condition (n=1) - unable to cannulate (n=7) - avulsed duct (n=6) - unknown (n=2) Visualisation failure: - unsuccessfully imaged (n=12)	Single surgeon LUS typically failing in patients with ducts of smaller diameter	?	?	?

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results: Intervention (LUS)	Results: Comparison (IOC)	Comments	Directness *	Study limitations *	Precision *
Hublet 2009 Belgium	Cross-sectional (inter-individual comparison)	I: 271 C: 730	0	2/271 <u>Application failure:</u> 0 <u>Visualisation failure:</u> - steatosis (n=2)	35+?/730 <u>Application failure:</u> - technically unsuccessful, mainly because of difficulty to catheterise the cystic duct, narrow lumen, cystic duct valves or excessively inflamed cystic duct (n=35) <u>Visualisation failure:</u> NR	Single surgeon	?	-	?
Li 2009 China	Cross-sectional (intra-individual)	103	0	27[1]/103 <u>Application failure:</u> 0 <u>Visualisation failure:</u> - unable to demonstrate common hepatic duct (n=1) - unable to demonstrate intrapancreatic part of CBD (n=27)	12[1]/103 <u>Application failure:</u> - unsuccessful, not further described (n=9) <u>Visualisation failure:</u> - unable to demonstrate common hepatic duct (n=0) - unable to demonstrate intrapancreatic part of CBD (n=3)	Number of surgeons NR Patients with a contraindication for IOC were excluded (iodine allergy, current pregnancy, preoperatively verified CBD or intrahepatic bile duct stones, and scoring <3 or >5 on a scale from 0 to 9 to select patients who might have occult choledocholithiasis)	-	-	?
Machi 1999 USA	Cross-sectional (intra-individual)	100	0	5/100 <u>Application failure:</u> 0 <u>Visualisation failure:</u>	8/100 <u>Application failure:</u> - unsuccessful cannulation (n=6) <u>Visualisation failure:</u>	Number of surgeons NR	?	?	?

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results: Intervention (LUS)	Results: Comparison (IOC)	Comments	Directness *	Study limitations *	Precision *
				- incomplete imaging of the bile duct, mainly because of inflammation or adhesions; usually the distal or intrapancreatic CBD was not visualised (n=5)	- poor image quality (n=2)				
Perry 2008 USA	Cross-sectional (inter/intra-individual comparisons)	I: 236 C: 239 (partly overlapping; 104 had both)	0	11/236 <u>Application failure:</u> - technical failure of equipment (n=3) <u>Visualisation failure:</u> - suboptimal visualisation of the distal bile duct (n=6) - equivocal findings for stones (n=2)	11/239 <u>Application failure:</u> - difficult cystic duct cannulation, cystic duct obstruction, or dye extravasation (n=11, not separately reported) <u>Visualisation failure:</u> 0	Single surgeon	?	?	?
Röthlin 1996a (Intra...) Switzerland	Cross-sectional (intra-individual)	158	0	0+?/158 <u>Application failure:</u> 0 <u>Visualisation failure:</u> NR	12+?/158 <u>Application failure:</u> - inability to cannulate a narrow cystic duct (n=11) - history of severe allergic reaction to a contrast medium (n=1) <u>Visualisation failure:</u> - unable to demonstrate intrahepatic bile duct (64%, n NR)	Number of surgeons NR	?	-	?
Röthlin 1996b (Laparo...) Switzerland	Cross-sectional (intra-individual)	200	0	0+?/200 <u>Application failure:</u> 0	17+?/200 <u>Application failure:</u> - technical problems (n=14) - allergy to contrast medium (n=3)	Single surgeon	?	-	?

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
- Major problems

Author Year Country	**Study design**	**Patients**	**Withdrawals - dropouts**	**Results**		**Comments**	**Directhness ***	**Study limitations ***	**Precision ***
				Intervention (LUS)	**Comparison (IOC)**				
				Visualisation failure: NR	Visualisation failure: NR				
Siperstein 1999 USA	Cross-sectional (intra-individual)	300	0	0+?/300 Application failure: 0 Visualisation failure: NR	18+?/300 Application failure: inability to cannulate the cystic duct (n=18) Visualisation failure: NR	Number of surgeons NR	?	-	?
Stiegmann 1995 USA	Cross-sectional (intra-individual)	209	I: 7 C: 8	24/202 Application failure: Not specified - small CBD (n NR) Visualisation failure: Not specified - usually the result of failure to visualise the terminal bile duct (n NR)	15/201 P=0.046 Application failure: Not specified - inability to cannulate cystic duct (n NR) Visualisation failure: Not specified	3 sites, number of surgeons NR Successful imaging defined as complete visualisation of the extrahepatic bile ducts, from cystic duct-common duct junction to the terminal CBD	+	?	?
Tranter 2003 UK	Cross-sectional (intra-individual)	135	0	3/135 Application failure: - not specified (n=2) Visualisation failure: - only part of biliary tree was visualised (n=1)	14/135 P=0.012 for the comparison Application failure: - x-ray equipment failed (n=1) - inability to cannulate the cystic duct (n=8) Visualisation failure: - incomplete anatomical demonstration (n=5)	Single surgeon	?	?	?

Project: Laparoscopic ultrasonography
Appendix 4.5
Outcome variable: Procedural failure

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	**Study design**	**Patients**	**Withdrawals - dropouts**	**Results**		**Comments**	**Directness ***	**Study limitations ***	**Precision ***
				Intervention (LUS)	**Comparison (IOC)**				
Wu 1998 USA	Before/after	I: 200 C: 407	~~0~~ I: 2 C: 14	14/198 <u>Application failure:</u> - equipment problems/unavailability of equipment (n=4) - IOC applied because of suspect ductal anomalies (n=5) - concurrent operations (n=4) - critically ill status (n=1) (- preoperative suspicion of CBD stones or acalculous cholecystitis, initial exclusion criteria for LUS, only applied within the first 55 cases, n=12) <u>Visualisation failure:</u> - unsuccessful visualisation of CBD (n=0)	23/393 <u>Application failure:</u> - equipment problems/unavailability of equipment (n=9) - critically ill status (n=2) - pregnancy (n=1) <u>Visualisation failure:</u> - unsuccessful visualisation of CBD (n=11)	Single surgeon	?	?	?

[1]Number of patients not summarised over the visualised bile duct segments, maximum number presented
CBD = common bile duct, CBDS = common bile duct stone, ERC = endoscopic retrograde cholangiography, LUS = laparoscopic ultrasonography, NA = not applicable, NPV= negative predictive value, NR = not reported, IOC = intraoperative cholangiography, PPV= positive predictive value, UK = United Kingdom

Project: Laparoscopic ultrasonography
Appendix 4.6
Outcome variable: Complications

*	+	No or minor problems
	?	Some problems
	-	Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Complications (LUS)
Deziel 2022 USA	Case series	732	NA	No major bile duct or vascular injury
Machi 2009 USA	Case series	1381	NA	Minor bile leaks secondary to a liver bed injury, Strasberg's classification type A, n=3 (0.2%)

LUS = laparoscopic ultrasonography, NA = not applicable

Project: Laparoscopic ultrasonography
Appendix 4.7
Outcome variable: Operation time and imaging time

* + No or minor problems ? Some problems - Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results (minutes) Intervention (LUS)	Results (minutes) Comparison (IOC)	Comments	Directness *	Study limitations *	Precision *
Barteau 1995 USA	Cross-sectional (intra-individual)	125	I: 3 C: 2	Operation time NR Imaging time mean±SEM: 6.6±0.3	Operation time NR Imaging time mean±SEM: 10.9±0.6 P<0.05 for the comparison	Number of surgeons NR	?	?	+
Birth 1998 Germany	Cross-sectional (intra-individual)	518	I: 2 C: 41	Operation time NR Imaging time mean (range): 7 (3–25)	Operation time NR Imaging time mean (range): 16 (5–45) P<0.001 for the comparison	Number of surgeons NR	?	+	+
Catheline 1999 France	Cross-sectional (intra-individual)	600	I: 0 C: 102	Operation time NR Imaging time mean (range): 10.2 (5–20)	Operation time NR Imaging time mean (range): 17.9 (7–38) P=0.0001 for the comparison	Number of surgeons: 7	+	?	+
Catheline 2002 France	Cross-sectional (intra-individual)	900	I: 0 C: 138	Operation time NR Imaging time mean (range): 9.8 (4–21)	Operation time NR Imaging time mean (range): 17.6 (7–42) P-value NR	Number of surgeons NR	+	+	+
Halpin 2002 USA	Before/after	I: 394 C: 400	I: 14 C: 26	Operation time NR Imaging time mean±SEM: 5.1±0.1	Operation time NR Imaging time mean±SEM: 16.0±0.5 P<0.0001 for the comparison	Single surgeon	?	?	+

Project: Laparoscopic ultrasonography
Appendix 4.7
Outcome variable: Operation time and imaging time

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results (minutes)		Comments	Directness *	Study limitations *	Precision *
				Intervention (LUS)	Comparison (IOC)				
Li 2009 China	Cross-sectional (intra-individual)	103	I: 0 C: 9	Operation time NR Imaging time mean±SD: 8.5±1.9	Operation time NR Imaging time mean±SD: 13.8±3.7 P<0.01 for the comparison	Number of surgeons NR Radiologist interpreted IOC, blinded for LUS results	-	+	+
Machi 1999 USA	Cross-sectional (intra-individual)	100	I: 5 C: 8	Operation time NR Imaging time mean±SD: 8.2±3.5	Operation time NR Imaging time mean±SD: 15.9±6.8 P<0.0001 for the comparison	Number of surgeons NR	?	?	+
Röthlin 1996a (Intra...) Switzerland	Cross-sectional (intra-individual)	158	I: 0 C: 12	Operation time NR Imaging time mean±SD (range): 4.8±1.9 (2–12)	Operation time NR Imaging time mean±SD (range): 14.1±4.1 (4–37) P=0.0001 for the comparison	Number of surgeons NR	?	?	+
Röthlin 1996b (Laparo...) Switzerland	Cross-sectional (intra-individual)	Cohort I: 100 Cohort II: 100	I: 0 C: 17 (cohort I: 7; cohort II: 10)	Operation time NR Imaging time mean±SD (range): Cohort I: 5.4±2.4 (2–12) Cohort II: 4.5±1.7 (2–10)	Operation time NR Imaging time mean±SD (range): Cohort I: 16.4±7.4 (4–37) Cohort II: 13.5±4.5 (7–30) P=0.0001 for both comparisons	Single surgeon	?	?	+
Stiegmann 1995 USA	Cross-sectional (intra-individual)	209	I: 31 C: 23	Operation time NR Imaging time mean±SD (range): 7.0±3.3 (2–25)	Operation time NR Imaging time mean±SD (range): 13.4±5.7 (3–30) P-value NR, but states significantly less time required for LUS	3 sites, number of surgeons NR	+	?	+

Project: Laparoscopic ultrasonography
Appendix 4.7
Outcome variable: Operation time and imaging time

* + No or minor problems
? Some problems
\- Major problems

Author Year Country	Study design	Patients	Withdrawals - dropouts	Results (minutes)		Comments	Directness *	Study limitations *	Precision *
				Intervention (LUS)	Comparison (IOC)				
Thompson 1998 USA	Cross-sectional (intra-individual)	140	NR	Operation time NR Imaging time mean±SEM: 6.6±0.3	Operation time NR Imaging time mean±SEM:10.9±0.6 P-value NR, but states that this is a statistically significant difference	Single surgeon	?	?	+
Wu 1998 USA	Before/after	I: 200 C: 407	I: 28 C: 26	Operation time NR Imaging time mean±SEM: 5.3±0.2	Operation time NR Imaging time mean±SEM: 15.1±0.4 P<0.0001 for the comparison	Single surgeon	?	?/+	+

LUS = laparoscopic ultrasonography, NA = not applicable, NR = not reported, IOC = intraoperative cholangiography, SD = standard deviation, SEM = standard error of the mean, UK = United Kingdom

Project: Laparoscopic ultrasonography
Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author Year Country	Study design	Problems contributing to downgrading the study in the assessment			
		Directness		Study limitations	
Barteau 1995 USA	Cross-sectional (intra-individual)	?	Number of surgeons performing LUS not reported. Indication for surgery not reported (consecutive inclusion).	?	Potential detection bias because of not blinded investigator, and LUS always performed prior to IOC.
Birth 1998 Germany	Cross-sectional (intra-individual)	?	Only elective cholecystitis (consecutive inclusion). Number of surgeons performing LUS not reported.	+	Random order of LUS/IOC
Catheline 1999 France	Cross-sectional (intra-individual)	+		?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Catheline 2002 France	Cross-sectional (intra-individual)	+		+	
Deziel 2022 USA	Case series	NA		NA	
Halpin 2002 USA	Before/after	?	Only one surgeon performing LUS (consecutive inclusion)	?	Some imbalances between groups in patient characteristics. Prevalence of acute cholecystitis not specifically reported.
Hublet 2009 Belgium	Cross-sectional (inter-individual comparison)	?	Only one surgeon performing LUS (consecutive inclusion)	-	Patient characteristics in comparison groups not reported. Not blinded assessments.
Li 2009 China	Cross-sectional (intra-individual)	-	Number of surgeons performing LUS not reported. Consecutive inclusion not described. Subgroup: inclusion according to score system (score 3 to 5, out of 9, included)	-	Numbers of procedural failure not clearly presented. Patients with iodine allergy and pregnancy excluded Not problematic for Imaging time
Machi 2009 USA	Case series	NA		NA	
Machi 1999 USA	Cross-sectional (intra-individual)	?	Number of surgeons performing LUS not reported. Consecutive inclusion.	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Perry 2008	Cross-sectional (inter/intra-	?	Only one surgeon performing LUS (consecutive inclusion)	-/?	Patient characteristics in comparison groups not reported. Not blinded assessments. For the outcome

Project: Laparoscopic ultrasonography

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author **Year** **Country**	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
USA	individual comparisons)				diagnostic failure, these aspects were assessed as less problematic
Röthlin 1996a (Intra...) Switzerland	Cross-sectional (intra-individual)	?	Number of surgeons performing LUS not reported. Consecutive inclusion not described.	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC. Patients (not all) included in Rothlin 1996b.
Röthlin 1996b (Laparo...) Switzerland	Cross-sectional (intra-individual)	?	Only one surgeon performing LUS (consecutive inclusion)	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Siperstein 1999 USA	Cross-sectional (intra-individual)	?	Number of surgeons performing LUS not reported. Characteristics of patients not reported. Consecutive inclusion.	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Stiegmann 1995 USA	Cross-sectional (intra-individual)	+		?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Thompson 1998 USA	Cross-sectional (intra-individual)	?	Only one surgeon performing LUS (consecutive inclusion)	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Tranter 2003 UK	Cross-sectional (intra-individual)	?	Only one surgeon performing LUS. Consecutive inclusion not described	?	Potential detection bias because of blinded investigator not reported, and LUS always performed prior to IOC.
Wu 1998 USA	Before/after	?	Only one surgeon performing LUS (consecutive inclusion)	?/+	Some imbalances between groups in patient characteristics. One surgeon: before/after comparison

LUS = laparoscopic ultrasonography, NA = not applicable, IOC = intraoperative cholangiography

Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- ✔ Metodbeskrivning
- ✔ PICO
- ✔ Uttömmande litteratursökning
- ✔ Flödesschema
- ✔ Urval relevans
- ✔ Kvalitetsgranskning
- ✔ Tabelldata
- ✔ Sammanvägning av resultat
- ✔ Metaanalys
- ✔ Evidensgradering enligt GRADE
- ✔ Sammanfattning
- ✔ Ekonomi
- ✔ Organisation
- ✔ Etik
- ✔ Pågående studier
- ✔ Exkluderade artiklar
- ✔ Expertgrupp deltar
- ✔ Extern granskning
- ✔ Kunskapsluckor identifierade
- ✔ Jävsdeklaration inhämtad från projektdeltagarna