Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA-report 2016:89

Surgical treatment of gallbladder cancer

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Surgical treatment of gallbladder cancer
[Kirurgisk behandling av gallblåsecancer]

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Published May 2016
2016:89
Suggested citation: Sternby Eilard M, Cahlin C, Lundgren L, Sandström P, Samuelsson O, Svanberg T, Strandell A. Surgical treatment of gallbladder cancer [Kirurgisk behandling av gallblåsecancer] Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum; 2016. Regional activity-based HTA 2016:89

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1. Abstract

Background
Gallbladder cancer is an aggressive cancer with high mortality. The severity of cancer is staged by the TNM-system. Stage T1 is the least and T4 is the most advanced stage of the primary tumour. In advanced stages, surgery is often not possible due to spread into the liver hilum, other organs or lymph nodes. Even in cases of radical surgery recurrence and mortality rates are high.
Early stages of gallbladder cancer are often incidentally diagnosed in conjunction with cholecystectomy due to gallstone disease. Radical surgery is the only potentially curative treatment. However, the extent of surgery is a matter of debate. In the very early stages (T1a) simple cholecystectomy seems to be radical enough, but there has been a discussion whether this applies also to when the cancer has engaged also the smooth muscle layer (T1b).

Objective
To evaluate whether extended surgery compared with cholecystectomy alone in the adult patient with gallbladder cancer in early and late stages lead to improved survival.

Methods
During May 2014, with an update in April 2015, systematic literature searches were conducted in PubMed, Embase and the Cochrane Library. At least two authors independently screened titles, abstracts, full-text articles for inclusion and thereafter extracted data. The certainty of evidence was appraised according to GRADE.

Main results
Forty-four observational studies (non-randomised, controlled studies) and seven case series fulfilled the inclusion criteria.
No study reported data or discussed the effects of surgery on health-related quality of life.
With regard to ***liver resection compared with cholecystectomy alone*** survival data from 24 cohort studies could be analysed according to the T-stages in a meta-analysis with a summary estimate of the effect for each stage. The odds ratios were significantly better for patients with stages T1b, T2 and T3 whom have had a liver resection. All studies had serious study limitations and the certainty of evidence was very low (GRADE ⊕◯◯◯).
Nine studies compared different extent of ***lymph node resection***. Studies of patients with stage T1b or higher observed a higher survival rate in patients undergoing lymph node resection compared with no such resection. This was most evident in patients with stage T2. The certainty of evidence that lymph node resection may improve survival was low (GRADE ⊕⊕◯◯).
The complication rate varied substantially between studies and included bleeding, infections, liver abscess, ascites, liver failure, bile leakage, pancreatic fistula, bile fistula, respiratory dysfunction, and renal failure. Overall serious complications were quite common.

Conclusion
Gallbladder cancer is a disease with high mortality. Data indicate that the prognosis can be improved if liver resection and lymph node resection is performed in patients with the early stages (T1b and T2) of gallbladder cancer. Morbidity is likely to increase with extensive surgery. The uncertain risk-benefit balance constitutes a difficult ethical dilemma, and the effects on health-related quality of life remains to be elucidated.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Gallblåsecancer är en aggressiv cancerform med hög dödlighet. Tumörens svårighetsgrad indelas i stadier enligt TNM-systemet. Stadium T1 innebär endast lokal tumörväxt i slemhinnan medan T4 är det mest avancerade stadiet med invasiv växt av primärtumören. I de mest avancerade fallen är kirurgisk åtgärd ofta inte möjligt på grund av tumörspridning till leverhilus, andra organ eller lymfkörtlar. Även i de fall där radikal kirurgi har utförts är återfall vanligt och dödligheten hög.
Patienter med tidiga stadier av gallblåsecancer upptäckts ofta incidentellt i samband med kolecystektomi på grund av gallsten. Radikalt kirurgiskt avlägsnande av tumören är den enda potentiellt botande behandlingen. Hur omfattande den kirurgiska åtgärden ska vara i dessa fall är omdiskuterat. I de allra tidigaste tumörstadierna (T1a) är troligen en enkel kolecystektomi tillräckligt, men om detta även gäller för gallblåsetumörer som även engagerar det glatta muskellagret (T1b) är oklart.

Syfte
Att utvärdera om utvidgade kirurgiska åtgärder jämfört med enbart kolecystektomi leder till ökad överlevnad hos vuxna patienter med gallblåsecancer i tidiga stadier.

Metoder
Under maj månad 2014 med uppdatering i april 2015 gjordes systematiska litteratursökningar i PubMed, Embase och Cochrane Library. Två författare gick oberoende av varandra igenom titlar, abstrakts och slutligen möjliga relevanta artiklar i fulltext för att avgöra om de uppfyllde kriterierna för att besvara frågeställningen. Resultaten i relevanta studier sammanställdes av samma personer. Evidensgraden bedömdes slutligen enligt GRADE-systemet.

Resultat
Fyrtiofyra observationsstudier (icke-randomiserade studier med kontrollgrupp) och sju fallserier inkluderades. Ingen av dessa studier rapporterade eller diskuterade effekter av olika kirurgiska åtgärder på hälsorelaterad livskvalitet.
Tjugofyra studier jämförde ***kolecystektomi plus leverresektion med enbart kolecystektomi***. En metaanalys med ett summaestimat för effekten på mortalitet för varje tumörstadium visade att överlevnaden hos de som även genomgått en leverresektion var signifikant högre hos patienter med stadium T1b, T2 och T3. Samtliga studier hade emellertid allvarliga begränsningar i sin kvalitet och evidensgraden bedömdes därför vara otillräcklig (GRADE ⊕○○○).
Nio studier jämförde olika omfattning av ***lymfkörtelresektion***. Med undantag av patienter med det lägsta stadiet av tumörutbredning (T1a) observerades en bättre överlevnad hos de patienter som opererats med lymfkörtelresektion jämfört med de som inte lymfkörtelresecerats. Effekten var mest påtaglig hos patienter i stadium T2. Evidensgraden till stöd för lymfkörtelresektion bedömdes vara begränsad (GRADE ⊕⊕○○).
Allvarliga komplikationer var vanliga och inkluderade blödningar, infektioner, leverabscesser, ascites, leversvikt, galläckage, pankreasfistlar, gallfistlar, andningssvikt, och njursvikt.

Slusatser
Gallblåsecancer är en sjukdom med hög dödlighet. Studieresultat indikerar att med leverresektion och lymfkörtelresektion kan prognosen förbättras hos patienter i tidiga stadier av sin cancersjukdom (T1b and T2) . Den postoperativa sjukligheten är hög efter extensiv kirurgi. Effekterna av mer extensiv kirurgi på den hälsorelaterade livskvaliteten är inte studerad. Osäkerheten i balansen mellan risk och nytta utgör ett svårt etiskt dilemma.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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Head of HTA-centrum of Region Västra Götaland, Sweden, 2016-04-27

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3. Summary of Findings

Outcomes Interventions	Study design Number of studies Total number of patients*	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE
5-year OS Radical resection vs. cholecystectomy	T1a: 3 cohort n=384 T1b: 5 cohort n=1389 T2: 14 cohort n=2270 T3: 7 cohort n=1665 T4: 1 cohort n=208	OR 1.0 (0.37-2.65) OR 2.75 (1.13-6.69) OR 2.39 (1.91-3.0) OR 3.56 (1.59-7.96)	Overall estimate 78.4% vs. 66.0% 80.3% vs. 43.4% 56.3% vs. 25.9% 22.8% vs. 9.1% 29.8% vs. 0%	⊕◯◯◯ Very low[1]
5-year OS Lymph node resection vs. no LN resection	9 cohort studies n=11,471	T1-T3: HR 0.70 (0.48-1.0) T1b: HR 0.82 (0.56-1.18) T2: HR 0.42 (0.33-0.53) T1: HR 0.64 (0.48-0.83)	Range 25-63% vs. 0-60%	⊕⊕◯◯ Low
5-year OS Bile duct resection vs. no resection	8 cohort studies n=1565	Not presented	Range 17-86% vs. 27-81%	⊕◯◯◯ Very low[2]
5-year OS Adjacent organ resection	1 cohort study n=4424 + 1 cohort study n=216	HR=0.79 (0.69-0.91) all stages (vs.cholecystectomy)	Stage III 39% vs 38% N+: 87% vs 17%	⊕◯◯◯ Very low[3]
1-year OS Resection vs. palliation	8 cohort studies	Not presented	Range 25-70% vs 0-17%	⊕◯◯◯ Very low[4]

Abbreviations:
OS = overall survival, LN= lymph node, N+=positive lymph nodes, T= tumor stage
OR=odds ratio from meta-analysis, OR>1 denotes better survival
HR=hazard ratio in separate studies, HR<1 denotes better survival
*Numbers refer to studies included in the meta-analysis
Footnotes:
[1] Serious study limitations; groups not comparable at baseline in several studies
[2] Serious study limitations; groups not comparable at baseline. Inconsistent results and imprecision.
[3] Serious study limitations and uncertain directness.
[4] Very serious study limitations

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

SweLiv	Swedish National Registry from tumours in the liver and bile ducts
GallRiks	Swedish national gallbladder registry
OS	Overall Survival
LN	Lymph Node
TNM	Tumor Node Metastases
R0/R1	Microscopically radical/ microscopically non-radical
OR	Odds Ratio
HR	Hazard Ratio
AHPBA	American Hepato-Pancreatico-Biliary Association,
ESMO	European Society for Medical Oncology
NCCN	National Comprehensive Cancer Network
BD	Bile Duct
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
MODS	Multi Organ Dysfunction Syndrome
D1 and D2	extent of lymph node dissection; along the hepatic ligament (D1) or more extensive dissection along the hepatic artery and behind the pancreatic head or more (D2)
MDT	MultiDisciplinary Team

5. Background

Disease/disorder of interest and its degree of severity

Gallbladder cancer is an aggressive cancer (adenocarcinoma) with high mortality. In advanced stages, surgery is often not possible due to spread into the liver hilum, other organs or lymph nodes. Even in cases of radical surgery recurrence and mortality rates are high. Surgery is the only chance of cure. In advanced stages the need for extensive surgery is associated with high morbidity and a very low possibility of cure.

Classification of gallbladder cancer

TNM-system

The severity of cancer in the gallbladder is staged by the TNM-system as follows:

T stage	Extent of the primary tumor
TX	Cannot be assessed
Tis	Cancer cells only in the epithelium and not in deeper layers of the gallbladder. *"Carcinoma in situ".*
T1	Cancer cells in the lamina propria (T1a) or muscle layer (T1b).
T2	Cancer cells in perimuscular fibrous tissue
T3	Cancer cells have grown through the serosa and/or from the gallbladder directly into the liver and/or a nearby organ or bile ducts outside the liver.
T4	Cancer cells have grown into one of the main blood vessels leading into the liver (portal vein or hepatic artery) or into 2 or more structures outside of the liver.

N stage	Local spread of cancer cells
NX	Regional lymph nodes cannot be assessed
N0	No cancer cells in nearby lymph nodes.
N1	Cancer cells in lymph nodes near the gallbladder, along the cystic duct and the hepatic ligament. (Along the common bile duct, hepatic artery, and portal vein.)
N2	Cancer cells in lymph nodes in the abdomen farther away from the gallbladder, such as along the aorta (periaortic), the vena cava (pericaval), the superior mesenteric artery, and the celiac artery.

M stage	Distant spread of cancer cells
M0	No cancer cells spread to tissues or organs far away from the gallbladder.
M1	Cancer cells spread to tissues or organs far away from the gallbladder.

Stage grouping
The information on T, N, and M categories is combined in *stage grouping*, expressed as Roman numerals from stage 0 (the least advanced) up to stage IV (the most advanced). Some stages are subdivided with letters.

Stage group	TNM
0	Tis, N0, M0
I	T1a or T1b, N0, M0
II	T2, N0, M0
IIIA	T3, N0. M0
IIIB	T1 – T3, N1, M0
IVA	T4, N0 or N1, M0
IVB	Any T group, N2, M0 or Any T group, any N, M1

R-classification
This classification refers to the surgical radicality.

R class	Extent of tumor resection
R0	Macroscopically radical resection and margins microscopically free of tumor
R1	Macroscopically radical resection, but with microscopic tumor growth in the resection surface
R2	Tumor not macroscopically resected

Early stages of gallbladder cancer, i.e. T1 and T2, are often incidentally diagnosed in conjunction with cholecystectomy due to gallstone disease. Radical surgery remains the only curative treatment. However, the extent of surgery is a matter of debate. In the very early stages (T1a) simple cholecystectomy seems to be radical enough, but there has been a discussion whether this applies also to T1b.

Another issue of debate is what extent of liver resection that is required in the more advanced T-stages. A further question is the importance and extent of lymph node dissection. Finally, there is a discussion whether a routine resection of the common bile duct should be performed.

The Swedish National Registry for tumours in the liver and bile ducts (SweLiv) was started in 2008 with a national coverage 2009-2013 of 87%. In the 2014 SweLiv report, 845 cases diagnosed with gallbladder cancer were reported 2009-2014. This corresponds to 141 cases per year.

Seventy-four percent of the patients were women. Overall 30 % of all patients were stage T1-T2 at diagnosis with a 5-years age-standardized survival of 40 % irrespective of treatment. Fifty percent of the patients were stage T3 and 20 % were stage T4 at the time of diagnoses. The 5-years survival in these patients was about 7 % and 6 %, respectively.

Since 1980 there has been a gradual decrease of the incidence of this disease, in women from 6.1 to 1.4 per 100 000, and in men from 2.2 to 0.9 per 100,000, Figure 1. Similar to other forms of cancer, gallbladder cancer is uncommon before the age of 60 (Figure 2), with a median age at diagnosis of 74 years according to the Swedish Board of Healthcare.

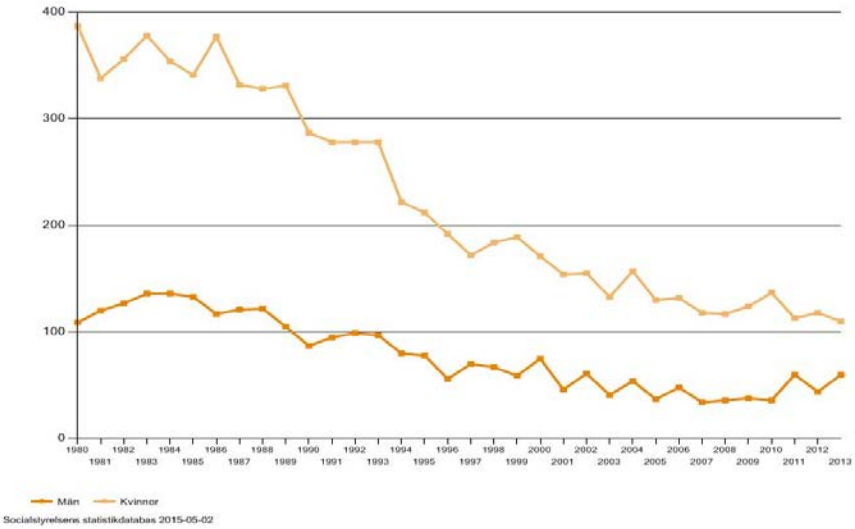


Figure 1. The incidence of gallbladder cancer in Sweden during 1980- 2013.

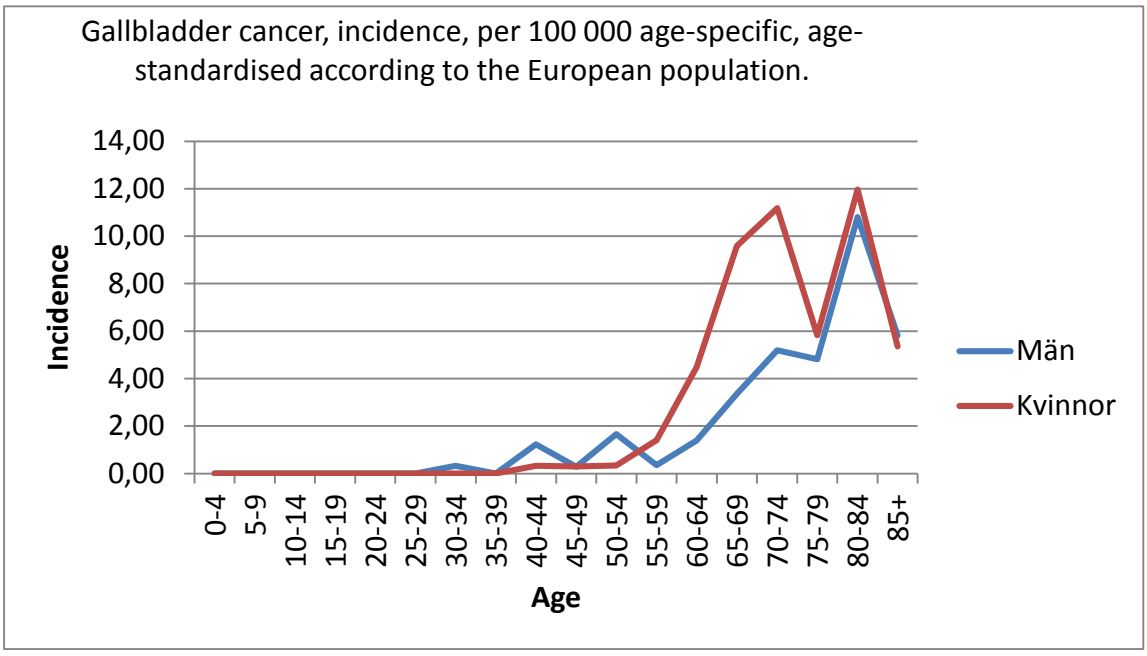


Figure 2. Age-standardised incidence of gallbladder cancer in Europe. Socialstyrelsens statistikdatabas 2015-05-20

In the national registry for cancer in the liver and bile duct system, SweLiv, gallbladder cancer varies in the different regions, Table 1. This could be due to low registration rates or different incidences in the regions. However, most probably this is due to less referral to the specialised clinics in some of the regions. Furthermore, according to the national gallbladder registry, GallRiks, many patients with gallbladder cancer are not registered in SweLiv. During the time period 2008-2014 almost 40 % of all the recorded gallbladder cancers in GallRiks are missing in SweLiv.

Table 1. The number of patients (percentage in parenthesis) who were diagnosed with gallbladder cancer in the six regions of Sweden during 2009-2013 and 2014. Data from SweLiv.

Region	Year		
	2009-13	2014	Total
North	67 (9.4)	5 (5.6)	72 (7.9)
Stockholm/Gotland	112 (15.8)	10 (11.2)	122 (15.3)
South	103 (14.5)	6 (6.7)	109 (13.6)
Southeast	128 (18.0)	21 (23.6)	149 (18.6)
Uppsala/Örebro	152 (21.4)	18 (20.2)	170 (21.3)
West	148 (20.8)	29 (32.6)	177 (22.2)
All	710 (100)	89 (100)	799 (100)

According to the national registry for cancer in the liver and bile duct system, SweLiv, 66 cases were diagnosed accidentally during or after cholecystectomy for gallstone disease during 2009-2014. In this group 54 % were stage T1-T2, while 38% were stage T3. The 5-years age-standardised overall survival in the group who underwent direct radical resection directly was 50%, while it was it was 39% in the accidentally diagnosed group, compared with 5% in the patients that did not have any resection of the tumour at all.

Present treatment of gallbladder cancer

Many cases of gallbladder cancer are incidentally diagnosed during or after simple cholecystectomy due to gallstone disease. Once the cancer diagnosis is established or suspected, the patient is normally referred to a regional liver surgery unit for radical surgery either directly or after a primary cholecystectomy. Radical gallbladder cancer surgery comprises a certain extent of liver and lymph node resection and sometimes also resection of the common bile duct. The extent of surgery depends on the cancer spread as well as the local clinical routines and opinions (see below Section 6. Surgery for gallbladder cancer, page 15). While simple cholecystectomy is mostly done with no more than one single night of hospital stay, radical surgery for gallbladder cancer requires hospital care for about a week, or even longer if extensive surgery is performed or postoperative complications occur.

The normal pathway through the health care system and current wait time for medical assessment and treatment

Patients with gallbladder cancer are diagnosed either during or after an operation for suspected benign gallstone disease, or radiologically in the preoperative setting. The patient is then referred to a specialised liver unit for direct or complementary radical resection. At this unit an evaluation is done at a multidisciplinary conference. Radiologic, clinical and sometimes histological variables are then considered.

In 2014, the median time from referral to the multidisciplinary conference was 10 days (73% within 21 days). The median time to surgery was 40 days (26% within 21 days).

Number of patients per year who undergo surgery for gallbladder cancer

There is a great variation between the different regions of Sweden with regard to the surgical procedures for gallbladder cancer (Table 2).

Table 2. The number of gallbladder cancer patients that did not have any surgery or underwent any kind of surgical resection in the six regions of Sweden during 2009-2014. Data from SweLiv.

Region	Type of surgical resection			Total
	None	Resection	En passent surgery	
North	53 (81.5)	6 (9.2)	6 (9.2)	65 (100)
Stockholm/Gotland	83 (72.8)	28 (24.6)	3 (2.6)	114 (100)
South	71 (67.0)	16 (15.1)	19 (17.9)	106 (100)
Southeast	110 (76.4)	30 (20.8)	4 (2.8)	144 (100)
Uppsala/Örebro	113 (69.8)	39 (24.1)	10 (6.2)	162 (100)
West	131 (75.7)	22 (12.7)	20 (11.6)	173 (100)
All	561 (73.4)	141 (12.7)	62 (8.1)	764 (100)

Present recommendations from medical societies or health authorities

A search on Medline and PubMed with the terms “Gallbladder cancer”,” Guidelines”, “National guidelines”, “Surgery” identified seven published guidelines. Four were national guidelines, and three were published by medical associations. They are summarised in Table 3.

Table 3. Treatment guidelines of gallbladder cancer.

Guidelines ref.	Liver resection	Wedge resection or resection of segment 4b/5	Lymph node resection	Prophylactic bile duct resection	Extensive surgery of adjacent organs	Extensive surgery in advanced stages
AHPBA Guidelines	T1b - T4		N1 yes N2 no benefit	no	selected cases	selected cases
Indian Guidelines	T1b - T4		N1 yes N2 no benefit	no	selected cases	selected cases
Korean Guidelines, 2014	T1b uncertain, T2 - T4	uncertain	N1 yes N2 no benefit	no	yes	selected cases
ESMO guidelines	T1b - T4	not analysed	not analysed	not analysed	yes	unclear
NCCN guidelines	T1b uncertain, T2 - T4		N1 yes N2 no benefit	no	unclear	unclear
Japanese guidelines 2015	T2 - T4	not analysed	not analysed	no	selected cases	selected cases
German guidelines 2007	T1b uncertain, T2 – T4	4b/5	N1 yes	not analysed	not analysed	unclear

Abbreviations: AHPBA= American Hepato-Pancreatico-Biliary Association, ESMO = European Society for Medical Oncology, NCCN = National Comprehensive Cancer Network, USA.

As can be seen in Table 3, six of the seven guidelines recommend liver resection in all stages from T1b and above, although three of them are uncertain about T1b. With regard to surgery with wedge resection or resection of liver segments S4b/5, the German guidelines recommend a bisegmentectomy. None of the other guidelines has any recommended statement. Five of the seven guidelines state that resection of N1 nodes (i.e. lymph nodes along the hepatic ligament) is beneficial, whereas this may not be the case for N2 lymph nodes. None of the guidelines recommend prophylactic resection of the bile duct, but the Japanese guidelines emphasises the need for bile duct resection in cases with lymph node tumour involvement, perineural growth and growth in the lower part of the gallbladder in order to reach an R0 stage.

6. Surgery for gallbladder cancer

The surgical strategy varies with the stage of the cancer of the gallbladder, all with the same intention to radically remove all cancer. The following surgical methods were evaluated and discussed below.

1. ***Simple cholecystectomy***. Resection of the gallbladder from the gallbladder fossa on the liver, but leaving all liver parenchyma. The cystic duct is divided with a good margin towards the common bile duct. Single lymph nodes may or may not be included. The operation can be done laparoscopically or as open surgery. It is performed in most hospitals in Sweden: Normally it requires only a very short hospital stay or can be performed as day surgery.

2. ***Extended or radical surgery***. Resection of the gallbladder including some extent of liver resection, lymph node resection, and sometimes also resection of the bile duct. In this HTA-report the various surgical procedures have been addressed separately, although the observed effects often are difficult to distinguish from one another
   a. ***Liver resection*** ranges from wedge resection of a few centimetres of the gallbladder fossa to resection of the anatomical segments 4b and 5, and sometimes more extensive procedures such as extended resection of the right liver lobe.
   b. ***Resection of the lymph node***s ranges from simple sampling of lymph nodes in the adjacent area around the cystic duct, to resection of lymph nodes along the hepatic ligament, or a more thorough cleaning of lymph nodes along the hepatic artery and behind the pancreatic head with dissection of the duodenum by a Kocher' manoeuvre.
   c. ***Resection of the bile duct*** means a division of the bile duct at the level of the entrance into the liver parenchyma proximally, and at the cranial rim of the pancreas distally. The continuity of the bile duct is restored with a Roux-en-Y-reconstruction where the jejunum is divided a few decimetres distal to the ligament of Treitz. The distal end is pulled cranially towards the liver and the bile duct to form a hepatico-jejunostomy, while the proximal end is anastomosed a couple of decimetres distally on the jejunum to form an entero-enteroanastomosis.

7. Objective

In the adult patient with gallbladder cancer in early and late stages does extended surgery compared with cholecystectomy alone lead to improved survival?

PICO (P= Population, I= Intervention, C= Comparison, O=Outcome)

P = Population

Adults with a radiologically or preoperatively diagnosed gallbladder cancer, or incidental finding in histology report from cholecystectomy because of gallstone disease.

I = Intervention

1. Liver resection; liver segments 4b and 5 or "radical" resection
2. Lymph node resection; standard or extended
3. Resection of the common bile duct
4. Extensive surgery of adjacent structures or/and organs.

The intervention was divided into separate questions regarding the evidence of benefit for different parts of these operations. In some studies the intervention was not described separately and the meaning of "extended surgery" could include both liver and lymph node resection together.

C = Comparison

- Cholecystectomy alone or wedge resection of gallbladder fossa
- No lymph node resection or standard resection
- No bile duct resection

O= Outcome

Overall survival
Disease-free survival
Health related quality of life
Complications/Risks

Subgroup evaluation has mostly been performed according to T-stage and sometimes full TNM-stage as follows

- T1a
- T1b
- T2
- T3
- Advanced stages including T4, N1 and M1

8. Methods

Systematic literature search (Appendix 1)

During May 2014 two authors (TS, UWA) performed systematic searches in PubMed, Embase andthe Cochrane Library. The literature search was later updated in April 2015. At least two authors assessed the obtained abstracts, deciding which articles to read in full text. All participants of the project group read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The articles were critically appraised using SBU's checklist regarding cohort studies (SBU 2015). A summary result for the outcome variables and the associated certainty of evidence are presented in a Summary of Findings table (page 4). The certainty of evidence was graded according to the GRADE system (Atkins et al, 2004; GRADE Working group). The grading of cohort studies started at the ⊕⊕OO level.

Ongoing research

The ClinicalTrials database (www.clinicaltrials.gov) was searched 2016-01-13 for studies of interest with the use of the terms (gallbladder AND (cancer OR cancers OR tumour OR tumours OR tumor OR tumors OR carcinoma OR carcinomas OR neoplasms OR neoplasm OR adenocarcinoma OR adenocarcinomas OR cholangiocarcinoma OR cholangiocarcinomas OR malignant OR malignancy OR malignancies)) AND (resection OR resections OR surgery OR surgical OR cholecystectomy OR cholecystectomies).

9. Results

Systematic literature search (Appendix 1)

The literature search identified 1960 articles after removal of duplicates. After reading the abstracts 1797 articles were excluded. Another 112 articles were excluded after reading the articles in full text (Appendix 3). The remaining 51 articles (44 cohort studies and seven case series) were finally included in the assessment (Appendix 2).

Liver resection

Thirty-one non-randomised, controlled cohort studies have reported overall survival after liver resection. Four of them reported the outcome after resection of the liver segments 4b and 5 compared with wedge-resection in patients with cancer stage T2 or T3.

Twenty-four studies reported overall survival in patients undergoing "radical" liver resection compared with cholecystectomy alone. The tumour stages of the patients in the different studies varied from T1b to T4. All of them reported survival data in relation to the separate T-stages with or without documentation of N-stage; N0 or N1.

No study reported data on health-related quality of life.

Liver resection versus cholecystectomy alone **(Appendix 4.1.1)**

Survival data from 18 cohort studies were analysed according to the T-stages in a meta-analysis with a summary estimate of the effect for each stage (Figure 3).

As can be seen in the forest plot cholecystectomy alone seems to be less beneficial than more radical liver resection in patients with more severe T-stages than T1a. However, the great majority of the studies had serious study limitations. The study groups were not well balanced with regard to baseline characteristics, which indicates selection bias. Furthermore, the simultaneous lymph node interventions seemed to have been more extensive in the patients undergoing more "radical" resection.

Conclusion**:** It is uncertain whether survival is improved by a more extensive liver resection compared with surgery to achieve R0-resection (i.e. resection macro-and microscopically) in patients with gallbladder cancer without obvious tumour infiltration of the liver (GRADE ⊕○○○).

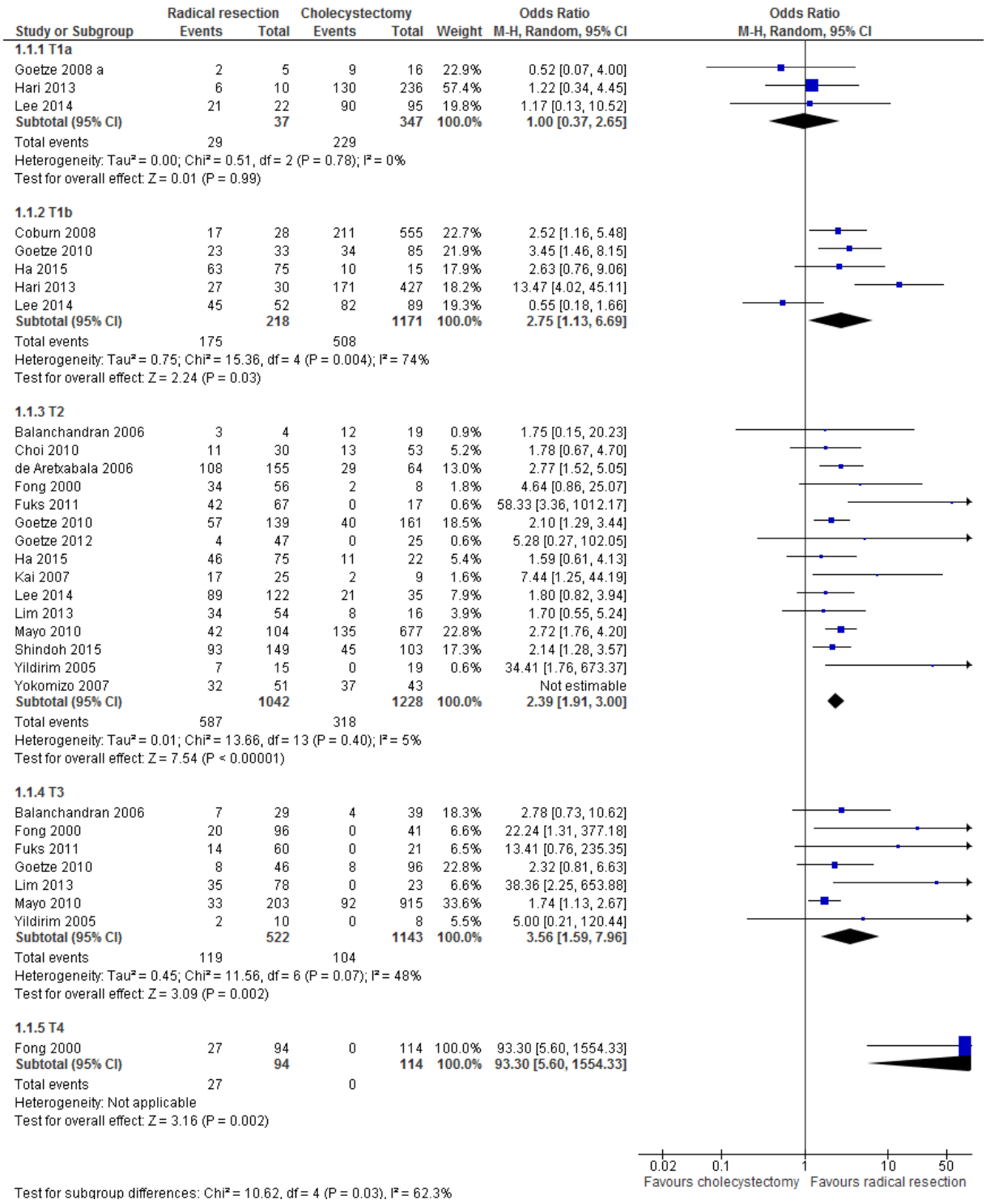
Resection of liver segment 4b and 5 versus wedge resection of the gallbladder fossa **(Appendix 4.1.1)**

The four cohort studies in which segment resection was compared with wedge resection had serious study limitations. There were no observed differences in survival in patients with stage T2 or T3.
Conclusion: It is uncertain whether survival is affected by resection of liver segment 4b/5 compared with wedge resection (GRADE ⊕○○○).

Complications **(Appendix 4.2.1)**

The complication rates were poorly described in all studies. Reported complications included bleeding, infections (including cholangitis), liver abscess, ascites, liver failure, bile leak, pancreatitis, ileus, MODS (multiorgan dysfunction syndrome), tachycardia, transitory ischemic attack, thrombosis or pulmonary embolism, pulmonary edema, respiratory dysfunction, urinary complications, and renal failure.

Figure 3. Meta-analysis of cohort studies comparing the effect of radical resection with cholecystectomy alone, on 5-year overall survival according to T-stage



Lymph node resection

Nine non-randomised, controlled cohort studies reported overall survival in patients who have had lymph node resection to different extent. Seven of them reported survival rates in patients with lymph node resection compared with patients without lymph node resection, and two compared "extended" with "standard" lymph node dissection.

The tumour stages of the patients in the different studies varied from T1 to T3. Six of the nine studies reported survival data in relation to separate T-stages.

No study reported data on health-related quality of life.

The studies had some study limitations with imbalances in the baseline patient characteristics.

Lymph node resection versus no lymph node resection **(Appendix 4.1.2)**
Eight studies reported numerically higher survival rates in patients with stage T1b or higher undergoing lymph node resection, of which all comparisons with regard to stage T2 were statistically significant. For patients with stage T1b and T3 the effect on survival data was less pronounced.
Conclusion: Lymph node resection may improve survival in patients with gallbladder cancer stage T1, T2 and T3 compared with no lymph node resection (GRADE ⊕⊕◯◯).

Standard lymph node resection versus extended lymph node resection **(Appendix 4.1.2)**
Two studies compared overall survival in patients having "standard" lymph node resection (D1) with "extended" lymph node resection (D2). Both reported a higher survival rate with "extended" lymph node resection for gallbladder cancer patients. A third study comparing extended, standard and no lymph node resection demonstrated significant better survival, only compared with no lymph node resection.
Conclusion: "Extended" lymph node resection may improve survival in patients with gallbladder cancer (GRADE ⊕⊕◯◯).

Complications **(Appendix 4.2.2)**
Perioperative complications were common varying from 14 % to 81 % across the studies. Serious complications were frequent. The reported complications included bleeding, infections, liver abscess, ascites, liver failure, bile leak, pancreatic fistula, bile fistula, respiratory dysfunction, and renal failure.

Resection of the common bile duct

Eight non-randomised, controlled cohort studies reported overall survival in patients who have had a bile duct resection compared with patients without bile duct resection. Resections have mainly been performed in patients with tumour invasion of the cystic duct, lower part of the gallbladder or for radical lymph node resection. Prophylactic bile duct resection in patients with gallbladder cancer was not evaluated in any of the studies.

The tumour stages of the patients in the different studies varied from T2 to T4. Five of the eight studies reported survival data in relation to separate T-stages.

No study reported data on health-related quality of life.

The studies had serious study limitations with imbalances in the baseline patient characteristics.

Bile duct resection versus no bile duct resection **(Appendix 4.1.3)**
The studies reported inconsistent results with regard to the overall survival rates in patients who underwent bile duct resection. Six of them reported better survival in the patients without bile duct resection, although there were no statistically significant differences, whereas two studies reported significantly better survival in the patients who have had a bile duct resection.
Conclusion: It is uncertain whether bile duct resection in patients with gallbladder cancer stage T2 to T4 affects overall survival compared with no bile duct resection (GRADE ⊕○○○).

Complications **(Appendix 4.2.3)**
Perioperative complications were common and varied from 8 % to 65 % in the different studies with higher complication rates in patients who underwent bile duct resection. The reported complications included bleeding, infections, ascites, liver failure, bile leak, pancreatic leak, duodenal leak, pulmonary embolism, respiratory dysfunction, and renal failure.

Resection of adjacent organs

Two small studies evaluated the effect of adjacent organ resection to achieve surgical radicality.

Adjacent organ resection versus no adjacent organ resection **(Appendix 4.1.4)**
One study reported prolonged overall survival with HPD (hepato-pancreatico-duodenectomy) compared with routine extended surgery in the absence of ligament infiltration for cases with lymph node infiltration, but not for lymph node negative patients. The other study found no survival benefit for more extended surgery (adjacent organ resection and/or hemihepatectomy) compared with common radical resection.
Conclusion: It is uncertain whether resection of adjacent organs for gallbladder cancer has any effect on overall survival (GRADE ⊕○○○).

Complications **(Appendix 4.2.4)**
Perioperative mortality rates after adjacent organ resection were high, with about 17% in the 1990s and about 10% during the last decade. The complications rates were very high and included bleeding, infections, ascites, liver failure, bile leak, pancreatic leak, duodenal leak, pulmonary embolism, respiratory dysfunction, and renal failure.

Surgery in advanced stages

Eight studies reported survival of patients who had resection of gallbladder cancer in advanced stages (Stage IVa and b).

No study reported data on health-related quality of life.

The studies had serious study limitations with major imbalances with regard to the patients who had surgery compared with those without or only palliative surgery, which indicates obvious selection bias.

Surgery versus no or only palliative surgery in advanced stages **(Appendix 4.1.5)**
Conclusion: It is uncertain whether resection compared with palliative treatments affects survival in advanced stages of gallbladder cancer (GRADE ⊕○○○).

Staged operations or direct radical surgery

Three studies compared survival of patients who underwent laparoscopy for staging before principal surgery or direct radical surgery.

No study reported data on health-related quality of life.

All studies had very serious study limitations with major imbalances between groups, indicating severe selection bias.

Staged operations vs direct radical surgery for gallbladder cancer **(Appendix 4.1.6)**

Conclusion: It is uncertain whether staged operations compared with direct radical surgery affects survival in patients with gallbladder cancer (GRADE ⊕◯◯◯).

10. Ethical issues

The main ethical issue is whether extensive surgery is balanced by the risk for complications. Complications may be very severe and the result of improved survival is based on studies with high risk of bias.

In Sweden there are presently no established guidelines for treatment of gallbladder cancer. If extended surgery with lymph node and liver resection would be generally accepted in all patients with stage T1b or higher, more patients than today would be referred to liver centres for surgery. Furthermore, if the treatment strategies were accepted in all counties and regions of the country, it would enable all patients to have an equal evaluation and treatment of this disease. As the total number of new cases of gallbladder cancer in Sweden is less than 200 patients per year the risk to adversely affect the treatment and care of other patient categories is low.

Serious complications are common following surgery for gallbladder cancer. If severe complications develop the patient may need prolonged treatment in the intensive care unit. Under these circumstances the patient will lose his or her autonomy, and it will also be difficult for family and other relatives. Therefore, it is of great importance that the patient is well-informed about the technical aspects with the consequent risks of morbidity and even mortality, as well as alternative options, and of the possibility to deny the proposed surgical treatment.

11. Organisational aspects

Surgery of gallbladder cancer is centralised to six regional cancer centres in Sweden. If more extended surgery with lymph node and liver resection will be generally accepted in patients with gallbladder cancer an increased number of patients will be referred to these centres. However, this will probably not require any organisational changes since the numbers of cases is rather small. The surgical technique and the evaluation of the patients will not be more demanding, but most probably will be more standardised. No new investments are expected for either the necessary work-up of the patients or the facilities for surgery.

Present use of surgery for gallbladder cancer in hospitals in Sweden

Surgery for gallbladder cancer is presently performed at the six university hospitals in Sweden (Karolinska University Hospital, Linköping University Hospital, Sahlgrenska University Hospital, Skåne University Hospital, Norrlands University Hospital, Uppsala University Hospital).

Consequences for other clinics or supporting functions at the hospital

The number of patients that will undergo surgery will increase slightly. This will increase the need for radiological examination and histopathology examinations to some extent.

12. Economic aspects

Present costs

The treatment of gallbladder cancer includes radiological evaluations, outpatient visits, MDT conference evaluation, surgical treatment, postoperative care and follow up visits.

Table 4 presents the costs for the perioperative care for different operations at the Sahlgrenska University Hospital. The figures do not include the costs for radiologic investigations, preoperative work up including MDT, or for follow up visits including radiologic examinations, or treatment of recurrence of the cancer.

Table 4. Cost for perioperative care at Sahlgrenska University Hospital.

Type of intervention	N*	Mean Cost Total[1]	Median Cost Total[1]	N*	Mean Cost InHospital	Median Cost InHospital	Mean/ Median Length of Stay
Extended cholecystectomy + standard LN-diss, no BD resection	1	209,096	209,096	3	140.463	128,334	7.3/8
Extended cholecystectomy + standard LN-diss, with BD resection				1	207,442	207,442	7/7
Reresection + standard LN-diss, no BD resection	7	191,056	194,530	8	161,843	150,706	7.4/8
Reresection + standard LN-diss, with BD resection + complications	1	863,578	863,578	1	835,533	835,533	36/36
Open cholecystectomy				10	111,247	95,852	14.9/7
Laparoscopic cholecystectomy				10	171,267	72,566	11.4

Footnotes: [1]Includes costs for pre- and postoperative visits in the region hospital, but not investigations or visits in the referral hospital.

[2]Refers to costs during the perioperative hospital stay.

* The number of patients that the cost estimation is based on.

As can be seen in the table the cost for the extended surgery is about two- or three-fold higher compared with simple cholecystectomy. Also, the cost for one simple cholecystectomy might be overestimated since cases with cholecystectomy treated at Sahlgrenska University Hospital might be more complicated than other cases who have surgery in other hospitals.

Available analyses of health economy or cost advantages or disadvantages

No health economy analyses has been identified.

13. Discussion

Summary of main results

Extended surgery with liver resection may result in longer overall survival in all stages of gallbladder cancer, except for stage T1a, compared with cholecystectomy alone. However, the data that support this conclusion are rather weak since the studied patient groups are confounded by selection bias.

We still do not have the evidence of what kind of liver resection achieves the best long-term survival, and whether or not we shall resect the extrahepatic bile duct in all cases with gallbladder cancer. On the other hand, we have been alerted of how important a thorough lymph node dissection may be, not only for staging, but also for survival, even though lymph node dissection has for long been a standard procedure in radical gallbladder surgery. The main ethical issue is whether extensive surgery is balanced by the risk for complications. Complications may be very severe and the result of improved survival is based on studies with high risk of bias.

The lack of knowledge in this field highlights the importance of a structured care to centralise expertise and to standardise the documentation to gain more knowledge in the future.

Overall completeness and applicability of evidence

The term radical resection comprises a combination of different surgical measures, i.e. liver resection, lymph node resection and sometimes resection of the extrahepatic bile ducts. To separate the effects of each of these measures on survival is difficult, since most studies were not designed for such comparisons, and detailed data is difficult to achieve retrospectively. All the published studies therefore lack essential data, especially for subgroups. They are often small and heterogeneous which further add to difficulties to interpret the results.

The specific question whether resection of liver parenchyma surrounding the gallbladder fossa will improve survival is poorly addressed. In our analysis, we defined “radical resection” as either wedge resection or resection of liver segments 4b and 5. However, some studies present their results for these procedures mixed with more extensive surgery. The combination of “radical resection” with lymph node intervention was often insufficiently described, as many of the studies separated the outcome data for liver interventions from those of lymph node interventions. Thus, they did not report lymph node status in relation to liver intervention or liver intervention in relation to different lymph node approaches.

Agreements and disagreements with other studies and reviews

Many issues of debate in gallbladder cancer surgery remain unanswered. Currently, most authors seem to support the recommendation to perform radical surgery for gallbladder cancer in all stages that are more advanced than T1a. In the most advanced stages, heterogeneity severely prevents the possibility to set up strict criteria for when to perform surgery or not, but it is interesting to note that there are a few long-term survivors even among patients with metastases.

The importance to perform a radical liver resection seems obvious, though the extent of liver resection for earlier stages has been insufficiently evaluated. An adequate lymph node resection seems important not only for staging, but also for survival. However, to what extent this should be done still remains unclear. The value of bile duct resection is also an unsolved matter of debate. Local practise differs in different regions and study results are inconsistent.

The effect of direct radical surgery versus staged operations in a controlled setting where histopathologic reports are rapidly analysed and the needed re-resections are scheduled within a very short time span has not been studied. The current practise is based on the general oncologic principle to aim at direct radical resection. The low survival rate of patients with residual cancer at the time of re-resection supports this principle, though the time passed from the first to the second operation might influence the rate of residual disease.

14. Future perspective

Scientific knowledge gaps

There is still a lack of knowledge with regard to the

- extent of liver resection needed in different stages
- extent of lymph node resection in different stages
- value of surgery in advanced stages
- value of bile duct resection
- effect of direct radical surgery vs staged operations in a controlled setting where histopathologic reports are rapidly analysed and the needed re-resections are scheduled within a very short time span
- what extent different surgical interventions affect the health-related quality of life

Gallbladder cancer is a rare form of cancer affecting older people and is often diagnosed in an advanced stage. This makes it difficult to perform randomised controlled trials. In Sweden we have a well-established national registry, SweLiv, for all patients with liver or bile duct tumours. The identified scientific knowledge gaps will be used to introduce relevant and standardised registry variables to increase our knowledge in this field.

The necessary extent of lymph node resection has not been evaluated in a standardised way. The data in this report indicate that lymph node resection has a positive impact on survival, but to what extent this is needed is still unclear. With new strict reporting criteria into the SweLiv registry of the surgical procedure as well as of the histopathology findings there is an opportunity to randomise patients to only resection of N1 nodes versus N2 nodes.

Another issue of interest is whether wedge resection or a formal segment 4b/5 resection is necessary in resection of gallbladder cancer of stage T2 or T3 (N0M0). In Sweden different centres have had different approaches in this respect. The SweLiv registry may be used to evaluate this issue.

There is a need to evaluate whether new modalities like neoadjuvant chemotherapy with the goal of downsizing the tumour tissue followed by surgery will improve the prognosis of patients with tumours in advanced stages that grow into hilar structures.

Ongoing research

The search in the Clinical Trials database (www.clinicaltrials.gov) identified 57 studies.
None of the studies was considered relevant for the questions at issue in this report.

Interest at the clinic/research group/organisation to start studies/trials within the research field at issue

See above (Scientific gaps).

15. Participants in the project

The question was nominated by
The National Consesus Group for Cholangiocellular Cancer

Participating health care professionals
Christian Cahlin, MD, PhD, Consultant, Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital
Linda Lundgren MD, Consultant, Department of Surgery, University hospital of Linkoping.
Per Sandström, MD, Associate professor, Consultant, Head of Upper Gastrointestinal Surgical Unit, Department of Surgery, University hospital of Linkoping.
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Therese Svanberg, librarian, HTA-centrum, VGR, Göteborg, Sweden.
Ulla Wikberg-Adania, librarian, Medical library, Sahlgrenska University Hospital, Göteborg, Sweden.

External reviewer
Olle Nelzén, MD, Associate professor, Department of Surgery, Skaraborg Hospital, Skövde, Sweden.

Declaration of interest
None

Project time
The HTA was accomplished during the period of autumn 2014 to April 2016. The latest literature search was made in April 30, 2015

Appendix 1, Search strategy, study selection and references

Question(s) at issue:

Does extended surgery compared with cholecystectomy alone in the adult patient with gallbladder cancer in early and late stages lead to improved survival?

PICO (P= Population, I= Intervention, C= Comparison, O=Outcome)

P = Population

Adults with a diagnosis of gallbladder cancer preoperatively by radiologic evaluation, or incidental finding in histology report from cholecystectomy because of gallstone disease.

I = Intervention

1. Liver resection; liver segments 4b and 5 or "radical" resection
2. Lymph node resection; standard or extended
3. Resection of the common bile duct
4. Extensive surgery of adjacent structures or/and organs.

The intervention was divided into separate questions regarding the evidence of benefit for different parts of these operations. In some studies the intervention was not described separately and the meaning of "extended surgery" could include both liver and lymph node resection together.

C = Comparison

- Cholecystectomy alone or wedge resection of gallbladder fossa
- No lymph node resection or standard resection
- No bile duct resection

O= Outcome

Overall survival
Disease-free survival
Health related quality of life
Complications/Risks

Subgroup evaluation has mostly been performed according to T-stage and sometimes full TNM-stage as follows

- T1a
- T1b
- T2
- T3
- Advanced stages including T4, N1 and M1

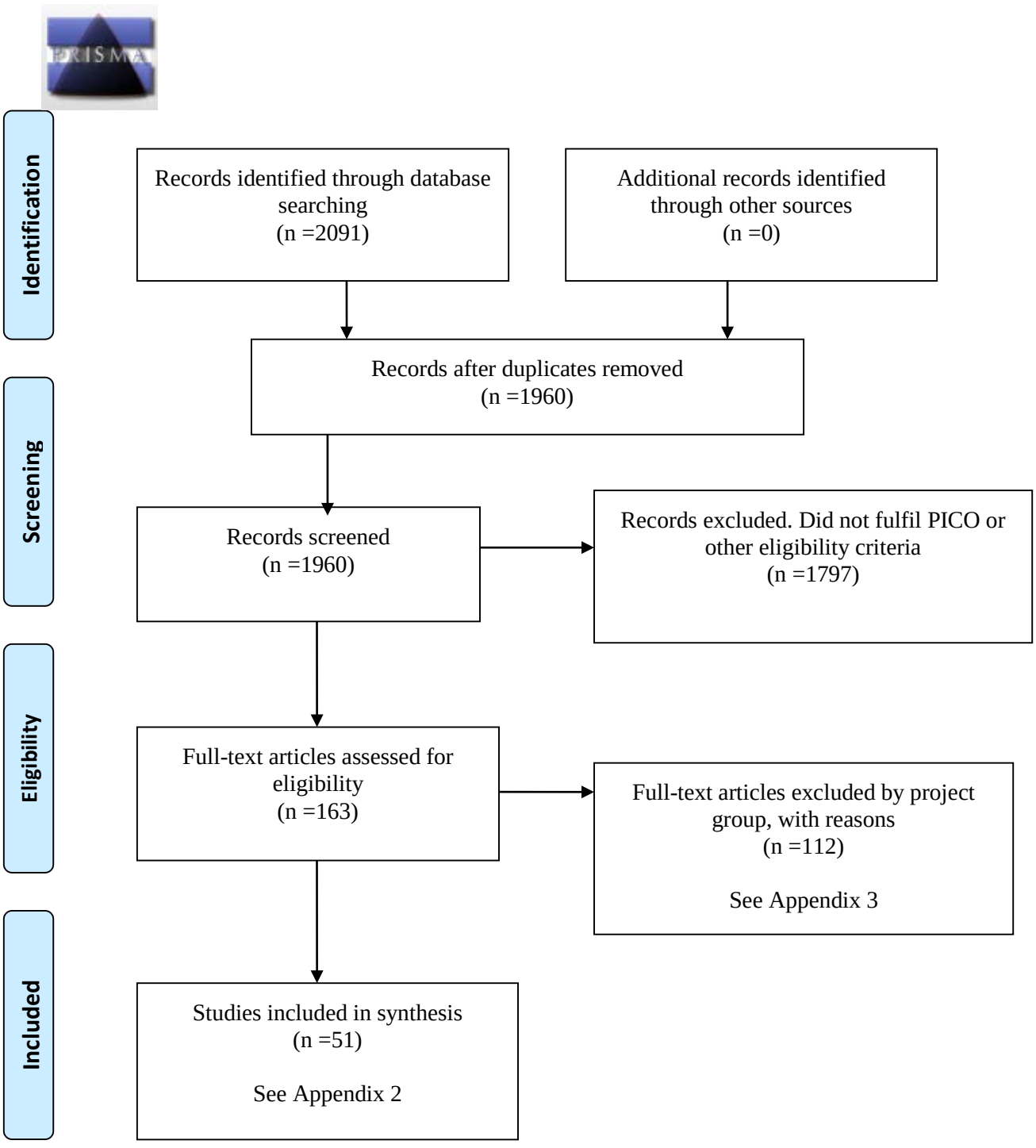
Eligibility criteria

Study design:
Randomised controlled studies
Non-randomised controlled studies
Case reports > 50 patients
Systematic reviews

Language:
English, German, French, Swedish, Norwegian, Danish, Greek

Publication date: 2000-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2014-05-23
No of results: 1519
Search updated: 2015-04-30, 199 results

Search	Most recent queries	Result
#24	**Search #11 NOT #15 Filters: Publication date from 2000/01/01; Danish; English; French; German; Greek, Modern; Norwegian; Swedish**	**1519**
#16	Search #11 NOT #15	3384
#17	Search #11 NOT #15 Filters: Publication date from 2000/01/01	1689
#15	Search #12 OR #13 OR #14	7375322
#14	Search ((child[mh] NOT (child[mh] AND adult[mh]))	950996
#13	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3889673
#12	Search editorial[ptyp] OR letter[ptyp] OR comment[ptyp] OR case reports[ptyp]	2820693
#11	Search #10 AND #5	4903
#10	Search #7 OR #8 OR#9	2258983
#9	Search cholecystectomy[Mesh Terms]	23969
#8	Search surgery[Mesh Subheading]	1613036
#7	Search resection[tiab] OR resection[tiab] OR surgery[tiab] OR surgical[tiab] OR cholecystectom*[tiab]	1329433
#5	Search #1 OR #4	10301
#4	Search (gallbladder[tiab]) AND (cancer[tiab] OR cancers[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR carcinoma*[tiab] OR neoplasms[tiab] OR neoplasm[tiab] OR adenocarcinoma*[tiab] OR cholangiocarcinoma*[tiab] OR malignan*[tiab])	7691
#1	Search gallbladder neoplasms[Mesh Terms]	7052

Database: Embase (Ovid SP)
Date: 2014-05-23
No of results: 276
Search updated: 2015-04-30, 56 results

No	Searches	Result
1	Exp gallbladder tumor/	9582
2	gallbladder.ti,ab.	28662
3	(cancer$1 or tumo?r$1 or carcinoma$1 or neoplasm$1 or adenocarcinoma$1 or cholangocarcinoma$1 or malignan$).ti,ab.	2622168
4	2 and 3	9307
5	1 or 4	12843

6	(resection$1 or surgery or surgical or cholecystectom$).ti,ab.	1597627
7	exp cholecystectomy/	34593
8	su.fs.	1680102
9	6 or 7 or 8	2558907
10	5 and 9	6524
11	(animal not (animal and human)).sh.	1179709
12	10 not 11	6512
13	(child not (child and adult)).sh.	810070
14	12 not 13	6469
15	limit 14 to (embase and (danish or english or french or german or greek or norwegian or swedish) and yr="2000 -Current" and (article or conference paper or "review"))	2345
16	Limit 15 to exclude medline journals	**276**

Database: The Cochrane Library
Date: 2014-05-23
No of results: 40
Cochrane reviews 3
Trials 35
Search updated: 2015-04-30, 1 result

No	Searches	Result
#1	MeSH descriptor: [Gallbladder Neoplasms] explode all trees	28
#2	gallbladder:ti,ab,kw (Word variations have been searched) cancer? or tum*r? or carcionoma? or adenocarcinoma? or cholangiocarcinoma? Or malignan*.ti,ab.kw (Word variations have been searched)	1088
#3	cholangiocarcinoma? or malignan*.ti,ab,kw (Word variations have been searched)	52382
#4	#2 and #3	93
#5	#1 or #4	93
#6	resection? or surgery or surgical or cholecystectom*.ti,ab,kw (Word variations have been searched)	89528
#7	#5 and #6	**40**

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Appendix 2 Included studies – design and patient characteristics

Author, year, country	Study design	Study duration	Study groups; Intervention vs control	Patients (n)	Mean age (years)	Gender distribution (% female)	Outcome variables
Araida T, 2009a, Japan	cohort	1994-2003	I: Bile duct resection N-/N+ C: No bile duct resection N-/N+	838 N- 593 N+ 245	N- 67 N+ 69	64	5yOS Complications
Araida T, 2009b, Japan	cohort	1994-2003	I : S4b/5 resection Hinf-/Hinf+ C: Wedge resection Hinf-/Hinf+	485	67	66	5yOS
Araida T, 2004, Japan	cohort	Missing (1979-1998?)	I : hepatopancreatoduodenectomy C: non-hepatopancreatoduodenectomy	216	Not reported	Not reported	5yOS
Balachadran 2006, Indien	cohort	1989-2000	I : Radical resection C: Cholecystectomy	117	53	68	Median overall survival 5yOS
Ballo, 2015, USA	cohort	2003-2012	I: single operation C: staged operation	20	64,8	70	1yOS Median survival
Birnbaum 2014, Italy	case series	1990-2011	Radicality as prognostic factor	78	67	56	3yOS 5yOS
Birnbaum 2015, Italy	cohort	1990-2011	I : D2-dissektion C: D1-dissektion	112	64	67	5yOS
Choi BG 2013, Korea	case series	2004-2011	I:>8 lymph nodes harvested C:<8 lymph nodes harvested Lymph node ratio as prognostic factor	123	Not reported	51	5yDFS

BD res = bile duct resection
D1 = Dissection of lymph nodes around the hepatic ligament
D2 = Extended dissection of lymph nodes beyond the hepatic ligament
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EHBD = Extra-hepatic bile ducts
GBC = Gallbladder cancer
Hinf+/- = Presence (+) of absence (-) of hepatic tumor invasion
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Choi SB 2010 Korea	cohort	1995-2007	I: radical surgery C: cholecystectomy I : lymph node dissection C: no lymph node dissection	83 T2	66	53	Median overall survival 3yOS 5yOS
Choi SB, 2013, Korea	cohort	2000-2010	I : EHBD resection C: no EHBD resection	71 (T2/T3)		55	3yOS 5yOS Complication
Coburn, 2008, USA	cohort	1988-2003	I: Cholecystectomy C: Radical resection I: LNdiss+ C: no LNdiss-	2835	71	72	5yOS
D'Angelica, 2009, USA	cohort	1998-2002	I: BP res+ C: no BD res-	104	65	71	Median overall survival 5yDSS
de Aretxabala, 2006, Chile	cohort	1988-2004	I: Radical resection C: Cholecystectomy	139 (T2)	58	56	5yOS
De Aretxabala, 2009, Chile	Case series	1988-2004		94	56,5	74	5yOS
Downing,SR, 2011, USA	cohort	1988-2005	I: Radical resection C: Cholecystectomy I: LNdiss+ C:LNdiss-	2945 T1b=462 T2=1533		75	HR
Endo, 2001, Japan	cohort	1985-2000	I: resection (ligament involvement high grade/low grade) C: no resection	78	65	74	5yOS

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Fong, 2000, USA	cohort	1986-2000	I: staged C: direct radical I: radical resection C: cholecystectomy	102 op of 410	65	67	5yOS Complications
Fuks, 2011, France	cohort	1988-2008	I: radical resection (re) C: cholecystectomy	218	64	69	1-, 3- and 5yOS
Goetze, 2008a, Germany	cohort	1997-	I: radical C: cholecystectomy	103 of 502 GBC	Not reported	75	5yOS
Goetze, 2008b, Germany	cohort	1997-	I: radical resection C: cholecystectomy	439			Median OS 5yOS
Goetze, 2010, Germany	cohort	1997-	I: early reresection C: cholecystectomy	624	74	76	5yOS
Goetze, 2012, Germany	cohort	1997-	I: reresection LN+/LN- C: cholecystectomy LN+	709	74	77	5yOS
Ha, 2015, South Korea	cohort	1996-2009	I: radical resection C: cholecystectomy I: direct radical resection C: staged I: BD res+ C: BD res-	203	62	55	5yOS
Hari, 2013, USA	cohort	1988-2008	I: cholecystectomy + LNdiss C: cholecystectomy I: radical resection C: cholecystectomy	1115			5yOS HROS HRDSS

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He, 2015, China	cohort	2003-2013	I: palliative resection C: radical resection	152	68	60	5yOS Complications
Higuchi, 2014, Japan	case series	1969-2012 (1969-1989) (1990-1999) (200-2012)		274	64	58	2y, 3y, 5yOS 5yDFS Complications
Horiguchi, 2013 Japan	cohort	1998-2004	I: BD res+ C: BD res- I: wedge C: S4b/5	109 T2N0 (24 missing data)	69	53	5yOS 5DFS Complications
Ishikawa, 2003, Japan	cohort	1986-2002	I:resection C: palliative cyt I: resection C: best supportive care	59	68.5	44	OS
Jensen, 2009a, USA	cohort	1988-2004	I: radical LN-/LN+ C: cholecystectomy LN-/LN+	4631	71	72	5yOS
Jensen, 2009b, USA	cohort	1988-2004	I: LNdiss+ C: LNdiss-	4614	71	72	Median OS
Kai, 2007, Japan	cohort	1990-2004	I: radical resection (wedge/S4b/5) C: cholecystectomy I: BDres+ C:BDres- I: standard LN dissection (D1) C: extended LN dissection (D2)	90	65	54	MedianOS OR

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Kang, 2012, South Korea	cohort	1996-2010	I: curative surgery C: palliative surgery	94	62	57	Median OS
Kayahara, 2008, Japan	cohort	1988-1997	I: extended (right-lobe, pancreas) C: cholecystectomy I: radical (wedge/S4b) C: cholecystectomy	4424	Not reported	64	5yOS
Kim, 2013, Korea	cohort	2000-2009	I: cholecystektomi + LN dissection N-/N+ C: cholecystectomy N-/N+	70 (T2)	63	63	5YOS
Lee H, 2014, Korea	cohort	2000-2011	I: radical resection (peritoneal/hepatic side) C: cholecystectomy (peritoneal/hepatic side)	157 (T2)	62	61	5yOS Complications
Lee SE, 2014, Korea	cohort	1995-2004	I: radical resection C: cholecystectomy	258	62.9	57	5DFS
Lim, 2013, South Korea	cohort	1999-2009	I: radical resection C: cholecystectomy	279	63	54	Median OS
Liu, 2013, China	cohort	1995-2010	I: extended LN dissection ≥4/≥6 C: standard LN dissection <4 /<6	78	59	59	Median DSS
Mayo, 2010, USA	cohort	1991-2005	I: radical resection C: cholecystectomy	2955	76.8	72	1-, 3-, 5 yOS Median OS Complication
Meng, 2011, China	cohort	1997-2004	I: radical resection C: chemotherapy I: radical resection C: other palliative treatment	55	64.1	64	Median survival

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Appendix 2 Included studies – design and patient characteristics

Author, year, country	Study design	Study duration	Study groups; Intervention vs control	Patients (n)	Mean age (years)	Gender distribution (% female)	Outcome variables
Niu, 2015, China	case series	Sept 2000-June 2011	Extended versus standard lymph node dissection	60			Complications
Ouchi, 2002, Japan	cohort	Before March 2000	I: radical resection C: cholecystectomy	498	63.6	63	5yOS
Qu, 2012, China	cohort		I: radical resection (hepatic/no hepatic invasion) C: palliative resection	139	62.8	67	1yOS
Shindoh, 2015, USA	cohort	1981-2011	I: radical resection (peritoneal side/hepatic side) C: cholecystectomy	437	63	69	5yOS
Wakai, 2012, Japan	cohort	1985-2000	I: Segm 4b/5 C: wedge	70	71	61	5yOS 3yOS Median OS
Wang, 2012, China	cohort	2002-2007	I: radical resection/palliative resection C: cholecystectomy	132	59	66	Mean survival time
Xiao, 2005, China	cohort	1993-2004	I: surgery with curative intent C: palliative op/laparotomy	70	58	66	1-, 3-, 5yOS
Yang, 2012, China	case series	2003-2011	Radical surgery Preoperative jaundice	76	59	66	5yrsOS Median survival Complications
Yildirim, 2005, Turkey	cohort	1990-2003	I: radical resection C: cholecystectomy	65	59	78	1-, 3-, 5yOS Complications

BD res = bile duct resection
D1 = Dissection of lymph nodes around the hepatic ligament
D2 = Extended dissection of lymph nodes beyond the hepatic ligament
DSS = disease specific survival
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Appendix 2 Included studies – design and patient characteristics

Author, year, country	Study design	Study duration	Study groups; Intervention vs control	Patients (n)	Mean age (years)	Gender distribution (% female)	Outcome variables
Yokomizo, 2007 Japan	cohort	1986-2005	I: Radical resection C: Cholecystectomy I: BD res+ C: BD res-	94 (T2)	68.6	59	5yOS 10yOS
Yoon, 2014, South Korea	cohort	1997-2010	I: radical resection C: cholecystectomy	54 (T1b)	5.1	69	5yOS

BD res = bile duct resection
D1 = Dissection of lymph nodes around the hepatic ligament
D2 = Extended dissection of lymph nodes beyond the hepatic ligament
DSS = disease specific survival
DFS = disease free survival
EHBD = Extra-hepatic bile ducts
GBC = Gallbladder cancer
Hinf+/- = Presence (+) of absence (-) of hepatic tumor invasion
HROS = Hazard Ratio for Overall Survival
HRDSS = Hazard Ratio for Disease-specific Survival
LN = lymph node
N+/- = Lymph node metastases present/ absent
OS= overall survival

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Agarwal AK, 2013	Wrong intervention
Agarwal AK, 2014	No survival data
Agarwal AK, 2015	Not correct PICO (comparison of laparoscopic or open procedure). No survival data.
Amini N, 2015	Not correct PICO (performance of different lymph node staging/scoring systems)
Alexander S, 2012	No subgroup analysis, no survival data
Ausania F, 2013	Not correct PICO (stageing before reresection)
Barbhuiya M, 2014	Wrong intervention
Barreto, 2014,	Wrong intervention (lymph node ratio)
Batra Y, 2005	Survival data not presented according to intervention
Birnbaum DJ, 2015	Wrong outcome (lymph node ratio)
Butte JM, 2011	Not correct PICO (stageing laparoscopi)
Butte JM 2011	Survival data not presented in relation to subgroup
Butte JM, 2014	No intervention
Cariati A, 2014	Not correct PICO (type of surgery not presented)
Cavallaro A, 2014	Wrong intervention
Cha BH, 2014	Survival data not presented according to intervention
Chakravarty KD, 2009	Survival data not presented according to intervention
Chan KM, 2005	Survival data not presented according to intervention
Chan SY, 2008	< 25 patients
Chijiiwa K, 2000	Survival data not presented according to intervention
Chijiiwa K, 2001	< 25 patients
Cho SY, 2012	Survival data not presented according to intervention
Choi SB, 2012	Survival data not presented according to intervention
Choi KS, 2015	Systematic review and meta-analysis No survival data
Cui HX, 2014	< 25 patients
Deng YL, 2015	Not correct PICO (no intervention)
D'Hondt M, 2013	Survival data not presented according to intervention
Dixon E, 2005	Not correct subgroup presentation, to few cases

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Ebata T, 2012	No survival data
Einama T, 2014	Case report and review of literature
Feng, 2012	Wrong intervention (jaundice)
Foster JM, 2007	< 25 patients with radical resection
Garg PK, 2015	Review
Glauser PM, 2010	< 25 patients
Glazer ES, 2012	No subgrop analysis
Goetze TO, 2013	Wrong intervention
Goetze TO, 2014	Not PICO (comparing high- and low-volume surgery)
Groot Koerkamp B, 2014	Survival data not presented according to intervention
Harada K, 2011	< 25 patients
He XD, 2010	Wrong outcome
Igami T, 2015	Old material
Itano O, 2015	Wrong intervention
Ito, 2011	Wrong intervention (total lymph node count)
Jarnagin WR, 2003	Wrong outcome (recurrence after gallbladder carcinoma)
Jin LX, 2013	No survival data
Kai K, 2014	Review
Kallianpur AA, 2014	No survival data
Kaneoka Y, 2003	No survival data
Kim WS, 2010	No survival data
Kiran RP, 2007	Old material
Kobayashi A, 2012	Wrong outcome
Kohya N, 2008	< 25 patients
Kondo S, 2000	Old material
Kwon YJ, 2014	Not correct PICO (perineural invasion as an prognostic factor)
Kondo S, 2002	Old material
Lee HY, 2012	Wrong intervention
Lee SE, 2014	Only guidelines for Korea, no new data
Liang JW, 2008	Old material
Mazer LM, 2012,	Wrong intervention
Müller BG, 2014	Not correct PICO (review of oncological treatment)
Murakami Y, 2011	Wrong outcome
Murakami Y, 2011	> 25 patients
Nadeem H, 2014	Not correct PICO (health economic model)

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Negi SS, 2011	< 25 patients
Nishio H, 2011	Old material
Nishio H, 2007	Old material
Noji T, 2015	Wrong intervention
Oh TG, 2013	No intervention
Okumura T, 2014	Case report
Onoyama H, 2002	Old material
Otero JC, 2006	Old material
Pais-Costa, 2012	Wrong intervention (different prognostic factors)
Park JS, 2007	No survival data
Pawlik TM, 2007	Old material
Piccolo G, 2014	Review
Pottakkat B, 2013	Not correct PICO (stageing)
Principe A, 2006	< 25 patients
Puhalla H, 2002	< 25 patients
Qu K, 2012	No subgroup analysis
Rakic M, 2014	Review
Randle RW, 2014	Wrong intervention
Sakata J, 2010	Old material
Sasaki R, 2006,	Old material
Schauer RJ, 2001	Old material
Shen, 2012	Wrong intervention (different time periods)
Shiba H, 2015	Not correct PICO (evaluation of prognostic score)
Shibata K, 2009	Old material
Shih SP, 2007	< 25 patients
Shimada H, 2000	< 25 patients
Shimada K, 2011	< 25 patients
Shimizu H, 2007	< 25 patients
Shirai Y, 2012	Wrong outcome
Shirai Y, 2012	Wrong outcome
Shirai Y, 2012	< 25 patients
Shirobe T, 2014	< 25 patients
Shukla PJ, 2008	No survival data
Taner CB, 2004	Old material
Toyonaga T, 2003	Old material

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Tsirlis T, 2015	Wrong intervention. No survival data.
Varma Z, 2009	< 25 patients
Wakai T, 2003	Old material
Wang, 2009	Intervention no well described in relation to stage
Wright BE, 2007	Data not possible to interpret
Yagi H, 2006	< 25 patients
Yang 2014	Wrong intervention (jaundice)
Yoshitomi H, 2015	Guidelines
You DD, 2008	Wrong outcome
Yu T, 2014	No intervention
Yun SP, 2015	No intervention
Zaydfudim V, 2008	Wrong outcome
Zhang WJ, 2015	< 25 patients
Zhu JQ, 2015	No intervention

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Liver intervention									
Liver resection vs Cholecystectomy									
Balachan-dran 2006 India	Cohort study	117 **Radical** T2 4 T3 29 (R0/R1 12/17) **Cholecyst** T2 19 T3 39	42 of which 5 in-hospital deaths	**Radical** T2 5yOS 75% T3 Median OS 18m 5yOS 23% (R0 33%, R1 12%)	**Cholecystectomy** T2 5yOS 61%, p=0.42 T3 Median OS 10m 5yOS 10% (p=0.01)	Large part R1-procedures 87/117. Heterogenous study.	-	-	-
Choi SB 2010 Korea	Cohort study	83 T2 30 vs 53 Only 32 R0, 18 R1 33 Rx	Mortality 1.1%	**Radical** T2 3yOS 63.8% 5yOS 37.6% Median OS 46.2m	**Cholecystectomy** T2 3yOS 39.8% 5yOS 24.1% Median OS 23.9m p=0.028	HR adjusted for other factors: R0, LN-dissection, op-method, infiltration, differentiation, LN invasion, perineural invasion, vascular invasion, R0, LN metastases	+?	?-	-
Choi SB 2013 Korea	Cohort study	71 (49 T2/22 T3) R1 (24) **Wedge** T2 29 vs 16 T3 10 vs 4 **S4/5+** T2 4 , T3 8		**Wedge** T2, T3 3yOS 73.5% 5yOS 45.9% **S4/5 or larger** T2 T3 3yOS 57.0% 5yOS 28.5%	**Cholecystectomy** T2 T3 3yOS 65.1% 5yOS 51.3% p=0.73 (all three comparisons)	More advanced cancer	+	-/?	?

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Coburn 2008 USA	Cohort study	2835	?	**Radical** (≥1 extra organ) Median OS T1 86m T2 25m T3 11m	**Cholecystectomy** Median OS T1 34m, p=0.02 T2 19m, p= 0.03 T3 10m NS	Also in presented in Appendix 4.1.2 (LN-table)	+/?	?	?
de Aret-xabala 2006 Chile	Retro-spective non-random ised controll ed	139 55 vs 64 Intention to do radical resection 74	Mortality 0%	**Radical** **T2** (subserosal) 5yOS 70% 7% with residual liver tumor	**Cholecystectomy** **T2** (subserosal) 5yOS 45%, p=0.07	LN+ 18,8% Neg prognostic factors: LN+ and residual tumor	+?	?	?
Downing 2011 USA	Retro-spective non-random ised controll ed	2495 T1b 462 T2 1533		**Radical** **T1b** HR 1.51 (0.78-2.90) **T2** HR 0.64 (0.46-0.90) (p= 0.01)	**Cholecystectomy** **T1b** p=0.22 **T2**		-?	?	?
Fong 2000 USA	Cohort singel-center	102 op of 410 T1 2 vs 0 T2 56 vs 8 T3 96 vs 41 T4 94 vs 114	?	**Radical** (102) 5yOS T2: 61% reresection T3: 21% T4: 28%	**Cholecystectomy** 5yOS T2: 19%, p<0.05 T3: 1/8 alive after 10m T4: All 4 dead after 11m	N-stage RR 2,8 T-stage RR 1,7 Size of resection and earlier resection did not influence the result	?	-	-

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Fuks 2011 France	Cohort register study	218 incidental All: 148 vs 70 **T2** 67 vs 17 **T3** 60 vs 21	No	**Radical (reresection)** 1-, 3-, 5-yOS 76, 54, 41% **T2** 98, 80, 62% **T3** 56, 25, 19%	**Cholecystectomy** 1-, 3-, 5-yOS 52, 20, 15% p<0.0001 **T2** 62, 9, 0%, p<0.0001 **T3** 29, 9, 0%, p=0.04	Not comparable groups Cholecyst-group did not have radical surgery because of age and/or advanced disease/cancer.	+/?	?	+
Goetze 2008a Germany	Retro-spective non-random ised controll ed	103 (of 502 iGBC) All T1 28 vs 75 T1a 5 vs 16 T1b 23 vs 49 4/5 vs wed 11 vs 12		**Radical** (wedge/S4/5) 5yOS **T1** 72% **T1a** 38% **T1b** 79% **4b/5 + extended**	**Cholecystectomy** 5yOS **T1** 40%, p=0.06 **T1a** 55% p=0.1 **T1b** 42%, p=0.03 **wedge** , p>0.05		+	-	?
Goetze 2008b Germany	Cohort study	439 radical of total T2 85/200 T3 35/85		**Radical** T2 5yOS 55% T3 5yOS 18% for all T3 irrespective of operation LN +/- 0/30%	**Cholecystectomy** T2 5yOS 35% p=0.0368 T3 p=0.6877		+	-	?

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Goetze 2010 Germany	Cohort study	624 (231 early) **Early reres** 231 vs **Cholecyst** 393 T1 33 vs 85 T2 139 vs 161 T3 46 vs 96	?	**Early reresection** (wedge, S4/5 or other within 45d) Mean 3219d Median 1245d <u>5yOS</u> 41% T1 71% T2 41% T3 17%	**Cholecystectomy** Mean 1322d Median 567d <u>5yOS</u> 25%, p=0.0075 T1 40%, p=0.04 T2 25%, p=0.0061 T3 8%, p=0.0075	Same as above	+/?	?/-	?
Goetze 2012 Germany	Cohort study	709 **N+** T1 3 vs 4 T2 47 vs 25 T3 20 vs 24 **N-*** T1 25 vs ? T2 94 vs ? T3 23 vs ?	No	**Radical** <u>5yOS</u> All TN+ 8% (p=0.05) T1 0% T2 9% T3 - N-*52% T1 75% T2 52% T3 30%	**Cholecystectomy** <u>5yOS</u> All TN+ 0% T1 - T2 0%, NS T3 - N-* T1 T2 T3	Partly same patients as in Goetze 2010 *"N-" was not used if less than 3 negative LNs had been dissected.	+/?	?/-	?

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Ha 2015 South Korea	Retro-spective non-random ised controll ed	203 R0 T1b 75/6 vs 15 N- 64/6 vs 6 N+ 11/0 vs 0 T2 75/22 vs 10 N- 55/18 vs 3 N+ 20/4 vs 1?		**Direct Radical / Staged** <u>5yOS</u> 76.0% / 66.7% **T1b** 84.4% / 83.3% **N-** 92.6% / 83.3% **N+** 34.3% **T2** 67.6% / 61.9% **N-** 74.4% / 73.3% **N+** 53.0% / 33.3% p=0.59*	**Cholecystectomy** <u>5yOS</u> 64.0%, p=0.61 **T1b** 68.8%, p=0.65 **N-** 100%, p=0.43 **N+** **T2** 50%, p=0.90 **N-** 100%, p=0.93 **N+ -**(only one)	*p-value refers to comparison "direct vs staged"	+	-	-
Hari 2013 USA	Retro-spective non-random ised controll ed	1115 55 vs 892 T1a 10 vs 236 T1b 30 vs 427 T1NOS n=279		**Radical** All T1 5yOS HR 0.742 (95%CI 0.490-1.122) <u>5yOS</u> T1a ca 65% T1b ca 47% All T1 5yDSS HR 0.410 (95% CI 0.22-0.77) <u>5yDSS</u> T1a ca 85% T1b ca 90% **Cholecys+LN/Radical** 5yOS 53%/48%	**Cholecystectomy** p=0.16 <u>5yOS</u> T1a ca 55%, p=0.93 T1b ca 40%, p=0.017 p=0.006 <u>5yDSS</u> T1a ca 70%, p=0.61 T1b ca 52%, p=0.0002 **Cholecystectomy** 5yOS 35%, p<0.001	Predictive factors DSS (Cox): age, T-stage, tumour group, radiation, type of surgery	+	?/+	+

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Jensen 2009a USA	Cohort SEER*-register	4631 443 Radical		**Radical** 5yOS T1b/T2 42% HR 0.681 (95% CI 0.485-0.956) N- 79% HR 0.432 (95% CI 0.189-0.986) N+ 40% HR 0.439 (95% CI 0.186-1.036)	**Cholecystectomy** 5yOS T1b/T2 30% p=0.027 N- 48% p=0.046 N+ 18% p=0.0060		-	-	?
Kai 2007 Japan	Cohort study	90 T2 34 (Wedge 21, S4/5 4 vs 9 cholecystectomy)		**Radical** 5yOS T2 wedge 60% 5yOS T2 S4/5 100%	**Cholecystectomy** 5yOS T2 25%, p=0.048	5yOS estimated from Kaplan-Meyer graph. P-value refers to log-rank test.	+	?/-	?
Kayahara 2008 Japan	Cohort study	4424		5yOS **Extended** Stage III 39% All stages vs cholecystect HR 0.789 (95% CI 0.686-0.909) **Radical** (wed/S45) Stage II 75% Stage III 51% All stages vs cholecystect HR 0.726 (95% CI 0.638-0.827)	5yOS **Cholecystect** Stage II 62% Stage III 38% p<0.01 vs chol p<0.01 vs chol	Extended resection includes right lobe, pancreas Radical includes wedge or seg 4/5 resection.	?	?/+	+

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Kim 2013 South Korea	Retro-spective non-random ised controll ed	70 33 vs 37		**Radical** **pT2 N-** 5yOS 69% **pT2 N+** 5yOS 78%	**Cholecystectomy only** **pT2 N-** 5yOS 75%, p=0.52 **pT2 N+** 5yOS 0%, p=0.001 vs C only **Cholecystectomy +LN dissection** **pT2 N-** 5yOS 84% **pT2 N+** 5yOS 68%, p=0.46 vs C + LN dissection	No postop mortality	?	?	-
Lee 2014 South Korea	Cohort register data	T1a 22 vs 95 T1b 52 vs 89		**Radical** 5yDFS **T1a** 97% **T1b** 87%	**Cholecystectomy** 5yDFS **T1a** 95%, p=0.18 **T1b** 92%, p=0.33	No postop mortality High N+ rate in T1b motivates reresection	?-	?/-	?

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Lim, 2013, South Korea	Cohort	279 All 169 vs 110 T1 18 vs 17 T2 54 vs 16 T3 78 vs 23 T4 19 vs 55		**Radical** <u>5yOS</u> T1 100% (NS) T2 62.9% (NS) T3 44.8% (p<0.001) T4 17.8% (p=0.007)	**Cholecystectomy** <u>5yOS</u> T1 87.5% T2 52.4% T3 0% T4 0%	129 R0/ 169 radical, 35 R0/ 110 cholecystectomy	+	?/-	+/?
Mayo 2010 USA	Cohort study	2955 (1899 T2+T3) Radical op T2 104 vs 677 T3 203 vs 915		**Radical op** T2 1yOS 85% 3yOS 55% 5yOS 40% Median OS 53.0m T3 1yOS 50% 3yOS 25% 5yOS 15% Median OS 11m	**Cholecystectomy** T2 1yOS 55% 3yOS 30% 5yOS 20% Median OS 16.0m p<0.001 T3 1yOS 35% 3yOS 15% 5yOS 10% Median OS 8m p<0.001	Mortality 30d 4.2%	+	?	?/+
Ouchi 2002 Japan	Cohort multi-center	498 238 vs 260	40% did not respond, but 470/498 with data	**Radical (reresection)** Significant advantage <u>5yOS</u> T2 T3 approx. 25%	**Cholecystectomy (laparoscopy)** <u>5yOS</u> T2, p=0.051 T3 0%, p<0.05	Bile spillage risk factor Mortality after reop 1.3% 5yOS all T2 70%, but not specified according to operation, although survival was non-significantly higher, for the reresected group.	?	?/- ?	?

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Yildirim 2005 Turkey	Cohort igbc at op	65 28 vs 37 T2 15 vs 19 T3 10 vs 8	0 30-d mortality	**Radical** (wedge) 1, 3, 5yOS T1a 100, 100, 100% T1b 100, 100, 100% T2 100, 100, 47% T3 88, 47, 16%	**Cholecystectomy** 1, 3, 5yOS T1a 100, 100, 100%, NS T1b 100, 100, 50%, NS T2 95, 44, 0% , p=0.01 T3 70, 10, 0%	Igbc means incidental gallbladder cancer, ie undiagnosed before operation	+	?	+
Yokomizo 2007 Japan	Cohort study	94 T2 51 vs 43 N+ 15 vs 9		**Hepatectomy T2** 5yOS 73.3% 10yOS 61.9% N- 5yOS 87.1% N+ 5yOS 46.2% 10yOS 34.6% (p=0.47)	**Cholecystectomy T2** 5yOS 87.2% 10yOS 68.6%, p=0.53 N+ 5yOS 77.8% 10yOS 51.9%	Figure 3 do not indicate the same results as the text. "Hepatectomy" included 39 wedge, 10 S4/5, 2 other Groups not comparable at baseline (Cholecyst-group older)	+	?	-
Yoon 2014 South Korea	Retro-spective cohort study	54 T1b with 2:1 matched propensity score (original cohort 85 T1b)		**Radical** (wedge or S4/5+LN) T1b 5yOS 93.3%	**Cholecystectomy** T1b 5yOS 88.8%, p=0.52	Cholecyst shorter op-time and hospital stay 11.1% (4) tumor recurrences after cholecystectomy vs 0% after radical.	+	?	?-

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Tumor localisation									
Lee 2014 South Korea	Cohort study	157 T2 122 vs 35 hepatic 98 vs 26 peritoneal 24 vs 9		**<u>Radical</u>** **Tumor localisation** **Liver side** 5yOS 67.5% **Peritoneal side** 5yOS 96%	**<u>Cholecystectomy</u>** **Tumor localisation** **Liver side** 5yOS 44.5%, p=0.007 **Peritoneal side** 5yOS 100%, p=0.574	Very few reached 5yrs in cholecyst-group peritoneal side. Uncertainty about reported data; 13 censored although only p in the group.	+	?/-	?
Shindoh, 2015, USA	Multicenter Cohort	437 hepatic 69 vs 30 peritoneal 80 vs 73		**Radical resection** **T2 Liver side** 5yOS 48.2% **T2 Peritoneal side** 5yOS 75.5%	**Cholecystectomy** **T2 Liver side** 5yOS 28.9%, p=0.19 **T2 Peritoneal side** 5yOS 49.8%, p=0.006		?	-	?-

Radical=any operation including gallbladder fossa and adjacent liver tissue, but less than one liver lobe, mostly in combination with some extent of lymph node dissection.
NR= not reported **NS**= non-significant
OS= overall survival **DFS**= Disease-free survival
DSS= Disease-specific survival
R0= macroscopically radical resection and margins microscopically free of tumour
R1= macroscopically radical resection, but with microscopic tumour growth in the resection surface
HR= hazard ratio **CI**= confidence interval
LN= lymph node
Binf +/- = Bile Duct infiltration present/absent
Igbc= incidental gallbladder cancer, i.e. undiagnosed before operation
SEER=National Cancer Institute's Surveillance, Epidemiology, and End Results database (USA)
pT2=T2-stage according to histopathology report

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Segment 4(b)/5-resection vs wedge-resection (T1) T2+T3									
Araida 2009b Japan	Cohort study	485 Binf-**S4/5 vs wedge** T2 30 vs 103 T3 15 vs 45 **Hepatectomy** 10		**S4b/5 resection** 5yOS 72% T2 86% T3 38% **Hepatectomy** T3 46% Hep vs S4/5, p=0.45	**Wedge resection** 5yOS 74% (p=0.77) T2 78% (p=0.98) T3 51% Hep vs wedge, p=0.98 S4/5 vs wedge, p=0.36		+	?	?
Horiguchi 2013 Japan	Retro-spective non-randomised controlled	109 T2N0 30 vs 55	24 wedge	**S4b/5 resection pT2 N0** 5yOS 65.9% 5yDFS 63.3%	**Wedge resection pT2 pN0** 5yOS 76.2%, p=0.53 5yDFS 74.4%, p=0.24	Prognostic factor: perineural invasion	?	?	?
Wakai 2012 Japan	Cohort	70 12 vs 58 T2 6 vs 45 T3 6 vs 13	No	**S4b/5 resection** 5yOS NR (p=0.52) 3yOS 60% T2 83% T3-4 0% Median OS 26m	**Wedge resection** 5yOS approx 70% 3yOS 74% T2 86%, p=0.78 T3-4 31%, p=0.52 Median OS 10m	5yOS estimated from survival-graphs. 5yOS not reached in the S4b/5 group due to short follow-up, though 4yOS was around 60%. P-value refers to log-rank test.	+	?	-

Project: Surgery for gallbladder cancer. Appendix 4.1.1
Intervention: Liver resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Goetze 2010 Germany	Cohort study	624 (231 early) T2 S4/5 vs wedge 31 vs 67 T2 S4/5 or wedge vs other less radical 98 vs 23	?	**S4/5 resection** T2 5yOS 54% ()	**Wedge resection** T2 5yOS 46%, p>0.05	Subgroup analysis of method, too small groups Same study as in the table "Radical vs cholecystectomy" below.	+/?	?/-	?

Project: Surgery for gallbladder cancer. Appendix 4.1.2
Intervention: Lymph node intervention. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Lymph node intervention									
Choi 2010 Korea	Cohort study	83 T2 LNdiss+ 31 LNdiss- 52	Mortality 1.1%	**LNdiss+** 3yOS 63.5% 5yOS 51.3% Median OS 63m	**LNdiss-** 3yOS 39.2% 5yOS 17.2% Median OS 23.5m p=0.024		+?	?-	-
Coburn 2008 USA	Cohort study	2835 LNdiss+ 149 LNdiss- 2686	?	**LNdiss+** <u>5yOS</u> T1 ~ 45% (p=0.55) T2 ~ 45% (p<0.01) T3 ~ 25% (p<0.01) HR 0.70 (95%CI 0.48-1.00)	**LNdiss-** <u>5yOS</u> T1 ~ 30% T2 ~ 20% T3 ~10%	Both liver and LN groups	+/?	?	?
Downing 2011 USA	Retro-spective non-randomised controlled	2495 T1b 462 T2 1533		**LNdiss+** <u>(1-4nodes)</u> **T1b** HR 0.82 (0.56-1.18) **T2** HR 0.42 (0.33-0.53) **LNdiss+** <u>≥5 nodes</u> **T1b** HR 0.42 (0.10-1.85) **T2** HR 0.26 (0.16-0.42)	**LNdiss-** **T1b** p=0.29 **T2** p<0.001 p=0.25 p<0.001	For HR, values below 1 favours survival.	-/?	?	+

Project: Surgery for gallbladder cancer. Appendix 4.1.2
Intervention: Lymph node intervention. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Hari 2013 USA	Retro-spective non-random ised controll ed	1115 T1a 300 T1b 536 T1x 279 Cholecyst+ LNdiss 168 T1a 54 T1b79 Cholecyst 892 T1a 236 T1b 427		**Cholecystectomy+LN diss** All T1 5yOS HR 0.638 (95% CI 0.488-0.834) <u>5yOS</u> T1a ~ 55% T1b ~ 55% **Cholecystectomy+LN /Radical** 5yOS 53%/48%	**Cholecystectomy** p<0.0001 <u>5yOS</u> T1a ~ 55% (p=0.93) T1b ~ 40% (p=0.017) **Cholecystectomy** 5yOS 35% p<0.001	Predictive factors DSS: age, T-stage, tumor grade, radiation, type of surgery OS: see above DSS also described with significant increase in intervention group	+	?/+	+
Jensen 2009b USA	Cohort study	4614		**LNdiss+** (≥ 1 LN) T1b/2 Median OS 123m T3 Median OS 10m	**LNdiss-** T1b/T2 Median OS 22m p<0.0001 T3 Median OS 6m p=0.014	Significant better with LNdiss+, erases effect of radical liverop	+	?	+
Kai 2007 Japan	Cohort study	90 34 T2 D2 19 D1 11 D0 3		**Extended LN-op (D2)** **Standard LN-op (D1)**	**No LN-op (D0)** Better survival with either extended or standard compared to no LN-op for T2 p=0.0012	No significant difference between D1 and D2.	+	?/-	?

Project: Surgery for gallbladder cancer. Appendix 4.1.2
Intervention: Lymph node intervention. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Kim 2013 South Korea	Retro-spective non-random ised controll ed	70 T2 Cholecyst +LN 28 Radical 33 Cholecyst ectomy 9	No mortality	**T2 N- Cholecyst+LN** 5yOS 84% **Radical op** 5yOS 69% **T2 N+ Cholecyst+LN** 5yOS 68% **Radical op** 78% 5yOS	**T2 N- Cholecystectomy** 5OS 75% p=0.52 **T2 N+ Cholecystect** 5yOS 0% p=0.019 vs C+LN p=0.001 vs Radical		?	?	-
Liu 2013 China	Cohort study	78	11	**Extended LN-op ≥4** 3 and 5yOS 40.4% 26.9% **N-** Median DSS 54m **N+** Median DSS 21m **LN-op ≥6** **N+** Median DSS 33 m	**Standard LN-op <4** 3 and 5yOS 15.4% 7.7% **N-** Median DSS 37m p=0.40 **N+** Median DSS 13 m p<0.001 **LN-op <6** **N+** Median DSS 13 m p<0.001		+	?	+/?

Project: Surgery for gallbladder cancer. Appendix 4.1.2
Intervention: Lymph node intervention. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Wang 2012 China	Cohort study	91 48 vs 43 TNM-stage II: 18 vs 15 III: 19 vs 18 IV: 11 vs 10		**Extended LN-op** (N2 or more) Approx 5yOS/3yOS TNM-Stage II 53/77% III 21/53% IV 24/45%	**Standard LN-op** (N1 - ligament) Approx 5yOS/3yOS TNM-Stage II 29/60%, p=0.11 III 0/22%, p=0.009 IV 0/10%, p=0.029	Wedge in all. Same age and clinical stage in groups	+	? /+	?

LNdiss+=Lymph node dissection has been done. **LNdiss-=**Lymph node dissection has not been done**.**
N+=lymph node metastases present, **N-=** lymph node metastases absent
OS= Overall survival
DSS= Disease specific survival
NS= not significant
"Radical"=operation with lymph node dissection and liver resection of either entire segment 4b and 5 or a wedge of a few centimeters from the gallbladder fossa within those segments.
"Cholecystectomy" refers to simple cholecystectomy with no liver resection and no lymph node dissection.

Project: Surgery for gallbladder cancer. Appendix 4.1.3
Intervention: Bile duct resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Bile duct interventions									
Araida 2009a Japan	Cohort study BDres+ 194 BDres- 399	838 **N-** T2 144 vs 323 T3 26 vs 44 T4 24 vs 32 **N+** T2 71 vs 77 T3 31 vs 21 T4 25 vs 20		**BDres+** 5yOS **N-** T2 72% T3 62% T4 38% **N+** T2 45% T3 17% T4 28%	**BDres-** 5yOS **N- ,** p=0.10 T2 81%, NS T3 46%, NS T4 52%, NS **N+,** p=0.12 T2 55%, NS T3 27%, NS T4 14% (3yOS), NS	No statistical difference between BDres+ and BDres- for the different T-stages. In the BDres- group older patients, less morbidity and more minor surgery	+/?	?	+
Choi SB 2013 Korea	Cohort study	71 (T2/T3) BDres+ 31 BDres- 40		**BDres+** 3yOS 55.6% 5yOS 34.8%	**BDres-** 3yOS 76.4% 5yOS 54.2% p=0.11	Not comparable groups by T-stage	+	-/?	?
D'Angelica 2009 USA	Cohort study	104 T1 4 (4%) T2 37(36%) T3 61(59%) T4 2 (2%)	Mortality 5/109 (5%) All after major hepatectomy+BDres (p=0,006)	**BDres+** (68) 5yDSS 37 % of which 36 had CBD involvement	**BDres-** (36) 5yDSS 50% (p=0.12) No CBD involvement	For patients with (36) and without (68) bile duct involvement 5yDSS was 20% and 49% respectively (p=0.01). Thus, unbalanced groups, affecting outcome.	+	-/?	?

Project: Surgery for gallbladder cancer. Appendix 4.1.3
Intervention: Bile duct resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Ha 2015 South Korea	Cohort study	203 T2 107 BDres+ 29 BDres- 68		**BDres+** 5yOS **T2** **N-** 70.6% (p=0.69) **N+** 40.0% (p=0.93)	**BDres-** 5yOS **T2** p=0.60 **N-** 76.7% **N+** 51.8%	excluded 10 T2 with only cholecystectomy	+	-	-
Horiguchi 2013 Japan	Cohort study	109 T2 BDres+ 37 BDres- 48		**BDres+** T2 5yOS 86.5%	**BDres-** T2 5yOS 61.6% p=0.038, univariable p=0.42, multivariable	Univar analysis identified BDres and perineural invasion as prognostic factors. In multivar analysis only perineural invasion was significant (p=0.001), but unknown which factors were included.	+	?/-	?
Kai 2007 Japan	Cohort study	90 T1 17 T2 17 vs 17 T3 5 vs 4 T4 25 vs 5		**BDres+** (no T1) 5yOS T2 NS (p=0.67)	**BDres-** (no T1) OR 1.939 univariable (95%CI 0.973–3.863) p=0.060 BDres- vs BDres+ T2 NS	Not comparable groups according to Tumour stage	+	?/-	?
Wakai 2012 Japan	Cohort study	70 BDres+ 55 BDres- 15 T2 51 T3-4 19 N+ 28 N- 42		**BDres+** <u>5yOS</u> 73%	**BDres-** <u>5yOS</u> 45% p=0.028 univariable p=0.048 multivariable	No postop mortality Older patients in BDres- T- and M-classification were significant prognostic factors in addition to BDres in multivariable analysis.	+	?	-

Project: Surgery for gallbladder cancer. Appendix 4.1.3
Intervention: Bile duct resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Yokomizo 2007 Japan	Cohort	94 T2 BDres+ 11 BDres- 83 N+ 5 vs 19		**BDres+ T2** (neck/duct localisation or suspicious invasion of bile duct) 5yOS 66.7% 10yOS 50.0% **N+** 3yOS 50% 5yOS NR	**BDres- T2** 5yOS 81.1% 10yOS 50.0% p=0.134 **N+** 5yOS 64.2% (p=0.08) 10yOS 44.9%	Multivariable analysis does not include BDres	+	?	-

BDres+=Bile duct resection **done, BDres-=** Bile duct resection **not done,**
N+=lymph node metastases **present, N-=** lymph node metastases **absent**
OS= overall survival
DSS= Disease-specific survival, **NS=** not significant
CBD=Common bile duct
"Radical"=operation with lymph node dissection and liver resection either of entire segments 4b and 5 or a wedge of a few centimeters from the gallbladder fossa within those segments.
"**Cholecystectomy**"=simple cholecystectomy with no liver resection and no lymph node dissection.

Project: Surgery for gallbladder cancer. Appendix 4.1.4
Intervention: Adjacent organ resection. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Adjacent organ resection									
Araida 2004 Japan	Cohort study	216 binf- N+ 16 vs 10 N- 11 vs 13	Selection method not presented (135)	44 **HPD** 5yOS binf- N+ 87% N- 73%	37 **non-HPD** 5yOS binf- N+ 17%, p<0.05 N- 63% p>0.05	Highly selected population For binf+, poor results.	-	-	-
Kayahara 2008 Japan	Cohort study	4424		5yOS **Extended** (right-lobe, pancreas etc) Stage III 39% All stages HR 0.789 (95% CI 0.686-0.909) **Radical** (wed/S45) Stage III 51% All stages HR 0.726 (95% CI 0.638-0.827) Stage IVa+b no diff between 3 op-groups	5yOS **Cholecystectomy** Stage III 38%		?	?	?/+

OS= Overall survival
HPD= Hepato-pancreatico-duodenectomy
Binf+ or **Binf-** =presence or abscence of tumor infiltration of the bile duct
HR= hazard ratio
CI= confidence interval

Project: Surgery for gallbladder cancer. Appendix 4.1.5
Intervention/subgroup: Surgery in advanced stages. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Surgery in advanced stages (n)									
Endo 2001 Japan	Cohort study	78 Op HLI+ 15 No op HLI+ 20		**Op with HLI +** 1yOS 25% 2yOS 0%	**No op because of HLI+** 1yOS 5% 2yOS 5%	High-grade lig invasion (>2 foci) op gave as low survival as no op OS estimated from Kaplan-Meier, p not reported	?	-	-
He 2015 China	Cohort study	152 Radical 57 (III 23, IVa 19) vs palliative 29 (III 19, IVa 2, IVb 7) vs no surgery 39 (IVa 3, IVb 36)	Not reported Lost to follow-up 19 (censor)	**Radical** 5yOS III 58% IVa 18%	**Palliative surgery** Median OS 6m 5yOS III 18%, p=0.04 IVa 20%, p=0.69 IVb palliative vs no surgery, p=0.001 **No surgery** Median OS 3-4m	Also liver resection	?	?	-
Kang 2012 South Korea	Cohort study	94 16 vs 78		**Curative surgery** Stage IVa Stage IVb Liver metastasis Median OS 31m Carcinomatosis Median OS 20m	**Palliative surgery** Stage IVa, p=0.764 Stage IVb Liver metatasis Median OS 9m, p<0.001 Carcinomatosis Median OS 6m, p=0.002		+	?/-	-

Project: Surgery for gallbladder cancer. Appendix 4.1.5
Intervention/subgroup: Surgery in advanced stages. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Kayahara 2008 Japan	Cohort study	4424 1127 vs 1397		**Resection** 5yOS IVb 10%	**Palliative treatments** 5yOS IVb 0%, p<0.001	R0 501/1127 in resected group	?	?	?/+
Ishikawa 2003 Japan	Cohort study	59 stage IV IVa 7R vs 1P vs 5 BSC IVb 22R vs 9P vs 15 BSC	6 lost to follow-up	**Resection** 1yOS 45.1%, 2yOS19.7%, 5yOS6.6% Radical res for M- (14) 1yOS 70.7%, 2yOS, 37.7% 5yOS 12.6%	**Palliative chemo.** 1yOS 10%, p=0.018 **Best supportive care** 1yOS 0%, p=0.0009 Radical res for M+ (12) 1yOS 16.7% 2yOS 0% p=0.0004	30-d mortality 10% Some longterm survivors.	+	?/-	+
Meng 2011 China	Cohort study	55, stage IV (a+b) 24 r vs 8 c vs 23 p		**Radical resection** Median OS 8m 1, 3, 5yOS 29, 12, 5%	**Chemotherapy** Median OS 3m, p=0.008 **Other palliative treatment** Median OS 3m, p=0.004 1 pat lived 13m	5/24 T4N1-2 lived for at least 34-64 months! Worse outcome for distant lymph node tumor. Survival for resected patients with distant LN metastases was not significantly different from chemotherapy and palliative groups.	-	-	-/?

Project: Surgery for gallbladder cancer. Appendix 4.1.5
Intervention/subgroup: Surgery in advanced stages. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Qu 2012 China	Cohort study	139 Stage III-IVb 83 vs 56 (Radical Hinv+ 33 Hinv- 50)	?	**Radical op** (Mix lobectomy, wedge/S4b/5/other organ) Hinv+ 1yOS 26.03% 2yOS 10% Hinv- 1yOS 37.9% 5yOS ca 20%	**Palliative op** (exploration, wedge, drain) Hinv+ , p>0.05 2yOS 10%, p=0.12 Hinv- , p<0.05 5yOS 0%, p<0.001		+	-	-
Xiao 2005, China	Cohort study	70 (Nevin stage IV/V) 22 c vs 15 p vs 33 lap Nevin IV 11 c vs 5 p vs 6 lap Nevin V 11 c vs 10 p vs 27 lap	2 loss to follow-up	**Curative op** <u>Median OS 22m</u> <u>1, 3, 5yOS</u> 69, 33, 8% p<0.01 vs other groups	**Palliative op** (not R0) <u>Median OS 9m</u> <u>1, 3, 5yOS</u> 27, 13, 0% p<0.01 vs laparotomy **Laparotomy** <u>Median OS 3m</u> <u>1, 3, 5yOS</u> 3, 0, 0%	Mortality 4,5%, morbidity 36% Nevin IV corresponds to N+ and V to T3.	+	?	?

HLI= High grade Ligament Invasion
OS= overall survival
R0= macroscopically radical resection and margins microscopically free of tumour
Chemo= chemotherapy
Hinv+/- = presence of absence of hepatic tumor invasion.

Project: Surgery for gallbladder cancer. Appendix 4.1.6
Intervention: Staged operations vs direct radical. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Staged operations versus direct radical									
Ballo 2015 USA	Cohort study	20 staged: 1 S?, 1 SI 3 SII 1 SIIIA 5 SIIIB, direct rad: 1 SII, 6 SIIIB, 2 SIV	Mortality 30d 0	**Staged** (laparoscopy first) 1yOS 57% Median OS 14.4m	**Direct radical** (more advanced stages, diagnosis preop) 1yOS 29%, p=0.592 Median OS 15.4m p=0.255		?	-	-
Fong, 2000 USA	Cohort singel-center	102 op of 410 80/248 vs 22/162 curative T1 2 vs 0 T2 32 vs 5 T3 31 vs 5 T4 15 vs 12	?	**Staged** <u>5yOS</u> approx 35%	**Direct radical** <u>5yOS</u> approx 35%, NS	N-stage RR 2.8 T-stage RR 1.7 Size of resection and earlier resection did not affect outcome	?	-	? /+

Project: Surgery for gallbladder cancer. Appendix 4.1.6
Intervention: Staged operations vs direct radical. Outcome: Survival

Author year Country	Study design	Number of patients n=	With drawal - drop-outs	Survival		Comments	Directness*	Limitations	Precision
				Intervention	Control				
Ha 2015 South Korea	Retro-spective non-random ised controll ed	203 R0 T1b 75/6 vs 15 N- 64/6 vs 6 N+ 11/0 vs 0 T2 75/22 vs 10 N- 55/18 vs 3 N+ 20/4 vs 1?		**Direct Radical / Staged** 5yOS 76.0% / 66.7% **T1b** 84.4% / 83.3% **N-** 92.6% / 83.3% **N+** 34.3% **T2** 67.6% / 61.9% **N-** 74.4% / 73.3% **N+** 53.0% / 33.3% p=0.59 (direct vs staged)	**Cholecystectomy** 5yOS 64.0%, p=0.61 **T1b** 68.8%, p=0.65 **N-** 100%, p=0.43 **N+** **T2** 50%, p=0.90 **N-** 100%, p=0.93 **N+ -**(only one)	(wedge or S4/5) BDres+ 13/28 in staged gr, 26/150 in direct group	+	-	-

OS= Overall Survival
RR= Risk Ratio
R0= macroscopically radical resection and margins microscopically free of tumour

Project: Surgery for gallbladder cancer
Appendix 4.2.1
Intervention: Radical liver resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
Radical resection versus Cholecystectomy						
Fuks 2011 France	Cohort registry	218 incidental	Mortality 3% (3 sepsis+ Multi Organ Failure, 1 liver failure)	**Reresection** (148) Complications: pulmonary (11) 20% bile-leak (10) 18%	**Cholecystectomy** (70)	Risk factor for complication: Bile duct resection
Lee 2014 South Korea	157 T2			**Radical** (122) Complication rate (8) 6.6%	**Cholecystectomy** (35) Complication rate (1) 2.9% (p=0.685)	Tachycardia, 3 fluid collections, 3 ileus, bile fistula, urinary complication, TIA
Yildrim 2005 Turkey	Cohort incidental gallbladder cancer	65	No mortality	**Radical (wedge)** (28) 27 complications (15pat) 54% 12 lymph-leak 2 bile-leak 12 transaminase-raise 2 wound infection 1 pneumonia	**Cholecystectomy** (37) Small bile-leak 5% (2)	
He 2015 China	Cohort	152 loss to follow-up 19 (censor)	-	**Radical** (57) 1 MODS death (Mortality 1.8%) 1 thrombosis 1 liver function impairment 1 skin infection + bleeding (Morbidity 5.3%) **Palliative** (28) 2 bile fistula 1 pulmonary embolism 1 deep infection 1 pulmonary oedema 1 subphrenic fluid	**Cholecystectomy** (28) 1 wound complication (Morbidity 3.6%) **No surgery** (39) 2 MODS (deaths)	

Project: Surgery for gallbladder cancer
Appendix 4.2.1
Intervention: Radical liver resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
de Aretxabala 2006 Chilie	Retrospective non-randomised controlled	139	Mortality 0%	**Radical** (wedge or S4b/5 res) **Morbidity** 16.6% 1 reoperation		Biliary leakage in 3 lymphorrhea 1, abdominal collection 1, pneumonia 1, fever 1.
Mayo 2010 USA	Cohort	2955	Mortality 4.2% 91-5 3.4 96-9 4.8 00-2 3.7 03-5 4.9	**Radical op + Cholecystectomy** Morbidity: 32.8% Postop infection: 4.0% Drain: 5.4% Postop bleed: 2.8%		
Fong 2000 USA	Cohort single-center	102 op of 410	Mortality postop 3.9%. (2 liver failure, 2 pneumonia+ respiratory failure	**Reresection** (80/ 248) + **Direct radical** (22/162) 45 complications in 29 pat. Bilomas 5 abscess 6 Infection 12 Wound complications 8		Risk factor complication: op size, op-time, intraoperative bleeding
Yang 2012 China	Case series	76	Mortality (1)	**Morbidity** (18) 23.7% Abdominal infection 2 Seroperitoneum 9 Bleeding 2 Bile leak 3 Wound infection 1 Liver abscess 1		
Ouchi 2002 Japan	cohort multi-center	498	Mortality 1.3% (liver failure, bleeding, GI-leak)	**Radical resection** (238)		

Project: Surgery for gallbladder cancer
Appendix 4.2.1
Intervention: Radical liver resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
Higuchi 2014 Japan	Case-series	274 1969-2012 A 69-89 (88) B 90-99 (76) C 00-12 (110)	Surgical mortality 1.9 % 2007-12 Mortality decrease A 19.3% B 17.1% C 3.6 % p = 0.00063	Different surgical methods in different time periods; BDR increases with time, PD decreased Clavien >3a decreased (p=0.0001) A 60.2% B 57.9% C 30.9% 3a-rate 26.4 % (14/53) 2007–2012.		
Horiguchi 2013 Japan	Cohort	85	1/85 1.2%	**S4/5resection** 13/30 Abdominal haemorrhage 1 Respiratory dysfunction 2 Pancreatitis 1 Wound infection 3 Bile leakage 4 Cholangitis 2 Ileus 0 Mortality 0	**Wedge resection** 12/55 (p=0.037) Abdominal haemorrhage 2 Respiratory dysfunction 3 Pancreatitis 0 Wound infection 1 Bile leakage 6 Cholangitis 0 Ileus 1 Mortality 1	Also Bile duct resection
Wakai 2012 Japan	Cohort	70	Mortality (1) 1.4% (wedge-group related to bleeding)	**S 4/5res** (12) Morbidity (6) 50% (p=0.341) Mortality 0 (p>0.999)	**Wedge res** (58) Morbidity (20) 34% Mortality (1) 1.7% (related to bleeding)	

BDR= bile duct resection
PD= pancreaticoduodenectomy
MODS=Multi Organ Dysfunction Syndrome
Clavien 3a corresponds to complication requiring surgical, endoscopic or radiological intervention not under general anaesthesia

Project: Surgery for gallbladder cancer
Appendix 4.2.2
Intervention: Adjacent organ resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
Birnbaum, 2013	cohort	78 T3-T4 67 R0	Surgical 90d-mortality (n=6) 8% (none in the S4/5 group)	**Major liver res or/and res of other organs** Mortality 11% (p=0.090), Overall morbidity 63% (p= 0.009) Grade III/IV morbidity 30% (p=0.002)	**Radical** (S4/5 res + LN-diss) Mortality 0% Overall morbidity 13% Grade III/IV morbidity 0%	Liver failure, Bile leakage, Hemoperitoneum, Abdominal collection ascites, Sepsis, Pancreatic leakage, Duodenal leakage, Pulmonary morbidity, Pulmonary embolus, Renal failure, AMI, Small bowel disorder
Birnbaum, 2015, Italy	Cohort	112	Mortality 90d (n=6) (5.4%) Hepatic failure 2, hemoperitoneum 1, septicemia 1, AMI 1, ARDS 1	**D2-diss** Overall morbidity 49.4% Grade III/IV complications 25.3%	**D1-diss** Overall morbidity 40.0% Grade III/IV complications 16.0%	Overall morbidity: (n=53) 47.3% Grade III/IV complications (n=20) Liver dysfunctions in 4, bile leak in 5, bile leak+hemoperitoneum in 4, abdominal collection in 2, duodenal leak+hemoperitoneum in 1, renal dysfunction in 1, AMI in 1, ARDS in 1, pleural effusion in 1 Standardop S4b5+LNdiss, (n=53) no mortality
Choi 2010 Korea	Cohort study	83 T2 LNdiss+ 31 LNdiss- 52	Mortality 1.1% (septicemia)	**LNdiss+/-** operative morbidity in 10 patients (11.1%) intra-abdominal abscess (4), jaundice (1), pleural effusion (1), angina (1), wound dehiscence (3).		

Project: Surgery for gallbladder cancer
Appendix 4.2.2
Intervention: Adjacent organ resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
De Aretxabala, 2009, Chile	Case series	45 T1a 49 T1b	Mortality 0%	Morbidity after resection 16.6% Bile leak 3, lymphorrea 1, abdominal collection 1, pneumonia 1, fever 1		
Niu, 2015, China	Cohort	60 Tx**N2** T2 (6), T3/T4 (54)	Mortality **Ext** (n=3) 9.3% **Standard** (n=2) 7.1%	**Extended Lgl** (N2) Mortality 9.34% (bleeding, hepatic failure, ARDS) Major morbidity 81.3%	**Standard Lgl** (N2) Mortality 7.14% (hepatic failure, ARDS) Major morbidity 64.3%	High morbidity, but extensive surgery, artery, porta, duodenum, pancreas, colon!!! Advanced stages, but not so bad survival

AMI= acute myocardial infarction
ARDS= Acute respiratory distress syndrome

Project: Surgery for gallbladder cancer
Appendix 4.2.3
Intervention: Bile duct resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
Bile duct intervention						
Araida, 2009a Japan	Cohort	838	Not reported	**BDres+** (194) Postop Complications 20.3%	**BDres-** (399) Postop Complications 18% (p=0.66)	
Birnbaum 2014 Italy	Cohort	78	(6) 8% 2 hepatic failure 1hemoperitoneum 1 acute myocardial infarction, 1 respiratory distress syndrome	**Major liver / res other organs** (CBD, pancreas, colon, gastric) Mortality 11% Overall morbidity 63% Grade III/IV complications 30%	**Radical** (S4/5 res + LN-diss) Mortality 0% (p=0,09) Overall morbidity 13% (p=0.009) Grade III/IV complications 0% (p=0.002)	Liver failure Bile leak, Hemoperitoneum, Abdominal fluid collection Ascites, Sepsis, Pancreatic leak, Duodenal leak, Pulmonary morbidity, Pulmonary embolism, Renal failure, Myocardial Infarction, Small bowel disorder
Choi SB 2013 Korea	Cohort	71 (T2/T3)	No postop mortality	**EBDres+** (31) Postop complications (10) 32.3% (p=0.007)	**EBDres-** (40) Postop complications (3) 7.5%	Abscess 4, Surgical site infection 5 Pleural effusion 2 Renal failure 1 Angina 1 No postop mortality.

Project: Surgery for gallbladder cancer
Appendix 4.2.3
Intervention: Bile duct resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
D'Angelica 2009 USA	Cohort	104 T1 4 (4%) T2 37(36%) T3 61(59%) T4 2 (2%)	Mortality 5/109 (5%) All after major hepatectomy +BDres (p=0.006)	**BDres+** 68 (65%) of which 36 had CBD involvment 29% grade 1-2 33% grade 3-4 (p=0.03)	**BDres-** 36 (35%) 20% grade 1-2 13% grade 3-4	Complication rate overall 53%
Igami 2015 Japan	Case series	52	Mortality 3.8% n=2 (bleed, liver failure)	**EBDres+** (52) Postop mortality 3.8% (2) (bleed d10, liver failure d51)		"micro-vessel-invasion" as a prognostic factor
BDres= bile duct resection CBD= common bile duct EBDres= extrahepatic bile duct resection						

Project: Surgery for gallbladder cancer
Appendix 4.2.4
Intervention: Adjacent organ resection
Outcome: Complications

Author year Country	Study design	Number of patients n=	Mortality	Complications		Comments
				Intervention	Control	
Birnbaum 2013 Italy	Cohort	78 T3-T4 67 R0	Surgical 90d-mortality (6) 8% (none in the S4/5 group)	**Major liver or/and res of other organs** 90d-mortality (6) 11% Overall Morbidity 63% Grade III-IV morbidity 30%	**Radical** (S4/5 res + LN-diss) No mortality (p=0.09) Overall Morbidity 13% (p=0.009) Grade III-IV morbidity 0% (p=0.002)	Liver fail, Bile leak, Hemoperiteum, Abdominal fluid collection, Ascites, Sepsis, Pancreatic leak, Duodenal leak, Pulmonary morbidity and embolism, Renal failure, AMI, Small bowel disorder
Higuchi 2014 Japan	Case series	Group B 1990-99 (76) Group C 2000-12 (110)	Surgical mortality 1.9% 2007-12	BDres increased with time, PD decreased Mortality decrease 17.1% group B to 3.6% Group C (p = 0.00063). 1.9% 2007-12 Morbidity 3b/4 decrease from 59.7% Group B to 30.9% Group C.		(Group A 1969-89 n=88, excluded from analysis – to old)
Niu 2015 China	Case series	60 TxN2 T2 (6), T3/T4 (54)	Mortality **5/60 (8%)**	**Extended LN-diss**(N2) Postop mortality 9.3% (bleed, liver fail, resp-failure) Major morbidity 81.3%	**Standard LN-diss**(N2) Postop mortality 7.1% (multi-organ failure 2) (NS) Major morbidity 64.3% (NS)	High morbidity, but extensive surgery, artery, porta, duodenum, pancreas, colon

LN-diss= lymph node dissection
BDres= bile duct resection
PD= pancreaticoduodenectomy
NS= not significant
Tx= uncertain T stage (T1, T2, T3 or T4)

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA

HTA

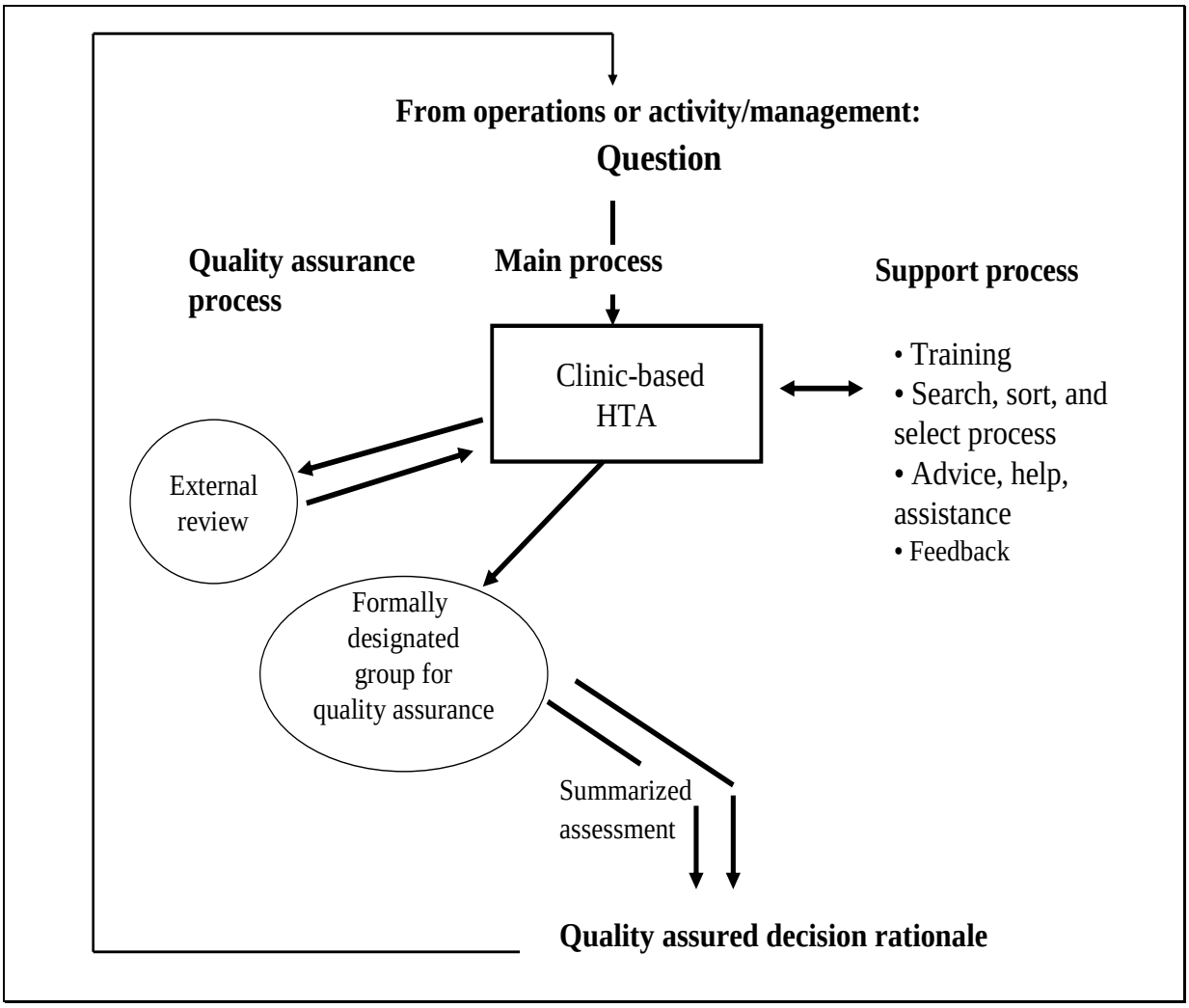
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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