Gallbladder Cancer. Risk Factors, Surgical Intervention and Survival.

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LUND
UNIVERSITY

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Abstract

Background and aims

Gallbladder cancer (GBC) is a rare malignancy with poor prognosis. Benign gallbladder disease, on the other hand, is very common and around 14 000 cholecystectomies are performed in Sweden anually. GBC discovered during a cholecystectomy or on histoptahological analysis, is defined as incidental gallbladder cancer (IGBC). The prognosis of GBC changes dramatically when identified at an early stage and surgery is a prerequiste for cure. This doctoral thesis aimed to identify predictors for IGBC and to create a validated preoperative risk score model for IGBC, to describe management and survival of rare malignancies of the gallbladder and to assess the management and surgical treatment of IGBC patients over one decade. Also, to analyze overall survival in IGBC patients, that either undergo cholecystectomy as the only procedure or a second operation compared to GBC patients undergoing surgery.

Methods

In paper I, II, III, IV and V data from cholecystectomies registered in the National Quality Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) was analyzed. In paper I: for IGBC between the years 2007-2014, II: for inclusion of the IGBC derivation cohort 2007-2014 and the IGBC validation cohort 2015-2016, III: 2007-2014 for rare malignancies of the gallbladder, IV: for IGBC 2007–2016. Data was crosslinked, for completion of the pathology report, with the National Quality Registry for Liver, Bile Duct and Gallbladder cancer (SweLiv) and/or the Swedish Cancer Registry. Medical records were retrieved if registry data was missing. In paper V, data from SweLiv, between 2009 and 2019 was collected for IGBC and GBC and crosslinked with GallRiks for IGBC between the years 2009-2016.

Results and conclusions

In paper I, several preoperative risk factors for IGBC were identified including older age, female sex, previous cholecystitis, and the combination of acute cholecystitis without jaundice and jaundice without acute cholecystitis. The preoperative risk model including these risk factors was further improved by adding the result of the macroscopic assessment of the gallbladder.

In paper II, the preoperative risk factors identified in paper I, created a risk score model that was validated in a separate patient material. The model was based on odds ratio and applied into three risk-groups, based on the risk of having IGBC. The high-risk group (>8 points) included 7 878 patients, with 154 observed and 148 expected IGBC. The AUROC score for predicting IGBC was 0.76 in the derivation cohort and 0.79 in the validation cohort, p=0.363, with an acceptable calibration.

In paper III, all patients underwent preoperative computer tomography or ultrasound, on which no metastases were identified. The survival was poor for patients with metastasis (from primary tumors of breast cancer, malignant melanoma, gastric cancer, renal cell carcinoma, colon cancer, upper gastrointestinal cancer and pancreatic cancer) and lymphoma, with a median survival of 5.8 months, compared to 23 months for IGBC patients.

In paper IV, median disease specific survival (DSS) improved after reresection in IGBC patients with pT2 and pT3 disease. Residual disease was proven to significantly lower disease specific survival compared to patients without residual disease.

In paper V, improved 5-year overall survival in pT3 GBC patients undergoing surgery or curative resection was seen, when compared to IGBC patients with simple cholecystectomy (SC) and IGBC patients undergoing a second operation or curative reresection. These results sustained through multivariable analysis, indicating that pT3 IGBC patients may benefit from one stage resection.

Key words: Gallbladder cancer, incidental gallbladder cancer, risk factors, predictors, metastases, lymphoma, risk score model, reresection, resection, disease specific survival, overall survival, one stage resection

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Gallbladder Cancer

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MADE IN SWEDEN

Till Edith och Rubinen

“All scientific work is incomplete”

Austin Bradford Hill

Table of Contents

List of papers and manuscript

This thesis is based on the following original papers, which will be referred to in the text by their roman numerals (I-V):

I. Muszynska C, Lundgren L, Lindell G, Andersson R, Nilsson J, Sandström P, Andersson B. Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease: Results from a population-based gallstone surgery registry. *Surgery*. 2017;162(2):256-63.

II. Muszynska C, Nilsson J, Lundgren L, Lindell G, Andersson R, Sandström P, Andersson B. A risk score model to predict incidental gallbladder cancer in patients scheduled for cholecystectomy. *Am J Surg.* 2020;220(3):741-744.

III. Muszynska C, Lundgren L, Andersson R, Søland T, Lindell G, Sandström P, Andersson B. Incidental metastases and lymphoma of the gallbladder - an analysis of ten rare cases identified from a large national database. *Scand J Gastroenterol*. 2019;54(3):350-358.

IV. Lundgren L, Muszynska C, Ros A, Persson G, Gimm O, Andersson B, Sandström P. Management of incidental gallbladder cancer in a national cohort. *Br J Surg.* 2019;106(9):1216-1227.

V. Muszynska C, Lundgren L, Jacobsson H, Sandström P, Andersson B. Preoperatively suspected gallbladder cancer has improved survival compared to incidental gallbladder cancer in pT3 patients. Manuscript.

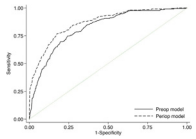
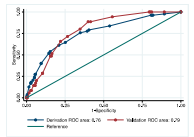
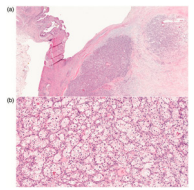
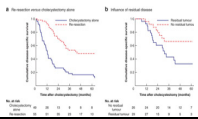
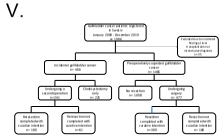
Related paper not included in this thesis:

Lundgren L, Muszynska C, Ros A, Persson G, Gimm O, Valter L, Andersson B, Sandström P. Are incidental gallbladder cancers missed with a selective approach of gallbladder histology at cholecystectomy? *World J Surg*. 2018;42(4):1092-1099.

Abbreviations

ADM	Adenomyomatosis
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiology score
AUROC	Area under receiver operating characteristic curve
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
DSS	Disease specific survival
ERCP	Endoscopic Retrograde Cholangiopancreatography
GallRiks	National Quality Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography
GBC	Gallbladder Cancer
HA	Hepatic artery
HL	Hosmer-Lemeshow test
HPB	Hepato-pancreatico-biliary
HR	Hazard ratio
IGBC	Incidental Gallbladder Cancer
MOL	Metastasis or Lymphoma
N	Nodal status
OR	Odds ratio
PGB	Porcelain gallbladder
pM	Pathological metastasis stage
pN	Pathological nodal stage
PSC	Primary sclerosing cholangitis
pT	Pathological tumor stage
PV	Portal vein
R	Resection margin
RCC	Renal Cell Carcinoma
SC	Simple cholecystectomy
SEER	The Surveillance Epidemiology and End Results
SweLiv	National Quality Registry for Liver, Bile Duct and Gallbladder Cancer

Thesis at a glance

Paper	Aims	Methods	Main results	Conclusions
I. 	To identify preoperative predictors of IGBC. To investigate the surgeons' intraoperative evaluation of the gallbladder and see if a risk model for IGBC could be improved by adding this information.	Data from GallRiks, 2007-2014, was analyzed for IGBC. Predictors for IGBC were identified using multivariable logistic regression.	In total 215 IGBC patients were included. Predictors for IGBC were; older age, female, previous cholecystitis and the combination of acute cholecystitis without jaundice and jaundice without acute cholecystitis. By adding macroscopic evaluation of the gallbladder by the surgeon, the AUROC increased to 0.87.	IGBC is more likely to be diagnosed in an older age, women, after previous cholecystitis and in patients with either jaundice or acute cholecystitis. Intraoperative inspection of the gallbladder improved the risk model.
II. 	To construct and validate a risk score model to predict IGBC in patients scheduled for cholecystectomy for benign gallbladder disease.	Data from GallRiks was analyzed, including the derivation cohort (n=2 8915, 2007-2014) and the validation cohort (n=7 851, 2015-2016). An additive risk score model based on odds ratio was created.	Predictors for IGBC from paper I were included in a validated scoring model. The model was applied into three risk-groups, based on the risk of having IGBC. The high-risk group (>8 points) included 7 878 patients, with 154 observed and 148 expected IGBC.	We created and validated a risk score model that estimates the expected risk of IGBC for the individual patient planned for cholecystectomy on a benign indication. This model may help to optimize treatment strategies.
III. 	To identify and characterize rare incidentally diagnosed malignancies of the gallbladder and describe the diagnostics, treatment and outcome.	Data from GallRiks, 2007–2014, was analyzed for IGBC, metastases or lymphoma involvement (MOL). Data was cross-linked with SweLiv and the Swedish Cancer Registry and medical journals were reviewed.	In total 215 IGBC, 7 patients with metastases and 3 patients with lymphoma involvement of the gallbladder were found. The median survival was 5.8 months in the MOL group and 23 months for IGBC patients. After 2 years, in the MOL group, only patients with lymphoma involvement of the gallbladder were alive.	Metastases and lymphoma of the gallbladder are rare. A liberal approach of histopathological analysis of the gallbladder should be applied in patients with previous history of malignancy.
IV. 	To assess the national cohort of IGBC patients in Sweden over a decade and to undertake a detailed analysis of management and survival outcomes.	Data was retrieved from GallRiks and cross-linked with SweLiv and the Cancer Registry. Medical records were collected if registry data was missing.	In total, 249 IGBC patients were identified. In pT2 and pT3, median DSS improved after reresection, 12 *versus* 44 months for pT2, and 10 *versus* 23 months for pT3. Residual disease impaired survival.	Reresection of pT2 and pT3 IGBC is associated with improved survival. Residual disease impairs survival.
V. 	To compare survival for IGBC and GBC, subjected to surgery for different pT-stage and in different treatment groups.	Data was collected and crosslinked from two national quality registers, SweLiv between 2009-2019 and GallRiks between 2009-2016.	In total 466 IGBC patients (of these 225 IGBC SC) and 477 GBC patients were included. Independent improved 5-year overall survival in pT3 GBC undergoing surgery and curative resection was seen.	GBC was an independent predictor for improved survival in pT3 patients. Radiological suspicion of gallbladder cancer should be evaluated at a liver tumor center to optimize patients´ outcome.

Introduction

Background

Gallbladder cancer is a rare disease with an incidence that vary geographically, with a worldwide occurrence of less than 2/100 000 individuals[1]. Meanwhile, benign gallbladder disease is very common and approximately 14 200 cholecystectomies are performed in Sweden annually (2019)[2]. The rarity of gallbladder cancer makes it somewhat difficult to study, in addition not all gallbladder specimens in Sweden are sent for histopathological examination, which also makes it difficult to estimate the true incidence of incidental gallbladder cancer (IGBC).

Gallbladder cancer is a disease with poor prognosis, often diagnosed at an advanced stage[3]. IGBC is diagnosed during cholecystectomy or during the histopathological examination of the gallbladder. When diagnosed at an early stage, usually incidentally, since early disease is not presented with concrete symptoms, the survival rate improves dramatically[4]. Gallbladder cancer is diagnosed in 0.11% to 3.0% of all cholecystectomies[5-10].

Anatomy

The gallbladder is a saccular organ located in the gallbladder fossa, adjacent to the liver. It consists of the fundus, body and neck that unfolds into the cystic duct, that continues into a junction of the common hepatic duct and further into the common bile duct, figure 1.

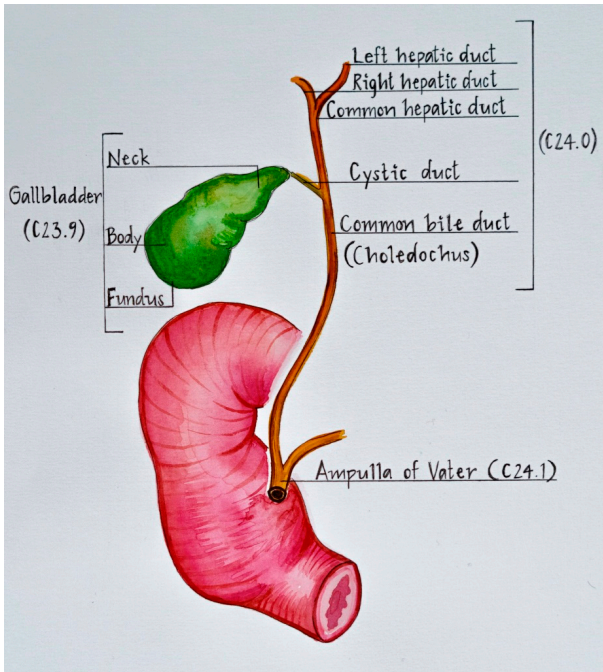


Figure 1. The anatomy of the gallbladder and bile ducts.
Illustration by Isabella Hylin and photographed by Michael Gartner.

The gallbladder wall is very thin and lacks a circular and transverse muscle layer, which can be found in the intestine. The gallbladder wall has a mucosa (thin epithelial lining and lamina propria), a smooth muscle layer, perimuscular connective tissue and serosa. Along the attachment to the liver there is no serosa, only the connective tissue that continues in to the interlobar space. The gallbladder is surrounded by regional lymph nodes[11].

Lymph nodes along the common bile duct, cystic duct, hepatic artery and portal vein are defined as hilar lymph nodes (N1) and are distinguished from lymph nodes along the coeliac trunk and superior mesenteric artery and the periduodenal and peripancreatic lymph nodes (N2). Gallbladder cancer usually metastasize to the liver and peritoneum, and sometimes to the lungs and pleura[11].

Physiology

The function of the gallbladder is mainly to store and concentrate bile between meals. The motoric function of the gallbladder is regulated by bile acids through receptors in the gallbladder membrane and by neurohormonal signals that are linked to digestion. These signals are responsible for triggering gallbladder emptying and refilling[12]. The emptying and refilling mechanism controls the flow of bile into the intestine[13]. The gallbladder epithelium produces and secretes bicarbonate and mucin, with the function of cytoprotection against bile acids[12]. The gallbladder epithelium also has the function of absorption of cholesterol and bile acids with a further passage through the cholecystohepatic shunt pathway[14]. When changes in gallbladder motor function occur, it contributes to changes in the bile acid composition and to gallstone formation[12, 15].

Epidemiology

The geographic pattern for gallbladder cancer varies greatly, with particularly high incidence in Latin America and Asia, relatively high in some Eastern and Central Europe countries[16, 17], yet low in the United States and most western and Mediterranean European countries[17], figure 2. Specific regions with a high incidence of gallbladder cancer include Mapuche natives from Valdivia, Chile, South America (12.3/100 000 for males and 27.3/100 000 for females)[18] and women from Delhi, India (21.5/100 000), La Paz, Bolivia (15.5/100 000), South Karachi, Pakistan (13.8/100 000) and Quito, Ecuador (12.9/100 000)[16].

The incidence of gallbladder cancer in Sweden based on SweLiv data (2020) was 1.3/100 000 for men and 2.4/100 000 for women. The completeness of the registry was 97% for the year of 2020[19].

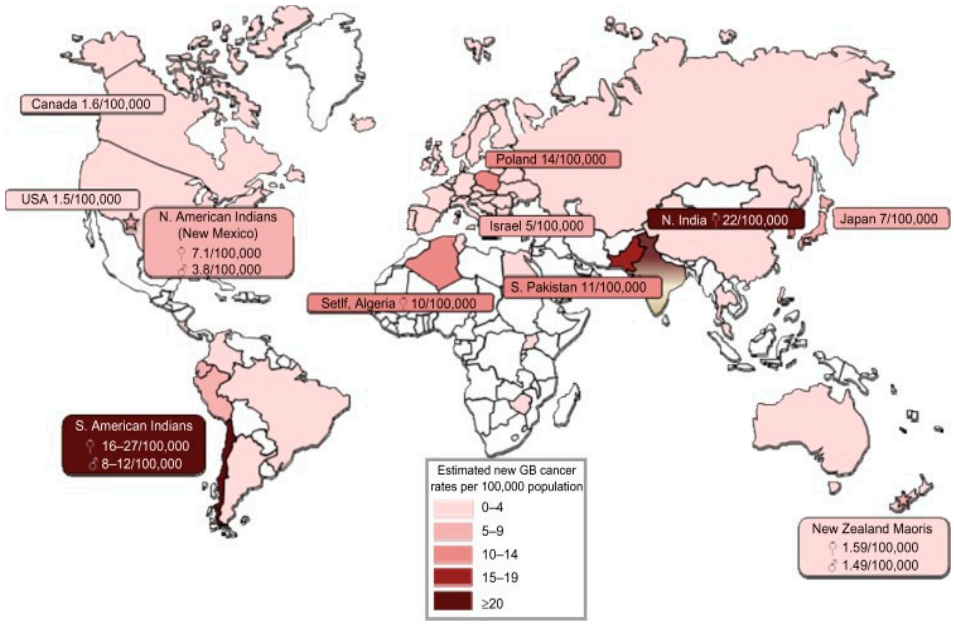


Figure 2. Incidence of gallbladder cancer in the world.
Reprinted with permission from Gut and Liver[17].

Risk factors

The identification of risk factors plays an important role in prevention and treatment strategies of cancer, including gallbladder cancer, since early detection of the tumor has an important impact on survival outcomes.

Age

The incidence rate of gallbladder cancer increase with advanced age. Age-adjusted incidence rate from US data from 2010 show an incidence of 0.16/100 000 (20–49 years), 1.47/100 000 (50–64 years), 4.91/100 000 (65–74 years), and 8.69/100 000 (≥75 years). This further matches with mortality rates per year; 0.08/100 000 (20–49 years), 0.77/100 000 (50–64 years) and to 2.68/100 000 (65–74 years), with the highest mortality rate of 5.05/100 000 in the age group over 75 years[20].

Sex

There is a clear predominance of female over male in the incidence of gallbladder cancer worldwide, especially in northern India, Pakistan, and in native American females[18]. Female-to-male incidence ratio is usually around 2 to 3, but range from 1 in Far East Asia to over 5 in Spain and Colombia. Gallbladder cancer is associated with high parity and greater number of pregnancies, secondary to the risk for gallstone disease in this patient chategory[16]. During pregnancy changes in the hepatobiliary function occur, including gallbladder stasis and secretion of bile, with increased amounts of cholesterol and decreased amounts of bile acids, creating an environment predisposing for gallstone formation[21].

Genetics

The risk of gallbladder cancer is associated with a family history of gallstone disease[22]. The genetic background accounts for approximately 25% of the total risk for gallstone disease[17]. Gene variations in ABCB1 and ABCB4 gene regions, that play a role in hepatobiliary phospholipid transporters, has been identified as a possible risk factors for gallbladder cancer[23]. Also, gene sequence variants encoding the bile acid transport [24], along with intestinal cholesterol transporters[25], are associated with a greater risk of gallstone disease.

Obesity

Obesity (body mass index [BMI] >30 kg/m^2) is related with an increased risk of developing gallbladder cancer. Particularly centripetal obesity, is a well-known risk factor for gallstone disease[17]. Between 15-30% of morbidly obese individuals have evidence of gallstone disease. Also, rapid weight loss is thought to contribute to gallstone formation, through the mobilization of cholesterol from tissue storage and deposition in the bile, adding to the cholesterol saturation[26].

Gallstones

A history of gallstone disease is the strongest risk factor for gallbladder cancer, with a relative risk of 4.9 [16]. Among patients with gallbladder cancer, 70–90% have a history of cholelithiasis[27]. The role of gallstones in development of gallbladder cancer is uncertain[28]. Chronic inflammation, due to chronic mucosal irritation by the gallstone and local production of carcinogens is thought to lead to development of metaplasia/hyperplasia, dysplasia and finally carcinoma[29]. Gallstones >3 cm bring a tenfold increased risk for gallbladder cancer compared to smaller stones[30].

Also, the duration of gallstone disease has an impact on the risk of developing cancer[31].

Gallbladder polyps

Gallbladder polyps are found on ultrasound in in 4-7% of examined patients[32, 33]. In patients undergoing surgery after ultrasound detected polyps, malignant or potentially malignant histology was seen in 3.7%[34]. Gallbladder polyps can become malignant over many decades, but their malignant potential is debated. Polyps ≥10mm in diameter are associated with cancer and a prophylactic cholecystectomy is recommended, as well as in patients with sessile polyps and if increased polyp size ≥2mm between radiologic exams[35]. In patients with polyps <10 mm in diameter, ultrasound imaging is recommended for at least 2 years until stability regarding the size of the polyp is documented[36].

Chronic inflammation

Prolonged inflammation is a major factor in carcinogenesis, causing DNA damage, tissue proliferation, release of cytokine and growth factors and consequently, predisposing cells to oncogenic transformation. Chronic inflammation can also contribute to deposition of calcium in the gallbladder wall, causing "porcelain gallbladder". Also, primary sclerosing cholangitis (PSC) is associated with a higher incidence of gallbladder cancer, due to chronic inflammation, supporting the metaplasia–dysplasia–carcinoma sequence[18].

Porcelain gallbladder

Porcelain gallbladder (PGB) is a condition where the inner gallbladder wall is coated with calcium. The gallbladder wall becomes thickened, hard and takes on a blueish tone. Most patients are asymptomatic and the condition is usually found on X-ray or CT scan as an incidental finding[37].

In a review published by Khan et al[38], PGB occurred in 0.2% of patients undergoing cholecystectomy, which is in line with previous studies[37]. The condition occurs more often in women and in patients over the age of 60 years. Gallstones are present in 95% of the patients with PGB. The role of PGB in the risk of developing gallbladder cancer has been debated and the risk is thought to be at a lower rate than previously valued, approximately 7%. It has been shown that the development of gallbladder cancer depends on the pattern of calcification, where a more selective mucosal calcification leads to a significant risk of cancer, while a diffuse intramural calcification does not[39]. Patients presented with symptoms and complications of

gallbladder disease should be recommended a cholecystectomy, as well as patients with selective mucosal calcification. Treatment recommendations for asymptomatic patients with complete intramural calcification are still under debate and patients age and comorbidities should be considered[40]. In Sweden, cholecystectomy is recommended for all types of PGB, if the patient is fit for surgery[41].

Primary sclerosing cholangitis

PSC is associated with an increased risk of gallbladder cancer[42], and prophylactic cholecystectomy is recommended in all PSC patients with gallbladder polyps regardless of the size of the polyp. However, most gallbladder polyps in PSC patients are benign, as shown by van Erp et al[43]. In their material, the gallbladder cancer rate was 8.8 per 1000 person-years in PSC patients with a radiologically detected gallbladder polyp.

In PSC patients, as well as in the general population, gallbladder cancer was correlated to interval growth of the polyp, mass lesion on preoperative imagining and polyp size ≥10mm[43]. In a study by Said et al[44] a gallbladder mass lesion with a mean size of 21 (± 9) mm was found in 6% of PSC patients and gallbladder cancer was found in 56% of these patients.

Chronic infection

The high rates of gallbladder cancer in South America and Asia have been partly attributed to high rates of *Salmonella typhi*, *Salmonella paratypi*, *Helicobacter bilis* and *Helicobacter pylori* infection. However, the studies on this topic have been of varying quality with small cohorts, unwell matched controls, and with a lack of standardized diagnostic methods[16].

Adenomyomatosis

Adenomyomatosis (ADM) of the gallbladder is a benign condition that can mimic gallbladder cancer on preoperative imagining. It is characterized by mucosal epithelium hypertrophy and muscularis forming called Rokitansky-Aschoff sinuses [45]. Three forms of ADM are present; segmental, fundal and more rarely diffuse [46]. Prophylactic cholecystectomy is not recommended in patients with asymptomatic ADM if the radiological diagnosis is certain[45, 47]. However, there have been cases of gallbladder cancer associated with ADM[48, 49,50]. Another study, presented an association with gallbladder cancer only in patients with segmental ADM[51]. There are no universal guidelines of how to manage ADM. In patients with symptomatic ADM, cholecystectomy should be offered[45].

Mirizzi syndrome

Mirizzi syndrome is an external bile duct compression syndrome, due to gallstone in the infundibulum or cystic duct leading to obstruction and intermittent or consistent jaundice. Cholecystectomy is the treatment of choice. The extent of surgery is highly depending on the subtype of the syndrome[52]. In some cases a cholecystocholedochal fistula may be present; Mirizzi syndrome type II-IV[53]. The presence of a fistula and the distorted anatomy predisposes for bile duct injury during cholecystectomy[54]. The surgical method is usually an incision in the gallbladder fundus and removal of the obstructed gallstone. Then, a careful dissection of biliary structures should be performed, identifying the common bile duct. Sometimes a perioperative ERCP is warranted. The type and location of the fistula should be defined and the defect repaired. In some cases, a hepaticojejunostomy must be established[55, 56]. There is a higher prevalence of coincidental gallbladder cancer and Mirizzi syndrome, compared to patients with uncomplicated gallstone disease. In a study by Schafer et al[57], gallbladder cancer was found in 11% of the patients with Mirizzi syndrome.

Choledochal cysts

Choledochal cysts are congenital cystic dilations of the biliary tract, when symptomatic usually presented in infants and young children[58, 59]. In a western population the incidence is 1/100 000 -150 000, with a higher incidence in East Asia[59]. Five types of choledochal cysts are described according to the Todani classification[60]. The etiology of choledochal cysts is not fully known, but anomalous pancreaticobiliary duct junction is seen in up to 87% of these patients[61-63], especially in Todani type I and IV[64]. The presented symptoms are usually abdominal pain, jaundice and right upper quadrant mass[65]. The presence of biliary malignancy is seen in around 10% of choledochal cysts[66], with a higher risk of malignancy in Todani type I, IV and V[67, 68]. In a review by Sastry et al[69], 24% of all biliary tract malignancies due to choledochal cysts were gallbladder cancer. The management of type I and IV cysts is cholecystectomy and total extrahepatic bile duct cyst excision with Roux-en-Y hepaticojejunostomy[62]. Symptomatic type V cysts are treated with liver resection if unilobular, but require liver transplantation if bilobular[70].

Anomalous pancreaticobiliary duct junction

In this rare congenital anomaly, the pancreatic and biliary ducts join outside the duodenal wall and form an abnormally long channel that lies beyond the sphincter of Oddi[71]. Sphincter of Oddi has no function in this case, meaning that pancreatic secretions can passage into the biliary system and the gallbladder, leading to malignant changes in the mucosa. Anomalous pancreaticobiliary duct junction can

be divided into two types; congenital biliary dilatation and without biliary dilatation[72].

Biliary tract cancers develop about 15–20 years earlier in this patient category (mean age, 50–60 years) than in the general population[73]. Previously, anomalous pancreaticobiliary duct junction associated gallbladder cancer was thought to be more common in Asia. However, the same prevalence seems to occur in the West, but tends to be undiagnosed. Anomalous pancreaticobiliary duct junction was present in 8% of all gallbladder cancer cases[74]. Prophylactic cholecystectomy is recommended for patients with anomalous pancreaticobiliary duct junction[75].

Histopathology

Gallbladder cancer can be difficult to diagnose macroscopically, especially in a situation with a thick gallbladder wall due to cholecystitis. The cancer may present in different ways on gross examination; as a mass lesion, localized wall thickening with induration of the wall and polypoidal growth. A neoplasm in the body may also constrict the lateral wall, causing an hour-glass deformity. The colour of these lesions is typically grey-white, while mucinous and signet ring lesions are presented with a gelatinous cut surface[27].

The most common histologic type of gallbladder cancer is adenocarcinoma not otherwise specified. Yadav et al[76], found adenocarcinoma in 87% of clinically or radiologically suspected gallbladder cancer cases, after fine needle aspiration of the gallbladder.

Different subtypes of Gallbladder Cancer

Papillary Adenocarcinoma may present as invasive and noninvasive. Histologically, malignant epithelial cells are seen, with a production of mucin in the gallbladder. Noninvasive papillary tumors grow in an intraluminal way, filling the gallbladder, usually without locoregional invasion. They are usually associated with a better prognosis than other adenocarcinoma subtypes of the gallbladder. Regardless of size and degree of differentiation, they do not metastasize and are usually treated with a simple cholecystectomy. In contrast, invasive papillary adenocarcinoma has a prognosis similar to other invasive types of adenocarcinoma of the gallbladder[77].

Mucinous Adenocarcinoma is defined as adenocarcinoma with >50% stromal mucin deposition and typically presents as a suspected acute cholecystitis[78].

Squamous/Adenosquamous Cell Carcinoma usually presents with a rapid and aggressive growth[79]. There is a lack of definition in the literature outlining the extent of squamous differentiation required to categorize the tumor as adenosquamous carcinoma and not as adenocarcinoma[80].

Small cell carcinoma is associated with paraneoplastic syndromes, like Cushing's syndrome and sensory neuropathy[81].

Hepatoid Adenocarcinoma typically has foci of both adenomatous differentiation and hepatocellular differentiation. They may also express alpha-fetoprotein, which is an important marker, but not all hepatoid adenocarcinomas are positive. Also, these tumors must be separated from hepatocellular carcinoma invasion into the gallbladder[82].

Clear Cell Adenocarcinoma presents with an infiltrative growth pattern and should be differentiated from a metastasis most commonly from Renal Cell Carcinoma[83].

Signet Ring Cell Carcinomas shows characteristically intracellular mucin containing cells, with nuclei pushed to periphery, with an infiltrative submucosal growth pattern[76].

Cribriform Carcinoma with histopathological features, similar to mammary gland cribriform carcinoma. The lack of estrogen and progesterone receptor immunoreactivity helps to differentiate from metastatic breast lesion[84].

Neuroendocrine Tumors are thought to originate from multipotent stem cells, as normal gallbladder mucosa does not contain neuroendocrine cells. Less than 1% of the patients show symptoms of carcinoid syndrome. The tumor is usually identified at an advanced stage, with a 5-year reported survival rate of ~20% [85].

Other extremely rare tumors of the gallbladder are *Undifferentiated Carcinoma,* including different subgroups such as spindle and giant cell type[86], and *Gallbladder Sarcoma* which are very aggressive tumors[87], with different subtypes including leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, Kaposi's sarcoma and liposarcoma[86].

American Joint Committee on Cancer staging system

A strong predictor of patient survival is tumor stage, figure 3 and figure 4, usually presented according to the American Joint Committee on Cancer (AJCC) staging system[88, 89].

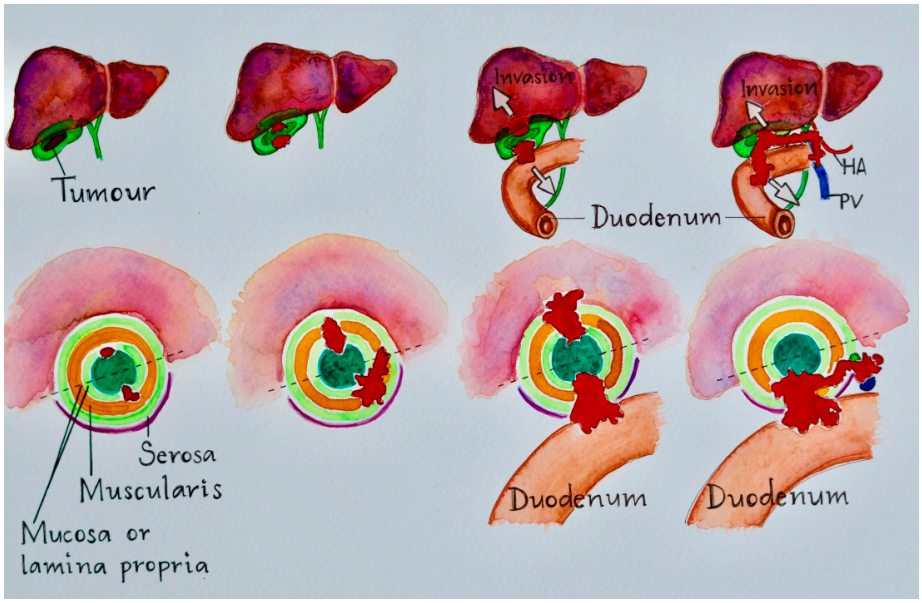


Figure 3. Gallbladder cancer pT-stage based on AJCC 8th edition.
Illustrated in relation to the gallbladder wall, liver and nearby structures. Above from the left: Tis or T1, T2: restricted to the gallbladder, T3: hepatic or organ invasion, T4: PV or HA or invasion of two organs. Lower part; cross section of the gallbladder. From left T1a and T1b, T2b and T2a, T3 and T4. PV; portal vein, HA; hepatic artery. Illustrations by Isabella Hylin and photographed by Michael Gartner.

The AJCC staging manual is based on T; defined as the local tumor growth in the primary organ, N; involvement of the lymph nodes and M; metastases. Further, these categories are grouped into stages.

The AJCC staging manual is update continually, the 6th edition was published in 2002[90]. In 2010 an updated 7th edition, that distinguishes between hilar (N1) and other regional nodes (N2) was released[91]. Also, the stage definition was modified to better correlate to surgical resectability. The 8th edition was released in 2017[92].

In the 8th edition of AJCC[93], T2 cancers are stratified depending on the location of the tumor on the peritoneal or hepatic side. This implementation is based on a study[94] of 252 patients with T2 disease, with worse OS in patients with curative intended surgery with hepatic side tumors, compared to patients with peritoneal side tumors (3-year and 5-year survival rates: 52% and 43%, respectively, for hepatic

side tumors and 74% and 65%, respectively, for peritoneal side tumors). The difference in prognosis may also be explained by the larger vessel and lymphatic drainage on the hepatic side of the gallbladder. After radical surgery, a higher recurrence in the liver and distant lymph nodes was noted in T2b patients[94-96].

In addition to the change on T2 tumors, the 8th edition of AJCC also includes a change in the staging groups for Stage II to Stage IIA (T2a) and Stage IIB (T2b). Further, the N-status was updated to N1 ("one to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes") and N2 ("four or more positive lymph nodes from the sites described for N1")[93].

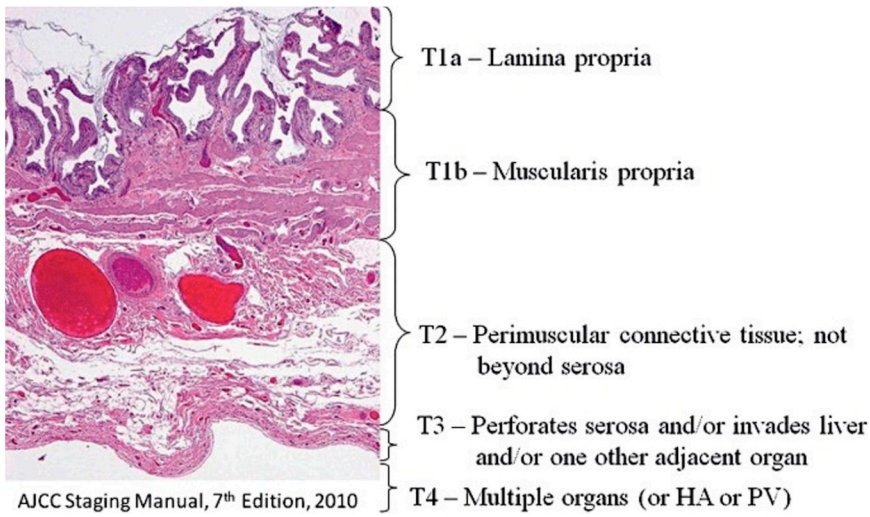


Figure 4. Histological illustration of different layers of the gallbladder with matching pT-stages in gallbladder cancer. HA Hepatic artery and PV Portal vein.
Reprinted with permission from Springer[97].

Lymphoma and metastasis of the gallbladder

Lymphoma of the gallbladder may be suspected when no typical signs of gallbladder cancer are present clinically. When a tumor in the gallbladder is noted on CT scan, with enlarged lymph nodes in the retropancreatic area and usually with a discrepancy between imaging findings and the patient's mild symptoms[98, 99]. Lymphoma of the gallbladder is extremely rare and is reported to occur as a primary tumor of the gallbladder in 0.1-0.2 of the cases[99]. MALT lymphoma represents approximately 40%[99, 100] of these cases and when isolated to the gallbladder, usually cholecystectomy is the curative treatment[100].

Metastasis to the gallbladder appear in 4.8% of all gallbladder malignancies in a study presented by Yoon et al[101], most commonly originating from primary tumors of malignant melanoma, stomach, pancreas, ovaries, bile ducts, colon, kidney and breast[101, 102].

Incidental Gallbladder Cancer

A patient with IGBC has undergone an elective cholecystectomy for a supposed benign disease. In previous studies, the majority of gallbladder cancer cases are found incidentally. These studies are often based on data from liver centers, where patients are referred to when surgical treatment is already planned[103]. The incidence is lower (20-50%) in studies based on data from hospitals performing cholecystectomies for benign indications[104-106]. In the case of IGBC, most patients are found to have pT2 disease (47%) followed by pT3 (25%) and pT1(23%)[103]. Usually information on pN status is missing, however, sometimes the cystic lymph node is included in the specimen [107, 108]. The histopathological evaluation of a routine gallbladder specimen should include the microscopic inspection of at least three sections of the gallbladder; the fundus, corpus, collum and the cystic duct margin. Specimens with dysplasia or malignancy should be more extensively examined[109].

When the histopathological diagnosis turns out to be IGBC, the patient should be referred to a HPB center for a multidisciplinary discussion concerning further treatment[41]. The histopathological report is often reviewed and additional imaging (CT of thorax and abdomen and often MRI of the liver) is performed[110]. PET-CT is considered if advanced disease is seen on the histopathological analysis or disseminated diseases is suspected[111].

Treatment recommendations

Treatment recommendations are based on TNM stage[93].

Tis and T1a tumors, since only invading the mucosa and not the muscularis, are considered to be cured with a simple cholecystectomy[112, 113] and estimated 5 year survival in T1a IGBC is up to 100%[4]. In a review by Lee et al[112], among 706 T1a gallbladder cancer patients, lymph node metastases were present in 1.8% of the cases and totally 1.1% of the patients died of recurrent gallbladder cancer. In a large study based on the SEER database[113], no benefit in DSS in T1a gallbladder cancer patients was seen with more extensive surgery (cholecystectomy and lymph node dissection or wedge resection) compared to patients treated with cholecystectomy alone.

For T1b tumors, with the invasion of the gallbladder muscle wall, and pT-stages above, there is a risk of residual disease in the liver and regional lymph nodes. Numerous multicenter studies show survival advantages with resection/reresection in T1b-T3 patients[106, 109, 114].

Surgical resection is considered only when a radical resection is thought to be possible[94]. R0 resection includes complete resection with macroscopical and microscopical negative margins. R1 resection is defined as macroscopic negative resection margins, but positive microscopical resection margins. R2 resection means both macroscopical and microscopical positive resection margins[115].

Time to reresection is affected by many logistic factors like additional histopathological and preoperative imaging, multidisciplinary meetings and surgical availability. In median 2 months between cholecystectomy and reresection was seen in a study by Barreto et al[116], which is in line with other studies[117-119]. The best outcome in median overall survival was seen with reresection at 4-8 weeks after index cholecystectomy[109, 119].

Surgical management

The usual surgical strategy is resection of the liver around the gallbladder fossa, involving wedge resection or resection of segment IVB/V, including lymphadenectomy of regional nodes, figure 5, including portal, gastrohepatic ligament, retroduodenal nodes and sometimes together with the evaluation of the aortocaval nodal basin[109, 120]. In some cases, more extensive liver and extrahepatic bile duct resections are required to achieve R0 resection[94, 121]. The extent of liver resection or lymphadenectomy is usually dependent on the intraoperative findings[94]. Lymphadenectomy provides a more accurate pathological staging and is a prognostic factor[113, 122]. Six lymph nodes are considered as a minimum for appropriate staging, however usually fewer lymph nodes are collected. Ito et al [123] showed that the median total lymph node count after resection was 3 (range 0-20). Bile duct resection, since associated with increased morbidity and does not increase the number of lymph nodes retrieved, is only recommended to achieve R0 resection. Intraoperative frozen section of the cystic duct, when positive, is a significant factor for the decision of bile duct resection[124]. Presence of malignancy in the resected cystic duct margin is showed to be a negative prognostic factor, even if residual disease is not present[125]. In patients with suspected peritoneal metastasis on preoperative imagining, a staging laparoscopy might be considered[126, 127].

Figure 5. The segments of the liver and lymph nodes along the choledochal duct.
Illustration by Isabella Hylin and photographed by Michael Gartner.

In recent years, numerous studies have shown comparable results of minimal invasive surgery to open surgery in patients with gallbladder cancer[128, 129]. There is a possibility to avoid unnecessary invasive procedures, but there is a difficulty in selecting suited patients, due to the difficulty of distinguishing between benign and malignant tumors and of defining wall depth invasion with preoperative imaging. Staging laparoscopy, laparoscopic ultrasonography and intraoperative pathological diagnosis may help to select the most suitable patient and technique[128, 129].

A review by Zhang et al[130] showed that the safety and effectiveness of laparoscopy in patients with gallbladder cancer is comparable with open surgery. In the laparoscopic group, significantly reduced intraoperative bleeding, time in surgery, hospitalization time and improved 1-year overall survival was seen, with no difference in morbidity and mortality rates. R0 resection, number of retrieved lymph nodes, 5-year recurrence-free survival and 5-year overall survival was comparable between the groups. Vega et al[131] showed similar results with laparoscopic reresection in IGBC patients, suggesting this procedure as a possible approach in selected patients. Robotic surgery show similar results to laparoscopy[132-134].

T1b

There are some split opinions in the literature concerning reresection in T1b patients. A large multicenter study from South Korea[135], along with other studies[136-140], showed no difference in overall survival in re-resected T1b patients compared to cholecystectomy alone. The results on survival, 5 year DSS 85%, presented by Lee et al[135] were regardless of if lymph node dissection was performed or whether lymph node metastasis were present. Further, Yoon et al[137] showed that recurrence was associated with simple cholecystectomy and incomplete lymph node dissection. However, these results did not have an impact on 5-year overall survival.

In contrast, two large studies by Kohn et al[141] and Xu et al[138] showed improved survival with lymphadenectomy in T1b patients. Further, from the SEER registry, it was found that reresection is associated with improved DSS and OS in T1b and not in T1a patients[113].

Wang et al[142] showed that pT1b patients with tumor size less than 1cm in diameter had no lymph node metastasis, whereas 14% of patients with larger tumor size were presented with lymph node metastasis. Concluding that simple cholecystectomy may be adequate treatment in patients with tumor size less than 1cm in diameter. In T1b patients up to 15% have nodal metastasis and concerning the benefits of adjuvant chemotherapy for lymph node positive gallbladder cancer[143, 144], failure to perform radical cholecystectomy and lymphadenectomy may lead to incomplete staging and under-treatment of T1b gallbladder cancer patients.

T2

There is a consensus regarding extended surgery with lymphadenectomy in T2, yet with the introduced subdivision into T2a and T2b, figure 6, the need for reresection in selected T2a patients has been questioned[145]. Estimated 5-year survival in IGBC T2a patients is 40-75% and in T2 b 28-50%[4]. In pT2, the tumor is not invading beyond serosa and theoretically, in T2b IGBC patients the subserosal plane has been disturbed during index cholecystectomy and there is also a risk of bile spillage when compared to one stage resection[94, 146]. Therefore, surgical management for T2 IGBC is an important question that can affect survival outcomes.

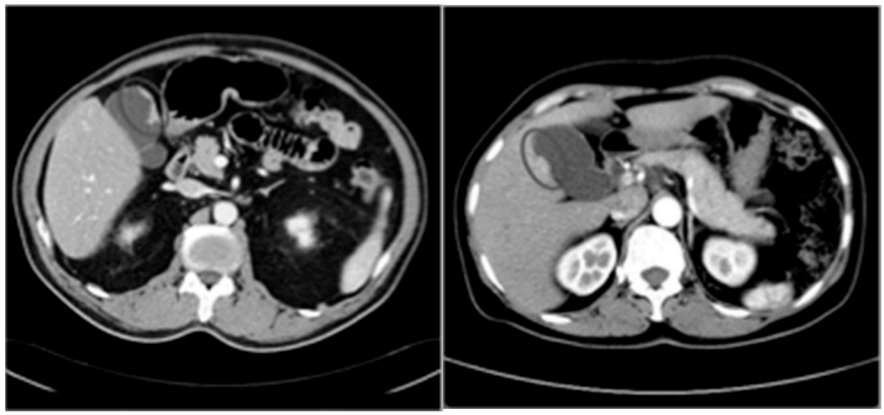


Figure 6. CT scan of peritoneal side (left) and liver side (right) gallbladder cancer.
Reprinted with permission from *Gut and liver*[147].

T3 and T4

Survival outcomes after curative resection of gallbladder cancer are highly dependent on the depth of tumor invasion through the gallbladder wall[94, 148]. Patients with T3 and T4 tumors (tumor invading beyond the serosa) have 5-year survival rates of 19% and 14%, respectively[149]. Extended surgery may be required for curative resection in pT3/pT4 patients, including vascular resection and reconstruction. Despite surgery, the prognosis after resection is extremely poor for these patients. Also, the high risk of postoperative complications decreases the chances of receiving adjuvant chemotherapy[150]. Further, Sahara et al[151] showed that lymph node dissection has a limited value in patients with pT4 or CA19-9 ≥200. These patients are likely to have micro-metastases and should be considered to have a systemic disease and over-invasive surgery should be avoided.

Perforation of the gallbladder

Accidental perforation of the gallbladder during index cholecystectomy has been showed to be a negative prognostic factor with increased risk of peritoneal carcinomatosis, and patients with bile spillage were less likely to undergo reresection. Also, shorter disease free survival was seen in these patients[8]. A higher recurrence rate was also shown by Goetze et al[152]; 38% in patients with accidental perforation *versus* 27% with no perforation. And a lower survival rate was seen in the same patient category in a Japanese survey[153].

Residual disease

Residual disease in patients with gallbladder cancer refers to recurrent or remaining tumoral growth in the gallbladder fossa, hepatoduodenal ligament or lymph nodes[154]. Residual disease is a strong negative predictor for disease free and disease specific survival and was reported in 54% of IGBC patients at reresection. No difference in DSS was seen, depending on the anatomical location of the residual site. pT-stage at index cholecystectomy was shown to be an independent predictive factor of residual disease[155]. The incidence of residual disease may be as high as 38% in pT1, 57% in pT2 and 77% in pT3[107].

Chemotherapy

In systemic trials of chemotherapy, gallbladder cancer has been included along with other biliary tract cancers, but when it comes to targeted- and immunotherapy the genetic differences must be taken into consideration. *HER2/neu*, DNA repair gene aberrations and *PI3-kinase* genetic alterations have been identified as potential areas of treatment in gallbladder cancer, which may result in a paradigm shift of treatment for this disease[156-159].

Neoadjuvant chemotherapy could be considered in patients with preoperatively staged T3 or T4 N1 disease[109]. However, Hakeem et al[160] conclude that there is insufficient data to support the routine use of neoadjuvant chemotherapy or chemoradiotherapy in advanced gallbladder cancer. In their review, neoadjuvant chemotherapy benefited a third of the whole cohort in patients who eventually achieved a R0 resection.

BILCAP[161] a randomised, controlled, multicenter, phase III study suggests Capecitabine as adjuvant chemotherapy as standard of care in patients with resected biliary tract cancer. In total, 447 patients with biliary tract cancer resected with curative intent were enrolled; 223 patients were randomly assigned to the Capecitabine group and 224 to the observation group. In the intention to treat group, median overall survival was 51 months in the Capecitabine group compared to 36 months in the observation group, HR 0.81, 95% CI 0.63-1.04, p=0.097. Although this study did not meet its primary endpoint of improving overall survival in the intention-to-treat population, when adjusting for nodal status, grade and sex, the overall survival HR was 0.71 (95% CI 0.55-0.92, p=0.010) and further subgroup analysis showed significant results on improved overall survival.

Adjuvant chemotherapy in case of R0 resection should be considered in T2-4 disease with pN1 gallbladder cancer. Patients with resected gallbladder cancer with positive margins could also be candidates for adjuvant chemoradiotherapy[109].

During the last years, many centers, including in Sweden, offer patients with gallbladder cancer adjuvant chemotherapy when the histopathological diagnosis is pT1bN0 and above. If Capecitabine is not tolerated, single Gemcitabine is an option.

Risk score models

Several risk score models have been created in the field of benign and malignant gallbladder surgery[162, 163]. Ethun et al[164] has developed a risk score model to predict locoregional and distant residual disease at reresection in IGBC patients to estimate overall survival. Advanced T-stage, grade, lymphovascular and perineural invasion were all associated with increased rates of locoregional and distant residual disease, followed by decreased overall survival. A validated nomogram to predict distant disease in T1 and T2 patients was presented in a recent study based on the large SEERs database and showed that younger age, high pathological grade, non-adenomcarcinoma, T1N1 and larger tumor size was associated with the risk of distant metastasis[162]. Baramgoudar et al[163] published a validated risk score model to predict prolonged operative time in patients undergoing cholecystectomy on benign indication.

Higuchi et al[165], reviewed patients with pT3/4 gallbladder cancer to identify poor prognostic factors that could be preoperatively diagnosed. With the intention of implementation of new treatment strategies, such as neoadjuvant chemotherapy for selected patients. Liver invasion ≥5 mm, invasion of the left margin or invasion of the hepatoduodenal ligament and ≥4 regional lymph node metastases were found to be negative prognostic factors. Five-year overall survival was 54% for patients with no negative prognostic factors, 34% for one factor and 4% for two factors.

Yamamoto et al[166] found CA19-9 values ≥250 U/mL in stage II-IV patients to be an independent prognostic factor for surgical outcome, proven to be equivalent to that of non-resected patients and that the indication for surgery in these patients should be taken into consideration.

Sahara et al[167], developed a validated gallbladder cancer recurrence risk score, available online, to determine early recurrence (within 12 months) after curative intended surgery. After registering preoperative CA19-9, surgical procedure, T stage, and histological grade, the patient is assigned a risk group from low to high risk of developing early recurrence.

Registries

Valuation of the quality and monitoring of the surgical procedures that are performed in Sweden has become more important over the last decades, and more than 100 national quality registers have been established[168]. These registries receive public funding from the Swedish Association of Local Authorities and Regions and are the main source of information regarding the quality of healthcare in Sweden[169].

When working with registry data, some definitions need to be clarified;

The **target population** in a registry is the population that fulfils the inclusion criteria and are intended to be included in the registry. The definition of the target populations is important since it reflects the aim of the registry. To define the target population inclusion and exclusion criteria must also be defined.

The **coverage** ("anslutningsgrad" in Swedish) represents the proportion of the target population covered by the registry. In a national registry, coverage reflects the units in the country that treat patients, that fulfil the inclusion criteria and are connected to the registry.

The **completeness** ("täckningsgrad" in Swedish) of a registry is defined by the number of individuals that fulfil the criteria to be included in the registry and are actually registered. A registry may have a high coverage but a low completeness. However, when the opposite is present, with high completeness the coverage is always high. Under-coverage is present when the observations from a registry population are too few compared to the actual amount of observations[170].

Data **validity** in a registry represents the extent of the input data being correct according to the source. Logic controls are used in registries to maintain validity. Logic controls in a registry are mandatory fields and values must be entered within established limits. Registries are usually validated by individuals that visit different units and compare input data to the source, usually medical records[170]. Data validation can also be performed by cross-linkage to other registries for example the Swedish National patient registry[171].

Reliability indicates the precision of a measured method. A precise measured method should give the same result when a measurement is done at different time intervals if the measured object has not changed. Data with deficient reliability leads to misleading results and may lead to misclassification bias[170].

Timeliness is defined as the time between the procedure and the registration. Usually, registration date is mandatory in a registry. The input data may contain misguided information if long time passes from the date of the procedure to the date of registration[170].

Comparability is the possibility for the registry data to be compared to registry data in other registries. It requires that the inclusion criteria are similar if not identical and that the definition of variables are the same and national or international criteria concerning e.g. diagnosis or performance status are used[170].

A registry usually changes over time and **variables** may change over time. When changes are being made, a documentation should be made to track these changes. Changes of a variable may include new inclusion or exclusion criteria, a new definition of a variable and new alternatives for a multi-choice variable. When defining a variable through golden standard the possibility of crosslinking with other registries increases if the variables are defined in the same way[170].

National Quality Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography

GallRiks, founded in 2005, is an intervention registry, including cholecystectomies (laparoscopic or open) and endoscopic retrograde cholangiopancreatography (ERCP). Additional variables concerning the histological examination of the gallbladder were added in 2007. The members of the GallRiks board are given their assignment from the Swedish Surgical Society. GallRiks is web-based, and the surgeon responsible for the procedure reports patient characteristics, indications for operation, surgical method, and intraoperative complications into a secure website. The response to the questions is mandatory. Also, a mandatory 30-day follow-up is performed by a non-physician coordinator at each participating hospital. The information is collected from medical records or as telephone interview with the patient. GallRiks consists of 466 pre-, intra-, and postoperative variables[172]. All participating surgeons can get immediate access to personal and local reports compared with nation-based results. These results are analyzed and the results are published online once a year[173].

Annually, approximately 14 200 cholecystectomies and 9 600 ERCPs are registered. The aims of the registry are to contribute to evidence-based management of gallstone disease, concerning surgical indication and choice of surgical technique and to identify patient benefits of treatment for gallstone disease. Also, to enable early detection of surprising adverse effects of new methods, to support local quality assurance for gallstone surgery and to contribute to increased knowledge on gallstone disease and its treatment[2].

In 2014 Rystedt et al[174], studied the completeness and correctness of entered data for cholecystectomies in GallRiks. In total 83% of the cholecystectomies were registered in GallRiks since the beginning of the registry and it was shown that the coverage increased over time. By two random samples the entries were found to be correct in 97% and 98% cases, respectively and 100% correctness for entered data

concerning bile duct injuries was seen. These results confirm that GallRiks qualifies as a reliable data source and enables scientific studies to be done.

All hospitals that register in GallRiks are being inspected every 3-years, on-site, by an appointed senior surgeon. The main purpose of the visit is to validate register data and provide support to the local surgeons and coordinator, and to become aware of the difficulties and ensure that adequate resources are assigned for this task. It is shown by Fine et al[175] that it is possible to improve the quality of a database by monitoring, independent validation and feedback.

It is not compulsory to register in GallRiks, however it is expected that all units that perform cholecystectomies participate. The national quality registries enable unique opportunities for studies to be performed on large prospectively collected data and this opportunity should be seized by our profession.

The National Quality Registry for Liver, Bile Duct and Gallbladder Cancer

SweLiv is the Swedish National Quality Registry for Liver, Bile Duct and Gallbladder Cancer. It was founded in 2008. All patients ≥16 years of age with primary tumors in the liver, gallbladder or bile ducts are registered. The registry consists of different chronological forms online; the first form consists of registration of the diagnosis, the second form includes tumor intervention and the last comprise complications and histopathological diagnosis[176].

The tumor intervention form includes information regarding the surgical procedure of gallbladder and bile duct cancers, as well as surgical or ablative interventions of primary and secondary tumors of the liver[176].

The variables contain detailed information regarding the patient (e.g. age, sex, performance status), tumor (e.g. date of diagnosis, way of diagnosis, TNM (for primary tumors), purpose of treatment; curative intent or palliation), intervention (e.g. date of surgery, type of surgical procedure) and the follow up (final histopathological diagnosis and complications)[176].

The registry was last validated 2014, and registered data was compared to source data through medical records at all six HPB centers in Sweden[177]. Yearly national reports with open access are published online[19]. Several studies have been published using SweLiv as a source.

Aims of the thesis

The overall aim of this thesis is to optimize preoperative treatment strategies for patients with gallbladder cancer, with a focus on incidentally diagnosed gallbladder cancer.

† To identify preoperative predictors of IGBC in patients treated with cholecystectomy for benign indication. To investigate the surgeons' intraoperative evaluation of the gallbladder and see if a risk model for IGBC could be improved by adding this information.

† To construct and validate an additive risk score model to predict incidental gallbladder cancer in patients scheduled for cholecystectomy for benign gallbladder disease.

† To identify and characterize rare incidentally diagnosed malignancies of the gallbladder and describe the diagnostic work-up, treatment and outcome in patients identified from a national registry for gallstone surgery.

† To assess the national cohort of patients with incidental gallbladder cancer in Sweden over a 10-year period, and to undertake a detailed analysis of management and survival outcomes.

† To analyze overall survival concerning different surgical treatment strategies in all IGBC patients, that either undergo cholecystectomy as the only procedure or are subjected for further surgery, compared to preoperatively suspected GBC patients that undergo surgery and to make the same comparison with the IGBC SC group excluded.

Methods

Study population

In paper I, all cholecystectomies registered in GallRiks during the study period were evaluated for inclusion in the study. Reasons for exclusion were; gallbladder not sent for histopathologic examination, cholecystectomy performed for other indication than gallbladder disease, if the indication for surgery was secondary to other major procedure or performed on the preoperative suspicion of GBC/gallbladder polyps and if the registered malignancy was not gallbladder cancer. Intraoperative suspicion of gallbladder cancer was not an exclusion criterion.

In paper II, the same cohort as in paper I was used as the derivation cohort. For the validation cohort, patients with the same inclusion and exclusion criteria as in paper I, but from a later period were included.

In paper III, the primary study group was patients with metastasis or lymphoma in the gallbladder retrieved from GallRiks. Except for this inclusion, the same exclusion criteria were used as in paper I. Surgical and oncological charts were collected from each hospital for these patients. This group was compared to IGBC patients and patients with benign histopathological outcome, identified in paper I.

In paper IV, IGBC patients were identified through GallRiks during the same study period as in paper I and II.

In paper V, IGBC and GBC patients were identified through SweLiv, and the registry was crosslinked with GallRiks to ensure inclusion of IGBC patients. Only the actual procedure concerning GBC was included. Patients with cholecystectomies performed as part of another procedure and if the registration was inconclusive concerning the primary diagnosis were excluded. Patients diagnosed with pT0, pTis, pT1a, pT4 and pTX were excluded from survival analysis, as well as patients with preoperatively known M1 status. The intention to treat analyses included all surgical attempts, also cases where no resection could be performed. In survival analysis concerning curative surgery patients with R2 and peroperatively found metastases were excluded.

Study design and data collection

In the present thesis, retrospective cohort studies have been performed.

Observational research is used when the studied exposure cannot be randomized. Cohort studies are either retrospective or prospective, and collect a group that share a central characteristic[178]. In our studies, data was collected retrospectively from registries and the defining characteristic was GBC or IGBC.

In paper I, II (derivation cohort) and III, data concerning cholecystectomies, was retrieved from GallRiks between January 2007 and September 2014. Data was linked with SweLiv and/or the Swedish Cancer Registry, for completion of the TNM classification. When TNM classification remained incomplete, the pathology report was retrieved.

In paper II, two cohorts were created; a derivation cohort and a validation cohort. For the validation cohort, patients from GallRiks, with the same inclusion criteria as in paper I, registered between October 2014 and November 2016 were included.

In paper IV, cholecystectomies registered in GallRiks between 1 January 2007 and 30 November 2016 were analyzed. Patient data were cross-linked to the National Board of Health and Welfare Cancer Registry if the histology report noted cancer or was incomplete. The TNM stage was retrieved from the Cancer Registry or by evaluation of the original pathology report. All IGBC cases were cross-linked to SweLiv for certain variables presented in the study. Since SweLiv was fully established one year later after the start in 2008, the variable data from 2007 until 2008 was retrieved from medical records for patients registered in GallRiks during this time. Data was grouped into two equal periods to evaluate changes over time.

In paper V, data from SweLiv between 2009 and 2019 was collected and crosslinked with GallRiks between 2009 and 2016. The GallRiks data for this period was available from paper IV and unfortunately not for the whole studied period. Also, seven IGBC patients registered in GallRiks, and not registered in SweLiv were included.

Statistical methods

Baseline characteristics were compared using the Mann-Whitney U tests, One Way ANOVA or Student t-tests for continuous variables, and the χ^2 test or Fisher exact tests for categorical variables.

In paper I, logistic regression was used in uni- and multivariable analysis. Clinically relevant predictors with less than 5% missing values were chosen as candidate

variables for the multivariable analysis. Forward and backwards stepwise selection was performed. The forwards stepwise selection begins with a model that contains no variables, and then starts by adding the most significant variables one after the other until a pre-specified stopping criteria (p>0.10) is reached or until all the variables under consideration are included in the model. The backwards elimination starts with all the variable under consideration (full model) and continues by removing the least significant variables one after the other until a pre-specified stopping criteria (p<0.10) is reached or until no variable is left in the model.

In a secondary analysis, the logistic regression method was used to test for possible interaction. For each identified interaction, we constructed a multiple dichotomous variable, representing the interaction, and recalibrated a separate model, including the multiple dichotomous variable and the same covariates as in the main effect model.

Odds ratios are presented with 95% confidence intervals. Predictive accuracy was assessed using the Hosmer-Lemeshow goodness-of-fit (HL) test. In a HL-test, the null hypothesis is defined by the model providing a good fit. The p-value is used to reject or not reject the null hypothesis. If the p-value is not significant the model is considered to provide a good fit. The area under receiver operating characteristic curves (AUROC) was used to illustrate the discriminatory power of the model. This plot has sensitivity (true positive rate) on the vertical axis and 1-specificity (the false positive rate) on the horizontal axis. A test producing a ROC curve that lays on diagonal from the origin, is a test with no discriminatory power and produces as many false positives as true positives[179, 180].

The Kaplan-Meier estimate of the survivor function was used to plot long-term survival and log rank test was used to compare the difference between the groups (paper I, III, IV and V). Log rank test is a non-parametric test that gives information on any difference in survival between two or more groups, at any point during the study period. A limitation of the log rank test is that it can only explore the influence of one variable on survival, meaning it does not eliminate the possibility of confounders.

In paper II, the independent risk variables from paper I were used to construct an additive risk score model based on odds radio. Logistic regression was used to recalibrate the model (including patients 40 years or older, divided in 10-year age interval groups). The model was further tested on a separate validation cohort.

The patients were divided, based on quartiles, into a low-risk group, intermediate-risk group and a high-risk group. The HL-test, was used to assess predictive accuracy and the AUROC was used to calculate the discriminatory power of the model.

In paper IV, survival was evaluated as DSS, measured from the date of diagnosis to the date of death from GBC or last follow-up. Patients with a cause of death other than GBC were censored at the date of death. Median follow-up was calculated by means of the reverse Kaplan Meier method. Univariable and multivariable Cox regression analyses were performed to analyze the effects of curative reresection in patients with pT2 and pT3 disease in the context of other clinically relevant variables, and to determine the prognostic significance of variables in patients undergoing curative reresection. Cox regression gives both estimates and confidence intervals for variables that affect survival and provides adjustment for confounders. The estimate is presented as a hazard ratio. The hazard ratio is a risk or probability of a clinical outcome, usually death, at any point during a defined time period.

In paper V, overall survival analysis concerning different surgical treatment strategies in IGBC SC patients and IGBC patients compared to GBC patients were performed. Overall survival was calculated from the date of diagnosis to the date of death of any cause or last follow up. Cox regression with uni- and multivariable analyses were performed for adjustment on survival concerning: GBC/IGBC, age, sex and N-status.

Ethics

The studies in this thesis were approved by the Regional Ethical Committee in Lund; Dnr: 2014/175 (paper I, II, III), Dnr: 2016/185 (paper III,) and the Regional Ethical Committee in Linköping; Dnr: 2014/39-31 and 2016/408-32 (paper IV and V).

Results

Paper I

A total of 36 355 patients were included in the analysis. Of these 215 patients were diagnosed with IGBC (0.59%). Patients in the IGBC group were older (70 ± 11 years vs 54 ± 16 years in the control group of benign patients) and were more often female (80% vs 60%). IGBC patients were more often scheduled for acute surgery (49% vs 39%), due to cholangitis or previous and ongoing cholecystitis, and more often in need of inpatient care. Injury to bile ducts was more common, as well as conversion to open surgery. Time in surgery was significantly longer in the IGBC group compared to the benign group. There was no significant difference in perforation of the gallbladder between the groups. Further, the use of antibiotics, reoperation, infection, and pancreatitis were more frequent in the IGBC group.

If the inspected gallbladder with gallstones showed signs of wall thickening, inflammation or obvious tumor, there was significantly increased risk of IGBC, OR 4.05 (95% CI: 2.31–7.10), $p<0.001$. Intraoperative suspicion of gallbladder cancer (n = 178) turned out to be gallbladder cancer in 31% (n=55) of the patients.

The distribution of the surgeons' suspicion of cancer divided by actual IGBC for each T-stage group was as follows: Tis 0/14, T1 5/42, T2 16/73, T3 20/51, T4 6/12, unknown histopathology 8/23. Gallbladder cancer diagnosis was *not* suspected during intraoperative inspection of the gallbladder in 160 IGBC cases. Nevertheless, only 14 (6.5%) of these specimens were considered to be macroscopically normal at the perioperative examination by the surgeon.

Acute cholecystitis was highly correlated to acute operation (r = 0.72). We evaluated acute cholecystitis to be more clinically relevant than acute surgery as a potential predictor for IGBC, and acute surgery was therefore not included in the multiple variable analysis.

Using the multivariable logistic regression method, we finally achieved five independent predictors for IGBC: age, sex, previous cholecystitis, acute cholecystitis without jaundice and jaundice without acute cholecystitis, table 1.

Table 1. Multivariable preoperative risk factors for IGBC.

Variable	OR	CI	P-value
Age	1.08	1.07–1.10	<.001
Female sex	3.58	2.55–5.02	<.001
Previous cholecystitis	1.37	1.01–1.87	.045
No jaundice* and No AC	1.00	Reference	
No jaundice* and AC	1.39	1.01–1.91	.041
Jaundice* and No AC	2.02	1.19–3.40	.009

*P-Bilirubin elevation (>50 mmol/L) and/or bile duct stones. AC, Acute cholecystitis.

Table 2. Multivariable risk factors for IGBC, preoperative factors and intraoperative evaluation of the gallbladder.

Variable	OR	CI	P-value
Preoperative risk variables			
Age	1.07	1.06–1.09	<.001
Female sex	3.50	2.46–4.96	<.001
No Jaundice and No AC	1.00	Reference	
Jaundice* and No AC	2.08	1.18–3.67	.011
Intraoperative risk variables			
Normal gallbladder with gallstones	1.00	Reference	
Acute cholecystitis with gallstones	2.14	1.06–4.30	.033
Cholecystitis without gallstones	4.67	1.83–11.90	.001
Gallbladder polyp (with or without gallstones)	7.00	2.48–19.72	<.001
Suspicion of malignancy (with or without gallstones)	141	74.39–269.05	<.001
Chronic cholecystitis (with gallstones)	3.00	1.68–5.35	<.001
Perforated gallbladder (spontaneously)	3.78	1.44–9.92	.007

*P-Bilirubin elevation (>50 mmol/L) and/or bile duct stones. AC, Acute cholecystitis.

The final model was tested using the HL-test and AUROC curves. Initially, the AUROC was 0.82 (95% CI: 0.80–0.85) when preoperative factors were included. By combining the preoperative factors with intraoperative assessment of the gallbladder, table 2, the AUROC increased to 0.87 (95% CI: 0.84–0.89), $p<0.001$, figure 7.

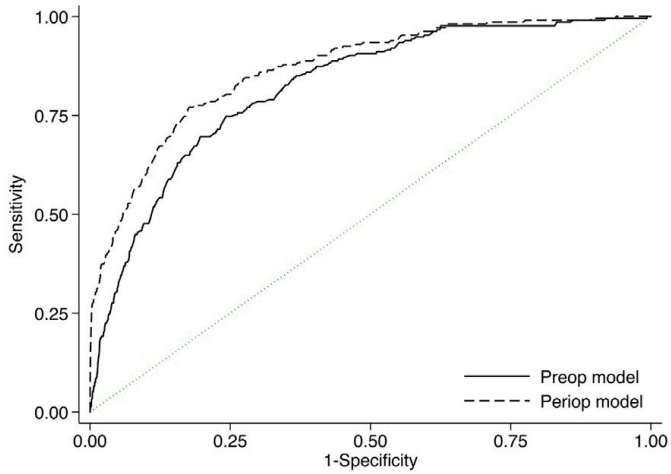


Figure 7. Area under the ROC curve (AUROC) 0.82 (preoperative model, solid line) and 0.87 (pre- and intraoperative model, dashed line), respectively, $p<0.001$.

Paper II

The derivation cohort (n=28 915) consisted of 214 (0.74%) IGBC patients compared to 35 (0.45%) IGBC patients in the validation cohort (n=7851).

Odds ratio (OR) was calculated from the recalibrated logistic regression model. Age>80 years resulted in the highest OR of 16.0 (CI: 8.9-30.0, p<0.001). Female sex resulted in OR of 3.7 (CI: 2.6-5.2, p<0.001) and elevated bilirubin levels/no acute cholecystitis in OR of 2.1 (CI:1.2-3.5, p=0.010).

Based on odds ratio an additive risk model was created and was rounded up to a point system, figure 8.

Risk score model to predict gallbladder cancer

Age:
<60: 0 points
60-69 years: 3.5 points
70-79 years: 6.5 points
≥80 years: 16 points
Female: 3.5 points
Previous cholecystitis: 1.5 points
No elevated bilirubin levels/acute cholecystitis: 1.5 points
Elevated bilirubin levels/no acute cholecystitis: 2.0 points

Total risk:	Odds Ratio (95% CI):
Low-risk: <3.5 points	Ref
Intermediate-risk: 3.5-8 points	3.6 (1.7-7.4)
High-risk: >8 points	17.8 (8.7-36.3)

Figure 8. Risk score model to predict gallbladder cancer.

The age range 50-59 years was not significant and was counted as 0 points in the model, as well as no elevated bilirubin level/no acute cholecystitis.

Three risk groups were created, based on quartiles; a low-risk group 0-3 points (n=7 149), an intermediate-risk group 3.5-8 points (n=21 739) and a high-risk group >8 points (n=7 878). In the low-risk group 8 IGBC patients were observed, whereas 18 IGBC patients were expected, in the intermediate-risk group 87 IGBC were observed and 108 IGBC were expected and in the high-risk group 154 IGBC were observed and 148 IGBC were expected.

Further, a high score group based on the ROC curve was created, including patients >12 points (n=2 080). Of these, 67 IGBC patients were observed, whereas 87 IGBC patients were expected, with a predicted incidence for IGBC of 4.2%.

The AUROC score for predicting incidental gallbladder cancer was 0.76 in the derivation cohort and 0.79 in the validation cohort with an acceptable calibration, HL-test: 8.3, p=0.219 and 14.3, p=0.027, respectively, figure 9.

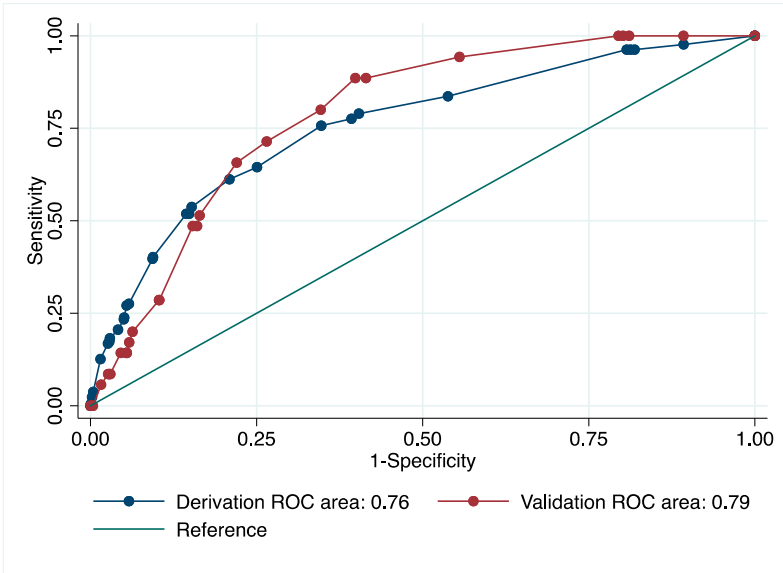


Figure 9. Receiver operation curve (ROC) for the derivation (blue line) and validation (red line) cohort, with no difference between the area under curve for the two groups, p=0.363.

Paper III

Seven patients with metastases to the gallbladder and three patients with lymphoma involvement of the gallbladder were included in the study. Metastasis to the gallbladder accounted for 3.1% of the incidental gallbladder malignances. The median age for patients in the metastasis and lymphoma group (MOL) was equal to IGBC patients, however patients with benign disease were younger compared to the MOL group. Most patients were female in all three groups. There was no significant difference in body mass index, if the surgery was performed as an acute procedure or if the patient had ongoing cholecystitis when comparing MOL cases with IGBC respectively benign cases. More patients had elevated bilirubin in the MOL group compared to the benign group, but no difference could be seen compared to the IGBC group, table 3.

Table 3. Preoperative characteristics of incidental gallbladder cancer (IGBC), the metastasis or lymphoma group (MOL) and benign cases.

Variable	IGBC (n=215)	MOL (n=10)	Benign cases (n=36 140)
Age (years)	70 (63-78)	70 (64-72)	55 (42-66)
Female	171 (80%)	8 (80%)	21 676 (60%)
BMI (kg/m²)	27	27	28
Acute surgery	106 (49%)	6 (60%)	14 096 (39%)
ASA classification III	45 (21%)	2 (20%)	3 302 (9%)
Elevated bilirubin*	35 (16%)	3 (30%)	3 509 (10%)
Ongoing cholecystitis	83 (39%)	3 (30%)	9 956 (28%)
Previous cholecystitis	60 (28%)	1 (10%)	6 518 (18%)

BMI: body mass index; ASA: American Society of Anesthesiologist. *P-Bilirubin elevation (>50 mmol/L) and/or bile duct stones.

During perioperative gross examination of the gallbladder specimen, a tumor was diagnosed in two cases by the surgeon, whereas the pathologist diagnosed a macroscopical tumor in 5 cases. Only four patients were discussed at a multidisciplinary conference postoperatively.

The median survival in the MOL group was 5.8 months compared to 23 months for IGBC patients and the 3-year overall survival was 30% respectively 42% for these groups, p=0.036. After 2 years, only the patients with lymphoma involvement of the gallbladder were alive, figure 10.

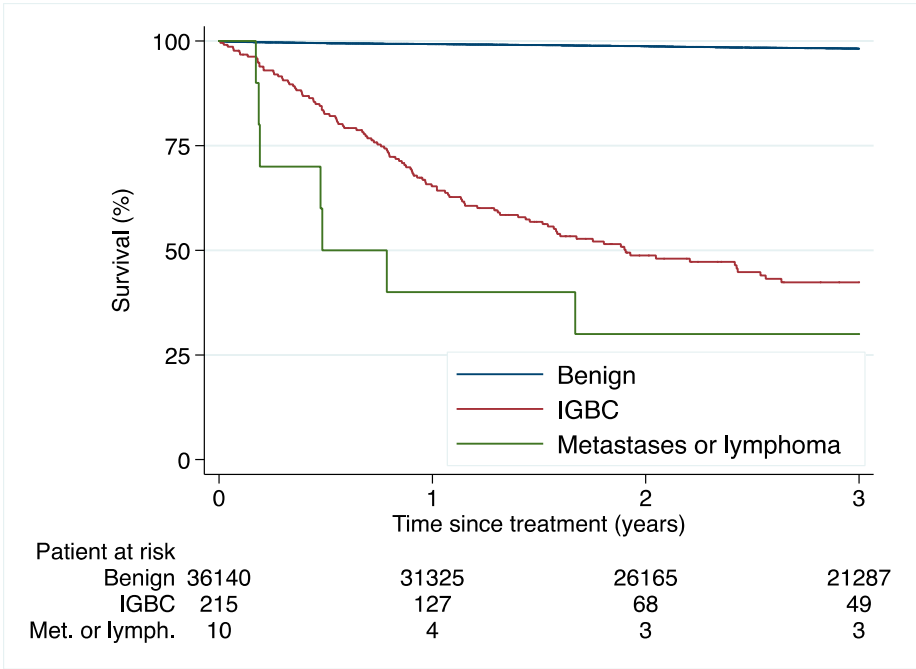


Figure 10. Kaplan-Meier curve on overall survival in benign, IGBC and metastases or lymphoma group.

Paper IV

During 1 January 2007 and 30 November 2016, 44 429 patients underwent cholecystectomy on the indication of benign gallbladder disease. In total, 249 IGBC patients were analyzed with an incidence of 0.56% relative to cholecystectomies performed. In patients with acute cholecystectomy the incidence of IGBC was 0.72%, compared to 0.49% if the cholecystectomy was performed without an acute indication. Accidental perforation of the gallbladder occurred more frequently if the operation was performed laparoscopically or if the procedure was converted to open surgery. No difference in the proportions of accidental perforations was noted between pT categories. The treatment strategy was discussed at a multidisciplinary team meeting in 67% of the cases. The proportion of patients discussed in a multidisciplinary setting increased in recent years.

Reresection was planned in 121 IGBC patients (49%). Disseminated disease was present during surgery in 29 (24%) of these patients and reresection was not performed. Patients in whom reresection was planned were younger and had a better ASA physical status grade.

The proportion of patients scheduled for reresection was higher in the late period, as was the proportion of completed curative reresection. In patients with pT2 disease, 36% underwent curative intended reresection during the early period compared with 77% during the late period. A comparison between 43 patients who underwent reresection within 60 days and 76 patients who had an operation after 60 days revealed no difference in the possibility of completing the reresection with curative intent.

In 92 patients, the reresection was completed with curative intent. Lymph node dissection was performed in 68 patients (74%).

The R0 resection rate among 92 patients who underwent reresection with curative intent was 85% and R0 resections were significantly higher during the second time interval. Residual disease was present in 48 (52%) of the 92 patients. The rate of residual disease increased with more advanced T stage.

Accidental perforation during index cholecystectomy occurred in 52 of 121 patients (43%) planned for reresection. There was a tendency towards a higher rate of completed reresection with curative intent in patients without previous gallbladder perforation.

The main reasons why reresection was not planned in the subgroup of patients with pT2 disease, were either that the cholecystectomy was considered sufficiently radical or patient co-morbidity. In patients with pT3 disease, the most common reasons were advanced tumor stage and patient co-morbidity.

Median follow-up was 71 months. A majority of patients with T1b disease had curative intended reresection (58%). Disease-specific survival did not significantly differ between pT1b patients with cholecystectomy alone and reresection. In the reresected group, median DSS was not reached, and 1-, 3- and 5-year DSS rates were 90%, 78% and 64%. In patients who did not undergo reresection, median DSS was 39 months, and 1-, 3- and 5-year DSS rates were 86%, 50% and 43% (p=0.102).

In reresected pT2 patients, median DSS was 44 months, compared with 12 months for patients who underwent cholecystectomy alone, figure 11a. Cox proportional hazards analysis adjusting for age, sex and co-morbidity revealed reresection to be a prognostic factor for longer survival in patients with pT2 disease (hazard ratio (HR) 0.26, 95% CI: 0.15 to 0.43, $p< 0.001$).

Among patients with pT3 disease, median DSS was significantly improved among 15 patients (20 months) who underwent reresection compared to 65 patients (10 months) who did not. Also, Cox proportional hazards analysis adjusted for age, sex and co-morbidity revealed reresection to be a prognostic factor for longer survival for patients with pT3 disease (HR 0.36, 95% CI: 0.19 to 0.67; $p = 0.001$).

In patients with residual disease and reresection, 1-, 3- and 5-year DSS rates were 79%, 34% and 25%, compared with 91%, 70% and 67% among patients without residual disease and reresection. Subgroup analysis of patients with pT2 showed a reduced DSS in patients with residual disease compared with no residual disease (median 32.2 months *versus* not reached; $p= 0.007$), figure 11b. pN1 status after reresection was associated with reduced DSS, regardless of pT stage.

For the entire cohort, median DSS was improved in the late period than the early period (27 *versus* 16 months; $p= 0.030$). In patients with completed reresection, there was no difference in survival between the early and late period.

No difference in median DSS was seen in patients when accidental perforation of the gallbladder occurred at index cholecystectomy compared to patients without accidental perforation. Nor did, time to reresection (within 60 days or after) affect median survival (19.8 *versus* 29.5 months respectively; $p = 0.664$).

Independent prognostic factors for impaired DSS in patients with curative intended reresection were proven to be pT3 and residual disease.

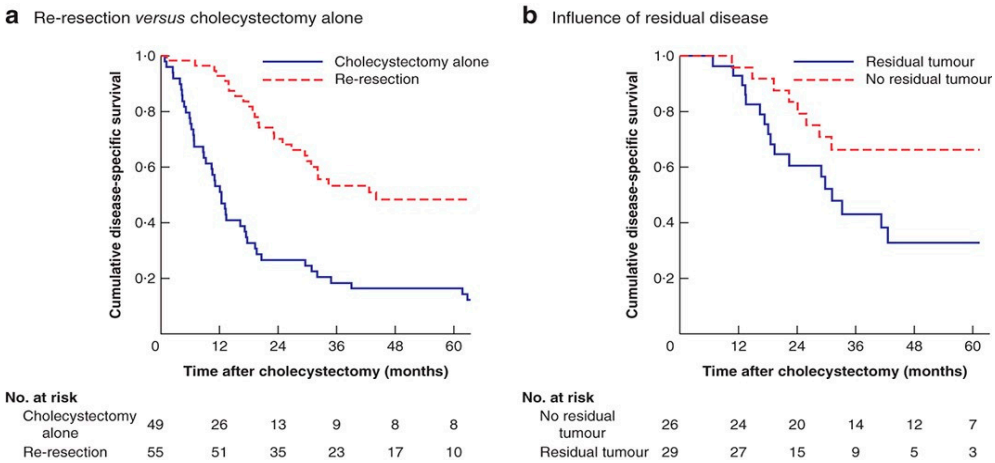


Figure 11. a. Patients with curative intended reresection *vs.* patients with cholecystectomy alone, $p < 0.001$ (log rank test). **b.** Patients with reresection with curative intent, with *vs.* without residual disease, $p = 0.007$ (log rank test), pT2

Paper V

Between January 2009 and December 2019, 1986 patients were registered in SweLiv as radiologically suspected or histopathologically proven gallbladder cancer. Thirty-five patients were excluded due to incidental finding of GBC during liver transplantation or due to uncertain diagnosis. Most patients were presented with GBC (76%) (n=1485) compared to IGBC (n=466, 24%), figure 12.

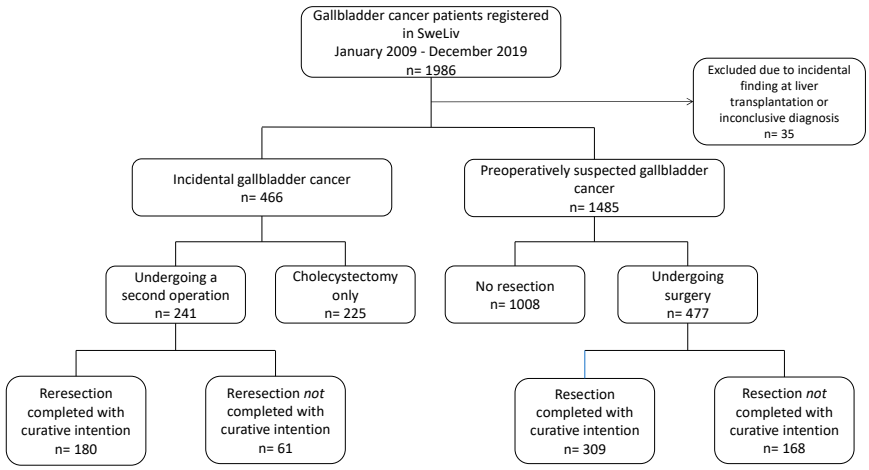


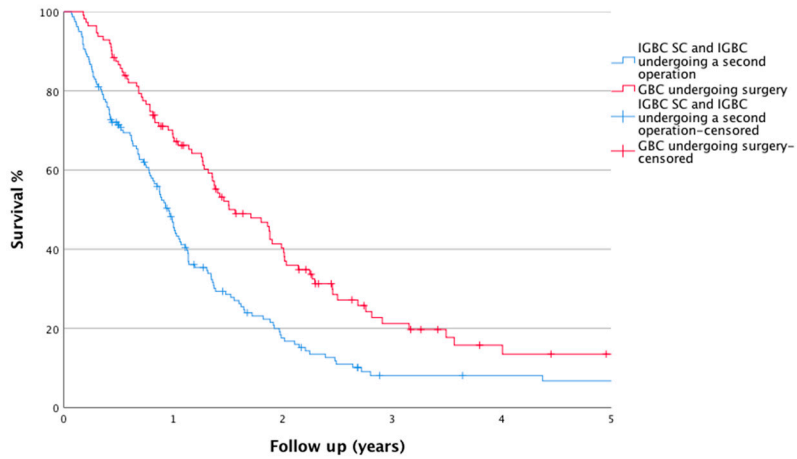
Figure 12. Flow chart, patients with gallbladder cancer registered in SweLiv during 2009-2019.

In total 225 IGBC patients underwent SC only, 241 IGBC patients underwent a second operation and 477 GBC patients underwent surgery, figure 12. Most patients were female (IGBC SC 73%, IGBC 72%, GBC 64%), and with small differences in mean age in all three groups (71 vs 67 vs 68 years, $p<0.001$). MDT meetings were applied in the majority of patients with an improvement over time. However, during the whole study period 20% of IGBC SC patients were not reviewed in a MDT meeting, compared to 15% of IGBC patients undergoing a second operation and 12% of GBC undergoing surgery ($p=0.018$).

Most patients in both the IGBC undergoing a second operation group (n=147, 68%) and GBC undergoing surgery group (n=252, 62%) were N0 and most patients in all three groups were M0. IVb/V segmentectomy with lymphadenectomy was the most common procedure in both IGBC and GBC patients, followed by wedge resection. Most IGBC/GBC patients that underwent surgery had a radical (R0) reresection/resection.

Overall survival analysis 1 - in IGBC SC and IGBC patients undergoing a second operation compared to GBC patients undergoing surgery, intention to treat

No difference in overall survival in pT1b patients (5-year overall survival of 65% in all IGBC and 79% in GBC, p=0.383) was seen. In pT2 patients a tendency of improved 5-year overall survival in GBC patients was seen (GBC 45% *vs*. all IGBC 40%, p=0.082). In pT3 patients, a significant difference in 5-year overall survival was seen, figure 13, with improved survival in the GBC group (GBC 13% *vs.* all IGBC 8%, p<0.001). GBC was shown to be an independent predictor for improved survival in pT3 patients (HR: 0.6; 95% CI: 0.4-0.8, p<0.001).



Patients at risk						
IGBC	158	66	22	7	6	5
GBC	112	71	37	14	7	4

Figure 13. Overall survival in IGBC SC and IGBC patients undergoing a second operation compared to GBC patients undergoing surgery, intention to treat, pT3. p<0.001 (log rank test).

Overall survival analysis 2 - in IGBC patients undergoing a second operation compared to GBC patients undergoing surgery, intention to treat

On pT-stage specific analysis (pT1b, pT2 and pT3) no significant difference was seen in overall survival in IGBC patients undergoing a second operation compared to GBC patients undergoing surgery. Five-year overall survival in pT1b GBC was 79% and in IGBC 76%, p=0.581. In pT2 GBC and IGBC patients, 5-year overall survival was 45% in both groups, p=0.456. In pT3 patients 5-year overall survival was 13% in the GBC group *vs*. 19% in the IGBC group, p=0.665.

Overall survival analysis 3 - in IGBC SC and IGBC patients with curative reresection compared to GBC patients with curative resection

In pT1b patients, no difference was seen on overall survival in all IGBC patients compared to GBC patients with curative resection (70% *vs.* 87 %, p= 0.275). In pT2 GBC patients with curative resection a tendency was seen towards improved 5-year overall survival compared to IGBC SC and IGBC patients with curative reresection (50% *vs*. 42%, p=0.051). In pT3 GBC patients with curative resection compared to IGBC patients with curative reresection, improved 5-year overall survival was seen in GBC patients (20% *vs*. 10%, p<0.001). GBC was shown to be an independent predictor for improved survival in pT3 patients (HR: 0.4; 95% CI: 0.3-0.7, p<0.001).

Overall survival analysis 4 - in IGBC patients with curative reresection compared to GBC patients with curative resection

No significant difference in overall survival in pT1b and pT2 IGBC patients with curative reresection compared to GBC patients with curative resection was seen. In pT3 IGBC patients a significant improved overall survival was seen, with 5-year overall survival of 50% compared to 20% in GBC patients, p=0.016. IGBC was proven to be an independent predictor for survival in pT3 patients undergoing curative reresection (HR: 0.4; 95% CI: 0.2-0.8, p<0.019).

Overall survival analysis 5 - in pT1b-pT3 patients, IGBC proven to be unresectable during second operation compared to IGBC with curative reresection

In IGBC patients proven to be unresectable compared to IGBC patients undergoing curative reresection, a significant improved 5-year overall survival in reresected IGBC patients was seen (58% in the IGBC reresected group *vs.* 12% in unresectable IGBC patients, p<0.001).

Overall survival analysis 6 - in pT1b-pT3 patients, GBC patients proven to be unresectable during surgery compared to GBC patients with curative resection

In GBC patients proven to be unresectable compared to GBC patients with curative resection a significant improved 5-year overall survival in resected GBC patients was seen (56% in resected GBC patients and 18% in unresectable GBC patients, p<0.001).

Discussion

Gallbladder cancer continues to be a highly lethal disease, with only less than half of all patients presenting at a stage suitable for curative intended surgical resection[181]. However, over the last decades improved surgical techniques and radical surgery has enhanced survival in this selected group of patients[27].

To preoperatively be able to identify patients at risk of having IGBC, may improve survival in patients undergoing surgery for a presumed benign diagnosis. IGBC was found to be more common in patients; 65 years of age or older, females, in patients with a history of cholecystitis, and the combination of acute cholecystitis without coincidental jaundice, as well as jaundice without acute cholecystitis. The accuracy of the risk model was higher when including the surgeons macroscopical evaluation of the gallbladder. Complications during and after the procedure (cholangitis, bile duct injury, postoperative infections and pancreatitis) were increased in the IGBC group compared to patients with benign gallbladder disease, indicating that the procedure may be more challenging in IGBC patients. To preoperatively identify patients with increased risk of IGBC gives the possibility to optimize the surgical procedure. This could mean not to schedule these patients during late shifts and ensure that the procedure is performed by an experienced surgeon. Also, by being more liberal of sending frozen section for histopathological analysis.

In 160 of the IGBC cases the surgeon responsible for the procedure did not suspect malignancy, but in 93% of the cases was sure of some kind of pathology in the gallbladder. It may be difficult to detect GBC especially in the presence of gallbladder wall thickening in the case of acute or chronic cholecystitis. You et al[182], presented the sensitivity of surgeons' macroscopic diagnosis of GBC in the presences of acute cholecystitis to be 46%, with a specificity of 97%[182]. In our present study, in the case of pT4 tumors, 50% were suspected to be cancer during the macroscopical inspection, the remaining 50% were suspected to be acute or chronic cholecystitis.

In our second study, we created a risk score model, based on five easily accessible clinical variables. The current risk model is greatly dependent on the patients age and the highest points are seen in patients over 80 years, in women and when elevated bilirubin level without concomitant acute cholecystitis is present. Previous studies support age[183] and female sex[184] as a risk factors as well as dilated bile ducts[183, 185]. The two last risk factors in the risk score model were acute cholecystitis

without elevated bilirubin and chronic cholecystitis. Acute cholecystitis has been showed to be a risk factor [186], however chronic cholecystitis has not. The patients were separated into three risk categories, making it possible for the surgeon to estimate the risk of gallbladder cancer in a patient scheduled for a cholecystectomy on a benign indication. Since the incidence of GBC is low [187, 188], it is difficult to distinguish these patients in a scoring model. However, the high odds ratio in the high-risk group and the AUROC of 0.79 in the validation cohort implies that this tool may be of value in clinical situations.

In our third study, seven cases of metastasis to the gallbladder, originating from different primary tumors; breast cancer, malignant melanoma, gastric cancer, renal cell carcinoma (RCC), upper gastrointestinal cancer, colon cancer and pancreatic cancer, are presented together with three cases of lymphoma involvement in the gallbladder; including B-cell lymphoma, mantel cell lymphoma and T-cell lymphoma.

These rare diagnoses may present with symptoms of gallstones or/and cholecystitis. If a history of previous malignancy is present, increased awareness of a possible metastasis in the gallbladder should occur. Metastasis of RCC may occur 8-27 years after the primary tumor[189], as in our RCC case the patient was diagnosed with a gallbladder metastasis 11 years after the primary diagnosis. Even in a palliative situation, a cholecystectomy could be of value for a patient with a cholecystitis, as was seen in our material. The procedure can be straight forward as well as very difficult and an aborted procedure is also an alternative, if there is a risk of bile duct injury or massive tumor involvement of hilar structures.

Not all metastasis to the gallbladder may have a bad prognosis, the primary tumor should be kept in mind when patients are dismissed of surgery. In the previously referred review[189] of RCC patients with metastasis to the gallbladder none of the 23 patients had a recurrence in the liver or the biliary tract after cholecystectomy.

Lymphoma of the gallbladder has a different prognosis in contrast to metastatic disease in the gallbladder. In our study two of three patients are alive, except for one who died of another cause.

If a patient has a history of malignancy, the gallbladder should be sent for histopathological examination in order not to miss incidental metastasis or lymphoma involvement of the gallbladder.

In the fourth study, we found that DSS among pT2 and pT3 patients was improved by reresection, with 5-year DSS rates of 48% and 13% respectively, when reresection was accomplished. This finding is in line with previous studies[114, 117, 190, 191].

In the late study period, a significant increase in median DSS was seen, by approximately a year for the whole study group and 15 months for the patients

planned for reresection. Increased knowledge, implementation of national guidelines and awareness over time, may have had an impact on survival. Also, R0 resections rates were higher in the late period.

During the whole study period, 37% of all patients underwent reresection with curative intent. The percentage of reresections increased significantly from 28% in the early period to 51% in the late period. The results from the late period are higher than results presented from a German registry (39%)[192] and a French multicenter database (34%)[117]. The number of patients evaluated at multidisciplinary team meetings increased over time, which may indicate that involvement of a liver surgeon early in the process improves outcome for these patients.

We found no significant difference in disease specific survival for cholecystectomy alone *versus* reresection in T1b patients, with the reservation of the small numbers in subgroup analysis. Swedish national guidelines[193] recommend reresection in T1b IGBC patients. The opinions are diverse; some studies[113, 194] support reresection for T1b IGBC, whereas others do not[135, 195]. Xu et al[138] showed that overall survival and disease specific survival was significantly improved in T1b patients with five or more lymph nodes dissected and no liver resection.

Two risk factors stand out when it comes to decreased survival; nodal status[96, 138] and residual disease, which is in line with previous studies[196-198]. Since nodal resection is not performed during index cholecystectomy (sometimes one lymph node is included in the specimen), the nodal status at primary surgery is probably underestimated in these patients. The overall rate of positive lymph nodes was 26% in this study, which is similar to previous results[103]. Residual disease was present in 52% of patients who underwent reresection, 5-year DSS rate was 25%, compared with 67% among those without residual disease. Further, multivariable analysis of the present data demonstrated that pT3 category and residual disease were prognostic factors for reduced survival. Ethun et. al[164] and Butte et. al[155] have reported that T category and tumor differentiation grade are predictors of residual disease at reresection.

In pT2 patients with residual disease at reresection, median DSS was longer compared to no reresection, however the groups were not totally comparable regarding possible selection bias, although neither age nor ASA were proven to be significant factors on multivariable analyses.

A surprisingly high rate of accidental perforation of the gallbladder during index cholecystectomy was seen (41%) compared to 22% presented by Goetze et. al[152], where also the recurrence rate was significantly increased in these patients. Our data show that accidental perforation at index cholecystectomy tended to decrease resectability among patients planned for reresection, and in contrast, accidental perforation had no impact on survival.

Timing of reresection has been discussed for IGBC patients, with the optimal time for reresection being 4-8 weeks[119]. In our material, reresection was performed at a median of 72 days after index cholecystectomy and the interval between cholecystectomy and reresection had no effect on resectability or survival.

In our last study, we managed to include a large number of patients due to two well established registries in Sweden; SweLiv and GallRiks. A tendency towards improved overall survival in pT2 and improved overall survival in pT3 GBC patients compared to IGBC patients was seen. Most patients were presented with nonincidental GBC (76%). In all three groups the majority of patients were women and the mean age was >65 years. MDT meetings were more frequent in the later period in all three groups. Concerning both periods, IGBC SC patients were less discussed at MDT meetings compared to IGBC patients undergoing a second operation or GBC patients undergoing surgery. This may have contributed to some of IGBC SC patients not being selected for further surgery. Unfortunately, we were not able to further investigate this in our study.

The Swedish guidelines recommend wedge resection and lymphadenectomy in pT1b-pT3 IGBC/GBC patients[193]. The dissection plane of a cholecystectomy disrupts natural layers and barriers between the tumor and the lymphovascular structures in the liver and may theoretically lead to dissemination of tumor cells in the liver bed and contribute to locoregional recurrence[96, 199]. In IGBC SC group most patients were diagnosed with pT3 and did not undergo further resection. These results are in line with the results in paper IV, were more IGBC pT2 patients were selected for reresection. The reason for not proceeding with further surgery in these patients was not studied, but there is a probability that they were disqualified for surgery because of disseminated disease and might have benefited from one stage resection.

In pT3 GBC patients undergoing surgery or curative surgery, an improved 5-year overall survival was seen, compared to IGBC SC and IGBC patients undergoing a second operation or curative reresection. GBC was proven to be an independent predictor for improved survival, indicating that pT3 patients may benefit from one stage resection. Further, overall survival in IGBC patients proven to be unresectable compared to IGBC patients undergoing curative reresection, in a merged group of pT1b, pT2 and pT3, showed a large difference in survival as expected, also illustrating the possible importance of one stage resection in these patients. The survival curves of unresectable IGBC patients are similar to unresectable GBC patients, which might indicate that simple cholecystectomy may have the same impact on survival as no surgery in certain pT stages. IGBC patients in pT3 stage undergoing reresection may be an extremely selected group, since they qualified for surgery despite the time interval from index cholecystectomy. The large difference

in 5-year overall survival in pT3 IGBC with curative reresection compared to GBC with curative resection may illustrate this.

Most patients were not suited for reresection in the present study as in previous studies[107, 117, 155]. Most patients were presented with Stage IV (AJCC 6th edition) and 22% of IGBC patients undergoing a second operation and 24% of GBC patients undergoing surgery were presented with M1 disease. Still, most IGBC/GBC patients that underwent reresection/resection had a radical (R0) procedure.

Methodical Considerations

The limitations in our studies are like those in all registry studies, with variables not registered properly or missing, constructing difficulties in interpretation of the data. Missing data is a factor of great concern in studies depended on registry data. To study a variable's effect on an outcome may not be possible, due to the variable not being registered separately or not even in the registry. Leading to the risk of decreased statistical power or bias.

In paper I and II, some risk factors identified in previous studies[166, 167, 185] could not be investigated, along with other possible risk factors as tumor markers, gallbladder wall thickening and results of ultrasonography, since these variables are not present in GallRiks. The presence and size of polyps were also not possible to study, without retrieving medical charts for each patient with this registration, since the variable is registered under the same heading as suspicion of GBC.

In paper III, the major limitation was the small sample size. Incidental metastasis to the gallbladder is an extremely rare condition as well as lymphoma involvement of the gallbladder, which makes it more demanding to study and interpret the results. However, when it comes to rare diagnosis even case studies can be of benefit.

The limitations of paper IV, are that the surgical treatment of the included patients took place over a long period and medical records were collected retrospectively, which can affect the evaluation of collected data. Of all gallbladder specimens, only a few were examined a second time by an experienced pathologist, which may lead to incorrect pT in some patients. The IGBC patients who underwent reresection were both younger and healthier, than the patients not selected for reresection, being a possible selection bias. However, age and ASA were not shown to be independent negative predictors on multivariable analysis.

In paper V, the missing data on pTNM status mainly in GBC patients made it not possible to include these patients in pT-specific survival analysis. Also, we were not able to cross-link SweLiv data with GallRiks during the entire study period, however the coverage of the registry has improved in recent years[19].

A limitation in all papers is that we do not know how many IGBC cases should have been included in the registries, since not all gallbladders are sent for histopathological analysis, when performing cholecystectomy for benign indication in Sweden.

By retrieving medical records, when information regarding histopathological diagnosis was missing, we minimized the risk of information bias.

Conclusions

We found five clinically, easily recognizable prognostic factors for IGBC; age ≥65years, female sex, previous cholecystitis, jaundice or acute cholecystitis. The developed preoperative risk score model for IGBC can be used as support regarding operative planning and to determine if the gallbladder should be sent for histopathological analysis postoperatively. By adding intraoperative assessment of the gallbladder, our risk model for IGBC was further improved. If a gallbladder is presented with cholecystitis, polyps, or spontaneous perforation it implies a higher risk for cancer, motivating a histopathological diagnosis.

The risk score model was validated through a separate cohort and has an ability to predict IGBC in adult patients before surgery. It can be used to distinguish patients with a greater risk of cancer, making it possible to optimize the preoperative investigations and treatment strategies.

Incidental metastasis and lymphoma of the gallbladder is a rare event. Traditional imaging methods like ultrasonography and CT may miss the diagnosis. Macroscopical examination of the gallbladder performed by the surgeon is challenging, which implies a liberal approach to histopathological analysis.

Reresection of pT2 and pT3 IGBC was associated with improved survival. When residual disease was present DSS was reduced. A higher reresection rate and more R0 resections in the later period may have been associated with improved survival.

pT3 IGBC patients and possibly pT2 IGBC patients, may benefit from one stage resections, which was proven to be an independent predictor for improved survival in pT3 patients. We recommend that radiological suspicion of malignancy should be evaluated at a liver tumor center.

Future perspectives

An interesting ongoing study from Netherlands, called the FANCY study will examine if a selective approach of histopathological analysis of appendices and gallbladders based on the intraoperative gross examination by the surgeon is safe and cost-effective[200]. The authors' take is; if a tumor is not detected by visual inspection or palpation it is usually of an early stage and if the organ is resected the tumor is already treated. The FANCY study is a nationwide, prospective, multicenter, observational, cohort study, where all gallbladders will be evaluated for tumors by gross examination by the operating surgeon. The surgeon will report the findings from gross examination and motivate if a histopathological analysis is considered to be necessary. Further, all specimens will be sent for histopathological examination. Then a hypothetical situation will be analyzed, where gallbladders are only examined by the pathologist on indication. Then an evaluation will be made concerning if any T1b-T4 IGBC cases would have been missed with a selective approach.

Goetze et al[201] with a phase III GAIN study, plan to investigate whether induction chemotherapy (Gemcitabine + Cisplatin 3 cycles) followed by radical reresection in IGBC (and, if feasible, postoperative chemotherapy, 3 cycles) improves overall survival compared to radical surgery alone.

An international retro- (years: 2010-2020) and prospective (years: 2022-2025) multicenter study; Operative Management of Early Gallbladder Cancer (Omega), with the ambition to evaluate the effect of extent of surgical resection and lymphadenectomy on overall survival and DSS. Also, to identify risk factors that can predict requirement for radical or extended resections compared to simple cholecystectomy is under process. The inclusion criteria are any operated patients with gallbladder cancer at any T- and N-stage, with the exclusion of metastatic disease.

Populärvetenskaplig sammanfattning

Gallblåsecancer (GBC) är en ovanlig sjukdom med kort överlevnad för många av de drabbade patienterna. Överlevnaden ändras dramatiskt till det bättre om diagnosen kan ställas tidigt. Godartad, det vill säga benign, gallblåsesjukdom, så som gallstensanfall eller akut inflammation i gallblåsan, är mycket vanligt. Vid benign gallblåsesjukdom är den vanliga behandlingen att operera bort gallblåsan, en så kallad kolecystektomi. I Sverige utfördes 14 231 kolecystektomier år 2019. Gallblåsecancer som upptäcks först under en kolecystektomi eller i samband med vävnadsanalys efter operationen benämns incidentell gallblåsecancer (IGBC) och förekommer i cirka 1% av alla vävnadsanalyser av gallblåsan. IGBC patienter opereras ofta i två steg: först med kolecystektomi; därefter remitteras patienten till ett levercentrum där så kallad lymfkörtelutrymning och leverkirurgi utförs. På förhand misstänkta fall av gallblåsecancer remitteras direkt till levercentra där patienten opereras med gallblåseoperation, lymfkörtelutrymning och leverkirurgi i samma seans. Det är inte känt om IGBC patienter har en bättre överlevnad jämfört med patienter med på förhand känd gallblåsecancer.

I studie I, var syftet att identifiera så kallade prediktiva faktorer som innan operation kunde förutse risken för IGBC, samt undersöka om kirurgens bedömning av gallblåsan kunde öka chansen att förutse denna risk. Följande prediktiva faktorer för IGBC identifierades: hög ålder, kvinnligt kön, genomgången inflammation i gallblåsan och akut inflammation i gallblåsan utan gulsot, samt gulsot utan akut inflammation i gallblåsan.

I studie II, användes de prediktiva faktorer som identifierades i studie I för att konstruera en så kallad ”risk score modell” med syftet att på ett kliniskt tillämpbart sätt, genom ett poängsystem, uppskatta risken av att drabbas av IGBC.

Metastaser, exempelvis från bröstcancer, njurcellscancer och malignt melanom, samt lymfomengagemang i gallblåsan, är mycket ovanligt. Syftet med studie III var att identifiera dessa ovanliga fall och beskriva dem avseende karakteristika, utredning, behandling och överlevnad. Alla patienter i studien hade innan operation genomgått ultraljud- eller skiktröntgenundersökning av buken utan att någon tumör kunde identifieras. Vid granskning av gallblåsan kunde kirurgen identifiera tumör i 2 av 7 fall, medan patologen i samband med vävnadsanalysen kunde identifiera tumör i 5 fall utan någon mikroskopisk undersökning.

I studie IV studerades behandling och överlevnad av IGBC patienter under en period av 10 år. IGBC patienter med tumörstadium pT2 och pT3 visade en högre sjukdomsspecifik överlevnad, efter att ha genomgått kompletterande leverkirurgi med lymfkörtelutrymning. Residualsjukdom, det vill säga kvarvarande sjukdom, sänkte sjukdomsspecifik överlevnad signifikant jämfört med patienter utan residualsjukdom.

I den avslutande studien V, studerades överlevnaden hos de IGBC patienter som enbart genomgick gallblåseoperation eller som gick vidare till leverkirurgi, jämfört med på förhand kända fall av gallblåsecancer, opererade i en seans. Patienter med tumörstadium pT3 och GBC som genomgick kirurgi, hade en bättre överlevnad jämfört med pT3 IGBC-patienter som opererades.

Sammanfattningsvis, genom identifierade prediktorer för gallblåsecancer kunde en risk score modell skapas, som är lätt att använda kliniskt och som kan hjälpa till att på förhand identifiera vilka patienter som löper en högre risk för gallblåsecancer när de söker sjukvård för benign gallblåsesjukdom. Metastaser och lymfomengagemang till gallblåsan är väldigt ovanligt och kan vara svårt att identifiera med bilddiagnostik innan operation. Hos patienter med prediktorer för IGBC och då det finns en historik av malign sjukdom, bör gallblåsan skickas för vävnadsanalys. IGBC-patienter i stadium pT2 och pT3 får en längre överlevnad om de genomgår kompletterande leverkirurgi och lymfkörtelutrymning. Residualsjukdom påverkar överlevanden negativt. GBC patienter som genomgår kirurgi har en bättre överlevnad än IGBC patienter som enbart opereras med kolecystektomi eller som genomgår vidare kirurgi i samma pT3-stadium, vilket kan tala för att patienter med gallblåsecancer bör opereras i en seans.

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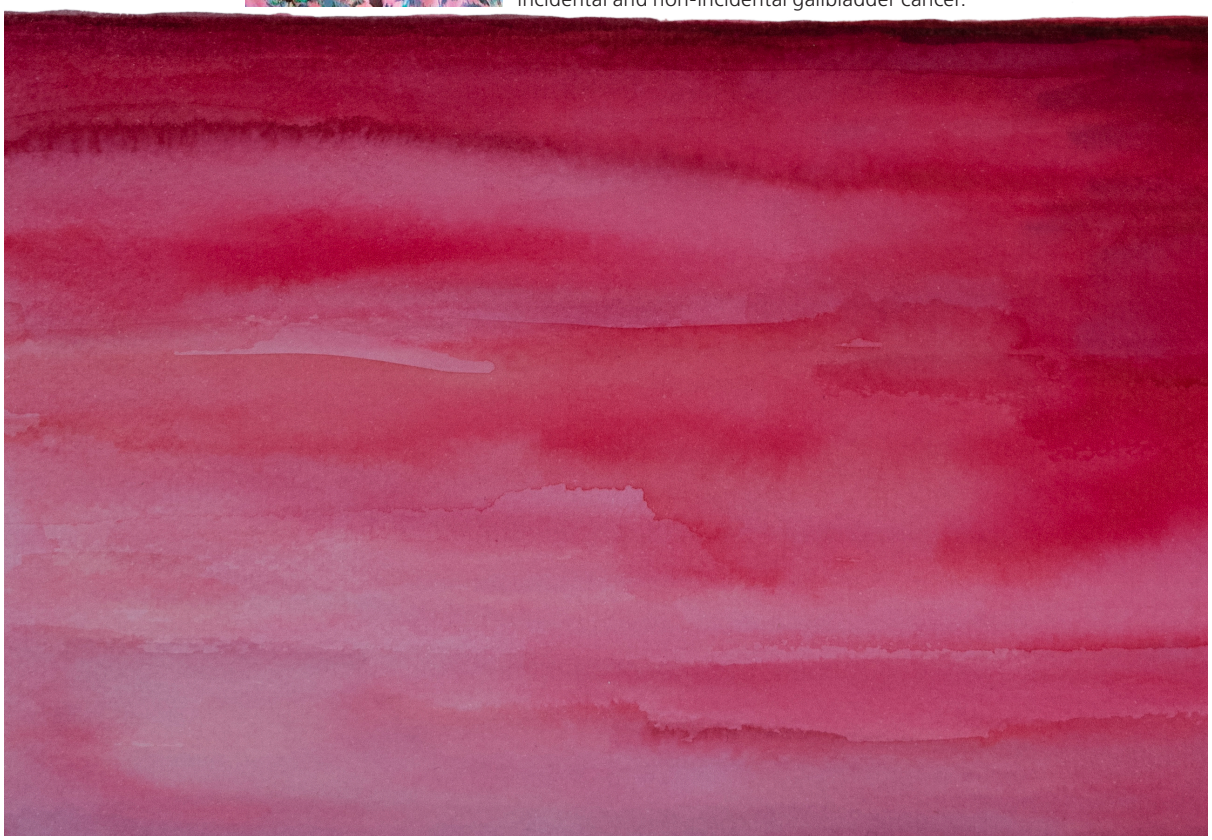
Gallbladder Cancer

Risk Factors, Surgical Intervention and Survival

CAROLINA MUSZYNSKA, is a general surgeon at the Department of Surgery, Skåne University Hospital in Malmö and has a special interest in HPB surgery. Her thesis examines risk factors, surgical treatment and survival in patients with incidental and non-incidental gallbladder cancer.



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