# Surgical Management of Gallbladder Cancer Patients

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## 2.1 Introduction

Gallbladder cancer (GBC) is the most prevalent biliary tract malignancy and the sixth most common gastrointestinal malignancy worldwide [1]. The global incidence is declining since the 1960s, which is probably a consequence of increased cholecystectomy rates secondary to gallstones [2]. Survival of GBC is poor, with overall 5-year survival across all stages of around 10% as most patients are diagnosed at an advanced stage [3]. GBC is rare and accounts for 1.2% of all cancers and 1.7% of all cancer mortality, respectively [4]. Best survival rates are obtained if GBC is diagnosed at an early stage and treated with complete (i.e., margin negative) resection.

### 2.1.1 Epidemiology and Risk Factors

GBC has a remarkable geographic distribution. The highest incidences are noted in Bolivia, Colombia, India, Chili, Eastern Europe (Poland, Hungary, Czech Republic), and among the American Indian, Alaska Native, and Hispanics. The incidence ranges from 12.3/100,000 for males and 27.3/100,000 for females in Chili, compared to 1/100,000 for males and 2/100,000 for females in the United States [4] (Fig. 2.1). The worldwide gender bias with a variable female-to-male incidence ratio of 5:1 is remarkable and attributed to the higher incidence of gallstone disease

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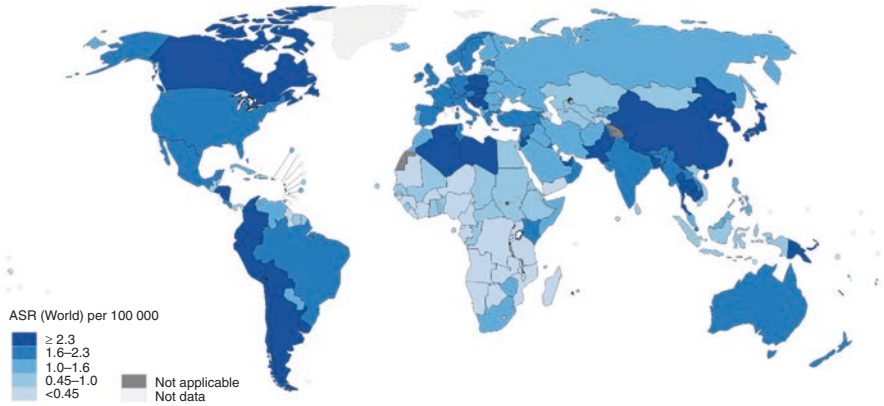


**Fig. 2.1** Global incidence of gallbladder cancer. Estimated age-standardized gallbladder cancer incidence rates per 100,000 per year in 2018 for both sexes. (Reprinted by permission from Springer Nature: Gamboa et al. [5])

and presence of the female hormone estrogen [6]. GBC is a disease of advancing age with a mean age of diagnosis in the seventh decade [7].

Cholelithiasis is considered to be the primary risk factor for GBC and is present in 85% of patients [8]. Furthermore, risk of GBC is increased tenfold in patients with larger gallstones (>3 cm) compared to smaller stones [9]. Gallstones provoke chronic mucosal inflammation promoting epithelial dysplasia and adenocarcinoma formation in the gallbladder wall. Nevertheless, only about 1% of patients with cholelithiasis develop GBC [10].

Calcifications in the gallbladder seen on imaging have been considered a risk factor for malignancy. Therefore, a "porcelain" gallbladder is regarded as an indication for cholecystectomy [11]. A review reported a GBC incidence of 21% ($n = 72$) in porcelain gallbladders ($n = 340$) [12]. Though, in a subgroup analysis of these patients ($n = 124$) without selection bias, the incidence of GBC was only 6% compared to 1% in a matched cohort of patients without gallbladder wall calcification. The most recent and largest review confirmed a 6% ($n = 21$) GBC incidence in porcelain gallbladders ($n = 333$) in an overall cohort of 60,781 cholecystectomies [13]. Therefore, prophylactic cholecystectomy should be considered based on symptoms, and a nonoperative approach is justified in those with significant comorbidities. Nevertheless, the pattern of calcification may be predictive of malignancy; it appears that selective mucosal calcification may be predictive of GBC, whereas complete intramural calcification is not associated with GBC [14]. In conclusion, cholecystectomy should be considered particularly in patients with selective mucosal calcification on imaging.

Other factors associated with higher rates of GBC occurrence include obesity, chronic inflammation caused by anomalous pancreaticobiliary ductal junction, primary sclerosing cholangitis, and infection with *Salmonella typhi* or *Helicobacter* species.

## 2.2 Preoperative Planning

### 2.2.1 Clinical Presentation

GBC may present in two ways: incidentally (intra- or postoperatively during/after routine cholecystectomy for cholecystolithiasis or cholecystitis) or in symptomatic patients with findings suspicious for malignancy. The majority of GBC patients (60%) is diagnosed incidentally (iGBC), whereas 40% of patients present with symptomatic disease. Symptoms of GBC include right upper quadrant or epigastric pain, jaundice, nausea and vomiting, anorexia, and weight loss [15]. Most symptomatic patients have advanced disease at diagnosis since symptoms often only occur late in the disease course [16]. In a series of 162 patients, only eight patients (5%) with symptomatic disease had a tumor that was limited to the gallbladder wall. All other patients had tumors invading the liver or other organs [17]. There are no sensitive nor specific tumor markers for the diagnosis of GBC. CEA and CA19.9 can be considered at baseline assessment but have no diagnostic value [18].

### 2.2.2 Staging: Anatomy and Imaging

The American Joint Committee on Cancer (AJCC) published the eighth edition of the AJCC staging manual in 2017 [19]. GBC is staged according to the depth of tumor invasion (T), presence and number of lymph node metastases (N), and presence of distant metastases (M) (Table 2.1, Fig. 2.2).

#### 2.2.2.1 Anatomy

The gallbladder is located in the inferior side between the right and quadrate lobe of the liver. The intraperitoneal part of the gallbladder is covered with peritoneum or serosa, whereas the extraperitoneal part, i.e., the part facing the liver, is covered by a perimuscular connective tissue called the cystic plate. Other organs, such as the stomach, duodenum, pancreas, or transverse colon, might be involved if cancerous cells extend beyond the peritoneal part. The tumor is located in the fundus in 60% of patients, in the body in 30%, and in the neck in 10% [20]. In case of neck involvement, inclusion of the biliary tree is more common because of the close relation to the right hepatic duct and biliary confluence [21]. In 98% of patients, GBC arises in the mucosal layer of the gallbladder. The majority of GBC are adenocarcinomas or their variants (adenosquamous, squamous) [22]. GBC's rare histologic variants include neuro-endocrine tumors, sarcomas, or metastases from other primary tumors such as melanoma. Subtypes have an infiltrative, nodular, or papillary growth pattern. Infiltrative GBC infiltrates the gallbladder in the subserosal plane, followed by invasion of the liver parenchyma and porta hepatis. Nodular GBC consists of circumscript lesions, whereas polypoid lesions characterize papillary GBC. Lymphatic flow from the gallbladder is primarily directed to the cystic duct node and the nodes around the bile duct, secondly to the hepatic vasculature and the posterior side of the pancreas, and finally to the aortocaval nodes near the left renal

**Table 2.1** Eighth edition of American Joint Committee on Cancer (AJCC) TNM staging for gallbladder cancer. (Adapted by permission from Oxford University Press: SØreide et al. (2019))

| | Description |
|---|---|
| *T-stage* | |
| Tis | Carcinoma in situ |
| T1a | Tumor limited to the lamina propria |
| T1b | Invades the muscle layer |
| T2 | Invades the perimuscular connective tissue |
| T2a | On the peritoneal side |
| T2b | On the serosal side |
| T3 | Perforates the serosa and/or directly invades the liver and/or other adjacent organs or structures |
| T4 | Invades the main portal vein or hepatic artery or two or more extrahepatic organs or structures[a] |
| *N-stage* | |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in 1–3 regional lymph nodes |
| N2 | Metastasis in 4 or more regional lymph nodes |
| *M-stage* | |
| M0 | No distant metastases |
| M1 | Distant metastases present |

| Stage | Tumor category | Node category | Metastasis category | Overall 5-year survival (%) |
|---|---|---|---|---|
| 0 | Tis | N0 | M0 | 80–100 |
| I | T1a/b | N0 | M0 | 80–100 |
| IIA | T2a | N0 | M0 | 40–75 |
| IIB | T2b | N0 | M0 | 40–75 |
| IIIA | T3 | N0 | M0 | 8–28 |
| IIIB | T1–3 | N1 | M0 | 8 |
| IVA | T4 | N0–1 | M0 | 7 |
| IVB | Any T | N2 | M0 | 4 |
| | Any T | Any N | M1 | 0–2 |

[a] Extrahepatic organs or structures include the stomach, duodenum, colon, pancreas, omentum, and extrahepatic ducts

vein, and coeliac lymph nodes (LNs) (Fig. 2.3) [23]. Involvement of LNs beyond the hepatoduodenal ligament (i.e., aortocaval and/or coeliac LNs) is considered metastatic disease [19]. Distant spread takes place mainly through hematogenous dissemination, either directly or through invasion of the liver parenchyma [24].

### 2.2.2.2 Imaging

Imaging plays a vital role in detecting, staging, surgical planning, and evaluation of treatment in GBC. Imaging may show a focal or diffuse gallbladder wall thickening, an intraluminal mass, or a mass in the gallbladder fossa.

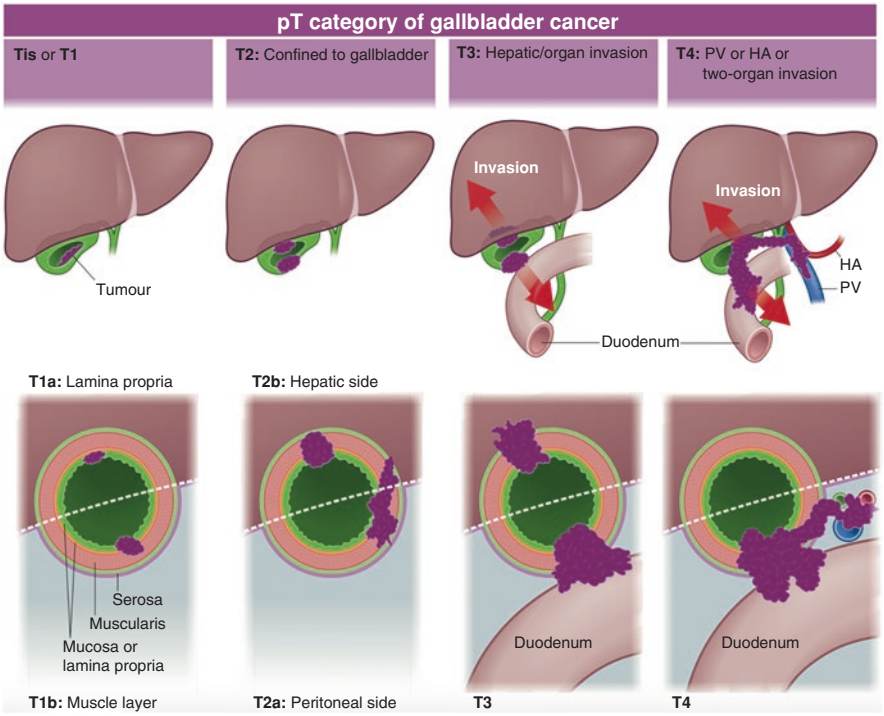


**Fig. 2.2** Illustration of pT categories of the TNM system for gallbladder cancer. (Reprinted by permission from Oxford University Press: SØreide et al. (2019))

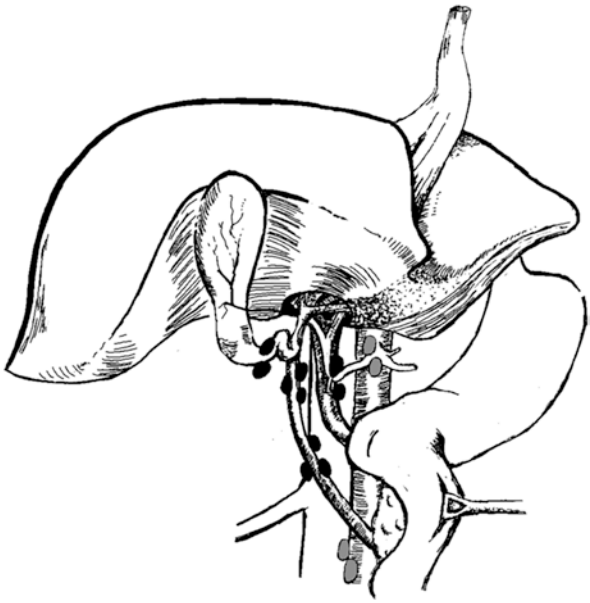

**Fig. 2.3** Illustration of lymphatic nodes typically involved in patients with gallbladder cancer. Black labeled lymph nodes are considered loco-regional, gray labeled lymph nodes as metastatic. (Courtesy of Gavin Chekpui Lo (MD))

### Ultrasonography

The primary modality by which GBC is detected is usually ultrasonography (US), as it is the initial imaging modality for evaluation of patients with abdominal pain or jaundice and has a high sensitivity to detect gallstones and gallbladder masses [16]. However, regular greyscale ultrasonography is limited in detecting early GBC, especially when attempting to differentiate GBC from gallbladder wall thickening due to cholecystitis [25, 26]. Evaluation of depth of invasion appears better in novel ultrasonography techniques such as endoscopic ultrasonography (EUS) and high-resolution ultrasonography (HRUS) [27–30]. Computed tomography (CT), however, has a similar sensitivity to detect malignant gallbladder lesions and is superior in detecting suspicious LNs or distant metastatic disease [27, 31]. The use of HRUS and EUS is therefore limited.

### Computed Tomography (CT)

CT is the primary staging modality for GBC. Its sensitivity and diagnostic accuracy to detect malignant gallbladder wall thickening are 90% and 92%, respectively [32–34]. Since CT is a cross-sectional study, it may be better suited to detect subtle variations of the gallbladder wall which are not visible on US. Moreover, CT is less operator dependent than US. The diagnostic accuracy of CT for the assessment of T-stage is about 85%, with 100% sensitivity for discrimination for T4 lesions, and 79% for the discrimination between T1 and T2 lesions. Nevertheless, overstaging by CT is not a rare occurrence. In one of the included studies (Kalra et al.), 12 of 20 patients were deemed resectable by CT, whereas during explorative laparotomy only 11 of 20 patients underwent definitive resection [35]. Overstaging in this particular patient was primarily caused by duodenal infiltration on CT, which was not present during surgery. Understaging on CT is primarily caused by the low sensitivity of CT for peritoneal (30%) and distant LN metastases (20%) [35].

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has a higher soft-tissue contrast resolution compared to CT MRI with gadolinium-enhanced contrast can be helpful to differentiate between chronic cholecystitis and malignant gallbladder wall thickening, which is challenging using other imaging modalities [36, 37]. In a cohort of patients with PSC, MRI showed a 100% sensitivity for malignancy in gallbladder lesions of over 0.8 cm in size [38]. Precise assessment of the local extent of disease (i.e., involvement of adjacent liver, bile duct invasion, LN invasion, and vascular invasion) is important because it determines the resectability and extent of resection. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive technique providing projection images of the biliary tree. MRI combined with MRCP and MR-angiography (MRA) is superior to CT for assessing the local extent of disease with a sensitivity of 100% for liver and bile duct invasion and 92% for loco-regional LN involvement [39–41]. MRI with MRCP and MRA as part of preoperative staging should be considered in any patient with suspected GBC. It may affect clinical decision-making as it augments the diagnostic accuracy of CT.

**Positron-Emission Tomography**

CT and MRI have a low sensitivity for distant LN and peritoneal metastases [40, 42, 43]. Positron-emission tomography (PET) detects high glucose uptake of tumor cells and is combined with standard CT image. The sensitivity of PET-CT to detect distant and LN metastases is 85–100% and 67–71%, respectively, and it may alter management in 15–23% of preoperatively diagnosed GBC patients [44–47]. One study showed that the yield of PET-CT is lower in patients with iGBC, changing management in only 13% of patients [47]. This is probably caused by the earlier stage of iGBC compared to symptomatic GBC. Another study, in which PET-CT was conducted in patients with ≥pT1b disease before re-resection, showed that PET-CT changed the clinical stage in 38% of patients [48]. PET-CT detected in 50% of patients with pNx disease distant nodal and/or metastatic disease and in 30% of patients with pN1 disease. In summary, PET-CT can be a useful tool in patients who have a high risk for distant disease (i.e., cT3 stage or higher) or in patients with iGBC with positive or suspicious LNs.

### 2.2.3 Histopathological Diagnosis

Histopathological confirmation of GBC is not needed prior to surgery for patients who have potentially resectable disease on imaging and are operable. Nevertheless, if patients are eligible for palliative systemic chemotherapy, pathological confirmation is required. This is typically obtained with percutaneous biopsy of lesions that are suspicious for metastatic disease, or of the primary tumor in patients without metastatic disease for whom a resection is not considered. If GBC patients present with obstructive jaundice, endoscopic retrograde cholangiopancreatography (ERCP) can be used for the drainage procedure, and a brush cytology or biopsy can in the meantime be performed. One study investigated the role of EUS-guided fine needle aspiration (EUS-FNA) in 101 patients with gallbladder masses and biliary obstruction [49]. EUS-FNA confirmed malignancy in 89 out of 98 patients with GBC; sensitivity was 90.8% and the negative predictive value (NPV) was 10%. These outcomes reflect that EUS-FNA is a sensitive tool in this clinical setting. EUS-FNA can also aid in staging by sampling LNs beyond the hepatoduodenal ligament, in particular, aortocaval and coeliac LNs.

### 2.2.4 Staging Laparoscopy

Four studies investigated the role of staging laparoscopy (SL) in patients with GBC; three studies in patients with preoperatively diagnosed GBC [50–52], and one in patients with iGBC [53]. The yield of laparoscopic staging in preoperatively diagnosed GBC is about 23% [52]. Agarwal et al. showed that the benefit of laparoscopic staging was higher in patients with advanced (T3/T4, yield 25.2%) compared to early (T1/T2, yield 10.7%) GBC. The study in patients with iGBC demonstrated a yield of only 4.3%, which might be biased due to a low rate of staging laparoscopy

(46/136 patients, 33.8%) but also due to low prevalence of advanced disease [53]. However, the risk of disseminated disease was closely correlated to T-stage, with up to 26% of T3 patients having disseminated disease. Additionally, patients with a positive resection margin at index cholecystectomy, i.e., margin <1 mm and tumoral involvement of at least one resected LN, were five times more likely to show disseminated disease at re-exploration. In summary, staging laparoscopy should be strongly considered in all patients with suspected locally advanced disease (i.e., T3/4 or N1) on preoperative imaging, and in all iGBC patients with T3 disease or positive (cystic duct) margins.

## 2.3 Management of Stage I-III GBC

Treatment of stage I and II disease is surgical (Tables 2.1 and 2.2). Patients with stage III and IVa GBC have nonmetastatic locally advanced disease, and resection is only performed in selected patients with good performance status after multidisciplinary consideration [16]. Table 2.2 represents the recommended T stage-adjusted resection in GBC. Stage IVB disease is considered as disseminated disease and can be managed with palliative chemotherapy. The treatment for stage IV disease is discussed in Sect. 2.4 "Management of stage IV GBC."

### 2.3.1 T1a Disease

The majority of T1a gallbladder tumors is diagnosed after laparoscopic cholecystectomy (LC) for presumed benign gallbladder disease. In T1a GBC the tumor is limited to the lamina propria and is consequently considered as local disease (Table 2.1, Fig. 2.2). This is supported by the fact that prevalence of LN metastases in patients with T1a GBC is less than 2% and 5-year survival after LC is reported to approach 100% [54–57]. A systematic review including 706 patients with T1a GBC showed no significant differences in survival between patients that underwent

**Table 2.2** T-stage-adjusted resection in gallbladder cancer

| T stage | Recommendation |
|---|---|
| Tis/T1a | Simple cholecystectomy |
| T1b-T2 | Extended cholecystectomy with regional lymphadenectomy: Cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 and lymphadenectomy of the hepatoduodenal ligament |
| T3 | Extended cholecystectomy as for T1b-T2, but GBC in the gallbladder neck or cystic duct may require right hepatectomy extended to segment 4b and/or bile duct resection with hepaticojejunostomy to obtain clear margins. Moreover, depending on involved organ: Wedge resection of duodenum or transverse colon. Only in patients with good performance status |
| T4 | As for T3, palliative care if involvement of main portal vein or proper hepatic artery. Most patients in this category are unlikely to benefit from resection even if technically feasible. Only in patients with good performance status |

simple versus extended cholecystectomy (EC), i.e., cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 and lymphadenectomy of the hepatoduodenal ligament [55]. Therefore, the consensus is that a simple cholecystectomy suffices for the treatment of T1a GBC.

### 2.3.2 T1b Disease

Like T1a GBC, T1b GBC is typically diagnosed after LC for benign indications and is generally classified as early GBC. However, some argue that T1b GBC should be considered regional disease. There have been reports of loco-regional spread at presentation and LN metastases found in approximately 0–10% of T1b GBC patients [55, 58, 59]. Several retrospective cohort studies comparing survival after simple versus EC, i.e., cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 and lymphadenectomy of the hepatoduodenal ligament, have been performed with conflicting outcomes [57–63]. Of three recently performed meta-analyses, two do not show prolonged survival after EC compared to simple cholecystectomy [57, 59]. The third meta-analysis did show favorable survival outcomes after EC (OR 2.75, 95% CI 1.13–6.69; $p = 0.03$). However, the authors considered the grade of evidence to be low as most included studies had serious limitations [64]. Nonetheless, several guidelines, including the National Comprehensive Cancer Network (NCCN) guideline, support EC as first-line treatment for T1b GBC [16, 18, 65]. The procedure is described in Sect. 2.5.2 "GBC suspicion before surgery."

### 2.3.3 T2/T3 Disease with or Without Lymphadenopathy

The standard of care treatment of T2 and T3 GBC is an EC, i.e., cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 and lymphadenectomy of the hepatoduodenal ligament [16, 64, 66]. Though, currently, no consensus exists on the extent of liver resection. A 2010 study found superior survival in T2 and T3 GBC after anatomical segmentectomy of 4b and 5 versus nonanatomical 2-cm wedge resection [67]. However, another study of 485 T2/T3 patients with R0 resection reported no difference in survival between patients undergoing a nonanatomical 2-cm wedge resection compared to either anatomical segment 4b and 5 resection or extended right hepatectomy [68]. A similar study in patients with T2 disease showed a higher rate of postoperative complications after anatomical segment 4b and 5 resection compared to a nonanatomical 2-cm wedge resection, without significant survival differences between both groups [69]. Finally, a study in 16 patients with T3 disease showed no difference in survival in patients who underwent formal hepatectomy compared to a nonanatomical 2-cm wedge resection alone [70]. In summary, anatomical segmentectomy does not provide a survival benefit compared to a nonanatomical 2-cm wedge resection. More extended liver resections should only be performed if required to achieve R0 resection margins. For example, in GBC in the neck or cystic duct, the right hepatic artery might be involved necessitating a formal right hemihepatectomy.

### 2.3.4 Survival and Prognostic Factors After (Re-)resection

Overall, 5-year survival of GBC is estimated to be 80–100% in stage 0 and I disease, 40–75% in stage II disease, 8–28% in stage IIIA disease, 8% in stage IIIB disease, and 0–8% in stage IV disease (Table 2.1) [4, 16]. Estimated 5-year overall survival (OS) after potentially curative resection is 21% with occurrence rate of at least 50%. Although pT-stage, pN-stage, and positive resection margin are major prognostic factors, additional independent prognostic factors can further improve the prediction of survival after resection [71]. These prognostic factors include serum CA 19.9 levels, vascular invasion, perineural invasion, and differentiation grade [72–75]. Other prognostic factors include intraoperative bile spillage at index cholecystectomy and jaundice at presentation. Blakely et al. showed in a small subset of GBC patients ($n = 12$) that intraoperative bile spillage is associated with decreased progression-free survival (HR 5.5, 95% CI 2.63–32.3, $p = 0.0014$) [76]. Also, in a population-based study in Canada with 82 GBC patients, peritoneal carcinomatosis occurred more frequently in cases with bile spillage at the index cholecystectomy (24% vs. 4%, $p < 0.01$) [77]. These patients were also less likely to undergo complete re-resection (25% vs. 56%, $p < 0.01$) and to achieve R0 resection (OR 0.19, 95% CI 0.06–0.55). Therefore, bile spillage should be avoided at any time when GBC is suspected. Jaundice at presentation in GBC reflects T3/T4 disease and is associated with poor survival as well. Regardless of the implemented treatment, a median survival of 6 months was observed in jaundiced GBC patients with no survivors beyond 2 years after diagnosis [78].

The benefit of survival of re-resection is mainly determined by the presence and location of residual disease (RD) [58, 79]. In a group of 36 pT2 and pT3 iGBC, OS after re-resection was significantly worse if RD was present in the EBD and/or distant sites (5-year OS: 14.3%) compared to no RD (5-year OS: 88.7%) or RD in the gallbladder bed, stump of cystic duct and/or regional LNs (5-year OS: 55.6%) [80]. Also, Ramos et al. observed no improved OS of patients with regional or distant RD [80]. Therefore, creating a model to predict RD in iGBC might lead to better selection of patients that most likely benefit from surgery. Ethun et al. published a pathology-based GBC Risk Score, and also Creasy et al. developed a model to stratify high-risk patients [74, 81]. It seems that benefit in survival of re-resection is especially observed in pT2 and pT3 iGBC. However, in pT2 patients, it remains unclear whether the increase in survival in patients who received re-resection is a result of the procedure itself or whether the apparent survival benefit is attributable to the upstaging of these patients.

## 2.4 Management of Stage IV GBC

In T4 GBC disease invasion of the main portal vein or hepatic artery or two or more extrahepatic organs or structures is present. It remains unclear whether locally advanced invasion into the porta hepatis, duodenum, or pancreas necessitating extended surgery such as hepatopancreatoduodenectomy should be considered as

resectable disease, which also accounts for vascular reconstructions. Select case series from high-volume expert centers have demonstrated the feasibility to achieve R0 resection [82–84]. However, these extended resections paired with high morbidity and mortality rates are generally not accepted. Moreover, R0 resections are only achieved in a subset of cases, and even then, over 50% of patients will suffer from a recurrence. In more than 90% of patients, GBC eventually metastasizes to the liver and extra-regional LNs. Other sites of metastatic spread are the lung, bones, and brain [85, 86]. If distant metastases are found at staging for GBC, a resection does not prolong survival [16]. Liver transplantation is not a viable treatment option for GBC due to the high risk of early distant disease, which is not resolved with a new liver [87–89]. No survival benefit by surgery is expected in patients with coeliac or aortocaval LN metastases [16, 43].

In summary, extended resection should only be considered by highly specialized teams in extremely fit patients. Even then, outcomes are poor, and risk of recurrence remains high.

## 2.5 Surgical Procedures for GBC

The surgeon can encounter GBC in the following two scenarios: incidentally (intra- or postoperatively during/after routine cholecystectomy) or in symptomatic patients with findings suspicious for malignancy on imaging. The majority of patients (60%) is diagnosed incidentally, whereas 40% of patients present with symptomatic disease [90]. According to the situation a different approach by the surgeon is required.

### 2.5.1 GBC Suspicion During Routine Cholecystectomy

GBC is found at pathological evaluation in about 1% of all laparoscopic cholecystectomies performed for cholelithiasis [91–93]. Gross intra-operative examination and opening the specimen to inspect the mucosa have a detection rate of 92% for iGBC [94]. If neoplasia at laparoscopy is suspected (e.g., due to the presence of a mass), the surgeon should strongly consider to not remove the gallbladder and first perform staging for GBC. Moreover, referral to a specialized hepatobiliary center is needed. The drawback of proceeding with surgery is that the resection may be futile (i.e., in patients with distant metastases). Also, a simple cholecystectomy may result in tumor spill and a R2 resection, while an EC may not be required. If abnormal mucosa is macroscopically noticed after the cholecystectomy, the gallbladder must be sent for frozen-section analysis, and definitive resection (i.e., nonanatomical 2-cm wedge resection of segment 4b and 5 with regional lymphadenectomy) may be undertaken during the same surgical procedure if a hepatobiliary surgeon is available.

In case of concomitant cholecystitis and high suspicion for GBC, it may be recommended to directly perform an EC. In the absence of GBC expertise, it is oncologically safe to abort the procedure and refer the patient to a tertiary center for

further evaluation [17, 95, 96]. EC might not be required, but will decrease the chances of gallbladder perforation and associated risk of tumor spill and peritoneal seeding, as stated in Sect. 2.3.4 "Survival and prognostic factors after resection".

In conclusion, in case GBC is suspected during routine cholecystectomy, it is recommended to refer the patient to a specialized hepatobiliary center and first perform staging. In the presence of concomitant cholecystitis, it is recommended to perform an EC to avoid risk of intra-operative bile spillage.

#### 2.5.1.1 Approach

Historically, a laparoscopic approach for GBC in general has been contraindicated due to concerns about increased risk of port site recurrences, peritoneal metastases due to bile spillage, and nonradical resection [97]. These risks have subsided due to improved recognition of GBC intraoperatively, improvements in laparoscopic skills of hepatobiliary surgeons, and the use of a retrieval bag [98]. Studies found that an initial laparoscopic approach does not influence the course of early-stage GBC if definitive resection during or after LC is performed [99, 100]. A recent meta-analysis by Zhao et al. showed a higher 5-year survival rate in patients who underwent laparoscopic compared to open surgery, though bias may have been present since the laparoscopic approach was more often used in earlier tumor stages [99].

### 2.5.2 GBC Suspicion Before Surgery

After a complete workup, stage-adjusted resection is scheduled (Table 2.1). Staging laparoscopy is strongly recommended in all patients, particularly in patients with suspected T3/T4 disease or positive resection margin in iGBC [49–51, 101]. If peritoneal or hepatic metastases are found, resection is futile [102]. Both open and minimal-invasive approaches are options for curative-intent resection of GBC. A minimal-invasive approach, however, is only recommended in expert centers [98].

#### 2.5.2.1 Open Approach

In an open approach, adequate exposure can be obtained through a right subcostal incision (Kocher) with or without extension to the left (Chevron) with installation of retractors (e.g., OmniTract, Thompson, or Rochard). The teres ligament is ligated and retracted cranially to expose the undersurface of the liver and the hepatoduodenal ligament. Re-inspection for undetected disseminated disease should be performed because staging laparoscopy may have missed occult metastatic disease. Intraoperative ultrasound can be used to evaluate depth of invasion, location of the primary tumor in relation to vascular structures, and rule-out liver metastases [103].

#### 2.5.2.2 Lymphadenectomy

Assessment of the distant nodal stations is performed to rule out stage IV disease because of extra-regional positive LNs [104]. A Kocher maneuver is executed to assess for aortocaval nodes. Frozen-section analysis of aortocaval nodes prevents a futile resection in 18.6% of GBC patients [105]. Coeliac LNs are also extra-regional

and should be sent for frozen section as well. The LN dissection starts posterior to the head of the pancreas and duodenum, also exposing the vena cava, aorta, and retroportal region. At the cranial border of the pancreas, the common hepatic artery is exposed, and dissection continues toward the celiac arteries. The gastroduodenal branch is preserved, but the right gastric artery is transected to facilitate LN retrieval. The portal vein, common hepatic artery, and common bile duct are freed up from surrounding lymphatic tissue. Regional lymphadenectomy of the hepatoduodenal ligament may be sent for pathological examination as a single specimen, but frequently the lymphadenectomy involves several separately resected LNs. A minimum of six LNs of the hepatoduodenal ligament should be harvested for adequate staging [16]. All lymphatic vessels should be tied to prevent postoperative chyle leak.

#### 2.5.2.3 Assessment of Main Portal Vein and Common Hepatic Artery

Involvement of the main portal vein and common hepatic artery is evaluated. If either structure is affected, or if more than one extrahepatic organ is involved, the tumor is classified as T4 GBC and a resection is futile for almost all patients. Inclusion of the main portal vein and common hepatic artery, however, is unlikely in the absence of jaundice and can be mostly ruled out on preoperative imaging. The cystic artery and duct are divided flush with the right hepatic artery and the common bile duct if no signs of tumor involvement are present, and frozen-section analysis of the cystic duct resection margin is performed.

#### 2.5.2.4 Assessment of the Extrahepatic Biliary Tree

If the cystic duct margin is positive or if the tumor directly invades the common bile duct, extrahepatic bile duct (EBD) resection is required to obtain R0 resection. Involvement of the bile duct is most likely in patients with a tumor in the neck of the gallbladder or in the cystic duct, or when jaundice was present at diagnosis. Jaundice in GBC is a sign of advanced disease with tumor involvement of the EBD. Though, Varma et al. reported 50% R0 resection in jaundiced GBC patients [106]. Tran et al. did observe in 108 patients presenting with jaundice in GBC a higher perioperative morbidity (69% vs. 38%, $p = 0.002$) but no higher 90-day mortality (6.5% vs. 3.6%, $p = 0.35$) compared to nonjaundiced patients who underwent curative-intent surgery. Japanese guidelines recommend preoperative biliary drainage in all jaundiced GBC patients, but there is no consensus regarding the approach and duration for drainage, nor the target bilirubin level. In conclusion, the presence of jaundice reflects T3/4 disease and is a poor prognostic factor [107]. Therefore, resection in GBC patients with jaundice at presentation, should only be considered in selected cases.

Routine EBD resection in nonjaundiced GBC patients to avoid isolated bile duct recurrences is not recommended. In a series of 26 nonjaundiced GBC patients who underwent a radical resection without EBD resection, no isolated recurrences at the EBD were found [108]. Moreover, EBD resection does not result in more harvested LNs [109]. The associated morbidity of an EBD resection has to be taken into account as well. D'Angelica et al. reported that 33% of patients had a complication requiring re-intervention or resulted in permanent disability or death, versus 13% of

patients who had no EBD resection [110]. Thus, only in highly selected patients, the common bile duct is divided as distal as possible posterior to the pancreatic head. The resection margin must be examined by frozen-section analysis. A 70 cm Roux-en-Y jejunal loop with jejuno-jejunostomy is prepared and positioned via a retrocolic route. The hepaticojejunostomy can be performed using running or separate sutures. The mesogap is closed with running or separate 3–0 Vicryl or PDS sutures.

#### 2.5.2.5 Assessment of Right Portal Vein and Right Hepatic Artery

If the right hepatic artery and/or right portal vein are involved, a right hemihepatectomy is required to achieve R0 resection. This should only be performed in highly selected patients and is typically suspected based on preoperative imaging. In order to adequately assess portal vein invasion, the liver is split along the umbilical fissure. R0 resection is possible if the tumor does not invade the left portal vein or left hepatic artery, obviously in a patient with a good performance status and an adequate liver remnant. Aberrant vascular and biliary anatomy should be noted on preoperative imaging. The left hepatic duct is transected and right hepatic artery ligated. Vascular clamps are placed on the main and left portal vein to transect the right portal vein. Transection is executed and depending on the extent of invasion of the right portal vein, either closure of the portal vein stump or a primary end-to-end anastomosis between the main and left portal vein is accomplished with a running, nonabsorbable suture (Prolene™ 5–0). Then, right hemihepatectomy with *en-bloc* resection of the gallbladder is completed preserving the middle hepatic vein. In-flow occlusion might be obtained by applying the Pringle maneuver in an intermittent or continuous fashion, and central venous pressure is kept below 5 mm Hg. The right liver lobe is mobilized by dividing the surrounding ligaments and ligating the short hepatic veins into the cava. Subsequently, the right hepatic vein is identified. The right hepatic vein is then transected, either by vascular stapler or suture ligature. Two traction sutures are placed at the inferior margin of the liver, one at each side of the demarcation line, and transection of the liver parenchyma is initiated. Superficial incision of the parenchyma takes place with diathermy, and further dissection can be performed with Kelly clamping or using an energy device, i.e., Thunderbeat® (Olympus Medical Systems Corp., Tokyo, Japan) or Enseal® (SurgRx Inc., Redwood City, CA, USA). During parenchymal transection, optimal exposure is obtained by either holding the right hemiliver with the left hand or performing a hanging maneuver, i.e., passing a tape between the anterior surface of the inferior vena cava and the liver. Hemostasis and biliostasis is verified with gauzes, and potential leaks should be suture-ligated. In order to prevent rotation of the left hemiliver, the falciform ligament is reattached. Abdominal drainage can be considered if a hepaticojejunostomy was performed or if a percutaneous transhepatic stent has been removed.

#### 2.5.2.6 Nonanatomical or Anatomical Segment 4b and 5 Resection

If the tumor does not invade the porta hepatis or liver parenchyma, the gallbladder is removed with a 2-cm nonanatomical wedge of the adjacent liver parenchyma using an energy device as aforementioned. The primary aim of liver resection in

patients with GBC is to achieve a negative resection margin on the hepatic side. Therefore, liver resection should be performed according to the extent of liver parenchyma invasion and might be more extensive. Intraoperative ultrasound can be useful to delineate the extent of the tumor [111]. The transection line is marked on the liver capsule with electrocautery. Traction sutures can be placed adjacent to the demarcation line at the inferior margin of the liver. Parenchymal transection is performed with Kelly clamping or an energy device, and vessels are ligated or clipped. A vascular stapler can be used to control large intrahepatic vessels. Transection can also be performed along the anatomical border of segment 4b and 5. Then, transection begins medially, encountering the middle vein first and then the segment 5 pedicle. The main anterior pedicle and pedicle adjacent to segment 8 are at risk for inadvertent injury during parenchymal transection. The gallbladder is removed en-bloc. Hemostatic agents can be used according to the surgeons' preference (i.e., TachoSil®, Surgicel®). Abdominal drainage is not needed [112].

#### 2.5.2.7 Laparoscopic and Robotic Approach

In a laparoscopic approach, the same principles as in open surgery are respected. Technical feasibility and safety of laparoscopic wedge resection, anatomical segment 4b and 5 resection, hepatoduodenal lymphadenectomy, and EBD resection have been reported but should only be carried out in expert centers [113–115]. These procedures require an expert advanced laparoscopic surgical team that will still have a long learning curve. For a systematic description of laparoscopic approach in GBC, we refer to a recent review of Vega et al. [116]. Recently, robotic approach for extended resections in GBC has also been described and considered safe and feasible [117, 118]. The surgical technique used in the robotic approach is depicted by Goel et al. [117]. The main advantage of robotic approach is the shorter learning curve.

### 2.5.3 GBC Diagnosed at Histopathological Analysis After Routine Cholecystectomy

If histopathology results are consistent with GBC, appropriate workup as described in Sect. 2.2.2 "Staging: anatomy and imaging" is warranted. In addition, review of initial imaging results, the operative note, and the histopathology report of the performed cholecystectomy is mandatory. A re-resection is recommended for patients with T1b, T2, or T3 iGBC in the absence of metastatic disease and/or poor performance status [16].

#### 2.5.3.1 Re-resection: Timing and Open Versus Laparoscopic Approach

Re-resection is considered more technically challenging than primary resection as adhesions from the index surgery are expected. Optimal timing for re-resection considering these technical aspects and tumor biology is between 4 and 8 weeks [119]. Data on outcomes of laparoscopic re-resection has only been reported by expert

centers [98]. One retrospective study did not detect survival differences between patients undergoing an open or laparoscopic re-resection [120].

#### 2.5.3.2 Extent of Re-resection

The aim of re-resection is twofold; to remove residual cancer and to perform adequate staging. Re-resection consists of either an open or laparoscopic nonanatomical 2-cm wedge resection of segments 4b and 5 and a lymphadenectomy with a minimum count of six LNs [16]. Rarely, more extensive procedures such as major liver resection, vascular resection, or common bile duct or adjacent organ resection are required to obtain negative resection margins. The same surgical principles apply for re-resection as for primary resection as described in Sect. 2.5.2 "GBC suspicion before surgery" with the exception that the gallbladder already has been removed.

#### 2.5.3.3 Port-Site Resection

Historically, port-sites resection at the time of re-resection for iGBC was recommended because of the high rate of wound recurrences. However, recent evidence shows that excision of port-sites is not correlated with improved overall or recurrence-free survival and causes a 10% rate of incisional herniation [121, 122]. Moreover, port-site resection is a disfiguring operation. If pathological examination of the specimen is positive, the patient has peritoneal metastasis. However, ESMO guidelines recommend resection of port-sites when the gallbladder was perforated at the index cholecystectomy or was not removed using a retrieval bag [123].

## 2.6 Postoperative Management

Postoperative care should be adjusted to the extent of surgery, with initial surveillance in an intensive care unit after major hepatectomy with bile duct reconstruction. Hemoglobin, coagulation parameters, liver function, and electrolytes should be monitored. Standard care includes adequate pain control, early ambulation, thrombosis prophylaxis, adequate fluid management, and early enteral diet to avoid general surgical complications such as pneumonia, deep vein thrombosis, pulmonary embolism, and pleural effusion.

### 2.6.1 Complications

Complications specific to liver resection include postoperative hemorrhage, bile leak with biloma formation, and liver failure. Posthepatectomy bleeding occurs in 1–8% of patients and management may be conservative (i.e., blood transfusion) or invasive (i.e., embolization or relaparotomy) depending on severity [124]. Parenchymal bile leaks are mostly self-limiting with percutaneous drainage, although in more severe cases endoscopic sphincterotomy and/or stent placement may be required. Injuries to the right anterior bile duct, segment 8 bile duct, or

extrahepatic bile ducts more likely require endoscopic and/or surgical management. Awareness for the risk of posthepatectomy liver failure in case of major liver resections is important, particularly in jaundiced patients [125].

### 2.6.2 Postoperative Surveillance

No high-quality studies regarding optimal postoperative surveillance strategies have been conducted. However, the general consensus is that surveillance should consist of physical examination, laboratory testing, and/or CT scan of the thorax and abdomen once every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter [123].

### 2.6.3 Adjuvant Therapy

At least 50% of patients with resected GBC will suffer from a recurrence [16, 126]. After a potential curative resection the median time to recurrence is only 12 months. 85% develop a distant recurrence without a concomitant loco-regional recurrence, and 15% has a loco-regional recurrence without distant recurrence [127]. In other cancers, adjuvant chemotherapy has shown to increase survival by increasing local control and decreasing distant disease. However, adequately powered trials investigating the value of adjuvant chemotherapy in GBC alone have not been performed. In the past decade, multiple RCTs have investigated the value of adjuvant chemotherapy in all patients with biliary tract cancer (BTC). The BILCAP trial compared adjuvant capecitabine to observation alone in all patients with resected BTC and did not find a significant difference in survival in the primary, intention-to-treat analysis; median overall survival was 51 months in the capecitabine group compared with 36 months in the observation group (HR 0.81, 95% CI 0.63–1.04; $p = 0.097$) [128]. In the per-protocol analysis, a survival benefit of 17 months was found (HR 0.75, 95% CI0.58–0.97, $p = 0.028$). No subgroup analysis, including only GBC patients was conducted.

## 2.7 Palliative Therapy

The plurality of patients with GBC has noncurable disease due to presentation at an advanced stage of disease or due to recurrence after curative-intent resection. In the palliative setting, obstructive jaundice develops in about half of the patients requiring adequate biliary drainage for symptomatic relief and/or initiation of chemotherapy [129]. Careful patient selection is mandatory for palliative chemotherapy [130, 131]. Endoscopic or percutaneous stenting is preferred to obtain biliary decompression. Saluja et al. performed an RCT comparing palliation of obstructive jaundice by endoscopic versus percutaneous drainage in 44 GBC patients with hilar biliary obstruction [132]. Compared to endoscopic drainage, patients who

underwent percutaneous drainage had a higher rate of relief of obstruction (89% vs. 41%, $p < 0.001$), lower rates of cholangitis (11% vs. 48%, $p = 0.002$), and similar quality of life. However, in both the drainage approaches, procedure-related deaths were reported; 4% in the percutaneous group versus 8% in the endoscopic group. Gastric outlet obstruction might occur due to duodenal compression or infiltration and may be resolved by surgical bypass in selected patients. Nevertheless, endoscopic stenting, decompressive gastrostomy, and endoscopic-guided gastroenterostomy are preferred in most patients [133].

## 2.8 Conclusion and Future Perspectives

The outcomes of GBC patients across all stages remain poor. Early detection, adherence to guidelines, referral to a hepatobiliary center with GBC expertise, better patient selection for surgery, fine-tuning the extent of surgery, reducing morbidity and mortality of surgery, and more effective systemic treatment options can improve the prognosis of GBC.

Given the rarity and heterogeneity of GBC, development of randomized controlled trials regarding surgical treatment is challenging. Trials investigating the value of (neo-) adjuvant chemotherapy are ongoing and targeted therapy may be the next step to improve treatment. Recent studies show that GBC patients carry several actionable genomic alterations for which targeted therapies are readily available and the first outcomes seem promising [134–136]. In conclusion, a multidisciplinary approach appears vital to further improve prospects of GBC patients.

**Key Points**

- GBC is the most prevalent biliary tract malignancy and remains highly lethal.
- The surgeon may be confronted with GBC in two scenarios: incidentally (intra- or postoperatively during/after cholecystectomy for cholelithiasis or cholecystitis), or in symptomatic patients with findings suspicious for malignancy on imaging.
- Imaging work-up of patients suspect for GBC includes at minimum local staging and assessment of potential distant metastases by CT. MRI and PET-CT may be considered in a more advanced stage.
- Histopathological confirmation is not required before planning surgery in patients with imaging findings suspect of GBC.
- Staging laparoscopy should be strongly considered in all patients with suspected locally advanced disease (i.e., T3/4 or N1) on preoperative imaging, and in all incidental GBC patients with T3 disease or positive (cystic duct) margins.
- Overall survival is mainly determined by tumor stage, lymph node status, and resection margin. Estimated 5-year overall survival after potentially curative resection is 21% with a recurrence rate of at least 50%.
- The presence of jaundice in GBC patients is a poor prognostic factor. Potential curative-intent surgery should only be considered in selected cases.

- If GBC is suspected during routine cholecystectomy and no expertise in GBC is available, it is recommended to abort the procedure and refer the patient to a specialized center for appropriate staging.
- If GBC is suspected during routine cholecystectomy with concomitant cholecystitis, a cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 might be recommended to avoid the risk of intra-operative bile spillage.
- The principal aim of surgical resection is attainment of negative margins.
- A simple cholecystectomy suffices for the treatment of T1a GBC.
- Resection for GBC with invasion in or beyond the muscular layer includes a cholecystectomy with nonanatomical 2-cm wedge resection of segments 4b and 5 and lymphadenectomy of the hepatoduodenal ligament (minimum of 6 LNs). If more extended resections are necessary to achieve R0 resection, shared decision-making should weigh surgical morbidity and mortality versus expected survival benefit.
- Re-resection for iGBC is recommended for patients with pT1b, pT2, or pT3 disease without metastatic disease and/or poor performance status.
- Extrahepatic bile duct resection should not be performed routinely and is only recommended for selected patients with a positive cystic duct margin or direct tumoral involvement of the hepatic duct.
- Resection of laparoscopic port-sites in patients with GBC is not recommended because it is not associated with better survival.
- A multidisciplinary approach appears vital to further improve prospects of GBC patients.

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