Gallbladder Cancer

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Learning Objectives
After reading this chapter, you should know how to manage patients with:

- A gallbladder polyp found on imaging
- Gallbladder cancer incidentally found at pathologic review after a cholecystectomy for cholelithiasis
- Gallbladder cancer suspected during cholecystectomy for cholelithiasis
- A gallbladder and/or liver mass found on imaging suspicious for gallbladder cancer

Background

Gallbladder cancer (GBC) is the most common biliary cancer: in the USA, each year about 6,000 patients are newly diagnosed with GBC [1]. Historically, surgery for GBC was rare because patients typically presented with advanced disease when symptoms develop. Only 5 % of GBC patients underwent surgical resection in a series of MD Anderson between 1940 and 1976 [2]. Nowadays, GBC patients are often diagnosed at an early (asymptomatic) stage, typically on pathologic review after laparoscopic cholecystectomy for cholelithiasis (i.e., incidental GBC). Also, surgical management of GBC improved with the introduction of ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) to determine the extent of disease. Currently, a cholecystectomy with en bloc liver resection of segments 4b and 5 with lymph node dissection of the hepatoduodenal ligament is recommended for most medically fit patients with resectable GBC [3]. Improvements in both anesthesia and surgery have reduced the postoperative morbidity and mortality [4].

The focus of this chapter is the surgical management of GBC patients. We first discuss risk factors, anatomy, and staging of GBC. The core of this chapter is structured based on the patient's presentation. The patient may present to the surgical oncologist with:

- A gallbladder polyp found on imaging (US, CT, or MRI)
- Incidental GBC found at pathologic review after cholecystectomy, typically for cholelithiasis
- Incidental GBC suspected during cholecystectomy, typically for cholelithiasis
- A gallbladder and/or liver mass found on imaging suspicious for GBC

Next, we describe the surgical procedures for GBC, postoperative care and complications, and adjuvant and palliative treatments. Because of the low incidence of GBC, no randomized controlled trials (RCTs) have been performed to evaluate surgical management. Guidelines are therefore based on anatomic studies, retrospective case

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series, and registries. RCTs evaluating adjuvant and palliative treatments typically randomize patients with any biliary cancer: conclusions regarding GBC patients are drawn from subgroup analyses or based on the assumptions that biliary cancers are similar.

Risk Factors

Chronic inflammation of the mucosa of the gallbladder is associated with GBC. GBC patients typically have coexisting cholelithiasis (90 %). However, by contrast, only about 1 % of patients with cholelithiasis are diagnosed with GBC. Cholelithiasis may cause chronic inflammation resulting in malignant transformation, or cholelithiasis and GBC may share pathogenetic features. Less common causes of chronic inflammation are pancreaticobiliary maljunction (especially in Asia), typhoid infection, and biliary-enteric fistula. These causes of chronic inflammation confer increased risks of GBC up to 10-fold.

Geography is an important risk factor for GBC: while in the Western world the incidence is 1–2 per 100,000, the incidence in India, Pakistan, Japan, Korea, and Ecuador is up to 20-fold higher [5]. In the USA, women are about twice as likely to develop GBC as men. Familial GBC is rare.

The progression of adenoma to carcinoma appears less important in the pathogenesis of GBC than in the pathogenesis of colorectal cancer. Adenomatous polyps are rare and typically do not harbor GBC unless very large; however, severe dysplasia is often found adjacent to GBC.

Anatomy and Staging

Understanding guidelines and controversies for surgical management of GBC requires knowledge regarding the relation of the gallbladder to surrounding structures, as well as patterns of lymphatic and venous drainage of the gallbladder. The gallbladder is located at the undersurface of segment 4b and segment 5 of the liver (Fig. 11.1a–c). In 60 % of GBC patients, the tumor is found in the fundus, 30 % in the body, and 10 % in the neck of the gallbladder [6]. Tumors in the gallbladder neck are more likely to involve the bile ducts because of the neck's close proximity to the right hepatic duct and the biliary confluence [7].

The intraperitoneal portion of the gallbladder is covered with (visceral) peritoneum or serosa (Fig. 11.1d). If the cancer extends beyond the serosa of the gallbladder, it may involve surrounding organs such as the stomach, duodenum, pancreas, or transverse colon (Fig. 11.1c). The part of the gallbladder facing the liver has no peritoneal covering: only a layer of perimuscular connective tissue called the cystic plate separates the muscularis of the gallbladder from the liver parenchyma (Fig. 11.1d). A simple cholecystectomy involves dissection between the muscularis of the gallbladder and the cystic plate. Consequently, if GBC is discovered at pathologic review after a simple cholecystectomy, the resection margin is likely involved, unless the tumor did not invade the muscularis and is limited to the lamina propria (T1a).

GBC typically arises in the mucosa of the gallbladder, with adenocarcinoma or its variants (adenosquamous, squamous) found in 98 % of all patients. Rare histologies of the gallbladder include neuroendocrine tumors, sarcomas, or metastatic diseases such as melanoma. The most common infiltrative subtype invades the entire gallbladder in the subserosal plane, followed by invasion of the liver and the porta hepatis. The nodular subtype forms a more circumscribed lesion; the papillary type forms polypoid lesions and is less invasive.

Dye studies have demonstrated the route of lymph flow from the gallbladder first to the cystic duct node and the nodes around the bile duct, then to nodes around the hepatic vessels and posterior to the pancreas, and finally to the aortocaval nodes near the left renal vein (Fig. 11.2) [8]. In some patients, additional lymphatics are found connecting regional lymph nodes directly to aortocaval nodes. Positive lymph nodes beyond the hepatoduodenal ligament (i.e., periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes) are considered stage IV disease since the seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification for GBC [9].

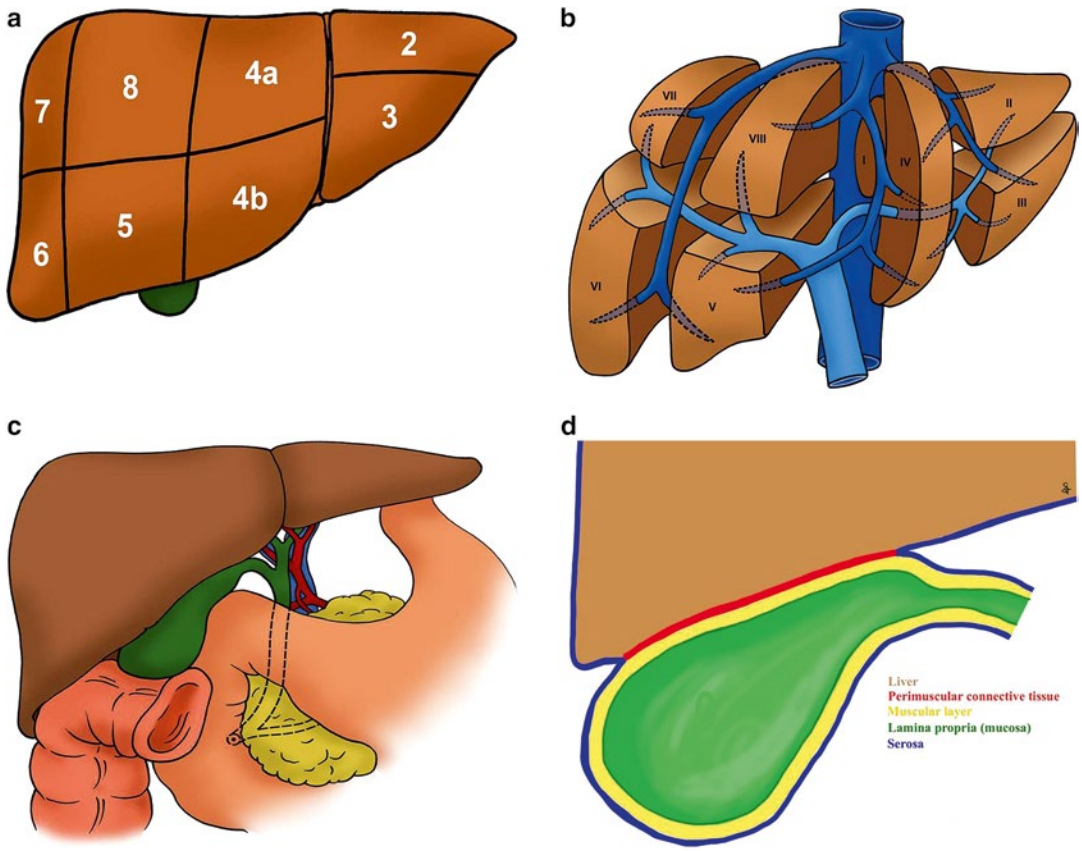

Fig. 11.1 (**a**) The gallbladder (*green*) is contiguous with segments 4b and 5 of the liver. Segment 1 (caudate lobe) is not shown. (**b**) Couinaud classification of the liver divides the liver into eight segments. (**c**) Illustration of the close relationship of the gallbladder to surrounding organs: the liver, duodenum, and transverse colon. Moreover, the cystic duct and neck of the gallbladder are in close proximity to the structures in the hepatoduodenal ligament: the common bile duct (*green*), portal vein (*blue*), and hepatic artery (*red*). (**d**) Layers of the gallbladder wall: the portion facing the liver is indicated in *red*, and the portion facing the peritoneal cavity is indicated in *blue* (Courtesy of Quyen D. Chu, MD, MBA, FACS)

Although lymphatic spread is important for staging, spread to distant sites occurs mainly through hematogenous dissemination, either directly or associated with invasion into the liver parenchyma [10]. When indocyanine green is injected in the cystic artery of GBC patients, the dye extends up to 4 cm into the parenchyma of segments 4b and 5 of the liver [11]. In an immunohistochemical study of liver resections for GBC, intrahepatic portal vein invasion was detected in more than half of the patients, up to 12 mm beyond the border of direct invasion. Metastatic nodules were found in 26 % of GBC patients, on average 16 mm beyond the border of direct invasion [12].

Table 11.1 presents the AJCC seventh edition guideline for staging of GBC, which is based on the anatomical considerations described above, as well as prognostic research [9]. Figure 11.3a presents overall survival of more than 10,000 patients with GBC diagnosed in the years 1989–1996 [9]. These data are from the National Cancer Data Base. Figure 11.3b presents overall survival of patients with GBC who had surgery, stratified by T stage and N stage [13]. These data are from the Surveillance, Epidemiology, and End Results (SEER) program, representing 26 % of the US population for the period 1991–2005. Patients with metastatic disease and stage T4 at the time of surgery were excluded [13].

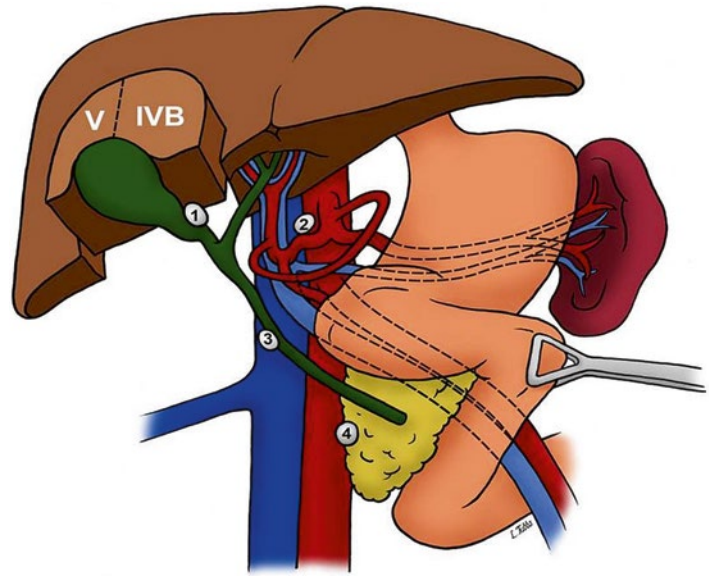

Fig. 11.2 Regional lymphadenectomy for gallbladder cancer includes lymph nodes in porta hepatis, hepatoduodenal and gastrohepatic ligament, and retroduodenal regions
Lymph Node Stations for Gallbladder Cancer
1: Cystic duct lymph node
2: Common hepatic artery lymph node
3: Portocaval lymph nodes
4: Common bile duct lymph nodes (Courtesy of Quyen D. Chu, MD, MBA, FACS)

Gallbladder Polyp on Imaging

Polypoid lesions and focal wall thickening of the gallbladder are found on ultrasound (US) in 3–7 % of healthy adults [14–16]. Their incidence has increased with more frequent use and improved resolution of US. Only rarely do they cause symptoms by obstructing the gallbladder outlet. Although most of these lesions are benign, some are premalignant (adenomatous polyps), and rarely GBC is found. The risk of malignant transformation of gallbladder polyps, while possible, is extremely low for small lesions (<1 cm) and appears to be lower than previously reported for larger lesions (>1 cm). Additionally, it should be recognized that small polypoid lesions are very often nonneoplastic.

Ultrasound cannot reliably distinguish premalignant polyps from pseudopolyps such as cholesterol polyps. The size of the polyp is an important predictor of malignancy. Based on a study in 1982, surgical resection has been recommended for polyps of at least 10 mm, because GBC was found only in polyps larger than 12 mm [17]. More recent studies confirmed that malignancy is extremely rare, if found at all, in polyps smaller than 10 mm, except in patients with primary sclerosing cholangitis (PSC) [18–20]. Of all polyps found on US, 7–29 % are larger than 10 mm. Risk factors for malignancy of polyps other than size and PSC are age above 50 years, Indian ethnic background, a sessile polyp, a single polyp, and the presence of gallstones [14, 19]. In patients with polyps smaller than 5 mm on US, no polyp or mass is found on pathologic examination in up to 83 %; for polyps larger than 20 mm, cancer may be present in up to 59 % [19]. Cholecystectomy for polyps of at least 10 mm remains a valid guideline based on recent series. In addition, cholecystectomy for polyps of more than 5 mm in patients with PSC appears justified, given the much higher risk of malignancy in that setting.

The resolution of conventional US is insufficient to distinguish the layers of the gallbladder wall (Fig. 11.1d). Therefore, US has a poor diagnostic accuracy for detecting a polyp that harbors GBC invading into or just beyond the lamina propria. Although CT can detect invasion of the liver parenchyma (T3) and distant metastases, its diagnostic accuracy for depth of invasion is also poor. Diagnostic accuracy for depth of invasion appears better for high-resolution US (63 %) and endoscopic ultrasound (56 %) [21]. In patients with a high likelihood of GBC

Table 11.1 American Joint Committee on Cancer (AJCC) TNM staging for gallbladder cancer (seventh edition)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one extrahepatic organ or structure*
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures*

*Extrahepatic organs or structures include the stomach, duodenum, colon, pancreas, omentum, and extrahepatic bile ducts

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to the periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups			
Group	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Adapted from Compton et al. [84]. With permission from Springer Verlag

(e.g., polyps larger than 15 mm), but no invasion on conventional US, a preoperative high-resolution US or endoscopic US may alter surgical management.

A simple cholecystectomy is sufficient for polyps and early (i.e., T1a) GBC (see below). Cholecystectomy can be performed open or laparoscopically. Bile spillage should be avoided because, if GBC cells are present in the bile, they can cause peritoneal or port-site metastases. The incidence of bile spillage during laparoscopic cholecystectomy for incidental GBC was about 20 % in a Japanese series of 498 patients and was associated with a higher recurrence rate of 27 % versus 14 % if no spillage occurred [22]. Other series showed that port-site or incisional recurrences occurred at least twice as often in laparoscopic versus open cholecystectomy for GBC [23, 24]. Even for in situ carcinoma, peritoneal dissemination has been described after gallbladder perforation [25]. A low threshold for conversion to open cholecystectomy is therefore recommended. A bag should be used for laparoscopic removal of the gallbladder. For patients with an increased risk of malignancy (e.g., polyp larger than 15 mm), open cholecystectomy should be considered because of the increased risk of bile spillage and peritoneal dissemination with laparoscopic resection. A simple cholecystectomy may not result in clear margins if GBC with invasion beyond the lamina propria is found. Frozen section of the gallbladder could be obtained to rule out GBC, if expertise is available for immediate liver resection (segments 4b and 5) and lymphadenectomy, but there is a high risk of sampling error in this setting. If the GBC is limited to the lamina propria (i.e., stage T1a), additional resection is not required [3].

Regarding polyps smaller than 10 mm that are not resected, the question arises whether follow-up is necessary. A study from 1962 found no GBC during a 15-year follow-up of patients with gallbladder polyps [26]. In a recent study, a follow-up US was available for 149 patients, 2–12 years after the initial US: increase in size was noted in only 1 polyp (from 3 to 5 mm, not clinically relevant), and two thirds of these small polyps were undetected at follow-up [27]. In another recent series, growth was seen in 8 out of 143 patients during follow-up, but no cancer developed [18]. On the other hand, in a small series of

patients with gallbladder polyps, rapid growth was found on repeat US in the months before surgery in five patients who eventually had GBC demonstrated [28]. Because of the conflicting data, follow-up at 6- to 12-month intervals for 2 years is generally recommended.

Several other gallbladder wall lesions can be found on imaging or during surgery. Calcification of the gallbladder wall, or porcelain gallbladder, appears to increase the risk of malignant transformation. However, the risk appears to be lower than was suggested based on older studies and also seems to be related to the nature of the calcifications (i.e., diffuse versus discontiguous or selective). In a number of studies, patients with diffuse calcification of the gallbladder had no GBC identified on histopathologic analysis [29–31]. However, one study of more than 25,000 resected gallbladders found GBC in 2 out of 27 patients with selective mucosal calcification of the gallbladder wall [30]. Cholecystectomy for patients with selective mucosal calcification is therefore recommended.

Adenomyomatosis of the gallbladder is characterized by focal thickening of the gallbladder wall with cystic-appearing spaces (Rokitansky-Aschoff sinuses) that are identified with high accuracy on US. Because these lesions are invariably benign and asymptomatic, they need no surgical management or follow-up [32].

Xanthogranulomatous cholecystitis is an uncommon inflammatory disease of the gallbladder with extensive fibrosis that can present with wall thickening, mass formation, and infiltration of the liver and other adjacent organs [33]. Typical findings on imaging include diffuse gallbladder wall thickening, hypo-attenuating intramural nodules, continuous mucosal line enhancement, and the presence of gallstones [34]. However, accuracy of these findings is often insufficient to rule out GBC, and xanthogranulomatous cholecystitis is typically diagnosed at pathologic review after extended cholecystectomy (i.e., segment 4b and 5 resection en bloc with gallbladder). In a series from India comprising 198 patients resected for presumed GBC, 16 % was found to have xanthogranulomatous cholecystitis [35].

Incidental Gallbladder Cancer at Pathologic Review

Incidental GBC is found on pathologic review of about 1 % of laparoscopic cholecystectomy specimens [36–38]. These patients comprise about two thirds of all patients with potentially curable GBC. In most of these cases, the gallbladder is resected for presumed symptomatic cholelithiasis, and GBC was not suspected on preoperative imaging or during surgery. Many of these patients benefit from reoperation and definitive resection. Re-resection may be beneficial if residual cancer is limited to the liver bed, cystic stump, common bile duct, or lymph nodes in the absence of distant metastasis. A large Western study showed that 14 % of these incidental GBC patients had disseminated disease on re-exploration, and 73 % of re-resected patients had residual disease on final pathology [39, 40].

The probability of both distant metastases and local residual cancer increases with the depth of invasion (i.e., T stage). In a Japanese nationwide survey of 498 patients with incidentally found GBC, 34 % had stage T1a, 14 % T1b, 41 % T2, 8 % T3, and 2 % T4 [22]. Table 11.2 presents the probability of residual disease in the liver or

Table 11.2 Residual disease found at re-resection for incidental GBC

T stage	Number of patients	Percentage of all stages (%)	Residual disease – any[a] (%)	Residual disease – liver (%)	Residual disease – nodes (%)
T1	8	8	38	0	13
T2	67	68	57	10	31
T3	22	22	77	36	46
All stages	97	100	59	15	33

[a]Also includes disease at the cystic duct margin and trocar sites (Reprinted from Pawlik et al. [41]. With permission from Springer Verlag)

regional lymph nodes stratified by T stage, found in re-resected patients with incidental GBC [41]. In another large Western series, the median survival time was 15 months if residual disease was found (73 % of patients), compared with 72 months if no residual disease was found [40]. The National Comprehensive Cancer Network (NCCN) guideline recommends re-resection for non-metastatic patients with T1b to T3 GBC [3]. Appropriate re-resection should include, at a minimum, resection of the liver segments contiguous with the gallbladder (segments 4b and 5) and regional lymphadenectomy, with selective bile duct resection (Fig. 11.2). The surgical procedures are described in more detail below.

Many studies have evaluated the benefit of a re-resection in patients with pT1a and pT1b GBC. A systematic review of T1 GBC identified 29 retrospective studies representing 1,266 patients [42]. T1a GBC was found in 56 % of all T1 GBC patients, of whom 16 % underwent re-resection. T1b was found in 44 %, of whom 33 % underwent re-resection. Patients with T1a GBC had lymph node metastases in 2 % and patients with T1b in 11 %. Eight patients (1 %) with T1a GBC died of recurrence. Fifty-two patients (9 %) of all patients with T1b died of recurrence: 13 % recurred after simple cholecystectomy alone and 3 % recurred after definitive re-resection. In a German prospective registry, 23 of 72 patients with T1b GBC underwent a re-resection [43], and this was associated with a 3-fold lower recurrence rate and a 5-year overall survival of 79 versus 42 months for simple cholecystectomy only ($P = 0.03$). In a study of more than 1,000 T1 GBC patients in the Surveillance, Epidemiology, and End Results (SEER) database, 80 % of both T1a and T1b patients underwent only a simple cholecystectomy [44]. For T1b patients, survival was better when combined with a liver resection and/or lymphadenectomy; for T1a patients, survival was similar with more extensive surgery (Fig. 11.3c). The NCCN guideline therefore recommends re-resection after an incidentally found T1b GBC [3]. For T1a GBC, the recurrence rate of a simple cholecystectomy alone is similar to the postoperative mortality rate for re-resection (approximately 1.5 %) [42]. Re-resection after an incidentally found T1a GBC is, therefore, not recommended.

Patients with T2 and T3 GBC may appear more likely to benefit from re-resection, because they are more likely to harbor residual disease than T1 GBC. However, they are also more likely to harbor occult distant metastatic disease, in which case re-resection is of no benefit. Several studies have suggested a benefit of re-resection for both T2 and T3 GBCs, using data from the SEER cancer registry [13, 45, 46]. In 781 patients with T2 GBC, the median survival time and the 5-year survival rate were 53 months and 37 %, respectively, after re-resection compared with 16 months and 21 % after cholecystectomy alone (Fig. 11.3d). In 1,118 patients with T3 GBC, the median survival and the 5-year survival rate were 11 months and 13 %, respectively, after re-resection compared with 8 months and 8 % with cholecystectomy alone (Fig. 11.3d) [13]. The benefit of re-resection persisted in node-positive patients with T1b or T2 tumors, but a benefit was not detected in node-positive patients with T3 tumors. In a German registry of 200 patients with incidental T2 GBC, 85 patients underwent re-resection, resulting in a 5-year survival of 55 % versus 35 % for patients subjected to a simple cholecystectomy [47]. In the same registry, of the 85 patients with T3 GBC, 32 underwent re-resection, but this did not result in an obvious improvement in the 5-year survival, which was only 18 %. Single institution series are smaller than these registries, but also found better survival after re-resection, especially for T2 tumors [48, 49]. The survival benefit found in these nonrandomized studies could be at least partly due to selection bias. In other words, there may well have been a good reason to exclude certain patients from re-resection that is not reflected in or is impossible to assess in retrospective analyses. Re-resection after incidentally found T2 and T3 GBCs is recommended, although the benefit is probably small for T3 GBC, and patients with node-positive T3 GBC may not benefit at all from re-resection. Unfortunately, nodal status is typically unknown after simple cholecystectomy and may not be known with certainty until the final histological analysis is complete. Table 11.3 summarizes the management of GBC patients based on T stage.

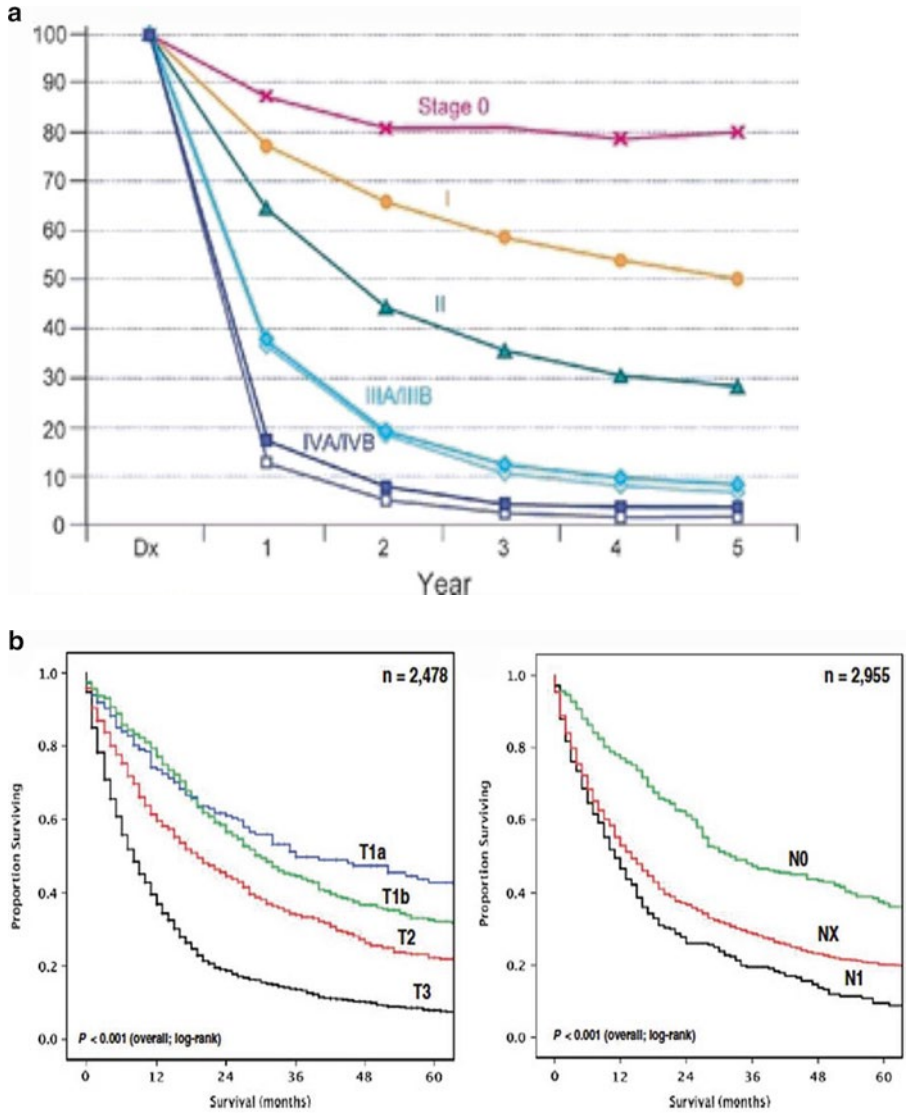

Fig. 11.3 (**a**) Overall survival of more than 10,000 patients with GBC diagnosed in the years 1989–1996. Data from the National Cancer Data Base [9]. (**b**) Overall survival for patients with gallbladder cancer who had surgery, stratified by T stage ($p<0.001$) and N stage ($P<0.001$). Data from the SEER database, representing 26 % of the US population, for the period 1991–2005. Patients with metastatic disease and stage T4 at the time of surgery were excluded. (**c**) Overall survival in patients with stage T1a ($n=300$) and T1b ($n=536$) GBC, stratified by type of surgery. C+LN, cholecystectomy with any lymph node dissection; RC, radical (i.e., extended) cholecystectomy including liver resection and regional lymph node dissection. Data from the SEER database, representing 26 % of the US population, for the period 1988–2008. (**d**) Overall survival in patients with stage T2 and T3 GBCs, further stratified by type of surgery. Radical, radical (i.e., extended) cholecystectomy including liver resection; simple, simple cholecystectomy [13]. Data from the SEER database, representing 26 % of the US population, for the period 1991–2005 ((**a**) Reprinted from Edge [9]. With permission from Springer Verlag. (**b**) Reprinted from Mayo et al. [13]. With permission from Springer Verlag. (**c**) Reprinted from Hari et al. [44]. With permission from John Wiley & Sons, Inc. (**d**) Reprinted from Mayo et al. [13]. With permission from Springer Verlag)

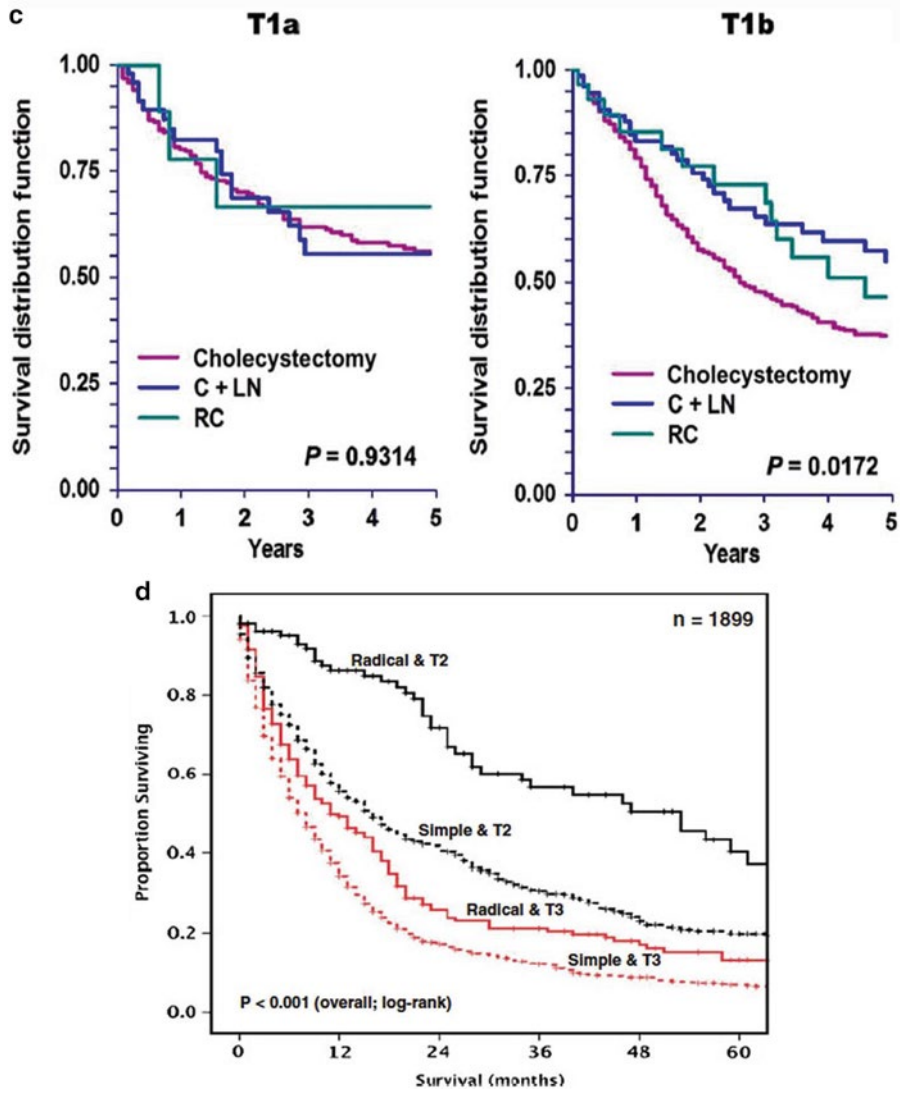

Fig. 11.3 (continued)

Before embarking on re-resection, distant metastases should be ruled out using abdominal CT or MRI and imaging of the chest. Positron-emission tomography (PET) may be of some benefit in avoiding futile surgery by detecting metastatic disease not found on cross-sectional imaging [50]. In one study, PET found distant metastasis in 3 out of 23 patients with incidental GBC [51]. As part of the work-up, it is important to review the initial imaging before cholecystectomy, the operative note, and the pathology report. These may inform on the precise location of the tumor within the gallbladder (on the peritoneal or liver side; near the fundus or near the cystic duct), inadvertent perforation of the gallbladder, and margin status at the cystic duct. If the cystic duct margin is positive for invasive cancer or high-grade dysplasia, bile duct resection is recommended to obtain clear margins. However, this information is often not included in routine histologic assessment for cholecystectomy performed for presumed benign disease. In a Western series, 8 out of 19 patients with a positive cystic duct margin had residual disease in the common bile duct [41]. Alternatively, re-resection of the cystic duct stump with frozen section could be considered [52].

Table 11.3 Management of GBC patients based on T stage

T stage	Recommendation
T1a	Simple cholecystectomy
T1b–T2	Cholecystectomy with en bloc liver resection of segments 4b and 5 (anatomical or wedge) with lymph node dissection of the hepatoduodenal ligament
T3	As for T1b–T2 but GBC in the gallbladder neck or the cystic duct may require right hepatectomy extended to segment 4b and/or bile duct resection with hepaticojejunostomy to obtain clear margins. To ensure negative margins, any adherent organ or structure[a] should also be resected
T4	As for T3, resection of two or more adherent organs or structures[a] can be considered. Palliative care if involvement of main portal vein or proper hepatic artery. Most patients in this category are not candidates for resection or will not benefit from resection even if feasible technically

[a]Adherent organs or structures other than liver include the stomach, duodenum, colon, pancreas, omentum, and extrahepatic bile ducts

Staging laparoscopy may prevent an unnecessary exploratory laparotomy if disseminated disease is found. The incidence of metastatic disease at re-exploration for GBC is 14–24 % [39, 41]. Of 46 patients undergoing staging laparoscopy in a Western series, 10 (22 %) had metastatic disease that was identified laparoscopically in only two patients, whereas in the other eight it was found at laparotomy [39]. Peritoneal metastasis is more likely in patients with poorly differentiated or T3 tumors, or after perforation of the gallbladder at cholecystectomy. The yield of staging laparoscopy would appear to be greater in such high-risk patients, and it is reasonable to use it routinely in these settings.

Incidental Gallbladder Cancer Found at Surgery

GBC is sometimes suspected during surgery, typically during laparoscopic cholecystectomy for cholelithiasis. If peritoneal or hepatic lesions are found and frozen section demonstrates GBC, the patient has metastatic disease and will not benefit from resection. If the diagnosis of GBC is suspected based on macroscopic assessment of the gallbladder and no expertise in GBC is available, it is probably best to not perform any resection and refer the patient to a specialized hepatobiliary center where the disease can be staged fully and the tumor resected in a single definitive procedure observing oncologic principles. Studies that report no difference in survival between patients undergoing two resections or a single definitive resection likely suffer from selection bias, since patients who develop disseminated disease prior to the second procedure are excluded [48, 53].

GBC may also be suspected after cholecystectomy by macroscopic assessment of the gallbladder mucosa. If the mucosa appears abnormal, then the gallbladder can be sent for frozen section histology, and definitive resection may be undertaken at that time.

Mass Found on Imaging, Suspicious for GBC

GBC is typically asymptomatic until advanced stages, when involvement of the liver and other surrounding structures occurs. At this stage, patients may present with constant right upper quadrant pain, weight loss, and nausea with vomiting. About 40 % of patients are jaundiced at presentation, an ominous finding [54]. At an advanced stage, US often demonstrates a heterogeneous mass in the gallbladder. Sometimes a diffuse thickening of the gallbladder wall is seen that can be difficult to distinguish from cholecystitis. Complete cross-sectional imaging, usually in the form of CT of the chest, abdomen, and pelvis, is recommended as the next step. PET scan may be justified in selected patients, to assess suspicious findings at distant sites, but is probably not helpful as a routine study [51].

The NCCN guideline has the same recommendations for these patients, as for patients in whom GBC was incidentally found [3]. In summary, most non-metastatic patients are expected to benefit from surgical resection. Exceptions are patients with positive lymph nodes beyond the hepatoduodenal ligament (i.e., the periaortic, pericaval, superior mesenteric artery, and/or

celiac artery lymph nodes), which is considered stage IV disease according to the seventh edition of the AJCC TNM classification. Moreover, patients with T4 tumors are unlikely to benefit from surgery even if their disease is amenable to resection. T4 tumors are locally advanced and include those that invade or encase the main portal vein and the hepatic artery or involve at least two extrahepatic organs or structures (e.g., the duodenum, pancreas, and transverse colon). If a patient has substantial comorbidities, a trade-off should be made between the expected postoperative morbidity and mortality and the long-term oncologic benefits of surgery.

The prognosis of symptomatic (non-incidental) GBC patients remains poor, even after liver segment 4b and 5 resection with lymphadenectomy of the hepatoduodenal ligament. In a Western series including 54 patients with non-incidental GBC, 48 patients underwent surgical exploration of which only 11 underwent a liver resection. The median survival was only 8 months [53].

Controversies in Surgical Management

In the absence of data from prospective, controlled trials, many issues pertaining to the treatment of patients with GBC remain unresolved. This section highlights three common controversies: the extent of liver resection, indications for extrahepatic bile duct resection, and the benefit of laparoscopic port-site resection.

The first controversy concerns whether GBC patients should undergo a liver wedge resection of 1–5 cm, an anatomic resection of segments 4b and 5, or an extended right hepatectomy. In 1954, Glenn and Hays first proposed a liver resection for GBC: the gallbladder was resected en bloc with a 1 cm wedge of liver parenchyma [55]. Since then, wider liver resections have been recommended to obtain clear margins, eliminate micrometastases in the liver, and ultimately avoid recurrence in the liver [56]. The results of histological studies support an anatomic resection of segments 4b and 5 (see section on anatomy) [12, 57]. However, in a Japanese multicenter series of 485 R0 T2/3 patients, no difference in survival or local recurrence was found between wedge resection, anatomical segmental resection, or extended right hepatectomy [58]. Metastases in the liver beyond segments 4b and 5 represent stage IV disease, and survival beyond 1 year is rare; extended hepatectomy appears futile for this indication. Moreover, the postoperative mortality of extended liver resections was between 9 and 18 % in several series [59–61]. Postoperative mortality occurred mainly in the setting of liver failure due to the extensive resection in combination with obstructive jaundice in 45–100 % of these patients. Therefore, most surgeons perform a wedge resection of about 2 cm liver parenchyma (en bloc with the gallbladder, if still in situ) or an anatomic liver resection of segments 4b and 5. An extended right hepatectomy (extended to segment 4b, with or without 4a and 1) could be considered in medically fit patients with GBC arising in the gallbladder neck, Hartmann's pouch, or the cystic duct. These tumors are close to the right hepatic pedicle at an early stage, and a conventional segment 4b and 5 liver resection is likely to result in a positive margin (see section on anatomy) [49].

The second controversy concerns resection of the extrahepatic bile duct (EBD) for patients with GBC. Involvement of the EBD often results in jaundice. EBD resection for jaundiced GBC patients was traditionally performed as a matter of routine, although enthusiasm has waned with the publication of poor outcomes [62]; however, this practice is still recommended by some Asian surgeons [60, 62]. In a Western series of 82 GBC patients who presented with jaundice, 55 were explored of whom 6 were resected (including EBD resection), of whom 4 had an R0 resection [62]. All six resected patients died or recurred within 6 months. The median survival of all jaundiced GBC patients was 6 months and all patients died before 28 months. Of the 82 jaundiced patients, only three patients had node-negative disease. Because of these poor outcomes, the NCCN guideline recommends to consider resection only in node-negative jaundiced GBC patients, at an experienced center; however, definitive determination of

nodal status prior to operation can be difficult [3]. Jaundice may be an early event in patients with GBC arising from the gallbladder neck, Hartmann's pouch, or the cystic duct. In theory, this small subgroup may benefit from resection. These patients have likely involvement of the right portal pedicle and require a combined extended right hepatectomy, EBD resection, and regional lymphadenectomy to obtain clear margins.

In the absence of jaundice, EBD resection in GBC patients is recommended to obtain clear margins for a positive cystic duct margin after a previous cholecystectomy. In one study, 8 of 19 patients (42 %) with a positive cystic duct margin had residual disease in the resected EBD [41]. Routine EBD resection for every GBC patient, even without evidence of tumor involvement, is recommended by some Japanese surgeons [63]. This approach is supported by a histological study that found cancer cells in the EBD in 19 of 44 (43 %) non-jaundiced patients with T2/3 GBC [64]. On the other hand, EBD resection and preservation were compared in a retrospective nationwide Japanese study including 838 T2–4 GBC patients [65]. These patients had no macroscopic involvement of the hepatoduodenal ligament and underwent an R0 resection with or without EBD resection. No difference was found in survival between EBD resection and preservation for any subgroup of T stage or N stage. A theoretical advantage of routine EBD resection is that it facilitates regional lymphadenectomy and avoids ischemia of the EBD. However, no difference in lymph node count was found between patients with and without bile duct resection [66]. Although the actual benefit of routine EBD resection remains disputed, the high complication rate is well established in both Western and Asian series. In a series of 104 GBC patients, 33 % of the patients undergoing an EBD resection had a complication that required re-intervention or resulted in permanent disability or death, versus 13 % of patients who had no EBD resection [66]. A postoperative biliary anastomotic leak may result in sepsis and death. In the long term, biliary strictures and recurrent cholangitis render the patient a "biliary cripple"[67]. The weight of evidence would support resection of the EBD only if involved with tumor or it is otherwise unavoidable in order to achieve an R0 resection.

The third controversy concerns the excision of laparoscopic port sites, simultaneous with definitive resection for incidental GBC, to avoid port-site recurrence. After spillage of bile, GBC has the unique ability to cause tumor implants on peritoneum, in biopsy tracts, and in abdominal wounds including port sites, as has been described as early as 1955 [56]. In a series of 113 patients with incidental GBC, 69 patients underwent port-site resection of which 13 (19 %) had port-site metastasis [68]. The presence of port-site metastasis was associated with a worse median survival (17 versus 42 months), but no difference in survival was detected between patients with and without port-site resection. Moreover, all 13 patients with resected port-site metastasis either had an R2 resection or recurred within 24 months. Consequently, port-site resection mainly has a role in staging and prognosis, rather than in prolonging survival, and appears to be the clinical equivalent of peritoneal metastasis. Because port-site resection can be a disfiguring operation, it is not recommended as part of the definitive operation for incidental GBC.

Description of Surgical Procedure for GBC

Before proceeding with surgery, medical evaluation and optimization is required, in particular for patients with coexisting cardiopulmonary disease. Blood products should be available because of potential blood loss associated with liver resection, although the likelihood of transfusion has decreased to low levels over the past several years [69]. The anesthesiologist should pursue low central venous pressure, which has been shown to reduce blood loss during parenchymal transection [70].

Staging laparoscopy should be considered in patients with an increased risk of disseminated disease. This includes patients with poor differentiation, T3 level of invasion, and perforation of

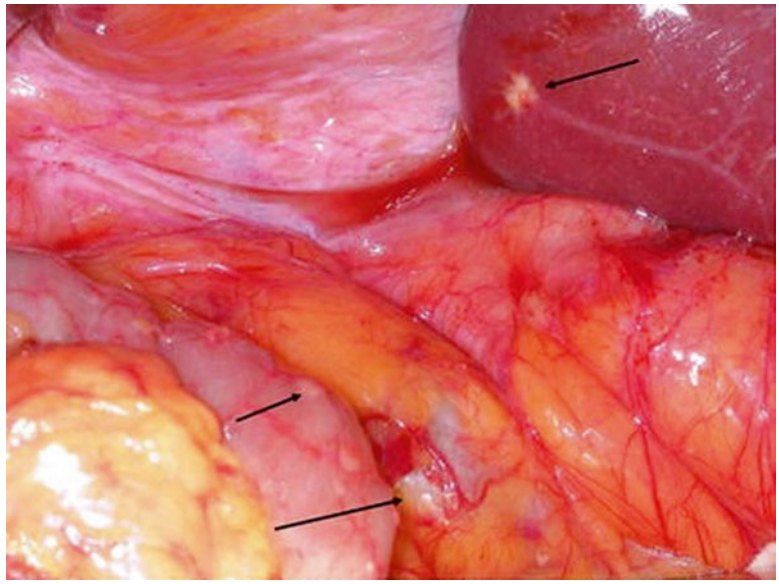

Fig. 11.4 Peritoneal metastases (*arrows*) found at re-exploration in patient with incidental gallbladder cancer (Reprinted from Hueman et al. [83]. With permission from Springer Verlag)

the gallbladder at previous cholecystectomy or symptomatic (non-incidental) GBC patients. The finding of peritoneal or hepatic metastasis (Fig. 11.4) signifies advanced, incurable disease and should terminate the procedure in nearly all cases. A right subcostal (Kocher) incision provides adequate exposure and can be extended to the left into a bilateral subcostal (chevron) incision. Alternatively, an inverted L (hockey stick) incision can be used. The teres ligament is divided and pulled upward to expose the undersurface of the liver and hepatoduodenal ligament. On inspection of the abdominal cavity, disseminated disease is often found that remained undetected at staging laparoscopy [39]. Exploration should include a Kocher maneuver to assess for suspicious retroperitoneal or aortocaval lymph nodes. If aortocaval, retropancreatic, or celiac lymph nodes are positive, the patient has the equivalent of stage IV disease and resection is futile [9].

If a single adjacent organ such as the transverse colon or duodenum is adherent to the gallbladder, en bloc resection is required to ensure clear margins. In a subgroup of 20 patients undergoing en bloc resection for adherence to the gallbladder, 10 patients had histological involvement of the organ adherent to the gallbladder [66]. If more than one adjacent organ is involved (stage T4), patients are less likely to benefit from resection, even if a complete resection can be achieved.

Regional lymphadenectomy should include the lymph nodes within the porta hepatis, gastrohepatic ligament, and retroduodenal regions [3] (Fig. 11.2). The right gastric artery is ligated, and the portal vein, hepatic artery, and common bile ducts are dissected free of surrounding lymphatic tissue, sweeping it upward toward the liver hilum. If during lymphadenectomy involvement of the main portal vein or common hepatic artery is found, the patient has T4 disease and resection is probably futile.

The segment 4b and 5 liver resection is commenced with opening of the umbilical fissure on the right side of the teres ligament. The inflow vessels to segment 4b are dissected and divided. The cystic duct is divided at the common bile duct. Next, the line of transection is marked on the liver capsule with electrocautery. Stay sutures are placed adjacent to the transection line at the anterior edge of the liver. A crushing technique is used for the parenchymal transection, and vessels are either clipped or ligated. Other parenchymal transection techniques

can be used if preferred. The Endo-GIA vascular stapler is used to control large intrahepatic vessels. Transection begins medially, where first the middle hepatic vein and then the segment 5 pedicle will be encountered and divided. The main anterior pedicle and the pedicle to segment 8 are at risk for inadvertent injury during parenchymal transection, and caution must be taken. Hemostasis is achieved with the argon beam coagulator. Abdominal drainage is not necessary [71].

En bloc bile duct resection may be required to obtain an R0 resection, for example, if the cystic duct margin of a previous cholecystectomy was positive. The common bile duct is divided just above the duodenum at the start of the regional lymphadenectomy. This will facilitate the lymphadenectomy and the assessment of involvement of the portal vein and hepatic artery. However, bile duct resection did not result in an increased lymph node yield [72]. The common hepatic duct is transected at its confluence. After the resection, a Roux-en-Y limb is created for a hepaticojejunostomy. We refer the reader to other textbooks for an illustrated description of the procedure [73, 74].

Postoperative Care and Complications

Postoperative care for GBC patients after a liver segment 4b and 5 resection with lymphadenectomy of the hepatoduodenal ligament is similar to the care for other patients after liver resection. The care focuses on minimizing the risk of cardiopulmonary and thromboembolic complications by effective pain relief, pulmonary toilet, early ambulation, thrombosis prophylaxis, maintaining fluid balance (avoiding fluid overload), and early enteral diet as tolerated.

Liver resections are considered major surgery, associated with cardiopulmonary complications and a postoperative mortality of 1 % or less in high-volume centers. Liver failure is the most serious complication specific to liver resections. Fortunately, in GBC patients without cirrhosis, the risk of liver failure is very low for the conventional resection of liver segments 4b and 5. The few resected jaundiced GBC patients and those who undergo an extended liver resection are at risk for liver failure. Bile leaks after resection of liver segments 4b and 5 arise mostly from the liver parenchyma and are self-limiting with percutaneous drainage, rarely requiring endoscopic sphincterotomy and/or stent placement. Inadvertent injuries to the right anterior bile duct, segment 8 bile duct, or extrahepatic bile ducts are more serious complications that likely require endoscopic and/or surgical management. A subhepatic or right subdiaphragmatic abscess typically resolves with percutaneous drainage.

Adjuvant Therapy

After a potentially curative resection for GBC, the median overall survival for patients in the SEER database was 16 months, and the 5-year survival rate was 21 % [13]. At a median follow-up of 24 months, 66 % of the patients with resected GBC had recurred. Of all patients that recur, 85 % will present with metastatic disease with or without locoregional recurrence [75]. As a result, there is interest in investigating the role of adjuvant therapies. While there is no good prospective data, many retrospective studies have evaluated whether adjuvant chemotherapy can reduce the recurrence rate and improve survival. A phase 3 randomized controlled trial (RCT) from Japan analyzed 112 patients with GBC and found an 8 % absolute increase ($P=0.02$) in 5-year disease-free survival in GBC patients receiving adjuvant mitomycin C and 5-fluorouracil (5-FU). The NCCN guideline recommends adjuvant treatment with 5-FU or gemcitabine, which is mainly based on RCTs in the palliative setting (see below) [3, 76, 77]. Addition of cisplatin or oxaliplatin could be considered in high-risk patients (T4, N1, or R1), although it has not been demonstrated that benefits observed in the palliative setting translate to the adjuvant setting.

About 15 % of patients will present with a locoregional recurrence without metastatic disease. These patients may have benefited from adjuvant radiotherapy. No phase 3 RCT has evaluated the benefit of adjuvant radiotherapy in

GBC. Adjuvant radiotherapy has been evaluated in about 4,000 GBC patients in the SEER database [78]. Radiotherapy was associated with 15-month overall survival (versus 8 months), but overall survival after 2 years was the same. Because of the retrospective nature of this study, the difference found may be partially or entirely attributed to patient selection; furthermore, this analysis did not take into account the adequacy of resection, and the benefits may extend only to those subjected to an inadequate resection. Adjuvant radiotherapy could be considered in particular in node-negative GBC patients with a positive margin.

Palliative Therapy

Most GBC patients will eventually undergo palliative treatment. Many patients are not eligible for surgical resection at the time of diagnosis: they either have distant metastases, have locally advanced disease (e.g., involvement of portal vein or hepatic artery), or are not medically fit to undergo a liver resection. Even after potentially curative surgery, the majority of patients will recur. A phase 3 RCT including 410 patients with biliary cancer demonstrated a 3.6-month improvement in median overall survival in patients who received gemcitabine with cisplatin versus gemcitabine alone [76]. In the subgroup of 149 patients with GBC, overall survival was also significantly better with a hazard ratio of 0.61 (95 % confidence interval: 0.42–0.89). More recently, several clinical studies evaluating targeted treatments in biliary cancer found improved response rates but have failed to demonstrate a survival benefit [79, 80]. The NCCN recommends the combination of gemcitabine and cisplatin as palliative treatment [3]. Alternatively, other gemcitabine-based or 5-FU-based regimens could be considered. Radiotherapy may have benefit in GBC patients with locally advanced disease, although no randomized data are available.

Locally advanced disease often causes obstruction of the intra- and extrahepatic bile ducts. The resulting jaundice and pruritus can be palliated with drainage. Optimal biliary drainage is also important to decrease the risk of biliary sepsis. Biliary drainage can be obtained with endoscopic or percutaneous interventions. In an RCT, endoscopic and percutaneous drainage were compared in 44 GBC patients with obstructive jaundice. Successful drainage was better in the percutaneous group (89 % versus 41 %, $P<0.001$), and early cholangitis was higher in the endoscopic group (48 % versus 11 %, $P=0.002$) [81]. However, both drainage approaches are associated with high morbidity. Patients undergoing percutaneous biliary drainage for malignant bile duct obstruction were found to have a 58 % rate of major complications and a median survival of only 5 months [82]. Therefore, biliary drainage is only recommended for symptomatic relief and not preemptively, or to allow for chemotherapy.

Future Perspective

The outcomes of patients with GBC remain poor. Improvements in outcomes for patients with GBC are possible in several ways: early detection, more effective systemic treatment, better patient selection for surgery, reduced mortality and morbidity of surgery, and better adherence to guidelines. Early detection or screening for GBC is unlikely to be effective anytime soon, since the prevalence is very low even in patients with increased risk, and no test is available other than imaging, which will mainly detect late-stage GBC. Most patients with GBC will eventually die of metastatic disease, regardless of the extent of surgery. Analysis of data from a prospective registry of GBC patients may improve selection of patients that are most likely to benefit from surgical resection. Postoperative mortality and morbidity are low in high-volume hepatopancreaticobiliary (HPB) centers; regionalization of care for these complex problems may further improve outcome. Randomized comparisons of systemic treatments for patients with GBC are also challenging, because of the rarity of the disease and heterogeneity among patients with GBC. Therefore, trials for systemic treatments often combine GBC patients with other biliary

cancers [76]. Several studies that used SEER data have shown that the compliance with the NCCN guideline for GBC is very poor [13, 45, 46]. In the most recent evaluated period (2003–2005), a liver resection was performed in only 16 % and a lymphadenectomy in only 5 % of all patients with non-metastatic GBC, stage T1b-3. At a population level, a substantial health gain for patients with GBC is anticipated by simply adhering to national guidelines regarding the indication for surgical resection. Finally, further molecular genetic studies will likely provide insights into disease pathogenesis and reveal novel targets for therapeutic intervention.

Salient Points

- Cholecystectomy is appropriate for patients with a gallbladder polyp larger than 10 mm.
- Open cholecystectomy is recommended for gallbladder polyps with an increased risk of malignancy (e.g., >15 mm): it decreases the chance of bile spillage and associated peritoneal seeding.
- Patients with gallbladder cancer diagnosed at pathologic review after cholecystectomy for cholelithiasis should undergo a (wedge) resection of segments 4b and 5 of the liver with lymphadenectomy of the hepatoduodenal ligament. Exceptions are patients with metastatic disease and nodal involvement beyond the hepatoduodenal ligament, patients with 2 or more extrahepatic organs involvement or invading or encasing the main portal vein and the hepatic artery or T4, and patients who are unfit for surgery.
- A staging laparoscopy prior to definitive resection is recommended in gallbladder cancer patients with an increased risk of peritoneal disease: poorly differentiated or T3 tumors, patients with bile spillage during the cholecystectomy, and patients with non-incidental (symptomatic) gallbladder cancer.
- If gallbladder cancer is suspected during surgery for cholelithiasis and no expertise is available in gallbladder cancer, it is appropriate to refer the patient to a specialized center for staging and a single definitive resection.
- Patients presenting with a mass in the gallbladder suspicious for gallbladder cancer should undergo staging including cross-sectional imaging of the chest, abdomen, and pelvis.
- A biopsy is not recommended before proceeding to surgery in a patient with a gallbladder mass suspicious for gallbladder cancer: the biopsy may cause peritoneal or abdominal wall seeding.
- A 2–3 cm wedge resection of segments 4b and 5 of the liver is sufficient for most patients with gallbladder cancer. Larger liver resections may be justified in some patients.
- Extrahepatic bile duct resection is recommended for patients with a positive margin at the cystic duct after cholecystectomy for presumed benign disease.
- Gallbladder cancer patients presenting with jaundice have a median survival of 6 months and are very unlikely to benefit from surgery.
- Extrahepatic bile duct resection in patients without macroscopic involvement of the extrahepatic bile duct does not improve survival and increases postoperative morbidity and mortality.
- Resection of laparoscopic port sites in patients with gallbladder cancer is not recommended because it does not improve survival.
- After a potentially curative resection for gallbladder cancer, the median overall survival for patients in the SEER database was 16 months, and the 5-year survival rate was 21 %.
- At a median follow-up of 24 months, 66 % of the patients with resected gallbladder cancer had recurred. Of all patients that recur, 85 % will present with metastatic disease with or without locoregional recurrence.
- Adjuvant treatment for gallbladder cancer is recommended with 5-FU or gemcitabine. Addition of cisplatin or oxaliplatin could be considered in high-risk patients.
- Adjuvant radiotherapy could be considered in particular in node-negative gallbladder cancer patients with a positive margin.
- As palliative treatment, the combination of gemcitabine and cisplatin is recommended, based on a large randomized controlled trial.

- Biliary drainage in the palliative setting is only recommended for symptomatic relief and not preemptively, or to allow for chemotherapy. Percutaneous drainage is more likely to be successful and less associated with cholangitis than endoscopic drainage.

Questions

1. A 55-year-old woman is found to have an abnormal gallbladder on ultrasound. Which abnormality does NOT require surgical management?
   A. A gallbladder polyp of 14 mm
   B. Selective mucosal calcification of the gallbladder wall
   C. A gallbladder polyp of 8 mm in a patient with primary sclerosing cholangitis
   D. Adenomyomatosis of the gallbladder wall
   E. A gallbladder mass invading the liver
2. A 69-year-old man is found to have a T3 gallbladder cancer on pathologic review after cholecystectomy for cholelithiasis. What is the next step in management?
   A. Liver resection of segments 4b and 5
   B. Staging laparoscopy
   C. Liver resection of segments 4b and 5 with lymphadenectomy of the hepatoduodenal ligament
   D. Imaging of abdomen and chest
3. A 67-year-old woman is found to have a T1a gallbladder cancer with a negative lymph node at the cystic duct on pathologic review after cholecystectomy for cholelithiasis. What is the next step in management?
   A. Liver resection of segments 4b and 5 with lymphadenectomy of the hepatoduodenal ligament.
   B. Liver resection of segments 4b and 5 without lymphadenectomy.
   C. Lymphadenectomy of the hepatoduodenal ligament without liver resection.
   D. No further surgery is recommended.
4. After introduction of the camera for a planned laparoscopic cholecystectomy in a 72-year-old woman with symptomatic cholelithiasis, the surgeon is concerned that the gallbladder looks suspicious for gallbladder cancer. What is the best next step in management?
   A. Liver resection of segments 4b and 5 en bloc with the gallbladder and bile duct with lymphadenectomy of the hepatoduodenal ligament.
   B. Abort the procedure and refer the patient to a specialized center for staging and a single definitive resection.
   C. Perform a laparoscopic cholecystectomy and refer the patient to a specialized center if pathologic review finds gallbladder cancer.
   D. Liver resection of segments 4b and 5 en bloc with the gallbladder.
5. A 75-year-old woman presents with constant right upper quadrant pain, weight loss, nausea, and vomiting. On ultrasound, she appears to have a large mass in her gallbladder. With which finding on CT of the chest, abdomen, and pelvis is she most likely to benefit from surgery?
   A. Encasement of the main portal vein
   B. Multiple bilateral pulmonary nodules ranging from 1 to 3 cm in diameter
   C. Involvement of the liver parenchyma contiguous with the gallbladder
   D. Enlarged lymph nodes at the root of the celiac artery of which biopsy shows adenocarcinoma
6. A 69-year-old man presents with a large mass in the gallbladder invading the liver on ultrasound. What is the next step in management?
   A. A laparoscopic cholecystectomy.
   B. Perform a percutaneous biopsy of the mass to distinguish gallbladder cancer from xanthogranulomatous cholecystitis.
   C. Perform a CT of the chest, abdomen, and pelvis.
   D. A (wedge) resection of segments 4b and 5 of the liver with lymphadenectomy of the hepatoduodenal ligament.
7. A 62-year-old woman was found to have a T2 gallbladder cancer on pathologic review after laparoscopic cholecystectomy for cholelithiasis. Which of the following procedures is an essential part of the definitive resection?
   A. Resection of the extrahepatic bile duct to clear disease in the submucosal lymphatics of the common bile duct

B. Resection of the port sites because patients often develop port-site metastasis
C. Lymphadenectomy of the hepatoduodenal ligament
D. Right hemihepatectomy because patients often have intrahepatic metastases beyond the segments contiguous with the gallbladder

8. Which patient with gallbladder cancer is most likely to benefit from an extrahepatic bile duct resection?
   A. A 67 year-old man presenting with severe jaundice is noted on CT scan to have a gallbladder mass that has invaded the hepatoduodenal ligament
   B. A 58-year-old woman presenting with a T1b gallbladder cancer incidentally found at pathologic review after cholecystectomy for cholelithiasis with a positive margin of the cystic duct
   C. An 81-year-old woman presenting with a T3 gallbladder cancer incidentally found at pathologic review after cholecystectomy for cholelithiasis with a positive lymph node at the cystic duct
   D. A 63-year-old man presenting with constant right upper quadrant pain and nausea and on CT a large mass in the fundus of his gallbladder invading the liver
9. Which of the following findings during an exploratory laparotomy for presumed gallbladder cancer is NOT a justification to refrain from a resection?
   A. A single small peritoneal nodule on the anterior abdominal wall demonstrating adenocarcinoma on frozen section
   B. A superficial nodule in segment 8 of the liver demonstrating adenocarcinoma on frozen section
   C. Adherence of the gallbladder to the transverse colon suspicious for involvement of the transverse colon
   D. A slightly enlarged aortocaval lymph node demonstrating adenocarcinoma on frozen section
   E. Encasement of the proper hepatic artery
10. A 64-year-old woman presents with right upper quadrant pain without jaundice and on CT a large mass in the fundus of the gallbladder with multiple large pulmonary lesions suspicious for metastatic disease. What is the next step in management?
    A. Endoscopic biliary drainage to prevent biliary obstruction
    B. A palliative resection to prevent biliary obstruction
    C. Percutaneous biliary drainage to prevent biliary obstruction
    D. Biopsy of the pulmonary lesions, followed by systemic chemotherapy
    E. Palliative radiotherapy to prevent biliary obstruction

Answers

1. D
2. D
3. D
4. B
5. C
6. C
7. C
8. B
9. C
10. D

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