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ORIGINAL ARTICLE

Surgical Management of Gallbladder Carcinoma

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Abstract
Gallbladder carcinoma is the commonest malignancy of the hepatobiliary system. It is plagued by the dismal outcome in terms of 5-year survival and high recurrence rate. The varying presentation from an incidental surprise during routine laparoscopic cholecystectomy for gallstone disease to presentation in advance stage. Surgical resection remains the only curative alternative; however, it is only possible in few patients at the time of diagnosis. Although, radical cholecystectomy is said to be the standard of surgical care, yet the extent of liver resection, lymphadenectomy, bile duct resection, adjacent organ resection, and palliative surgical treatment needs to be elaborately discussed. The resection of tumor with R0 margin with appropriate lymphadenectomy is the only hope for long-term survival. Revision surgery should be considered in patients who underwent simple cholecystectomy with incidentally diagnosed gallbladder carcinoma that invaded muscularis propria or beyond. The advance lesions are treated non-operatively with palliative intension. This review discusses the current surgical treatment options in patients with gallbladder cancer depending on the stage of disease.

Keywords Gallbladder cancer · Radical cholecystectomy · Liver resection · Lymph node dissection · Stage · Prognosis

Introduction

Gallbladder carcinoma (GBC) is the most frequent biliary malignancy worldwide and ranks fifth in GI tract malignancy [1]. It is usually detected in advance stage due to vague sign and symptoms and has poor prognosis. Surgical resection is only amenable in 15–47% of preoperatively diagnosed GBC [2]. GBC may be diagnosed as incidental findings during cholecystectomy in 0.09–2% patients [3]. The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5% [4]. In early-stage disease, a 5-year survival rate of 75% can be achieved if stage-adjusted therapy is performed [5].

The cancer of the gallbladder has a very diverse geographical variation both worldwide as well as within India [6]. Globally, there is an increased incidence of gallbladder cancer seen in Asia, South America, and some parts of central Europe (Hungary, Germany, and Poland) [1]. Data from Mapuche Indians from Valdivia, Chile, South America, shows the rate of gallbladder cancer as 12.3/100000 for males and 27.3/100000 for females [1]. Although the worldwide occurrence of gallbladder cancer is less than 2/100000 individuals, this has been recorded with extensive variance [7]. In Asia, high incidence is seen among the residents of Indo-Gangetic belt particularly females of northern India (21.5/100000) and south Karachi in Pakistan (13.8/100000) which has been reported as one of the highest affected regions in the whole world [8]. Gallbladder cancer is also found in high frequency in Eastern Europe including Poland (14/100000 in Poland), Czech Republic, and Slovakia and Asia, whereas South Americans of Indian descent (3.7 to 9.1 per 100,000), Israel (5/100000), and Japan (7/100000) have shown intermediate prevalence of gallbladder cancer [7, 8]. The residents of Andean area, North American Indians and Mexican-Americans, are especially predisposed of GBC [9].

The incidence increases with age and is significantly higher in women (3:1) [7]. Although gallbladder cancer is more common in females still in some countries like Korea, Iceland, and Costa Rica, higher mortality rate has been reported for males as compared to females [10]. It is diagnosed in the seventh decade of life, with a median age of 62–66 years [8]. The incidence of GBC is based on important etiological factors as cholelithiasis; however, its incidence also varies with geography and race. Most patients of GBC have advance disease at

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the time of diagnosis except for patients diagnosed incidentally intraoperatively or at histopathological examination. With the advent of laparoscopic cholecystectomy, the incidence of incidentally diagnosed gallbladder carcinoma (IGBC) has increased despite the increasing incidence of gallbladder cancer in the last 20 years, laparoscopic cholecystectomy has permitted earlier detection and improved survival of what was once considered a disease associated with a dismal prognosis [11, 12].

Risk Factors

The development of gallbladder cancer has been linked to various genetic and environmental factors. The most common risk factors for developing gallbladder cancer are gallbladder stones, advanced age, female sex, tobacco and alcohol abuse, multiple pregnancies, low physical activity, obesity, and infectious diseases. Chronic infection of the gallbladder or/and environmental exposure to specific chemicals, heavy metals, and even many dietary factors have been found to be associated with GBC formation. Ample literature exists to suggest the association of GBC with female gender and certain geographical regions (mostly developing countries) has been proposed to be influenced by various female hormones, cholesterol cycling and salmonella infections [13, 14].

Cholelithiasis is the best-known risk factor; it results in chronic mucosal inflammation, dysplasia, and subsequent malignant transformation [15]. The incidence of GBC correlates with the prevalence of cholelithiasis [16]. The risk of GBC is four to five times higher in patients with cholelithiasis than in a calculus gallbladder. The large stone size and duration of gallstone symptoms are associated with the development of gallbladder neoplasia. It is reported that stone larger than 3 cm are associated with tenfold higher of developing GBC [17, 18]. The type of gallstone also affects the development of GBC and cholesterol stone is a reported higher risk of developing cancer [4]. A review article by Shrikhande et al. [19] has also supported the fact that for populations reporting high incidence of gallbladder cancer with associated gallstones, prophylactic cholecystectomy should be done only after correlating with the epidemiological profile of the place. The common pathogens implicated in the development of gallbladder cancer are *Salmonella typhi*, *Salmonella paratyphi*, and *Helicobacter* [20, 21].

Worldwide GBC affects females 2–3 times more commonly than males, but this bias varies greatly in different parts of the world mostly in high prevalent regions of GBC [8]. To some extent, the female hormone estrogen causes increased cholesterol super saturation in bile and hence can be implicated in gallstone-mediated GBC pathogenesis; however, the association of female hormone receptor expression to tumor differentiation has still not been established [22]. So the extent of female hormones contribution in gallbladder cancer is still not certain and requires more investigation. Gallbladder polyps, the porcelain gallbladder, and anatomical abnormalities of the ampulla of Vater, which causes bile reflux, are also predisposing factors [4]. The adenoma-carcinoma progression has been stipulated in gallbladder cancer with increased incidence of cancer seen in isolated, broad-based sessile adenomatous polyps, particularly of size more than 1 cm in patients > 60 years of age, are considered higher risk, and these patients should undergo cholecystectomy [4, 13]. Primary sclerosing cholangitis is also an increased factor for development of GBC [23].

Family history of gallstones, tobacco consumption, chemical exposure, residence in Gangetic belt and high concentrations of secondary bile acids and excessive intake of fried foods (reused oil) increases the risk for GBC [24]. Comorbid diseases associated with western diet such as obesity and diabetes are also associated with gallbladder cancer [25, 26]. Diet is an important risk factor in the development of gallbladder cancer; increased intake of fried foods, consumption of red meat, or those that cause constipation increases the risk [27]. On the other hand, the intake of boiled beans or fish, fibers, and vitamins C and E lowers the incidence of gallbladder cancer [28, 29]. Some drugs, such as methyldopa and isoniazid, have been implicated as the risk agents while [30] any association between oral contraceptives and gallbladder cancer is unclear [7]. The involvement of environmental factors such as heavy metals (high levels of nickel, cadmium, manganese, copper, chromium, and lead, as well as low levels of selenium or zinc) is not yet fully understood and needs prospective studies conducted on large groups of patients [4, 31]. Tobacco consumption is a significant risk factor [24]. Miners are often exposed to radon, an inhaled gas, which has been associated with cancer of the gallbladder [32].

The loss of genetic heterozygosity in 2.1–47.8% of preneoplastic lesions at 8 different loci for several tumor suppressor genes is associated with gallbladder cancer compared to its absence in normal gallbladder [33]. P53 gene mutation is an important role in progression of atypia to dysplasia, to carcinoma in situ and finally invasive carcinoma. Mutations of K-ras or p53 are studied in gallbladder carcinoma [34]. The reported prevalence of p53 gene mutation is in the range from 35 to 92%. Both K-ras and p53 mutations are reported in gallbladder cancer patients with abnormal junction of pancreatic and biliary duct [35]. In one study, it was seen that high incidence of carcinoma of the gall bladder observed in patients with blood groups A and AB [36].

Pathology

The dysplasia-carcinoma sequence has also been proposed in gallbladder cancer. The estimated time of progression from

dysplasia to carcinoma is approximately 10–15 years [37]. It is not typically present with adenomatous polyp; however, it is commonly seen with chronic mucosal inflammation. Gallbladder cancer most often presents as monocentric lesions and multifocal forms are extremely rare. The most common localization is at the fundus of the gallbladder (60%), followed by the body (30%) and the infundibulum/neck (10%) [38].

The most common histological type of gallbladder malignant tumor is adenocarcinoma. The papillary form of adenocarcinoma has the best prognosis because this type of tumor tends to be noninvasive or minimally invasive [38]. The other histological types are squamous cell or adenosquamous carcinoma, mucinous carcinoma, signet ring cell carcinoma, lymphomas, and neuroendocrine tumors [39]. The rare forms are represented by melanomas or secondary tumors localized at the level of the gallbladder.

Gallbladder cancers most commonly metastasize to the lymph node and adjacent liver in gallbladder bed [40]. The gallbladder lymphatic is drained by lymphatic plexus into the first level of lymph nodes i.e. cystic duct, and pericholedochal lymph nodes [40]. The spread then occurs down into the pancreaticoduodenal lymph nodes and nodes along the common hepatic artery and celiac axis. The nodes in interaortocaval regions are considered as metastatic disease [41].

The venous drainage of the gallbladder occurs through veins draining directly to segment IV b or V or via venous collaterals along the bile duct [42]. The majority of venous drainage occurs into the right lobe (2/3); however, in 28% to left lobe only and in 28% it occurs to both lobes of the liver. The close proximity of the gallbladder to the liver, the connective tissue of the gallbladder is continuous with the interlobular connective tissue of the liver, and venous drainage explains the predisposition of the gallbladder cancer to involve liver bed. The perineural invasion is also reported in approximately 25% patients [43].

Advanced cases of the disease determine enlarged lymph nodes at the level of the hepatic hilum, which erode and invade the portal vein wall, causing thrombosis and all the consequences of portal hypertension. Spreading to the peritoneum, which determines the occurrence of paraneoplastic ascites, as well as pulmonary and hepatic metastases, determines the infaust evolution of terminal cases.

Clinical Presentation and Workup

Gallbladder cancer can be diagnosed either preoperatively or intraoperatively during surgical treatment for another disease and even as a histopathological surprise of the specimen resulting from cholecystectomy for gallbladder stones. The patients with early-stage disease are usually asymptomatic or may be diagnosed as acute or chronic cholecystitis [44]. However, most common symptom in gallbladder cancer is pain and jaundice. The other symptoms include weight loss, palpable mass, and ascites. The less common presentations are duodenal obstruction, gastrointestinal bleeding, or hemobilia. In spite of these, many lesions are diagnosed as incidental findings during surgery [45].

Incidental gallbladder cancer is detected in approximately 0.2% to 1.1% of all laparoscopic cholecystectomy [46]. Imaging is crucial for diagnosing and staging of gallbladder cancer. Ultrasound is usually the first imaging performed in patients presenting with biliary tract disease. On USG, it is difficult to differentiate gallbladder cancer from chronic cholecystitis especially in early lesions of GBC. However, its sensitivity for detection of GBC increases with tumor infiltration to the liver or lymph node. The features on ultrasonography that may raise suspicion of malignancy are mass in the gallbladder, irregular and thickened gallbladder wall, a polyp > 10 mm in size, suspicious invasion into the liver, and enlarged pericholedochal nodes [47]. Kim et al. [48] reported gallbladder wall thickening > 1 cm and hypoechoic internal echogenicity to be independent predictive factors for neoplastic gallbladder thickening.

Contrast-enhanced CT scan of the abdomen is the most important and reliable imaging for the staging and detection of extent of locoregional spread. It strongly suggests the presence of lymph node metastases, local invasion of the liver and vascular involvement. In early lesions of gallbladder carcinoma or wall thickening, the accuracy increases in dual-phase CT [47]. This modality enhances visualization of gallbladder wall in arterial and venous phase and helps to differentiate malignancy from chronic cholecystitis. Kim et al. [49] reported CT scan findings in differentiating T1 versus T2 lesions, T2 versus T3 lesions, and T3 versus T4 lesions with sensitivity of 79.3%, 92.7%, and 100%, respectively and corresponding specificity were 98.8%, 86%, and 100%, respectively. CT provided details about the local extent of carcinomas of the gallbladder with accuracy of 83 to 86% [50]. It has acceptable sensitivity and specificity for the T2 and more advanced lesions but poor sensitivity for the T1 lesions. The overall accuracy of CT scan in predicting the stage in GBC was 71%, 79% for T1 and T2 tumors, 46% for T3 tumors, and 73% for T4 tumors [50]. Combining CT with multiplayer reconstruction (MPR) can differentiate T-stage with > 80% accuracy [30]. MRI has better sensitivity for both identifying possible lymph node metastases and for revealing any invasion at the level of the adjacent hepatic parenchyma. This is best evidenced by MRI T2 sections [30].

Color Doppler may detect high flow within the lesions reported in malignant lesions. Endoscopic ultrasonography (EUS) has been incorporated in preoperative staging of GBC. The EUS staging was used to report the macroscopic tumor appearance (pedunculated versus sessile), the wall thickness (localized versus diffuse), and the layer structures

of the gallbladder (maintenance or disruption of the outer hyperechoic layer). EUS-guided FNAC may be one from primary tumor, enlarge lymph nodes or liver metastases, where the diagnostic accuracy approaches up to 100% [30]. ERCP (endoscopic retrograde cholangiopancreatography) allows tissue biopsy in selected patients identifies AJPBD and also used to place stent for palliation of jaundice.

The relevant tumor markers in GBC are CEA and CA 19-9 [51]. A high level of CEA has a specificity of 90% for malignant tumors of the gallbladder but has a low sensitivity (50%) when it is used for screening because it is also elevated by benign tumors. The tumor markers have a low utility for gallbladder cancer's diagnosis but they are extremely important for the follow-up of these patients. As a single tumor marker for GBC diagnosis, CA 19-9 has a sensitivity of 71.7%. Diagnostic accuracy with a combination of CA199, CA242, and CA125 diagnostic accuracy was 69.2% [52].

These tumors are considered highly aggressive and rapidly involve hepatic parenchyma, mostly segments IVb and V. The tumor extension can occur towards the cystic duct and its confluence with the common hepatic duct and may have presentation similar to a Klatskin tumor. Malignant tumors of the gallbladder can invade the branches of the hepatic artery or portal vein, which leads to the atrophy of the ipsilateral lobe and compensatory hypertrophy of the contralateral lobe.

FDG PET is an emerging modality that may be used for the diagnosis of ambiguous primary lesions and detection of residual disease in gallbladder bed in post-cholecystectomy patients and distant metastases not diagnosed by conventional imaging studies. FDG PET causes change in management in 31% of patients. Anderson et al. [53] evaluated 14 patients of GBC with after cholecystectomy and reported sensitivity and specificity of 78% and 80% respectively. The addition of PET to standard staging CT may be helpful in 17% of patients to improve classification of equivocal lesions by CT or MRI and identify distant metastatic disease [54].

Diagnostic laparoscopy is superior in identifying possible peritoneal spread and small liver metastases, which are difficult to detect on standard imaging modality. These are absolute contraindications for radical surgery [55]. Diagnostic laparoscopy combined with intraoperative ultrasound techniques, with or without contrast, has better sensitivity in identifying liver metastases and allows for a more precise evaluation of tumor-adjacent blood vessel involvement. The invasion of adjacent organs (liver, stomach, duodenum, pancreas, colon, greater omentum, and abdominal wall) can also be revealed through laparoscopy [56]. The preoperative histopathological diagnosis is not considered necessary as biopsy may cause peritoneal or biopsy tract seedlings. In addition, the rate of false-negative results of biopsies is significant.

The IGBC on histopathological examination of specimen needs high-resolution imaging to evaluate for the residual disease, nodal metastases, and identification of distant metastases. Both CT/MRI provide crucial information and restaging of the disease. Recently, 18 FDG PET-CT has been reported to improve the sensitivity for detecting non-clinically evident metastatic disease in GBC. FDG PET causes a change in management in 13% patients with incidental GBC [54]. Thus, 18 FDG PET-CT is not established in the evaluation of this incidental diagnosed GBC. Shukla et al. [57] evaluated IGBC with PET-CT in 24 patients and reported a sensitivity of 100% in predicting resectability, which was not significantly superior to conventional CT. The residual disease was demonstrated with a sensitivity of 28.5% and specificity of 80.9% [57]. PET-CT scan is useful to stratify patients with incidentally diagnosed gallbladder cancer for effective treatment. Goel M et al. [58] reported that patients with pT1b lesions and wedge liver resection should be avoided in PET negative and patients may be observed as chance of relapse is low.

Surgical Treatment of Gallbladder Cancer

The treatment of GBC is a multimodal one and implicates a multidisciplinary team. The aim of surgical resection is to achieve Ro resection, thus extent of resection required to achieve may vary with the disease extent [59, 60]. The R1 or R2 resection in gallbladder carcinoma has no long-term survival [61]. The radical (extended) cholecystectomy involves wedge resection of liver segment IVb and V to at least a 3-cm depth from gallbladder bed along with regional lymphadenectomy [62]. Stage I and II carcinoma gallbladder is potentially resectable with curative intent. However, stage III indicates mostly unresectable disease from vascular invasion or multiple adjacent organ involvement. Stage IV is an unresectable disease secondary to distant metastases [63].

Surgical resection remains the only curative alternative; however, it is only possible in 15–47% patients at the time of diagnosis [2].

It is necessary to identify the absolute contraindications for radical surgery and these are the following non-contiguous liver metastases, peritoneal nodule, encasement of main portal vein or proper hepatic artery, gross para-aortic lymphadenopathy or malignant ascites [64]. The invasion of adjacent organs (colon, duodenum, and liver) does not represent an absolute contraindication to radical surgery as en bloc resection of the tumor and invaded organs could be performed [7]. The presence of jaundice in gallbladder carcinoma patients occur due to extension of disease into the lumen of common bile duct, engulfment or invasion of the bile duct by the gallbladder cancer, pressure or invasion of the bile duct by lymph nodes in the hepatoduodenal ligament, or the presence of associated stone in the bile duct. Thus, the presence of jaundice is not always considered as a sign of unresectability. In all patients with resectable lesions, staging laparoscopy helps to assess for

the presence of peritoneal and discontiguous liver disease [7, 65].

Extent of Hepatic Resection

The primary aim of surgical treatment for carcinoma gallbladder is to achieve Ro resection as R1 or R2 resections have survival similar to patients not undergoing surgery [64, 66]. The extent of hepatic resection includes extended cholecystectomy or Glenn resection (approximately 2–3 cm from gallbladder bed) or anatomical resection of liver segment IV b and V. Both wedge and segmental resection are accepted as long as tumor-free margin (R0) is achieved in the liver parenchyma [64]. Pawlik et al. [67] reported that patients with major hepatic resection (anatomical segmentectomy of IVa and V or hemihepatectomy) had a similar risk of specific death to patients who have undergone hepatic wedge resection. Thus, it is not the type of hepatic resection but the Ro resection margin is the important factor in determining the final outcome.

The extensive liver invasion may require major hepatectomy in the form of extended right hepatectomy. The decision for such major liver resection in locoregionally advanced disease requires careful judgment and is only recommended when R0 resection is achieved. Extended hepatic resection is also useful in providing negative resection margins for patients with inflammation near the cystic plate following cholecystectomy [68]. Thus, in the absence of right portal pedicle involvement, segmental resection is adequate. The various margins have been proposed in wedge resection of the liver varying from 1 to 5 cm and have shown similar results [69].

There are no conclusive data to show that routine resection of segments IV and V is mandatory in patients with Tis, T1, or T2 disease if negative margin has been achieved with wedge hepatic resection [70]. However, hepatic wedge resection (2–3 cm) has problem of maintaining constant thickness around gallbladder. The non-anatomical hepatic resections are also associated with high risk of bleeding and bile leak. In the patients with extended hepatic resection, portal vein embolization (PVE) is indicated if future liver remnant is less than 25% of original liver volume [68].

Lymph Node Dissection

The extent of nodal disease in GBC patients is also an important concern. The regional lymph nodes of the gallbladder include the cystic duct, pericholedochal, posterior superior pancreaticoduodenal, retroportal, right celiac, and hepatic artery node groups. The cystic duct and pericholedochal node groups have been regarded as the first echelon nodes of the gallbladder, whereas the second echelon lymph nodes were located posterosuperior to the head of the pancreas (the posterosuperior pancreaticoduodenal nodes) or posterior to the portal vein (the retroportal nodes) and common hepatic artery (the right celiac nodes) [71, 72]. The lymph from the gallbladder flows in hepatofugal direction around the common bile duct, into the first echelon nodes then reaching to the second echelon nodes (other than hilar node), and finally to the para-aortic nodes [71, 72].

Glenn and Hays [73] first described the procedure of radical cholecystectomy in 1954 with portal lymph node dissection referred as “skeletonization of the lesser omentum”. In 2005, Dixon and colleagues [74] described complete portal lymph node dissection with skeletonization of the portal structures up to the suprapyloric region. This dissection does not include the second echelon lymph nodes of the gallbladder and is practiced in most western countries. Extended portal lymph node dissection includes resection of both the first and second echelon nodes en bloc [71]. Lymph nodes in the hepatoduodenal ligament are dissected if they are not infiltrating the vascular structures. However, enlarged nodes behind the head of the pancreas or behind the duodenum are dissected with good kocherization. This extended dissection clears both the first and second echelon lymph node groups of the gallbladder and is widely practiced among Japanese surgeons [71, 72]. The extended regional lymphadenectomy may combine with pancreaticoduodenectomy in selected group of patients in the presence of peripancreatic (head only) nodal disease adherent to or invading the pancreatic parenchyma [75, 76].

The advantage of nodal dissection on long-term survival has been proven [72, 75]. It is the most important prognostic information in the absence of distant metastases. The T stage is the ultimate predictor of nodal involvement. The frequency of nodal status with T stage includes 0–4% in T1a, 12.5–20% in T1b, 20–60% in T2, and 60–81% in T3/T4 lesions [77, 78]. The prognosis of GBC correlates with the lymph node involvement than the depth of infiltration [77, 79]. Recent reports by Western groups have uniformly suggested that radical resection with portal lymphadenectomy provides a survival benefit for patients with pN0 disease [80, 81]. Japanese groups have suggested that a considerable proportion of patients with pN1 disease survive for 5 years after potentially curative (R0) resection with extended portal lymphadenectomy [77, 78]. However, the majority of these long-term survivors have nodal disease restricted to the first echelon lymph nodes [77, 79].

Assessment of the nodal status in GBC is a critical issue. The three conventional parameters of nodal status include anatomical location of positive lymph nodes, number of positive lymph nodes, and lymph node ratio (LNR, ratio of number of positive nodes to the number of nodes (TLNC) evaluated). Shirai et al. [82] reported only the number of positive lymph nodes as potent parameter in assessing the nodal status in GBC and not the anatomical location of lymph node or LNR. However, Negi et al. [83] found LNR as independent prognostic factor rather than number of positive nodes in

study cohort of 57 patients with relatively small TLNC (median of 5 in node-negative and 6 in node-positive patients). In a study published from the USA, 122 patients underwent portal lymph node dissection for GBC and reported a median TLNC of 3 nodes only [84]. In contrast, Japanese studies reported retrieval of a large number of nodes (median of 14 nodes), showing proved 5-year survival statistics [82]. The studies suggest that retrieval and evaluation of at least six lymph nodes improve risk stratification in node-negative patients [83, 84].

It is important to note that lymph node metastasis is present in 19–25% of patients [85]. The radical resection with paraaortic lymphadenectomy does not provide survival advantage in patients with GBC [85]. Studies have reported that interaortocaval nodes (16b1) are considered as final abdominal nodal station and metastases to this LN has poor survival similar to patients with hepatic or peritoneal metastases [85]. Thus, frozen section of interaortocaval LN is recommended and radical surgical procedure should be deferred on histological confirmation of metastases [86].

Bile Duct Resection

Extrahepatic bile duct resection has not shown improvement in survival in patients with GBC, it rather increases morbidity [67, 87]. Its resection is performed if the cystic duct stump margin is positive with tumor or lesion in neck of gallbladder infiltrating directly into the common bile duct. Intraoperative frozen section of cystic stump margin should be done and resection bile duct may be required if negative margin is not achieved [88]. The surgeons who are proponent of bile duct excision propose to have better lymph node yield however, it is not proven [87, 88]. Pawlik et al. [67] showed that the median number of lymph nodes harvested at the time of lymphadenectomy was the same with or without common bile duct excision. Araida et al. [89] reported that patients with advanced GBC, in absence of hepatoduodenal ligament and/or of the cystic duct invasion, and resection of bile duct showed no differences in terms of recurrence and overall survival. However, it also predisposes these patients with bilioenteric anastomosis complications. The other reason for bile duct excision is to avoid occurrence of ischemic biliary stricture after aggressive periductal nodal dissection. The studies have shown that patients with microscopically positive cystic duct stump margin were more likely to have a disease in the common bile duct (42% versus 4%) and bile duct excision may require to achieve R0 margin [67]. A few studies from Japan proposed survival advantage with resection of extrahepatic biliary tree [89, 90]. In contrast, other studies have shown no additional survival benefit [91, 92]. The malignant invasion of cystic duct is an indicator of poor prognosis because of high incidence of concomitant perineural invasion and lymph node metastasis. The two important indications for bile duct resection are positive cystic duct margin and as part of extended right hemihepatectomy because of the concern about encroachment of tumor to right main or posterior sectoral ducts compromising Ro resection [67, 90, 91].

Adjacent Organ Involvement

The involvement of portal vein and hepatic artery are not amenable for resection. The direct involvement of the colon, duodenum, or liver is not a contraindication for surgery. There are several reports of extended resections like extended right hepatectomy or combined hepatic and pancreatic resections as pancreaticoduodenectomy with improved long-term survival [3, 93]. However, major resection for the pancreas or duodenal involvement such as pancreaticoduodenectomy is associated with high morbidity and mortality [94]. Duodenal infiltration can also be treated with duodenal sleeve resection or distal gastrectomy with resection of first part of duodenum. Similarly, colonic involvement may need segmental resection or right hemicolectomy [95, 96]. It should be emphasized that multiple liver metastases are a contraindication for radical procedure as it represents disseminated disease.

Surgical Management of IGBC

In patients where diagnosis of GBC is made intraoperatively during laparoscopic cholecystectomy, it is paramount not to violate the oncological principles during first operation, if a two-stage approach is necessary. The accidental opening of the gallbladder or bile leak has worse prognosis [97, 98]. Intraoperative staging should be done as it identifies the occult disseminated disease. The suspected metastatic disease or lymph node may be sent for frozen section procedure. The procedure, extended cholecystectomy, should be performed after conversion to an open procedure or if expertise is not available then surgery should be differed. The patient should be transferred to an experienced center. In incidental diagnosed GBC, the extent of surgery depends on the depth of invasion (T-stage) of tumor [46]. The reoperation for incidentally diagnosed gallbladder carcinoma has two fundamental objectives: Ro resection of liver parenchyma and clearance of locoregional lymph nodes. Re-exploration of incidentally diagnosed GBC patients on histology reveals residual tumor in 40–76% cases [46].

In cases of carcinoma in situ or tumor invading the mucosa (Tis and T1a), simple cholecystectomy alone is the curative procedure and no further treatment is required [46, 77]. No data support re-exploring these patients for lymphadenectomy. With negative margins, cure rate following simple cholecystectomy ranged between 85 and 100% [77]. However, if

the tumor invades the muscle layer (pT1b), the incidence of lymph node metastasis reported is 10–20%; lymphatic, venous, or perineural infiltration is up to 50%; and future risk of recurrence up to the tune of 20–50% [11, 99]. In contrast to some series, no lymphatic, venous, or perineural invasion has been reported in the patients with T1b. Thus, some controversy exists for the management of T1b lesion. The simple cholecystectomy in pT1b lesion has shown 1-year survival rate of 40–50% [100, 101]. On re-exploration of these patients, residual disease was found in liver bed in 10% [102]. There are reports of an increase in 5-year survival after radical cholecystectomy for T1b tumors is 62–100%) [101–103]. Thus, radical re-resection as radical cholecystectomy is needed as a second procedure.

In cases where tumor invaded the muscularis propria (T2 and beyond), a radical cholecystectomy is mandatory. In these cases, simple cholecystectomy was performed with dissection in subserosal plane that resulted in positive margins and increased risk of liver involvement. Various studies have compared 5-year survival of patients following simple cholecystectomy and radical re-do surgery. The marked difference in 5-year survival has been reported for T2 lesion (30–40% vs 80–90%) [11, 99, 104]. Radical cholecystectomy is also recommended for T2 as occult lymphatic metastases reported in range of 30–50% [67, 102].

Recently, Shindoh et al. [105] have analyzed T2 disease with tumor location and categorized into hepatic side or peritoneal side of the gallbladder. They reported that patients with tumors on the hepatic side had higher rates of vascular invasion, neural invasion, and nodal metastases when compared with tumors located on the peritoneal side (51% vs. 19%, 33% vs. 8%, and 40% vs. 17%, respectively). The 5-year survival of patients for hepatic and peritoneal tumors was also different (42.6% versus 64.7%). Thus, based on poor survival of patients with tumor on hepatic side of the gallbladder, 8th edition AJCC staging system on carcinoma gallbladder has divided T2 into separate categories as T2a (stage IIA) and T2b (stage IIB).

In T3 lesions, incidence of residual disease and lymph node metastases are 36% and 46% respectively [67]. In patients after complete resection, the outcome ranges between 30 and 40% [74, 80]. Thus, redo-surgery as radical cholecystectomy is recommended. With advanced disease stage, the need for more extensive hepatic and bile duct resections are often indicated in the attainment of negative surgical margins [106]. T4 classified tumors are in most cases unresectable without any oncologic radicality pretention. In this stage, the palliative surgical approach combined with chemoradiotherapy is the only therapeutic alternative [7]. In exceptional cases, with main portal vein invasion, resection and reconstruction of the portal vein can be performed. However, the survival benefit of these procedures is unclear. The operative morbidity and mortality associated with extensive reconstructions generally outweigh any survival benefit, thus it is generally not recommended [46].

The GBC diagnosed incidentally during laparoscopic cholecystectomy are usually T1–3 lesions. However, T4 tumors are mostly diagnosed in preoperative work-up. The tumor of the neck of the gallbladder or patients with positive cystic duct margin requires bile duct excision and hepaticojejunostomy [67]. In patients with IGBC on histology following laparoscopic cholecystectomy, cystic duct stump was positive in 29.6% and residual disease in bile duct reported in 42.1% [67]. It is an important consideration to look for the cystic stump margin in patients presenting with simple cholecystectomy performed previously and reported as malignant on histology.

In post-cholecystectomy patients with incidental diagnosed GBC, resection of previous port sites during reresection is not performed routinely. As port site resection was not associated with increased overall survival or recurrence-free survival when Ro resections patients are compared with adjusted T and N stage [106, 107]. An associated increased incidence of incisional hernia is reported with port site excision. Thus routine port site resection is not performed in redo surgery.

Laparoscopic radical cholecystectomy has been performed in a few centers [108–110]. Port site recurrence and peritoneal dissemination are the major concern with the laparoscopic technique. It has been proposed that these complications occur due to inadequate manipulation of the gallbladder, gallbladder perforation during the procedure, and CO2 pneumoperitoneum. Prevention of the gallbladder perforation, bile leak during surgical procedure, and the retrieval of the gallbladder specimen in plastic bag can avoid dissemination. The 5-year survival rate following laparoscopic radical cholecystectomy for T1b and T2 was similar to an open procedure (100 and 83.3% versus 100 and 90% respectively) [108]. Robotic radical cholecystectomy has also emerged as a feasible alternative to open or laparoscopic resection. However, oncological adequacy of the procedure is unknown [108, 111].

Palliative Treatment

In patients with unresectable GBC, it is important to aid palliative treatment to improve quality of life. Patients in an advanced stage of the disease are often presenting with jaundice, pruritus, pain in the right upper abdomen, or bowel obstruction [112]. The optimal palliative procedure is one that provides the remission of symptoms with minimum morbidity [112]. The palliation for jaundice can be performed either endoscopically or surgically, although surgical palliation for jaundice has higher rate of complications compared to the endoscopic approach [113]. In unresectable disease on exploration, segment III bypass can be done for palliation of jaundice, however, higher complication rate is reported. In small

bowel obstruction, commonly seen in advance peritoneal disease intestinal bypass should be undertaken with caution because of higher morbidity.

Adjuvant Treatment

The data on the use of adjuvant therapy for GBC are conflicting, thus consensus regarding the optimal adjuvant therapy has not been reached. However, due to a high rate of recurrence, adjuvant treatment comes in the form of radiotherapy, possibly combined with chemotherapy [114]. Gemcitabine-based therapies have shown improved efficacy over 5 fluorouracil (5-FU) regimens. Sharma et al. [115] have shown improved median overall survival in GBC with the use of gemcitabine when compared with 5FU and best supportive care. Phase III trial from Japan showed improved year survival by adjuvant mitomycin and 5 FU versus resection alone (20.3% versus 11.6%) [116]. Few trials have also reported a beneficial effect of combining gemcitabine with oxaliplatin or cisplatin [117, 118].

In the case of patients who have positive resection margins, combined treatment (chemotherapy and radiotherapy) is recommended. An option is to perform intraoperative radiotherapy. This is meant to improve the prognosis but there is little evidence indicating a real benefit of this treatment [119]. One advantage of intraoperative radiotherapy is the possibility of targeted administration of a high dosage of radiation directly on the tumor, while protecting the adjacent, highly radiosensitive tissues [119]. Houry et al. [120] have shown slight improvement with radiation therapy in GBC and future of incorporating gemcitabine-based radiation regimens. The data on neoadjuvant therapies in GBC are limited. However, few studies have reported the beneficial effect of gemcitabine-based combination in neoadjuvant setting [121, 122].

In cases of unresectable tumors, palliative chemoradiotherapy can be performed. In the past, the used chemotherapeutic treatment was 5-FU, methotrexate, mitomycin C, and doxorubicin, with a response rate of 10–20% [63]. More recently, the use of gemcitabine and cisplatin has improved the response rate up to 64% [123]. On the other hand, radiotherapy has a palliative effect for locally advanced tumors (stages T3 and above) and is usually well-tolerated and ensures the remission of symptoms [63]. Radiotherapy is most commonly used in combination with chemotherapy.

Outcomes

The perioperative risk depends on the stage of the disease and the biological status of the patient. It is important to balance the risk of surgery to the risk of the untreated disease. Surgery should be performed with curable intent just when the patient is capable to support it. If the biological status of the patient does not support a radical approach it should be ameliorated preoperatively. Gallbladder cancer surgery is accompanied by a lot of possible complications, some of them very difficult to manage. Most feared complications are postoperative bleeding, bile leak, and perihepatic abscess. The perioperative mortality rate is significantly higher in patients with extended hepatic resections compared with those who underwent limited resections (resection of segments IVb and V), radical cholecystectomy, or simple cholecystectomy [124]. An improvement in the outcome of patients who underwent extended liver resection has been obtained by the progress made in the field of surgical techniques, anesthetic and intensive care management. Long-term outcome is extremely poor due to the highly aggressive nature of this type of cancer. Only patients staged T1 have better long-term outcome, but unfortunately only approximately 10% of symptomatic patients present with T1 disease with up to 20% of the incidentally diagnosed patients having T1 tumors.

The survival rate of patients undergoing surgery for gallbladder cancer depends of the disease's stage. For T1a tumors limited to the lamina propria, the 5-year overall survival rate is reported to range between 85 and 100% [77]. For T1b after radical cholecystectomy, 5-year survival is 62–100% [101–103]. Patients with T2 lesion, the oncologic radicality is easy to obtain by performing a liver resection including segments IVb and V, combined with lymphadenectomy at the level of the lesser omentum. The 5-year survival rate ranges between 80 and 90%. [11, 104]. The survival of the patients with T2 tumors depends on the lymph node status and negative margin achieved during resection or not. Now, difference in the survival is reported in T2 lesions present on hepatic versus peritoneal side of the gallbladder, with worse for hepatic side. For T3 and T4 tumors, it becomes challenging to balance the surgical risk of an extensive resection with the possible benefit. It is known that if a more extensive liver resection is performed, a higher rate of complications may occur. However, by recent improvement of the surgical techniques, the rate of complications after major liver surgery has decreased and more extensive resections can be made with a diminished morbidity and mortality rate. The 5-year survival rate in T3 lesions after complete resection ranges between 30 and 40% [74, 80]. The outcome of the T4 tumors is disappointing with survival of few months.

Patients presenting unresectable gallbladder tumors benefit from palliative treatment to increase their quality of life. The overall survival rate is not significantly improved by palliative treatment, but there may be some benefits of chemoradiotherapy. Advanced gallbladder cancer has a very poor survival rate without any treatment even if the patient has a good performance status. The overall survival is 4.4 months for unresectable and untreated gallbladder cancers [125]. The presence of metastases at the

moment of the diagnosis appeared to decrease the survival rate.

Gallbladder carcinoma is the most frequent biliary tract malignancy and mostly diagnosed in advance stage. Surgical resection is the only curative treatment; however, it is only possible in 15–47% patients at the time of diagnosis. The early-stage GBC is mostly diagnosed as incidental finding. The resection of tumor with Ro margin with lymphadenectomy is the only hope for the long-term survival. Multicentric randomized controlled trials are needed to address the various surgical issues to generate sufficient evidence to adopt uniform and standard surgical technique related to the stage of disease. The benefit of chemotherapy is to be explored further as adjuvant treatment to improve outcome in GBC.

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