

## Research

### Surgical Procedures for Gall Bladder Cancer

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#### Introduction

Gall bladder cancer (GBC) is the commonest biliary tract cancer worldwide but has not received much attention as it is an uncommon cancer in the West, including north America, western Europe and Australia & New Zealand; incidence of GBC has peculiar geographical distribution, being higher in central and south America, central and eastern Europe, Japan, South Korea and northern India [1].

There was a lot of confusion about the nomenclature related to the clinical presentation of GBC. In an earlier publication [2], we had introduced the terms obvious, suspected, unsuspected and incidental GBC depending upon the time/ stage at which diagnosis of GBC is first made. The terminology of surgical procedures for GBC is also not uniform and standardized, with different groups using different terms for the same surgical procedure or meaning different surgical procedures while using the same term. We now propose standardization of the nomenclature for surgical procedures for GBC.

#### Staging Laparoscopy

GBC is a biologically aggressive cancer [3]; in addition to the usual lymphatic and vascular routes, it spreads by peritoneal dissemination also, resulting in small surface deposits on the peritoneum (both parietal and visceral) and omentum which cannot be detected on ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) or even positron emission tomography (PET). They are, however, easily visualized on laparoscopy and can be biopsied to confirm metastatic disease. Presence of histologically confirmed peritoneal dissemination contraindicates laparotomy for resection as prognosis of GBC in presence of peritoneal metastasis is very poor. Staging laparoscopy, therefore, must be done in all patients with GBC thought to have possibly resectable disease on CT (including those who are PET negative) as detection of peritoneal dissemination on laparoscopy will avoid an unnecessary laparotomy [4,5] NCCN guidelines also recommend strong consideration of staging laparoscopy [6]. We suggest that it should be rightly called staging (NOT diagnostic, as erroneously referred to in some reports) laparoscopy.

#### Distant Lymph Node Biopsy

The first step at laparotomy (after a negative staging laparoscopy) should be to look for an enlarged distant (celiac, superior mesenteric or aorto-caval) lymph node – if present, the lymph node should be removed and subjected to a frozen section histopathology. A positive distant lymph node indicates metastatic disease and poor prognosis, and contraindicates resection [7]. Distant lymph node biopsy can be performed laparoscopically also. Extended retroperitoneal lymphadenectomy [8], including distant lymph nodes, has been described but is not practised by most groups as it does not lead to increased survival.

#### Simple Cholecystectomy

Simple cholecystectomy, wherein the plane of dissection is between the gall bladder wall and the cystic plate, which is left intact attached to the gall bladder bed in liver, is adequate for mucosal (T1a) GBC because these tumors are not associated with lymph node spread [9]; this can be performed laparoscopically also. The clinical problem, however, is definitive preoperative diagnosis of T1a GBC which is difficult on US or CT and can be made by endoscopic ultrasonography (EUS) alone. T1a GBC is, therefore, hardly ever a preoperative diagnosis and simple cholecystectomy will hardly ever be performed for an obvious GBC. The clinical application of this knowledge is, however, useful when dealing with incidental GBC. If it was T1a disease AND if the cystic duct margin was negative AND if the cystic lymph node was negative, simple cholecystectomy alone will be enough and no more intervention

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(in the form of CEC, *vide infra*) is required.

### Non-Curative Simple Cholecystectomy

Some patients with disease confined to the gall bladder i.e. T1/ T2 disease may have distant lymph node spread or distant metastases. In such cases, while R0 resection is not possible, the gall bladder can be safely removed without breaching any tumor plane thus resulting in an obvious R2 resection. This, combined with postoperative adjuvant chemo-radio therapy, may result in better survival than no treatment/ chemotherapy alone [10]. While we do not recommend it as a procedure of choice, we suggest that it may be performed if the distant lymph node spread or distant metastasis is detected for the first time after laparotomy has been performed. Non-curative resections have been performed by other groups also - 13 out of 165 resections performed for T3/ T4 GBC at Nagoya were simple cholecystectomy [11].

### Full Thickness Cholecystectomy

Kinoshita [12] introduced the term full thickness cholecystectomy (FTC) which includes removal of the gall bladder with the cystic plate i.e. the plane of dissection is between the cystic plate and the liver parenchyma. This procedure is also adequate for T1a (mucosal) GBC only [13] and can be performed laparoscopically [14] but its clinical application is limited (*vide supra*).

### Extended Cholecystectomy (EC)

EC, initially described by Glenn and Hays [15], according to us [16], includes removal of

1. Gall bladder
2. Resection of a non-anatomical 2 cm wedge of liver around the gall bladder bed in segments IVB and V. The margin of 2 cm is arbitrary – just 1 cm may also be adequate if there is no liver infiltration or even 3 cm may be required in some patients with liver infiltration. Liver parenchyma is divided but no major bilio-vascular pedicle is encountered except a branch of segment V pedicle and few terminal tributaries of the right hepatic vein (RHV) and middle hepatic vein (MHV). Wedge resection can be performed with virtually no bleeding using high wattage cautery and ultrasonic scalpel. It must, however, be kept in mind that the liver wedge can be taken around the gall bladder fundus/ body only and not around the gall bladder neck where the right main portal pedicle lies at a depth of only a few mm from the gall bladder bed.
3. Dissection of lymph nodes in the hepato-duodenal ligament (cystic, pericholedochal, porta hepatis and retroportal), those behind pancreas head and duodenal C loop (retropancreatic and retroduodenal) and along the common hepatic artery (to the right of the celiac axis). Adequacy of lymph node dissection is reflected in the number of lymph nodes identified in the specimen; a minimum of 6 lymph nodes is considered adequate for GBC [17]. EC does

NOT include a formal/ anatomical liver resection (as in segment IVB+V resection, *vide infra*) and dissection of celiac (to the left of the celiac axis), superior mesenteric or aorto-caval lymph nodes. EC is curative for early GBC i.e. confined to the gall bladder wall (T1, T2) and lymph node spread limited to the hepato-duodenal ligament (N1). EC may be performed for GBC at fundus/ body with minimal liver infiltration (T3) but for GBC at neck with liver infiltration (T3) EC is not technically possible as the right main portal pedicle lies at a depth of only a few mm in the gall bladder bed at its neck and a 2 cm margin of liver will sacrifice the right main pedicle thus necessitating right hepatectomy (which in GBC translates into extended right hepatectomy because segment IV also has to be removed). EC has been performed laparoscopically also [18,19] but we do not recommend it because of the aggressive biology of GBC [3]. If it is to be performed, it should be done in patients with T1/T2 disease (no liver infiltration, no adjacent organ involvement) only – this should be confirmed by both CT and EUS and preferably laparoscopic US also. The terms extended and radical cholecystectomy have been used as synonyms to describe the same/ similar surgical procedures. We, however, prefer to use the term EC for describing the surgical procedure for GBC, which defines the extent of the surgical procedure. We do not use and do not recommend the term radical cholecystectomy because the term radical defines the oncological adequacy of the surgical procedure based on the result of histological examination of the specimen i.e. R0 resection. Radicality of a surgical procedure depends both on the stage of the disease and the extent of the surgical procedure. Thus, while even simple cholecystectomy (with no liver resection and no lymph node dissection) will be radical for mucosal, node negative (T1aN0) GBC, even hepato-ligamentopancreato duodenectomy (HLPD) may not be radical for locally advanced GBC infiltrating liver, hepato-duodenal ligament (containing the common bile duct, hepatic artery and portal vein), and pancreas.

### Extended Resections

Procedures more extensive than EC should be described as follows

#### Segment IVB+V Resection

Also, erroneously though, called bisegmental resection [20] and central inferior subsegmentectomy [21] While most groups differentiate between liver wedge and segment IVB+V resection, some groups, erroneously though, use the term standard radical cholecystectomy to include both procedures [22].

Segment IVB is the lower (caudal) part of segment IV of liver; Japanese surgeons, however, call the lower part of segment IV as IVA and upper part as IVB

.Segment IVB+V is an anatomical liver resection. The technique of segment IVB+V resection has been best described by Miyazaki [23]. Vessels, usually 2-3, to segment IVB from the left hepatic

artery (LHA) and left portal vein (LPV) are taken to the right of the base of the falciform ligament resulting in discoloration of segment IVB. The border between segment V and segment VI is identified by temporarily clamping the right posterior sectoral portal pedicle in the gall bladder bed which demarcates the right posterior sector (segments VI+VII) from the right anterior sector (segments V+VIII). Parenchyma is then divided where terminal tributaries of RHV and MHV are encountered. Segment IVB+V resection may be required to achieve R0 resection for GBC at fundus/ body with liver infiltration (T3) but is not suitable for GBC at neck with liver infiltration (T3) for reasons cited above.

Segment IVB+V resection is expected to take care of occult intrahepatic metastases as a result of spread via portal venous branches [24] but whether and why these metastases are confined to segment IVB+V only and do not involve the rest of the liver is not certain. A major disadvantage of segment IVB+V resection is division of branches from LHA and LPV to segment IV as in some cases these are common branches to both segments IVB and IVA and their division may devascularize segment IVA also.

In a review of 85 patients with T2N0 GBC, 5 year survival did not differ between those who underwent bed resection (n=55) and segment IVb+V hepatectomy [25].

#### Extended Right Hepatectomy (ERH)

Also, erroneously though, called trisectionectomy Right hepatectomy alone, described for the first time by Pack [26], is never adequate for GBC; in GBC, segment IV also has to be removed thus resulting in ERH [27]. Modified ERH (removing only segment IVB and preserving segment IVA) has been described to preserve more liver parenchyma.

Patients with locally advanced GBC, especially at the gall bladder neck, often present with obstructive jaundice due to involvement of the common hepatic duct. Preoperative biliary drainage has to be performed to bring the serum bilirubin down to less than 3 mg/ dL before a major liver resection. This can be endoscopic if the biliary ductal confluence is patent but percutaneous transhepatic biliary drainage (PTBD) will be required if the biliary ductal confluence is involved.

If the functional liver remnant (FLR) is not adequate (<30% in patients without jaundice and <40% in patients with jaundice), hepatic failure may occur after a major liver resection and is responsible for high mortality. FLR may be increased by portal vein embolization (PVE) which causes atrophy – hypertrophy. For GBC, however, RPV as well as segment IV branch of LPV have to be embolized because ERH will be performed. If RPV alone is embolized, segment IV (which will also have to be resected) will also hypertrophy and cause technical difficulties during ERH. Staging laparoscopy should be performed before PVE and once

again before operation. Nagoya group performed PVE in 141 patients with GBC (1991-2010) but only 80 (57%) could be resected and mortality of resection was 13/80 (16%); 5 year survival was 23% - only 10 patients lived for 5 years [28].

#### Central Hepatectomy

Central hepatectomy (resection of segments IV, V and VIII) is an alternative to ERH which preserves the right posterior sector (segments VI and VII) which is not involved in GBC. It can, however, be performed only if RHA/ RPV is not involved. It has, however, not become very popular, probably because of technical difficulties.

#### Taj Mahal Resection

Kawarada [29] described Taj Mahal resection including segments IVB+V with total resection of the caudate lobe (segment I). This is a dome-shaped liver resection ending at the root of the middle hepatic vein (MHV) which then lies exposed at the pinnacle of the dome which looks like the Taj Mahal at Agra in India. The limits of the dome on the left side are B2+3 bifurcation and the right margin of the umbilical portion of the LPV and on the right side B8 of the right anterior sectoral branch and B6+7 bifurcation of the right posterior sectoral branch. Taj Mahal resection requires multiple intra-hepatic biliary-enteric anastomoses in the form of intra-hepatic cholangio-jejunostomy.

Taj Mahal resection is suitable for GBC at neck involving the biliary ductal confluence but without involvement of the RHA or RPV. It has also not become very popular, again probably because of technical difficulties. Also, it cannot be performed if RHA and/ or RPV are involved.

#### Combined Resection Of Adjacent Organs (CRAO)

##### Common Bile Duct (CBD)

Some groups [30] recommend CBD excision as a routine during EC to take care of occult periductal and perineural spread. CBD excision, however, increases the morbidity of EC [31]. In our opinion, CBD excision is not a mandatory component of EC; it may be performed in some selected cases e.g.

GBC with surgical obstructive jaundice due to direct infiltration of the CBD

Tumor in gall bladder neck/ cystic duct which is close to the CBD so that a clear margin cannot be obtained or if the cystic duct margin is positive on frozen section

iii. Some surgeons advocate CBD excision in presence of extensive lymph node involvement in the hepato-duodenal ligament to ensure adequate lymph node dissection, especially if the lymph nodes are adherent to the CBD. In a recent study, CBD resection in 41/112 patients did not increase the number of retrieved lymph nodes [32]

iv. For papillary tumors in the gall bladder which are more likely to be multi-centric or have intra-ductal spread to the CBD

v. GBC with choledochal cyst

Extrahepatic biliary (CBD) involvement (EBI) is a poor prognostic factor – in an analysis of 100 patients with T3/T4 GBC who underwent resection, survival was much poorer in those with EBI than in those without EBI - 5 year 23% vs. 54% and median 1.5 vs. 15.4 years [33].

#### Vessels

Involvement of major vessels in the hepato-duodenal ligament viz. hepatic artery and portal vein, indicates poor prognosis and is a contraindication for resection in GBC [34]. There are a few reports of resection and reconstruction of these vessels [35] but resection of major vessels does not improve survival in GBC, unlike in cholangiocarcinoma, where it may be helpful [36].

#### Colon

Right transverse colon is often involved in GBC (especially at fundus) and can safely be resected to achieve an R0 resection.

#### Duodenum

Involvement of the duodenum may contraindicate resection unless pancreato-duodenectomy is planned. Segmental or sleeve resection of the duodenum [37] has been described (if pancreas is free).

#### Pancreas

Involvement of the pancreas may contraindicate resection unless pancreato-duodenectomy (PD) is planned. PD, when combined with EC or segment IVB+V resection, will have the morbidity and mortality similar to PD itself but hepato-pancreato-duodenectomy (HPD) i.e. major hepatectomy combined with PD is still associated with high mortality and does not offer survival advantage in GBC [38] The role of HPD in GBC is questionable [39] and it is not recommended for GBC [40]. Wedge resection of pancreas has been described for involvement of (head of) pancreas [41] but has not become popular because of technical difficulties.

#### Right Upper Quadrantectomy

There are anecdotal reports of supra-radical surgical procedures including major hepatectomy, hepato-duodenal ligamentectomy (including CBD, hepatic artery and portal vein), pancreato-duodenectomy, right hemicolectomy, right nephrectomy, etc for loco-regionally advanced GBC but their benefit in terms of long term survival is questionable.

Combined resection of adjacent organs (CRAO) other than liver and CBD is a poor prognostic factor 5 year survival was 16% vs. 36%, median survival 0.8 vs. 3.8 years [33].

#### Completion Extended Cholecystectomy (CEC)

We have proposed the term completion extended cholecystectomy (CEC) for the surgical procedure performed for the diagnosis of an incidental GBC diagnosed for the first time on histopathological examination of a gall bladder removed for a presumed diagnosis of gall stone disease [42]. CEC, recommended for all except T1a tumors, includes resection of non-anatomical 2 cm wedge of liver in the gall bladder bed in segments IVB and V and lymph nodes as in EC.

At the time of reoperation, the cystic duct stump should be excised and sent for frozen section histological examination. If positive, CBD excision should be added to the CEC [43].

Based on the reports of high incidence of port site metastases (which usually occur in the port of gall bladder extraction but can very well occur in other ports also) after laparoscopic cholecystectomy for GBC [44], we recommend full thickness (skin to peritoneum) excision of all 4 ports of LC as a part of the CEC. The upper 2 ports (midclavicular and epigastric) can actually be included in the subcostal incision used for CEC. Some recent reports, however, indicate that port site excision may not offer any survival advantage and only helps in deciding the need for adjuvant therapy and to predict the prognosis [45]. In a recent analysis of 113 patients with incidental GBC who underwent resection at MSKCC, New York between 1992 and 2009, port site resection (n=69) did not improve survival [46].

CEC with liver wedge [47] and segment IVB+V resection [48] has been performed laparoscopically also but we do not recommend it and prefer open operation for CEC for the same reasons as for EC (*vide supra*).

#### Anticipatory Extended Cholecystectomy (AEC)

We have recently introduced the term anticipatory extended cholecystectomy (AEC) for a thick-walled (wall >3 mm) gall bladder (TWGB) on US with low suspicion of cancer. All TWGBs should be evaluated by CT to define whether the wall thickness is focal or irregular (highly suspicious of GBC) or diffuse and regular (more likely to be inflammatory and less suspicious of GBC). A highly suspicious TWGB should be treated as GBC i.e. staging laparoscopy followed by open EC. A small number of these cases may turn out to be inflammatory on histological examination but that should be acceptable [49]. The diffuse regular TWGB is more likely to be inflammatory but may be malignant in about 3% of cases [50]. An EC in these cases will be an over kill in a vast majority of cases and is not recommended. Laparoscopic simple cholecystectomy, where the plane of dissection lies between the gall bladder wall and the cystic plate, will be suboptimal for the

few cases which turn out to be GBC because the tumor plane may be breached. Also, laparoscopic cholecystectomy frequently causes gall bladder opening and bile spill which may be responsible for dissemination of disease including port site metastases. In such low suspicious cases with diffuse and regular TWGB, we propose and recommend AEC i.e. removal of the gall bladder with 1 cm wedge of liver so that the plane of dissection is kept outside the cystic plate into the liver parenchyma. This ensures that the tumour (if present) plane is not breached. The specimen is subjected to frozen section histological examination - if the frozen section histological examination is positive for cancer, the EC is completed by adding lymph node dissection; if the frozen section histological

examination is negative, nothing more needs to be done. Only 2 out of 13 such cases in which AEC was performed turned out to be malignant [51]. Han and Cho [52] have reported laparoscopic cholecystectomy with cystic plate and some attached liver tissue in 30 patients with suspected GBC without liver invasion on CT, EUS or laparoscopic US - 12 turned out to be benign while 18 were GBC.

### Conclusion

We suggest the formation of an International Study Group on Gall Bladder Cancer (ISGGBC), on the patterns of similar study group for pancreatic surgery (ISGPS), to define and standardize the surgical procedures for GBC.

### Summary Of Surgical Procedures For Gall Bladder Cancer

|                                  |   |
|----------------------------------|---|
| T1, T2 (GB fundus/ body)         | Extended cholecystectomy  |
| (GB neck)                        | Extended cholecystectomy + CBD excision                                     |
| T3 liver (GB fundus/ body)       | Segment IVB+V resection   |
| (GB neck)                        | Extended right hepatectomy  |
|                                  | T3 colon Extended cholecystectomy + segmental colonic resection             |
|                                  | T3 duodenum Extended cholecystectomy + sleeve/ segmental duodenal resection |
|                                  | T3 pancreas Extended cholecystectomy + pancreato-duodenectomy               |
| T4 hepatic artery or portal vein | Unresectable  |
| Distant lymph nodes              | Inoperable  |
| Distant metastases               | Inoperable  |
| CBD common bile duct             |   |
| GB gall bladder                  |   |

**NOTE** In all cases, the intent of resection should be to achieve R0 resection status i.e. no microscopic residual disease; R2 resection (gross residual disease) is NOT acceptable and should not be performed.

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