**Short Review**

# Surgical Management of Gall Bladder Carcinoma

Muhammad Hanif Shiwani
.Barnsley General Hospital, and Honorary Senior Clinical Lecturer, University of Sheffield.

Carcinoma of gall bladder (CaGB) is extremely rare, affecting 7,100 people in the US per year. In the UK in 2002, only 394 new cases of CaGB were registered, with a rate of 1.5 per 100,000 population. Women are more commonly affected than men. The peak incidence is for people in their 60s, but the disease age range is from 29 to 90 years of age and there is great geographic and ethnic variation.[1] CaGB is one of the five most common malignancies of the gastrointestinal (GI) tract and the most common biliary malignancy.

## Association of CaGBwith Benign Diseases

There is a direct link between gall stones and CaGB. In patients with CaGB, the incidence of cholelithiasis ranges from 54% to 97%.[2,3] CaGB is more common in patients with Mirizzi's syndrome,[4] and typhoid carriers are a high-risk group. Moreover, porcelain (calcified) gall bladder has a high malignant potential and large, sessile polyps (more than 10mm) are more likely to be malignant than multiple, small, pedunculated ones.[5,6] The incidence of CaGB increases 14.7-fold 20 years after surgery for gastric ulcer.[7]

## Pathology

The adenocarcinoma is the most common histological type (approximately 80%) of CaGB, but histology varies. Cases of undifferentiated carcinoma occur in 6% and squamous carcinoma in 3%. Cases of adenosquamous, carcinosarcoma and spindle-cell sarcoma of gall bladder have also been reported. A variety of other lesions, including carcinoid tumours, sarcoma, melanoma and lymphomas, have also been found.[8–10]

## Symptoms

CaGB either remains asymptomatic for a long time or presents with very non-specific symptoms. Commonly, symptoms are related to associated gall stones and include (in descending order of frequency) pain, anorexia and weight loss, jaundice, pruritis, fever, vomiting, gall bladder mass, enlarged liver and ascites.

## Investigations

Abnormal serum alkaline phosphatase and gamma glutamyl transferase may be elevated in the absence of jaundice. An ultrasound (U/S) scan may show irregular thickening of the gall bladder wall, polypoidal lesion protruding into the gall bladder lumen and a mass in the gall bladder fossa replacing the gall bladder.[11] A U/S scan may give a false positive result as patients with acute cholecystitis may have an inflammatory mass that could be mistaken for the CaGB.

Computed tomography (CT) is better at detecting lesions than U/S. CT has a low sensitivity for detecting lymph node metastasis, although its positive predictive value is more than 90%.[12] Both US and CT may fail to show local GI and omental infiltration and peritoneal deposits.

Cholangiography, both percutaneous (PTC) or endoscopic (ERC), may not be helpful in diagnosis of CaGB at an early stage. ERC or PTC may detect obstruction due to external compression on the bile duct caused by either direct infiltration from CaGB or enlarged metastatic lymph nodes.

Fine needle aspiration cytology (FNAC) provides 90% sensitivity, 100% specificity and 90% accuracy in the presence of a gall bladder mass.[13] Endoscopic ultrasonography (EUS) may detect early lesion and better assess local infiltration. Laparoscopy, laparoscopic U/S and FNAC may prevent unnecessary laparotomy.

## Diagnosis

Despite advances in hepatobiliary imaging techniques, the pre-operative diagnosis of CaGB is difficult; only approximately 8.6% of the diagnoses are correct.[14] Incidental diagnosis of CaGB (occult) with gall stone is approximately 4%.[15]

A difficult gall bladder at surgery should raise the suspicion of cancer. In the presence of unusual findings at surgery – such as gall bladder mass, dense adhesions of the omentum and adjacent organs to the gall bladder – the neck of the gall bladder adhering to the bile ducts and difficult dissection of the gall bladder from its liver bed should raise the suspicion of carcinoma. Laparoscopic procedure should be converted to open procedure. Close evaluation of the extent of the disease should be carried out. Biopsy of any lymph node should be taken and frozen section should be considered. Intra-operative U/S or intraportal EUS could be used to assess portal vessels. In the presence of ascites, fluid should be obtained for cytology; otherwise, a peritoneal wash-out can be considered for cytology.

In the era of laparoscopic cholecystectomy, a failure to diagnose CaGB at an early stage can result in presentation of a trocar-site metastasis or widespread intraperitoneal disseminated disease.[16]

## Staging

The management, outcome and prognosis of CaGB depend on the stage of the disease. The most commonly used staging classification is tumournode-metastasis (TNM) classification, which was proposed by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer (AJCC-UICC) and subsequently modified by Beahrs et al. (Table 1).[17]

## Management

The decision as to which therapeutic option to use depends on whether CaGB is diagnosed preoperatively, perioperatively or post-operatively, as well as on the stage of the disease – that is, whether it is localised resectable, localised unresectable or advanced disease. The surgical options are summarised in Table 3.

## Surgical Procedures in the Management of CaGB

## Simple Laparoscopic or Open Cholecystectomy

Laparoscopic or open cholecystectomy is curative if the diagnosis is unknown and the cancer is diagnosed to be in in situ stage on histological examination of the specimen. In case of laparoscopic approach, the use of a specimen retrieval bag should be considered if cancer is suspected. Examination of the specimen by the surgeon has also been suggested.

## Extended Cholecystectomy

Extended cholecystectomy involves excision of the gall bladder with regional lymphadenectomy combined with excision of the liver substance adjacent to gall bladder bed. It involves en bloc removal of the adventitia and contained lymphatics surrounding the bile duct, portal vein and hepatic artery. The limits of this dissection extend from the nodes behind the first and second part of duodenum and the head of pancreas and across to the coeliac axis and extend upwards to the base of the liver and porta hepatis.

## Liver Resection

The recommended extent of the liver resection varies from a non-anatomical wedge resection of the gall bladder bed to formal removal of segment IV and V, including the gall bladder fossa and even right hepatic lobectomy, according to the following:

* wedge excision is apparently less radical, but it is a non-anatomical and difficult procedure that carries significant risk of fatal bleeding. In various reports, the extent of wedge

**Table 1. AJCC-UICC Tumour-node-metastatis (TNM) classification.**

| | |
|---|---|
| **Primary Tumour (T)** | |
| Tx | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Tis | Carcinoma in situ |
| T1 | Tumour invades mucosa or muscle layer |
| | a Tumour invades mucosa |
| | b Tumour invades mucosal layer |
| T2 | Tumour invades perimuscular connective tissue; no extension beyond serosa or into liver |
| T3 | Tumour perforates serosa (visceral peritoneum) or directly invades into one adjacent organ or both (extension 2cm or less into liver) |
| T4 | Tumour extends more than 2cm into liver and/or two or more adjacent organs |
| | (Stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of liver) |
| **Regional Lymph Nodes (N)** | |
| NX | Regional lymph nodes cannot be assessed |
| NO | No regional lymph node metastasis |
| N1 | Metastasis in cystic, pericholedochal and/or hilar lymph nodes (i.e. in the hepatoduodenal ligament) |
| N2 | Metastasis in peripancreatic (head only), periduodenal, periportal, coeliac and/or superior mesenteric lymph nodes |
| **Distant metastasis (M)** | |
| MX | Presence of distant metastasis cannot be assessed |
| MO | No distant metastasis |
| M1 | Distant metastasis |

**Table 2. Stage grouping.**

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T1, T2 | N1 | M0 |
| | T3 | N0, N1 | M0 |
| Stage IVA | T4 | N0,N1 | M0 |
| Stage IVB | Any T | N2 | M0 |
| | Any T | Any N | M1 |

varies from 2cm to 5cm from the margins of the gross tumour;

* right hepatectomy does not prolong survival if cancer is locally advanced;[18] and

* segmental liver resection is a better option if liver resection is at all indicated.

There is controversy over some aspects of the surgical treatment of locally advanced CaGB. The in-hospital mortality varies from 5.3% to 18% in a selected group of patients and surgical morbidity is 31.6%.[3,19,20] The surgical excision of the tumours extending up to serosa of gall bladder or liver involvement has shown 13% survival at five years.[21] If the cancer is resectable and aggressive radical surgery is performed, including radical lymphadenectomy or liver resection, disease free survival can be improved.[3,22] The aggressive surgical approach for localised disease is associated with improved results in selected patients.[23] The proponents of the radical surgery recommend extended cholecystectomy or radical lymphadenectomy with or without resection of extrahepatic bile duct in selected patients with stage 1, 2 or 3 (except T3N1) tumour of gall bladder.[24,25]

## Palliative Procedures

A majority of patients with CaGB have advanced or unresectable disease. The results of any kind of surgery in the form of laparotomy, debulking or bypass are generally poor with survival rates of only a few months.[3] The following procedures are indicated for symptom control.

## Surgical Biliary Bypass

Biliary obstruction in CaGB is high (near the confluence), so extrahepatic hepaticojejunostomy using the common or left hepatic duct is either not feasible or not recommended because the anastomosis may soon become blocked with tumour. Relief of biliary obstruction in gall bladder cancer requires an intrahepatic segment III cholangiojejunostomy. The 30-day mortality for this procedure has been reported to be up to 12% and the median survival is five months.[26]

## Surgical Gastric Bypass

If there are signs and symptoms of existing or impending gastric outlet obstruction, open or laparoscopic gastrojejunostomy can be considered.

However, due to malignant gastroparesis in some patients, this drainage procedure might not palliate the

**Table 3. Surgical Management of Carcinoma of Gall Bladder.**

| Stage of Disease | Pre-operative Diagnosis | Perioperative Diagnosis | Post-operative Diagnosis |
|---|---|---|---|
| Localised resectable disease | Extended cholecystectomy + lymphadenectomy | Extended cholecystectomy + radical lymph adenectomy, with or without hepatic resection | Simple cholecystectomy enough for in situ disease and stage T1a<br>Excision or irradiation of the retrieval port site and for stage beyond T1a, re-operation is debatable |
| Localised unresectable disease | Symptomatic palliative radiologic/endoscopic or surgical biliary and gastric bypass if obstruction is impending | Accurate assessment of the extent of the disease<br>Biopsy/nodes to confirm diagnosis<br>Surgical biliary or gastric bypass if obstructed | If resected margins are positive, then palliative therapy is needed (surgery/chemotherapy/ radiotherapy) |
| Advanced disease | Percutaneous needle cytology to confirm diagnosis<br>Symptomatic treatment<br>Chemotherapy/radiotherapy | Manage as localised unresectable disease + ascitic fluid for cytology | Palliative therapy |

symptoms adequately.[27]

## Endoscopic or Percutaneous Stent

The biliary obstruction and gastric outlet obstruction can be relieved by endoscopic stent. Radiology-guided percutaneous internal or external bile drainage is an option to relieve symptoms of obstructive jaundice. Endoscopic biliary stent can be placed successfully with a 30-day hospital mortality rate of 18%.[28] Techniques of endoscopic duodenal stents are rapidly evolving.

## Prognosis

Survival for patients with CaGB depends more on the stage of the disease than the type of treatment provided. A number of authors have reported between 71% and 100% five-year actuarial survival with stage 1 carcinoma following both a simple and extended cholecystectomy.

The overall five-year survival for CaGB patients has been reported as 4.1% and one-year survival 11.8%.14

## Summary

CaGB is a rare form of cancer and its association with gallstone disease should be recognised. Although overall prognosis is poor, early diagnosis of CaGB and radical surgery provides better outcome. Careful examination of the specimen should be performed to determine the short-term outcome and long-term prognosis.

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