Gall Bladder Cancer – Is the Stage Set? Yet!

Anu Behari and Vinay Kumar Kapoor
Department of Surgical Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India

Abstract

The current Tumor Node Metastasis (TNM) staging of Gall Bladder Cancer (GBC) has some shortcomings. We propose some changes in the current TNM staging of GBC. We propose that involvement of muscularis propria should be classified as T2 (instead of current T1b) and stage grouped as II (instead of current I). T4 in GBC should be sub-divided into T4a (perforation of serosa, involvement of omentum, CBD, stomach/duodenum and colon) and T4b (involvement of pancreas, hepatic artery and portal vein). Hepato-Duodenal Ligament (HDL) Lymph Nodes (LNs) alone should be classified as N1; peri-duodenal, peri-pancreatic and common hepatic artery LNs should be classified as N2 and stage grouped as IVA; non-regional (distant) LNs should be classified as M1a and distant (non-nodal) metastases should be classified as M1b. We also propose changes in the TNM stage grouping of GBC – stage I (T1 N0 M0), II (T2 N0 M0), III (T3 N0 M0, T1-3 N1 M0) and IV (T4 Any N M0, Any T N2 M0, Any T Any N M1). Tumors at GB neck are difficult to resect and have poorer prognosis even after resection. Surgical Obstructive Jaundice (SOJ) in GBC makes resection difficult and is associated with poorer prognosis even after resection. We also propose inclusion of non TNM factors viz. site of tumor (fundus/body or neck) and SOJ in staging of GBC.

Keywords: Gall bladder; Liver; Gall bladder cancer; Gastric cancer; Small bowel perforation

Abbreviations:

TNM: Tumor Node Metastasis; GBC: Gall Bladder Cancer; SOJ: Surgical Obstructive Jaundice; HDL: Hepato-Duodenal Ligament; LN: Lymph Node; CBD: Common Bile Duct.

Introduction

The current TNM staging of GBC has some shortcomings and needs revision to bring it in conformity with the TNM staging of other GI and HPB cancers. We propose some changes in the T, N and M stages and the stage grouping of GBC and also propose inclusion of non TNM factors viz. site of tumor (fundus/body or neck) and SOJ in the staging of GBC.

GBC though the commonest cancer of the biliary tract worldwide, has not received much attention as it is not a common cancer in the western world i.e., North America (USA and Canada), UK and Western Europe, and Australia and New Zealand [1]. GBC is common in central and south America, central and Eastern Europe, Japan and Korea, and the northern Indian sub-continent [2]. GBC was relatively neglected by the International Classification of Diseases (ICD) as it was included in liver and biliary tract in the 6th edition (1950), in biliary tract in the 7th edition (1957) and with extrahepatic bile duct and ampulla in the 8th edition (1967). It was only in the 9th edition (1977) that GBC received its own identity as 156 and later as C23 in the recent 10th edition (2010). Rarity of the disease, lack of awareness, delayed diagnosis and inappropriate management are responsible for poor survival (less than 10% at 5 years in stages II-IV) [3].

The most commonly followed staging system for GBC is the AJCC TNM staging. TNM system of staging of cancers was developed by Pierre Denoix in the 1940s and 1950s; American Joint Committee on Cancer (AJCC) adopted it in its Cancer Staging Manual. TNM staging for GBC has undergone changes in various editions of the AJCC Cancer Staging Manual (from the 1st Edition in 1977 to the 7th Edition in 2009).

Staging of a cancer should be able to direct management and predict prognosis. Based on these considerations, we had proposed some changes in the TNM staging of GBC [4]. involvement of muscular layer should be classified as T2 (instead of T1b) and staged as II (instead of I) and distant LNs should be classified as N3 (instead of N2) and staged as IV (instead of III); some of these proposals have been accepted while others remain to be considered.

T (Primary tumor) stage

The current T stages of GBC are as follows in the Table 1.

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumor cannot be assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or muscular layer.</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria.</td>
</tr>
</tbody>
</table>
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 other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts.

T4  Tumor invades main portal vein or hepatic artery or invades at least two extrahepatic organs or structures.

Table 1: Current T stages of GBC.

<table>
<thead>
<tr>
<th>Other Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>In esophagus, stomach and colon, T1 includes involvement of lamina propria and submucosa only; involvement of muscularis propria is classified as T2.</td>
</tr>
<tr>
<td>In pancreas, if the tumor invades unresectable structures e.g., celiac axis and superior mesenteric artery it is classified as T4.</td>
</tr>
<tr>
<td>In many cancers, T4 has been subclassified. In esophageal cancers, infiltration of resectable adjacent structures viz. pleura, pericardium and diaphragm is classified as T4a and infiltration of unresectable structures viz. aorta, trachea/bronchus and vertebra is classified as T4b.</td>
</tr>
</tbody>
</table>

Observations

GB has no submucosa; lamina propria thus includes mucosa only. GBC involving lamina propria (mucosa) does not have LN metastases and can be treated with simple cholecystectomy only whereas GBC involving muscularis propria can have LN metastases because of a rich lymphatic network in the muscle plane and requires extended cholecystectomy. GBC, once it perforates the serosa, has potential to spread in the peritoneal cavity.

NX  Regional LNs cannot be assessed.

N0  No regional LN metastasis.

N1  Metastases to nodes along the cystic duct, CBD, hepatic artery and/or portal vein.

N2  Metastases to periaortic, pericaval, superior mesenteric artery and/or celiac artery LNs.

Table 2: Current N stages of GBC.

<table>
<thead>
<tr>
<th>Other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>In esophagus and stomach, LNs are grouped as N1-N3 based on the number of LNs involved, viz. N1 (1-2), N2 (3-6), N3 (&gt;6); non-regional (distant) LNs e.g., celiac for upper esophagus and cervical for lower esophagus are classified as M1a and staged as IVB; distant (non-nodal) metastases are classified as M1b and staged as IVB.</td>
</tr>
<tr>
<td>In colorectal cancers also, LNs are grouped as N1-N3 based on the number of LNs involved, viz. N1 (1-3), N2 (4-6) and N3 (&gt;6); non-regional (distant) LNs e.g., para-aortic, are classified as M1a and staged as IVB and distant (non-nodal) metastases are classified as M1b and staged as IVB.</td>
</tr>
<tr>
<td>In hilar cholangiocarcinoma, only cystic duct, CBD, hepatic artery and portal vein LNs are described as N1; celiac, superior mesenteric, periaortic and pericaval LNs are classified as N2 which are staged along with M1 as IVB.</td>
</tr>
</tbody>
</table>

Observations

In GBC, omentum, Common Bile Duct (CBD), stomach/duodenum and colon are easily resectable structures whereas pancreas, hepatic artery and portal vein, though technically resectable, require major surgical procedures with high mortality and doubtful survival benefit.

Proposed changes

- T1 Tumor invades lamina propria (mucosa).
- T2 Tumor invades muscular layer or perimuscular connective tissue; no extension beyond serosa or into liver.
- T3 Tumor perforates the serosa (visceral peritoneum).
- T4 Tumor directly invades an adjacent organ or structure.
- T4 should be subdivided into: T4a Tumor directly invades the liver, CBD, stomach/duodenum, colon or omentum and T4b Tumor directly invades the pancreas, main portal vein or hepatic artery.

N (regional LNs) stage

The current N stages of GBC are as follows (Table 2).
involved nodes to the total LN count in GBC, it is essential to have a minimum of 6 LNs in the lymphadenectomy specimen for proper staging and risk stratification [8-10].

**Proposed changes**

LNs in GBC should be classified as follows:

- N1 Cystic duct, CBD, proper hepatic artery and portal vein LNs (which should be called HDL LNs).
- N2 Periduodenal and peripancreatic and common hepatic artery LNs.
- Non-regional (distant) e.g., celiac, superior mesenteric and aorto-caval LNs should be classified as M1a.

**M (distant metastases) stage**

The current M stages of GBC are as follows (Table 3).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis.</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
</tbody>
</table>

**Other cancers**

In esophagus, stomach and colon, non-regional (distant) LNs are classified as M1a and distant (non-nodal) metastases are classified as M1b.

In colorectal cancers, M1 has been subdivided into M1a (single site including non-regional LNs) and M1b (multiple sites).

**Proposed changes**

M stage in GBC should be classified as,

- M1a Non-regional (distant) i.e., celiac, superior mesenteric and aorto-caval LN metastases.
- M1b Distant (non-nodal) metastases.

**Stage grouping**

The current stage groups in GBC are as follows (Table 4).

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>N0–1</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M0/M1a/M1b</td>
</tr>
</tbody>
</table>

**Non TNM factors**

While TNM staging is used for most cancers, in some cancers non-TNM staging systems are still used e.g., Ann Arbor staging for lymphomas, Barcelona Clinic for Liver Cancer (BCLC) staging for hepatocellular carcinoma (HCC) in cirrhosis; in some other cancers, other features have been added to the TNM stages e.g., Gleason score in prostate. C (CEA) stage has been proposed to be added to the TNM staging of colo-rectal cancers [13].

In GBC, the site of tumor viz. whether fundus/body or neck, is important for management. GBC at any site (fundus/body or neck) with no liver infiltration can be managed with extended cholecystectomy. While GBC at fundus/body with liver infiltration can still be managed with extended cholecystectomy or segment IVB+V resection, GBC at neck with liver infiltration requires extended right hepatectomy because the right portal pedicle lies at a depth of 2-6 mm from the GB bed and even 1 cm margin cannot be obtained without sacrificing the right portal pedicle [14]. In addition, GBC at neck requires CBD excision with hepatico-jejunostomy. Patients with GBC neck have SOJ and require preoperative biliary drainage and portal vein embolization before a major hepatectomy is performed [14]. GBC at neck has poorer prognosis than GBC at fundus/body even after resection – 3 and 5 year survival for GBC neck being 13% and 10% vs. 44% and 36% for GBC fundus/body, respectively; on multivariate analysis, tumor location and LN metastases were the only factors for poor survival [15].

Some reports suggest that the location of the tumor on the peritoneal side carries better prognosis in terms of recurrence and survival than tumor on the hepatic side but the depth of infiltration viz. mucosa, muscular layer, perimuscular connective tissue, serosa and adjacent organ and T stage are probably more important and decide the extent of resection.
SOJ can be caused in GBC due to metastatic LNs in the HDL or due to CBD involvement. SOJ due to CBD involvement is an important factor for management and prognosis of GBC. In one report, 55 patients with GBC and SOJ were operated – curative resection could be performed in only 6 – none survived for 2 years [4]. None of the 32 patients with CBD involvement in another report survived for 5 years [16]. Another report found CBD involvement to be a predictor of poor prognosis [17]. Resection in 47 patients with SOJ was associated with poor survival than in 145 patients without SOJ (5 year survival 6% vs. 37% and median survival 14 mol vs. 43 mol) [15-21].

We propose that in GBC, the site of tumor viz. whether fundus/body or neck and presence or absence of SOJ should also be used in staging.

The proposed changes will need validation with large databases. The 8th edition of AJCC Cancer Staging Manual is due for publication in 2016. We suggest that our observations be studied and our proposed changes be considered while finalizing the TNM staging of GBC.

References