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Gall Bladder Cancer – Is the Stage Set? Yet!

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Abstract

The current 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 subdivided 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 lymph nodes alone should be classified as N1; periduodenal, peripancreatic and common hepatic artery lymph nodes should be classified as N2 and stage grouped as IVA; non-regional (distant) lymph nodes 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

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 & 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 surgical obstructive jaundice (SOJ) in the staging of GBC.

Gall bladder cancer (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 subcontinent [2]. GBC was relatively neglected by the International Classification of Diseases (ICD) as it was included in liver + 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.

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma in situ.
T1	Tumor invades lamina propria or muscular layer.
T1a	Tumor invades lamina propria.
T1b	Tumor invades muscular layer.
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver.
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one 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.

Other Cancers

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

Observations

GB has no submucosa; lamina propria thus includes mucosa only. GBC involving lamina propria (mucosa) does not have lymph node (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.

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 lymph nodes) stage

The current N stages of GBC are as follows (Table 2).

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

Table 2: Current N stages of GBC.

Other cancers

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 (>6); non-regional (distant) LNs e.g. celiac for upper esophagus and cervical for lower esophagus are classified as M1a and staged as IVA; distant (non-nodal) metastases are classified as M1b and staged as IVB.

In colo-rectal cancers also, LNs are grouped as N1-N3 based on the number of LNs involved, viz. N1 (1-3), N2 (4-6) and N3 (>6); non-regional (distant) LNs e.g. para-aortic, are classified as M1a and staged as IVA and distant (non-nodal) metastases are classified as M1b and staged as IVB.

In hilar cholangiocarcinoma, only cystic duct, common bile duct, 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.

Observations

In the current N stages of GBC, there is no mention of periduodenal and peripancreatic LNs. Japan Society of Biliary Surgery (JSBS) describes 3 echelons of LNs for GBC [5]. N1 Hepato-duodenal ligament (HDL) nodes where a standard lymphadenectomy achieves R0 resection. N2 Nodes beyond HDL i.e. along the common hepatic artery (CHA), behind pancreas head and duodenum which are included in standard lymphadenectomy but R0 resection is not achieved. N3 Celiac, superior mesenteric, aorto-caval (including para-aortic) nodes, involvement of which is beyond standard lymphadenectomy and prognosis is as bad as metastatic disease. Despite anecdotal reports of long-term survival of patients who underwent extended lymph node dissection in presence of involved para-aortic nodes, involvement of para-aortic lymph nodes in GBC is most often associated with a prognosis as grim as that of metastatic disease and this cannot be improved with extended lymph node dissections also [6,7]. With more and more reports stressing the importance of total number of lymph nodes involved as well as the ratio of involved nodes to the total lymph node count in GBC, it is essential to have a minimum of 6 lymph nodes 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, common bile duct, 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).

M0	No distant metastasis.
M1	Distant metastasis.

Table 3: Current M stages of GBC.

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 colo-rectal 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).

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4	N0–1	M0
IVB	Any T	N2	M0
	Any T	Any N	M1

Table 4: Current stage groups in GBC.

Oh [11] compared the 7th edition of the tumor node metastasis (TNM) staging system with the 6th edition to validate its usefulness in predicting prognosis for GBC and concluded that the 7th edition was not much better than the 6th and suggested further improvement in the GBC staging system [12] had earlier proposed staging T2N0M0 as stage II and N2 as IVB – this has been accepted in the 7th edition. We propose the following stage groups for GBC using the new (proposed) T, N and M classification are as follows (Table 5).

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4a	N0–1	M0
	Any T	N2	M0
IVB	T4b	Any N	M0
	Any T	Any N	M1a/ M1b

Table 5: Stage groups for GBC using the new (proposed) T, N and M classification.

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 hepato-cellular 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 can not 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 surgical obstructive jaundice (SOJ) and require preoperative biliary drainage and portal vein embolization before a major hepatectomy is performed [15]. 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 lymph node metastases were the only factors for poor survival [16].

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 [17] 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 lymph nodes in the hepato-duodenal ligament 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 [18]. None of the 32 patients with CBD involvement in another report survived for 5 years [19]. Another report found CBD involvement to be a predictor of poor prognosis [20]. 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 mo vs. 43 mol) [16].

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.

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