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Staging of Biliary Tract and Primary Liver Tumors

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Synopsis

For patients with hepatobiliary malignancies, various therapeutic options are currently available. To optimize the selection of these treatment options, adequate stratification of patients according to their prognosis is practically important. To date, a variety of staging systems have been introduced and utilized in the field of hepatobiliary malignancies. However, current staging systems have both strengths and limitations, and there has been no perfect staging system addressing both patient prognosis and the best treatment strategy for individual patient. In addition, hepatic function of the underlying liver is also a potent prognostic factor for patients with hepatobiliary malignancies. Therefore, interpretation of tumor staging and selection of treatment should be done with care understanding individual characteristics of each staging system.

Keywords

Staging; Hepatocellular carcinoma; Intrahepatic cholangiocarcinoma; bile duct cancer; gallbladder cancer

Introduction

For patients with hepatobiliary malignancies, various therapeutic options are currently available including surgical resection, ablation, transarterial chemoembolization (TACE), systemic therapy, or radiotherapy. To optimize the selection of these therapeutic options, adequate stratification of patients according to their prognosis is practically important. Among the hepatobiliary malignancies, hepatocellular carcinoma (HCC) is the most studied malignancy and various staging systems have been proposed from both clinical and pathological standpoints, such as Cancer of the Liver Italian Program (CLIP) score, Barcelona Clinic Liver Cancer (BCLC) staging system, the Liver Cancer Study Group of

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Conflicts of Interest

The authors report no conflicts of interest relevant to this article.

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Japan (LCSGJ) staging system, or the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system. However, these staging systems have their relative strengths and weaknesses. In addition, for biliary tract cancers, there also remain several controversies in prognostic impacts of tumor location or definition of regional lymph nodes. This article reviews currently utilized staging systems for hepatobiliary malignancies and highlights their clinical relevance and controversies.

Staging of Primary Liver Cancer

Hepatocellular carcinoma

Cancer of the Liver Italian Program (CLIP) Score—The Cancer of the Liver Italian Program (CLIP) score was developed using data on 435 Italian HCC patients treated with a range of surgical and non-surgical therapies [1] (Table 1), and several subsequent validation studies confirmed the clinical relevance of this prognostic score. [2–4] The CLIP score includes more tumor-specific factors and offers better prognostic stratification compared to conventional Okuda Staging System, which included tumor morphology, presence of ascites, serum albumin level, and serum bilirubin level as parameters for prognostic score. [5] However, the limitation of this staging system is poor discriminatory power of prognosis within early and advanced stages of HCC. The parameter of tumor morphology includes wide range of tumor sized. Also vascular invasion, which is a potent prognostic factor for HCC, is not counted unless forming portal vein tumor thrombus. Therefore, the clinical usability of the CLIP score is limited especially for the purpose of selection of therapeutic options.

Barcelona Clinic Liver Cancer (BCLC) Staging System—The BCLC staging system [6] (Figure 1) is one of the popular staging systems used especially in European countries for patients with HCC. This system includes liver function, tumor characteristics and performance status to address the progression of disease, and offers adequate treatment options based on the treatment algorithm. Although its usefulness was validated in several studies,[7–9] one of the major drawbacks of this staging system is that it is based on a single institutional experience. Furthermore, mixture of staging system and treatment algorithm may cause several problems in actual clinical settings. First, the surgical management is rather conservative in this system and patient who has HCC >5 cm is not a candidate for surgery. Because treatment for HCC has been changing over time and some patients actually benefit from multidisciplinary and/or sequential approach (e.g, resection after TACE + portal vein embolization, or orthotopic liver transplantation after TACE), simplified therapeutic recommendation for each tumor stage does not fit with actual clinical practice. Second, although the BCLC staging system considers both underlying liver disease and cancer progression, this system is rather a treatment algorithm than pure cancer staging system, and accordingly, simple comparison with other staging system is difficult.

Liver Cancer Study Group of Japan (LCSGJ) Staging System—The LCSGJ 4th edition staging system was developed by a working group of the International Hepato-Pancreato-Biliary Association using data on 21,711 Japanese patients who underwent liver resection for HCC.[10] T factor is determined by how many following factors are present:

tumor size (≤ 2 cm or >2 cm), tumor number (solitary or multiple), and macrovascular invasion (present or absent). The stage is determined according to the T factor and presence of regional node metastasis (N) or distant metastasis (M) (Table 2). Strength of this staging system is that it is based on large number of cohort from a Japanese nationwide survey by the LCSGJ. However, the limitations are that this staging system places equal weight on each of three tumor-specific factors and only macroscopic evidence of vascular invasion is accounted for in determining T factor.

American Joint Committee on Cancer/International Union against Cancer

(AJCC/UICC) Staging System—The AJCC/UICC 7th edition TNM staging system [11] is a modification of simplified TNM staging system based on a study from the International Cooperative Study Group on Hepatocellular Carcinoma that included data on 591 surgical patients from the United States, Japan, and France [12] (Table 3). The strength of this staging system was the use of centralized pathological review and its clinical relevance has been validated in various subsequent studies in patients treated with liver resection.[13–19] In addition, validation was also performed using transplanted patients in a multicenter study. [20] Because explanted liver enables complete removal of the cancerized liver, full staging of HCC is feasible purely depending on progression of initial HCC.

However, the limitation of current edition of AJCC/UICC staging system is that solitary HCC is not stratified with respect to size. Recent studies have reported excellent long-term outcomes in patients with solitary HCC up to 2 cm.[21–26] The size cutoff of 2 cm has been adopted in the LCSGJ staging system and in the BCLC staging system. Although the presence of microvascular invasion has been reported to be a strong prognostic factor in HCC,[10, 27–29] its significance in small HCC has not yet been clarified.

Recent study from the International Cooperative Study Group on Hepatocellular Carcinoma has been reported that microvascular invasion does not affect the patient prognosis in small HCC up to 2 cm, and possibility of reclassification of current version of AJCC/UICC staging system has been shown (Table 4 and Figure 2). This result is practically important because various curative therapeutic options can be selected for small tumors up to 2 cm and this result also suggests that resection for the purpose of pathologic evaluation might not be necessary in patient selection for liver transplantation.[30, 31]

Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma is a relatively uncommon disease accounting for 5–30% of all primary liver malignancies.[32] Historically, the staging system for intrahepatic cholangiocarcinoma has been identical to that of HCC. However, with increasing clinical evidences, current version of AJCC/UICC staging system is a unique staging system (Table 5). This is based on a study using 598 patients from the Surveillance, Epidemiology, and End Results (SEER) database,[33] and later validated in studies using international multicenter data.[34, 35] Tumor size had no independent effect on survival, and multiple tumors and vascular invasion had similar prognostic influence.

Staging of Biliary Tract Cancer

Extrahepatic bile duct cancer

For extrahepatic biliary tract cancers, different staging systems are used according to the location of the tumor (Table 6 and Figure 3). Because complete surgical resection is the single most effective treatment for patients diagnosed with extrahepatic biliary tract cancer, preoperative evaluation of progression of tumor is clinically important. However, most factors determining T stages are histopathologic parameters and it would not change the surgical management for the extrahepatic bile duct cancers. Accordingly, the staging system is less useful for the selection of treatment unless remarkable vascular involvement, invasion to adjacent organs, or nodal/distant metastases are present on preoperative imaging studies. Furthermore, because the bile duct cancer extend both laterally and longitudinally, it is difficult to apply current staging system for the patients with wide cancer spread along the biliary tract.

In clinical settings, distribution of cancer is of most importance for determining the surgical procedure especially in patients with hilar cholangiocarcinoma. Bismuth-Corlette classification [36] is a simple and useful classification offering adequate surgical management (Figure 4). For types I, II, and IIIa hilar cholangiocarcinoma, an extended right hepatectomy is usually performed, whereas for type IIIb hilar cholangiocarcinoma, a left or extended left hepatectomy is needed.

Gallbladder cancer

Gallbladder cancer is a relatively uncommon malignancy and majority of cases are detected incidentally in cholecystectomies for cholelithiasis or cholecystitis. Unlike in the remainder of the gastrointestinal tract, the gallbladder lacks muscularis mucosa and the presence of Rokitanski-Aschoff sinus forming microscopic diverticulae in the gallbladder wall would facilitate early tumor progression deep into the gallbladder wall. T stage is based on the depth of the tumor invasion in gallbladder cancer (Table 6). Because the depth of invasion is associated with increased incidence of liver metastasis and nodal metastasis, T stage is a useful guide for concomitant or additional resection of the gallbladder bed and regional lymph node.[37] However, the limitation of the current staging system is that it does not offer a difference of clinical presentation according to the tumor location (ie, serosal side vs. hepatic side). Our preliminary data from 586 patients receiving curative surgical resection for gallbladder cancer revealed that incidences of lymphovascular invasion and lymph node metastasis may be affected in T2 gallbladder cancer (Figure 5). These results suggest that location of tumor would have prognostic difference and further investigation may be needed to further optimize the staging system for better surgical management of gallbladder cancer.

Summary

In the field of hepatobiliary malignancies, a variety of staging systems have been introduced in an effort to stratify patients on the basis of prognosis and facilitate the selection of appropriate treatment strategies. However, each staging system has strengths and limitations and there has been no perfect staging system for these disease entities because of the variability in nature of population used for development of a staging system. In addition,

because the hepatic function of the underlying liver is also a potent prognostic factor in hepatobiliary malignancies, interpretation of tumor staging and selection of treatment should be done with case based on the comprehensive assessment of the status of the patients.

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Key Points

- Tumor staging is practically important to stratify patient prognosis and select adequate treatment options.
- A variety of staging systems are available for hepatobiliary malignancies. However, each staging system has its own strengths and weaknesses, and there has been no perfect staging system.
- Patients with hepatobiliary malignancies are often affected with decreased hepatic function due to underlying liver disease.
- Interpretation of tumor staging should be done with care according to the status of patients and understanding of the nature of each staging system

Figure 1.**BCLC Staging System**

From Llovet JM, Burroughs A, Bruix J., Hepatocellular carcinoma. Lancet. 2003 Dec 6;362(9399):1907-17; with permission.

Figure 2.

Reclassification of AJCC/UICC staging system for solitary HCC *Adapted from Shindoh J, Andreou A, Aloia TA, Zimmitti G, Lauwers GY, Laurent A, Nagorney DM, Belghiti J, Cherqui D, Poon RT, Kokudo N, Vauthey JN. Microvascular Invasion Does Not Predict Long-Term Survival in Hepatocellular Carcinoma up to 2 cm: Reappraisal of the Staging System for Solitary Tumors. Ann Surg Oncol 20(4):1223–9, 4/2013; with permission.*

	N0	N1	N2, M1
Tis	0		
T1	I	IIIB	IVB
T2	II		
T3	IIIA		
T4	IVA		

	N0	N1	M1
Tis	0		
T1	IA	IIB	IV
T2	IB		
T3	IIA		
T4	III		

Figure 3.

Staging for extrahepatic biliary cancers

N0, no regional lymph node metastasis; N1, regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein; N2, Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph node; M0, no distant metastasis; M1, presence of distant metastasis.

Data from Edge, S.B.; Byrd, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. (Eds.) AJCC Cancer Staging Manual, 7th ed. 2010, XV, 649 p.

Figure 4.

Extent of hepatic resection according to Bismuth-Corlette classification of hilar cholangiocarcinoma.

Adopted from Parikh AA, Abdalla EK, Vauthey JN. Operative considerations in resection of hilar cholangiocarcinoma HPB 2005; 7:254–8; with permission

Figure 5.
Location of tumor and incidences of vascular invasion and lymph node metastasis

Table 1

Cancer of the Liver Italian Program (CLIP) score

Variable	Points		
	0	1	2
Child-Pugh grade	A	B	C
Tumor morphology	Solitary and 50%	Multifocal and 50%	Massive or >50%
Serum α -fetoprotein	<400 ng/mL 400 ng/mL		
Portal vein thrombosis	Absent	Present	

From The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998;28:751–5; with permission

Table 2**The Liver Cancer Study Group of Japan Staging System**

T	T1	None of following factors
	T2	one of following factor
	T3	two of following factors
	T4	three or following factors or tumor rupture/direct invasion
		<ul style="list-style-type: none"> • Size >2cm • Multiple tumor • Macrovascular invasion
Stage I	T1N0M0	
Stage II	T2N0M0	
Stage III	T3N0M0	
Stage IVA	T4N0M0 or T1-3N1M0	
Stage IVB	AnyT AnyN M1	

From Makuuchi M, Belghiti J, Belli G, et al. IHPBA concordant classification of primary liver cancer: working group report. J Hepatobiliary Pancreat Surg 2003;10:26–30; with permission.

Table 3

American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) 7th edition staging system

T	T1	Solitary with no vascular invasion
	T2	Solitary with vascular invasion or Multifocal ≤ 5 cm
	T3a	Multifocal >5 cm
	T3b	Involvement of a major branch of the portal vein or hepatic artery
	T4	Invasion of adjacent organs or rupture of HCC
Stage I	T1N0M0	
Stage II	T2N0M0	
Stage IIIA	T3aN0M0	
Stage IIIB	T3bN0M0	
Stage IIIC	T4N0M0	
Stage IVA	AnyT N1M0	
Stage IVB	AnyT AnyN M1	

From Edge, S.B.; Byrd, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. (Eds.) AJCC Cancer Staging Manual, 7th ed. 2010, XV, 649 p; with permission.

Current AJCC classification (7th ed) and new classification *Adapted from* Shindoh J, Andreou A, Aloia TA, Zimmitti G, Lauwers GY, Laurent A, Nagorney DM, Belghiti J, Cherqui D, Poon RT, Kokudo N, Vauthey JN. Microvascular Invasion Does Not Predict Long-Term Survival in Hepatocellular Carcinoma up to 2 cm: Reappraisal of the Staging System for Solitary Tumors. *Ann Surg Oncol* 20(4):1223–9, 4/2013; with permission.

Table 4

AJCC 7 th	OS, months, median (range)	New classification	OS, months, median (range)
Solitary HCC without			
T1			
MVI	84.7 (76.1–100.4)	T1a Solitary HCC ≤ 2 cm	126.9 (83.8–NE)
		Solitary HCC >2 cm	
		T1b without MVI	81.4 (69.0–97.2)
		Solitary HCC >2 cm	
Solitary HCC with			
T2			
MVI	60.6 (50.4–75.8)	T2 with MVI	55.0 (44.2–65.6)
Multiple HCC ≤ 5 cm	55.9 (48.6–72.0)	Multiple HCC ≤ 5 cm	55.9 (48.6–72.0)
T3a			
Multiple HCC >5 cm	27.7 (22.5–38.7)	T3a Multiple HCC >5 cm	27.2 (22.5–38.7)
T3b			
Major vascular invasion	28.0 (15.4–43.3)	T3b Major vascular invasion	28.0 (15.4–43.3)

AJCC, American Joint Committee on Cancer; OS, overall survival; NE, not estimated; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

Table 5

AJCC/UICC classification (7th ed) for intrahepatic cholangiocarcinoma

T	
Tis	Carcinoma in situ
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
Stage IVA	T4 N0 M0, AnyT N1 M0
Stage IVB	Any T Any N M1

From Edge, S.B.; Byrd, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. (Eds.) AJCC Cancer Staging Manual, 7th ed. 2010, XV, 649 p; with permission.

Table 6**AJCC. UICC 7th Classification for extrahepatic biliary cancer**

Hilar and Proximal Cholangiocarcinoma	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Gallbladder Cancer	
Tis	Carcinoma in situ
T1	The tumor has grown into the lamina propria or the muscle layer (muscularis)
T2	The tumor has grown into perimuscular fibrous tissue
T3	The tumor has grown through the serosa and/or it has grown from the gallbladder directly into the liver and/or one nearby structure such as the stomach, duodenum, colon, pancreas, or bile ducts outside the liver
T4	The tumor has grown into one of the main blood vessels leading into the liver or it has grown into 2 or more organs outside of the liver
Distal Cholangiocarcinoma	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
T4	Tumor involves the celiac axis, or the superior mesenteric artery
Ampulla of Vater	
Tis	Carcinoma in situ
T1	Tumor limited to ampulla of Vater or sphincter of Oddi
T2	Tumor invades duodenal wall
T3	Tumor invades pancreas
T4	Tumor invades peripancreatic soft tissues or other adjacent organs or structures other than pancreas

From Edge, S.B.; Byrd, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. (Eds.) AJCC Cancer Staging Manual, 7th ed. 2010, XV, 649 p; with permission.