The 8th Edition American Joint Committee on Cancer Staging for Hepato-pancreato-biliary Cancer

A Review and Update

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• ***Context.***—**Cancer staging provides critical information for patients and treating physicians to battle against cancer, predict prognosis, and guide treatment decisions. The American Joint Committee on Cancer (AJCC) staging system uses a tumor, node, metastasis (TNM) scoring algorithm and is the foremost classification system for adult cancers. This system is updated every 6 to 8 years to allow sufficient time for implementation of changes and for relevant examination and discussion of data validating those changes in staging.**

Objective.—**To review the updates in the 8th edition American Joint Committee on Cancer staging system on hepato-pancreato-biliary cancer.**

Data Sources.—**Literature review.**

Conclusions.—**The 8th edition, published in 2016 and implemented on January 1, 2018, has been in use for approximately 3 years. Compared with the 7th edition, some of the changes are quite radical. This review aims to provide a summary of the changes/updates of the 8th edition with focus on hepato-pancreato-biliary cancers, and evaluate its performance through literature review.**

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The 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual has been in use for approximately 3 years.[1] Developed by the joint efforts of AJCC and the Union for International Cancer Control, this newest edition is a compendium of all available information for staging adult cancers of clinically important anatomic sites, representing the standard of defining prognosis, determining treatment approaches, and providing basis for understanding population cancer incidence changes. Like its previous versions, the 8th edition continues to use the tumor, node, metastasis (TNM) scoring system, where the size and extent of primary tumor (T), involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M) are basic measurements to stratify cancer stages.[2] Those parameters are modified in response to updated clinical and pathologic data, improved understanding of cancer biology, or newly identified biologic factors affecting prognosis. Thus, refining and revising those factors to provide the best possible staging system is a never-ending process. Dedicated efforts from all health professionals are continuously validating those changes while investigating new measurements that can better predict cancer outcome and treatment response.

Hepato-pancreato-biliary (HPB) cancers are relatively rare. The complex anatomy surrounding those organs often requires technically demanding surgery. Improving the cancer staging system is particularly critical, correlating directly with high-quality surgery, accurate pathologic analysis, and reliable follow-up after treatment.[3] For HPB cancer, the revisions are largely based on single-institution series from centers of excellence in both surgery and pathology, some of which have been validated at other centers of excellence. A big and unified change in the 8th edition is the harmonized N category for cancers of gallbladder, perihilar bile ducts, distal bile duct, ampulla, and exocrine pancreas, where N1 is now uniformly defined as metastasis to 1 to 3 lymph nodes and N2 as metastasis to 4 or more lymph nodes. In addition, subjective measurements such as size of tumor, depth of invasion (DOI), vascular invasion, and involvement of large vessels are generally given more distinguishing power on staging purposes compared with the previous editions. Are those changes implemented better in practice? The aim of this review is to provide a concise summary of changes/updates from the 8th edition of the AJCC staging manual in HPB cancers and review literature that validates those changes after 3 years' application in practice.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the most common primary malignancy in the liver, the fifth most common malignancy worldwide, and the third most common cause

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Table 1. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Hepatocellular Carcinoma[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
T1	Solitary, <2 cm, or >2 cm without vascular invasion	Solitary, without vascular invasion
T1a	Solitary, **≤2 cm**	
T1b	Solitary, **>2 cm without vascular invasion**	
T2	Solitary, **>2 cm with vascular invasion**; or multiple, none >5 cm	Solitary with vascular invasion, or multiple tumors none >5 cm
T3	Multiple, at least one >5 cm	
T3a		Multiple, >5 cm
T3b		Any tumor involving a major branch of the portal vein or hepatic vein
T4	**Any tumor involving a major branch of the portal vein or hepatic vein**, or with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	Direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis
AJCC stage groupings		
IA	**T1a N0 M0**	
IB	**T1b N0 M0**	
I		T1 N0 M0
II	T2 N0 M0	T2 N0 M0
IIIA	T3 N0 M0	T3a N0 M0
IIIB	**T4 N0 M0**	T3b N0 M0
IVA	Any T N1 M0	Any T N1 M0
IVB	Any T any N M1	Any T any N M1
Rationale for changes: Vascular invasion and size and number of tumors determine tumor staging		
Validation of changes: T: Not better or similar to 7th edition		
Potential future modifications: T2 substratification. Staging modification by combining stages IB/II and stages IIIB/IVA		

[a] Bold entries in the 8th Edition column indicate changes.

of cancer-related deaths globally.[4,5] Current treatment choices include hepatic resection, liver transplantation, radiofrequency ablation, and transcatheter arterial chemoembolization, yet optimal management remains controversial owing to the heterogeneity of HCC and underlying diseases attributable to different risk factors such as viral hepatitis, metabolic disorders, or toxins.[6,7] Given the considerable geographic and institutional variations, there are currently many different staging and scoring systems developed for HCC,[8] among which the AJCC TNM staging system is widely accepted and is the most frequently used.

In the 8th edition, T1 is subdivided into T1a and T1b based on a size cutoff of 2 cm. Despite controversial opinions on the importance of vascular invasion in small HCCs,[9] T1a includes tumor 2 cm or smaller with or without vascular invasion, whereas the presence of vascular invasion in tumor >2 cm distinguishes T2 from T1b. T3 (multiple, at least one >5 cm) was T3a in the 7th edition,[10] whereas tumors involving a major branch of the portal vein or hepatic vein are upstaged from T3b in the 7th edition to T4 in the 8th edition. The N stage remains unchanged (Table 1). There is no minimal requirement for lymph node harvest for HCC, likely because the incidence of lymph node metastasis in HCC patients is low.[11]

Right after the publication of the AJCC 8th edition, a study evaluated its performance on HCC using the Surveillance, Epidemiology, and End Results (SEER) database (1998–2013), and found that the 8th edition performed similarly to the 7th edition.[12] Yet the authors suggested that the T2 category should be substratified, because survival was better for T2 solitary tumors larger than 2 cm with vascular invasion than for T2 multifocal tumors smaller than 5 cm. Further, for multifocal tumors 5 cm or smaller, those with vascular invasion had worse survival than those without, suggesting that vascular invasion and tumor size each have prognostic power.[12] A similar study also used the SEER database (2010–2013) to assess the discriminating value of the 8th edition AJCC stage grouping, and found minimal improvement in the 8th compared with the 7th edition.[13] Particularly, there was notable overlap in outcomes observed between stages IB (T1bN0M0)/II(T2N0M0) and IIIB (T4N0M0)/IVA (any TN1M0), and thus, a modified system combining stages IB/II and stages IIIB/IVA was proposed.[13]

Currently AJCC cancer staging for all solid tumors is based on anatomic measurements. Molecular information is not yet incorporated. A recent study identified differentially expressed stage-specific genes in HCC, which may enhance our understanding of the molecular determinants of HCC progression and serve as biomarkers that potentially underpin diagnosis as well as pinpointing therapeutic targets.[14]

CARCINOMA OF THE INTRAHEPATIC BILE DUCT

Intrahepatic cholangiocarcinoma (ICC) is the second most common malignancy arising in liver, making up about 10% of all cholangiocarcinomas in the biliary tree.[15] Treatment of

Table 2. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Carcinoma of the Intrahepatic Bile Ducts[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
Tis	Carcinoma in situ (intraductal tumor)	Carcinoma in situ (intraductal tumor)
T1	Solitary, without vascular invasion	Solitary, without vascular invasion
T1a	Solitary, **≤5 cm** without vascular invasion	
T1b	Solitary, **>5 cm** without vascular invasion	
T2	Solitary, with vascular invasion; or multiple, with or without vascular invasion	
T2a		Solitary, with vascular invasion
T2b		Multiple, with or without vascular invasion
T3	Perforating the visceral peritoneum	Perforating the visceral peritoneum or involving local extrahepatic structures by direct invasion
T4	**Involving local extrahepatic structures by direct invasion**	Periductal invasion
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis
AJCC stage groupings		
IA	**T1a N0 M0**	
IB	**T1b N0 M0**	
I		T1 N0 M0
II	T2 N0 M0	T2 N0 M0
IIIA	T3 N0 M0	
IIIB	**T4 N0 M0; any T N1 M0**	
III		T3 N0 M0
IV	Any T any N M1	
IVA		T4 N0 M0; any T N1 M0
IVB		Any T any N M1
Rationale for changes: Vascular invasion and tumor size of more importance. Equivalent prognostic value of vascular invasion and tumor multifocality		
Validation of changes: T: Slightly better than 7th edition		
Potential future modifications: Restaging of T1 as tumor ≤2 cm. Keeping periductal invasion in T4. Removing visceral peritoneum invasion. Incorporating serum tumor markers		

[a] Bold entries in the 8th Edition column indicate changes.

ICC has recently been improved with the advent of hepatectomy and gemcitabine-based chemotherapy, but prognosis remains poor because of a high rate of recurrence.[16] The construction of a reliable staging system to precisely predict the prognosis is important for developing a treatment strategy and assessing disease outcomes. ICC was previously staged the same as HCC in the AJCC staging manual until the 7th edition, where T category was determined by tumor numbers, vascular invasion, and invasion to adjacent organs. The 8th edition includes several significant modifications, particularly in the T category, where a size cutoff of 5 cm is set up to divide T1 into 1a (≤5 cm) and 1b (>5 cm). Previous T2a (solitary, with vascular invasion) and 2b (multiple, with or without vascular invasion) are combined as T2 to reflect the equivalent prognostic value of vascular invasion and tumor multifocality. Local direct invasion into extrahepatic structure, previously T3, is now upgraded to T4, and periductal invasion is removed from the T4 category. The N stage remains unchanged. For stage grouping, the previous T4 tumors and regional lymph node metastasis (N1) are downgraded from stage IV to IIIB, with stage IV designated only when there is distant metastasis (M1) (Table 2).

The prognostic performance of the 8th edition was overall not markedly improved over the 7th edition based on several validation studies, and potential modifications have been proposed.[17–20] Interestingly, although one study from a Korean group concluded that the new T3 did not provide good prognostic contrast,[17] a much larger study across 14 major hepatobiliary centers worldwide found the new T3 and stage III to stratify the risk of death for ICC patients.[20] On the other hand, a Japanese group found significant overlaps between T2, T3, and T4 on 5-year disease-specific survival rate, and the authors suggested modifying the size cutoff point at 2 cm for T1 (T1, size ≤2 cm without other factors; T2, size >2 cm without other factors), and keeping periductal infiltrating in T4 because of its prognostic significance.[21] Similarly, a Chinese study using a multicentric cohort found visceral peritoneum invasion not an independent risk factor and modified the 8th edition staging system by removing this factor, combining T1b into T2, and incorporating serum tumor markers (CA19-9 and CEA) into stage classification.[19] The authors claimed that their modifications had better discriminatory capacity and validated it through a SEER cohort.[19] It was not the first time incorporating serum tumor markers for staging ICC has been proposed.[22] Likewise, tumor budding at the invasive front as a known risk factor in

Table 3. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Carcinoma of the Perihilar Bile Ducts[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
Tis	Carcinoma in situ/high-grade dysplasia	Carcinoma in situ
T1	Confined to the bile duct, with extension up to the muscle layer or fibrous tissue	Confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	**Invades beyond the wall of the bile duct, or adjacent hepatic parenchyma**	
T2a	Invades beyond the wall of the bile duct to surrounding adipose tissue	Invades beyond the wall of the bile duct
T2b	Invades adjacent hepatic parenchyma	Invades adjacent hepatic parenchyma
T3	Invades unilateral branches of the portal vein or hepatic artery	Invades unilateral branches of the portal vein or hepatic artery
T4	Invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement	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
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	**Metastasis to 1–3 regional lymph nodes**	Regional lymph node metastasis
N2	**Metastasis to ≥4 regional lymph nodes**	Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes
AJCC stage groupings		
I	T1 N0 M0	T1 N0 M0
II	T2a–b N0 M0	T2a–b N0 M0
IIIA	T3 N0 M0	T3 N0 M0
IIIB	**T4 N0 M0**	T1–3 N1 M0
IIIC	**Any T N1 M0**	
IVA	**Any T N2 M0**	T4 N0–1 M0
IVB	**Any T any N M1**	Any T N2 M0; any T any N M1
Rationale for changes: Number of positive lymph nodes affects staging		
Validation of changes: T: Not better or similar to 7th edition. N: Better than 7th edition		
Potential future modifications: A depth-based rather than layer-based measurement to define T stage. Incorporating more biologic factors		

[a] Bold entries in the 8th Edition column indicate changes.

colorectal carcinoma has recently been investigated in ICC and other tumors of the biliary tree,[23–25] which may be incorporated in the future AJCC edition for ICC.

CARCINOMA OF THE PERIHILAR BILE DUCTS

Cholangiocarcinoma develops anywhere within the biliary tree from the most proximal intrahepatic bile duct to the most distal intraduodenal bile duct. Extrahepatic cholangiocarcinoma was separated into perihilar cholangiocarcinoma (PHC) and distal cholangiocarcinoma because of the distinct characteristics in pathology, treatment, and prognosis.[26] PHC, also known as Klatskin tumor, arises in the area of the biliary duct bifurcation proximal to the cystic duct and accounts for 60% to 70% of all cholangiocarcinomas.[27] Because of its unique local and regional growth patterns, it is staged predominantly according to tumor relationship with surrounding tissues in both the 7th and 8th editions of the AJCC staging system. Major changes in the 8th edition include incorporation of high-grade biliary intraepithelial neoplasia into carcinoma in situ (Tis) and removal of bilateral second-order biliary radical invasion from T4. Based on a large 8-institution study from Japan,[28] a unified staging theme for the N category in the pancreatobiliary system was adopted, in which N1 is designated as metastasis in 1 to 3 lymph nodes and N2 as metastasis in more than 3 lymph nodes. Accordingly, the stage group for T4 tumors is downgraded from stage IVA to stage IIIB, the N1 category is upgraded from IIIB to IIIC, and N2 is classified as stage IVA (Table 3). There is currently no requirement for a minimal number of lymph nodes to be evaluated for PHC.

The performance of the newly released 8th edition AJCC staging system in PHC, particularly the modified T category, is still unsatisfactory based on 2 European studies, 1 from the Netherlands and the other from Italy.[29,30] Further refinements were suggested. One proposal is to follow the same staging algorithm as that for the distal common bile duct, where a depth-based rather than layer-based measurement is applied to define T stage.[31] Using a 4-tier invasive tumor thickness with cutoff points of 1, 5, and 8 mm, these new defining parameters appear to be an adequate alternative, improving the concordance index from 0.589 to 0.598.[31] Other proposals include incorporating more biological factors such as microvascular invasion, perineural invasion, and tumor differentiation to ensure a personalized approach for prognostication and treatment.[32] In contrast to the T category, the new N category in the 8th edition appeared to perform better than that in the previous edition.[30] Besides the total number of positive lymph nodes, the parameters of lymph node ratio or log odds of metastatic

Table 4. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Carcinoma of the Distal Extrahepatic Bile Ducts[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
Tis	Carcinoma in situ/high-grade dysplasia	Carcinoma in situ
T1	**Invades the bile duct wall with a depth <5 mm**	Confined to the bile duct histologically
T2	**Invades the bile duct wall with a depth of 5–12 mm**	Invades beyond the wall of the bile duct
T3	**Invades the bile duct wall with a depth >12 mm**	Invades the gallbladder, pancreas, duodenum or other adjacent organs
T4	Involves the celiac axis, superior mesenteric artery, **and/or common hepatic artery**	Involves the celiac axis, or the superior mesenteric artery
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	**Metastasis in 1–3 regional lymph nodes**	Regional lymph node metastasis
N2	**Metastasis in ≥4 regional lymph nodes**	
AJCC stage groupings		
I	T1 N0 M0	
IA		T1 N0 M0
IB		T2 N0 M0
IIA	**T1 N1 M0; T2 N0 M0**	T3 N0 M0
IIB	**T2 N1 M0; T3 N0–1 M0**	T1–3 N1 M0
IIIA	**T1–3 N2 M0**	
IIIB	**T4 any N M0**	
III		T4 any N M0
IV	Any T any N M1	Any T any N M1
Rationale for changes: Depth of invasion predicts outcomes		
Validation of changes: T: Better than 7th edition. N: Better than 7th edition		
Potential future modifications: Including organ invasion to T staging. Revising cutoff value for depth of invasion		

[a] Bold entries in the 8th Edition column indicate changes.

lymph nodes were also proposed to improve predicting power.[33]

CARCINOMA OF THE DISTAL EXTRAHEPATIC BILE DUCT

Distal bile duct cholangiocarcinomas (DCCs), located between the cystic duct entry and the end of the common bile duct in the ampullary region, account for 20% to 30% of all bile duct carcinomas. The incidence rate varies considerably owing to varying prevalence of risk factors such as stone disease, parasitic infection, abnormal junction, and ulcerative colitis. DCCs are usually mass forming, displaying variable growth patterns. Traditionally, bile duct tumors were grouped as proximal, middle, and distal, but staged as a single entity with one TNM classification. The AJCC 7th edition started to separate PHC and DCC, but using a common anatomic layer–based staging system, which was described as vague and resulting in wide interobserver variations.[34,35] The 8th edition kept the layer-based approach for PHC, while adopting a more subjective depth-based approach for DCC, in that the DOI with cutoff values of 5 and 12 mm defines the T category (T1, <5 mm; T2, 5–12 mm; T3, >12 mm). Tumor infiltration into adjacent organs such as the pancreas, duodenum, and gallbladder (previously T3) is excluded from staging. Similar to PHC, Tis includes high-grade biliary intraepithelial neoplasia, and the N category is unified based on the number of lymph node metastases (N1, 1–3; N2, >3; Table 4). A minimum number of 12 lymph nodes examined for accurate staging has not been determined but has been suggested. Other changes include adding high-grade neuroendocrine carcinoma for consistency with other gastrointestinal and hepatobiliary designators and updated histologic types to match current World Health Organization terminology.

A Korean study[36] evaluated those changes in the AJCC 8th edition staging system and concluded that both the new T and N categories accurately predict patient prognosis in a way superior to the 7th edition. However, another study from Korea[37] found little survival difference using the new T criteria, and the authors believed that organ invasion should be still included as one of the factors that determine the AJCC stage given that those with dual-organ invasion had a shorter survival time than those with single-organ invasion. Nevertheless, DOI is a validated approach for categorizing T stages in many other organ systems, including the distal bile duct. A potential modifiable measurement is to find the best cutoff value for DOI. For example, revising the DOI cutoff points to 1, 5, and 10 mm was validated as a better T system,[38] whereas DOI cutoff points at 3 mm or smaller, 3–10 mm, and 10 mm or larger seemed to perform better in another multi-institutional study.[35] The superior N category in the 8th edition was validated in another study with a proposal of a minimum of 12 regional lymph nodes to be retrieved for accurate staging.[39]

CARCINOMA OF THE GALLBLADDER

Gallbladder cancer (GBC) is the most common biliary tract malignancy, relatively rare in Western countries but a substantial health issue in certain regions of the world.[40] It usually presents at a late stage, as there are no specific symptoms in its early stages. The 5-year survival rate is estimated to be 5%.[40,41] Compared with other HPB cancers, the 8th edition AJCC cancer staging system for GBC did not

Table 5. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Carcinoma of the Gallbladder[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
Tis	Carcinoma in situ	Carcinoma in situ
T1	Invades the lamina propria or muscular layer	Invades the lamina propria or muscular layer
T1a	Invades the lamina propria	Invades the lamina propria
T1b	Invades the muscular layer	Invades the muscular layer
T2	Invades perimuscular connective tissue, with no extension into the liver	Invades perimuscular connective tissue; with no extension into the liver
T2a	**Invades perimuscular connective tissue on the peritoneal side**	
T2b	**Invades the perimuscular connective tissue on the hepatic side**	
T3	Perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure	Perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure
T4	Invades main portal vein or hepatic artery or ≥2 extrahepatic organs or structures	Invades main portal vein or hepatic artery or ≥2 extrahepatic organs or structures
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	**Metastasis to 1–3 regional lymph nodes**	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	**Metastasis to ≥4 regional lymph nodes**	Metastases to periaortic, pericaval, superior mesentery artery and/or celiac artery lymph nodes
AJCC stage groupings		
I	T1 N0 M0	T1 N0 M0
IIA	**T2a N0 M0**	
II		T2 N0 M0
IIB	**T2b N0 M0**	
IIIA	T3 N0 M0	T3 N0 M0
IIIB	T1–3 N1 M0	T1–3 N1 M0
IVA	T4 N0–1 M0	T4 N0–1 M0
IVB	Any T N2 M0; any T any N M1	Any T N2 M0; any T any N M1
Rationale for changes: Hepatic side invasion predicts outcome		
Validation of changes: T: Mixed opinions. N: Better than 7th edition		
Potential future modifications: T3 substratification		

[a] Bold entries in the 8th Edition column indicate changes.

change dramatically, but continued to use the layer-based approach for T classification, with slight changes for T2, where tumors involving the perimuscular tissue on the peritoneal side are T2a and those on the hepatic side are T2b, as the latter were found to be associated with lower survival rates.[41,42] For N category, the 8th edition adopted the unified number-based approach,[43] where N1 is designated as metastasis in 1 to 3 lymph nodes and N2 as metastasis in 4 or more lymph nodes (Table 5). Metastases to celiac, superior mesenteric, and peripancreatic lymph nodes, previously N2 in the 7th edition, are now considered distant metastasis (M1) in the 8th edition. To avoid underestimation of disease stage, especially in node-positive patients, a minimum of 6 lymph nodes to be harvested for histologic evaluation is recommended.

The new GBC staging system was validated by a study performed on a National Cancer Institute database, confirming that it offers adequate discrimination, especially for node-positive patients.[44] Yet, there are mixed opinions in other studies, especially for the T category.[45,46] Some proposed potential modifications including further dividing T3 into T3a (tumors penetrating serosa but not directly invading liver and/or an adjacent organ or structure) and T3b (tumor penetrating serosa and directly invading liver and/or an adjacent organ or structure).[45] The number-based N category appears to be prognostic if 6 or more lymph nodes are available for examination. Evidence that patients without nodal dissection had significantly poorer survival than those with N0 supports the 8th edition recommendation of a minimum of 6 lymph nodes to be examined. The regrouping for tumors metastatic to celiac, superior mesenteric, and peripancreatic lymph nodes as M1 (stage IVB) was challenged by a study showing that those patients with R0 resection had longer survival than patients with true distant metastatic (M1) diseases.[47]

CARCINOMA OF THE AMPULLA OF VATER

The ampulla of Vater is a complex structure referring to the confluence of the distal common bile duct and the main pancreatic duct in the second portion of the duodenum, or the termination of the common bile duct if the pancreatic duct enters the duodenum separately. Although ampullary carcinoma (AC) is the most common small intestinal malignancy, its incidence is rare, representing less than 0.5% of all gastrointestinal cancers, much less common than carcinoma of the pancreas or bile ducts.[48] Ampullary carcinoma may arise within ampulla (intra-ampullary) or in periampullary duodenum, and sometimes can be difficult

Table 6. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Carcinoma of the Ampulla of Vater[a]

	8th Edition[1]	7th Edition[10]
T category (pT)		
Tis	Carcinoma in situ	Carcinoma in situ
T1	Limited to ampulla of Vater or sphincter of Oddi **or invades into the duodenal submucosa**	Limited to ampulla of Vater or sphincter of Oddi
T1a	**Limited to ampulla of Vater or sphincter of Oddi**	
T1b	**Invades beyond the sphincter of Oddi and/or into the duodenal submucosa**	
T2	Invades into the **muscularis propria** of the duodenum	Invades duodenal wall
T3	Invades the pancreas **or extends into peripancreatic/ periduodenal tissue or duodenal serosa**	Invades pancreas
T3a	**Invades the pancreas (≤0.5 cm)**	
T3b	**Invades the pancreas (>0.5 cm) or peripancreatic/ periduodenal tissue or duodenal serosa**	
T4	**Involves the celiac axis, superior mesenteric artery, and/or common hepatic artery**	Invades peripancreatic tissues or other adjacent organs or structures
N category (pN)		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	**Metastasis to 1–3 regional lymph nodes**	Regional lymph node metastasis
N2	**Metastasis to ≥4 regional lymph nodes**	
AJCC stage groupings		
IA	**T1a N0 M0**	T1 N0 M0
IB	**T1b–2 N0 M0**	T2 N0 M0
IIA	**T3a N0 M0**	T3 N0 M0
IIB	**T3b N0 M0**	T1–3 N1 M0
IIIA	**T1a–3b N1 M0**	
IIIB	**T4 any N M0; any T N2 M0**	
III		T4 any N M0
IV	Any T any N M1	Any T any N M1
Rationale for changes: Depth of invasion predicts outcomes. Invading into artery is important. Peripancreatic soft tissue invasion is difficult to define		
Validation of changes: T: Not improved. N: Better than 7th edition		
Potential future modifications: Reclassifying T1 and T2 (controversial among studies). Including histologic subtypes in staging		

[a] Bold entries in the 8th Edition column indicate changes.

to differentiate from periampullary carcinomas of pancreas, common bile duct, or duodenum. It is also highly challenging to stage AC because of its rarity, marked anatomic complexity, and 3-dimensional spread of the tumors in this area.[49] Since 2010, AC has been staged in the 7th edition AJCC/Union for International Cancer Control system using a "sphere model" where the ampulla is presumed to be sequentially covered by duodenum, pancreas, and then peripancreatic soft tissues, so that the stage increases when tumor invades further in that hypothetical order.[50] This model oversimplified the structural complexity and has been proved to be irreproducible and lack clinical relevance. The 8th edition modified both T and N classifications, where T stage is divided based on DOI into the duodenum (T1b, invasion into the duodenal submucosa, versus T2, invasion into the duodenal muscularis propria) and pancreas (T3a, invasion into the pancreas ≤0.5 cm, versus T3b, invasion into the pancreas >0.5 cm). T4 is limited to tumors involving the celiac axis, superior mesenteric artery, and/or common hepatic artery. Similar to pancreas and biliary duct carcinomas, the N classification is based on positive lymph nodes (N1, 1–3; N2, >3), and a minimum number of 12 lymph nodes in Whipple (pancreaticoduodenectomy) resection is recommended for optimal staging (Table 6).

Two studies have since investigated the clinical relevance of the 8th edition AJCC staging system on AC, both showing satisfactory results in the N category but not the T category. Specifically, Imamura et al[51] analyzed 104 consecutive patients from a single institution and found that the T classification failed to discriminate T1b (invading duodenal submucosa) and T2 (invading duodenal muscularis) tumors, yet worked to separate T3a (invading pancreas ≤0.5 cm) from T3b (invading pancreas >0.5 cm). Therefore, the authors suggested reclassifying T1b into T2. Kim et al[52] analyzed 369 operatively resected AC patients and also showed unsatisfactory stratification for T staging. However, they proposed a different method of modification by eliminating the current subcategories, that is, merging T1a/T1b as new T1, keeping T2, and merging T3a/T3b as new T3. The discrepancies of results leading to different proposals call attention to the challenges of validating staging systems based on retrospective single-institution series. The unique constraints that pertain specifically to AC, which is not uncommonly misdiagnosed as pancreatic ductal adenocarcinoma (PDAC), distal common bile duct carcinoma, or duodenal adenocarcinoma, also contributes to different conclusions. Further, AC can be subdivided into intestinal or pancreatobiliary subtypes based on histomolecular profiling, which contributes significantly to different

Table 7. Comparison of 8th and 7th American Joint Committee on Cancer (AJCC) Staging for Tumors of the Pancreas[a]

	8th Edition—Exocrine pancreas[1]	8th Edition—Endocrine Pancreas[1]	7th Edition—Exocrine and Endocrine Pancreas[10]
T category (pT)			
Tis	Carcinoma in situ		Carcinoma in situ
T1	≤2 cm	Limited to the pancreas, <2 cm	Limited to the pancreas, ≤2 cm
T1a	**≤0.5 cm**		
T1b	**>0.5 cm and <1 cm**		
T1c	**1–2 cm**		
T2	**>2 cm and ≤4 cm**	**Limited to the pancreas, 2–4 cm**	Limited to the pancreas, >2 cm
T3	**>4 cm**	**Limited to the pancreas, >4 cm; or invading the duodenum or common bile duct**	Extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Involves the celiac axis, superior mesenteric artery, **and/or common hepatic artery**	**Invading adjacent organs or the wall of large vessels**	Involves the celiac axis or the superior mesenteric artery
N category (pN)			
N0	No regional lymph node metastasis	No regional lymph node involvement	No regional lymph node metastasis
N1	**Metastasis in 1–3 regional lymph nodes**	Regional lymph node involvement	Regional lymph node metastasis
N2	**Metastasis in ≥4 regional lymph nodes**		
AJCC stage groupings			
IA	T1 N0 M0		T1 N0 M0
IB	T2 N0 M0		T2 N0 M0
I		**T1 N0 M0**	
IIA	T3 N0 M0		T3 N0 M0
IIB	T1–3 N1 M0		T1–3 N1 M0
II		**T2–3 N0 M0**	
III	**T1–3 N2 M0;** T4 any N M0	**T4 N0 M0; any T N1 M0**	T4 any N M0
IV	Any T any N M1	Any T any N M1	Any T any N M1
Rationale for changes (exocrine): Debate on the ambiguity of "peripancreatic soft tissue." Size-based definitions are more objective. Resectability is subjective. Better prognosis stratification is provided based on number of positive lymph nodes			
Validation of changes (exocrine and endocrine): T and N: Significant advantage over the 7th edition			
Potential future modification (exocrine): Combining stage IIA with IIB and further subclassifying stage III			

[a] Bold entries in the 8th Edition column indicate changes.

prognosis and treatment responses.[53] Lack of subtype data in studies trying to validate the AJCC staging system may also potentially bias the results. Overall, there is still much work to do before a reliable staging system on AC is available.

CARCINOMA OF THE EXOCRINE PANCREAS

Despite tremendous scientific efforts and advancing knowledge in cancer biology, PDAC remains an aggressive malignancy prone to metastasize and difficult to treat. The 5-year survival rate is less than 10%, and all patients are eventually expected to die from the disease.[54] Accurate tumor staging is a prerequisite for further treatment and prognostic prediction. The AJCC T stage for pancreatic cancer originally applied a measurement of tumor extension (limited to pancreas versus extending to peripancreatic soft tissue) in its previous editions. After decades of debate on the definition of invasion into peripancreatic soft tissue and its reliability in survival prediction,[49] the 8th edition finally introduced a completely different size-based T staging system, where stages T1 through T3 are redefined purely by tumor size (T1, ≤2 cm; T2, >2 cm and ≤4 cm; T3, >4 cm), with T1 further divided into 1a (≤ 0.5 cm), 1b (>0.5 and <1 cm), and 1c (1–2 cm) to encompass small invasive carcinoma increasingly detected in association with cystic neoplasms such as intraductal papillary mucinous neoplasms (IPMNs), intraductal tubulopapillary neoplasms, and mucinous cystic neoplasms.[49] Whether tumor is confined to pancreas or invading into peripancreatic soft tissue does not affect staging. T4 is defined when tumor involves large blood vessels (celiac axis, common hepatic artery, and/or superior mesenteric artery). Resectability is removed from staging purpose because of its subjectivity and more tumors becoming resectable. As for PHC, DCC, GBC, and AC, the N classification for PDAC is further subdivided into N0, N1 (1–3) and N2 (>3). T1-3N2M0 is classified as stage III, whereas the other stages remain unchanged (Table 7). Microscopic evaluation of at least 12 lymph nodes is also recommended for Whipple resections. Lastly, the AJCC 8th edition clearly documents the following surgical resection margins to be evaluated: pancreatic neck/parenchymal, uncinate (retroperitoneal/superior mesenteric artery), bile duct, proximal (gastric or duodenal), and distal (duodenal or jejunal), with a new rule stating that "the presence of tumor at or within 1 mm of resection constitutes a positive margin." Although controversial, there is no specification which margin(s) should meet the 1 mm requirement, and it is

interpreted that this rule applies to all true resection margins.[55,56]

The 8th edition of the TNM staging system in exocrine pancreas, particularly PDAC, is generally well received and considered superior to the 7th edition, with more even distribution among stages and more powerful discrimination.[57–62] Yet slightly varied opinions and some refinements have been brought up in different studies. Two studies,[60,61] one from China and one from Germany, found that the new T classification had a significant advantage over the previous edition in predicting overall survival whereas the new N classification did not, which is opposite to the results of an international multicenter cohort study[62] where the revised N stage was highly prognostic, but the revised T stage was not. A Chinese study[63] using the SEER database proposed to combine stage IIA with IIB and further subclassify stage III for better discriminative power. The latter proposal was endorsed by authors of another study[64] using the SEER database, who suggested subclassifying stage III into IIIA (T[1–3]N2/T4N[0–1]) and IIIB (T4N2) because of significant differences in overall and disease-specific survival. For node-positive patients, some studies again advised using positive lymph node ratio as a better nodal parameter compared with the total number of positive lymph nodes.[65]

The validation of the 8th edition staging system was done mostly on PDAC, yet one study investigated on IPMN with associated invasive carcinoma.[66] Using the SEER database, the authors found that tumor size of invasive IMPN was not a predictor of survival in patients with a resectable tumor larger than 2 cm (size >4 cm versus >2 and ≤ 4 cm), and that the 7th edition was more applicable than the 8th edition staging classification. However, a major caveat is how tumor size was defined in those studies: did it include the whole tumor with IMPN component, or was only the size of the invasive component included? Further studies may be warranted with a clear definition of tumor size and then comparison with the 7th edition to validate IPMN or mucinous cystic neoplasm with an associated invasive carcinoma.

The new size-based tumor classification and the new 1 mm or smaller positive margin rule brought up considerable controversies on how to best gross a Whipple specimen to yield best information for staging, particularly tumor origin, size, margin status, and lymph node yields.[67] The 2 most commonly used grossing protocols are axial sectioning[68,69] and bivalving methods,[70,71] each having pros and cons. The axial sectioning method is more accurate for tumor size and margin status, but may lead to repeated lymph node counting, and is not suitable for AC or IPMN. The bivalving method is beneficial in evaluating AC or IPMN, with a better lymph node yield and more accurate positive lymph node ratio, but is not ideal for margin status. Which methods to use may also depend on clinical setting; for example, cancer status post chemotherapy is generally difficult to resect and an axial sectioning method may be preferred in order to accurately evaluate margin status in such cases. Thus, standardization of Whipple grossing protocol may not be possible or necessary, and different techniques should be applied on a case-by-case basis. Knowing the complete clinical history, radiographical findings, and any presurgical treatment is critical to decide which technique to use so as to yield the most helpful information for tumor staging in the proper clinical context. For studies validating the changes of AJCC staging, the Whipple grossing methods may be taken into account for data analysis in order to reach a comparable and reliable conclusion.

TUMOR OF THE ENDOCRINE PANCREAS

Neuroendocrine tumors (NETs) of the hepatobiliary system are extremely rare. Currently no separate staging system is available for NETs of liver, bile ducts, or gallbladder. However, NET is relatively common in the pancreas, accounting for approximately 1% to 2% of all pancreatic tumors with unique pathologic features and clinical behavior. The World Health Organization classified pancreatic NETs into 3 grade groups according to mitotic count and Ki-67 labeling index. Pancreatic NETs were originally staged the same as exocrine cancers in the AJCC/TNM system. The European Neuroendocrine Tumor Society was the first to introduce a size-based staging parameter for pancreatic NETs, which is now incorporated and modified into the AJCC 8th edition (Table 7). Since its release, several studies have validated and supported the clinical use of this new staging system over the 7th edition or the European Neuroendocrine Tumor Society system.[72,73]

CONCLUSIONS

There have been major advancements in our understanding of cancer biology and discovery of new factors that predict cancer outcomes and treatment responses, which have led to some of the radical changes in the 8th edition AJCC cancer staging manual, particularly in HPB cancers. This new edition of the staging system has been validated worldwide. Some changes appear to perform better, and some do not. Generally, for the T category, a more objective method (tumor size, DOI, etc) appears to work better, particularly for DCC and PDAC, and a more subjective anatomic layer–based approach, such as for AC and GBC, remains suboptimal. The unified number-based N category for pancreatobiliary cancers and ACs is well received and is considered superior to its previous versions. It also rationalizes a minimal number of lymph nodes to be evaluated, although this requirement is not recommended for all HPB cancers yet. Lastly, although most of the publications on validating those changes/updates are of good quality, larger studies with solid databases are still needed to solve the remaining controversial issues in the 8th edition.

In summary, the TNM-based AJCC cancer staging system has been widely accepted and used for solid tumors; however, in an era of personalized medicine some nonanatomic factors, such as serum and molecular biomarkers, have been gaining attention for potential inclusions into the staging system. Because the AJCC promulgates staging practices through each new edition in an effort to provide a powerful, knowledge-based resource for the battle against cancer, this review summarizes the major changes of the 8th edition on HPB cancers and reviews literature validating those changes, hoping that this information will provide the reader with a better understanding of the rationales behind the changes and potential exciting developments in future editions.

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