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EDITORIAL – HEPATOBILIARY TUMORS

# 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers

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The American Joint Committee on Cancer (AJCC) Staging Manual represents the standard for classifying patients with pancreas and hepatobiliary cancers, predicting prognosis, and guiding treatment decisions. For the new 8th edition, the AJCC Hepatobiliary Task Force, a multidisciplinary team of international experts, conducted two face-to-face meetings. At the first meeting, specialists in individual disease sites presented analysis of the literature and reviewed questions and issues from the 7th edition. Recommendations for revisions were proposed and discussed. At the second meeting, additional data to support the proposed revisions were reviewed, and revisions were approved by the full task force, including representatives from the Union for International Cancer Control (UICC) and the AJCC Editorial Board. Chapters were submitted to the Editorial Board for editing and final approval.

The cornerstone of staging of hepatobiliary cancers is high-quality surgery, detailed pathologic analysis, and reliable follow-up, which are not available from large datasets and registries. Owing to the relative rarity of hepatobiliary cancers and the complex anatomy, often requiring technically demanding surgery, the AJCC staging system is largely based on single-institution series from centers of excellence in surgery and pathology. Much of the evidence that forms the basis for the revised 8th edition has been validated at other centers of excellence in hepatobiliary cancer. Importantly, the revisions also drew heavily on international expertise, particularly from Asia, where the incidence of hepatobiliary cancers is high.



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For the 8th edition, the N category has been harmonized for gallbladder, perihilar bile ducts, distal bile duct, ampulla, and pancreas. For these disease sites, N1 is defined as one to three metastatic lymph nodes, and N2 as four or more metastatic lymph nodes. A number-based categorization of metastatic lymph nodes results in better prognostic stratification.[1,2] Other key modifications in the AJCC 8th edition are described below.

## LIVER

T1 is subdivided into T1a and T1b based on a cutoff size of 2 cm.[3] The separation of early-stage hepatocellular carcinoma (HCC), based on a size of $\leq$2 or >2 cm, is particularly relevant for applicability to the Eastern experience with HCC, as many patients in Asia undergo routine ultrasound surveillance and are diagnosed with small, solitary HCCs. Furthermore, the T1a and T1b subgroups have practical implications for local therapies, such as ablation and chemoembolization, which can be curative for HCC $\leq$2 cm in size.

## INTRAHEPATIC BILE DUCTS

The 7th edition introduced a new staging for intrahepatic bile duct cancers, which were previously staged the same as HCC.[4] For the 8th edition, a cutoff size of 5 cm is introduced to separate the T1 category into T1a and T1b subgroups. Periductal invasion is removed from the T4 category due to the paucity of recent data on the prognostic impact of periductal invasion. T4 is now defined as involvement of local extrahepatic structures by direct invasion and is classified as stage IIIB. In the 7th edition, invasion of local extrahepatic structures was classified as stage III (T3). Recovery of at least six lymph nodes is

recommended for complete nodal staging, consistent with recommendations for gallbladder cancer.

## GALLBLADDER

Stage II (T2) gallbladder cancer is often diagnosed incidentally after laparoscopic cholecystectomy and requires re-resection for adequate treatment and staging. For the 8th edition, the T2 category is separated into T2a (stage IIA) and T2b (stage IIB), based on tumor location on the peritoneal or hepatic side of the gallbladder, respectively. This change is based on a study from four international centers with review by expert pathologists, demonstrating worse survival for tumors on the hepatic side of the gallbladder.[5]

## PERIHILAR BILE DUCTS

For the 7th edition, a new staging system for perihilar bile ducts was established, separate from distal bile ducts. For the 8th edition, the T4 category excludes bilateral second-order bile duct extension, which does not affect prognosis, independent of nodal metastases and vascular invasion.[6] In addition, T4 tumors are downstaged from IVA to IIIB, since these tumors are considered resectable at centers with expertise in extended hepatectomy and combined vascular resection and reconstruction.

## DISTAL BILE DUCT

Definitions of the T subgroups are revised from a descriptive extent of tumor invasion of the bile duct to the measured depth of invasion. A study on Eastern patients, with corroboration from a Western center, demonstrated that stratification of patients by depth of tumor invasion $<5$, 5–12, and $>12$ mm strongly predicted overall survival.[7,8]

## AMPULLA OF VATER

The T category is expanded with more precise definitions, reflecting the complex three-dimensional anatomy of the ampulla. To address the ambiguity of the previous T2 definition, duodenal invasion is separated into invasion of the duodenal submucosa (T1b), muscularis propria (T2), and serosa (T3b). The T3 category also includes invasion of the pancreas, which is separated into T3a and T3b subgroups, according to the depth of pancreatic invasion $\leq 0.5$ or $>0.5$ cm.[9] The T4 category is harmonized with pancreas and distal bile duct cancers to reflect the prognostic significance of tumor involvement of the celiac axis, superior mesenteric artery, and/or common hepatic artery.

## EXOCRINE PANCREAS

For the 8th edition, staging of exocrine and endocrine pancreatic cancers is separated. The T category is revised from descriptive to size-based definitions. Currently, size is the best surrogate of tumor biology following resection of pancreatic cancer. A size-based classification was able to stratify overall survival well in a series from two high-volume centers, with independent validation from a large multi-institutional series.[10,11] In addition, resectability is removed from the T4 category, since the definition of resectability is not consistent among institutions and evolves with advances in surgical technique.

## CONCLUSION

Often considered orphan diseases, hepatobiliary cancers are relatively rare, with few well-designed, adequately powered, randomized trials. However, the incidence of hepatobiliary cancers is rising, particularly primary cancers of the liver, intrahepatic bile ducts, and pancreas. An important limitation of the current and previous AJCC editions is the lack of level I evidence to support the staging proposals. The future 9th edition will be strengthened by a coordinated international effort to rigorously analyze, improve, and validate the staging system.

Revisions for the AJCC 8th edition rely heavily on detailed pathologic analysis of resected specimens from international centers of excellence. Since these data are derived from surgical series, AJCC staging is most applicable to surgically treated patients. Subgroups are better stratified by precise definitions on size and depth of tumor invasion. Key descriptors, including the N and T4 categories, have been harmonized across disease sites. The 8th edition affirms that the anatomic extent of disease remains the strongest predictor of outcome in hepatobiliary cancers.

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