Intrahepatic cholangiocarcinoma is the second most common primary liver cancer after hepatocellular carcinoma and is increasing in incidence worldwide (1). Surgical resection remains the only potentially curative treatment but is associated with high tumor recurrence rates. The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual introduced a new staging system for intrahepatic cholangiocarcinoma, which was previously staged the same as hepatocellular carcinoma. The recently published 8th edition has subdivided the T1 category to T1a and T1b based on a size cutoff of 5 cm, removed periductal invasion from the T4 category, and downstaged T4 tumors and regional lymph node metastasis from stage IV to IIIB. Continued international efforts to accurately stratify prognosis are important to counsel patients and guide treatment decisions.

Keywords: Intrahepatic cholangiocarcinoma; American Joint Committee on Cancer (AJCC); Union for International Cancer Control (UICC); staging

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intrahepatic cholangiocarcinoma into large duct and small duct subtypes, which correlate with macroscopic growth patterns (12,13). The small duct type is found in mass-forming tumors and is associated with chronic liver disease. The large duct type occurs in patients with chronic biliary disease and exhibits a variable macroscopic growth pattern.

**AJCC 7th edition**

The 7th edition of the AJCC staging system for intrahepatic cholangiocarcinoma included tumor number, vascular invasion, and direct extrahepatic extension as defining components of the T category (Table 1) (7). Tumors with periductal invasion were classified as T4, stage IVA. This T4 classification was based on limited analyses suggesting a prognostic significance of tumor growth patterns for intrahepatic cholangiocarcinoma (9). Compared to the more common mass-forming type, periductal-infiltrating type of intrahepatic cholangiocarcinoma is reportedly associated with a poor prognosis. The T4 category included diffuse periductal-infiltrating tumors and mixed mass-forming plus periductal-infiltrating tumors. The 7th edition of the AJCC staging system was validated in several independent patient populations (14,15).

**Changes in AJCC 8th edition**

Significant changes in the 8th edition of the AJCC staging of intrahepatic cholangiocarcinoma are presented below.

**Size**

The revised AJCC 8th edition incorporated a tumor size cutoff of 5 cm to separate the T1 category into T1a and T1b subgroups. Institutional and registry studies have shown that maximum tumor diameter >5 cm is an independent prognostic factor for overall survival.
Furthermore, tumor size >5 cm is associated with microscopic vascular invasion and higher tumor grade (18).

**Serosal invasion**

In both the 7th and 8th editions of the AJCC staging system of intrahepatic cholangiocarcinoma, the T3 category is defined as perforation of the visceral peritoneum. The LCSGJ staging system also includes serosal invasion as a component of the T category (8).

**T4 category**

In the 7th edition, periductal invasion defined the T4 category and was classified as stage IVA. For the 8th edition, periductal invasion is removed from the T4 category because of a lack of recent data on the prognostic effect of periductal invasion. T4 is now defined as tumor involving local extrahepatic structures by direct invasion and is categorized as stage IIIB. Sakamoto et al. reported that in patients undergoing resection of intrahepatic cholangiocarcinoma, invasion of the first-order branch of the bile duct is an independent factor for worse prognosis (19). However, other surgical series on intrahepatic cholangiocarcinoma exclude tumors involving the hepatic hilum from analysis (8,20).

The definition of periductal invasion remains an area of controversy. The 7th and 8th editions of the AJCC Staging Manual define intrahepatic cholangiocarcinoma anatomically as extending from the periphery of the liver to the second-order bile ducts. This definition does not differentiate between hilar cholangiocarcinoma with an intrahepatic component and intrahepatic cholangiocarcinoma involving the hepatic hilum. A solution to this ambiguous definition proposed by Ebata et al. is to define the center of the tumor in relation to the umbilical portion of the left portal vein and the right posterior portal vein as anatomic boundaries for the hilar bile duct (21).

**Tumor number and vascular invasion**

The 7th edition T2 category was subdivided into T2a, solitary tumor with vascular invasion, and T2b, multiple tumors, with or without vascular invasion. In the 8th edition, the T2 category is no longer subdivided, indicating an equivalent prognostic effect of vascular invasion and multifocal disease.

**Lymph nodes**

In the 7th edition, intrahepatic cholangiocarcinoma with regional lymph node metastasis was classified as stage IVA. In surgical series, up to one-third of patients have node-positive disease (22). For the 8th edition, regional lymph node metastasis was downstaged from IVA to IIIB. A challenge with the N1 category in intrahepatic cholangiocarcinoma is that routine lymphadenectomy is not standardized across institutions. According to an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, information on lymph node status was available in only 49% of patients undergoing resection of intrahepatic cholangiocarcinoma (23). In addition, there are no guidelines on the minimum number of lymph nodes that should be harvested. In the 8th edition of the AJCC staging of intrahepatic cholangiocarcinoma, recovery of at least 6 lymph nodes is recommended for complete nodal staging, consistent with recommendations for gallbladder cancer.

**Validation of AJCC 8th edition staging of intrahepatic cholangiocarcinoma**

Three studies have been published on the prognostic value of the 8th edition of the AJCC staging for intrahepatic cholangiocarcinoma (Table 2) (24-26). These studies show that the new 8th edition is similar or better than the 7th edition in stratifying patients’ overall survival.

An analysis by Kim et al. of the SEER registry found that the 8th edition was comparable to the 7th edition (24). Harrell’s concordance index for overall survival was 0.669 for the 8th edition and 0.667 for the 7th edition.

Spolverato et al. evaluated the 8th edition of the AJCC staging using a multi-institutional cohort of patients who underwent curative-intent hepatic resection (25). Compared to the 7th edition, the 8th edition staging was able to better stratify survival in stage III patients. Paradoxically, patients categorized by the 8th edition staging with T3 tumors had 5-year overall survival rates that surpassed those of patients with T1b and T2 tumors. The T3 category is defined as perforation of the visceral peritoneum, or serosal invasion. The LCSGJ staging system also includes serosal invasion as a component of the T category (8). Sakamoto et al. proposed removing serosal invasion from the LCSGJ staging system, since serosal invasion was not significantly associated with survival (19).

Kang et al. assessed the prognostic impact of the 8th...
and found that in patients without lymph node metastasis, median overall survival rates with T2 and T3 tumors were 25 months and 27 months, respectively (26). Median time to recurrence with T2 and T3 tumors was 14 and 15 months, respectively. Similar to the findings by Spolverato et al., this study suggests that the 8th edition T3 category does not accurately reflect patient prognosis and tumor biology.

**Conclusions**

The revisions to staging of intrahepatic cholangiocarcinoma in the 8th edition of the AJCC Staging Manual build upon the foundation of the 7th edition, which represented the first unique AJCC staging for intrahepatic cholangiocarcinoma. These revisions were based upon detailed pathologic analysis of resected surgical specimens from international hepatobiliary centers of excellence. The future 9th edition will be further improved by continued international efforts to share and rigorously analyze data.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

**References**
