

# Intrahepatic cholangiocarcinoma: the AJCC/UICC 8<sup>th</sup> edition updates

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**Abstract:** Intrahepatic cholangiocarcinoma accounts for 5% to 30% of all primary liver cancers, and its incidence has increased in the last 3 decades. Surgical resection remains the only potentially curative treatment but is associated with high tumor recurrence rates. The 7<sup>th</sup> 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 8<sup>th</sup> 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 is the second most common primary liver cancer after hepatocellular carcinoma and is increasing in incidence worldwide (1). Surgical resection is the only potentially curative therapy and results in 5-year overall survival rates between 15% and 40% (2). Unfortunately, disease relapse after resection occurs in up to two-thirds of patients (3). Prognostic factors associated with higher recurrence include positive surgical margin, lymph node metastasis, vascular invasion, and multiple tumors (4,5). The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system represents a standard for stratifying patients with cancer, predicting prognosis, and guiding treatment decisions (6). The recently published 8<sup>th</sup> edition of the AJCC Staging Manual represents the first revision of the previously novel staging of intrahepatic cholangiocarcinoma introduced in the 7<sup>th</sup> edition (7). Before the 7<sup>th</sup> edition,

intrahepatic cholangiocarcinoma shared the same staging as hepatocellular carcinoma.

Both the 7<sup>th</sup> and 8<sup>th</sup> editions of the AJCC Staging Manual recommend data collection of tumor growth patterns, classified as mass-forming, periductal-infiltrating, or mixed types, based on the Liver Cancer Study Group of Japan (LCSGJ) classification (8). The LCSGJ also defines an intraductal growth type, which is rare and associated with a favorable prognosis. The mass-forming type is the most common and characterized by an intraparenchymal mass with distinct borders. The periductal-infiltrating type is marked by tumor infiltration along the bile duct, often causing dilatation of a peripheral bile duct. Some studies show worse survival after resection of the periductal-infiltrating type compared with the mass-forming type, whereas other reports show no difference in survival (5,9-11). Recently, histologic studies have divided

**Table 1** AJCC staging of intrahepatic cholangiocarcinoma: comparison of 7<sup>th</sup> and 8<sup>th</sup> editions

7 <sup>th</sup> edition	8 <sup>th</sup> edition
<b>T category</b>	
T1: solitary tumor without vascular invasion	T1a: solitary tumor ≤5 cm without vascular invasion T1b: solitary tumor >5 cm without vascular invasion
T2a: solitary tumor with vascular invasion T2b: multiple tumors, with or without vascular invasion	T2: solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3: tumor perforating the visceral peritoneum or involving local hepatic structures by direct invasion	T3: tumor perforating the visceral peritoneum
T4: tumor with periductal invasion	T4: tumor involving local extrahepatic structures by direct invasion
<b>N category</b>	
N0: no regional lymph node metastasis	N0: no regional lymph node metastasis
N1: regional lymph node metastasis present	N1: regional lymph node metastasis present
<b>TNM stage</b>	
I: T1 N0 M0	IA: T1a N0 M0 IB: T1b N0 M0
II: T2 N0 M0	II: T2 N0 M0
III: T3 N0 M0	IIIA: T3 N0 M0 IIIB: T4 and/or N1, M0
IVA: T4 N0 M0/any T, N1, M0	IV: any T, any N, M1
IVB: any T, any N, M1	

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 7<sup>th</sup> 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 7<sup>th</sup> edition of the AJCC staging system was validated in several independent patient populations (14,15).

### Changes in AJCC 8<sup>th</sup> edition

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

#### Size

The revised AJCC 8<sup>th</sup> 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

(5,16,17). Furthermore, tumor size >5 cm is associated with microscopic vascular invasion and higher tumor grade (18).

### **Serosal invasion**

In both the 7<sup>th</sup> and 8<sup>th</sup> 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 7<sup>th</sup> edition, periductal invasion defined the T4 category and was classified as stage IVA. For the 8<sup>th</sup> 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 7<sup>th</sup> and 8<sup>th</sup> 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 7<sup>th</sup> edition T2 category was subdivided into T2a, solitary tumor with vascular invasion, and T2b, multiple tumors, with or without vascular invasion. In the 8<sup>th</sup> edition, the T2 category is no longer subdivided, indicating an equivalent prognostic effect of vascular invasion and multifocal disease.

### **Lymph nodes**

In the 7<sup>th</sup> 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 8<sup>th</sup> 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 8<sup>th</sup> 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 8<sup>th</sup> edition of the AJCC staging for intrahepatic cholangiocarcinoma (Table 2) (24–26). These studies show that the new 8<sup>th</sup> edition is similar or better than the 7<sup>th</sup> edition in stratifying patients' overall survival.

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

Spolverato *et al.* evaluated the 8<sup>th</sup> edition of the AJCC staging using a multi-institutional cohort of patients who underwent curative-intent hepatic resection (25). Compared to the 7<sup>th</sup> edition, the 8<sup>th</sup> edition staging was able to better stratify survival in stage III patients. Paradoxically, patients categorized by the 8<sup>th</sup> 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 8<sup>th</sup>

**Table 2** Studies on prognostic performance of the 8th edition AJCC staging of intrahepatic cholangiocarcinoma

Author	Year	Institution/data source	Number of patients	Independent factors for overall survival	Prognostic performance of AJCC 8 <sup>th</sup> edition staging
Kim (24)	2017	SEER database	1,008	8 <sup>th</sup> edition AJCC stage; age >65 years; tumor grade	Similar prognostic discrimination as 7 <sup>th</sup> edition
Spolverato (25)	2017	International multi-institutional cohort	1,154		T3 patients had lower hazard ratio of death compared with T1b and T2
Kang (26)	2018	Asan Medical Center, South Korea	626, all R0 resection	Multiple tumors; CA 19-9 >200 U/mL; size >5 cm; direct invasion to extrahepatic structures; lymph node metastasis	Patients with T2 and T3 tumors had same overall survival

edition AJCC staging of intrahepatic cholangiocarcinoma 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 8<sup>th</sup> edition T3 category does not accurately reflect patient prognosis and tumor biology.

## Conclusions

The revisions to staging of intrahepatic cholangiocarcinoma in the 8<sup>th</sup> edition of the AJCC Staging Manual build upon the foundation of the 7<sup>th</sup> 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 9<sup>th</sup> 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.

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