



AJCC 8th edition staging system for pathologically versus clinically staged intrahepatic cholangiocarcinoma (iCCA): ready for prime time?

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Comment on: Kamarajah SK. Evaluation of the AJCC 8th Edition Staging System for Pathologically Versus Clinically Staged Intrahepatic Cholangiocarcinoma (iCCA): a Time to Revisit a Dogma? A Surveillance, Epidemiology, and End Results (SEER) Analysis. *J Gastrointest Cancer* 2019;50:392-9.

Submitted Apr 17, 2019. Accepted for publication Apr 20, 2019.

doi: 10.21037/cco.2019.04.04

View this article at: <http://dx.doi.org/10.21037/cco.2019.04.04>

Biliary tract cancers (BTC) are a rare, heterogeneous group of malignancies that arise from the neoplastic proliferation of cholangiocytes or epithelium of the bile ducts (1). They are comprised of three anatomic subgroups: intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (EHCC), and cancers of the gallbladder. In patients who present with early stage disease, patients are offered a potential curative treatment through surgical resection. Our increased understanding of the biology of these diseases has allowed us to understand the heterogeneity that exists between these anatomic subgroups (2), which is observed from the differences in prognosis and clinical outcomes.

These nuanced variances are further supported in the staging and classification of these malignancies. The American Joint Committee on Cancer (AJCC) staging system provides physicians a standardized measure to prognosticate patient outcomes based on tumor-related characteristics. The AJCC 7th edition staging system was the first revision of the previous staging of iCCA, which previously shared the same staging system with hepatocellular carcinoma (3). Recently, the AJCC 8th edition provided several updates, which included new definitions for T classification (size, tumor number, serosal invasion, vascular invasion) and lymph node categorization (4). Revisions in the 8th edition were based upon pathologic assessments from various institutions,

which suggested a prognostic effect based on certain tumor specific characteristics (5,6). Changes in the AJCC 8th edition include T staging revisions based off tumor size, where a cutoff of 5 cm stratified T1 into T1a and T1b. Additional changes within the 8th edition include the refinement of T2 tumors as those with vascular invasion, and the reclassification of T4 as tumors that directly involve local extrahepatic structures. While the refinement and reclassification may potentially better prognosticate patient outcomes compared to the 7th edition, the new AJCC 8th edition has not been validated.

Several studies have accessed the validity and prognostic utility of the AJCC 8th edition for iCCA. Utilizing prospectively collected data from the Surveillance, Epidemiology and End Results (SEER) database, a recent study identified patients who underwent surgical resection for iCCA from 1998 to 2013 evaluated the impact of the AJCC 8th edition classification on patient survival (7). A total of 1,008 patients with iCCA who underwent surgical resection were identified. Patient outcomes were similar from the AJCC 8th edition compared to the 7th edition. Spolverato *et al.* also evaluated the impact from the AJCC 8th edition on patients who underwent hepatic resection for iCCA (8). Multi-institution patient data was pooled and patients were staged according to the AJCC 7th and 8th edition. According to the AJCC 8th edition, patients with T1b, T2 and T4 tumors were at increased risk of

death compared those with T1a tumors [T1b, hazard ratio (HR) 1.91, $P < 0.001$; T2, HR 2.29, $P < 0.001$; T4, HR 4.16, $P = 0.001$] (8). Similar to the AJCC 8th edition, based off the 8th edition, T3 patients had a higher HR of death (HR 1.65; $P = 0.001$) compared to patients with T1 tumors, but paradoxically, patients with T3 tumors had a lower risk of death than those with T1b and T2 tumors. The C-index T staging showed a higher degree of concordance with the AJCC 7th edition than with the 8th edition (0.609 versus 0.590). Another study that investigated the prognostic impact of AJCC 8th edition demonstrated similar survival outcomes in patients with T2 and T3 tumors, with a median survival of 25 versus 27 months, respectively (9). A more recent, larger study utilized the SEER database to validate the prognostic value of the 8th edition in patients with iCCA. From 1998 to 2013, 2,630 patients with iCCA were identified, with 37% of which underwent surgical resection. Similarities in patient overall survival and concordance index for the staging system were observed between the 7th and 8th edition.

The findings observed across these various studies suggest comparable results in stratifying patient outcomes between the AJCC 7th edition and AJCC 8th edition staging system. Subtle differences were noted in patient outcomes in those who underwent surgical resection. Further refinement should include the identification and validation of the appropriate subset of patients to apply these new changes prior to the uniform implementation of this new staging classification.

Acknowledgments

None.

Footnote

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

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Cite this article as: Ahn DH, Bekaii-Saab T. AJCC 8th edition staging system for pathologically versus clinically staged intrahepatic cholangiocarcinoma (iCCA): ready for prime time? *Chin Clin Oncol* 2019;8(Suppl 1):S19. doi: 10.21037/cco.2019.04.04