



The power to predict with biomarkers: carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) serum markers in intrahepatic cholangiocarcinoma

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Carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are the most studied tumor markers in intrahepatic cholangiocarcinoma (iCC) and are elevated in 85 and 40%, respectively (1). A recent publication proposed that serum biomarkers enhance the predictive power of the American Joint Committee on Cancer 8th edition (AJCC/UICC) and the Liver Cancer Study Group of Japan (LCSGJ) staging systems in resectable iCC (2). The authors of this multicenter study come from 16 experienced hepatobiliary centers in North America, Asia, Australia, and Europe. The study is based on a large patient population of 805 patients undergoing resection for histologically proven iCC. Patients with missing CA 19-9 data, R2 resection, or presence of extrahepatic disease at time of surgery were excluded from the study. The objectives of the study was to define the best survival cut-off values for CA 19-9 and CEA and to investigate whether the integration of these biomarkers increase survival prediction of the AJCC/UICC and the LCSGJ classification for iCC (2). The study identified best cut-offs of CA 19-9 and CEA, which were associated with postresectional survival. In addition, the authors suggest that the inclusion of preoperative CA 19-9 and CEA in AJCC/UICC and LCSGJ staging systems may improve the prognostic survival prediction after resection for iCC.

Although the extent and spread of the tumor disease has obviously an important impact on the prognosis, it has to be emphasized that the primary goal of traditional

staging systems such as TNM classification was to stage the anatomic macroscopic and later microscopic extent of the malignant tumor disease rather to come up with prognostic survival prediction. In the recent past, the AJCC/UICC 6th edition did not provide tumor-specific staging for iCC and hepatocellular carcinoma (HCC), and both tumor entities were not distinguished from each other. However, the following 7th edition of the AJCC Staging Manual, published in 2009, first recognized the importance of iCC and incorporated this tumor entity into the tumor-node-metastasis (TNM) staging system, which was distinct from HCC and extrahepatic bile duct malignancies. Additional new staging characteristics of iCC in this edition were local extension, periductal infiltration, lymph nodal metastasis, vascular invasion, and tumor burden (3,4). In the most recently published 8th edition of AJCC Staging Manual in 2016, iCC remained an independent staging systems, which is different from HCC and extrahepatic bile duct cholangiocarcinoma (5). Both the LCSGJ and AJCC/UICC staging scheme are widely comparable in terms of staging of distant and lymph node metastases but have considerable variations in the classification of T stage as well as tumor number and tumor growth pattern including periductal versus intraductal subtypes and mass forming lesions (3). Because iCC represents the second most common primary hepatic cancer with increasing incidence (6), there has been an expanding number of investigative efforts to identify prognostic predictors allowing a more precise staging of

Table 1 Published studies on cut-off values of CA19-9 and median survival times after liver resection for intrahepatic cholangiocarcinomas

Author (ref.)	No of patients	Cut-off value, CA 19-9 (U/L)	Median survival time (months)*
Yamada <i>et al.</i> (7)	18	≥100	12.0
	26	<100	59.0
He <i>et al.</i> (6)	50	≥200	15.1
	141	<200	42.5
Yamamoto <i>et al.</i> (9)	19	≥300	15.3
	54	<300	46.9
Sasaki <i>et al.</i> (2)	120	≥500	15.5
	171	≥100, <500	28.1
	541	<100	50.0

*, refers to postresectional overall survival. CA, carbohydrate antigen; U/L, units per liter.

iCC (3).

Surgical resection is the only established curative treatment for iCC; however, recurrence occurs frequently and the prognosis after resection is generally suboptimal. Therefore, useful biomarkers are necessary for assisting the prediction of the post-operative prognosis of patients with iCC (7). The use of alpha-fetoprotein (AFP) in the HCC Exception Criteria Guidelines of the United Network for Organ Sharing (UNOS) is an example how biomarker assist clinical decision making in patients awaiting liver transplantation (8). Various iCC studies investigated the predictive potential of CA 19-9 for survival. Although these studies come up with different CA 19-9 cut-off values, the predictive power of biomarker for overall survival is mirrored in the fact that higher CA 19-9 levels are associated with inferior prognosis (Table 1). In the current study by Sasaki *et al.*, the discriminative power of CA 19-9 cut-offs of <100 versus >500 U/L translated in an overall survival difference of 34 months (2).

Despite the clinical usefulness of CA 19-9 and CEA, a wide variation in sensitivity (50–90%) and specificity (54–98%) have been reported for both serum biomarkers (10). In addition, 10% of individuals do not express the Lewis antigen and, therefore, do not produce CA 19-9. Furthermore, tumor cells occasionally lose the ability to express tumor markers (11). Nevertheless, serum levels of CA19-9 are also elevated in patients with non-malignant biliary conditions such as primary sclerosing cholangitis

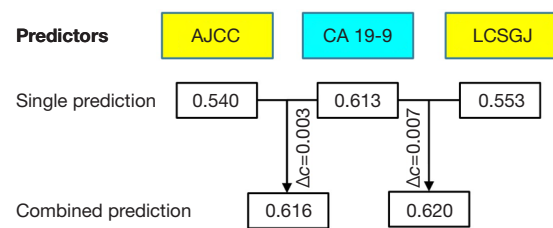


Figure 1 Discriminatory ability of single and combined survival prediction. C-statistics for single prediction of postresectional overall survival was 0.613 for CA 19-9, 0.540 for AJCC/UICC, and 0.540 for LCSGJ staging system. When CA 19-9 was combined either with AJCC or LCSGJ, the discriminatory ability of combined prediction increased only marginally by 0.003 and 0.007, respectively. CA 19-9, carbohydrate antigen 19-9.

or pure biliary obstruction. This implies that CA-19-9 might not be the perfect marker for surveillance in patients with cholangitis or obstructive jaundice (6,12). CEA, which is a powerful tumor marker in many gastrointestinal malignancies, has gained increasing attention as potential tumor marker in hepatobiliary malignancies as well. In one study, CEA was more predictive for long-term survival after resection of cholangiocarcinoma than CA 19-9 (13).

The authors of the commented study (2) claim that the central finding of their study is the improved survival prediction of the AJCC/UICC and LCSGJ staging systems for patients undergoing resection for iCC when preoperative CA 19-9 and CEA are included. This sounds reasonable at first sight but requires considering some important statistical issues. First, Harrell's *c*-statistics for single prediction using either the AJCC/UICC or LCSGJ staging system was close to 0.5 (Figure 1) and is, therefore, not useful for clinical prediction. We have to keep in mind that a perfect prediction corresponds to a *c*-statistics of 1.0 while a value of 0.5 indicates random prediction. Second, single prediction of CA 19-9 or CEA is clearly superior to single prediction by either staging systems but is still weak at 0.613 and 0.579 regardless of staging of the disease. Third and most importantly, the additional gain in prediction of combining biomarkers (CA 19-9) and T4 staging is very marginal for both AJCC/UICC (Δ*c*=0.003) and LCSGJ (Δ*c*=0.003) staging systems (Figure 1). However, the incremental increase in prognostic power by integrating CA 19-9 and CEA into the prediction model is true for using the staging system as statistical reference but would be different when biomarkers would be the gold standard. In other words, an additional prediction by either staging

systems on top of a statistical biomarker reference would be statistically as well as clinically irrelevant. However, the work of the authors underlines the importance of integrating novel non-anatomic biomarkers into the staging system, which better reflect stage and extension of the disease in relation to the predicted prognosis. Additional staging variable candidates might not only be restricted to established and novel serum biomarkers (14) but may also apply to genetic tumor characteristics (15,16) or even PET-based metabolic information (17).

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None.

Footnote

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

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