https://doi.org/10.1016/j.hpb.2018.04.005 HPB

ORIGINAL ARTICLE

Serum tumor markers enhance the predictive power of the AJCC and LCSGJ staging systems in resectable intrahepatic cholangiocarcinoma

Kazunari Sasaki[1,*], Georgios A. Margonis[3,*], Nikolaos Andreatos[3], Qinyu Chen[2], Carlotta Barbon[3], Fabio Bagante[4], Matthew Weiss[3], Irinel Popescu[5], Hugo P. Marques[6], Luca Aldrighetti[7], Shishir K. Maithel[8], Carlo Pulitano[9], Todd W. Bauer[10], Feng Shen[11], George A. Poultsides[12], Olivier Soubrane[13], Guillaume Martel[14], Bas Groot Koerkamp[15], Alfredo Guglielmi[4], Itaru Endo[16], Federico N. Aucejo[1] & Timothy M. Pawlik[2]

[1]Department of Surgery, Cleveland Clinic, Cleveland, [2]Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, [3]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, USA, [4]Department of Surgery, University of Verona, Verona, Italy, [5]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania, [6]Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal, [7]Department of Surgery, Ospedale San Raffaele, Milan, Italy, [8]Department of Surgery, Emory University, Atlanta, GA, USA, [9]Department of Surgery, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia, [10]Department of Surgery, University of Virginia, Charlottesville, VA, USA, [11]Eastern Hepatobiliary Surgery Hospital, Shanghai, China, [12]Department of Surgery, Stanford University, Stanford, CA, USA, [13]Department of Hepatobiliopancreatic Surgery and Liver Transplantation, AP-HP, Beaujon Hospital, Clichy, France, [14]Division of General Surgery, Department of Surgery, University of Ottawa, Ottawa, Canada, [15]Department of Surgery, Erasmus University Medical Centre, Rotterdam, Netherlands, and [16]Gastroenterological Surgery Division, Yokohama City University School of Medicine, Yokohama, Japan

Abstract

Background: While several prognostic models have been developed to predict long-term outcomes in resectable intrahepatic cholangiocarcinoma (ICC), their prognostic discrimination remains limited. The addition of tumor markers might improve the prognostic power of the classification schemas proposed by the AJCC 8th edition and the Liver Cancer Study Group of Japan (LCSGJ).

Methods: The prognostic discrimination of the AJCC and the LCSGJ were compared before and after the addition of CA 19-9 and CEA, using Harrell's C-index, net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) in an international, multi-institutional cohort.

Results: Eight hundred and five surgically treated patients with ICC that met the inclusion criteria were identified. On multivariable analysis, CEA5 ng/mL, 100IU/mL CA 19-9< 500IU/mL and CA 19-9500 IU/mL were associated with worse overall survival. The C-index of the AJCC and the LCSGJ improved from 0.540 to 0.626 and 0.553 to 0.626, respectively following incorporation of CA 19-9 and CEA. The NRI and IDI metrics confirmed the superiority of the modified AJCC and LCSGJ, compared to the original versions.

Conclusion: The inclusion of preoperative CA 19-9 and CEA in the AJCC and LCSGJ staging schemas may improve prognostic discrimination among surgically treated patients with ICC.

Received 3 November 2017; accepted 15 April 2018

Correspondence

Timothy M. Pawlik, Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University Wexner Medical Center, 395 W. 12th Avenue, Suite 670 Columbus, OH 43210, USA. E-mail: tim.pawlik@osumc.edu

No preregistration exists for the reported studies reported in this article.

Georgios Antonios Margonis was supported by the Bodossaki Foundation.

[*]These authors contributed equally to this work.

Please cite this article in press as: Sasaki K, et al., Serum tumor markers enhance the predictive power of the AJCC and LCSGJ staging systems in resectable intrahepatic cholangiocarcinoma, HPB (2018), https://doi.org/10.1016/j.hpb.2018.04.005

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a primary hepatic malignancy that constitutes approximately 10% of all cholangiocarcinomas.[1] ICC generally arises in the intrahepatic peripheral bile ducts, proximal to the secondary biliary radicals; abnormal trans-differentiation of hepatocytes may also be responsible for the development of ICC in some cases.[2,3] Importantly, the incidence of ICC has steadily increased over the last several decades and currently accounts for approximately 5–30% of all primary hepatic malignancies.[4,5] Of note, the age-adjusted incidence of ICC increased by 165% from the 1970s to the 1990s in the United States alone.[6] In turn, the rise in disease incidence has led to the gradual recognition of ICC as a distinct entity from hepatocellular carcinoma (HCC) with a different pathogenesis and natural history. To this end, an independent ICC staging system was first proposed in 1997 by the Liver Cancer Study Group of Japan (LCSGJ).[7] Subsequently, in 2010, the 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging manual became the first AJCC/UICC staging schema to address ICC separately from HCC.[8] More recently, the staging for ICC was revised in the 8th edition of the AJCC/UICC manual.[9] While the LCSGJ and AJCC/UICC staging systems were important steps to stage ICC patients, both suffer from relatively poor discriminatory ability.[10–12] The overreliance of classification systems on tumor-related morphometric factors, rather than quantifiable indicators of tumor biology, may in part account for the limited discriminatory ability of these prognostic schemas.[13]

The AJCC/UICC has begun to incorporate quantifiable tumor markers into the traditional TNM staging schema for some tumors. For example, AJCC/UICC staging of testicular cancer now includes measurements of alpha-fetoprotein (AFP), beta human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH), which has resulted in increased prognostic discrimination.[8] Similarly, in colon cancer, the AJCC/UICC has proposed the inclusion of pretreatment serum carcinoembryonic antigen (CEA) levels (C-stage) into the conventional TNM staging system as CEA improved prognostic stratification after surgery.[14] For ICC, CA 19-9 may have prognostic utility independent from tumor morphologic characteristics and nodal metastases.[15–18] Similarly, CEA has been reported to have prognostic implications for patients with ICC.[16] The optimal prognostic cut-off values for CA 19-9 and CEA in ICC have yet to be identified, with most previous studies being limited by small sample size. In addition, the relative value of incorporating either CA 19-9 or CEA into the traditional AJCC/UICC staging of ICC has not been examined. As such, the objective of the current study was to define optimal cut-off values for CA 19-9 and CEA, as well as investigate whether the addition of these biomarkers into the AJCC/UICC 8th edition and LCSGJ classification schemas increase prognostic discrimination of patients with ICC.

Methods

Patients and definitions

Patients who underwent liver surgery for histologically confirmed ICC between January 1, 1990, and July 1, 2016 at one of the 16 participating tertiary-care hepatobiliary centers in North America (Cleveland Clinic Foundation, Cleveland, Ohio; The Ohio State University, Columbus, Ohio; Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia and Ottawa General Hospital, Ottawa, Canada), Asia (Eastern Hepatobiliary Surgery Hospital, Shanghai, China and Yokohama City University, Yokohama, Japan), Oceania (Royal Prince Alfred Hospital, Sydney, Australia) and Europe (Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; San Raffaele Hospital, Milan, Italy; Erasmus University Medical Centre Rotterdam, Rotterdam, the Netherlands and University of Verona, Verona, Italy) were identified. Patients who underwent macroscopically incomplete resection (R2) or patients with concurrent extrahepatic disease at the time of hepatectomy were excluded from the study. In addition, patients who had no information on CA 19-9 were excluded. The respective institutional review boards from each hospital approved the study.

For each patient, data collected included preoperative CA 19-9 (normal range, 0–37 IU/mL) and CEA (normal range, 0–5 ng/mL) levels, as well as demographic (age, sex and region) and clinicopathologic information (tumor size, histologic grade, performance of lymphadenectomy, presence of nodal metastases, margin status and presence of vascular and/or perineural invasion).

Determination of optimal cut-off levels for preoperative CA 19-9 and CEA

The optimal prognostic cut-off levels for preoperative serum CA 19-9 and CEA were determined using iterative multivariable models of overall survival (OS). Specifically, various cut-off values for CA 19-9 and CEA [ranging from 20 to 1000 IU/mL and 3–15 ng/mL for CA19-9 and CEA, respectively] were employed. The multivariable models adjusted for other relevant demographic and clinicopathologic factors, such as age, sex, tumor size, tumor number (solitary vs multifocal), vascular invasion, tumor differentiation, and lymph node (LN) status. The Hazard Ratios (HRs) derived from the multivariable models for each cut-off value of CA 19-9 and CEA were plotted and assessed. The value that corresponded to the "steepest" shift in the slope of the graph was selected as the optimal cut-off value.

Statistical analysis

Summary statistics were reported as frequencies with percentages or median values using interquartile ranges (IQR). Differences between categorical values were estimated using the chi-squared

Please cite this article in press as: Sasaki K, et al., Serum tumor markers enhance the predictive power of the AJCC and LCSGJ staging systems in resectable intrahepatic cholangiocarcinoma, HPB (2018), https://doi.org/10.1016/j.hpb.2018.04.005