March 31st, 2018

Re: 2017-2018 Kenneth W. Warren Fellowship Progress Report #1

Dear IHPBA Research Committee,

I would like to express my gratitude to the IHPBA Research Committee for awarding me the 2017-2018 Kenneth Warren Fellowship. This grant supports my study entitled “Patterns of Gene Mutations in Biliary Tract Cancers” under the mentorship of Dr. Timothy M. Pawlik at the Ohio State University.

Liver and bile duct cancers are an emerging global health problem with more than 50,000 expected new cases and about 35,000 estimated deaths in the United States in 2018.[1] For biliary tract cancers (BTCs), including gallbladder cancer (GBC), intra- (ICC) and extra-hepatic (EHCC) cholangiocarcinoma. While surgical resection remains the only potentially curative treatment, 5-year overall survival (OS) results only 20-30% after curative-intent surgery. Moreover, while several clinical-pathological variables have been associated with prognosis, optimal staging schemes for BTCs have not been identified resulting in a poor ability to predict the prognosis of the BTCs patients after surgery.[2]

Jusakul et al. performed an integrative clustering analysis defining four distinct groups of cholangiocarcinoma (CCA): Clusters-1/2 with characterized by *TP53* and *ARID1A* mutations as well as poor prognosis and Clusters-3/4 mostly Fluke-Negative CCAs that exhibited high *IDH1/2*, *BAP1* mutations.[3] Furthermore, Farshidfar et al. reported the Cancer Genome Atlas (TCGA) analysis of 38 CCA samples and noted four distinct clusters identified using analyses on multiple platforms.[4] The clusters identified in the two analyses presented strong correlations and might increase the prognostic staging of BTCs patients undergoing surgery.

In a preliminary analysis, we used a cohort of 105 patients who underwent curative-intent surgery for BTCs (53% PHCC, 33% ICC, and 14% GBC). We classified patients based on gene mutation profiles according to recent data of literature regarding mutation profile analysis. A total of 23 patients with mutations of *IDH1/2*, *BAP1*, and *PBRM1* genes and 49 patients with mutations of *KRAS*, *NRAS*, *TP53*, and *ARID1A* genes were identified. Importantly, this classification based on gene mutation profiles (*PBRM1/IDH1/BAP1* vs. *KRAS/TP53*) was strongly associated with survival in a multivariable analysis adjusted for margin status, tumor grade, T, and N stages (Figure 1).

Based on these preliminary findings, we aim to increase the sample size to confirm the prognostic role of the two gene mutation profiles and to investigate the genetic mutations status of patients without *PBRM1/IDH1/BAP1* and *KRAS/TP53* mutations.

Thank you for your support, and I look forward to presenting the completed study at the 2020 IHPBA meeting in Melbourne, Australia.

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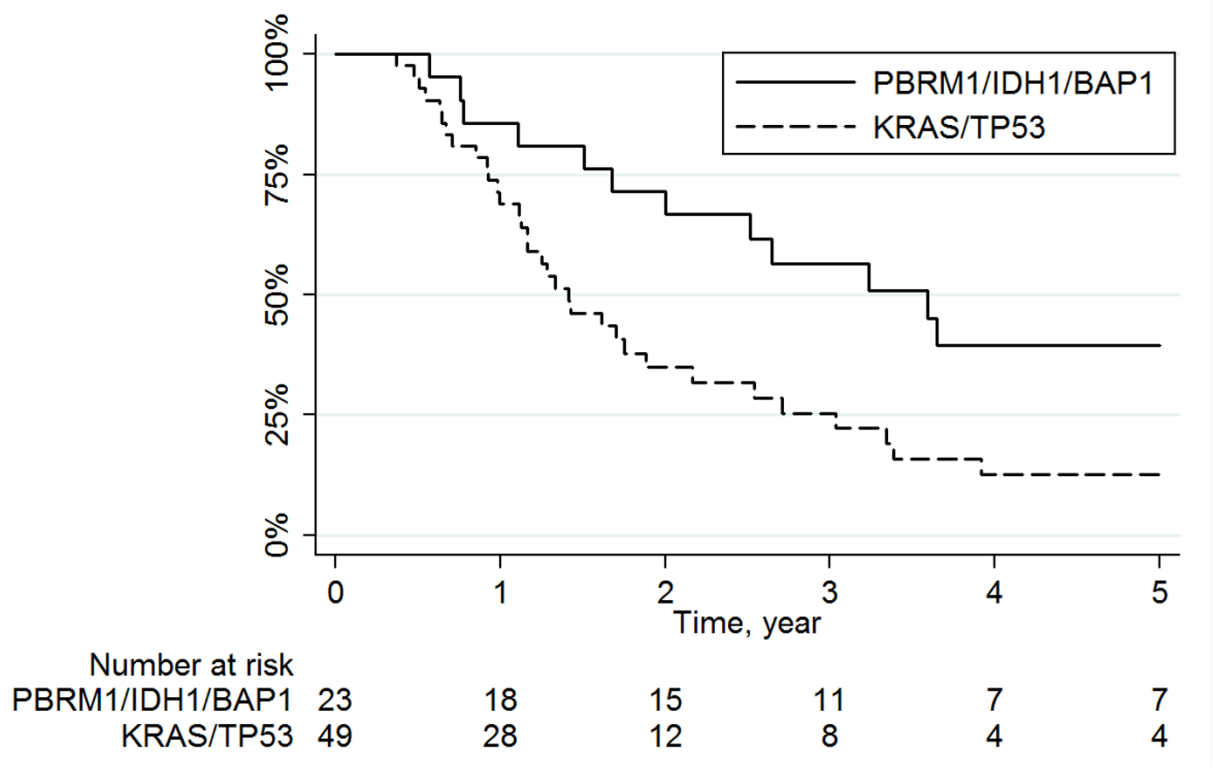
Figure 1. Kaplan-Meier Curve Comparing the Overall Survival of Patients Undergoing Curative-Intent Surgery for Biliary Tract Cancers Stratified by the Gene Mutation Profiles (IDH1/2, BAP1, PBRM1 mutated genes vs. KRAS, NRAS, TP53, and ARID1A mutated genes).



References

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