

March 11, 2019

Re: 2018-2019 Kenneth W. Warren Fellowship Progress Report #1

Dear IHPBA Research Committee,

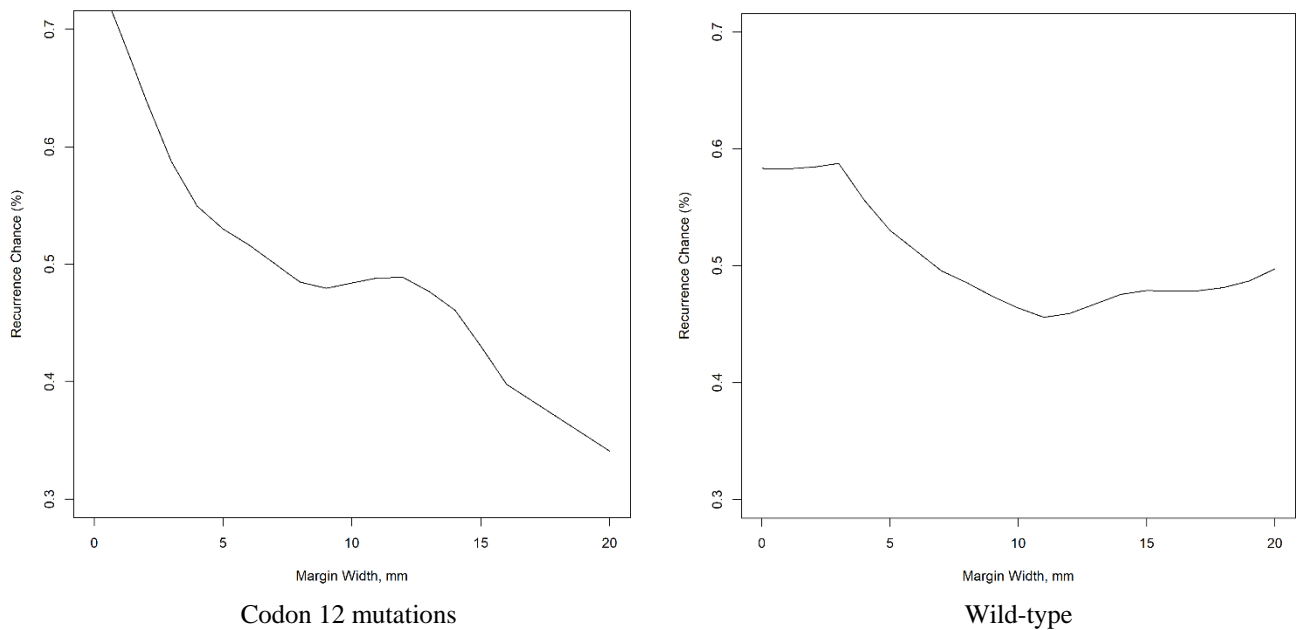
I would like to express my gratitude to the IHPBA Research Committee for awarding me the 2018-2019 Kenneth Warren Fellowship. This grant supports my study entitled “Genetic information to address two current challenges in colorectal cancer liver metastases surgery: a multi-institutional effort” under the mentorship of Dr. Martin E. Kreis, Chair of the Department of Surgery and Professor of Surgery at the University of Berlin – Charité Campus Benjamin Franklin and Dr. Matthew J. Weiss, Associate Professor of Surgery and Oncology and Surgical Director of the Liver Cancer Multidisciplinary Clinic at the Johns Hopkins University.

An R0 resection is thought to constitute a necessary precondition for achieving very long-term survival (i.e. 10-year survival) among patients with colorectal cancer liver metastasis (CRLM). This hypothesis is supported by a hallmark study by Tomlinson et al and a study from our group that, in spite of employing distinct statistical methodologies and patient cohorts, concurred on the central importance of negative margins for favorable long-term outcomes.^{1,2} While these findings give grounds for optimism as the surgical margin can be directly influenced by operative skill, the optimal margin width that would provide the maximal survival advantage for patients with CRLM remains controversial. Given the risk for postoperative complications, such as liver failure, with extensive resections and the recent trend in favor of parenchymal sparing hepatectomy whenever feasible (so that a re-resection can be performed in case of recurrence), it is necessary that the association of margin width with survival should be fully clarified, before resection extent can be appropriately optimized.

Neoplastic growth patterns that are, in turn, dictated by underlying tumor biology have long been thought to determine the effect of margin width on patient survival. On the basis of this hypothesis, recent studies have assessed the impact of KRAS mutational status, a widely-employed surrogate of tumor biology, on the prognostic implications of margin width.^{3,4} While the authors of these reports concur on the possible importance of KRAS mutational status as a guide to resection extent, their specific findings and conclusions are conflicting. In turn, this might stem from the fact that the aforementioned studies treated KRAS mutational status as a binary variable (yes or no), while it is known that codon-specific KRAS mutations may be associated with distinct tumor biology and long-term outcomes.⁵

In an attempt to transcend this limitation and reconcile previous discordant findings, we assembled an international, multi-institutional cohort of patients with surgically resected CRLM that was sufficiently large to allow for different KRAS codon mutations to be analyzed separately, without negating statistical power. A new analysis was employed to formally ascertain the margin widths associated with maximal survival (optimal margin widths) in patients with wild-type KRAS lesions and different codon-specific mutations, respectively. Specifically, B-splines were fitted to account for non-linearity of the margin distance. Knots after which no improvement in survival was observed were compared across mutational groups. All analyses were performed using SPSS 24.0 (IBM, New York) and the `bs`, `rms` and `mice` packages for R 3.3.4 (<https://cran.r-project.org/>). All tests were 2-sided and $p < 0.05$ defined statistical significance. We present herein some preliminary results of a cohort of >1000 patients with known KRAS mutational status. This cohort will further expand thanks to more tertiary centers joining this international, multi-institutional effort. For example, Erasmus University of Rotterdam has joined this collaboration and we expect to increase the size of our dataset at least

by 50%. According to our preliminary results, a 11mm margin is enough to minimize chance of recurrence for wild-type tumors. Interestingly, this is consistent with a very recent meta-analysis of the long-term outcomes in >11000 patients with CRLM which reported that a margin >1 cm may result in even better oncologic outcomes and should be considered if possible.⁶ Although the KRAS mutational status was not considered in that analysis, wild-type tumors are the majority and in turn may drive outcomes to their direction. In contrast, plots for codon 12 KRAS mutations differed according to our preliminary analysis (Figure). Our findings may confirm the hypothesis that different tumor biology may mandate distinct surgical management thus potentially contributing to the individualized treatment of patients with CRLM.



References

1. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25:4575-4580.

2. Margonis GA, Buettner S, Andreatos N, et al. Prognostic Factors Change Over Time After Hepatectomy for Colorectal Liver Metastases: A Multi-institutional, International Analysis of 1099 Patients. *Annals of surgery*. 2018.
3. Brudvik KW, Mise Y, Chung MH, et al. RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases. *Annals of surgical oncology*. 2016;23:2635-2643.
4. Margonis GA, Sasaki K, Andreatos N, et al. KRAS Mutation Status Dictates Optimal Surgical Margin Width in Patients Undergoing Resection of Colorectal Liver Metastases. *Annals of surgical oncology*. 2017;24:264-271.
5. Margonis GA, Kim Y, Spolverato G, et al. Association Between Specific Mutations in KRAS Codon 12 and Colorectal Liver Metastasis. *JAMA surgery*. 2015;150:722-729.
6. Margonis GA, Sergentanis TN, Ntanasis-Stathopoulos I, et al. Impact of Surgical Margin Width on Recurrence and Overall Survival Following R0 Hepatic Resection of Colorectal Metastases: A Systematic Review and Meta-analysis. *Annals of surgery*. 2018;267:1047-1055.

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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