Ann Surg Oncol (2023) 30:3182–3183
https://doi.org/10.1245/s10434-023-13343-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – HEPATOBILIARY TUMORS

Modeling the Prediction of Early Treatment Failure After Hepatectomy for Colorectal Liver Metastases

Seth Concors, MD, Antony Haddad, MD, and Jean Nicolas Vauthey, MD

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Nearly two thirds of patients experience recurrence 5 years after hepatectomy for colorectal liver metastases (CLM), and more than 30 % have recurrence within the first year after resection.[1] Recurrence within the first year after hepatectomy is associated with worse survival for patients with CLM.[2] Two decades ago, Fong et al.[3] published a clinical score to predict recurrence after hepatectomy for CLM based on primary tumor node positivity, disease-free interval, metastatic tumor size and number, disease-free interval, and carcinoembryonic antigen (CEA) level. Our understanding of recurrence risk in CLM has subsequently evolved and is informed by tumor biology. A decade ago, our group demonstrated RAS mutational status to be a dominant risk factor for recurrence and survival among patients with CLM.[4] In fact, RAS/TP53 co-mutation is the only factor associated with recurrence-free survival 2 years after hepatic resection.[5]

Recently, Berardi and colleagues[6] proposed a nomogram based on clinical variables that would predict the risk of early recurrence after upfront resection of CLM. In their manuscript, Berardi et al.[6] present a nomogram to predict treatment failure after upfront surgery for CLM based on a cohort of 783 patients who underwent surgery at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1991 and 2019. Of 3085 patients who underwent hepatectomy for CLM, 1008 had upfront surgery. Of these 1008 patients, 225 did not receive adjuvant chemotherapy for unknown reasons. The majority of the 783 patients (57 %) in the final cohort presented with metachronous disease, and 49 % of these patients received adjuvant chemotherapy after primary tumor resection. After curative intent hepatectomy, 28 % of the patients had recurrence within the first year, which the authors defined as treatment failure. Whereas 32 % of the patients presented with liver-only recurrences, 68 % had recurrence in other organs with or without liver involvement. The population was split into a training cohort (n = 535) and a validation cohort (n = 248). Based on historical data, the patients who had more than a 40 % probability of failure according to the nomogram were considered as high risk, and the patients who had a probability of less than 40 % were considered low risk. The 2-year overall survival was compared between the two groups and found to be 70 % for the high-risk patients and 82 % for the low-risk patients.

The nomogram presented by the authors successfully predicts the risk of treatment failure, but the utility and generalizability of their model is limited by patient selection and heterogeneity. Although the cohort was substantial, the patients constituted a subset of the patients who underwent resection for CLM (783 of 3008) at MSKCC during a 20-year period. This cohort of 783 patients was heterogeneous and did not stratify by several factors. The choice of operative approach including addition of ablation, one- versus two-stage approach, or adjuvant hepatic artery infusion (HAI) pump placement was not clearly defined. The extent and use of combined resection and ablation was not included in the multivariate model despite its effect on recurrence-free survival.[7] It is likely that the two-stage hepatectomy patients who were excluded from the final cohort and at high risk of treatment failure were the most likely to receive perioperative chemotherapy. Clarifying their treatment selection algorithm would allow for greater generalizability. Moreover, the inclusion of patients who received HAI (n = 222, 28 %)

First Received: 9 January 2023
Accepted: 27 February 2023
Published Online: 23 March 2023

J. N. Vauthey, MD
e-mail: jvauthey@mdanderson.org

may have decreased the incidence of early hepatic recurrence in the highest-risk cohort. The MSKCC group has previously demonstrated 1-year improvements in the cumulative incidence of intrahepatic recurrence for HAI with systemic therapy versus systemic therapy alone (11.2 % vs 24.4 %), without evidence of longer-term benefit on extrahepatic recurrence (64.2 % vs. 63.4 %).[8] Finally, tumor mutational profile, a key stratification factor, was not included in the model. Findings have shown that RAS mutation status, which is widely available, affects survival of patients with tumors of similar size and number.[9]

It also is important to note that long-term outcomes after treatment failure differ by site of recurrence. The management and survival of patients with isolated single-site recurrence, particularly hepatic recurrence, is quite different from those of patients with multiple areas of recurrence.[2, 10] For instance, 5-year overall survival (OS) is reported to be 64.3 % (median, 6.9 years) for patients who have repeat resection of isolated hepatic recurrence. Clearly delineating the site of recurrence enhances our understanding of local or distant failure, thereby allowing for specific analysis of the effect of treatment methods.

We congratulate Berardi et al.[6] for their nomogram, which provides a model to stratify patients after upfront surgery who are at high risk of early recurrence. Identifying patients at highest risk of early intrahepatic and distant failure is critically important and warrants ongoing study. However, when using clinical risk scores and nomograms, the underlying patient populations and treatment pathways must be clearly delineated to understand the applicability of proposed models.

DISCLOUSURE There are no conflicts of interest.

REFERENCES

1. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg*. 2009;250:440–8.
2. Tan MC, Butte JM, Gonen M, et al. Prognostic significance of early recurrence: a conditional survival analysis in patients with resected colorectal liver metastasis. *HPB Oxford*. 2013;15:803–13.
3. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230:309–18.
4. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann Surg*. 2013;258:619–26.
5. Kawaguchi Y, Lillemoe HA, Panettieri E, et al. Conditional recurrence-free survival after resection of colorectal liver metastases: persistent deleterious association with RAS and TP53 co-mutation. *J Am Coll Surg*. 2019;229(286–294):e281.
6. Berardi G, Chou J, Gonen M, et al. A model to predict treatment failure in patients undergoing upfront surgery for resectable colorectal liver metastases. *Ann Surg Oncol*. 2023. https://doi.org/10.1245/s10434-023-13113-2.
7. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239(6):818–25.
8. Srouji RM, Narayan RR, Boerner T, et al. Extrahepatic recurrence rates in patients receiving adjuvant hepatic artery infusion and systemic chemotherapy after complete resection of colorectal liver metastases. *J Surg Oncol*. 2020;122:1536–42.
9. Kawaguchi Y, Kopetz S, Tran Cao HS, et al. Contour prognostic model for predicting survival after resection of colorectal liver metastases: development and multicentre validation study using largest diameter and number of metastases with RAS mutation status. *Br J Surg*. 2021;108:968–75.
10. Panettieri E, Kim BJ, Kawaguchi Y, et al. Survival by number and sites of resections of recurrence after first curative resection of colorectal liver metastases. *J Gastrointest Surg*. 2022;26:2503–11.