Editorial

Association between the lymph node ratio and hepatic tumor burden: importance for resectable colorectal liver metastases?

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Ahmad A, Reha J, Saied A, *et al.* Association of primary tumor lymph node ratio with burden of liver metastases and survival in stage IV colorectal cancer. Hepatobiliary Surg Nutr 2017;6:154-61.

Submitted Feb 02, 2018. Accepted for publication Feb 26, 2018.
doi: 10.21037/hbsn.2018.03.02
View this article at: http://dx.doi.org/10.21037/hbsn.2018.03.02

Prognosis in patients with stage IV colorectal cancer (CRC) and liver-only metastases is first and foremost determined by resectability of the liver metastasis (as well as the primary disease), which can usually be entertained in about 20% (1). However, within the resected group of patients, there is a wide variability in outcome, related to a number of factors. Thus, identification of reliable prognostic factors that may aid in decision-making and treatment choice is welcomed. Recently, in this Journal (2), Ahmad and colleagues reported an association with primary tumor lymph node ratio (LNR) and intrahepatic tumor burden in patients with stage IV CRC and resectable liver metastasis. Notably, patients with a high LNR and greater liver tumor burden also did worse in overall survival analysis (2). The study has several limitations as addressed by the authors, including a small sample size, including patients which had neoadjuvant (radio)chemotherapy (which may influence the post-radiochemotherapy nodal status; ypN) and including patients with extrahepatic disease. Thus, the true association between the LNR and the hepatic tumor burden may be difficult to confirm per se. Still, however, the study addresses a number of interesting questions.

Presence of lymph node metastasis (pN+) remains among the strongest prognosticators for long-term outcome in CRC, despite its debated role and controversies (3,4). In primary CRC, the lymph nodes have been investigated in relation to their total numbers, the quality of lymphadenectomy, their role as "sentinels", and by using metrics including the log odds or the ratio of positive-to-number of harvested nodes (LNR) in outcome prediction. In resectable colorectal liver metastasis there is consensus that the primary tumor lymph node status is associated with outcome, both before and after the introduction of modern chemotherapy (5,6).

In patients with resectable colorectal liver metastases, reports have identified subgroups of patients with good prognostic factors (e.g., lymph node negative disease, RAS wild type and metastases less than 5 cm in diameter) with 5-year survival rates after hepatectomy exceeding 75% (5). Interestingly, this is higher than the expected 5-year survival in unselected patients with stage IIIB CRC (Colorectal Cancer Facts & Figures 2016, American Cancer Society) and also in contrast to the overall 5-year survival in the total group of patients with stage IV CRC, reported at a mere 10–15%. The discrepancy in overall survival figures illustrate the challenge and heterogeneity of stage IV disease and, thus, the challenge in estimating prognosis in this group of patients.

A number of factors have been proposed to predict prognosis in stage IV CRC. With the introduction of modern effective chemotherapy regimens (such as oxaliplatin or irinotecan based ± monoclonal antibody), traditional prognostic factors (including pN+ status, number and size of metastasis) may become less important and their practical use more complicated. In patients with

metachronous metastases, the timeframe from adjuvant chemotherapy for the primary to emergence of metastasis is likely a relevant factor. In patients with synchronous metastases, response to neoadjuvant chemotherapy could be of greater importance than the total number of metastases or the size of the largest metastasis. Neoadjuvant chemotherapy has been associated with a reduction of the absolute number of retrieved nodes and may affect the LNR (4,7). This may be particularly important in rectal cancer (representing up to 60% of patients with stage IV disease) that undergo concomitant radiochemotherapy, after which lymph node metastasis (or, clinically suspected metastatic nodes, cN+) may be "sterilized" in patients with response to therapy (thus, presenting as, ypN0). Furthermore, a recent study suggests prognostic factors may change over time after the hepatectomy. Biology related factors may be main drivers of early prognosis, while surgically related factors gain significance in a longer time-frame (8).

The primary tumor LNR, defined by the number of positive lymph nodes divided by the total number of retrieved nodes, has been proposed as an alternative to the conventional lymph node status. LNR showed superiority to other factors in predicting oncologic outcome in patients undergoing surgery and chemotherapy for CRC, at different TNM stages (9-11). The LNR has been suggested to overcome the dependence of the number of harvested nodes, a limitation of the conventional lymph node status. A standard lymphadenectomy should include harvested 12 nodes in CRC. It is interesting to note that the proposed cut-off of LNR at 0.25 in Ahmad's paper in the Journal would match with a pN1 status (three metastatic nodes) in the 8th edition of the AJCC staging, in a patient with 12 nodes harvested (3/12=0.25).

There could be certain limitations with the use of the LNR. With the concept of sentinel lymph nodes, you may expect the majority of metastatic lymph nodes to be located in the mesentery within a short proximity of the tumor. If that is the case, the LNR could be a surrogate marker of poor surgery: few total lymph nodes, dissection not following anatomical planes and a potentially higher risk of tumor at the resection margin. On the other hand, the clinical importance of an extensive harvesting of lymph nodes is undergoing debate. Extended surgery and focused pathological examinations are not practiced similarly and an increased risk of complications are measured against the potential and unsure survival and staging benefit of removing metastatic lymph nodes. Another challenge with the LNR may be to identify a common cut-off value. It is likely this could be different from each cohort of patients with resectable stage IV CRC. Thus, validation of any given value becomes increasingly important in order to generalize results beyond the initial cohort and make robust predictions available.

In the study by Ahmad *et al.*, the majority of patients had resectable metastatic disease, and was overrepresented in the group with a low LNR. When determining the independence of a prognostic factor in patients with stage IV CRC, it may be problematic to pool patients with resectable and unresectable disease. It is likely that being unresectable and not having a resection performed are the two main drivers of poor prognosis and will skew the significance of any other factor included in analysis. One example could be the association between survival and *RAS* mutations which, irrespective of treatment targeting the epidermal growth factor receptor, has been found to be of stronger influence on survival in patients with resectable liver metastases than in patients with unresectable stage IV CRC (12). Less important factors may gain significance in the absence of major disease drivers and this could be similar for studies on the implication of lymph node status in stage IV CRC.

Ahmad and colleagues used the presence of bilateral disease and more than three liver metastases as a measurement of tumor burden in the liver. To our knowledge, no correlation has been observed between the number of metastases and the size of the largest metastasis or distribution of metastases and, thus, this estimate of tumor burden may be unprecise. For example, the volume of three subcentimeter metastases would be less than the volume of one metastases measuring 3 cm in diameter. Another study recently combined size and numbers of liver metastases to create a tumor burden score associated with survival after hepatectomy (13). Nevertheless, Ahmad and colleagues interestingly showed an association between a high LNR and bilateral liver metastases and more than three liver metastases. The correlation is intriguing and begs the question whether the tumor load found in the lymph nodes is directly correlated to the tumor load in the liver? And if so, what makes pN0 *vs.* pN+ different in terms of molecular biology, drivers of progression and growth rate except for a larger number of tumor volume? Clearly, these questions cannot be addressed in the current study and would need further research to pursue new answers and directions for this subtype of patients with stage IV disease.

There has been increasing interest in the field of immune oncology and the tumor microenvironment. The latter may contribute with genomic and epigenomic aberrations

to enhance the survival of malignant cells. The immune landscape has been investigated in colorectal primaries and its liver metastases (14). The microenvironment within the metastatic lymph nodes may be interesting with respect to survival of metastatic cells and also concepts such as tumor immune escape (15). The adverse outcome observed in patients with lymph node metastases are undoubtedly related to adverse biology, but lymph node related anti-tumor immunological effects may also play a role in this.

Taken together, better understanding of the tumor phenotype in patients with lymph node disease is needed. Further, how this reflects on liver tumor burden is an intriguing biological question that needs new answers. The extent of lymph node involvement (the LNR) may be correlated to the extent of liver involvement and represent both a prognostic indicator as well as a mirror into aggressive tumor behavior. Currently, it is not clear if this association represents a true indicator of outcome or simply mirrors the overall tumor burden in a given patient. Our efforts to better understand biological drivers of outcome are essential. Improved molecular and immunological understanding of the primary tumor and the metastatic processes in CRC may help to tailor selection and personalize the available treatment strategies.

Acknowledgements

None.

Footnote

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

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Cite this article as: Brudvik KW, Søreide K. Association between the lymph node ratio and hepatic tumor burden: importance for resectable colorectal liver metastases? HepatoBiliary Surg Nutr 2018;7(3):206-208. doi: 10.21037/hbsn.2018.03.02

