Primary lymph node ratio and hepatic resection for colorectal metastases

Daniel Ansari, William Torén, Roland Andersson

Colorectal cancer (CRC) is a leading cause of death worldwide (1). The liver is the most common site for distant metastases, and approximately 50% of patients diagnosed with CRC develop hepatic metastases during the course of their disease (2). Improvements in surgical techniques, anesthesia and multimodal treatment regimens (e.g., neoadjuvant chemotherapy and portal vein embolization) have expanded the indications for liver resection (3). Hepatic resection is nowadays offered to patients previously deemed unresectable, such as those with multiple or bilobar metastases, extrahepatic disease and recurrent tumors. The 5-year overall survival rate after resection for CRC liver metastases is close to 60% at specialty units, with low perioperative morbidity and mortality (4,5).

Over the years, many prognostic scoring systems have been developed to risk stratify patients with CRC liver metastases in order optimize clinical management (6). Detailed histopathological analysis of the primary tumor is worthwhile, as it may assist in prognostic assessment of CRC patients with liver metastases (7). However, no scoring system has been sufficiently validated. Still, the tumor, node, and metastasis (TNM) classification is the gold standard to estimate prognosis and guide treatment decisions in routine clinical practice.

The N-stage of the primary tumor has been reported to be a strong prognostic factor in patients with CRC liver metastases, but the data remain inconclusive (6,7). Lymph node ratio (LNR, positive lymph nodes/examined lymph nodes) has been introduced in the hope that it may provide more comprehensive information. The definition of N-stage is affected by the extent of lymph node dissection by the surgeon and the node retrieval by the pathologist. LNR may overcome some of these limitations. However, optimal cut-off levels for LNR are debatable.

In a previous issue of Hepatobiliary Surgery and Nutrition, Ahmad et al. (8) report a clear association between primary LNR and the extent of hepatic tumor burden and survival in CRC patients. High-LNR (>0.25) was correlated with the number of liver metastases as well as bilobar disease. Furthermore, high-LNR was associated with decreased survival in patients undergoing hepatic resection.

Is CRC spread to lymph nodes a prerequisite for metastatic dissemination to the liver? Recent molecular phylogenetic analyses have shed new light on this topic (9). It was reported that lymph node and hepatic metastases have distinct origins in about 2/3 of cases, indicating that hepatic metastases can be generated independent of cancer cell deposits in the lymph node, likely by the hematogenous route (portal vein). Only about 1/3 of cases of lymph and liver metastases were reported to share a common origin.

What is then the mechanism behind the associations between lymph node involvement and hepatic tumor burden and survival seen in the study presented by Ahmad et al.? A theory is that metastatic dissemination to lymph nodes occurs early during tumor evolution and that seeding to distant locations requires genetic properties attained...
later in the tumor evolution. This would explain why the metastatic lesions found in lymph nodes and distant locations are genetically diverse. In the minority of cases where the lesions seemed to have a common origin, the primary tumor may stochastically have acquired a genetic setup allowing dissemination to both niches.

Clearly, more research is mandated in order to understand the metastatic cascade in CRC and molecular features of primary, lymphatic and distant metastatic lesions. Further knowledge in this area may ultimately lead to more precise methods for prediction, prevention and treatment of metastatic disease.

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Footnote

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References