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Hepatic vascular inflow occlusion is associated with reduced disease free survival following resection of colorectal liver metastases

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Abstract

Background: Hepatic vascular inflow occlusion (VIO) can be applied during resection of colorectal liver metastases (CRLM) to control intra-operative blood loss, but has been linked to accelerated growth of micrometastases in experimental models. This study aimed to investigate the effects of hepatic VIO on disease-free and overall survival (DFS and OS) in patients following resection for CRLM.
Methods: All patients who underwent liver resection for CRLM between January 2006 and September 2015 at our center were analyzed. Hepatic VIO was performed if deemed indicated by the operating surgeon and severe ischemia was defined as ≥20 min continuous or ≥45 min cumulative intermittent VIO. Cox regression analysis was performed to identify predictive factors for DFS and OS.
Results: A total of 208 patients underwent liver resection for CRLM. VIO was performed in 64 procedures (31%), and fulfilled the definition of severe ischemia in 40 patients. Patients with severe ischemia had inferior DFS (5-year DFS 32% vs. 11%, $P < 0.01$), and inferior OS (5-year OS 37% vs. 64%, $P < 0.01$). At multivariate analysis, a high clinical risk score (Hazard ratio (HR) 1.60 (1.08–2.36)) and severe ischemia (HR 1.89 (1.21–2.97)) were independent predictors of worse DFS. Severe ischemia was not an independent predictor of OS.
Conclusion: The present cohort study suggests that prolonged hepatic VIO during liver resection for CRLM was associated with reduced DFS. A patient-tailored approach seems advisable although larger studies should confirm these findings.

Keywords: Vascular inflow occlusion; Liver resection; Colorectal liver metastases; Disease-free survival

Introduction

Surgical indications for resection of CRLM have been extended during the last decades.[1] Limitations regarding number, size and localization of CRLM have been replaced by one main criterion, namely sufficient future remnant liver volume and function.[2] Surgery for CRLM has increasingly become part of a multimodality approach, including downstaging systemic therapy, local ablation modalities and treatment of limited extrahepatic metastases.[1,3]

The extended indications and extended resections within a multimodality approach have increased the risks of postoperative morbidity.[4] Intra-operative blood loss has mainly been associated with compromised clinical outcomes[5] and reduced survival,[6] and therefore, vascular inflow occlusion (VIO, or Pringle maneuver) is frequently used during parenchymal transection to reduce blood loss[7,8] VIO, however, inevitably leads to temporary ischemia of the liver parenchyma. Although most livers can tolerate up to 120 min of (intermittent) ischemia, subsequent reperfusion induces hepatic ischemia/reperfusion (IR) injury of which the impact is correlated with the duration of ischemia.[9]

Hepatic IR is characterized by the formation of reactive oxygen species and inflammation causing hepatocellular necrosis, which can compromise postoperative function of

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the liver remnant.[10] Furthermore, hepatic IR has been shown to accelerate outgrowth of hepatic colorectal micro-metastasis up to 6-fold in animal models.[11–13] The clinical oncological impact of hepatic IR is still subject of debate. A recent systematic review reported no influence of VIO on overall survival (OS) following resection of CRLM.[14] The impact of VIO on disease free survival (DFS) is less well established with contradictory findings in literature.[15,16] While some confirmed the preclinical finding of increased recurrence with application of VIO,[16] others found a protective effect of VIO on recurrence.[15] This study aimed to investigate the effects of hepatic VIO during resection of CRLM on DFS and OS.

Methods

Patients

All consecutive patients who underwent liver resection with curative intent for CRLM between January 2006 and September 2015 at the Academic Medical Center, Amsterdam, The Netherlands, were included. Data were retrospectively collected from prospective data registrations. The institutional medical ethics committee was consulted and the need for ethics approval and individual informed consent was waived.

Preoperative evaluation

Standard preoperative work-up included computed tomography (CT) of the abdomen and chest as well as measurement of plasma carcinoembryonic antigen (CEA) levels along with other routine blood tests. Magnetic resonance imaging (MRI) of the liver and positron emission tomography (PET) were selectively performed. All patients were discussed in a multidisciplinary meeting including surgeons, medical oncologists and radiologists.

Major liver resection was defined as resection of at least three Couinaud liver segments.[17] In the case of suspected major liver resection, future remnant liver (FRL) volume was routinely assessed by CT-volumetry, along with FRL function using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy.[2] When considered insufficient (FRL volume $<$ 25% and/or HBS $<$ 2.7%/min/m^2), portal vein embolization was performed prior to resection.

Surgery

Abdominal exploration and liver ultrasonography were performed in all cases to confirm tumor resectability and to evaluate the presence of extrahepatic disease. Parenchymal dissection of the liver was routinely done using the ultrasonic dissector (Cavitron Ultrasonic Aspirator, Valleylab, Boulder, CO, USA) and bipolar forceps. Minor liver resections and metastasectomies were performed laparoscopically since 2011 when considered feasible. Major liver resections were selectively performed using a laparoscopic approach since 2014; currently only as part of an ongoing randomized clinical trial comparing open and laparoscopic hemihepatectomy (clinicaltrials.gov identifier NCT01441856). Hepatic VIO was performed when deemed indicated by the operating surgeon in order to reduce intra-operative blood loss. Intermittent VIO using cycles of 20 min ischemia followed by 10 min of reperfusion was the preferred regimen.

Follow-up included hepatic ultrasonography or abdominal CT with imaging of the thorax (plane X-ray or CT) every 3–6 months during the first 2 years and every 6–12 months thereafter. CEA was measured every 3–6 months. Adjuvant chemotherapy is not part of standard treatment protocols and guidelines in the Netherlands, due to the absence of a benefit in OS.[18]

Study variables

Study variables included patient characteristics, CEA level before resection, primary tumor T and N stage, number of hepatic lesions, size of the largest lesion, synchronous or metachronous presentation of metastases and operative details. Severe ischemia was defined as $\geq$20 min continuous or $\geq$45 min cumulative intermittent ischemia, according to a previous report.[16] Considering that VIO is liberally applied even when blood loss is limited, severe ischemia was chosen as study variable and lesser durations of ischemia were defined as mild. Primary outcome parameters were DFS, defined as the time from liver resection until first recurrence or loss to follow-up, and OS, defined as the time between surgery for hepatic metastasis and death or loss to follow-up. Secondary outcome parameters included morbidity according to Clavien-Dindo classification, with at least grade IIIa defined as major complications,[19] mortality defined as death within 90 days after surgery, and intrahepatic recurrence. Survival was obtained via the national municipal personal records database.

Statistical analysis

DFS and OS were analyzed and visualized using Kaplan–Meier analysis. Differences in actuarial survival probabilities between relevant subgroups were analyzed using log-rank tests. Multivariate analysis of predictive factors for DFS and OS was performed using cox regression and repeated for hepatic recurrence only. Variables with a P-value below 0.20 at univariate analysis were included in the model, with backward selection. The clinical risk score according to Fong[20] was used for the purpose of multivariate analysis of prognostic factors instead of the separate criteria. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Chicago, IL).

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