Chemotherapy-Induced Splenic Volume Increase Is Independently Associated with Major Complications after Hepatic Resection for Metastatic Colorectal Cancer

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BACKGROUND: In patients with colorectal cancer liver metastases (CRCLM), chemotherapy-induced hepatic injury is associated with increased splenic volume, thrombocytopenia, and decreased long-term survival. The current study investigates the relationship between change in splenic volume after preoperative chemotherapy and development of postoperative complications.

STUDY DESIGN: The study group consisted of 80 patients who underwent resection of CRCLM; half received neoadjuvant chemotherapy for 6 months before resection ($n = 40$) and the other half did not ($n = 40$). The study group was compared with two control groups: a normal group composed of patients undergoing cholecystectomy for benign disease ($n = 40$) and a group of untreated, nonmetastatic colorectal cancer (CRC) patients ($n = 40$). Splenic volume was measured by CT/MRI volumetry. In the study group, the nontumoral liver was graded for steatosis and sinusoidal injury; operative and outcomes characteristics were also analyzed.

RESULTS: Before chemotherapy, CRCLM patients had normalized spleen volumes of 3.2 ± 1.1 mL/kg, significantly higher than normal (2.5 ± 0.8 mL/kg; $p < 0.001$) and nonmetastatic CRC (2.6 ± 1.3 mL/kg; $p < 0.05$) patients, with higher splenic volume after 6 months of chemotherapy (4.2 ± 1.7 mL/kg; $p < 0.01$). After chemotherapy, splenic volume increase was associated with any perioperative complication ($p < 0.01$) and major complications ($p < 0.05$). Patients with $\geq$39% splenic volume increase (maximal chi-square test) were significantly more likely to have major complications ($p < 0.01$). Spleen volume changes were not correlated with change in platelet count ($R^2 = 0.03$; $p = 0.301$).

CONCLUSIONS: In patients with CRCLM, the presence of liver metastases and chemotherapy are associated with higher splenic volume. Percent splenic volume increase after 6 months of chemotherapy can aid preoperative risk stratification, as it was an independent predictor of major postoperative complications. (J Am Coll Surg 2015;220:271−280. © 2015 by the American College of Surgeons)

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Abbreviations and Acronyms

BSA = body surface area
CRC = colorectal cancer
CRCLM = colorectal cancer liver metastases
NSV = normalized spleen volume

Hepatic resection is the only potentially curative treatment for colorectal cancer liver metastases (CRCLM),[1] but it is possible in <25% of patients.[2] Some patients with initially unresectable disease can benefit from conversion chemotherapy to downsize CRCLM, and at the same time maximize remnant liver volume. The use of neoadjuvant chemotherapy in patients with resectable disease before resection is controversial. Reported series of hepatic resection combined with systemic chemotherapy have demonstrated 5-year survival rates of 40% to 50%, and cure in approximately 20% of selected patients.[3-5] Although the largest prospective trial, by the European Organisation for Research and Treatment of Cancer Intergroup, demonstrated an improved 3-year progression-free survival rate with perioperative FOLFOX4 compared with surgery alone, there was no difference in 5-year overall survival.[6]

The controversy surrounding the use of neoadjuvant chemotherapy in patients with resectable CRCLM partially stems from reports of chemotherapy-related hepatotoxicity. Pathologic liver injury related to systemic chemotherapy includes steatosis, steatohepatitis, and sinusoidal dilation. In addition, this toxicity has been associated with increased perioperative morbidity in retrospective series and prospective trials.[6-9] In contrast, a study of 384 patients from the authors' institution showed no association between neoadjuvant chemotherapy, steatohepatitis, and early postoperative mortality and morbidity.[10] Oxaliplatin is associated with splenomegaly, which might be secondary to portal hypertension due to hepatic sinusoidal injury.[11-14] The implications of this phenomenon, however, are unclear. Although chemotherapy remains a part of the treatment strategy in CRCLM patients, prediction of associated liver injury and its sequelae are currently limited. Biologic correlates of liver toxicity are needed for improved risk stratification before surgery. To this end, the current study investigates whether an increase in splenic volume after chemotherapy is associated with pathologic liver injury and postoperative complications.

METHODS

Patients

The IRB at Memorial Sloan Kettering Cancer Center approved this study via a waiver of the Health Insurance Portability and Accountability Act. The prospectively maintained liver resection database from the hepatopancreatobiliary service was queried for all patients that underwent liver resection for CRCLM from April 2003 to March 2007. Of these 506 patients, 384 had sufficient non-neoplastic liver tissue for follow-up pathology assessment as part of a previously reported study.[10] From these 384 patients, 80 consecutive patients were chosen from the database to form the study group: 40 patients who received 6 months of neoadjuvant chemotherapy and 40 patients who received no chemotherapy before resection of CRCLM. Demographic, laboratory, histopathologic, operative, perioperative, and survival data were collected prospectively and analyzed retrospectively. Preoperative evaluation and surgical management at the institution have been described previously.[15] Neoadjuvant chemotherapy for resectable patients is not standard of care at our institution, minimizing selection bias in the study group. Splenic volumes were measured preoperatively in the no-chemotherapy group. In the chemotherapy group, splenic volumes were measured at baseline before chemotherapy and at approximately 3 months and 6 months (preoperative) after initiation of chemotherapy.

Two control groups were used to study potentially confounding factors relating to splenic volume. Forty patients either undergoing laparoscopic cholecystectomy for benign disease, or being followed for benign pancreatic cysts were identified from a prospectively maintained institutional database from June 2000 to January 2013 as a normal (no cancer) control group. A second control group composed of 40 patients with stage III untreated nonmetastatic colorectal cancer (CRC) was also formed. Scans from the initial assessment were used for spleen volume measurement. To investigate changes in spleen volume over time in normal patients, spleen volume was measured in patients followed for benign pancreatic cysts during a 5-year period. Review of the medical records of the patients in the control groups was undertaken to exclude patients with incidental disease or treatment that could potentially bias the study of spleen volume, including history of chemotherapy, splenic vessel abnormalities, previous or concurrent malignancy, autoimmune disease, primary blood dyscrasia, and/or systemic inflammatory disease.

Postoperative staging and follow-up

As reported previously,[10] in the CRCLM resection cohorts, hematoxylin and eosin–stained slides prepared from routinely processed liver tissue samples were reviewed by two pathologists blinded to the patients' treatment history and clinical outcomes. Steatosis of the resected specimen was graded based on the