# 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 ≥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

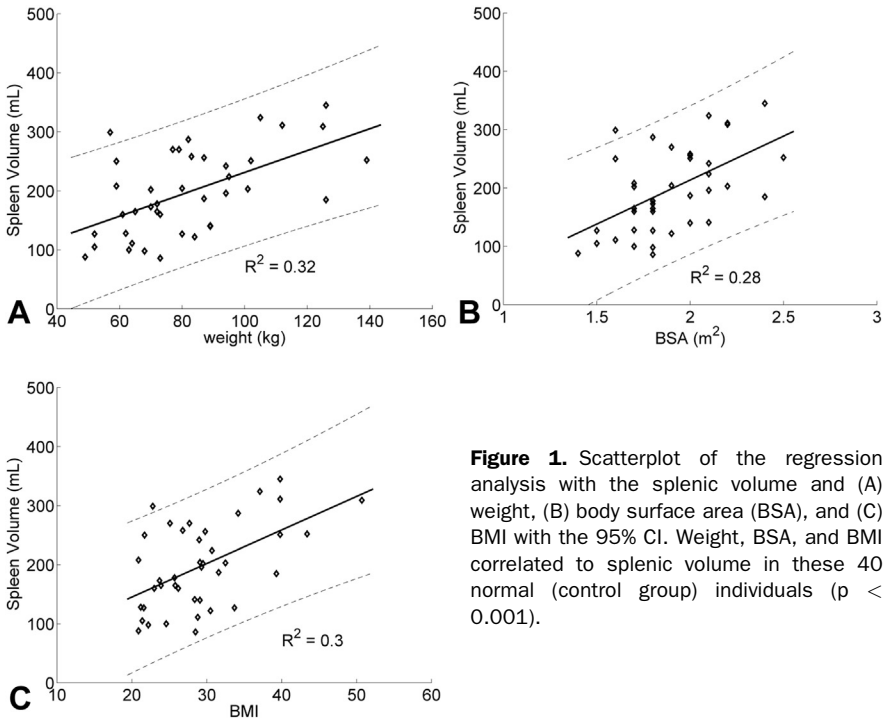


**Figure 1.** Scatterplot of the regression analysis with the splenic volume and (A) weight, (B) body surface area (BSA), and (C) BMI with the 95% CI. Weight, BSA, and BMI correlated to splenic volume in these 40 normal (control group) individuals ($p < 0.001$).

Kleiner-Brunt histologic scoring system; patients were considered to have steatosis if >5% of the examined parenchyma was involved.[16] Patients with a steatosis grade of ≥4 were considered to have steatohepatitis. Sinusoidal injury was scored in accordance with the Rubbia-Brandt grading system.[14] All patients with a score of ≥1 were considered to have sinusoidal injury.

### Patient demographics and perioperative outcomes assessment

In the study group (80 patients with resected CRCLM), patient demographics and comorbidities, as well as perioperative characteristics, including platelet count; estimated blood loss; and operative time, were recorded. Postoperative outcomes, including blood product transfusion; ICU admission; 90-day mortality; and complications characterized as infectious; liver; and major were recorded. Liver-related complications were defined, consistent with our previously reported study, as the development of ascites, bile leak, or postoperative liver dysfunction (total bilirubin of ≥3 mg/dL or international normalized ratio of ≥1.8).[10] Infectious complications were defined as any diagnosis of a surgical site infection, pneumonia, urinary tract infection, or intra-abdominal abscess. Morbidity was graded according to the Memorial Sloan Kettering Secondary Events Program database,[17] consistent with the Common Terminology Criteria for Adverse Events from the National Institutes of Health and National Cancer Institute, where grades range from 0 (no complications) to 5 (resulting in death). Complications of grade 3 or higher were considered major.

### Splenic volume measurement

Splenic volume was measured from patients' MRI or CT scans using Scout Liver commercial software (Pathfinder Technologies) for preoperative liver planning. The software enables the user to pull MRI and CT scans directly from institutional storage, segment regions of interest from surrounding structures in a semi-automatic fashion, generate a 3-dimensional model, and calculate organ volumes. Splenic volume was correlated with body surface area (BSA), BMI, and weight to find an appropriate normalization constant.

### Statistical analysis

Clinicopathologic factors were expressed as mean (SD) or median (range), as appropriate. Spleen volumes were expressed as mean (SD). All statistical analyses were performed with SPSS software, version 21 (IBM SPSS) and Matlab software (MathWorks). Continuous variables were assessed with Wilcoxon's signed rank test and categorical variables were assessed with Pearson's chi-square test, where $p < 0.05$ defined statistical significance. To determine the best method of normalization of splenic

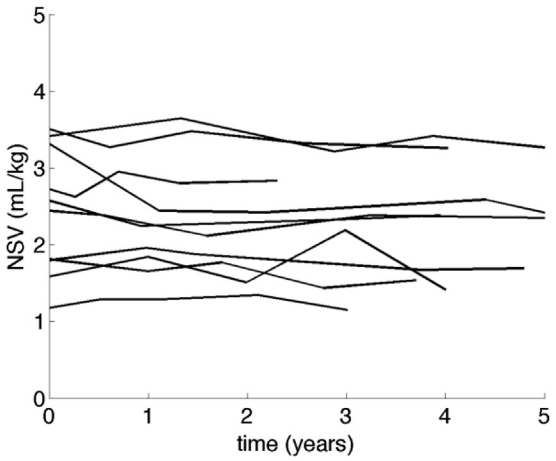


**Figure 2.** Spleen volume normalized by weight during a 5-year period in 10 normal individuals (control group). NSV, normalized spleen volume.

volume, regression lines were generated separately between spleen volume and weight, BSA, and BMI, and Pearson correlation coefficient was calculated. The 95% CIs for the predicted values and $R^2$ were calculated for each regression. The relative percentage of spleen volume increase from baseline to 6 months of chemotherapy was calculated. Cut points in this value were calculated with the maximal chi-square test.[18] This test statistic can help identify abrupt changes in the relationship between the response and some explanatory variables. The technique was used here to determine the splenic volume increase associated with the largest (most clinically relevant) change in complication rate.

## RESULTS

### Splenic volume in normal patients

The mean ± SD splenic volume in the normal control group (patients with benign disease) of 40 patients was 198 ± 72 mL. In this cohort, splenic volume correlated with weight ($R^2 = 0.32$; $p < 0.001$), BSA ($R^2 = 0.28$; $p < 0.001$), and BMI ($R^2 = 0.30$; $p < 0.001$), as shown in Figure 1. Splenic volume correlated with sex, but when weight was factored into the regression, sex was no longer significant, suggesting sex as a surrogate for weight. Height and age did not correlate with spleen volume. Because splenic volume best correlated with weight, all volumes were subsequently normalized by this value. The mean ± SD of normalized spleen volume (NSV) for the normal control group was 2.5 ± 0.8 mL/kg. Normal spleen volumes during a 5-year period for a subset of 10 normal control patients with available imaging are shown in Figure 2. The spleen did not vary significantly over time in this group.

### Preoperative factors associated with increased splenic volume

Demographic and preoperative characteristics of CRCLM patients are summarized in Table 1. The study population was composed of 80 patients, of which 30 (38%) were male. Median age of the study population was 63 years (range 28 to 83 years) with BMI of 26.8 kg/m$^2$ (range 16.6 to 38.6 kg/m$^2$). Thirty-nine patients (49%) underwent major hepatic resection (≥3 segments). Median size of the largest metastases was 2 cm (range 0.3 to 12 cm).

Of the 40 study group patients receiving preoperative chemotherapy, 23 (58%) were treated with irinotecan and 27 (68%) with oxaliplatin. All chemotherapy regimens included 5-FU. Twelve (30%) patients were treated with bevacizumab and 2 (5%) with cetuximab. Table 1 shows stratification of demographic and perioperative characteristics in the study group by presence or absence of chemotherapy. No statistical difference was found between preoperative chemotherapy and age, sex, BMI, BSA, diabetes, cardiac or pulmonary comorbidity, synchronous disease, major resection, size of the largest metastasis, and number of metastases. Patients treated with chemotherapy were more likely to have a node-positive primary tumor ($p < 0.05$) and lower preoperative platelet counts ($p < 0.01$).

Normal spleen volume in the nonmetastatic, untreated stage III CRC patient control group was 2.6 ± 1.3 mL/kg, which was not significantly larger than in the normal (no cancer) group ($p = 0.939$). Normal spleen volume in the no-chemotherapy CRCLM patients was 3.2 ± 1.1 mL/kg, and was significantly higher than in the normal ($p < 0.001$) and untreated stage III CRC ($p < 0.05$) groups. After 3 months of chemotherapy, NSV increased to 3.8 ± 1.6 mL/kg, which was significantly higher than their baseline NSV before chemotherapy ($p < 0.05$). After 6 months of chemotherapy, NSV increased to 4.2 ± 1.7 mL/kg. Figure 3 summarizes this gradual increase in NSV at baseline (before treatment) and after 3 and 6 months of chemotherapy, compared with the normal control and untreated stage III CRC groups.

### Factors associated with pathology of the nontumoral liver

Treatment, operative, and perioperative characteristics of the study group stratified by pathologic assessment are summarized in Table 2. Sinusoidal dilation was present in 8 patients (10%), steatosis in 27 patients (34%), and steatohepatitis in 4 patients (5%). Normalized spleen volume did not vary according to the type of liver injury. Any chemotherapy, 5-FU, and irinotecan were all associated with steatosis ($p < 0.05$). Cardiac and any major comorbidity were also associated with steatosis ($p < 0.05$).

**Table 1.** Univariate Analysis of Metastatic Colorectal Cancer Patient Demographics and Perioperative Characteristics with Respect to Chemotherapy

| Variable | All (n = 80) | No chemotherapy (n = 40) | Chemotherapy (n = 40) | p Value |
|---|---|---|---|---|
| Age, y, median (range) | 63 (28–83) | 65 (33–81) | 64 (28–83) | — |
| Sex, male, n (%) | 30 (38) | 14 (35) | 16 (40) | — |
| BMI, kg/m$^2$, median (range) | 26.8 (16.6–38.6) | 26.3 (17.2–38.4) | 27.2 (16.6–38.6) | — |
| BSA, m$^2$, median (range) | 1.9 (1.4–2.8) | 1.9 (1.4–2.8) | 2.0 (1.4–2.3) | — |
| Diabetes, n (%) | 13 (16) | 6 (15) | 7 (18) | — |
| Cardiac comorbidity, n (%) | 49 (61) | 25 (63) | 24 (60) | — |
| Pulmonary comorbidity, n (%) | 2 (3) | 0 (0) | 2 (5) | — |
| Synchronous disease, n (%) | 52 (65) | 22 (55) | 30 (75) | — |
| Preoperative platelets | 219 (78–420) | 273 (164–420) | 192 (78–374) | <0.01 |
| Nodal stage primary, n (%) | 37 (46) | 13 (33) | 24 (60) | <0.05 |
| Major resection, n (%) | 39 (49) | 20 (50) | 19 (48) | — |
| Largest metastasis, cm, median (range) | 2 (0.3–12) | 1 (0.3–12) | 2 (1–12) | — |
| No. of tumors, median (range) | 2 (1–2) | 2 (1–2) | 2 (1–2) | — |

BSA, body surface area.

No associations with steatosis were found between liver pathology, other variables, including ICU admission; 90-day mortality; liver-specific or infectious complications, and NSV.

### Outcomes associated with splenic volume increase after chemotherapy

In the study group of patients treated with chemotherapy, splenic volume increase was associated with any perioperative complication ($p < 0.01$), infectious complications ($p < 0.01$), and major complications ($p < 0.05$). Patients with greater changes in splenic volume were even more likely to have major complications. Major complications were significantly more likely to occur if the percentage change in spleen volume was $\geq$39%, as assessed by the maximal chi-square test ($p < 0.01$). Analysis of this spleen volume change threshold with respect to outcomes is detailed in Table 3.

The relationship between complications and other factors was assessed to determine whether splenic volume changes are an independent predictor of complications in patients treated with chemotherapy (Table 4). Complications were not associated with any other variables, including male sex, diabetes, thrombocytopenia, blood product transfusion, estimated blood loss, or major resections.

### Factors associated with changes in splenic volume after chemotherapy

Increase in the percentage change in spleen volume after chemotherapy was associated with oxaliplatin ($p < 0.05$) use. No association was found between percentage change in spleen volume and other chemotherapy regimens or any abnormal liver pathology. These characteristics are summarized in Table 3.

To assess whether thrombocytopenia was a surrogate for spleen volume change, splenic volume changes were compared with platelet changes within the same time period. Change in spleen volume was not correlated with change in platelet count from baseline to 6 months of chemotherapy ($R^2 = 0.03$; $p = 0.301$, data not shown).

## DISCUSSION

In carefully selected patients, complete resection with systemic chemotherapy of CRCLM is associated with 5-year survival rates ranging from 40% to 50%, with 20% of

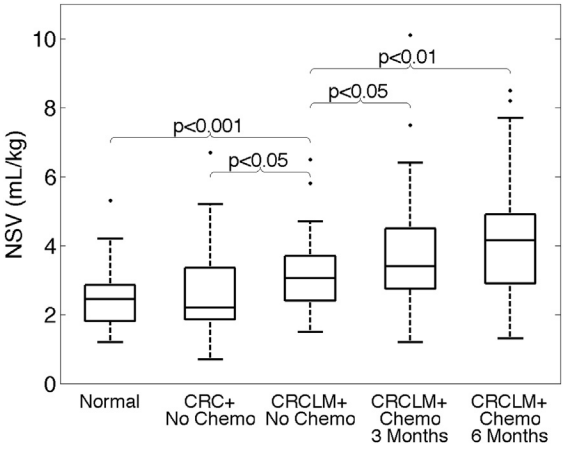


**Figure 3.** Boxplot of normalized spleen volume (NSV) for individuals with colorectal cancer liver metastases (CRCLM) before chemotherapy (n = 40), with 3 months (n = 40) and 6 months (n = 40) of chemotherapy, compared with the colorectal cancer (CRC) group and a normal control group (n = 40).

**Table 2.** Univariate Analysis of Nontumor Liver Injury Stratified by Patient, Chemotherapy, Operative, and Spleen Volume Characteristics (n = 80)

| | | Sinusoidal dilation (n = 8 [10%]) | | | | Steatosis (n = 27 [34%]) | | | | Steatohepatitis (n = 4 [5%]) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **n** | **n** | **%** | **Mean (range)** | **p Value** | **n** | **%** | **Mean (range)** | **p Value** | **n** | **%** | **Mean (range)** | **p Value** |
| NSV | | | | 4.2 (1.5–7.7) | — | | | 3.6 (1.4–6.5) | — | | | 3.4 (1.4–5.7) | — |
| Any chemotherapy | 40 | 4 | 10 | | — | 18 | 45 | | <0.05 | 3 | 8 | | — |
| 5-FU | 40 | 4 | 10 | | — | 18 | 45 | | <0.05 | 3 | 8 | | — |
| Irinotecan | 23 | 2 | 9 | | — | 13 | 57 | | <0.05 | 2 | 9 | | — |
| Oxaliplatin | 27 | 4 | 15 | | — | 9 | 33 | | — | 1 | 4 | | — |
| Bevacizumab | 12 | 2 | 17 | | — | 3 | 25 | | — | 1 | 8 | | — |
| Cetuximab | 2 | 0 | 0 | | — | 0 | 0 | | — | 0 | 0 | | — |
| Comorbidity | | | | | | | | | | | | | |
| Cardiac | 49 | 3 | 6 | | — | 21 | 43 | | <0.05 | 3 | 6 | | — |
| Pulmonary | 2 | 0 | 0 | | — | 0 | 0 | | — | 0 | 0 | | — |
| Diabetes | 13 | 1 | 8 | | — | 5 | 38 | | — | 1 | 8 | | — |
| Any comorbidity | 67 | 7 | 10 | | — | 25 | 37 | | — | 4 | 6 | | — |
| Any major comorbidity | 54 | 3 | 5 | | — | 23 | 43 | | <0.05 | 4 | 7 | | — |
| Preoperative | | | | | | | | | | | | | |
| Platelets | | | | 198 (101–299) | | | | 219 (128–418) | | | | 226 (145–268) | |
| Operative | | | | | | | | | | | | | |
| EBL, mL | | | | 713 (100–3,000) | — | | | 506 (20–2,000) | — | | | 575 (150–1000) | — |
| Operative time, min | | | | 348 (229–420) | — | | | 283 (90–480) | — | | | 334 (240–480) | — |
| Blood product transfusion | 24 | 4 | 17 | | — | 5 | 21 | | — | 1 | 4 | | — |
| Outcomes | | | | | | | | | | | | | |
| ICU admission | 2 | 1 | 50 | | — | 0 | 0 | | — | 0 | 0 | | — |
| 90-day mortality | 0 | 0 | 0 | | — | 0 | 0 | | — | 0 | 0 | | — |
| Any complication | 39 | 4 | 10 | | — | 13 | 33 | | — | 3 | 8 | | — |
| Major complication | 17 | 1 | 6 | | — | 5 | 29 | | — | 1 | 6 | | — |
| Liver complication | 3 | 0 | 0 | | — | 0 | 0 | | — | 0 | 0 | | — |
| Infectious complication | 15 | 3 | 20 | | — | 5 | 33 | | — | 1 | 7 | | — |

EBL, estimated blood loss; NSV, normalized spleen volume.

patients actually cured.[4,19,20] Chemotherapy before or after hepatic resection is associated with modest improvements in recurrence-free survival when compared with resection alone.[5,6,21] However, some reports have demonstrated that preoperative chemotherapy is associated with increased rates of postoperative complications.[6] Consequently, reported improvements in progression-free survival associated with use of preoperative chemotherapy must be weighed against the increased risk of postoperative complications.[6] With reports showing the close association between splenic volume increases and chemotherapy-related hepatotoxicity, thrombocytopenia, and worse long-term survival,[22,23] splenic volume might provide an alternative biomarker for predicting postoperative outcomes. To date, no studies have correlated splenic volume increase with postoperative outcomes, perhaps due to the technical limitations of software for computing splenic volume, or the lack of appropriate controls (normalization of spleen volume and selection of normal control groups).

In the normal spleen, volume was correlated with weight, BSA, and BMI, but no relationship was found with respect to height, sex, or age. Biologic correlates to splenic volume are debated in the literature. In Japanese populations, splenic volume correlated with age (with a gradual volume decrease later in life), weight, sex, and height.[24-26] with non-normalized mean splenic sizes 127 ± 63 $cm^3$ (compared with 198 ± 72 mL in the current study), but these relationships are unexplored in North American populations. In other populations, splenic volume was correlated with age,[27,28] but not other factors.[28] Although ethnic considerations, including body habitus, can explain gross differences in spleen volume, methodologic differences in spleen volume calculations cannot be excluded. These earlier studies calculated volume using a summation of areas technique (counting pixels in each slice and multiplying the sum by slice thickness),[29] and the software used in this study computes volume directly from the 3-dimensional object, a method known to be

**Table 3.** Univariate Analysis of Change in Spleen Volume Stratified by Patient, Chemotherapy, and Operative Characteristics of Patients Treated with Neoadjuvant Chemotherapy (n = 40)

| Variable | Spleen volume increase <39% (n = 32) | Spleen volume increase ≥39% (n = 8) | p Value |
|---|---|---|---|
| Chemotherapy, n (%) | | | |
| Irinotecan | 18 (56) | 5 (63) | — |
| Oxaliplatin | 19 (59) | 8 (100) | <0.05 |
| Bevacizumab | 8 (25) | 4 (50) | — |
| Cetuximab | 2 (6) | 0 (0) | — |
| Comorbidity, n (%) | | | |
| Cardiac | 20 (63) | 4 (50) | — |
| Pulmonary | 1 (3) | 1 (13) | — |
| Diabetes | 5 (16) | 2 (25) | — |
| Any comorbidity | 26 (81) | 6 (75) | — |
| Any major comorbidity | 23 (72) | 4 (50) | — |
| Preoperative | | | |
| Platelets, mean (range) | 204 (101–374) | 135 (78–213) | <0.01 |
| Thrombocytopenia, n (%) | 8 (25) | 6 (75) | <0.05 |
| Operative | | | |
| EBL, mL, mean (range) | 492 (0–3,000) | 906 (0–3,000) | — |
| Operative time, min, mean (range) | 292 (130–480) | 339 (222–433) | — |
| Blood product transfusion, n (%) | 9 (28) | 4 (50) | — |
| Major resection, n (%) | 14 (44) | 5 (63) | — |
| Largest metastasis, cm, median (range) | 2 (1–6) | 3 (1–12) | — |
| No. of tumors, median (range) | 2 (1–2) | 2 (1–2) | — |
| Pathology, n (%) | | | |
| Sinusoidal dilation | 3 (9) | 1 (13) | — |
| Steatosis | 16 (50) | 2 (25) | — |
| Steatohepatitis | 3 (9) | 0 (0) | — |
| Outcomes | | | |
| ICU admission, n (%) | 0 (0) | 1 (13) | — |
| 90-day mortality, n (%) | 0 (0) | 0 (0) | — |
| Any complication, n (%) | 9 (28) | 7 (88) | <0.01 |
| Major complication, n (%) | 3 (9) | 5 (63) | <0.05 |
| Liver complication, n (%) | 0 (0) | 1 (13) | — |
| Infectious complication, n (%) | 4 (13) | 4 (50) | <0.01 |
| Recurrence, mo, mean (range) | 7 (0–48) | 8 (0–27) | — |

EBL, estimated blood loss; ICU, intensive care unit.

more accurate.[30] Scout software has undergone extensive accuracy assessment for liver applications and was found to be reproducible and accurate when compared with manual techniques. Because the spleen is a homogenous mass easily distinguished from surrounding structures on CT, we believe that the accuracy and reproducibility are comparable with our liver studies. This functionality is also available on most modern radiographic workstations; Scout software is not the only mechanism for providing these measurements.[31,32] The volume of the spleen in normal controls did not change during a 5-year assessment period, but was widely variable across the patients (even after normalization), suggesting that an equation for predicting spleen volume as proposed in other studies[26,28] might not be sufficient for capturing inter-patient variability.

The principal finding of the current study is that in patients with CRCLM, the presence of liver metastases and the use of preoperative chemotherapy are associated with higher spleen volume. Spleen volume changes were assessed after 3 and 6 months of chemotherapy because higher morbidity and longer hospital stay have been associated with 6 cycles of adjuvant chemotherapy.[33] The percentage of splenic volume increase after 6 months of chemotherapy was associated with (but not a surrogate for) preoperative thrombocytopenia and a higher rate of major postoperative

**Table 4.** Univariate Analysis of Complications Stratified by Patient, Operative, and Pathology Characteristics of Patients Treated with Neoadjuvant Chemotherapy

| | | Any complication (n = 16 [40%]) | | | | Major complications (n = 8 [20%]) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **n** | **n** | **%** | **Mean (range)** | **p Value** | **n** | **%** | **Mean (range)** | **p Value** |
| Age, y | | | | 59 (35 to 80) | — | | | 62 (48 to 80) | — |
| Sex, male | 16 | 9 | 56 | | — | 5 | 31 | | — |
| BMI, kg/m$^2$ | | | | 27 (19 to 39) | — | | | 28 (19 to 39) | — |
| Diabetes | 7 | 5 | 71 | | — | 2 | 29 | | — |
| Cardiac comorbidity | 24 | 9 | 38 | | — | 3 | 13 | | — |
| Pulmonary comorbidity | 2 | 1 | 50 | | — | 1 | 50 | | — |
| Preoperative | | | | | | | | | |
| Thrombocytopenia | 14 | 9 | 64 | | — | 5 | 36 | | — |
| Spleen volume change, % | | | | 37 (−14 to 90) | <0.01 | | | 43 (0 to 90) | <0.05 |
| Operative | | | | | | | | | |
| EBL, mL | | | | 722 (0 to 3,000) | — | | | 956 (0 to 3,000) | — |
| Blood product transfusion | 13 | 8 | 62 | | — | 3 | 23 | | — |
| Major resection | 19 | 9 | 47 | | — | 6 | 32 | | — |
| Pathology | | | | | | | | | |
| Sinusoidal dilation | 4 | 2 | 50 | | — | 0 | 0 | | — |
| Steatosis | 18 | 7 | 39 | | — | 3 | 17 | | — |
| Steatohepatitis | 3 | 2 | 67 | | — | 0 | 0 | | — |

EBL, estimated blood loss.

complications. Complications were not associated with any other factors; therefore, spleen volume change was an independent predictor of complications. Although other studies have correlated spleen volume increases with worse long-term survival and liver injury,[22,23] to our knowledge, the relationship between spleen volume and postoperative complications appears to be a new result. Patients were more likely to have a major complication if the increase in spleen volume from baseline to 6 months of chemotherapy was ≥39%. The number of patients undergoing a major resection was similar between these two groups and spleen size seemed to predict complications independent of this variable. Additional studies incorporating detailed data on future liver remnant volume might elucidate the relationships among future liver remnant, spleen size, and postoperative morbidity; addressing the question of whether future liver remnant volumes change the ability of spleen size to predict complications. This analysis was beyond the scope of our study. Increase in spleen volume was associated with oxaliplatin-based chemotherapy use, consistent with reports from two other major centers.[13,22] Overman and colleagues[22] observed that increase in spleen volume by 50% due to oxaliplatin use correlated with hepatic sinusoidal injury in 55% of patients at the time of resection, and that this increase in splenic volume correlated with reductions in platelet count. A correlation between sinusoidal injury and spleen volume increase could not be observed in the current study because there were few events of sinusoidal injury for analysis. Recently, Katayama and colleagues[23] showed that overall survival was considerably shorter in patients with spleen volume increases ≥30% before resection. The effect of spleen changes before resection of CRCLM on overall survival was not evaluated in the current study.

Patients with untreated CRCLM had significantly larger spleen volumes than patients in the normal control group ($p < 0.001$) and patients with untreated CRC ($p < 0.05$). This observed increase in spleen volume with hepatic metastases alone (in the absence of chemotherapy) could be due to mechanical factors or change in immune composition. It is unclear why we do not see correlations between sinusoidal obstruction and splenomegaly in this dataset. The spleen enlarges during liver regeneration[34,35]; a recent study reports a correlation between hepatic and splenic hypertrophy.[36] In addition, the liver and spleen play important roles in the maintenance of the reticuloendothelial system,[34,37] which might suggest that both share common regulatory pathways. The spleen has been shown to regenerate after partial splenectomy or autotransplantation,[38] but the mechanisms for its growth and regulation are largely unknown. Although the mechanisms are likely multifactorial, related to both the presence and treatment of the CRLM, and not formally addressed by the current study, these data can still contribute to this richly complex topic.

## CONCLUSIONS

The current study demonstrates that increase in spleen volume due to the presence of hepatic metastases and chemotherapy before surgery is associated with preoperative thrombocytopenia and major postoperative complications. Chemotherapy before resection of colorectal liver metastases is safe,[10] but patients with spleen volume changes $\geq$39% are significantly more likely to have major postoperative complications. Consequently, these data suggest that formal monitoring/evaluation of spleen volume change should be considered as a means to risk stratify patients before undergoing resection of CRCLM.

### Author Contributions

Study conception and design: Simpson, Leal, Pugalenthi, Fong, Gönen, D'Angelica

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