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# Blood loss and outcomes after resection of colorectal liver metastases

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ABSTRACT

*Background:* The influence of intraoperative blood loss (IBL) on long-term outcomes of patients undergoing liver resection for colorectal cancer liver metastases (CRLM) remains not well defined.

*Materials and methods:* A total of 433 patients who underwent curative-intent hepatic resection for CRLM between 2000 and 2013 at Johns Hopkins were identified. Demographics, IBL data, and long-term outcomes were collected and analyzed. Clinicopathologic predictors of IBL and the association of IBL and outcomes were assessed.

*Results:* The median patient age was 54 y (interquartile range, 44–64), most patients were male (58.9%; $n = 255$). At surgery, the median IBL was 400 mL (range, 10–5100 mL). Two-hundred eighty-seven patients (66.3%) had an IBL of >250 mL. Factors associated with increased IBL (>250 mL) on multivariate analysis were male sex (odds ratio [OR], 2.62; 95% confidence interval [CI], 1.68–4.09; $P < 0.001$), tumor size >3 cm (OR, 1.88; 95% CI, 1.18–2.99; $P = 0.008$), and major hepatic resection (OR, 3.08; 95% CI, 1.92–4.92; $P < 0.001$). At a median follow-up time of 30.6 mo, the median survival times were 70.5, 56.4, and 36.9 mo for IBL <250, 250–1000, and >1000 mL, respectively ($P = 0.004$). IBL >250 mL remained an independent prognostic factor of overall survival in multivariate analysis (hazard ratio, 1.41; 95% CI, 1.01–1.97; $P = 0.04$) after adjusting for other factors including the receipt of blood transfusion.

*Conclusions:* The magnitude of IBL during CRLM resection was related to biologic characteristics of the tumor and the extent of surgery. Increased IBL during CRLM resection was an independent prognostic factor for worse patient survival. Furthermore, a dose–response relationship between increasing IBL and worsening survival was evident.



## Introduction

Liver surgery is increasingly being performed with roughly 11,000 hepatectomies performed annually in the United States [1]. In the Western world, the main indication for liver resection is colorectal liver metastasis (CRLM) [2]. Liver-directed surgery is the only potentially curative option for these patients with an estimated 5-y survival ranging from 40%–50% [3,4]. To date, most studies reporting on prognosis after curative-intent resection of CRLM have focused on disease-related factors [5]. In turn, a large number of clinicopathologic and molecular prognostic factors has been identified

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including primary tumor stage, liver metastasis size, surgical margin status, carcinoembryonic antigen (CEA) level, as well as KRAS mutational status [6–10]. A few studies have examined the impact of perioperative factors such as complications on long-term outcomes; however, most of these reports have analyzed complications in aggregate [11–13].

Intraoperative blood loss (IBL) is a potential complication of liver surgery. In fact, blood loss and receipt of transfusion are well-established predictors of short-term morbidity. Several studies have shown that as blood loss and transfusion requirements increase, there is a corresponding increase in the risk of serious morbidity and death from surgery [14–16]. Furthermore, massive blood transfusions can add to the risk of coagulopathy as well as exert immunosuppressive effects. Although several techniques have been adopted to minimize blood lose, IBL remains a concern during major hepatic resections. Interestingly, the magnitude of IBL has been associated with long-term outcomes of patients after resection of gastric cancer and prostate cancer [17–22]. The independent impact of IBL on long-term prognosis has been difficult to interpret, however, due to the frequent related use of intraoperative transfusion, which can also have immunomodulatory effects and potentially influence outcomes [23,24]. Sohn *et al.* [25] reported that IBL had an independent prognostic effect on prognosis among patients with pancreatic cancer who underwent resection—even after controlling for transfusion. In a separate study, Katz *et al.* [26] similarly noted that operative blood loss independently predicted recurrence and survival after resection of hepatocellular carcinoma (HCC). However, other investigators have questioned the independent association between IBL and long-term outcomes [27–30].

To date, only one single-institution study with a limited sample size has investigated the impact of IBL on long-term outcomes among patients undergoing surgery for CRLM [31]. In addition, this sole study examined an exclusively Asian population from a Chinese center. Given the importance of surgical blood loss in liver surgery, as well as the lack of data from a Western center, the objective of the present study was to define whether IBL was independently associated with long-term prognosis. In addition, we sought to identify those factors associated with IBL.

## Materials and methods

### *Study design*

Patients who underwent curative-intent surgery for CRLM between 2000 and 2013 and who had available data on the magnitude of IBL were identified. Patients with CRLM who underwent only an ablative procedure without concurrent hepatic resection, as well as patients with extrahepatic disease, were excluded. Standard demographic data were collected including age, sex, and race. Information on preoperative factors such as CEA levels, tumor number and size, receipt of preoperative chemotherapy, as well as the disease-free interval from the time of primary tumor diagnosis until diagnosis of liver metastases, tumor location (colon *versus* rectum), American Joint Committee on Cancer primary tumor T stage, and nodal status was also recorded. Data on operative details included IBL, receipt of perioperative transfusion, as well as the extent of liver resection and concomitant use of ablation; a major hepatectomy was defined as a resection of at least three Couinaud liver segments [32]. On pathology, surgical margin status was categorized as negative (R0), microscopically positive (R1), or macroscopically positive (R2). Perioperative mortality was calculated based on the number of patients who died within 90 d of the operation. The primary outcome variable analyzed was overall survival (OS). The Institutional Review Board of Johns Hopkins Hospital approved the study.

### *Statistical analysis*

Summary statistics for the population were presented as totals and frequencies for categorical variables or as median values with interquartile ranges (IQRs) for continuous variables. IBL was categorized using the cutoff value of 250 mL as proposed by Jiang *et al.* [31]. In the study by Jiang *et al.* of IBL in CRLM patients, the authors reported that an IBL volume of 250 mL corresponded to the maximum joint sensitivity and specificity on the receiver operating characteristic (ROC) plot [31]. To maintain consistency across studies, we performed preliminary analyses using the same cutoff value and similarly found 250 mL to represent the most appropriate point of stratification between low and high levels of blood loss. As such, patients were subsequently categorized as low IBL ($\leq$250 mL) *versus* high IBL (>250 mL). Univariable comparisons for continuous variables were performed using the Kruskal–Wallis test, whereas categorical variables were assessed using the chi square or the Fisher exact test, as appropriate. Logistic regression analysis was used to explore factors associated with high blood loss; results were reported as odds ratio (OR) with 95% confidence intervals (95% CI). OS was estimated by the Kaplan–Meier method calculated from the date of surgery, and differences between patient groups were compared by the log-rank test. A Cox proportional hazards model was used in multivariate analyses to identify independent prognostic factors. All analyses were carried out with Stata version 12.0 (StataCorp, College Station, TX), and a $P$ value of $<0.05$ (two-tailed) was considered statistically significant.

## Results

### *Demographic, clinicopathologic, and perioperative characteristics*

A total of 433 patients who underwent curative-intent liver resection for CRLM at the Johns Hopkins Hospital and who met inclusion criteria were identified. Table 1 lists the baseline characteristics of the entire cohort stratified by the magnitude of IBL. Median patient age was 54.4 y (IQR, 44.0–64.0 y); the majority of patients were male ($n = 255$; 58.9%) and Caucasian ($n = 253$; 79.8%).

Most patients had a primary colon tumor ($n = 325$; 75.1%), whereas about one-fourth of patients ($n = 108$; 24.9%) had a primary rectal tumor. Most patients had T3–T4 colorectal