Impact of Autologous Blood Transfusion on Survival and Recurrence among Patients Undergoing Partial Hepatectomy for Colorectal Cancer Liver Metastases

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BACKGROUND: Autologous transfusion (AT) has long been considered unsafe in major oncologic operations due to a theoretic risk of spreading metastatic disease, however, few data support this assumption.

STUDY DESIGN: We conducted a retrospective analysis of 147 patients who underwent partial hepatectomy for colorectal cancer metastases at a single institution. Seventy-four patients received AT only and 73 received no transfusion (NT). We compared the overall survival and recurrence-free survival of these groups using Kaplan-Meier survival curves and adjusted hazard ratios.

RESULTS: Patients who received AT had greater blood loss, more extensive resections, and longer procedure times. There were no differences in age, sex, proportion colon vs rectal cancer, or Fong Clinical Risk Score. Mean follow-up was 54 months. Median overall survival in the AT group was 59 months compared with 54 months in the NT group ($p = 0.69$) on log-rank test. No difference in overall survival was noted after adjusting for age, sex, Fong score, type of cancer (colon vs rectal), receipt of neoadjuvant therapy, receipt of adjuvant therapy, extent of resection and blood loss (hazard ratio AT vs NT 0.58; 95% CI 0.31 to 1.11; $p = 0.10$). Recurrence-free survival was also similar in the AT and NT groups (27% vs 37%; $p = 0.22$). The adjusted hazard ratio for recurrence-free survival was 0.95 (95% CI 0.54 to 1.65; $p = 0.85$).

CONCLUSIONS: Autologous blood transfusion is not associated with an increased recurrence risk or a higher mortality rate. Surgeons performing liver resections for patients with colorectal cancer metastases can safely transfuse filtered autologous blood. (J Am Coll Surg 2019;228:902–908.

Despite strategies to minimize blood loss during a partial hepatectomy, blood loss is common and transfusions are often necessary. However, surgeons are hesitant to transfuse in this situation secondary to concerns surrounding the safety of allogenic and autologous blood.

Allogenic transfusions confer a known risk of infectious transmission and immunomodulation.[1-5] The hypothesis that immunomodulation secondary to allogenic transfusions can be a mechanism for decreased survival among patients undergoing major oncologic procedures emerged from the observation of improved renal allograft survival in patients that received pretransplantation allogeneic transfusions. Subsequently, several studies have shown that transfusion of allogeneic blood to patients undergoing liver resection for colorectal cancer metastases is associated with increased risk of tumor recurrence and decreased overall survival.[6-9] Further, a meta-analysis of 36 studies established that transfusion of allogeneic blood is also associated with increased risk of tumor recurrence after resection of colorectal primary tumors.[10] It is clear that allogeneic transfusions should be avoided, if possible, during resection of primary colorectal cancer and metastases to the liver.

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The use of autologous blood for transfusion mitigates the immunomodulatory risks associated with allogenic transfusions. However, there is a theoretical concern that blood collected intraoperatively contains cancer cells and autotransfusion could result in the spread of metastatic disease.[11] Although it has been demonstrated that filtration of salvaged blood will remove cancer cells, this concern has persisted and limited the widespread adoption of autologous transfusions (ATs).[12-14] Consequently, little is known about the impact of intraoperatively collected autologous blood on tumor recurrence and survival.[15,16] The few studies that have investigated this topic either evaluate a heterogenous group of patients with different underlying primary cancers or focused on hepatocellular carcinoma. These studies note that AT does not lead to increased recurrence rates.[17-19] We are not aware of any previous studies that have specifically evaluated patients undergoing partial hepatectomy for colorectal cancer.

It was our objective to evaluate the risk of recurrence and overall survival among patients who received filtered AT during resection of colorectal liver metastases. To understand the baseline risk of ATs, we compared outcomes with those individuals who received no intraoperative transfusions, as this latter group would be spared the downstream effects of blood transfusions.

METHODS

Study population

We identified all patients who underwent a partial hepatectomy in the setting of liver metastases for a primary colorectal cancer at our institution from 1999 to 2016 via a departmental database. The database is prospectively maintained and includes clincopathologic details, including patient age, sex, cancer type (colon or rectal), CEA levels at diagnosis, size of largest liver metastases, number of liver metastases, and receipt of neoadjuvant/adjuvant therapy. We then extracted operative details, including length of operation, estimated blood loss, and extent of liver resection from operative and pathology reports. Information about the receipt of a blood transfusion, type of transfusion, and volume were confirmed via the operative report, anesthesia record, perfusionist notes, and the electronic medical record.

Transfusion protocol

Intraoperative blood loss was strictly calculated as described previously by Barth and colleagues.[20] Blood was evacuated from the operative field by a Cell Saver (Haemonetics Corporation). Blood-soaked laparotomy pads were wringed into a basin, and the resultant volume included in the aspirate for accurate quantitation of blood loss. The estimated blood loss recorded was the volume in the collection reservoir of the Cell Saver. The autologous blood was then filtered (Haemonetics SQ40S filter) and if the volume of the filtered blood was $\geq$200 mL, it was transfused. In the event that a patient underwent resection of both the hepatic lesion(s) and the primary colorectal cancer during one operative encounter, the hepatic resection was completed first and the blood loss from the hepatic resection was recorded separately.

Primary exposure

The primary exposure was receipt of autologous blood. We compared patients that received AT with those that received no transfusion (NT). If patients experienced substantial blood loss during their procedure and were transfused allogenic blood in addition to autologous blood, they were excluded from the analysis to limit confounding. We also excluded patients that received allogenic blood postoperatively at any point during their hospital admission.

Primary end point

Our primary end point was overall survival. We reviewed all clinical encounters (outpatient visits, telephone encounters, and hospitalizations). If a death was noted, we calculated the number of days between the index procedure and death. For patients who had been lost to follow-up (no clinical encounters in the 12-month period before this analysis), we used their Social Security numbers to query the National Death Index. Follow-up time was calculated from the index procedure to their last clinical encounter or date of death.

Our secondary end point was recurrence-free survival (RFS). Again, for each patient we reviewed all clinical encounters, radiology, laboratory, and pathology studies for any reports of a recurrence. For those patients that experienced recurrence, RFS was calculated as the number of days from the index procedure to the detection of the recurrence. For patients who did not have a recurrence, RFS was calculated as the time between the index operation and their last clinical encounter.

Statistical analysis

We used descriptive statistics to compare patients who received autologous blood to those that received no blood. Comparisons were made using *t*-test, chi-square analysis, and Fisher's exact test. We reported continuous variables as means with SDs and categorical variables as percentages. Crude overall survival and RFS were calculated using Kaplan-Meier survival analysis and log-rank test. An adjusted hazard ratio was also calculated, adjusting for

patient age, sex, cancer type (colon vs rectal), Fong Clinical Risk Score, extent of resection (lobectomy vs segmentectomy/multiple wedges vs wedge resection), estimated blood loss, receipt of neoadjuvant therapy, and receipt of adjuvant therapy. All statistics were performed using STATA, version 14 (Stata Corp).

Human subjects protection

Medical record review for this study was approved by the Committee for the Protection of Human Subjects at Dartmouth College.

RESULTS

A total of 162 patients underwent partial hepatectomy in the setting of colorectal cancer metastasis between 1999 and 2016. Seven of these patients were excluded, as they received both allogenic and autologous blood intraoperatively. An additional 6 patients were excluded because they received allogenic blood postoperatively during the same hospital admission (3 in the NT group and 3 in the AT group). Lastly, an additional 2 patients were excluded for missing transfusion details. The final cohort consisted of 147 patients, of which 74 received AT and 73 received no intraoperative or postoperative transfusions. Mean volume of autologous blood transfused per patient was 427 mL.

Patient characteristics

Patients that received AT were similar in age to those who received no transfusion (AT: 61.6 ± 10.0 years vs NT: 59.5 ± 11.8 years; p = 0.24) (Table 1). The percentage of female patients was also similar; 33.8% of patients who received autologous blood and 46.6% of patients that received no transfusions were female (p = 0.11). The majority of patients had a primary

Table 1. Characteristics of Patients Who Underwent Partial Hepatectomy in the Setting of Metastatic Colorectal Cancer Stratified by Receipt of Autologous Blood Transfusion

Characteristic	No blood transfusion (n = 73)	Autologous blood transfusion (n = 74)	p Value
Clinical			
Age, y, mean (SD)	59.5 (11.8)	61.6 (10.0)	0.24
Female sex, n (%)	34 (46.6)	25 (33.8)	0.11
Primary cancer, n (%)			0.43
Colon	50 (68.5)	55 (74.3)	
Rectal	23 (31.5)	19 (25.7)	
Neoadjuvant chemotherapy, n (%)	20 (27.4)	22 (29.7)	0.75
Adjuvant chemotherapy, n (%)	57 (79.2)	56 (75.7)	0.62
Fong Clinical Risk Score,* n (%)			0.41
0	9 (12.3)	5 (6.8)	
1	19 (26.0)	15 (20.3)	
2	24 (32.9)	28 (37.8)	
3	15 (20.6)	16 (21.6)	
4	6 (8.2)	7 (9.5)	
5	0 (0.0)	3 (4.0)	
Operative			
Year of operation, n (%)			0.91
1999 to 2005	22 (30.1)	20 (27.0)	
2006 to 2010	20 (27.4)	22 (29.7)	
2011 to 2016	31 (42.5)	32 (43.3)	
Length of operation, min, mean (SD)	219.2 (80.8)	284.7 (77.8)	<0.001
Extent of resection, n (%)			0.001
Lobectomy	5 (6.9)	21 (28.4)	
Segmentectomy†	48 (65.7)	43 (58.1)	
Single wedge	20 (27.4)	10 (13.5)	
Estimated blood loss, mL, mean (SD)	342.1 (266.0)	937.3 (520.7)	<0.001

*The Fong Clinical Risk Score is used to predict risk of recurrence, where higher scores indicate greater risk of recurrence. The Fong score incorporates, nodal status, number of hepatic tumors, size of largest tumor, preoperative CEA level, and disease interval between detection of the primary tumor and hepatic lesions.

†Segmentectomy or multiple wedge resection.

colon cancer (AT: 74.3% and NT: 68.5%; p = 0.43). In addition, there was no difference in the percentage of patients that received neoadjuvant therapy (AT: 29.7% and NT: 27.4%; p = 0.75) or adjuvant therapy (AT: 75.7%; NT: 79.2%; p = 0.62). As shown in Table 1, the predicted risk for recurrence, as calculated by the Fong Clinical Risk Score, was similar between the 2 groups.

There were differences in the operative characteristics of these 2 groups. Patients that received autologous blood had longer operation time (283.7 ± 77.8 minutes vs 219.2 ± 80.8 minutes; p < 0.001), greater blood loss (937.3 ± 520.7 mL vs 342.1 ± 266.0 mL; p < 0.001), and more extensive resections (AT: 28.4% underwent lobectomy vs NT: 6.9% underwent lobectomy, p = 0.001) than those that did not receive any transfusions.

Overall survival

Mean follow-up for survival was 54 months. Median survival in the AT group was 59 months compared with 54 months in the NT group (p = 0.69 on log-rank test) (Fig. 1). On our multivariable Cox regression model, where we adjusted for clinical factors including age, sex, type of primary cancer (colon vs rectal), receipt of neoadjuvant therapy, receipt of adjuvant therapy, and Fong Clinical Risk Score, as well as operative factors, including extent of resection and estimated blood loss, overall survival was similar between those who received autologous blood and those who did not (hazard ratio 0.58; 95% CI 0.31 to 1.11) (Fig. 2).

Recurrence-free survival

Recurrence-free survival, which includes any recurrence local or distant, was similar among patients that received autologous blood and those who received no transfusions. Median RFS time was 13.7 months in the AT group and 18.7 months in the NT group (p = 0.22 on log-rank test) (Fig. 3). On our multivariable Cox regression model, which adjusted for the clinical and operative factors mentioned, the RFS remained similar between these 2 groups (hazard ratio 0.95; 95% CI 0.54 to 1.65).

DISCUSSION

Autologous blood transfusion during an oncologic hepatic resection is often avoided, secondary to concerns of spreading metastatic disease. In this study, we evaluated the impact of salvaged autologous blood on survival and recurrence. We found no difference in overall survival or RFS between patients that received autologous blood and those that did not receive any transfusions. Patients who received blood were clinically similar to those who did not. However, there were differences in operative factors; patients who received blood, unsurprisingly, had more extensive resections, longer operations, and greater blood loss. After adjusting for these operative factors as well as clinicopathologic features, we still found no difference in outcomes.

Our findings in a cohort of patients undergoing partial hepatectomy for colorectal cancer metastases are aligned with the observations of others who have shown no deleterious effects of AT among patients undergoing hepatectomy for hepatocellular carcinoma, pancreatic resection

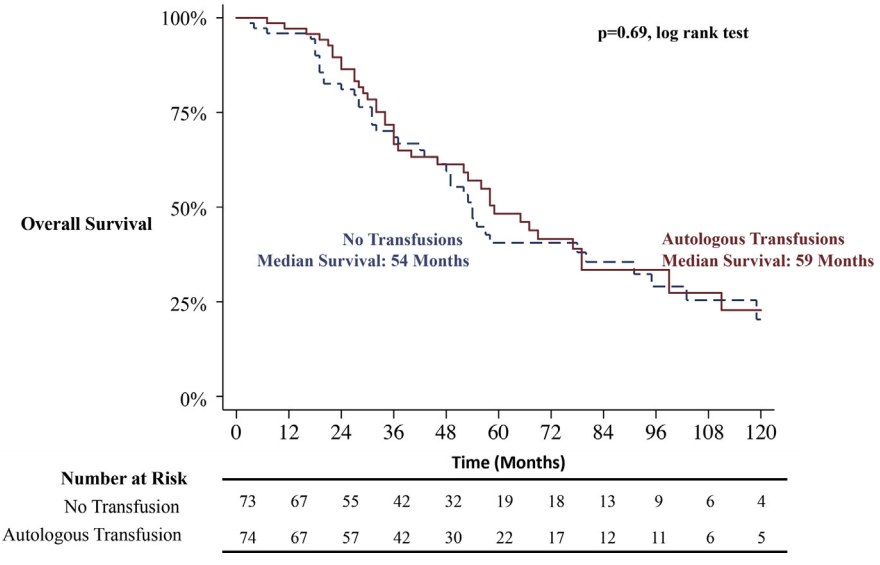

Figure 1. Overall survival for patients that received autologous blood and those that received no transfusion.

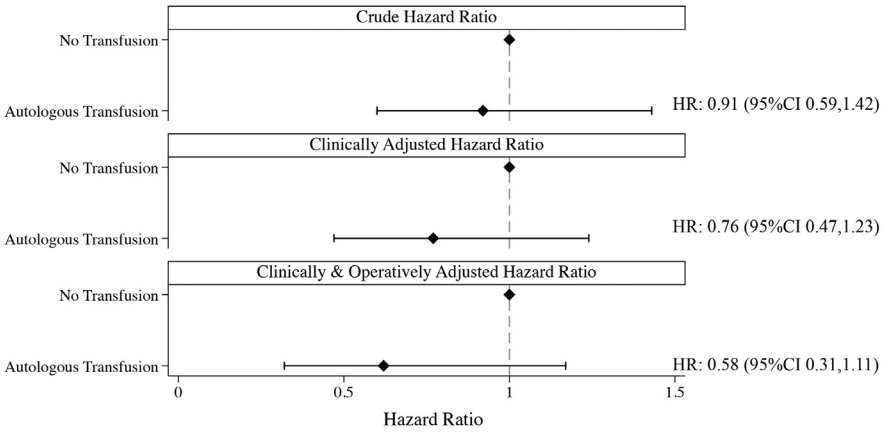

Figure 2. Hazard ratios (HR) for overall survival among patients that received autologous blood, with patients who received no transfusion serving as the reference group. Clinically adjusted HR, adjusted for age, sex, primary cancer type, Fong Clinical Risk Score, receipt of neoadjuvant therapy, and receipt of adjuvant therapy. The clinically and operatively adjusted model adjusted for the clinical factors mentioned, estimated blood loss, and extent of surgical resection. A lower HR indicates a lower likelihood of death.

for pancreas cancer, or prostatectomy for prostate cancer.[16,21,22] In fact, it is thought that salvaged autologous blood transfusions can actually be beneficial, as it counters the immunosuppression associated with operative trauma.[23] However, transfusion of autologous blood is not without risk. Like allogenic transfusions, ATs can predispose patients to a dilutional coagulopathy and hypothermia when large volumes of blood are transfused.[24,25] In addition, the process of salvaging intraoperatively collected blood involves heparin and, theoretically, this could increase the risk of postoperative bleeding. Lastly, we specifically examined the effects of salvaged autologous blood, and cannot comment on the use of pre-donated autologous blood. The latter has been shown to increase the need for any transfusion and induce iatrogenic anemia.[26]

Ultimately, efforts to minimize blood loss during hepatectomy must be pursued, if the need for allogeneic transfusions is to be eliminated.[27] These methods include vascular inflow occlusion, techniques to lower central

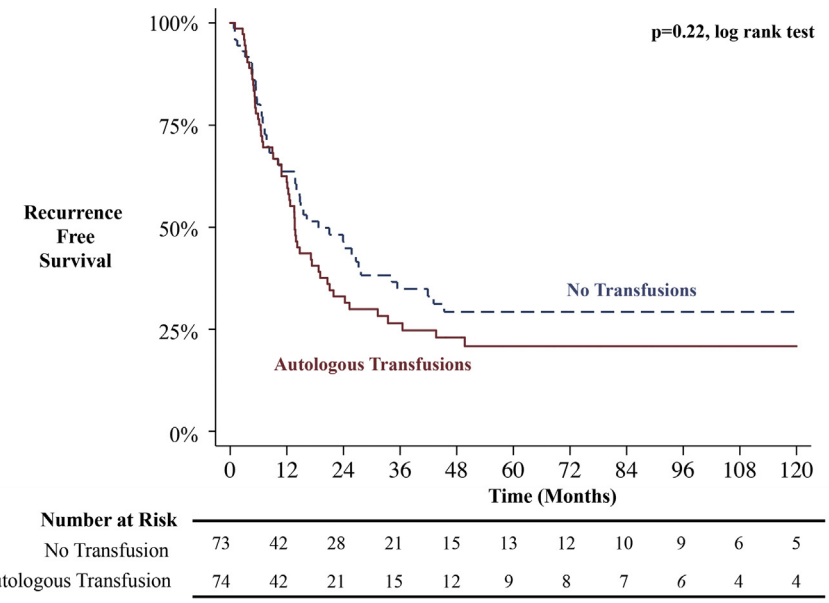

Figure 3. Recurrence-free survival for patients that received autologous blood and those that received no transfusion.

venous pressure, parenchymal transection devices, cut surface sealants, and pharmacologic interventions.[28] In addition, a 1-week, low-calorie, low-fat preoperative diet has also been shown to substantially decrease blood loss during liver operation.[20] In our cohort, very few patients (7 of 162 [4%]) had substantial bleeding requiring allogeneic transfusions in addition to ATs.

There are limitations to this study. First, although we controlled for clinical and operative factors, there might be other unmeasured or unmeasurable factors that influenced clinical outcomes. Second, although both Kaplan-Meier analysis and adjusted Cox Regression found no difference in overall survival and RFS, the possibility for a type II error exists. The RFS curve in particular diverged and remained parallel after 24 months. This was due to a low number of patients being at risk for recurrence beyond this time interval. It is unknown if a larger cohort would have resulted in a statistically significant difference in recurrence. We were powered to detect a hazard ratio of approximately 1.6, where ATs are associated with a 60% higher likelihood of death or recurrence. This hazard ratio is within the range reported in earlier studies comparing allogenic with NT, however, there is no earlier literature to inform the sample size calculation for autologous blood transfusion.[10,29] Of note, our experience is that of a single academic center and largely of a single experienced surgeon, and our overall survival at 10 years was fairly high.

CONCLUSIONS

We found no deleterious effect of using salvaged autologous blood intraoperatively during partial hepatectomy in the setting of colorectal cancer metastasis. Our experience indicates that the use of filtered autologous blood is a safe alternative to the use of allogeneic blood for patients undergoing hepatectomy who require transfusion. A multicenter trial is warranted to assess whether our findings are reproducible and generalizable.

Author contributions

Study conception and design: Kang, Barth
Acquisition of data: Kang, Huang, Barth
Analysis and interpretation of data: Kang, Seath, Huang
Drafting of manuscript: Kang, Barth
Critical revision: Kang, Seath, Huang, Barth

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Invited Commentary

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Transfusion of allogenic red blood cells is associated with adverse effects including transfusion reaction, transmission of disease, lung injury, volume overload, and immunosuppression. In the operative patient, allogenic red blood cell transfusion is associated with an increased risk of postoperative wound infection and poorer outcomes.[1] Retrospective studies have suggested a link with poorer disease-free and overall survival in patients who receive allogenic blood transfusion and have resection of colorectal cancer[2] as well as in patients having resection of colorectal liver metastases.[3,4] The deleterious impact of allogenic red blood cell transfusion on postoperative and cancer-related outcomes is multifactorial, but is likely related to transfusion-related immunomodulation.

Recognition of poorer outcomes in patients who receive allogenic red blood cell transfusion associated with liver resection for colorectal cancer metastases has resulted in strategies to limit intraoperative blood loss and to restrict autologous red blood cell transfusion. These interventions have resulted in a steady and significant decrease in allogenic red blood cell transfusions given to patients having liver resection. Despite this awareness and these interventions, in contemporary reports, an average of 38% of patients having liver resections receive allogenic red blood cell transfusions.[4]

Restoring lost blood to patients undergoing liver resection can involve allogenic and autologous blood transfusion. Autologous blood transfusion can be addressed by strategies that involve preoperative and intraoperative autologous blood collection, including preoperative autologous donation, intraoperative acute normovolemic hemodilution, and intraoperative salvage of shed blood.

Circulating tumor cells are present in patients with cancer, and surgery increases the shedding of tumor cells into the circulation.[5] The complex, multifactorial changes involving inflammation and immune modulation that occur with surgery may enhance the survival and propagation of circulating tumor cells.[5] This has led to reluctance to using autologous blood salvage in patients having liver resection for colorectal metastases. The American Medical Association Council on Scientific Affairs has endorsed the use of autologous red blood cell transfusion as the preferred method of transfusion in many situations, but has listed bacterial contamination in the operative field and malignancy as contraindications to its use.[6] Although more current reviews have not found transfusion of intraoperative salvaged blood to be inferior to allogenic blood in cancer surgery,[7] this recommendation against using autologous blood recovered during surgery has contributed to reluctance to use it and a lack of data regarding the outcomes of patients who received autologous red blood cell transfusions after liver resection for colorectal liver metastases.

In their report, Kang and colleagues provide important information regarding the long-term outcomes of patients who received autologous red blood cell transfusion of blood salvaged during resection of colorectal liver metastases. Their study is based on the innovative and careful work done at the Dartmouth-Hitchcock Medical Center under the direction of Dr Richard Barth. This is a retrospective study of a prospectively maintained database, which is consistent with most studies addressing the effect of red blood cell transfusion on the outcomes of patients having liver resection for colorectal liver metastases. In this study, the outcomes of patients who had resection of colorectal liver metastases and received autologous blood transfusions of blood salvaged during the operation were compared with outcomes of patients who did not receive any blood transfusion. Both groups were similar and well matched in terms of their characteristics, dates of operation, and durations of follow-up. The primary outcome of the study was overall survival and the secondary outcome was recurrence-free survival. The patients who received autologous blood transfusion had significantly longer and more extensive operations and more intraoperative blood loss than the patients who did not receive any blood transfusion. Despite these differences, there was no difference in overall survival or recurrence-free survival in patients who received transfusions of autologous blood salvaged during their liver resection and those who did not receive any blood transfusion.

The retrospective design, single institutional experience, and sample size of this study do not allow for definitive conclusions regarding the use of intraoperatively salvaged autologous blood transfusions in patients having liver resection for colorectal liver metastases. This important study does expand our knowledge and provides solid and supportive information regarding the use of autologous blood transfusion salvaged intraoperatively in patients having resection of colorectal liver metastases.