JAMA Surgery | Original Investigation

Anterior Approach vs Conventional Hepatectomy for Resection of Colorectal Liver Metastasis
A Randomized Clinical Trial

Nuh N. Rahbari, MD; Emrullah Birgin, MD; Ulrich Bork, MD; Arianeb Mehrabi, MD; Christoph Reißfelder, MD; Jürgen Weitz, MD

Invited Commentary

Supplemental content

IMPORTANCE Tumor relapse after partial hepatectomy for colorectal liver metastasis (CRLM) remains an unsolved issue. Intraoperative manipulation of the liver during conventional hepatectomy might enhance hematogenous tumor cell spread. The anterior approach is an alternative approach that may reduce intraoperative tumor cell dissemination.

OBJECTIVE To determine the efficacy and safety of the anterior approach compared with conventional hepatectomy in patients undergoing resection for CRLM.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical study evaluated the efficacy and safety of the anterior approach compared with conventional hepatectomy in adult patients with CRLM who were scheduled for hepatectomy from February 1, 2003, to March 31, 2012, at a tertiary-care hospital. A total of 80 patients with CRLM were randomized to the anterior approach and conventional hepatectomy groups in a 1:1 ratio. Bone marrow and blood samples were analyzed for disseminated tumor cells and circulating tumor cells (CTC) using cytokeratin 20 reverse transcriptase–polymerase chain reaction analysis. Data were analyzed from April 1 to December 1, 2018, using intention to treat.

INTERVENTIONS Anterior approach vs conventional hepatectomy.

MAIN OUTCOMES AND MEASURES The primary end point was intraoperative CTC detection in central blood samples after liver resection. Secondary end points included postoperative morbidity, mortality, and long-term survival.

RESULTS Among the 80 patients included in the analysis (48 men [60%]; mean [SD] age, 61 [10] years), baseline characteristics, including preoperative CTC detection, were comparable between both groups. There was no statistically significant difference in intraoperative CTC detection between patients in the conventional hepatectomy (5 of 21 [24%]) and anterior approach (6 of 22 [27%]) groups ($P = .54$). Except for a longer operating time in the anterior approach group (mean [SD], 171 [53] vs 221 [53] minutes; $P < .001$), there were no significant differences in intraoperative and postoperative outcomes between both study groups. Although detection of CTC was associated with poor overall (median, 46 [95% CI, 40-52] vs 81 [95% CI, 54-107] months; $P = .03$) and disease-free (median, 40 [95% CI, 34-46] vs 60 [95% CI, 46-74] months; $P = .04$) survival, there was no significant difference in overall (median, 73 [95% CI, 42-104] vs 55 [95% CI, 35-75] months; $P = .43$) and disease-free (median, 48 [95% CI, 40-56] vs 40 [95% CI, 28-52] months; $P = .88$) survival between the conventional hepatectomy and anterior approach groups. Also, there was no significant difference in patterns of recurrence between both groups.

CONCLUSIONS AND RELEVANCE This randomized clinical trial found that the anterior approach was not superior to conventional hepatectomy in reducing intraoperative tumor cell dissemination in patients undergoing resection of CRLM.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN45066244

JAMA Surg. doi:10.1001/jamasurg.2020.5050
Published online November 4, 2020.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jürgen Weitz, MD, Department of Gastrointestinal, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany (juergen.weitz@uniklinikum-dresden.de).

Partial hepatectomy remains the most effective therapeutic modality for patients with colorectal liver metastasis (CRLM). Within a multimodal setting, partial hepatectomy may result in 10-year survival rates of as high as 24%.[1] However, after curative resection, as many as 70% of patients develop hepatic or extrahepatic disease recurrence.[2,3] Although approximately one-quarter of patients with intrahepatic recurrence may undergo repeated hepatectomy, most patients with disease recurrence after potentially curative partial hepatectomy for CRLM are candidates for palliative therapy only.[4]

Circulating tumor cells (CTC) represent the key element within the metastatic cascade. Numerous studies have demonstrated the prognostic value of CTC in primary and metastatic colorectal cancer.[5-7] Selective analyses of CTC in the hepatic inflow and outflow compartments have recently revealed the ability of CRLM to shed intact tumor cells into the circulation.[8] Mechanical manipulation of the liver during conventional hepatectomy might further enhance dissemination of CTC into the circulation and thereby result in higher recurrence rates. This hypothesis is backed by previous studies that proved an increased detection rate of CTC in the circulation of patients after partial hepatectomy for CRLM.[9,10]

For patients requiring a right hepatectomy, the anterior approach presents an alternative surgical strategy with transection of the parenchyma and division of the right hepatic vein before mobilization of the right hepatic lobe. In patients with hepatocellular carcinoma (HCC), the anterior approach has been shown to be associated with improved survival compared with conventional hepatectomy, potentially owing to decreased hematogenic dissemination of cancer cells.[11,12] Based on the hypothesis that the anterior approach without initial mobilization of the liver might reduce intraoperative CTC dissemination, we performed a prospective randomized clinical trial to investigate the efficacy and safety of the anterior approach compared with conventional hepatectomy in patients with CRLM.

Key Points

Question Does anterior approach hepatectomy reduce tumor cell dissemination during resection of colorectal liver metastasis compared with conventional hepatectomy?

Findings In this randomized clinical trial including 80 participants, no statistically significant difference in tumor cell dissemination (5 of 21 [24%] vs 6 of 22 [27%]) and overall (median, 73 vs 55 months) and disease-free (median, 48 vs 40 months) survival was found between conventional hepatectomy and the anterior approach.

Meaning These findings suggest that both techniques offer safe and comparable postoperative and survival outcomes in patients undergoing right-sided hepatectomy for colorectal cancer.

Methods

The trial was approved by the Ethics Committee of the University of Heidelberg, Heidelberg, Germany, and all patients provided written informed consent before surgery. A complete copy of the study protocol is available in Supplement 1. In addition, the rationale and design of the study was published previously.[13] This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients

From February 1, 2003, to March 31, 2012, patients with CRLM who were scheduled for potentially curative resection were screened for inclusion in the trial at the Department of General, Visceral and Transplantation Surgery, University of Heidelberg. Eligible patients were 18 years or older and planned to undergo elective right-sided or extended right-sided hepatectomy. Patients with history of other malignant neoplasms, extrahepatic disease of colorectal cancer, liver cirrhosis, and grossly positive lymph nodes in the hepatoduodenal ligament were excluded, as were patients with expected lack of adherence or impaired mental state. Furthermore, patients with positive margins after liver resection (R1), intraoperative blood loss exceeding 2000 mL, and positive preoperative tumor cells in blood samples were excluded from the analysis of intraoperative tumor cell detection in blood samples but not from the analysis of secondary end points.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to the anterior approach or the conventional hepatectomy arm. Randomization was performed in the operating room after surgical exploration before hepatic resection by using consecutively numbered opaque and sealed envelopes. Stratification was performed for patients' clinical risk score (0-2 vs 3-5). Patients were blinded to the study intervention. Perioperative outcomes were assessed by blinded observers (third party).

Outcomes

The primary end point was intraoperative CTC detection rate in blood samples obtained immediately after liver resection using cytokeratin 20 (CK20) reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. Predefined secondary end points included intraoperative blood loss, need of the Pringle maneuver, operating time, blood transfusion, postoperative complications, and length of hospital stay. In addition, resection margin status, long-term outcomes from the date of randomization (overall and disease-free survival), and the site of disease recurrence were assessed.

Collection and Processing of Blood and Bone Marrow Samples

Preoperative blood samples (10 mL) were collected through a central venous catheter after induction of general anesthesia. Bone marrow samples (10 mL) were aspirated from both iliac crests after the patient was prepped and draped in a sterile fashion. Intraoperative blood samples (10 mL) were drawn immediately after completion of hepatectomy through the central venous catheter. Blood and bone marrow samples were processed according to a standardized protocol and stored at −80 °C for further central analysis. In brief, blood samples were diluted with 10 mL of phosphate-buffered solution and centrifugated through sterile medium (Ficoll-Paque; Amersham Pharmacia Biotech) for 30 minutes (at 400*g*). After harvesting the mononuclear peripheral blood cell pellet, RNA extraction and complementary DNA synthesis was performed using commercially available kits (Life Technologies, Inc). The CK20 RT-PCR protocol has been described in detail previously.[13] Technicians and physicians involved in the laboratory analyses were blinded to patients' clinical data and allocated study arms.

Trial Interventions and Perioperative Care

All surgeons were instructed on the study interventions before the start of the trial. Only surgeons who had already performed 25 or more partial hepatectomies performed operations within the setting of this trial. In both study groups, perioperative care was identical except for the study intervention. In brief, a reversed L-shape incision was made. For cases in which the surgeon confirmed resectability by (extended) right-sided hepatectomy, patients were randomized. In the anterior approach group, a hanging liver maneuver was performed after ligation and division of right portal vein and hepatic artery (inflow control) with subsequent parenchymal transection. This was followed by outflow control and finally mobilization of the liver out of the retroperitoneal plane. In the conventional hepatectomy group, the liver was first mobilized from the retroperitoneal plane. Parenchymal transection was performed after completion of inflow and outflow control. In both study groups, hepatic transection was performed according to surgeon's preference under low central venous pressure without routine vascular inflow control (Pringle maneuver).

Sample Size Calculation and Statistical Analysis

The sample size was calculated with regard to the primary end point of hematogenous tumor cell dissemination. The incidence of intraoperative hematogenous tumor cells was expected to be 50% to 55% in the conventional hepatectomy group (19 of 38 patients) and 15% to 20% in the anterior approach group (2 of 14 patients) based on previous results of tumor cell dissemination for patients undergoing resection of primary colorectal cancer and liver metastases.[10,14] Assuming a 30% difference between the 2 groups in the proportion of patients with CTC, a total of 112 patients were calculated (1:1 ratio) to be needed for the primary analysis, with a significance level $\alpha = .05$ and a power of $(1 - \beta) = 0.9$ (2-sided test). The study protocol required an interim analysis of the primary end point when at least 75 patients were randomized and completed the follow-up. According to the study protocol, the study was terminated owing to an overall $P > .65$ between both groups, indicating futility of the assessment of whether the anterior approach is superior to conventional hepatectomy in reducing intraoperative tumor cell dissemination in patients undergoing resection of CRLM.

Data were analyzed from April 1 to December 1, 2018, using the intention-to-treat population. The primary end point was analyzed using the Fisher exact test. Categorical variables were expressed by absolute and relative frequencies (percentage) and compared using the Pearson χ^2 or the Fisher exact test. Continuous variables were summarized as mean (SD) or median (interquartile range [IQR] or 95% CI) and compared using the unpaired 2-tailed *t* test or the Wilcoxon rank sum test, depending on the pattern of distribution. Analyses for overall survival and disease-free survival were performed using the Kaplan-Meier method and the log-rank test between the groups. Patients who reached the final point of follow-up or who were lost to follow-up were censored. The prognostic relevance of tumor cell detection in bone marrow and blood samples was assessed using the Cox proportional hazards regression method. The following explanatory variables were included: clinical risk score, operating technique, and detection of CTC. The Cochran *Q* test was performed to correlate the RT-PCR results with timing of blood sampling, and the McNemar test was conducted to compare tumor cell detection rates in blood vs bone marrow samples. All statistical tests were evaluated for significance at 2-sided $P < .05$. Statistical analysis was performed using SPSS software, version 25 (IBM Corp), and R, version 3.5.2 (R Project for Statistical Computing).

Results

Patient Characteristics

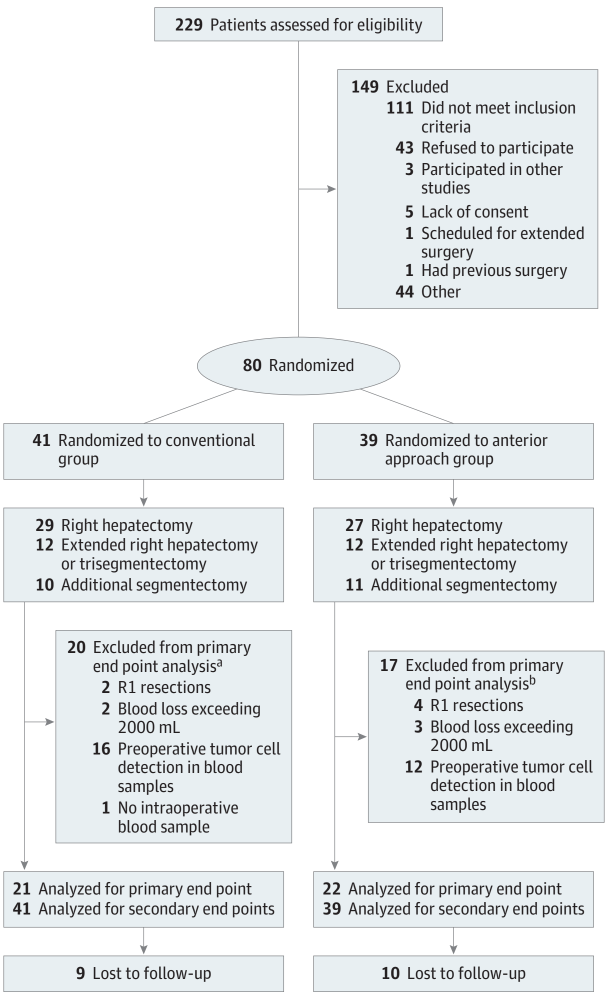
A total of 80 patients (48 men [60%] and 32 women [40%]; mean [SD] age, 61 [10] years) were randomized to the conventional hepatectomy (n = 41) and anterior approach (n = 39) groups. **Figure 1** displays the CONSORT flow diagram. Patients' baseline characteristics were equally distributed between groups (**Table 1**). Between study groups, oncological characteristics of the primary tumor were well balanced with regard to pathological findings of the primary tumor (AJCC/UICC stage I, 3 [7%] vs 3 [8%]; AJCC/UICC stage II, 5 [12%] vs 4 [10%]; AJCC/UICC stage III, 13 [32%] vs 15 [38%]; AJCC/UICC stage IV, 19 [46%] vs 16 [41%]; $P = .97$) and perioperative oncological treatment strategies (neoadjuvant chemotherapy, 3 [7%] vs 3 [8%; $P = .95$]; adjuvant chemotherapy, 23 [56%] vs 17 [44%; $P = .26$]). In particular, we found no significant differences in the onset (synchronous metastases, 20 [49%] vs 16 [41%]; $P = .49$), timing (mean [SD], 17 [27] vs 14 [16] months, $P = .54$), and size (mean [SD], 48 [27| vs 44 [27] mm; $P = .49$] of CRLM between the conventional hepatectomy and anterior approach groups.

Operative Details and Perioperative Outcome

Data on perioperative outcomes are outlined in **Table 2**. The kind of surgical procedures were similar between both groups. Although the need for the Pringle maneuver was comparable between groups (19 of 41 [46%] vs 13 of 39 [33%]; $P = .24$), the anterior approach was associated with a longer duration of inflow control (mean [SD], 10 [6] vs 24 [15] minutes; $P < .001$). There was no significant difference in intraoperative blood loss (mean [SD], 763 [484] vs 1051 [1150] mL; $P = .15$). However, the anterior approach resulted in a significantly longer operating time (mean [SD], 171 [53] vs 221 [53] minutes; $P < .001$).

There was no statistically significant difference between study groups in grades I to IV complications (16 of 41 [39%] vs

Figure 1. CONSORT Diagram



[a] One patient had a positive resection margin and blood loss exceeding 2000 mL simultaneously.

[b] Two patients had positive resection margins, blood loss exceeding 2000 mL, and preoperative positive tumor cells simultaneously.

16 of 39 [41%]; *P* = .16). There was no mortality in the conventional hepatectomy group, whereas 2 patients in the anterior approach group died of septic multiorgan failure postoperatively. The incidence of specific complications, such as bile leakage, abdominal fluid collection, wound infection, postoperative cholangitis, pneumonia, or sepsis, did not differ significantly between the groups. Median length of hospital stay was comparable among the study groups (11 [IQR, 9-15] vs 12 [IQR, 10-17] days; *P* = .74).

Detection of Tumor Cells in the Blood and Bone Marrow

In preoperative blood samples, 12 patients (32%) were positive for CTC in each study group (*P* = .57). A total of 9 of 34 patients in the conventional hepatectomy group (26%) and 12 of 38 patients in the anterior approach group (32%) had disseminated tumor cells detected in the bone marrow before surgery (*P* = .80). In line with the study protocol, patients with a positive resection margin, excessive intraoperative blood loss, and preoperative CTC detection were excluded from the analysis of the primary end point. After exclusion of these patients, a total of 21 patients remained in the conventional hepatectomy group and 22 remained in the anterior approach group for the analysis of the primary efficacy end point of intraoperative detection of CK20-positive CTC. The analysis of the primary end point revealed no significant difference in intraoperative CTC detection between both groups (5 of 21 [24%] vs 6 of 22 [27%]; *P* = .54) (**Table 3**). Further analyses showed no statistically significant differences between the timing of blood sampling and detection of tumor cells for all patients (24 of 75 [32%] for preoperative vs 21 of 73 [29%] for intraoperative; *P* = .70) and for patients in the conventional hepatectomy (12 of 37 [32%] for preoperative vs 11 of 35 [31%] for intraoperative; *P* > .99) or anterior approach (12 of 38 [32%] for preoperative vs 10 of 38 [26%] for intraoperative; *P* = .62) group (eTable 1 in Supplement 2). Furthermore, there was no statistically significant difference in preoperative detection of disseminated tumor cells in blood and bone marrow samples of the respective patients (13 of 21 [62%] had both positive tumor cells detected in blood and bone marrow samples, whereas 8 of 21 [38%] had positive tumor cells detected in blood but no tumor cells detected in bone marrow samples; *P* > .99) (eTable 2 in Supplement 2).

Long-term Outcomes

Median follow-up time was 46 (IQR, 0-116) months for the total cohort. During follow-up, 16 patients (39%) in the conventional hepatectomy group and 19 patients (49%) in the anterior approach group died. There was no significant difference in median overall survival between patients in the conventional hepatectomy group (73 [95% CI, 42-104] months) compared with patients in the anterior approach group (55 [95% CI, 35-75] months) (*P* = .43) (**Figure 2**A).

On last follow-up, a total of 8 patients (20%) in the conventional hepatectomy group and 6 patients (15%) in the anterior approach group showed no evidence of disease (*P* = .47). Recurrence of colorectal cancer developed in 23 patients (56%) in the conventional hepatectomy group and in 17 (44%) in the anterior approach group (*P* = .46). The median disease-free survival was 48 (95% CI, 40-56) months in the conventional hepatectomy group and 40 (95% CI, 28-52) months in the anterior approach group (*P* = .88) (Figure 2B). There was no significant difference in the pattern of disease recurrence between both study groups. Most patients with recurrent disease had the first recurrence of CRLM within the liver (10 [24%] in the conventional hepatectomy vs 8 [21%] in the anterior approach groups; *P* = .82). Although we observed a higher incidence of disease recurrence in the lungs in patients after conventional hepatectomy (n = 9) vs anterior approach (n = 5), this difference did not reach statistical significance (*P* = .52). Five patients in the conventional hepatectomy group (3 lung, 1 liver, 1 colon) and 6 patients in the anterior approach group (2 liver, 2 lung, 1 bone, 1 pelvis) underwent repeated metastasectomy for recurrent disease. Chemotherapy for recurrent disease was administered in a total of 18 patients in the conventional hepatectomy and 12 patients in the anterior approach

Table 1. Baseline Characteristics

Characteristic	Study group[a] Conventional hepatectomy (n = 41)	Anterior approach (n = 39)	P value[b]
Age, mean (SD), y	60 (11)	63 (10)	.22
BMI, mean (SD)	25 (3)	24 (4)	.80
Sex ratio (No. M:F)	24:17	24:15	.78
ASA grade			
I/II	22 (54)	17 (44)	.19
III/IV	8 (20)	14 (36)	
Missing	11 (27)	8 (21)	
Cardiovascular comorbidities	3 (7)	7 (18)	.15
Preoperative laboratory test results, mean (SD)			
Albumin level, g/dL	4.3 (0.5)	4.2 (0.7)	.67
Bilirubin level, mg/dL	0.8 (1.1)	0.6 (0.5)	.41
AST level, U/L	46 (72)	50 (120)	.85
ALT level, U/L	60 (174)	48 (85)	.72
CEA level, ng/mL	168 (430)	40 (81)	.10
Primary tumor location			
Hemicolon			.50
Right	7 (17)	5 (13)	
Left	12 (29)	17 (44)	
Rectum	20 (49)	17 (44)	
Synchronous lesions	2 (5)	0	
Primary tumor T stage			
pT1/pT2	7 (17)	8 (21)	.28
pT3/pT4	33 (80)	30 (77)	
pTx	1 (2)	1 (3)	
Primary tumor nodal status			
pN0	18 (44)	12 (31)	.33
pN1/pN2	22 (54)	26 (67)	
pNx	1 (2)	1 (3)	
AJCC/UICC stage			
I	3 (7)	3 (8)	.97
II	5 (12)	4 (10)	
III	13 (32)	15 (38)	
IV	19 (46)	16 (41)	
Missing	1 (2)	1 (3)	
Onset of metastasis			
Synchronous	20 (49)	16 (41)	.49
Metachronous	21 (51)	23 (59)	
Time to liver metastasis, mean (SD), mo	17 (27)	14 (16)	.54
Characterization of CRLM, mean (SD)			
Preoperative No. of CRLM	2 (2)	2 (2)	.35
Preoperative size of largest CRLM, mm	48 (27)	44 (27)	.49
Histologic size of largest CRLM, mm	68 (121)	47 (33)	.31
Neoadjuvant chemotherapy before primary tumor resection	3 (7)	3 (8)	.95
Fluorouracil or capecitabine with or without oxaliplatin	2 (5)	2 (5)	
Bevacizumab with or without cetuximab	1 (2)	1 (3)	
Adjuvant chemotherapy after primary tumor resection	23 (56)	17 (44)	.26
Fluorouracil or capecitabine with or without oxaliplatin	19 (46)	10 (26)	
Bevacizumab with or without cetuximab or panitumumab	4 (10)	6 (15)	
Fluorouracil plus oxaliplatin plus regorafenib	0	1 (3)	
Neoadjuvant chemotherapy before CRLM resection	16 (39)	11 (28)	.81
Fluorouracil or capecitabine with or without oxaliplatin	6 (15)	3 (8)	
Fluorouracil or capecitabine plus irinotecan hydrochloride	1 (2)	1 (3)	
Bevacizumab with or without cetuximab or panitumumab	9 (22)	6 (15)	
Fluorouracil plus oxaliplatin plus regorafenib	0	1 (3)	

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union Internationale Contre le Cancer; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; pNx, nodal status not available; pTx, T stage not available.

SI conversion factors: To convert albumin to g/L, multiply by 10.0; ALT and AST to μkat/L, multiply by 0.0167; bilirubin to μmol/L, multiply by 17.104; and CEA to μg/L, multiply by 1.0.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] The unpaired 2-tailed *t* test was performed for continuous parameters. Pearson χ^2 test or Fisher exact test was performed for categorical parameters dependent on sample size.

Table 2. Operative Details and Perioperative Outcomes

Variable	Study group[a] Conventional hepatectomy (n = 41)	Study group[a] Anterior approach (n = 39)	P value[b]
Surgical procedure			
Hemihepatectomy			
Right-sided	29 (71)	27 (69)	.88
Extended right-sided	12 (29)	12 (31)	
Additional segmentectomy	0	2 (5)	.14
Additional wedge resection	10 (24)	9 (23)	.89
Extrahepatic resection	6 (15)	4 (10)	.81
R1 resection	2 (5)	4 (10)	.43
Pringle maneuver	19 (46)	13 (33)	.24
Duration of Pringle maneuver, mean (SD), min	10 (6)	24 (15)	<.001
Need for intraoperative transfusion	9 (22)	10 (26)	.70
No. of PRBC units transfused, mean (SD)	2.6 (1.0)	2.8 (2.5)	.81
No. of FFP units transfused, mean (SD)	4.0 (0)	5.5 (3.0)	.54
Operating time, mean (SD), min	171 (53)	221 (53)	<.001
Blood loss, mean (SD), mL	763 (484)	1051 (1150)	.15
Postoperative complications			
Grade I	4 (10)	8 (21)	.16
Grade II	5 (12)	2 (5)	
Grade IIIa	2 (5)	5 (13)	
Grade IIIb	3 (7)	1 (3)	
Grade IV	2 (5)	0	
Grade V (death)	0	2 (5)	
Specific complications			
Bile leakage	3 (7)	4 (10)	.64
Abdominal fluid collection	2 (5)	4 (10)	.36
Wound infection	4 (10)	4 (10)	.94
Postoperative cholangitis	2 (5)	2 (5)	.96
Pneumonia	3 (7)	3 (8)	.95
Sepsis	0	2 (5)	.14
Postoperative blood transfusion	10 (24)	7 (18)	.48
No. of PRBC units transfused, mean (SD)	1.8 (0.4)	1.8 (0.5)	.85
No. of FFP units transfused, mean (SD)	2.8 (1.3)	2.7 (1.2)	.86
Length of hospital stay, median (IQR), d	11 (9-15)	12 (10-17)	.74

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; PRBC, packed red blood cell; R1, residual tumor.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] The unpaired 2-tailed *t* test was performed for continuous parameters. Pearson χ^2 test or Fisher exact test was performed for categorical parameters dependent on sample size.

group. Overall, detection of CTC (preoperative and intraoperative) independently of the study group was associated with significantly decreased overall survival (median, 46 [95% CI, 40-52] vs 81 [95% CI, 54-107] months; *P* = .03) (Figure 2C). Similarly, disease-free survival was significantly shorter in patients with positive CTC detection (median, 40 [95% CI, 34-46] vs 60 [95% CI, 46-74] months; *P* = .04) (Figure 2D). On Cox proportional hazards regression analysis, detection of positive CTC was associated with poor survival (hazard ratio, 2.18; 95% CI, 1.09-4.37; *P* = .03) (eTable 3 in Supplement 2).

Discussion

The anterior approach technique was first described by Ozawa[15] in 1992. Several liver surgeons adopted this approach as a no-touch technique without tumor manipulation, and refinements were made by the hanging liver maneuver.[16] Although this approach was shown to be safe and potentially superior to the conventional approach in terms of morbidity, survival, and CTC dissemination in HCC, its efficacy and safety for resection of CRLM has remained unclear.[11,12,17] This randomized clinical trial addressed this lack of evidence using intraoperative CTC detection as the primary efficacy end point. Based on an a priori interim analysis, the trial was stopped prematurely, and the null hypothesis was not rejected. In the entire cohort, however, CTC detection was associated with poorer overall and disease-free survival, whereas CTC detection in the study groups was comparable and reflected a similar oncological outcome. Perioperative results revealed no significant differences between both surgical techniques except for a longer operating time in the anterior approach group.

Detection of CTC is associated with poor outcome in patients with primary as well as metastatic colorectal cancer.[6,7,18,19] Using the US Food and Drug Administration–approved CellSearch device for CTC detection in patients with colorectal cancer, moreover, Rahbari et al[8] demonstrated the ability of liver metastases to shed intact tumor cells into circulation. Measures to limit detachment of tumor cells from metastatic lesions are therefore urgently needed to decrease

Table 3. Oncological Outcomes

Outcome	Study group[a] Conventional hepatectomy (n = 41)	Anterior approach (n = 39)	*P* value[b]
Tumor cell detection			
Preoperative blood[c]	12 (32)	12 (32)	.57
Preoperative bone marrow[d]	9 (26)	12 (32)	.80
Intraoperative blood[e]	5 (24)	6 (27)	.54
Follow-up			
No evidence of disease	8 (20)	6 (15)	.47
Alive with disease	8 (20)	4 (10)	
Death from disease	15 (37)	16 (41)	
Death from other reason	1 (2)	3 (8)	
Recurrence (first site)	23 (56)	17 (44)	
Liver	10 (24)	8 (21)	.46
Adrenal gland	2 (5)	0	
Lung	9 (22)	5 (13)	
Bone	1 (2)	2 (5)	
Nodal	0	1 (3)	
Pelvic recurrence	0	1 (3)	
Colon	1 (2)	0	
Therapy of recurrence			
Chemotherapy	15 (37)	10 (26)	.36
Surgery	2 (5)	4 (10)	
Chemotherapy + surgery	3 (7)	2 (5)	
Loss to follow-up	3 (7)	1 (3)	

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] The Wilcoxon rank sum test was performed for continuous parameters. Pearson χ^2 test or Fisher exact test was performed for categorical parameters dependent on sample size.

[c] Preoperative blood samples were available for 37 patients in the conventional and 38 in the anterior approach group.

[d] Preoperative bone marrow samples were available for 34 patients in the conventional and 38 in the anterior approach group.

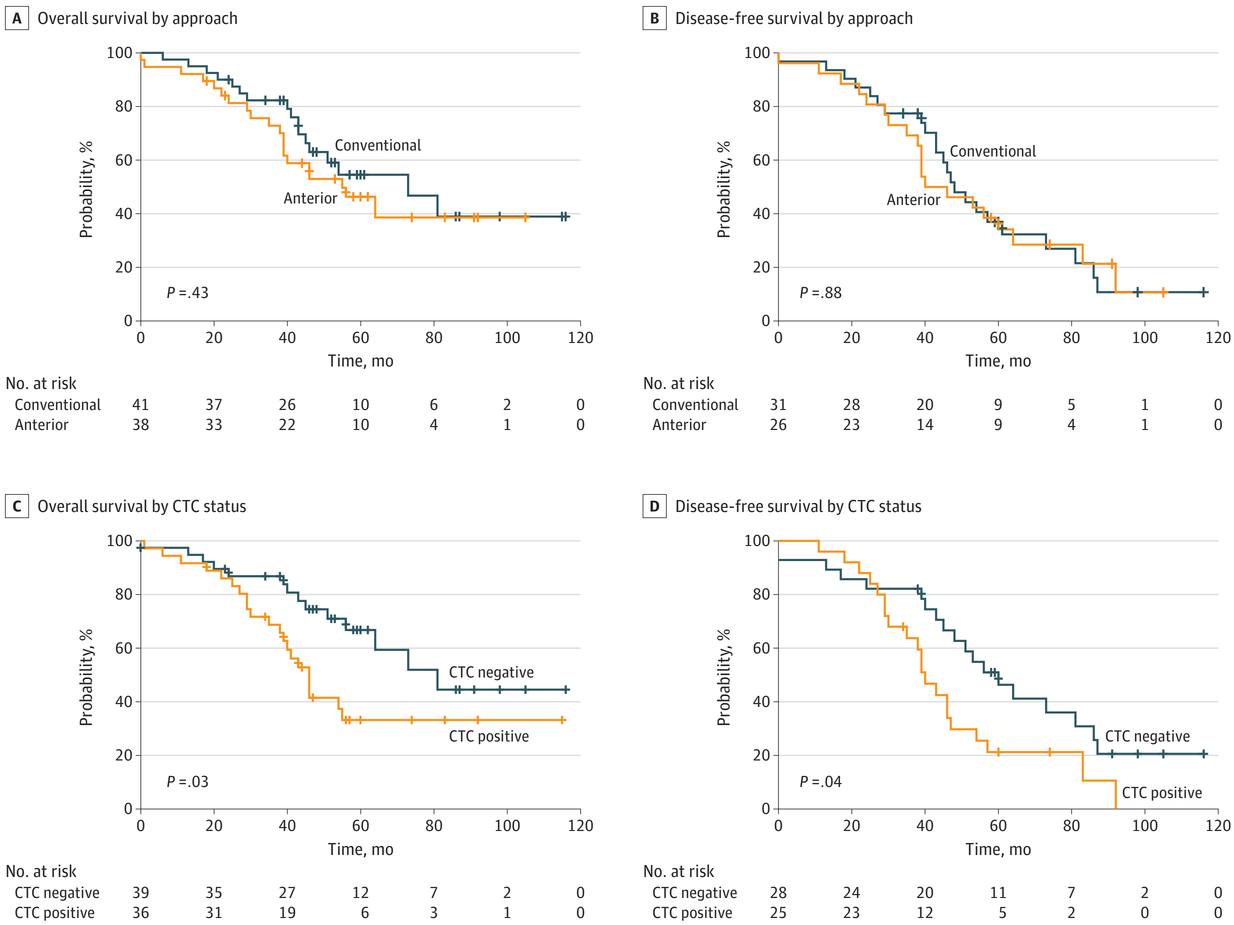
[e] Intraoperative blood samples of 21 patients in the conventional and 22 in the anterior approach group were considered in this analysis.

potential further spread of tumor cells. However, increasing data suggest that CTC spontaneously leaving the cellular union of a tumor mass are phenotypically and genotypically different from tumor cells that are detached from the original mass secondary to mechanical manipulation.[20-22] Although the anterior approach failed to reduce the intraoperative CTC detection rates, these data do not support further efforts to reduce tumor cell dissemination and subsequent disease recurrence by minimizing intraoperative manipulation. They should rather prompt strategies to prevent spontaneous tumor cell dissemination and to target minimal residual disease after potentially curative resection.

Most data on the oncological effect of the anterior approach are available for patients undergoing resection for HCC. The first randomized clinical study on this topic by Liu et al[12] analyzed patients with large HCC (>5 cm) and revealed a significant overall survival benefit after the anterior approach, whereas disease-free survival and perioperative outcome were comparable between the study groups. Although the recurrence rate was 56% in both study groups, recurrent disease was amenable to local ablative or surgical therapy in 80% of patients after the anterior approach compared with 17% after conventional hepatectomy. Furthermore, the anterior approach was associated with intraoperative lower plasma levels of albumin messenger RNA, supporting the evidence of lower levels of circulating liver cells during the anterior approach; however, CTC were not evaluated. Another recent randomized clinical trial by Hao et al[11] assessed patients with a heterogenous size of HCC and detected less mean and median epithelial cell adhesion molecule-positive CTC after the anterior approach compared with conventional hepatectomy in the first 10 postoperative days. Unfortunately, long-term outcome was not reported, but 2-year overall and recurrence-free survival was significantly reduced after the conventional approach. Thus far, perioperative outcome and long-term survival of patients with CRLM who underwent anterior approach and conventional hepatectomy were only assessed in 2 nonrandomized cohort studies.[23,24] Finally, these studies revealed no significant differences between the study groups, which is consistent with the results of the present study.

Morbidity after major hepatectomy remains high and ranges from 35% to 69% depending on the patient population, preexisting liver disease, and volume of the future liver remnant.[25-27] Although the anterior approach failed to provide a benefit with respect to patients' oncological outcome, advantages in perioperative outcomes might still justify its use in clinical routine. Our results showed a significantly prolonged operating time and duration of portal triad clamping for patients in the anterior approach group with no statistically significant difference in any further perioperative parameters, including blood loss, morbidity, and length of hospital stay. These data are in line with previous data from randomized trials that reported similar perioperative outcomes for patients who underwent a right-sided hepatectomy with the anterior approach and the conventional hepatectomy approach.[11,12,28] Owing to the lack of benefits in perioperative outcomes, the anterior approach does not appear superior to conventional hepatectomy. However, it is useful in patients with large masses that render primary mobilization of the right lobe difficult.[29] Previous studies on CTC detection using CK20 RT-PCR reported higher rates of CTC-positive findings.[30]

Figure 2. Kaplan-Meier Plots for Overall and Disease-Free Survival



The graphs depict Kaplan-Meier estimated overall survival (A) and disease-free survival (B) stratified by anterior approach vs conventional hepatectomy (log-rank test) and Kaplan-Meier estimated overall survival (C) and disease-free survival (D) stratified by perioperative positive and negative findings for circulating tumor cells (CTC) (log-rank test).

We used a highly sensitive and specific RT-PCR assay to identify CTC as described and standardized previously.[14,31] The number of patients with intraoperative positive tumor cells were comparable in both groups. In total, we found a considerably lower rate of CTC as described in the literature[31,32]; however, this could be owing to modern chemotherapy protocols with subsequent reduction of tumor cells.

Limitations

Our study has some limitations. First, our sample size is relatively small, which is primarily owing to a premature termination of the study. Because there were no statistically significant differences for the primary end point on interim analysis, the study was discontinued in line with the study protocol. Second, 8 patients had no bone marrow samples because of patient's preference to avoid an additional procedure. Third, evaluation of the primary end point was limited to a relatively small group of patients owing to a high number of patients with preoperative positive tumor cells in blood as well as intraoperative blood loss of more than 2000 mL, resulting in loss of statistical power and inconclusive results. Fourth, to minimize reporting bias, all patients were evaluated for secondary outcomes.

Conclusions

In this randomized clinical trial, patients undergoing right hepatectomy for colorectal cancer by anterior or conventional resection bore a similar risk of tumor cell dissemination. Findings suggest that both techniques are safe and indicate no statistically significant difference in postoperative outcome or long-term survival.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2020.

Published Online: November 4, 2020. doi:10.1001/jamasurg.2020.5050

Author Affiliations: Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany (Rahbari, Mehrabi, Reißfelder); now affiliated with Department of Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (Rahbari, Reißfelder); Department of Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (Birgin); Department of Gastrointestinal, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus at the Technische Universität Dresden, Dresden, Germany (Bork, Weitz).

Author Contributions: Drs Rahbari and Birgin contributed equally to this study. Drs Rahbari and Birgin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Weitz.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Rahbari, Birgin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Rahbari, Birgin.
Administrative, technical, or material support: Bork, Mehrabi, Weitz.
Supervision: Rahbari, Bork, Reißfelder.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Department of Surgery, University of Heidelberg.

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; interpretation of the data; and preparation, review, or approval of the manuscript. The sponsor was involved in the collection, management, and analysis of the data and granted approval to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? *Surgery*. 2018;163(6):1238-1244. doi:10.1016/j.surg.2018.01.004

2. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest Surg*. 2009;13(12):2141-2151. doi:10.1007/s11605-009-1050-0

3. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg*. 2009;250(3):440-448. doi:10.1097/SLA.0b013e3181b4539b

4. Rahbari NN, D'Angelica MI. Surgical salvage of recurrence after resection of colorectal liver metastases: incidence and outcomes. *Hepat Oncol*. 2017;4(1):25-33. doi:10.2217/hep-2017-0002

5. Bork U, Rahbari NN, Schölch S, et al. Circulating tumour cells and outcome in non-metastatic colorectal cancer: a prospective study. *Br J Cancer*. 2015;112(8):1306-1313. doi:10.1038/bjc.2015.88

6. Groot Koerkamp B, Rahbari NN, Büchler MW, Koch M, Weitz J. Circulating tumor cells and prognosis of patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer: a meta-analysis. *Ann Surg Oncol*. 2013;20(7):2156-2165. doi:10.1245/s10434-013-2907-8

7. Rahbari NN, Aigner M, Thorlund K, et al. Meta-analysis shows that detection of circulating tumor cells indicates poor prognosis in patients with colorectal cancer. *Gastroenterology*. 2010;138(5):1714-1726. doi:10.1053/j.gastro.2010.01.008

8. Rahbari NN, Bork U, Schölch S, et al. Metastatic spread emerging from liver metastases of colorectal cancer: does the seed leave the soil again? *Ann Surg*. 2016;263(2):345-352. doi:10.1097/SLA.0000000000001341

9. Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE. Liver resection for metastatic colorectal cancer. *Surgery*. 1986;100(4):804-810.

10. Weitz J, Koch M, Kienle P, et al. Detection of hematogenic tumor cell dissemination in patients undergoing resection of liver metastases of colorectal cancer. *Ann Surg*. 2000;232(1):66-72. doi:10.1097/00000658-200007000-00010

11. Hao S, Chen S, Tu C, Huang T. Anterior approach to improve the prognosis in HCC patients via decreasing dissemination of EpCAM$^+$ circulating tumor cells. *J Gastrointest Surg*. 2017;21(7):1112-1120. doi:10.1007/s11605-017-3410-5

12. Liu CL, Fan ST, Cheung ST, Lo CM, Ng IO, Wong J. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. *Ann Surg*. 2006;244(2):194-203. doi:10.1097/01.sla.0000225095.18754.45

13. Schmidt T, Koch M, Antolovic D, et al. Influence of two different resection techniques (conventional liver resection versus anterior approach) of liver metastases from colorectal cancer on hematogenous tumor cell dissemination: prospective randomized multicenter trial. *BMC Surg*. 2008;8:6. doi:10.1186/1471-2482-8-6

14. Weitz J, Kienle P, Magener A, et al. Detection of disseminated colorectal cancer cells in lymph nodes, blood and bone marrow. *Clin Cancer Res*. 1999;5(7):1830-1836.

15. Ozawa K. *Nonconventional Approaches to Advanced Liver Cancer: Liver Surgery Approached Through the Mitochondria.* Medical Tribune; 1992:117-165.

16. Liddo G, Buc E, Nagarajan G, Hidaka M, Dokmak S, Belghiti J. The liver hanging manoeuvre. *HPB (Oxford)*. 2009;11(4):296-305. doi:10.1111/j.1477-2574.2009.00068.x

17. Li Y, Xu KS, Li JS, et al. The research of no-touch isolation technique on the prevention of postoperative recurrence and metastasis of hepatocellular carcinoma after hepatectomy. *Hepatogastroenterology*. 2014;61(131):784-791.

18. Arrazubi V, Mata E, Antelo ML, et al. Circulating tumor cells in patients undergoing resection of colorectal cancer liver metastases: clinical utility for long-term outcome: a prospective trial. *Ann Surg Oncol*. 2019;26(9):2805-2811. doi:10.1245/s10434-019-07503-8

19. Seeberg LT, Waage A, Brunborg C, et al. Circulating tumor cells in patients with colorectal liver metastasis predict impaired survival. *Ann Surg*. 2015;261(1):164-171. doi:10.1097/SLA.0000000000000580

20. Gasch C, Bauernhofer T, Pichler M, et al. Heterogeneity of epidermal growth factor receptor status and mutations of *KRAS/PIK3CA* in circulating tumor cells of patients with colorectal cancer. *Clin Chem*. 2013;59(1):252-260. doi:10.1373/clinchem.2012.188557

21. Mostert B, Jiang Y, Sieuwerts AM, et al. *KRAS* and *BRAF* mutation status in circulating colorectal tumor cells and their correlation with primary and metastatic tumor tissue. *Int J Cancer*. 2013;133(1):130-141. doi:10.1002/ijc.27987

22. Soler A, Cayrefourcq L, Mazard T, et al. Autologous cell lines from circulating colon cancer cells captured from sequential liquid biopsies as model to study therapy-driven tumor changes. *Sci Rep*. 2018;8(1):15931. doi:10.1038/s41598-018-34365-z

23. She WH, Chan ACY, Ma KW, et al. Anterior approach to major resection for colorectal liver metastasis. *J Gastrointest Surg*. 2018;22(11):1928-1938. doi:10.1007/s11605-018-3840-8

24. Llado L, Muñoz A, Ramos E, Torras J, Fabregat J, Rafecas A. The anterior hanging-approach improves postoperative course after right hepatectomy in patients with colorectal liver metastases: results of a prospective study with propensity-score matching comparison. *Eur J Surg Oncol*. 2016;42(2):176-183. doi:10.1016/j.ejso.2015.11.009

25. Fritzmann J, Kirchberg J, Sturm D, et al. Randomized clinical trial of stapler hepatectomy versus LigaSure™ transection in elective hepatic resection. *Br J Surg*. 2018;105(9):1119-1127. doi:10.1002/bjs.10902

26. Fretland AA, Dagenborg VJ, Bjørnelv GMW, et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. *Ann Surg*. 2018;267(2):199-207. doi:10.1097/SLA.0000000000002353

27. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg*. 2012;255(3):405-414. doi:10.1097/SLA.0b013e31824856f5

28. Capussotti L, Ferrero A, Russolillo N, Langella S, Lo Tesoriere R, Viganò L. Routine anterior approach during right hepatectomy: results of a prospective randomised controlled trial. *J Gastrointest Surg*. 2012;16(7):1324-1332. doi:10.1007/s11605-012-1894-6

29. Coppa J, Citterio D, Cotsoglou C, et al. Transhepatic anterior approach to the inferior vena cava in large retroperitoneal tumors resected en bloc with the right liver lobe. *Surgery*. 2013;154(5):1061-1068. doi:10.1016/j.surg.2013.05.027

30. Hinz S, Hendricks A, Wittig A, et al. Detection of circulating tumor cells with CK20 RT-PCR is an independent negative prognostic marker in colon cancer patients: a prospective study. *BMC Cancer*. 2017;17(1):53. doi:10.1186/s12885-016-3035-1

31. Koch M, Kienle P, Hinz U, et al. Detection of hematogenous tumor cell dissemination predicts tumor relapse in patients undergoing surgical resection of colorectal liver metastases. *Ann Surg*. 2005;241(2):199-205. doi:10.1097/01.sla.0000151795.15068.27

32. Soeth E, Vogel I, Röder C, et al. Comparative analysis of bone marrow and venous blood isolates from gastrointestinal cancer patients for the detection of disseminated tumor cells using reverse transcription PCR. *Cancer Res*. 1997;57(15):3106-3110.