Original Study

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Perioperative Bevacizumab-based Triplet Chemotherapy in Patients With Potentially Resectable Colorectal Cancer Liver Metastases

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Abstract

Neoadjuvant triplet chemotherapy plus bevacizumab achieved pathologic response in 63% of colorectal cancer liver metastases. Early tumor shrinkage and posttreatment positron emission tomography predicted pathologic findings.

Background: In colorectal cancer liver metastases (CRCLM), bevacizumab-based neoadjuvant strategies provide increased pathologic response. We aimed at assessing the activity of perioperative capecitabine, oxaliplatin, irinotecan, and bevacizumab (COI-B regimen) in patients with potentially resectable CRCLM, and investigating biomarkers for early prediction of pathologic response. **Patients and Methods:** This was a single-center phase II study enrolling patients with liver-limited, borderline resectable disease and/or high-risk features. Patients received 5 preoperative and 4 postoperative cycles of biweekly COI-B (irinotecan 180 mg/m^2 and bevacizumab 5 mg/Kg on day 1, oxaliplatin 85 mg/m^2 on day 2, and capecitabine 1000 mg/m^2 twice a day on days 2 to 6). The primary endpoint was pathologic response rate in the intention-to-treat population. A Simon 2-stage design was adopted to detect an increase from 30% to 50% with a power of 90%. Dynamic imaging biomarkers (early tumor shrinkage [ETS], deepness of response, maximum standardized uptake volume [SUVmax]/regression index) and next generation sequencing data were explored as surrogates. **Results:** From June 2013 to March 2017, 46 patients were enrolled. Pathologic response was achieved in 63% patients (endpoint met), and responders achieved significantly better survival outcomes with respect to non-responders. The most frequent grade 3/4 adverse events were diarrhea and neutropenia (8.7%) in the preoperative phase and thromboembolic events (5.9%) in the postoperative phase. ETS and lower SUV-2 were significantly associated with pathologic response. **Conclusion:** The COI-B regimen is a feasible and highly active perioperative strategy in patients with molecularly unselected, potentially resectable CRCLM. ETS and SUV-2 have a promising role as imaging-based biomarkers for pathologic response.

Clinical Colorectal Cancer, Vol. 18, No. 1, 34-43

Keywords: Colorectal cancer liver metastases, FGD-PET/CT, Pathologic response, Triplet chemotherapy, Tumor regression grade

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Submitted: May 3, 2018; Revised: Aug 10, 2018; Accepted: Nov 19, 2018; Epub: Nov 24, 2018

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1533-0028/$ - see frontmatter
https://doi.org/10.1016/j.clcc.2018.11.004

Introduction

Despite the heterogeneity of prognosis and clinical presentation of colorectal cancer liver metastases (CRCLM),[1,2] neoadjuvant strategies are usually adopted for potentially resectable disease, and highly active combinations (such as triplet FOLFOXIRI [5-fluorouricil, leucovorin, oxaliplatin, and irinotecan] regimen plus bevacizumab or doublets plus anti-epidermal growth factor receptors [EGFRs] in RAS wild-type tumors) are the preferred conversion regimens for borderline resectable/unresectable disease.[3-6] Perioperative oxaliplatin-based chemotherapy remains the standard of care in resectable CRCLM[7] because the addition of cetuximab had a detrimental effect on survival even in patients with *RAS* wild-type status.[8]

The association between pathologic response of CRCLM following neoadjuvant treatment and overall survival has been demonstrated in several studies.[9-14] In particular, the use of bevacizumab in the neoadjuvant setting (particularly with oxaliplatin-based regimens) increases the pathologic response, even if the incidence of complete regressions (defined as tumor regression grade 1 [TRG1]) remains below 5%.[11-13]

In a previous retrospective dataset, we showed that bevacizumab-based neoadjuvant strategies seem to increase the pathologic response rate when compared with anti-EGFR-based ones.[15] Also, we showed that triplet chemotherapy plus cetuximab achieved a relatively low pathologic response rate (33%, none complete), despite significant radiologic response, in patients with RAS wild-type CRCLM and borderline resectability.[16] Drawing from these considerations, we supposed that bevacizumab added to a triplet chemotherapy backbone could achieve the maximal pathologic response, while maintaining the Response Evaluation Criteria in Solid Tumors (RECIST), early tumor shrinkage (ETS), and depth of response (DoR) activity expected with the use of intensive regimens.[17] In addition, the potential role of fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) as noninvasive prediction surrogates of pathologic responses has not extensively been studied in the bevacizumab era, despite the widespread use of this agent.

Here we primarily aimed at assessing the activity − in terms of pathologic response on the resected tumors − of perioperative COI-B (capecitabine, oxaliplatin, and irinotecan plus bevacizumab) regimen in patients with potentially resectable CRCLM and, secondarily, at investigating novel dynamic imaging or molecular biomarkers for early prediction of pathologic response.

Materials and Methods

This single-center, open-label, single-arm phase II study was approved by our Institutional Review Board (EudraCT number 2013-001362-42; clintrials.gov identifier: NCT02086656). Written informed consent was obtained from each patient before study procedures.

Study Population

Key inclusion criteria were: age > 18 years old; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; histologic diagnosis of colorectal adenocarcinoma; borderline resectable or high-risk liver-limited metastases, with or without previous resection of the primary tumor; previous adjuvant therapy terminated from at least 6 months before the diagnosis of metastases; and adequate organ function. Borderline resectability was defined by multidisciplinary team discussion according to at least 1 of the following criteria: planning of portal embolization/"2-stage hepatectomy" or radiofrequency ablation; tumor involvement of > 1 hepatic vein or ≥ 4 hepatic segments or any lesion ≥ 5 cm. Technically resectable patients had to bear at least 1 of the following adverse prognosis factors: > 4 metastatic nodules; carcinoembryonic antigen (CEA) > 200 ng/mL; synchronous metastases. Key exclusion criteria were: tumor involvement of liver > 75% and insufficient liver remnant (<25%) after surgery. Other inclusion and exclusion criteria are listed in the Supplemental Methods (in the online version).

Study Procedures and Treatments

Study procedures are summarized in Supplemental Figure 1 (in the online version). Initial resectability status was assessed at a multidisciplinary team meeting as per screening criterion. The preoperative phase consisted of 4 cycles of biweekly COI-B: irinotecan (180 mg/m^2) and bevacizumab (5 mg/Kg) on day 1 followed by oxaliplatin (85 mg/m^2) on day 2 and capecitabine 1000 mg/m^2 twice daily on days 2 to 6. CT or magnetic resonance imaging (MRI) scans and resectability assessment were repeated after 8 weeks from enrollment; 1 additional chemotherapy cycle (COI) without bevacizumab was given with the aim of avoiding the occurrence of a long interval between the last COI-B administration and surgery, according to previous studies.[13,18] No additional imaging was performed prior to surgery. Surgery was planned between 4 and 7 weeks from the last treatment dose and was conducted in a high-volume center with intraoperative ultrasound and intensive care assistance according to international standards. Lymph nodal hilar sampling was performed in all cases. Patients received prophylactic low molecular weight heparin for 4 weeks postsurgery as per internal institutional guidelines. In patients with rectal cancer and unresected primary tumor at study enrollment, standard preoperative chemo-radiotherapy was not compatible with the study treatment design; adjuvant radiotherapy was therefore discussed at multidisciplinary team meeting, to minimize the risk of local recurrence according to international guidelines.[19] At least 4 weeks and within 8 weeks from surgery, the patients received the COI-B regimen for additional 4 postoperative cycles.

Study Endpoints and Evaluations

The primary endpoint of the study was the intention-to-treat (ITT) pathologic response rate defined as TRG ≤ 3 according to Rubbia-Brandt et al.[9] Secondary objectives were overall response rate (ORR) according to RECIST v1.1 criteria, progression-free survival (PFS), overall survival (OS), R0 resection rate, and safety. Pretreatment evaluations included the following: medical history and physical examination; complete blood count and biochemical profile; electrocardiogram; and chest x-ray, CT scan of the chest, abdomen, and pelvis, with segmental localization and measurement of each tumor deposit. During chemotherapy, complete blood cell count and biochemical profiles, physical examinations, and assessment of toxicities were done before each treatment cycle. CT scans were repeated after 4 preoperative cycles, and a double-blinded radiologic review was performed.

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0.

Exploratory Biomarkers

Prespecified biomarkers potentially correlated to pathologic response were of 2 kinds: (1) Dynamic imaging-based. On top of ETS, defined as $\geq$ 20% reduction of target lesions at 8 weeks from treatment start and DoR, baseline and posttreatment FDG-PET/CT scans were performed in order correlate maximum standardized uptake values (SUVmax)/changes and the observed pathologic response in a subset of consenting patients. (2) Molecular-based. In both primary tumors and liver metastases, next-generation sequencing (NGS) using the Ion AmpliSeq Cancer Hotspot Panel v2 with the Ion-Torrent platform was employed as previously described,[20,21] whereas microsatellite instability was assessed as previously reported.[22]

Statistical Analysis

According to the Simon's optimal 2-stage design, the trial planned to enroll a maximum of 46 patients. Such a size yielded 90% power to test the hypothesis of a 50% pathologic response with the COI-B regimen in comparison to 30% baseline, using a 1-sided test at the 10% significance level. Estimation and testing of the response rate was determined on the basis of the exact binomial distribution.

All the analyses were conducted on the ITT population, defined as all subjects who provided informed consent, satisfied all baseline screening inclusion and exclusion criteria, and who received at least 1 treatment cycle.

Descriptive statistics were used to summarize patient characteristics, diagnoses, treatment administration and compliance, and efficacy and safety endpoints, as well as exploratory biomarkers. PFS was defined as the interval from treatment start to disease progression or death for any reason. OS time was calculated as the interval from treatment start date to the date of death for any cause, with censoring at the date of last contact for patients alive.

Possible association between pathologic response and other factors was investigated by means of univariable logistic models. Logistic model results are reported as odds ratios (OR), together with corresponding 95% confidence intervals (CIs) and Wald's test *P* values. An OR greater than 1 indicates an increased chance of pathologic response, whereas a decreased chance is indicated by an OR lower than 1. PFS and OS were described using Kaplan-Meier curves, whereas the log-rank test was used to perform statistical comparisons. For PFS analysis, Cox models were also fitted either in the univariable or multivariable setting, including in the latter an Akaike information criterion-based backward selection procedure. Results are reported in terms of hazard ratios (HRs), together with corresponding 95% CIs and the Wald test *P* values.

Any 2-sided $P < .05$ was considered statistically significant. Statistical analyses were carried out using SAS (version 9.4, SAS Institute, Cary, NC) and R software (version 3.4.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' Characteristics

From June 2013 to March 2017, 46 patients were enrolled in the ITT population, and 44 were treated as per protocol. One patient experienced a liver progression after the third cycle of preoperative chemotherapy and was deemed not amenable of surgery, whereas another patient did not receive primary tumor resection owing to rapid multi-site progression after liver-first surgery. Patient and disease characteristics are summarized in Table 1. At the multidisciplinary team baseline screening, the disease was judged as borderline resectable in 22 (48%) patients for the reasons detailed in Supplemental Figure 2 (in the online version). In 18 (39%) patients, the primary tumor had not been resected at time of study enrollment. Of these, 4 patients underwent a liver metastases-first resection, 10 a concomitant primary and liver metastases removal, and 3 a primary tumor-first surgery. Only 1 patient underwent 2-stage hepatectomy (initially foreseen in 4), whereas 2 additional patients underwent radiofrequency ablation plus R0 resection procedures (initially foreseen in 4). Adjuvant radiation was given to all but 1 patient with rectal cancers. No microscopic involvement of hilar lymph nodes was detected in all patients undergoing surgery.

Tumor-related Outcomes

The primary endpoint of the study was met, as pathologic response (TRG1-3) was achieved in 63% (95% CI, 48%-77%) of patients (29 out of 46). Major responses (TRG1-2) were observed in 24% (95% CI, 13%-39%), although complete pathologic response was observed in only 2 (4.3%) patients (95% CI, 0.5-14.8%) (Figure 1).

Additionally, activity was assessed through radiologic parameters. The ORR was 65% (95% CI, 50%-79%), the ETS was 83% (95% CI, 69%-92%), and the median DoR was −34%; (interquartile range [IQR], −42% to −25%). R0 resection was performed in 37 (80%) patients (95% CI, 66%-91%) of 45 patients who underwent liver surgery.

Patient-related Outcomes

At a median follow-up of 26 months (IQR, 14-37.4 months), 25 (54%) patients had disease recurrence, but only 9 (20%) of them subsequently died. The median PFS was 20.8 months (IQR, 8.0-38.9 months), whereas the median OS was not reached (IQR, 34.9-NR). Two-year PFS and OS rates were 40.1% (95% CI, 26.7%-60.2%) and 84.8% (95% CI, 74.4%-96.8%), respectively (Figure 2, panels A and B). In patients with pathologic response (TRG1-3), 2-year PFS and OS were 56.8% (95% CI, 39.3%-81.9%) and 96.0% (95% CI, 88.6%-100%), whereas in non-responders such rates dropped to 9.5% (95% CI, 1.6%-58%) ($P = .0007$) (Figure 2, panel C) and 66.3% (95% CI, 46.0%-95.5%), respectively ($P = .003$) (Figure 2, panel D).

Exploratory Biomarkers

Of note, ETS was experienced more frequently by patients with pathologic response (TRG1-3, 93.1%) as compared with non-responders (TRG 4-5, 64.7%), whereas neither RECIST criteria nor DoR had a significant association with pathological response (Figure 3, panel A) (see Supplemental Table 1 in the online version).

In 25 (54%) patients in which FDG-PET/CT data were available, baseline SUV-1 values did not predict pathologic response (Figure 3, panels B-D) (see Supplemental Table 1 in the online version). Conversely, patients with pathologic response showed

Table 1 Patient and Disease Characteristics in the Intent-to-treat Population

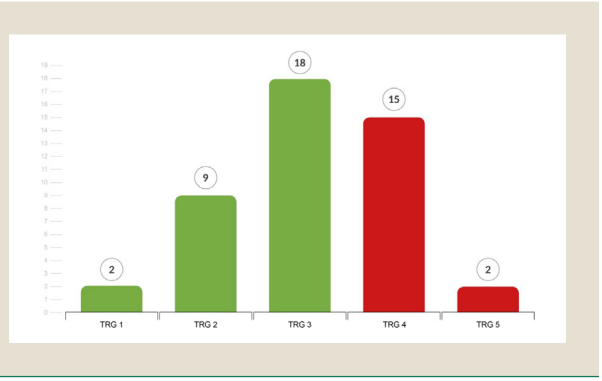
Characteristics	N = 46 N (%)
Gender	
Male	28 (60.9)
Female	18 (39.1)
Age, y	
Median (IQR)	62 (54-66)
ECOG PS	
0	39 (84.8)
1	7(15.2)
Disease-free interval, mos	
≥ 12	8 (17.4)
< 12	38 (82.6)
Primary tumor location	
Right colon	10 (21.7)
Left colon	24 (52.2)
Extraperitoneal rectum	12 (26.1)
Resected primary tumor at enrollment	
Yes	28 (60.9)
No	18 (39.1)
N stage primary tumor	
N0	14 (30.4)
N1-2	31 (67.4)
NA[a]	1 (2.2)
No. of liver metastases	
Single	12 (26.1)
2-3	18 (39.1)
≥ 4	16 (34.8)
Diameter of liver metastases, cm	
< 5	36 (78.3)
≥ 5	10 (21.7)
No. of hepatic segments	
< 4	30 (65.2)
≥ 4	16 (34.8)
Involvement of > 1 hepatic vein	
Yes	4 (8.7)
No	42 (91.3)
Bilobar involvement	
Yes	26 (56.5)
No	20 (43.5)
CEA level, mg/mL	
Median (IQR)	6.9 (2.7-52.1)
≥ 200	5 (10.9)
RAS and BRAF mutational status	
RAS mutated	29 (63.0)
BRAF mutated	-
RAS and *BRAF* wild-type	17 (37.0)
TP53 mutational status	
Mutated	25 (54.3)
Wild-type	19 (41.3)
NA[b]	2 (4.3)
PI3KCA mutational status	
Mutated	13 (28.3)
Wild-type	31 (67.4)
NA[b]	2 (4.3)
MMR status	
MSI-high	1 (2.2)
MSS	45 (97.8)

Abbreviations: CEA = CARCINOEMBRYONIC antigen; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; MMR = mismatch repair; MSI = microsatellite instable; MSS = microsatellite stable; NA = not available.
[a]One patient failed to undergo primary tumor resection.
[b]Next generation sequencing analysis failed for 2 patients owing to insufficient DNA quality.

lower SUV-2 values (median SUV-2, 7.1; IQR, 4.8, 10.2) and higher regression index (RI) (median RI, −51%; IQR, −63%, −39%) as compared with non-responders (median SUV-2, 14.9; IQR, 11.1, 25.2; median RI, −32%; IQR, −48%, +41%).

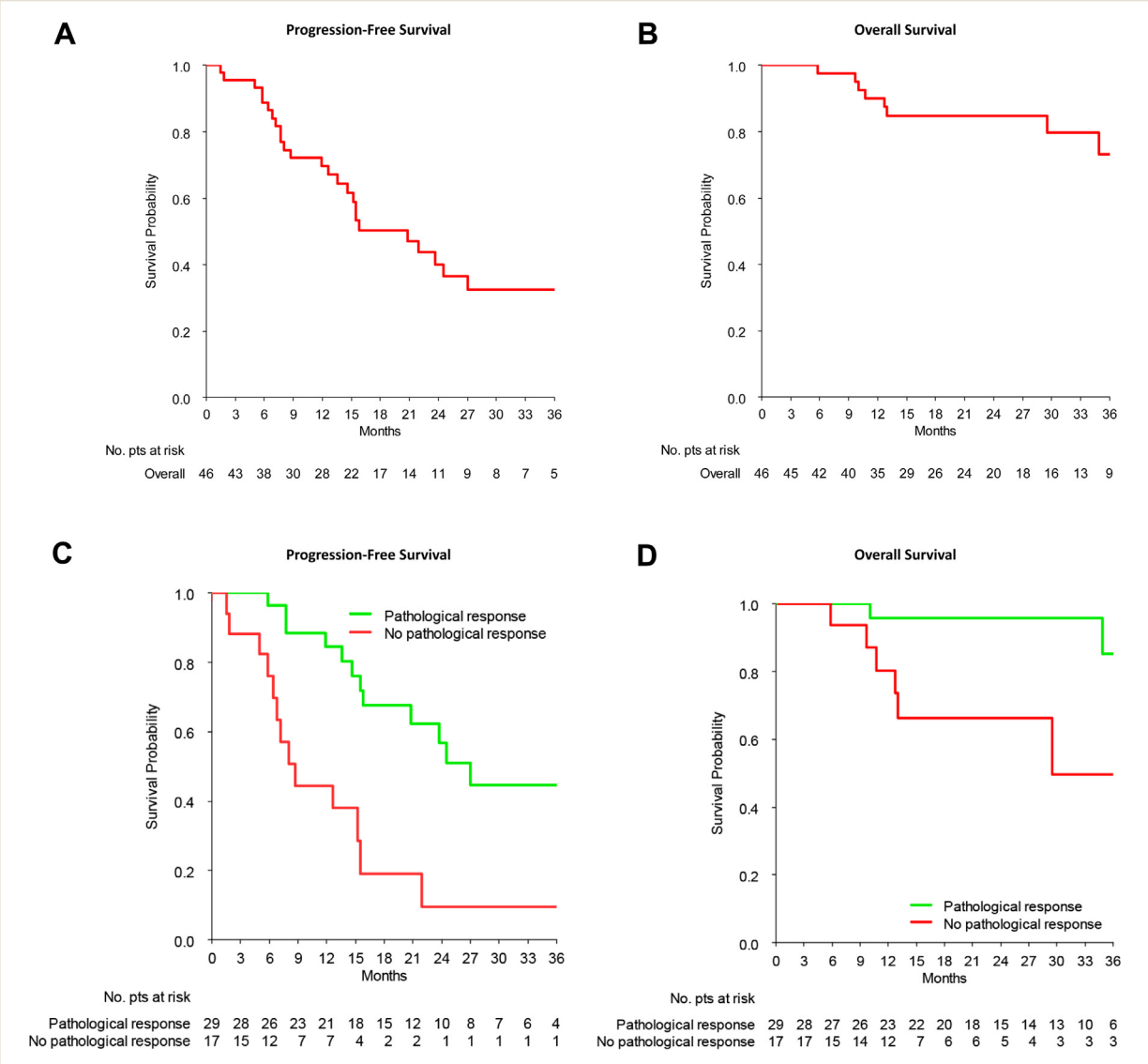
Regarding molecular data, *RAS* or *TP53* mutations were not associated with poorer outcome (Table 2). However, the presence of *PI3KCA* mutations conditioned a poorer median PFS, but only in the univariable model (HR, 2.508; 95% CI, 1.099-5.724; $P = .029$). Intriguingly, the only patient with high microsatellite instability was among the 2 achieving a pathologic complete response.

Figure 1 Bar Graph for Pathologic Responses According to Rubbia-Brandt et al. TRG1 Corresponded to Absence of Tumor Cells Replaced by Abundant Fibrosis; TRG2 to Rare Residual Tumor Cells Scattered Throughout Abundant Fibrosis; TRG3 to More Residual Tumor Cells Throughout a Predominant Fibrosis; TRG4 to Large Amount of Tumor Cells Predominating Over Fibrosis; and TRG5 Most Exclusively to Tumor Cells Without Fibrosis. Because the Analysis was Planned in the Intent-To-Treat Population, the 1 Patient With Liver Progression During Preoperative Chemotherapy and Deemed Not Amenable to Surgery Was Considered to Have a TRG5 Pathologic Response



Abbreviation: TRG = tumor regression grade.

Figure 2 Kaplan-Meier Curves for Progression-free Survival and Overall Survival in the Intent-to-Treat Population (A, B) and According to Pathologic Response (C, D). In Panel C and D, Red Lines Indicate Patients With Pathologic Response (TRG1-3), Whereas Green Lines Indicate Patients Without Pathologic Response (TRG4-5). Patients With Pathologic Response had Higher Progression-free Survival and Overall Survival Compared With Patients Without Pathologic Response



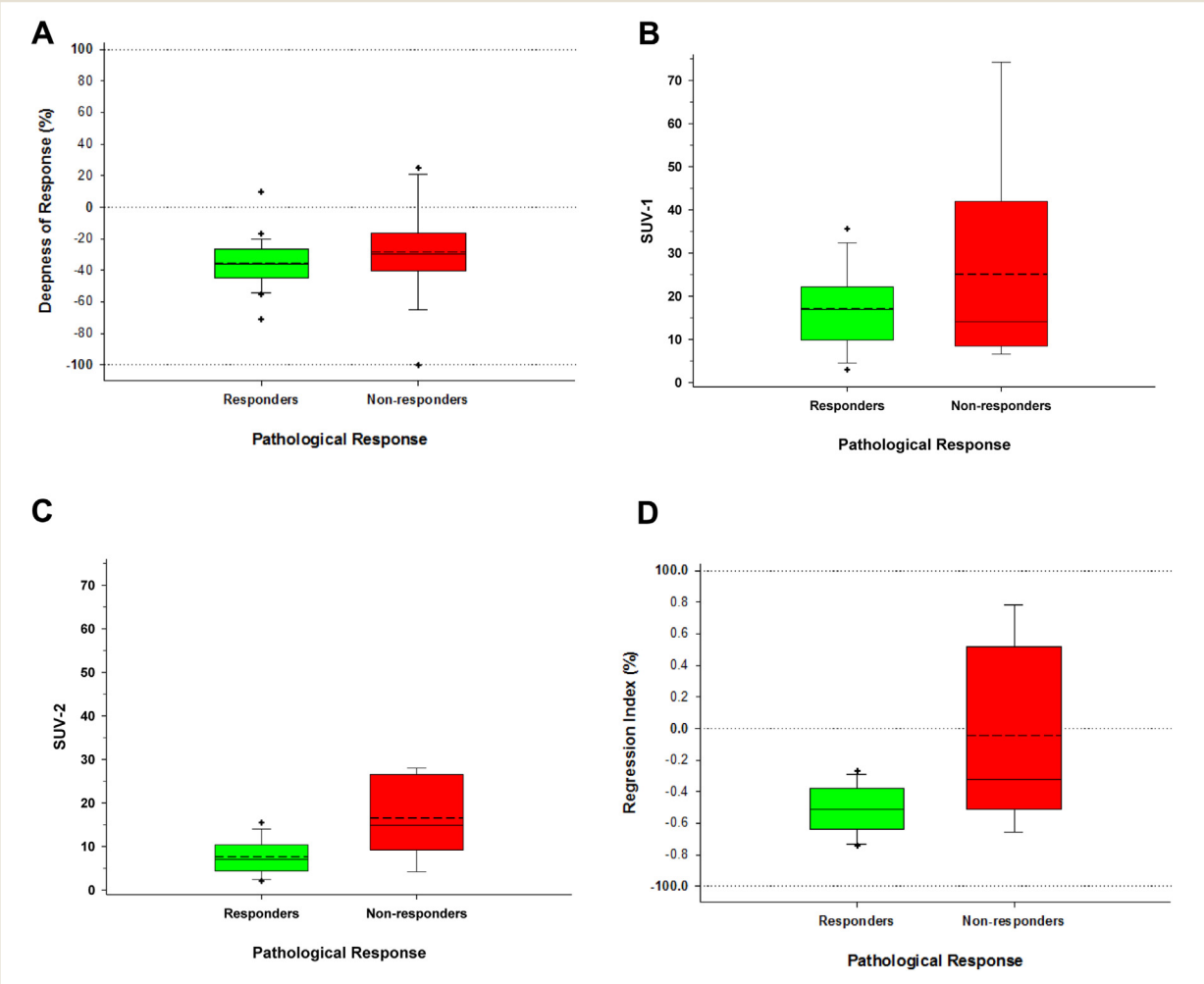
Abbreviation: TRG = tumor regression grade.

The ability of baseline variables to predict the chance of pathologic response was assessed by univariable logistic regression models (Table 3) that showed significant correlation with female gender ($P = .017$), lower SUV-2 ($P = .036$), and presence of ETS ($P = .046$).

Prognostic Modeling

Univariable analysis showed that male gender, younger age, no ETS, no pathologic response, R1 margins, involvement of ≥ 4 hepatic segments, and *PI3KCA* mutations were associated with a shorter PFS (Table 2). At multivariable analysis, only male gender (HR, 3.710; 95% CI, 1.216-11.324; $P = .021$) and no ETS (HR, 4.704; 95% CI, 1.583-13.974; $P = .005$) maintained their poor prognostic role, whereas a strong trend was observed for R1 margins (HR, 2.515; 95% CI, 0.995-6.357; $P = .051$) (Table 2). Given the low number of death events, the same analysis was not feasible for OS at the time of data cutoff. The FDG-PET/CT data were not included in the Cox model because they were restricted to a patient subgroup. To overcome this limitation, SUV-2 optimal cutoff was assessed with Cox modeling, and a value of 11.1 yielded maximum prognostic separation in terms of PFS. Accordingly, Kaplan-Meier survival curves showed better PFS for patients with SUV-2 $\leq$ 11.1 versus $>$ 11.1 (HR, 3.338; 95% CI, 0.857-12.998; trend for significance $P = .0822$), as shown in Supplemental Figure 3 (in the online version).

Figure 3 Box Plots of Deepness of Response (A), SUV-1 (B), SUV-2 (C), and Regression Index (D), According to Pathologic Response. Green Boxes Indicate Patients With Pathologic Response (TRG1-3), Whereas Red Boxes Indicate Patients Without Pathologic Response (TRG4-5). Baseline SUV-1 Values and Deepness of Response Were Not Associated With Pathologic Response; on the Contrary, Patients With Pathologic Response had Lower SUV-2 Values and Higher Regression Index



Abbreviations: SUV = standardized uptake value; TRG = tumor regression grade.

Safety

All patients received at least 1 treatment dose. Based on our previous experience,[23] all patients were screened for *DPYD* and *UGT1A1* single nucleotide polymorphisms, and initial dose reductions were performed for patients with homozygous *28/*28 *UGT1A1* status or high-risk *DPYD* genotype. Table 4 summarizes the frequency of all grades of adverse events (AEs). During the preoperative phase, the most frequent grade 3/4 AEs were diarrhea and neutropenia — both with an incidence of 8.7%. The median number of cycles for the preoperative phase was 5 (range, 3-5 cycles). Preoperative treatment interruption was owing to AEs in 3 patients, tumor progression in 1 patient, and medical decision in 4 patients. After surgery, 34 (74%) patients received the post-operative protocol treatment (see Supplemental Figure 4 in the online version). The most frequent grade 3/4 AEs during the postoperative phase were thromboembolic events (5.9%) followed by diarrhea, anemia, and peripheral neuropathy (2.9%). The median number of postoperative cycles was 4 (range, 2-4 cycles). Postoperative treatment interruption was owing to AEs in 3 patients and tumor progression in 1 patient. Chemotherapy dose reductions were performed according to the protocol in 7 patients in the preoperative phase and 8 more patients in the postoperative phase.

Liver resection complications of any grade occurred in 15 (33%) patients. Fever and pleural effusion were the most commonly observed, occurring in 5 (11%) and 4 (9%) patients, respectively, with no impact on the length of hospitalization. Primary tumor resection complications of any grade occurred in 4 (9%) patients. Anastomotic leakage leading to peritonitis was the most serious complication, occurring in 1 (2%) patient. No surgical mortality was observed (see Supplemental Table 2 in the online version). These results were consistent with previous studies.[18,24]

Table 2 Univariable and Multivariable Proportional Hazard Regression Models on PFS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Gender						
Male versus female	4.907	1.623-14.829	**.005**	3.710	1.216-11.324	**.021**
Age, y						
66 versus 54[a]	0.548	0.337-0.892	**.016**	—	—	—
ECOG PS						
PS 1 versus PS 0	1.343	0.455-3.965	.593	—	—	—
Disease-free interval, mos						
$<$ 12 versus $\geq$ 12	1.107	0.376-3.259	.853	—	—	—
Primary tumor location						
Left versus right colon	0.725	0.298-1.768	.480	—	—	—
N stage primary tumor						
N1-2 versus N0	1.858	0.684-5.048	.225	—	—	—
No. of liver metastases			.096	—	—	—
2-3 versus single	1.884	0.588-6.039	.286	—	—	
$\geq$ 4 versus single	3.615	1.093-11.952	.035			
Diameter of liver metastases, cm						
$\geq$ 5 versus $<$ 5	0.705	0.240-2.069	.525	—	—	—
No. of hepatic segments						
$\geq$ 4 versus 1-3	3.697	1.484-9.209	**.005**	—	—	—
Bilobar involvement						
Yes versus no	2.175	0.939-5.035	.070	—	—	—
CEA level, ng/mL						
52.1 versus 2.7[a]	0.914	0.761-1.098	.338	—	—	—
RAS mutational status						
Mutated versus wild-type	1.604	0.663-3.879	.295	—	—	—
TP53 mutational status						
Mutated versus wild-type	1.153	0.495-2.682	.742	—	—	—
PI3KCA mutational status						
Mutated versus wild-type	2.508	1.099-5.724	**.029**	—	—	—
RECIST v1.1 response						
Yes versus no	0.938	0.387-2.271	.887	—	—	—
Early tumor shrinkage						
No versus yes	5.193	1.777-15.179	**.003**	4.704	1.583-13.974	**.005**
Deepness of response						
−25% versus −42%[a]	1.344	0.826-2.185	.234	—	—	—
Pathologic response						
No versus yes	3.462	1.517-7.903	**.003**	—	—	—
TRG			**.012**			
TRG3 versus TRG1-2	0.708	0.228-2.200	.550	—	—	—
TRG4-5 versus TRG1-2	2.870	1.054-7.813	.039	—	—	
Surgical margins						
R1 versus R0	3.370	1.370-8.289	**.008**	2.515	0.995-6.357	.051

Bold *P* values indicate statistically significant results.
Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; RECIST = Response Evaluation Criteria in Solid Tumors; TRG = tumor regression grade.
[a]The 2 values are, respectively, the 3rd and 1st quartiles of the variable distribution.

Table 3 Univariable Logistic Models Evaluating the Chance of Pathologic Response

Variable	OR	95% CI	*P* Value
Gender			
Male versus female	0.133	0.026-0.695	**.017**
Age, y			
66 versus 54[a]	1.424	0.647-3.134	.379
ECOG PS			
PS 1 versus PS 0	0.500	0.088-2.830	.433
Disease-free interval, mos			
< 12 versus ≥ 12	2.083	0.443-9.790	.353
Primary tumor location			
Left versus right colon	1.278	0.301-5.420	.740
N stage primary tumor			
N1-2 versus N0	1.111	0.294-4.205	.877
No. of liver metastases			
2-3 versus single	0.167	0.017-1.623	.064
≥ 4 versus single	0.071	0.007-0.686	
Lesion diameter, cm			
≥ 5 versus < 5	0.783	0.185-3.319	.740
No. of hepatic segments			
≥ 4 versus 1-3	0.579	0.164-2.045	.396
Bilobar involvement			
Yes versus no	0.424	0.118-1.532	.191
CEA level, ng/mL			
52.1 versus 2.7[a]	1.074	0.810-1.423	.619
RAS mutational status			
Mutated versus wild-type	0.982	0.279-3.461	.977
TP53 mutational status			
Mutated versus wild-type	0.750	0.212-2.658	.656
PI3KCA mutational status			
Mutated versus wild-type	0.750	0.208- 2.703	.660
SUV-1			
21.8 versus 10.1[a]	0.664	0.350-1.259	.210
SUV-2			
13.4 versus 6.4[a]	0.225	0.056-0.909	**.036**
Response index			
−32% versus −62%$_a$	0.268	0.066-1.080	.064
Early tumor shrinkage			
No versus yes	0.163	0.027-0.970	**.046**
Deepness of response			
25% versus −42%[a]	0.839	0.483-1.456	.532

Bold *P* values indicate statistically significant results.
Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; OR = odds ratio; SUV = standardized uptake value.
[a]The 2 values are, respectively, the 3rd and 1st quartiles of the variable distribution.

Discussion

This is a study designed to investigate the pathologic response achievable with a triplet chemotherapy plus bevacizumab (COI-B regimen) in patients with potentially resectable CRCLM. A semi-quantitative score of the quality/extent of pathologic response (TRG)[9] has been proposed by several studies as an independent prognostic factor associated with outcomes (disease-free survival and OS) following CRCLM resection, and is improved by both oxaliplatin- and bevacizumab-based neoadjuvant regimens.[9,12,13] However, previous studies in this setting were biased by the most frequent use of doublets — inherently heterogeneous — and above all, by their retrospective nature. Therefore, our primary endpoint was based on activity of COI-B regimen in patients with borderline resectable/high risk CRCLM. Such hypothesis was met, as pathologic response was observed in 63% of ITT patients, being major/complete in about one-quarter (24%). These results are strengthened by the statistically significant (at least on univariable analysis) correlation of pathologic response with survival endpoints,[9,10,12] with 2-year PFS being 16.7% higher in patients with pathologic response compared with the overall study population.

Liver resection was associated in all cases with hilar nodal sampling. Even if this procedure granted a more precise liver staging, the absence of any positive finding of microscopic nodal involvement may question its utility. However, the sample size may have influenced our results on this point.

The observed ORR and R0 resection rate are in line with previous randomized trials demonstrating the high activity of triplet regimens plus bevacizumab, both in the first-line and conversion settings. In detail, our 63% ORR is similar to 65% with FOLFOXIRI plus bevacizumab compared with 53% with doublet plus bevacizumab in the TRIBE (TRIplet plus BEvacizumab) study.[4,25] In addition, we showed that ETS — significantly increased by highly active regimens[26,27] — is associated with pathologic response. This suggests that also treatment intensification with 3-drug regimens may impact the TRG scoring, as previously shown for oxaliplatin and bevacizumab-based regimens: a hypothesis that awaits confirmation in a randomized setting, with the availability of a control arm of doublets (ideally FOLFOX) plus bevacizumab.[28]

Noteworthy, the tumor-related variables with independent prognostic impact were only ETS and, marginally, resection margins (Table 2), whereas pathologic response was no longer significant. Several interpretations may be given for this observation. First, initial studies on pathologic response did not investigate thoroughly novel radiologic parameters such as ETS and DoR, as well as molecular status.[9-12] Furthermore, ETS and DoR may influence not only pathologic response but also resection margin status,[29] leaving open the possibility that highly active regimens may be "per se" associated with better outcomes of liver surgery for patients with more rapid and profound responses. Incidentally, our 5-trial pooled analysis of triplets plus bevacizumab versus cetuximab has shown that bevacizumab-based triplets achieve a significantly higher pathologic response rate than anti-EGFRs-based ones.[30] Finally, because pathologic response may be permissive to R0 margins,[11,15] bevacizumab-based regimens (particularly with triplet-based backbones) may further improve the outcomes of resections independently from other variables.

Another crucial aspect of our study lies in the attempt to identify biomarkers that might be exploited to improve patient management. Previous retrospective studies showed that *KRAS* mutations may be associated with poorer outcomes following curative resections.[31-33] We could not prospectively confirm such results. Regarding pathologic response, no molecular marker was found to

Table 4 Treatment-related Adverse Events According to Common Terminology Criteria for Adverse Events v4.0

Adverse Events	Preoperative Treatment (N = 46), N (%)				Postoperative Treatment (N = 34), N (%)			
	G1	G2	G3	G4	G1	G2	G3	G4
Nausea/vomiting	3 (6.5)	4 (8.7)	–	–	4 (11.8)	4 (11.8)	–	–
Diarrhea	9 (19.6)	10 (21.7)	4 (8.7)	–	3 (8.8)	10 (29.4)	1 (2.9)	–
Mucositis	1 (2.2)	1 (2.2)	–	–	–	–	–	–
Peripheral neuropathy	3 (6.6)	–	–	–	1 (2.9)	2 (5.9)	1 (2.9)	–
Anemia	2 (4.3)	1 (2.2)	–	–	3 (8.8)	1 (2.9)	1 (2.9)	–
Asthenia	6 (13.0)	3 (6.5)	1 (2.2)	–	2 (5.9)	1 (2.9)	–	–
Hepatobiliary disorders	–	2 (4.5)	–	–	2 (5.9)	–	–	–
Anorexia	2 (4.3)	1 (2.2)	–	–	–	–	–	–
Hypertension	3 (6.6)	–	–	–	–	–	–	–
Hypotension	–	1 (2.2)	–	–	–	–	–	–
Neutropenia	6 (13.0)	1 (2.2)	4 (8.7)	–	–	3 (8.8)	–	–
Thromboembolic event	1 (2.2)	–	1 (2.2)	–	1 (2.9)	–	1 (2.9)	1 (2.9)
Thrombocytopenia	1 (2.2)	–	–	–	–	–	–	–

Abbreviation: G = grade.

be predictive. This for at least 3 reasons: (1) the extended *RAS* evaluation carried out by means of NGS could have detected a higher proportion of mutated samples; (2) the ability of highly active triplets plus bevacizumab to counteract several adverse prognostic factors, including *RAS* or *BRAF* mutations[29]; and (3) the more homogeneous patient population enrolled in this study. Regarding PFS, only the "relatively uncommon" *PI3KCA* mutations (that are usually found in *RAS*-mutated cancers) seemed to be associated with poorer outcomes, but only at univariable analysis; therefore, a larger sample size is needed to retest such hypothesis. So far, only 1 study reported worse resection outcomes in patients with double *APC* and *PIK3CA* mutations.[34]

In the present study, prespecified exploratory biomarkers were intentionally selected, in order to predict early pathologic response prior to surgery. This is because early prediction of the chance of pathologic response prior to liver resection may lead to "in vivo" assessment of treatment sensitivity and, potentially, treatment shifts towards non−cross-resistant regimens in patients at unacceptable risk of poor resection outcomes.

Intriguingly, in the ancillary FDG-PET/CT study, only SUV-2 − as early assessment at 8 weeks from treatment start − was predictive of pathologic response. Although the role of FDG-PET/CT is well established for improving the sensibility of hepatic and extra-hepatic detection/staging,[35,36] only 1 study in patients receiving chemotherapy without bevacizumab found a moderate correlation between SUVmax regression and pathologic response.[37] Given the higher pathologic response achieved by our regimen and, in general, with bevacizumab-based regimens,[10,12,13] further prospective validation of SUV-2 is required in more modern patient populations.

Despite its prospective nature, our study has several limitations. First, capecitabine-based triplets are not considered a standard, even if we previously showed that the COI regimen may be safely used in several advanced or perioperative settings.[16,17,38] Second, in absence of clear evidence on the optimal postoperative regimen when triplet chemotherapy and/or bevacizumab-based therapies are chosen preoperatively, we administered bevacizumab also in the postoperative phase. However, in other studies including our previous experience with triplet chemotherapy plus the anti-EGFR monoclonal antibody cetuximab, the same regimen in the postoperative setting was adopted, with acceptable toxicity profiles.[16,18,25,28,39] The choice of giving 18 weeks of treatment instead of 24 is another limitation of our study.

A relevant proportion of patients enrolled in this study, although resectable, presented with high-risk features predicting recurrence. As mentioned above, 63% of cases harbored RAS mutations, which may be associated with poorer outcome.[31-33] Moreover, the nonrandomized nature of the investigation leaves opens the possibility that several investigated factors such as imaging and biomarkers may be prognostic rather than predictive, even if prediction of pathologic response is directly related to a treatment effect rather than being inherently linked to tumor or patient characteristics. Finally, pathologic response cannot be regarded as a validated surrogate for OS following neoadjuvant treatment of CRCLM. However, this phase II nonrandomized study must be considered as exploratory in its nature. Given the large body of evidence regarding the role of bevacizumab in improving pathologic response, we selected the latter as an objective and measurable activity marker for resected CRCLM, assuming that R0 resection may be mostly related to the quality of surgery technique in a monocenter study conducted at a tertiary cancer center.

Conclusions

Triplet capecitabine-based chemotherapy plus bevacizumab (COI-B regimen) is a feasible and highly active perioperative strategy in patients with molecularly unselected, potentially resectable CRCLM. Further investigation of triplets plus bevacizumab versus anti-EGFRs-based doublets as conversion therapy for *RAS* wild-type unresectable or borderline resectable CRCLM are needed to establish the optimal treatment strategies for this patient population.

Clinical Practice Points

- The activity in terms of pathologic response of highly active regimens such as triplets plus bevacizumab has never been prospectively investigated in patients with CRCLM.
- Triplet plus bevacizumab achieved a 63% pathologic response rate in patients with potentially resectable disease.
- We could predict pathologic response by means of early tumor shrinkage and PET-2.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.11.004.

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Supplemental Methods

Inclusion Criteria

- Histologic diagnosis of colorectal adenocarcinoma.
- Liver-limited metastases or metastases mainly (≥80% total disease burden) limited to the liver. Primary tumor may be resected or not, but patient must not be symptomatic for T.
- Potential resectability of liver metastases by major liver surgery according to at least one of the following criteria:
    - Portal embolization preceding resection;
    - "Two-stage epatectomy" of any kind;
    - Tumor involvement of more than 1 hepatic vein;
    - Tumor involvement of ≥ 4 hepatic segments.
- Should those criteria not apply, inclusion will be extended to regular candidates to liver resection carrying at least 1 of the following adverse prognosis factors:
    - > 4 metastatic nodules;
    - CEA > 200 U/L;
    - Synchronous metastases.
- Previous adjuvant therapy is allowed if it had been terminated for at least 6 months.
- Previous first-line treatment (irinotecan or oxaliplatin-containing regimen) with stable or partial response after no more than 3 months of treatment.
- An interval of at least 6 weeks must be allowed from resection of the primary tumor.
- Age ≥ 18 years.
- ECOG performance status < 2.
- Adequate organ function including the following:
    - Adequate bone marrow reserve: WBC count > 3.0×10^9/L, absolute neutrophyl count > 1.5×10^9/L, platelet count > 100×10^9/L, and hemoglobin > 10 g/dL.
    - Hepatic: bilirubin < 1.5 × ULN, alkaline phosphatase, aspartate transaminase, and alanine transaminase < 2.5 × ULN.
    - Renal: serum creatinine < 2.0 × ULN.
- Patients' compliance and geographic proximity that allow for adequate follow-up.
- Patients must sign an informed consent document.
- Male and female patients with reproductive potential must use an approved contraceptive method.

Exclusion Criteria

- Extra-hepatic metastatic disease > 20% of total disease burden.
- Tumor involvement of the liver > 75%.
- Chance of a liver remnant after surgery < 25%.
- More than 6 hepatic segments involved.
- Eligibility for concurrent radiotherapy treatment.
- Disease progression during first-line chemotherapy with FOLFOX, XELOX, FOLFIRI, or XELIRI plus bevacizumab.
- Previous treatment of more than 3 months of FOLFOX, XELOX, FOLFIRI, or XELIRI.
- Previous therapy with cetuximab or panitumumab or bevacizumab.
- Administration of other experimental drugs during the study.
- Body mass index > 35.
- Brain metastases.
- Pregnancy and/or breast-feeding.
- Serious or uncontrolled medical pathologies or active infections that would jeopardize the possibility of receiving the investigated treatment. Disorders that could influence the absorption of capecitabine (eg, malabsorption), intestinal occlusion, Crohn's disease, or ulcerative colitis.
- Psychiatric disorders, neurologic disease, or other conditions that would make it impossible to comply with the protocol procedures. Peripheral neuropathy not related to oxaliplatin previous administration.
- Previous dangerous life-threatening toxicities from fluoropirimidine.
- Positive history with regard to other neoplastic diseases except for the ones that have been cured for more than 3 years.

Abbreviations: CEA = carcinoembryonic antigen; ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = 5-fluorouricil, leucovorin, and irinotecan; FOLFOX = 5-fluorouricil, leucovorin, oxaliplatin, and irinotecan; XELIRI = capecitabine and irinotecan; XELOX = capecitabine and oxaliplatin; ULN = upper limit of normal; WBC = white blood cell count.

Supplemental Table 1 CT and FDG-PET/CT Parameters in the Overall Population and by Comparison of Patients With and Without Pathologic Response

	Overall Population	No Pathologic Response	Pathologic Response	
	N (%)	N (%)	N (%)	*P* Value[a]
No. patients	46	17	29	
RECIST response	30 (65.2)	10 (58.8)	20 (69.0)	.534
Early tumor shrinkage	38 (82.6)	11 (64.7)	27 (93.1)	**.038**
Deepness of response, %				.196
Median	−34%	−30%	−36%	
1st, 3rd quartile	−42%, −25%	−39%, −17%	−44%, −27%	
SUV-1[b]				.835
Median	14.4	14.1	17.0	
1st, 3rd quartile	10.1, 21.8	10.1, 21.8	10.0, 22.0	
SUV-2[b]				**.009**
Median	8.5	14.9	7.1	
1st, 3rd quartile	6.4, 13.4	11.1, 25.2	4.8, 10.2	
Regression index,[b] %				**.031**
Median	−47%	−32%	−51%	
1st, 3rd quartile	−62%, −32%	−48%, 41%	−63%, −39%	

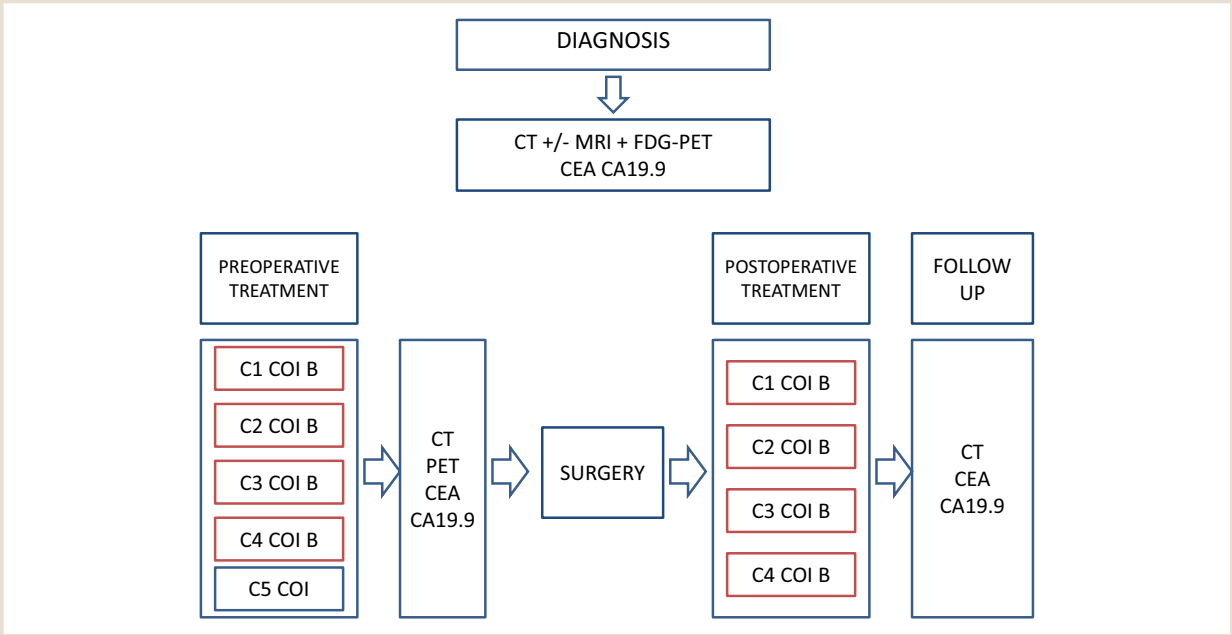
Bold *P* values indicate statistically significant results.
Abbreviations: CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; SUV = standardized uptake value.
[a]Fisher exact test or Anderson-Darling test as appropriate.
[b]FDG-PET/CT parameters reported for the subset of 25 patients included in the ancillary study.

Supplemental Table 2 Postoperative Complication Rating: Postoperative Complications

Liver Resection[a]	N = 46 N (%)	Primary Tumor Resection	N = 46 N (%)
Fever	5 (11)	Anastomotic fistula	2 (4)
Pleural effusion	4 (9)	Bleeding	1 (2)
Biliary fistula	2 (4)	Anastomotic leakage	1 (2)
Hepatic failure (ascites)	2 (4)		
Pneumonitis	1 (2)		
Bleeding	1 (2)		
Wound infection	1 (2)		

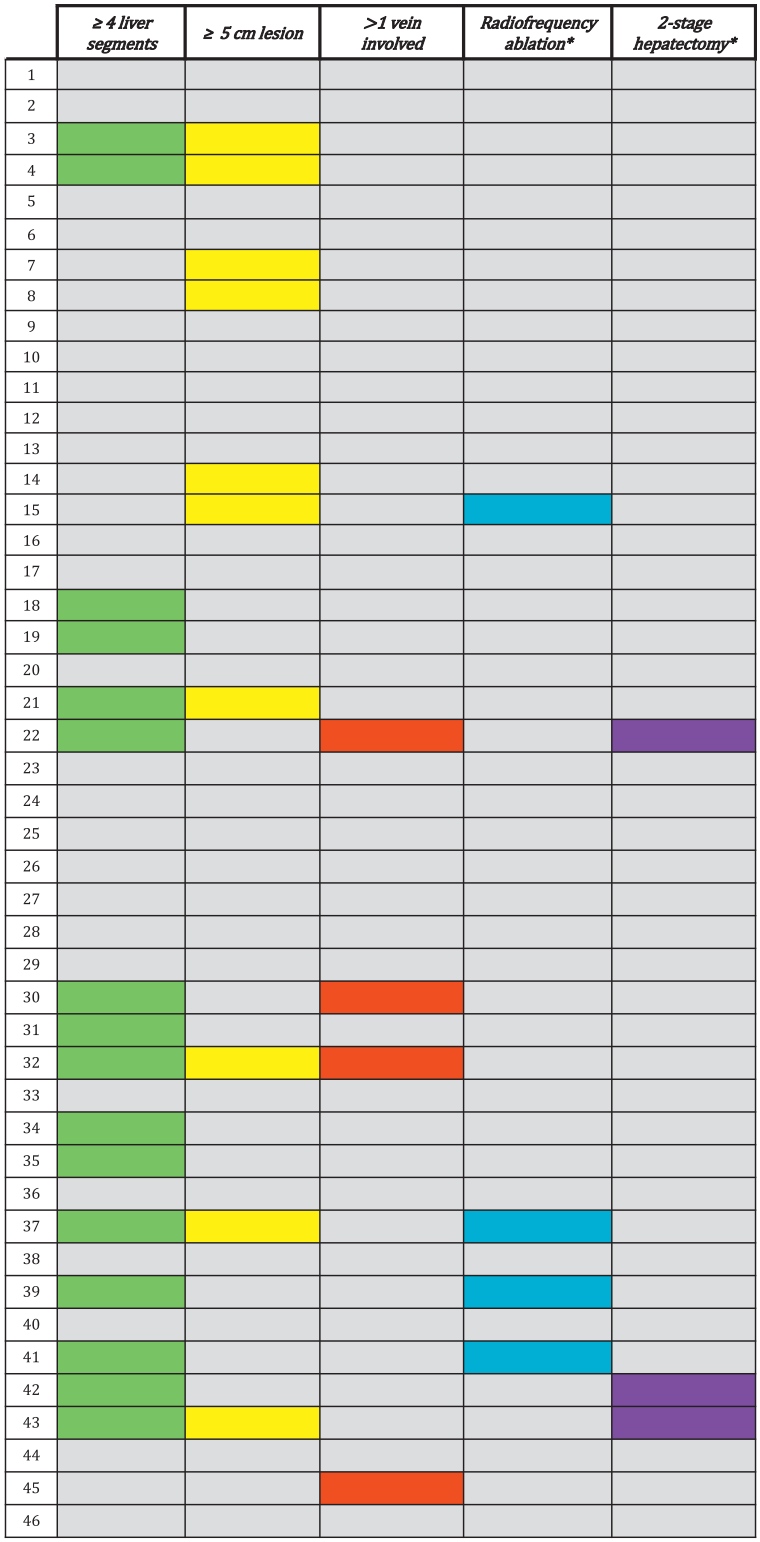
Liver resection complications of any grade occurred in 15 patients (33%). Fever and pleural effusion were the most commonly observed complications occurring in 5 (11%) and 4 (9%) patients, respectively, with no impact on the length of hospitalization. Primary tumor resection complications of any grade occurred in 4 (23%) patients. Anastomotic leakage leading to peritonitis was the most serious complication and occurred in 1 patient (2%). No surgical mortality was observed.
[a]Three patients experienced 2 concomitant complications.

Supplemental Figure 1 **Flow Diagram Showing Study Procedures. After Complete Staging, Initial Resectability Status Was Assessed at a Multidisciplinary Team Meeting. The Preoperative Treatment Phase Consisted of 4 Cycles of COI-B. Resectability Was Reassessed After 8 Weeks From Enrollment and 1 Additional Cycle of COI Without Bevacizumab Was Administered. Surgery Was Planned Between 4 and 7 Weeks From the Last Treatment Dose. At Least 4 Weeks and Within 8 Weeks From Surgery, the Patients Received the Same COI-B Regimen Postoperatively for an Additional 4 Cycles**



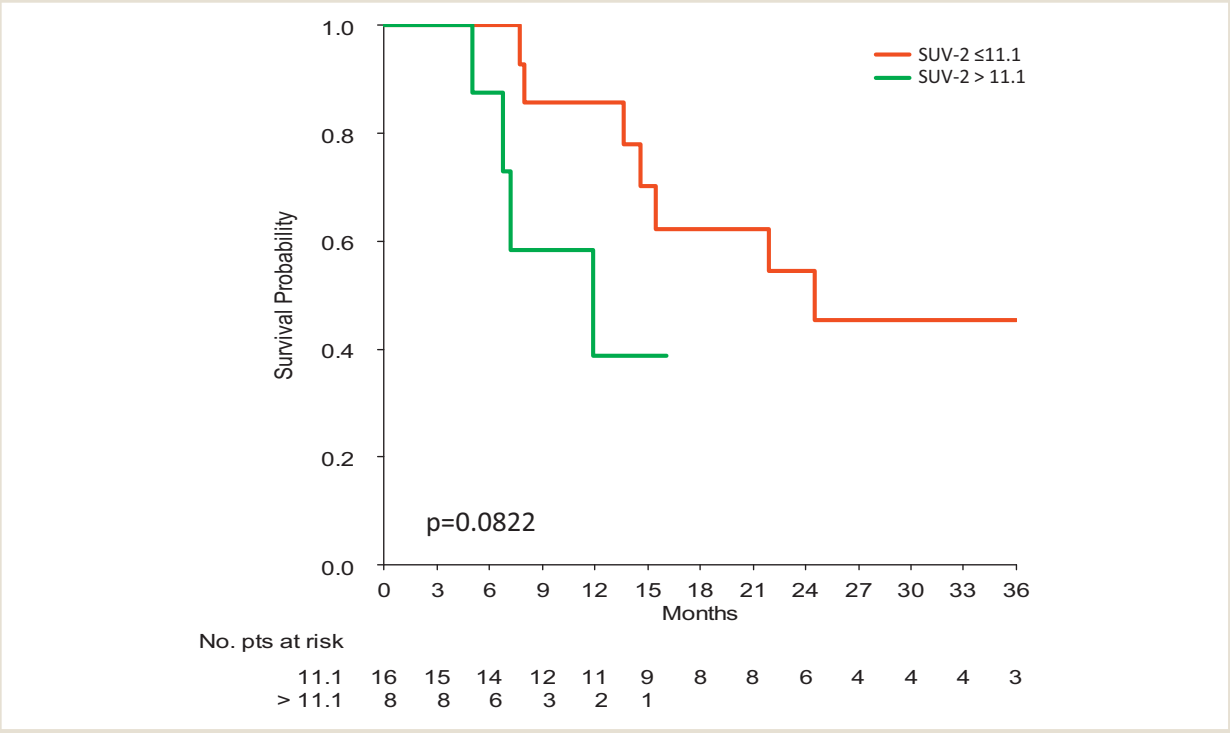
Abbreviations: CEA = carcinoembryonic antigen; COI-B = capecitabine, oxaliplatin, irinotecan, and bevacizumab; CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; RMI = Magnetic Resonance Imaging.

Supplemental Figure 2 Borderline Resectability Criteria in the Intent-to-Treat Population According to Baseline Multidisciplinary Team Assessment. The Disease Was Judged as Borderline Resectable in 22 out of 46 Patients. *Planned Based on Baseline assessment



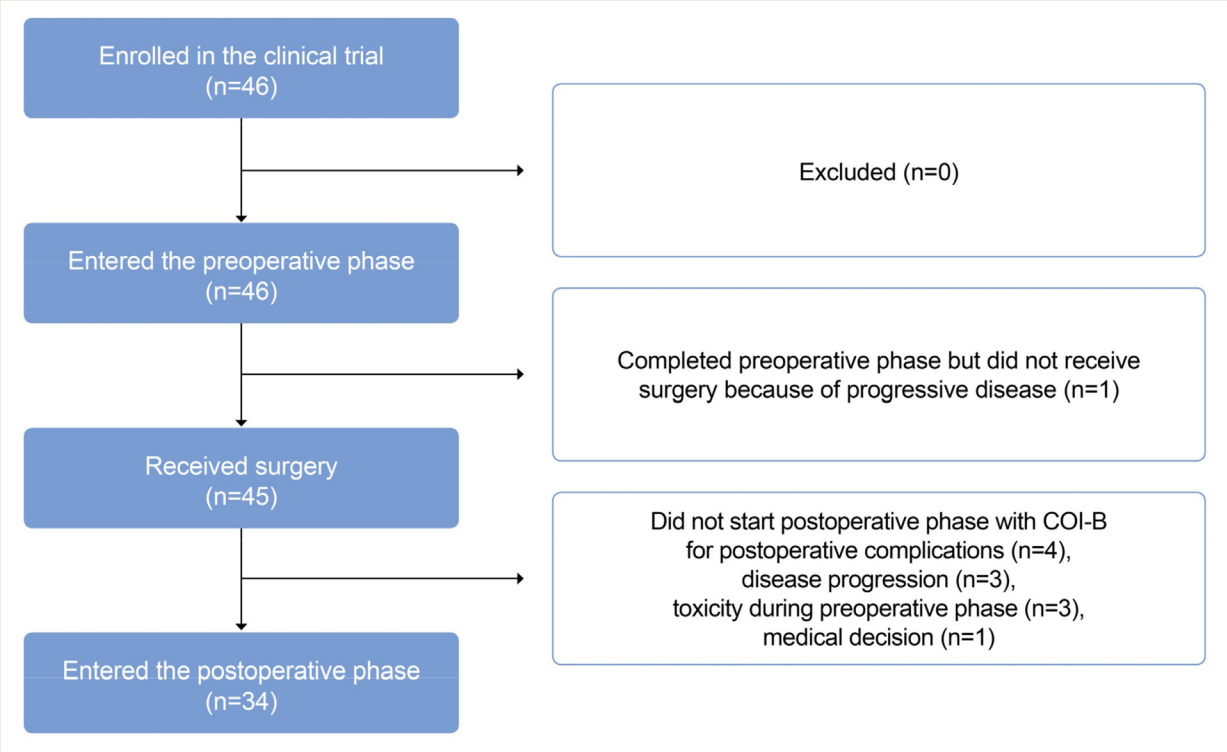
* planned based on baseline assessment

Supplemental Figure 3 **Kaplan-Meier Curves for Progression-free Survival According to SUV-2 Cutoff Values. Red Lines Indicate Patients With SUV-2 ≤ 11.1, Whereas Green Lines Indicate Patients With SUV-2 > 11.1. Patients With SUV-2 ≤ 11.1 had Better Progression-free Survival Compared With Those With SUV-2 > 11.1**



Abbreviation: SUV = standardized uptake value.

Supplemental Figure 4 **Flow Chart of the Study. One Patient did Not Receive Surgery Because of Progressive Disease; 11 Patients did not Start Postoperative Phase With COI-B for Postoperative Complications (n = 4), Disease Progression (n = 3), Toxicity During Preoperative Phase (n = 3), or Medical Decision (n = 1)**



Abbreviation: COI-B = capecitabine, oxaliplatin, irinotecan, and bevacizumab.