Association of computed tomography morphological criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases

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Abstract

Context—The standard criteria used to evaluate tumor response, the Response Evaluation Criteria in Solid Tumors (RECIST), were developed to assess tumor shrinkage after cytotoxic chemotherapy and may be limited in assessing response to biologic agents, which have a cytostatic mechanism of action..

Objective—To validate novel tumor response criteria based on morphologic changes observed on computed tomography (CT) in patients with colorectal liver metastases (CLM) treated with bevacizumab-containing chemotherapy regimens.

Design, Setting, and Patients—234 CLM were analyzed in 50 patients who underwent hepatic resection after preoperative chemotherapy that included bevacizumab at a comprehensive US cancer center from 2004 to 2007; date of last follow-up was March 2008. All patients underwent routine contrast-enhanced CT at the start and end of preoperative therapy. Three blinded, independent radiologists evaluated images for morphologic response, based upon metastases changing from heterogeneous masses with ill-defined margins into homogeneous

lesions with sharp borders. These criteria were validated with a separate cohort of 82 patients with unresectable CLM treated with bevacizumab-containing chemotherapy.

Main Outcome Measures—Response determined using morphologic criteria and RECIST was correlated with pathologic response in resected liver specimens and with patient survival.

Results—Interobserver agreement for scoring morphologic changes was good among three radiologists (κ=0.68–0.78; 95% confidence interval, 0.51–0.93). In resected tumor specimens with morphologic optimal, incomplete, and no response, the median percentages of residual tumor cells were 20% (interquartile range [IQR], 10%–30%), 50% (IQR, 30%–60%), and 70% (IQR, 60%–70%), respectively ($P<.001$). With RECIST partial response, stable disease, and progressive disease, the median percentages of residual tumor cells were 30% (IQR, 10%–60%), 50% (IQR, 20%–70%), and 70% (IQR, 65%–70%), respectively ($P=.04$). Among patients who underwent hepatic resection, median overall survival was not yet reached with optimal morphologic response and 35 months (95% CI, 20.2 to 29.8 months) with incomplete or no morphologic response ($P=.03$). In the validation cohort, patients with optimal morphologic response had median overall survival of 31 months (95% CI, 26.8 to 35.2 months) compared to 19 months (95% CI, 14.6 to 23.4 months) with incomplete or no morphologic response ($P=.009$). RECIST did not correlate with survival in neither the surgical nor validation cohort.

Conclusions—Among patients with CLM treated with bevacizumab-containing chemotherapy, CT-based morphologic criteria had a statistically significant association with pathologic response and overall survival.

INTRODUCTION

The addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, to cytotoxic chemotherapy is associated with improved survival in patients with stage IV colorectal cancer and higher pathologic response rates in patients undergoing resection of colorectal liver metastases (CLM).[1, 2] Response to bevacizumab, which exerts an antiangiogenic mechanism of action, may be inadequately assessed by traditional size-based radiologic criteria, the Response Evaluation Criteria in Solid Tumors (RECIST), which were designed for assessing tumor volume reduction following cytotoxic chemotherapy.[3–5] In support of this, a recent phase III trial showed that the addition of bevacizumab to oxaliplatin-based chemotherapy for metastatic colorectal cancer improved progression-free survival without affecting RECIST-defined response rates.[6]

Recently, pathologic response to preoperative chemotherapy has been shown to correlate with improved survival and has been proposed as a new outcome endpoint after resection of CLM.[7–9] To date, a noninvasive method of predicting pathologic response to chemotherapy in CLM, particularly biologic agents, is lacking. We observed that after bevacizumab-containing therapy, CLM tend not only to decrease in size but also to undergo unique morphological changes on computed tomography (CT). Metastases that have heterogeneous attenuation, variable degree of enhancement, and ill-defined borders before treatment transform into homogeneous, hypoattenuating lesions with well-defined borders. We hypothesized that these changes on CT reflect the pathologic response in patients treated with bevacizumab-containing chemotherapy before hepatic resection of CLM. To test this

hypothesis, we correlated tumor response based on these morphologic criteria and tumor response based on RECIST with pathologic response. We then tested the morphologic criteria in patients with unresectable CLM treated with bevacizumab. The morphologic criteria and RECIST were correlated with survival in both resected and unresectable patients.

METHODS

Initial Patient Cohort

From a prospective hepatobiliary database at The University of Texas M. D. Anderson Cancer Center, we identified 234 CLM in 50 consecutive patients who received first-line chemotherapy with bevacizumab before undergoing hepatic resection between March 2004 and March 2007. All patients underwent contrast-enhanced CT scans of the abdomen at the start and end of preoperative therapy as part of their standard evaluation. Patients who had undergone prior liver resection were excluded. Postoperatively, patients were followed with history and physical examination, CT scans, and serum carcinoembryonic antigen levels at 3- to 6-month intervals for the first 2 to 3 years after resection and at more extended intervals thereafter. The median follow-up time was 18 months (range, 3–42 months). Date of last follow-up was March 2008. This study involved retrospective review of medical information and was conducted under the approval of the institutional review board, which waived the requirement for informed consent.

Validation Patient Cohort

From a prospective gastrointestinal medical oncology database at The University of Texas M. D. Anderson Cancer Center, we identified 82 patients with unresectable CLM treated with bevacizumab combined with cytotoxic chemotherapy between March 2004 and April 2007. Patients were considered unresectable if two contiguous hepatic segments could not be preserved, vascular inflow and outflow or biliary drainage was inadequate, or the volume of the future liver remnant was 20% of the total estimated liver volume.[10] All patients underwent contrast-enhanced CT scans of the abdomen before starting chemotherapy and at 2–3 month intervals thereafter. Median follow-up was 25 months (range, 6–57 months). Date of last follow-up was April 2009.

Imaging Analysis

CT scans were performed with 4- or 16-slice CT (LightSpeed, GE Healthcare, Piscataway, NJ) using a collimation of 5 mm and reconstruction at 2.5 mm. Images were acquired with one of two methods: a triphasic liver protocol following a noncontrast evaluation of the liver or a single-phase technique. For the triphasic liver protocol, images were obtained 30, 50, and 70 seconds after the start of intravenous injection of ioversol at a rate of 5 cc/sec. For the single-phase technique, images were obtained 60 to 70 seconds after the start of ioversol injection at a rate of 2 to 3 cc/sec. Because of the routine concomitant acquisition of chest CT and delayed images through the kidneys, single-phase scans also permitted partial evaluation of the liver during the early and delayed phases of enhancement.

Response to treatment was assessed independently by three radiologists with 2, 15, and 20 years of experience in abdominal oncologic imaging. Radiologists were blinded to pathologic results, patient treatment, and outcomes. Discrepancies between radiologists were resolved by consensus review. Response was evaluated using new morphologic criteria, assigning each metastasis to one of three groups (Table 1). A group 3 metastasis was characterized by heterogeneous attenuation and a thick, poorly defined tumor-liver interface (Fig 1A and 1C). A group 1 metastasis was characterized by homogeneous attenuation with a thin, sharply defined tumor-liver interface (Fig 1B). A group 2 metastasis had morphology that could not be rated as 3 or 1 (Fig 1D). When present, a peripheral rim of hyperattenuating contrast enhancement was designated a group 3 characteristic, and resolution of this enhancement was classified group 1.

Morphologic response criteria were defined as optimal if the metastasis changed from a group 3 or 2 to a 1, incomplete if the group changed from 3 to 2, and none if the group did not change or increased. In patients with multiple tumors, morphologic response criteria were assigned based on the response seen in the majority of tumors. Response by RECIST was defined as previously described: complete response, disappearance of all tumors; partial response, > 30% decrease in sum of the longest diameter of target tumor; progressive disease, > 20% increase in the sum of the longest diameter of target tumor; and stable disease, none of the complete response, partial response, or progressive disease criteria met.[11] The appearance of new metastases was defined as progression by RECIST and morphology assessment.

Assessment of Pathologic Response to Chemotherapy

Hematoxylin and eosin-stained specimens sectioned into 5-mm-thick slices were evaluated by two gastrointestinal pathologists who were blinded to treatment regimen, radiologic results, and patient outcomes. The extent of residual carcinoma was assessed semiquantitatively as a percentage relative to the total tumor surface area, as previously described.[2, 8] Pathologic response was scored as minor if 50% residual tumor cells were present, major with 1% to 49% residual tumor cells, and complete if no residual tumor cells were detected.

Statistical Analysis

Continuous variables were compared using the Kruskal-Wallis or Mann-Whitney test; discrete variables, expressed as number and percentage, were compared using the chi-square test or Fisher exact test, when appropriate. A post hoc power analysis showed that based on the actual number of patients enrolled in the current study, there was greater than 95% statistical power to detect a difference in pathologic response rate of 32% between patients with optimal v incomplete or no morphologic response at a conventional P value of .05. Kappa statistics were used to determine interobserver agreement of the proposed morphologic criteria among three radiologists. Survival was determined from time of hepatic resection until the time of death or last follow-up. If more than 3 months had lapsed since the date of last follow-up, then survival was calculated according to whether patients were alive at the time the study was closed, as recorded in tumor registry data or medical records. Five patients with residual disease in the liver, lung, or an intact primary tumor at

the time of hepatectomy were excluded from the survival analysis. Among unresectable patients, survival was calculated from the start of bevacizumab-containing chemotherapy. Survival curves were generated using the Kaplan-Meier method, and differences were evaluated with the log-rank test. Analyses were performed with SPSS software (version 12.0, SPSS Inc., Chicago, IL). All statistical tests were two- sided, and significance was set at *P*<.05.

RESULTS

Initial Surgical Cohort

Two hundred thirty-four lesions in 50 patients were evaluated; their demographic and clinicopathologic characteristics are presented in Table 2. Of the 130 CT scans reviewed, 53 were performed with triphasic liver protocol and 77 with single-phase technique. Among the 33 patients with multiple tumors, the morphologic responses of the metastases within the same patient were concordant in all but two patients.

Morphologic response was significantly associated with the percentage of residual tumor cells: median values were 70% (interquartile range [IQR], 60%–70%), 50% (IQR, 30%–60%), and 20% (IQR, 10%–30%) residual tumor in patients with no response, incomplete response, and optimal response, respectively (*P*<.001, Fig 2A). RECIST was also significantly associated with the percentage of residual tumor cells: median values were 70% (IQR, 65%–70%), 50% (IQR, 20%–70%), and 30% (IQR, 10%–60%) in patients with progressive disease, stable disease, and partial response, respectively (*P*=.04, Fig 2B).

When pathologic response was stratified as minor, major, or complete, using previously determined cutoff values for the percentage of residual tumor cells,[8] two patients had a complete response, 27 had a major response, and 21 had a minor response. Metastases with major pathologic response were characterized by replacement of tumor cells by fibrosis. Necrosis was observed in less than 5% of tumors. Complete or major pathologic response corresponded to morphologic optimal response in 22/29 (76%) patients, while minor pathologic response was associated with morphologic partial or no response in 17/21 (81%) patients. When correlated with RECIST, complete or major pathologic response corresponded to RECIST partial response in 23/29 (79%) patients, while minor pathologic response was associated with RECIST stable or progressive disease in 10/21 (48%) patients. None of the patients had RECIST complete response. Therefore, incomplete or no response by morphology was more specific for predicting minor pathologic response than RECIST stable or progressive disease (17/21, morphology *v* 10/21, RECIST, *P*=0.02). Morphologic optimal response and RECIST partial response had similar sensitivities for predicting complete or major pathologic response (22/29, morphology *v* 23/29, RECIST, *P*=0.75).

Outcome among Resected Patients

Thirty patients (60%) had disease recurrence during the study period, and 9 (18%) died of disease. Five patients (10%) with residual disease in the liver, lung, or an intact primary tumor at the time of hepatectomy were excluded from the survival analysis. Patients with optimal response by morphology were classified as responders, while the remaining patients

were classified as nonresponders. When morphologic criteria were used in tumor response evaluation, median overall survival was not yet reached for responders and 35 months (95% CI, 20.2 to 29.8 months) for nonresponders (*P*=.03, Fig 3A). When RECIST were used, median overall survival was not yet reached in patients who achieved partial response and 34 months (95% CI, 20.0 to 48.0 months) with stable or progressive disease (*P*=.25, Fig 3B). On univariate analysis of traditional predictors of survival and potential radiologic predictors of outcome, only morphologic criteria demonstrated a significant correlation with overall survival (Table 3).

Validation in Unresectable Patients

To validate the CT response criteria in assessing clinically significant tumor response of liver metastases, a separate cohort of 82 patients with unresectable CLM treated with bevacizumab-containing chemotherapy was analyzed. Their clinicopathologic features are presented in Table 2. Among the 78 patients with multiple liver metastases, the morphologic responses of the metastases within the same patient were concordant in all but 10 patients; in these patients, morphology score was assigned based on the dominant pattern observed.

Among the 82 patients with stage IV colorectal cancer treated with chemotherapy only, those with optimal response by morphologic criteria had significantly better overall survival than patients with incomplete or no response, with median overall survival of 31 months (95% CI, 26.8 to 35.2 months), and 19 months (95% CI, 14.6 to 23.4 months), respectively (*P*=.009, Fig 4A). In contrast, response by RECIST was not associated with an improvement in survival; median overall survival was 28 months (95% CI, 22.5 to 33.5 months) in patients with partial response and 22 months (95% CI, 15.3 to 28.7 months) in those with stable or progressive disease (*P*=.45, Fig. 4B). The following variables did not significantly affect overall survival: gender, age, size or multiplicity of hepatic metastases, rectal primary, and the presence of extrahepatic metastases.

Interobserver Agreement for Morphologic Criteria

The interobserver agreement between the three radiologists for scoring morphologic changes was good: κ=0.78 (95% confidence interval [CI]: 0.63–.93) between readers 1 and 2, κ = 0.72 (95% CI: 0.56–0.88) between readers 1 and 3, and κ 0.68 (95% CI: 0.51–0.85) between readers 2 and 3. Among the radiologists, there were discrepancies in scoring morphologic criteria in 13 of the 50 surgical patients, which were resolved by consensus review.

DISCUSSION

We present novel qualitative morphologic CT criteria for predicting response to bevacizumab-containing chemotherapy in patients with CLM. These criteria were reproducible, as shown by the good interobserver agreement in scoring morphologic changes among three independent radiologists with varied experience in abdominal oncologic imaging. Morphologic criteria correlated strongly with the percentage of residual tumor cells and also with pathologic response stratified as complete, major, or minor, using 50% residual tumor cells as the cutoff value between major and minor pathologic response. Optimal morphologic response to preoperative therapy translated into a survival benefit after

hepatic resection. In a separate validation cohort of patients with unresectable CLM, response by morphologic criteria was also associated with improved overall survival. RECIST was also sensitive for predicting complete or major pathologic response but with a significantly lower specificity for predicting minor pathologic response. RECIST was neither associated with the stratified pathologic response nor survival.

Optimal morphologic response was defined as a change in metastases from lesions with heterogeneous attenuation and thick, irregular borders into bland, homogeneously hypodense masses with a sharp interface between the tumor and adjacent normal liver parenchyma, which in some cases could mimic a cyst. This homogeneous attenuation of metastases responding to treatment likely reflects the replacement of treated tumor by fibroconnective tissue rather than tumor necrosis, which was present in less than 5% of patients in this study. Rubbia-Brandt et al. also observed that histological tumor response is characterized by fibrous replacement of tumor rather than tumor necrosis in CLM.[7] In patients with multiple liver metastases, the morphologic responses of the metastases within the same patient were uniform in 99 of 111 (89%) patients. This result confirms a previous study demonstrating that in patients with multiple CLM, the histological tumor responses within the same patient were similar.[7]

The impact of pathologic response to preoperative therapy on survival in patients with solid tumors is well-established.[12, 13] In patients with CLM, histologic tumor regression, graded by the extent of fibrosis and presence of residual tumor cells, has been shown to correlate with survival.[7] In this study, we scored pathologic response semiquantitatively as the percentage of residual tumor cells relative to the total tumor surface area. Pathologic response was scored as minor if 50% residual tumor cells were present, major with 1% to 49% residual tumor cells, and complete with 0%. Using this 50% cutoff to define major versus minor pathologic response, we recently showed that in patients with CLM, major pathologic response to preoperative chemotherapy independently predicted improved patient survival.[8] In the present study, overall survival was correlated with morphologic response but not RECIST-based prognostic factors, such as tumor size and number. Although the sample size in the surgical cohort is small, these results highlight the importance of response rather than baseline clinical factors in determining patient outcome after liver resection.[8, 14]

The limitations of this study include its retrospective nature and potentially the predominant use of a single-phase CT technique. Although triphasic liver protocol CT is not required to apply the morphologic criteria and is probably not needed routinely in non-surgical patients with CLM, it might improve sensitivity by allowing evaluation of early and delayed phases of tumor enhancement. Recent studies on evaluating response to antiangiogenic agents with CT or MRI have focused on tumor perfusion.[15–18] Although tumoral enhancement was a component of our morphology response criteria, the degree of enhancement could not be consistently assessed because of variations in scanning techniques. While CLM are considered hypovascular tumors, enhancement does occur and is characterized by an ill-defined rim of peripheral enhancement which is maximal during the arterial phase and fades away during the portal phase.[19, 20] We reviewed many CTs that were single phase studies, lacking an arterial phase. Nevertheless, in cases where an early hyperattenuating rim of enhancement was present before treatment, it disappeared in all patients with an optimal

morphologic response. In addition, the applicability of these criteria in assessing response to other biologic agents approved for CLM requires investigation.

In conclusion, we present novel qualitative radiologic criteria that predict the pathologic response to preoperative bevacizumab-containing chemotherapy in patients undergoing resection of CLM. Morphologic response correlated with pathologic response stratified as complete, major, or minor, as well as overall survival, whereas RECIST did not. This correlation between survival and morphologic response, but not RECIST, was confirmed in a non-surgical cohort. Thus, our results indicate that morphologic response may be a useful, noninvasive surrogate marker of pathologic response and improved survival in patients with CLM receiving a bevacizumab-containing regimen. It provides complementary information to traditional size-based criteria in assessing CT response to bevacizumab in CLM

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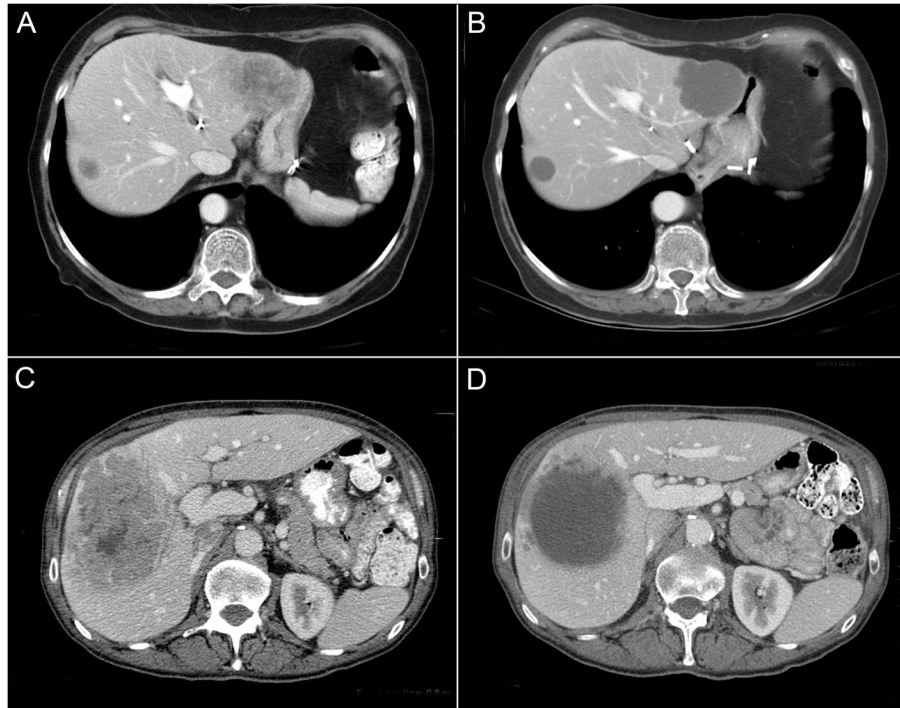
Fig 1.
Pre- and posttreatment CT scans showing RECIST stable disease and morphologic optimal response (A, B), characterized by homogeneous attenuation and sharp tumor-liver interface; morphologic incomplete response (C, D), with homogeneous attenuation but ill-defined tumor-liver interface remaining after treatment.
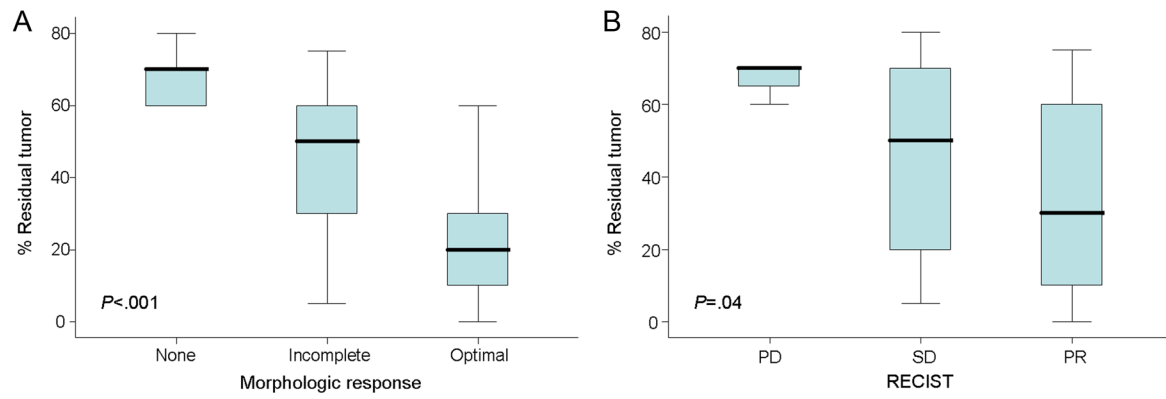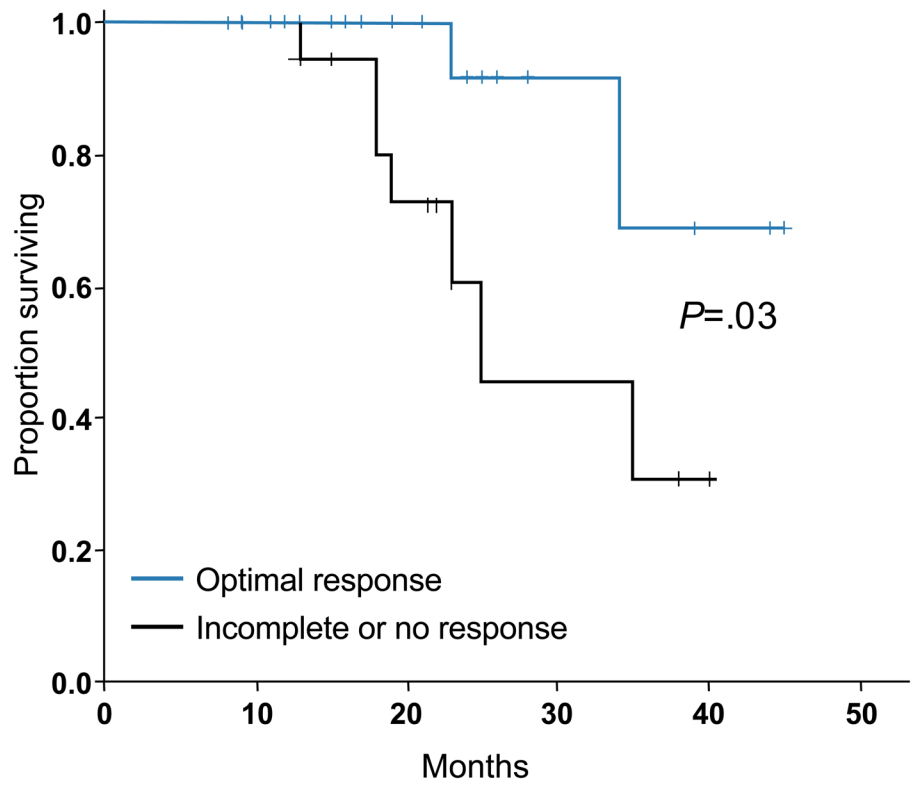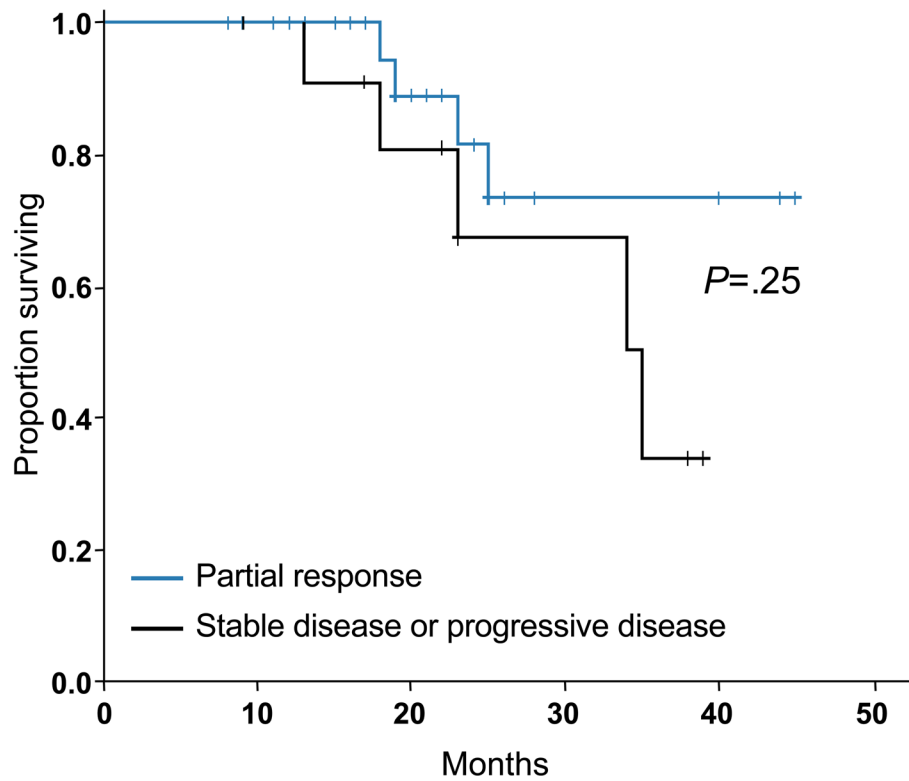
Fig 2.
Correlation between morphologic response (A) or RECIST (B) and percentage of residual tumor cells. Lines inside boxes represent the median; endpoints of whiskers represent minimum and maximum values. Lower and upper edges of boxes represent 25th and 75th percentiles.

Figure 3A

Figure 3B

Fig 3.
Overall survival in responders and nonresponders by morphologic criteria (A) and RECIST (B) in surgical cohort.

P=.009

Optimal response

Incomplete or no response
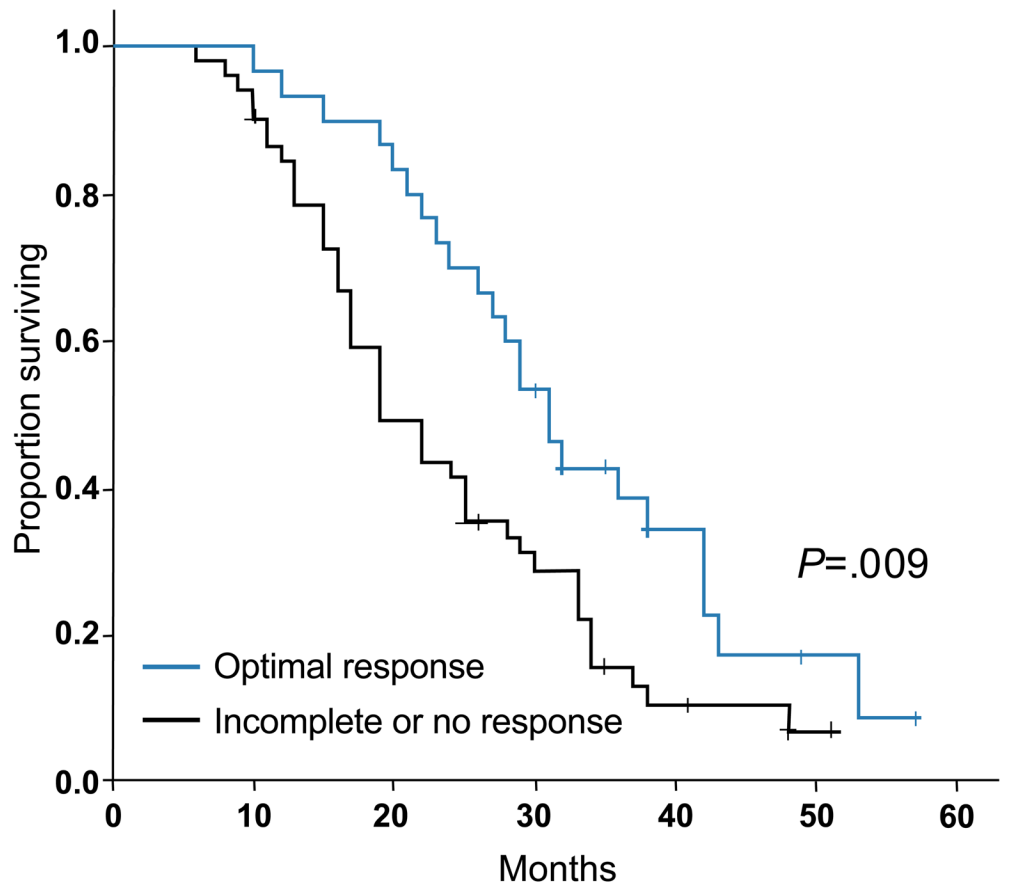
No at risk						
Responder	30	30	26	16	6	2
Non-responder	52	49	25	14	4	1

Figure 4A

Figure 4B

Fig 4.
Overall survival in responders and nonresponders by morphologic criteria (A) and RECIST (B) among 82 unresectable patients.

Table 1

CT morphologic groups

Morphology group	CT tumor characteristics		
	Overall attenuation	**Tumor-liver interface**	**Peripheral rim of enhancement**
3	Heterogeneous	Ill-defined	May be present
2	Mixed	Variable	If initially present, partially resolved
1	Homogeneous and hypoattenuating	Sharp	If initially present, completely resolved

Table 2

Baseline characteristics

	No. (%) of patients	
	Initial Surgical Cohort (n=50)	Unresectable Patients (n=82)
Age		
Median	57 years	57 years
Range	34–84 years	26–69 years
Sex		
Female	21 (42%)	37 (45%)
Male	29 (58%)	45 (55%)
Primary tumor		
Colon	36 (72%)	63 (77%)
Rectum	14 (28%)	19 (23%)
Sites of metastases		
Liver only	48 (95%)	45 (55%)
Liver and extrahepatic	2 (4%)	37 (45%)
Liver metastases		
Solitary	17 (34%)	4 (5%)
Multiple	33 (66%)	78 (95%)
Tumor size[a]		
Median	2.3 cm	4.9 cm
Range	0.4–13 cm	1.5–18 cm
Chemotherapy		
FOLFIRI with bevacizumab	7 (14%)	47 (57%)
FOLFOX with bevacizumab	43 (86%)	35 (43%)
Hepatectomy		
Minor	24 (48%)	N/A
Major	26 (52%)	
Radiofrequency ablation at time of hepatectomy	8 (16%)	N/A
No. of chemotherapy cycles before hepatectomy		
Median	6	N/A
Range	3–12	
Interval between last CT scan and surgery		
Median	18 days	N/A
Range	2–56 days	
Overall survival[b]		

	No. (%) of patients	
	Initial Surgical Cohort (n=50)	Unresectable Patients (n=82)
Median	Not reached	25 months
3-year	51%	24%

Abbreviations: FOLFIRI, infusional 5-fluorouracil (5-FU) and leucovorin with irinotecan; FOLFOX, infusional 5-FU and leucovorin with oxaliplatin; CT, computed tomography; NA, not applicable.

[a]Based on the largest diameter of the resected tumor specimen in surgical patients and largest diameter on pre-chemotherapy CT in unresectable patients.

[b]From time of hepatectomy in surgical cohort and from start of bevacizumab-containing chemotherapy in unresectable cohort.

Table 3

Univariate Analysis of Predictors of Overall Survival among 45 Surgical Patients

Variable	No. of Patients	Actuarial 2-Year Survival Rate	P
Gender			.71
Male	26	79%	
Female	19	74%	
Age, years			.83
60	17	71%	
> 60	28	89%	
Primary site			.24
Colon	33	78%	
Rectum	12	76%	
Primary tumor			.90
Node-negative	16	83%	
Node-positive	29	74%	
Prehepatectomy serum CEA			NA
200 ng/ml	45	77%	
> 200 ng/ml	0		
Resection margin			.11
Negative	43	79%	
Positive	2	50%	
Disease-free interval			.55
12 months	15	69%	
< 12 months	30	81%	
No. of tumors			.79
1	16	75%	
> 1	29	78%	
Tumor size, cm[a]			.11
5	40	79%	
> 5	5	50%	
Morphologic response			.03
Optimal	22	90%	
Incomplete or none	23	42%	
RECIST			.25
Partial response	31	80%	
Stable or progressive disease	14	64%	

Abbreviations: CEA, carcinoembryonic antigen; NA, not applicable.

[a]Based on the largest diameter of the resected tumor specimen.