

Association of Computed Tomography Morphologic Criteria With Pathologic Response and Survival in Patients Treated With Bevacizumab for Colorectal Liver Metastases

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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.^{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 3 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 sur-

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 treated with bevacizumab-containing chemotherapy regimens.

Design, Setting, and Patients A total of 234 colorectal liver metastases were analyzed from 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 on metastases changing from heterogeneous masses with ill-defined margins into homogeneous hypoattenuating lesions with sharp borders. These criteria were validated with a separate cohort of 82 patients with unresectable colorectal liver metastases 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 3 radiologists (κ , 0.68-0.78; 95% confidence interval [CI], 0.51-0.93). In resected tumor specimens, the median (interquartile range [IQR]) percentages of residual tumor cells for optimal morphologic response was 20% (10%-30%); for incomplete response, 50% (30%-60%); and no response, 70% (60%-70%; $P < .001$). With RECIST, the median (IQR) percentages of residual tumor cells were for partial response 30% (10%-60%); for stable disease, 50% (20%-70%); and for progressive disease, 70% (65%-70%; $P = .04$). Among patients who underwent hepatic resection, median overall survival was not yet reached with optimal morphologic response and 25 months (95% CI, 20.2-29.8 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, 26.8-35.2 months) compared with 19 months (95% CI, 14.6-23.4 months) with incomplete or no morphologic response ($P = .009$). RECIST did not correlate with survival in either the surgical or validation cohort.

Conclusion Among patients with colorectal liver metastases treated with bevacizumab-containing chemotherapy, CT-based morphologic criteria had a statistically significant association with pathologic response and overall survival.

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vival and has been proposed as a new outcome end point after resection of colorectal liver metastases.⁷⁻⁹ To date, a noninvasive method of predicting pathologic response to chemotherapy in colorectal liver metastases, particularly biologic agents, is lacking. We observed that after bevacizumab-containing therapy, colorectal liver metastases tend not only to decrease in size but also to undergo unique morphologic 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 colorectal liver metastases. 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 colorectal liver metastases treated with bevacizumab. The morphologic criteria and RECIST were correlated with survival in patients who underwent resection and those who did not.

METHODS

Initial Patient Cohort

From a prospective hepatobiliary database at the University of Texas M. D. Anderson Cancer Center, we identified 234 colorectal liver metastases 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 up with history and physical examination, CT scans, and serum carcinoembryonic antigen levels at 3- to

Table 1. Computed Tomographic Morphologic Groups

Morphology Group	Computed Tomographic 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

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 colorectal liver metastases treated with bevacizumab combined with cytotoxic chemotherapy between March 2004 and April 2007. Patients were considered unresectable if 2 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% or less of the total estimated liver volume.¹⁰ All patients underwent contrast-enhanced CT scans of the abdomen before starting chemotherapy and at 2- to 3-month intervals thereafter. Median follow-up was 25 months (range, 6-57 months). Date of last follow-up was April 2009.

Imaging Analysis

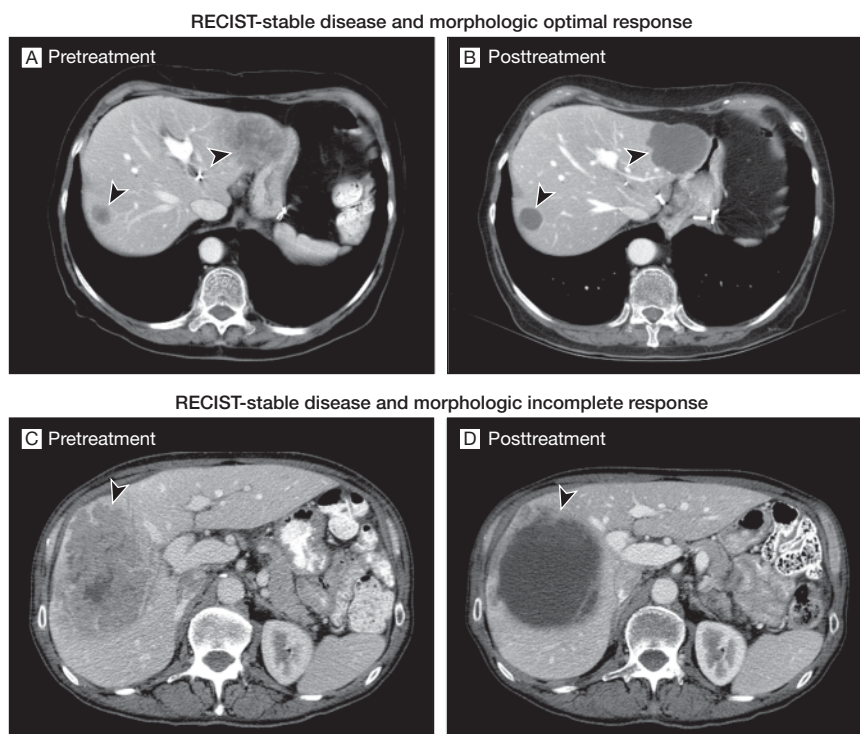
Computed tomographic scans were performed with 4- or 16-slice CT (Light-Speed, GE Healthcare, Piscataway, New Jersey) using a collimation of 5 mm and reconstruction at 2.5 mm. Images were acquired with 1 of 2 methods: a triphasic liver protocol following a noncontrast evaluation of the liver or a single-phase 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 mL/s. 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 mL/s. Because of the routine concomitant acquisition of chest CT scans 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 3 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 1 of 3 groups (TABLE 1). A group-3 metastasis was characterized by heterogeneous attenuation and a thick, poorly defined tumor-liver interface (FIGURE 1A and C). A group-1 metastasis was characterized by homogeneous low attenuation with a thin, sharply defined tumor-liver interface (Figure 1B). A group-2 metastasis had morphology that could not be rated as 3 or 1 (Figure 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 had not changed or increased. In patients with multiple tumors, morphologic response criteria

Figure 1. Representative Pretreatment and Posttreatment Computed Tomographic Scans Evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) and Morphologic Criteria



Arrowheads indicate the tumor-liver interface. Morphologic optimal response is characterized by decreased attenuation and sharp tumor-liver interface (B); morphologic incomplete response is characterized by decreased attenuation but persistent ill-defined tumor-liver interface remaining after treatment (D).

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, more than a 30% decrease in sum of the longest diameter of target tumor; progressive disease, more than a 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 a gastrointestinal pathologist who was 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% or more of 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 χ^2 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 a pathologic response rate of 32% between patients with optimal vs incom-

plete or no morphologic response at a conventional *P* value of .05. κ Statistics were used to determine interobserver agreement of the proposed morphologic criteria among 3 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 patients with unresectable tumors, 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, Illinois). All statistical tests were 2-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 the 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 2 patients.

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

(20%-70%) for patients with stable disease, and 30% (10%-60%) for patients with partial response ($P = .04$, Figure 2).

When pathologic response was stratified as minor, major, or complete using previously determined cutoff values for the percentage of residual tumor cells,⁸ 2 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 of 29 patients (76%), while minor pathologic response was associated with morphologic partial or no response in 17 of 21 patients (81%). When correlated with RECIST, complete or major pathologic response corresponded to RECIST partial response in 23 of 29 patients (79%), while minor pathologic response was associated with RECIST stable or progressive disease in 10 of 21 patients (48%). 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 of 21, morphology vs 10 of 21, RECIST, $P = .02$). Morphologic optimal response and RECIST partial response had similar sensitivities for predicting complete or major pathologic response (22 of 29, morphology vs 23 of 29, RECIST, $P = .75$).

Patients Who Underwent Resection

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 25 months for nonresponders (95% confidence interval [CI], 20.2-29.8 months; $P = .03$, FIGURE 3).

When RECIST were used, median overall survival was not yet reached in patients who achieved partial response and

34 months with stable or progressive disease (95% CI, 20.0-48.0 months; $P = .25$, Figure 3). On univariate analysis of tra-

Table 2. Baseline Characteristics

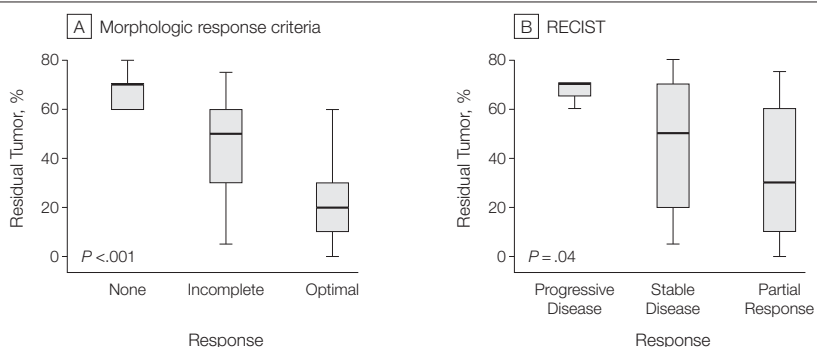
	No. (%) of Patients	
	Initial Surgical Cohort (n = 50)	Patients With Unresectable Tumor (n = 82)
Age, median (range), y	57 (34-84)	57 (26-69)
Sex		
Female	21 (42)	37 (45)
Male	29 (58)	45 (55)
Primary tumor		
Colon	36 (72)	63 (77)
Rectum	14 (28)	19 (23)
Sites of metastases		
Liver only	48 (95)	45 (55)
Liver and extrahepatic	2 (4)	37 (45)
Liver metastases		
Solitary	17 (34)	4 (5)
Multiple	33 (66)	78 (95)
Tumor size, median (range), cm ^a	2.3 (0.4-13)	4.9 (1.5-18.0)
Chemotherapy		
FOLFIRI with bevacizumab	7 (14)	47 (57)
FOLFOX with bevacizumab	43 (86)	35 (43)
Hepatectomy		
Minor	24 (48)	NA
Major	26 (52)	NA
Radiofrequency ablation at time of hepatectomy	8 (16)	NA
No. of chemotherapy cycles before hepatectomy, median (range)	6 (3-12)	NA
Interval between last CT and surgery, median (range), d	18 (2-56)	NA
Overall survival ^b		
Median, mo	Not reached	25
3 years, %	51	24

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

^aBased on the largest diameter of the resected tumor specimen in surgical patients and largest diameter on prechemotherapy computed tomography in unresectable patients.

^bFrom time of hepatectomy in surgical cohort and from start of bevacizumab-containing chemotherapy in unresectable cohort.

Figure 2. Correlation Between Morphologic Response or Response Evaluation Criteria in Solid Tumors (RECIST) and Percentage of Residual Tumor Cells



Lines inside boxes represent the median; end points of whiskers represent minimum and maximum values. Lower and upper edges of boxes represent 25th and 75th percentiles. P values were derived from the Kruskal-Wallis test comparing the percentage of residual tumor cells among patients with optimal, incomplete, or no morphologic response; and RECIST partial response, stable disease, or progressive disease.

ditional predictors of survival and potential radiologic predictors of outcome, only morphologic criteria demonstrated a significant correlation with overall survival (TABLE 3).

Validation in Patients With Unresected Tumors

To validate the CT response criteria in assessing clinically significant tumor response of liver metastases, a separate cohort of 82 patients with unresectable colorectal liver metastases 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, the 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, 26.8-35.2 months) and 19 months (95% CI, 14.6-23.4 months), respectively (P = .009, Figure 3). In contrast, response by RECIST was not associated with an improvement in survival. Median overall survival was 28 months (95% CI, 22.5-33.5 months) in patients with partial response and 22 months (95% CI, 15.3-28.7 months) in those with stable or progressive disease (P = .45, Figure 3). The following variables did not significantly affect overall survival: sex, age, size or multiplicity of hepatic metastases, rectal primary tumor, and the presence of extrahepatic metastases.

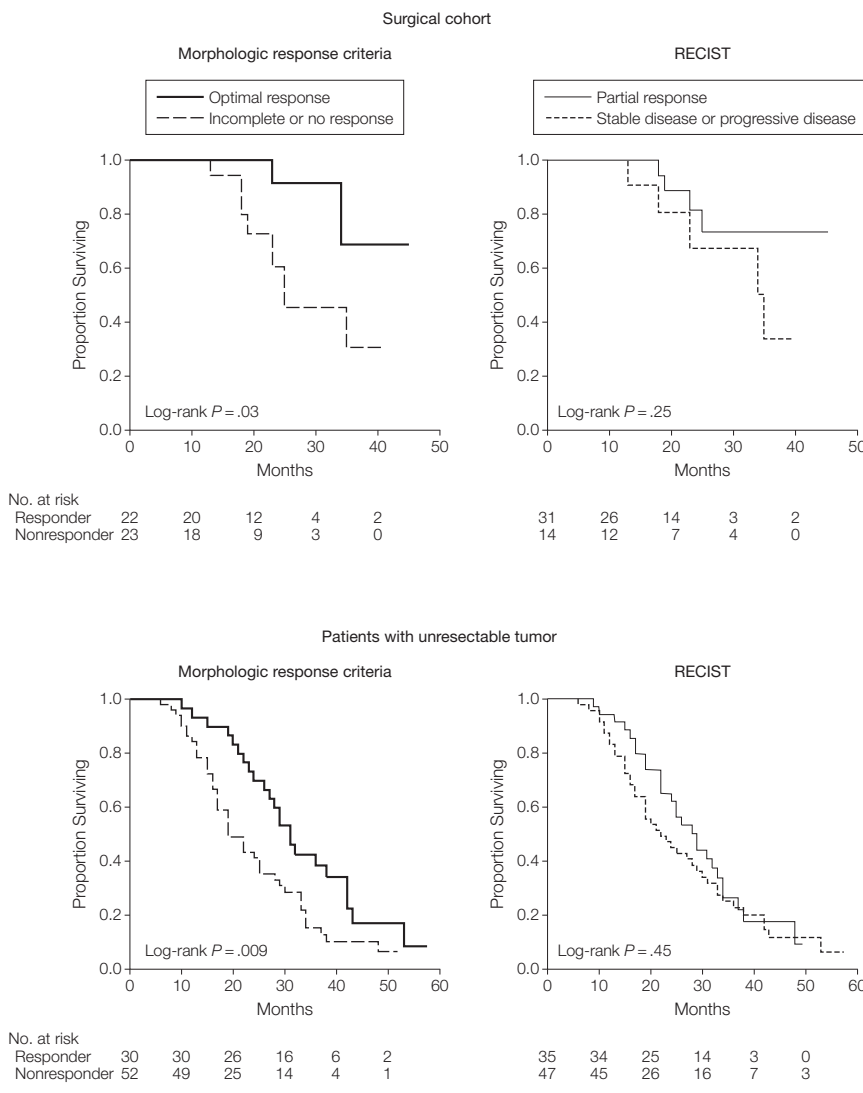
Interobserver Agreement for Morphologic Criteria

The interobserver agreement between the 3 radiologists for scoring morphologic changes was good: κ , 0.78 (95% CI, 0.63-0.93) 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.

COMMENT

We present novel qualitative morphologic CT criteria for predicting response to bevacizumab-containing chemotherapy in patients with colorectal liver metastases. These criteria were reproducible, as shown by the good interobserver agreement in scoring morphologic changes among 3 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

Figure 3. Overall Survival in Responders and Nonresponders by Morphologic Criteria and Response Evaluation Criteria in Solid Tumors (RECIST) in the Initial Surgical Cohort and in Patients With Unresectable Tumor (Validation Cohort)



Survival was evaluated in 45 surgical patients who underwent complete resection.

patients with unresectable colorectal liver metastases, 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 associated with neither 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 al⁷ also observed that histological tumor response is characterized by fibrous replacement of tumor rather than tumor necrosis in colorectal liver metastases. In patients with multiple liver metastases, the morphologic responses of the metastases within the same patient were uniform in 99 of 111 patients (89%). This result confirms a previous study demonstrating that in patients with multiple colorectal liver metastases, the histological tumor responses within the same patient were similar.⁷

The effect of pathologic response to preoperative therapy on survival in patients with solid tumors is well-established.^{12,13} In patients with colorectal liver metastases, histological 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% or more of residual tumor cells were present, major with 1% to 49% residual tumor cells, and complete with 0%. Using this 50% cutoff to define major vs minor pathologic response, we recently showed that in patients with colorectal liver

metastases, 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 nonsurgical patients with colorectal liver metastases, 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 magnetic resonance imaging 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 colorectal liver metastases are considered hypovascular tumors, enhancement does occur and is characterized by an ill-defined rim of peripheral enhancement that is maximal during the arterial phase and fades

Table 3. Univariate Analysis of Predictors of Overall Survival Among 45 Surgical Patients

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

Abbreviations: CEA, carcinoembryonic antigen; NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumors.
^aBased on the largest diameter of the resected tumor specimen.

away during the portal phase.^{19,20} We reviewed many CTs that were single-phase studies, lacking an arterial phase. Nevertheless, in cases for which 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 colorectal liver metastases 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 colorectal liver metastases. Morphologic response correlated with pathologic response stratified as com-

plete, 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 nonsurgical cohort. Thus, our results indicate that morphologic response may be a useful, noninvasive surrogate marker of pathologic response and improved survival in patients with colorectal liver metastases receiving a bevacizumab-containing regimen. It provides complementary information to traditional size-based criteria in assessing CT response to bevacizumab in colorectal liver metastases

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Author Contributions: Dr Vauthey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Vauthey and Loyer contributed equally as senior authors of this article.

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Statistical analysis: Chun, Vauthey.

Administrative, technical, or material support: Vauthey, Loyer.

Study supervision: Vauthey, Loyer.

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