

Modified two-dimensional response as surrogate marker of overall survival in patients with metastatic colorectal cancer

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Key words

Bevacizumab, colorectal cancer, overall survival, quantitative measurement, surrogate marker

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The identification of surrogate markers for long-term outcomes in patients with metastatic colorectal cancer (mCRC) may help in designing treatment regimens. The aim of this study was to assess whether two-dimensional response (2-DR) can serve as a new surrogate marker for overall survival (OS) in patients with mCRC. The study group consisted of 99 patients with mCRC from two independent cohorts who were treated with oxaliplatin-based chemotherapy plus bevacizumab. Two-dimensional response was defined as an area enclosed by coordinate points, including early tumor shrinkage at 8 weeks, depth of response at nadir, and 20% increase over nadir at progression. Each variable was weighted by its contribution rate to OS. The model was developed and internally validated in the learning cohort, and the performance of this model was externally verified in the validation cohort. Spearman correlation coefficients for 2-DR and OS in the learning and validation cohorts were 0.593 and 0.661, respectively. The C-indexes in predicting OS were 0.724 (95% confidence interval, 0.623–0.815) in the learning cohort and 0.762 (95% confidence interval, 0.651–0.873) in the validation cohort. Overall survival was significantly longer in patients with high 2-DR values than in patients with low 2-DR values in both the learning (37.0 vs. 24.1 months, $P < 0.001$) and validation (41.2 vs. 20.4 months, $P < 0.001$) cohorts. In contrast, differences in early tumor shrinkage and depth of response were not statistically significant. Multivariate analyses showed that 2-DR was an independent prognostic factor for OS.

The evaluation of treatment response in patients with metastatic colorectal cancer (mCRC) is estimated by the Response Evaluation Criteria in Solid Tumors (RECIST) as a binary all-or-none measurement to assess the potential advantages of tumor shrinkage and to serve as a surrogate for survival benefits.⁽¹⁾ Recently, the assessment of quantitative linear measurements, such as early tumor shrinkage (ETS) and depth of response (DpR), have been highlighted to better explain the actual status of tumor regression or dynamics in response to treatment, particularly with anti-EGFR antibodies.

Retrospective analyses of several clinical trials have indicated that ETS, which is usually defined as percent tumor shrinkage at 6–8 weeks compared with baseline, was predictive of survival outcomes in several regimens for mCRC, including irinotecan plus cetuximab in the BOND trial, irinotecan with fluorouracil and folinic acid (FOLFIRI) plus cetuximab in the CRYSTAL trial, oxaliplatin with fluorouracil and folinic acid (FOLFOX) plus cetuximab in the

OPUS trial, and FOLFOX plus panitumumab in the PRIME trial.^(2–4) Retrospective analyses have also shown that DpR, which is defined as the ratio of tumor shrinkage at nadir relative to baseline, was significantly associated with post-progression survival in the CRYSTAL and OPUS trials.⁽⁵⁾ These findings suggest that quantitative analysis of tumor shrinkage could be relevant to survival outcomes in patients treated with anti-epidermal growth factor receptor (EGFR) agents.

In contrast, the significance of tumor shrinkage on survival outcomes has been equivocal in therapies using the anti-angiogenic agent bevacizumab. Analyses of the AVF2107 and N9741 trials, involving patients with mCRC receiving first-line bevacizumab-containing regimens, suggested that the objective response rate was not a predictor of survival outcomes.⁽⁶⁾ Furthermore, overall survival (OS) and progression-free survival (PFS) did not differ significantly between patients who achieved stable disease as the best response and patients who showed an objective response.⁽⁶⁾ A limited number of studies

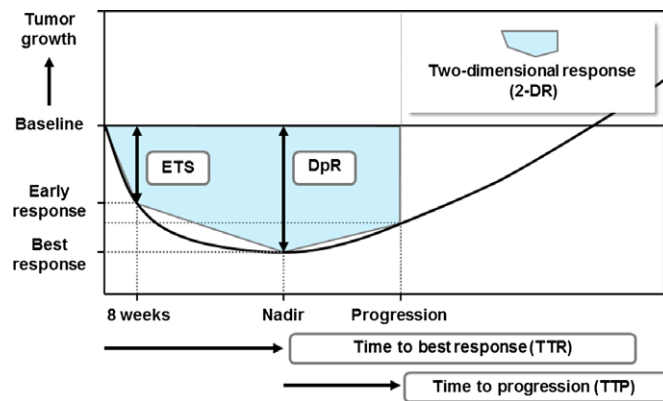


Fig. 1. Model of the two-dimensional response (2-DR), developed as a surrogate marker for overall survival in patients with metastatic colorectal cancer. The 2-DR was defined as the area enclosed by the coordinate points including early tumor shrinkage (ETS) at 8 weeks, depth of response (DpR) at the nadir, and 20% increase over nadir at disease progression.

Table 1. Patient characteristics and treatment statuses in two independent cohorts of patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab

Variable	Learning cohort (n = 47)		Validation cohort (n = 52)		P-value
	n	%	n	%	
Patient characteristics					
Age, years					
Median (range)	63 (40–74)		66 (40–80)		0.091
Sex					
Male	31	66.0	31	59.6	0.540
Female	16	34.0	21	40.4	
Performance status, WHO					
0	29	61.7	38	73.1	0.284
1	18	38.3	14	26.9	
Primary site					
Colon	31	66.0	28	53.8	0.305
Rectum	16	34.0	24	46.2	
Number of metastatic sites					
1	33	70.2	37	71.2	1.000
>1	14	29.8	15	28.8	
Metastatic site					
Liver	22	46.8	30	57.7	0.317
Liver only	12	25.5	16	30.8	0.657
Lung	21	44.7	20	38.5	0.547
Peritoneum	3	6.4	9	9.6	0.127
Lymph nodes	10	21.3	5	17.3	0.160
Tumor diameter at baseline, mm					
Median (range)	50.0 (5.0–946.0)		46.5 (9.9–200.0)		0.768
KRAS status					
Wild type	18/35	51.4	24/41	58.5	0.859
Mutant type	17/35	48.6	17/41	41.5	
Treatment status					
Total dose of oxaliplatin, mg					
Median (range)	1178 (262–3927)		1052 (470–4346)		0.391
Total dose of bevacizumab, mg					
Median (range)	3002 (500–10401)		2400 (960–9000)		0.864
Treatment after first-line therapy					
Second-line therapy	42	89.4	46	88.5	1.000
Anti-EGFR agents	14	29.8	17	32.7	0.830
Bevacizumab (BBP)	33	70.2	35	67.3	0.830
Resection of metastasis	7	14.9	8	15.4	1.000

BBP, bevacizumab beyond progression; EGFR, epidermal growth factor receptor.

focused on the relevance of ETS and DpR in patients receiving bevacizumab-based therapy. The results of the FIRE-3 trial, which compared first-line FOLFIRI plus either cetuximab or bevacizumab, showed that a higher percentage of patients in the cetuximab arm compared to the bevacizumab arm achieved ETS (68.2% vs. 49.1%, $P = 0.0005$) and that median DpR was significantly higher in the cetuximab than in the bevacizumab arm (48.9% vs. 32.2%, $P < 0.0001$).⁽⁷⁾ Furthermore, retrospective comparison of second-line therapy with FOLFIRI plus either cetuximab or bevacizumab showed a statistically significant positive correlation between DpR and OS in the cetuximab arm but not in the bevacizumab arm.⁽⁸⁾ These results suggest that assessments of tumor shrinkage based on both binary qualitative and linear quantitative parameters may be insufficient for predicting long-term survival outcomes in individual patients, at least for those patients receiving bevacizumab-based chemotherapy.

With the goal of finding new surrogate makers to evaluate the impact of bevacizumab on long-term survival outcome, we have developed a marker called the two-dimensional response

(2-DR), which was designed along the new concept of combining the parameters of tumor shrinkage with time factors.

Materials and Methods

Study design and setting. This retrospective analysis was undertaken to establish and validate the 2-DR model as a new surrogate measurement for OS in two independent cohorts, a learning cohort and a validation cohort. In total, 99 patients treated with first-line regimens containing bevacizumab and oxaliplatin were analyzed.

The learning cohort consisted of 47 patients who participated in the multicenter, single-armed phase II clinical trial of the Chubu Clinical Oncology Group (CCOG)-0801 (UMIN trial no. 000006818).⁽⁹⁾ Patients were treated with bevacizumab (5 mg/kg) plus FOLFOX, consisting of 85 mg/m² oxaliplatin and 200 mg/m² folinic acid, followed by a bolus infusion of 400 mg/m² fluorouracil and a subsequent continuous infusion of 2400 mg/m² fluorouracil, repeated every 2 weeks. After a median follow-up period of 55.4 months, 46 disease progressions (97.9%) and 37 deaths (78.7%) occurred in the 47 enrolled patients. Using this cohort, the modified 2-DR model was established and validated internally. The validation cohort consisted of 52 patients who participated in the CCOG-0902 trial (UMIN trial no. 000006478).⁽¹⁰⁾ Patients were treated with 7.5 mg/kg bevacizumab plus CapeOX, consisting of 130 mg/m² oxaliplatin on day 1 and oral capecitabine (1000 mg/m² twice daily) for 14 days, followed by a 7-day treatment-free interval, with the regimen repeated every 3 weeks; these treatments were followed by maintenance therapy with capecitabine plus bevacizumab. After a median follow-up period of 49.5 months, 49 disease progressions (94.2%) and 35 deaths (67.3%) occurred in the 52 enrolled patients. The model performance was externally validated in this cohort.

The end-points of both the trials included: (i) overall response rate, defined as the proportion of patients achieving a best response of complete response or partial response; (ii) disease control rate, defined as the proportion of patients who achieved a best response of complete response, partial response, or stable disease; (iii) PFS, defined as the time from

the date therapy was initiated to the date of disease progression or death from any cause; and (iv) OS, defined as the time from the date that therapy was initiated to the date of death from to any cause. Tumor size was assessed at baseline and every 8 weeks thereafter according to RECIST version 1.1.

The study protocol was approved by the institutional review board of each participating institution. Informed consent was waived owing to the retrospective design of this study.

Surrogate measurements of OS. Early tumor shrinkage and DpR were defined as the ratio of tumor shrinkage observed at 8 weeks after treatment initiation and nadir to baseline, which was expressed as a percentage.

The 2-DR model was designed as a new concept that combined the parameters of tumor shrinkage with time factors. The previously developed 2-DR model was defined as the area enclosed by coordinate points, including ETS at 8 weeks, DpR

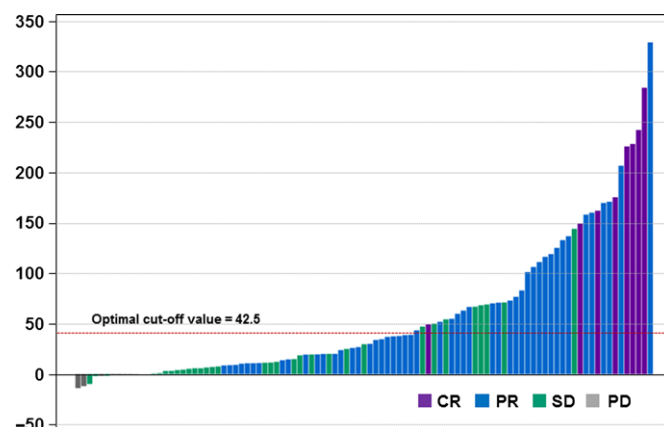


Fig. 2. Distribution of the two-dimensional response (2-DR), developed as a surrogate marker for overall survival, in patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab. Each plot was characterized according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Variable	Learning cohort (n = 47)		Validation cohort (n = 52)		P-value
	n	%	n	%	
RECIST response					
Objective response	26	55.3	31	59.6	0.841
Disease control	42	89.4	49	94.2	0.472
ETS, %					
Median (range)	22.7 (-33.3-71.5)		29.6 (-71.4-76.0)		0.196
≥20%	25	53.2	36	69.2	0.147
DpR, %					
Median (range)	31.3 (-33.3-100.0)		35.8 (-71.4-100.0)		0.651
≥30%	27	57.4	32	61.5	0.842
2-DR					
Median (range)	25.0 (-9.8-328.9)		36.7 (-13.9-242.1)		0.563
≥42.5	17	36.2	24	46.2	0.414

2-DR, two-dimensional response; DpR, depth of response; ETS, early tumor shrinkage; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Distribution of surrogate measurements for overall survival in two independent cohorts of patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab

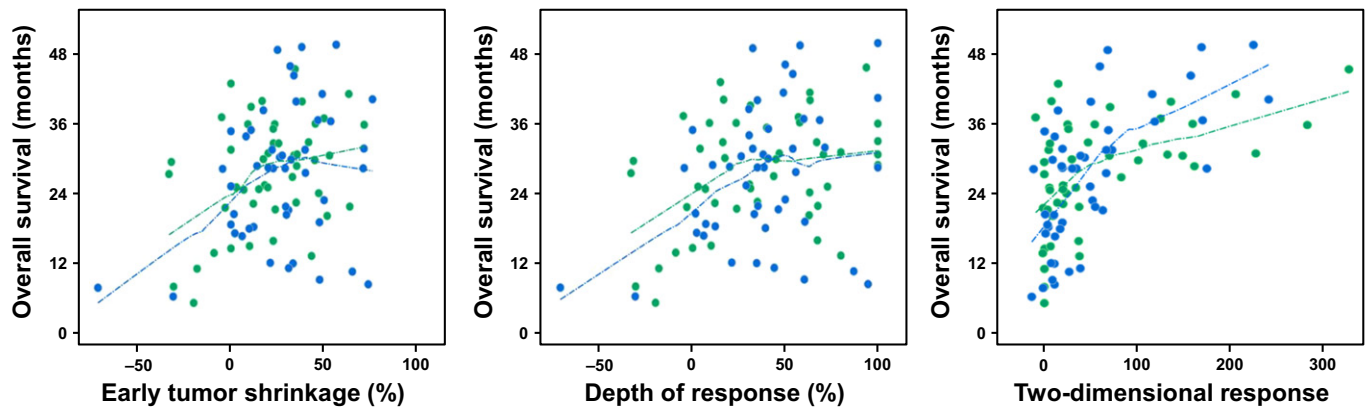


Fig. 3. Correlations between surrogate measures and overall survival in two independent cohorts of patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab. Green and blue dots represent patients in the learning and validation cohorts, respectively. Loess smoothing curves were used to indicate the functional relationship between each parameter and overall survival.

at nadir, and a 20% increase over nadir at disease progression (Fig. 1).⁽¹¹⁾ In this study, the 2-DR was refined as a modified model whose variables were weighted by the contribution rate (CR^{variable}) to OS in the learning phase. The modified 2-DR value was calculated as follows:

Modified 2-DR

$$= [(0.5 \times TTR \times CR^{\text{TTR}}) + (0.9 \times TTP \times CR^{\text{TTP}}) - (4 \times CR^{\text{TTP}})] \times [(DpR \times CR^{\text{DpR}}) + (0.5 \times TTR \times CR^{\text{TTR}} \times ETS \times CR^{\text{ETS}})]$$

where time to best response (TTR) is the time from initiation of therapy to maximum tumor shrinkage and time to progression (TTP) is the time from the date of maximum tumor shrinkage to 20% increase over nadir.

Statistical analysis. Differences in the characteristics of cohorts were analyzed using the χ^2 -test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Spearman's rank correlation coefficient was used to assess the correlation between each surrogate end-point and OS. The percent contribution of each parameter was calculated as the square of Spearman's correlation coefficient with OS. Loess smoothing curves with 70% of fit points were used to analyze the functional relationship between each measurement and OS. The concordance index (C-index) and calibration curves were compared with actual observed survival probability to determine the performance of the established model. Receiver–operating characteristic (ROC) curve analysis was used to assess the optimal cut-off value for 2-DR; the area under the ROC curve was also calculated. The cut-off values for ETS and DpR were defined in accordance with previous reports as 20%^(3,4,12,13) and 30%,⁽⁸⁾ respectively. Survival curves were estimated using the Kaplan–Meier method and compared using the log–rank test. After baseline characteristics and other outcome measures were corrected for, univariate and multivariate analyses of OS were carried out using a Cox proportional hazards model to determine whether 2-DR was an independent prognostic factor for OS. *P*-values below 0.05 were considered statistically significant. Statistical analyses were carried out using SPSS statistical package version 23 (SPSS, Chicago, IL, USA) and R version 3.1.3 (The R Foundation, <http://www.r-project.org/>).

Results

Baseline characteristics and treatment status. The learning and validation cohorts consisted of 99 patients total; the baseline characteristics of the two cohorts were comparable (Table 1). Treatment status, including total dose of key drugs and post-progression treatments, did not differ significantly between these cohorts.

Survival outcomes and surrogate measures of OS. The median PFS was 11.3 months (95% confidence interval [CI], 8.7–13.9 months) in the learning cohort and 12.4 months (95% CI, 10.0–14.8 months) in the validation cohort (hazard ratio, 1.025; 95% CI, 0.683–1.538; *P* = 0.905). The median OS was 30.0 months (95% CI, 27.8–32.2 months) in the learning cohort and 30.6 months (95% CI, 27.9–33.3 months) in the validation cohort (hazard ratio, 0.756; 95% CI, 0.471–1.214; *P* = 0.248). Surrogate measures of OS, including overall response rate according to RECIST version 1.1 criteria, ETS, and DpR, are presented in Table 2. No significant differences in survival outcomes or surrogate measures were found between the learning and validation cohorts.

Derivation of the 2-DR model. Spearman's rank correlation analysis showed that the degrees of correlation between OS and the parameters ETS, DpR, TTR, and TTP were 0.28, 0.30, 0.13, and 0.64, respectively, in the learning cohort and 0.24, 0.30, 0.07, and 0.65, respectively, in the validation cohort. The contribution of each parameter to OS showed a similar trend in both cohorts. By applying these coefficients in the learning cohort, the contribution rates were calculated as 0.078 for CR^{ETS} , 0.089 for CR^{DpR} , 0.017 for CR^{TTR} , and 0.415 for CR^{TTP} .

The performance of the 2-DR model was assessed by ROC curve analysis; the area under the ROC curve was 0.785 (95% CI, 0.650–0.919; *P* = 0.001) in the learning cohort and 0.817 (95% CI, 0.698–0.936; *P* < 0.001) in the validation cohort. The ROC curve analysis for predicting OS over 30 months showed that the optimal cut-off value for 2-DR was 42.5 (Fig. 1). Using this cut-off value, the 2-DR had positive and negative predictive values of 82.4% and 73.3%, respectively, in the learning cohort, and 70.8% and 78.6%, respectively, in the validation cohort.

Validation of the 2-DR model. The 2-DR model was validated internally in the learning cohort and externally in the validation cohort. Median values of 2-DR for internal and external

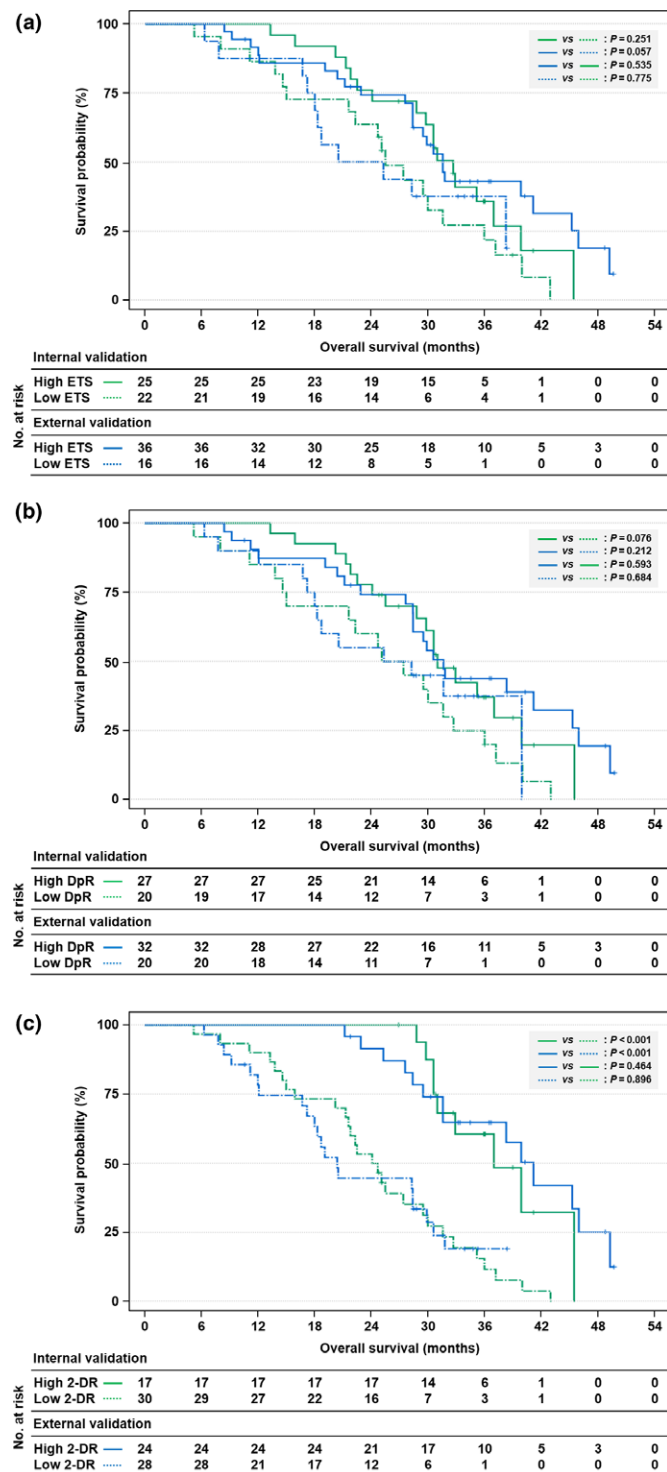


Fig. 4. Kaplan–Meier curves for overall survival in patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab, according to the surrogate measures. (a) Early tumor shrinkage. (b) Depth of response. (c) Two-dimensional response (2-DR).

validation were 25.0 (range, -9.8 to 328.9) and 36.7 (range, -13.9 to 242.1), respectively. The distribution of 2-DR is shown in Figure 2.

Spearman's correlation coefficients for 2-DR and OS were 0.593 ($P < 0.001$) in the learning cohort and 0.661

($P < 0.001$) in the validation cohort. The correlation plots of 2-DR and other surrogate measurements are presented in Figure 3.

The C-indexes of the 2-DR model in predicting OS were 0.724 (95% CI, 0.623 – 0.815) in the internal validation and 0.762 (95% CI, 0.651 – 0.873) in the external validation; the C-indexes of ETS and DpR were 0.623 (95% CI, 0.504 – 0.740) and 0.640 (95% CI, 0.525 – 0.751) in the internal validation and 0.588 (95% CI, 0.477 – 0.699) and 0.593 (95% CI, 0.482 – 0.704) in the external validation, respectively.

Overall survival was significantly longer in patients with high 2-DR values than in patients with low 2-DR values during the internal validation (37.0 months [95% CI, 29.8 – 44.2 months] vs. 24.1 months [95% CI, 20.4 – 27.8 months], $P < 0.001$) and external validation (41.2 months [95% CI, 36.6 – 45.8 months] vs. 20.4 months [95% CI, 17.4 – 23.4 months], $P < 0.001$) (Fig. 4). In contrast, the differences in ETS (internal validation, 32.7 months [95% CI, 29.5 – 36.0 months] vs. 25.5 months [95% CI, 21.8 – 29.2 months], $P = 0.121$; external validation, 31.6 months [95% CI, 29.1 – 34.1 months] vs. 20.5 months [95% CI, 7.6 – 33.4 months], $P = 0.141$) and DpR (internal validation, 31.0 months [95% CI, 26.8 – 35.2 months] vs. 25.5 months [95% CI, 21.3 – 29.7 months], $P = 0.094$; external validation, 31.6 months [95% CI, 22.4 – 40.8 months] vs. 28.4 months [95% CI, 19.3 – 37.6 months], $P = 0.431$) were not statistically significant in either validation.

Univariate analyses showed that TTP and 2-DR were significantly associated with OS. Multivariate analyses showed that 2-DR was the only independent prognostic factor of OS in both the learning and validation cohorts (Table 3).

Discussion

This study is the first to evaluate the modified 2-DR as a new surrogate marker of OS in patients with mCRC. This model was developed and verified in two independent cohorts consisting of patients who participated in phase II trials of first-line oxaliplatin-based chemotherapy plus bevacizumab. The correlation between 2-DR and OS was statistically significant in both internal and external validations. The C-index showed that this model could predict actually observed survival. Overall was significantly greater in patients with high 2-DR values than in patients with low 2-DR values, with a cut-off of 42.5 being a clear prognostic value in both cohorts.

Linear quantitative parameters, including ETS and DpR, have been shown to be useful in assessing the value of chemotherapy, especially regimens consisting of anti-EGFR antibodies.^(2–4,12,14) However, in our patients, these parameters showed only weak correlations with long-term OS. These differences may be owing to differences in the mechanisms of action of bevacizumab and anti-EGFR agents. Bevacizumab has a cytostatic effect rather than a direct cytotoxic effect, which may be reflected more by disease control than by tumor shrinkage.⁽⁶⁾ In addition, the profile of molecules predictive of tumor response and survival might be different in the case of bevacizumab. The levels of vascular endothelial growth factor (VEGF), the molecular target of bevacizumab, have been associated with tumor response, but not with survival. However, upstream promoters of angiogenesis and hypoxia, such as CA9 and HIF-2 α , were significantly associated with survival outcomes.⁽¹³⁾

Moreover, radiologic responses to bevacizumab-containing regimens in patients with colorectal liver metastasis included

Table 3. Impact of surrogate measurements on overall survival in two independent cohorts of patients with metastatic colorectal cancer who were treated with oxaliplatin-based chemotherapy plus bevacizumab

Variables	Internal validation (n = 47)				External validation (n = 52)			
	n	HR	95% CI	P-value	n	HR	95% CI	P-value
Univariate analysis								
ETS, %								
<20%	22	Ref.			16	Ref.		
≥20%	25	0.597	0.308–1.155	0.126	36	0.578	0.274–1.219	0.150
DpR, %								
<30%	23	Ref.			27	Ref.		
≥30%	24	0.557	0.289–1.074	0.081	25	0.635	0.308–1.307	0.217
TTR, weeks								
<Median	23	Ref.			25	Ref.		
≥Median	24	0.600	0.306–1.177	0.137	27	1.094	0.561–2.133	0.792
TTP, weeks								
<Median	24	Ref.			26	Ref.		
≥Median	23	0.322	0.161–0.646	0.001	26	0.325	0.163–0.647	0.001
2-DR								
<Cut-off value	30	Ref.			28	Ref.		
≥Cut-off value	17	0.239	0.108–0.529	<0.001	24	0.244	0.110–0.545	0.001
Multivariate analysis								
TTP, weeks								
<Median	24	Ref.			26	Ref.		
≥Median	23	0.604	0.265–1.377	0.230	26	0.644	0.255–1.622	0.350
2-DR								
<Cut-off value	30	Ref.			28	Ref.		
≥Cut-off value	17	0.322	0.125–0.827	0.019	24	0.334	0.116–0.958	0.041

2-DR, two-dimensional response; CI, confidence interval; DpR, depth of response; ETS, early tumor shrinkage; HR, hazard ratio; Ref., reference; TTP, time to progression; TTR, time to response.

not only shrinkage of tumor size but also morphological changes, such as homogeneous low attenuation with a thin and sharply defined tumor interface.⁽¹⁵⁾ The optimal morphologic response correlated significantly with OS.⁽¹⁶⁾ These findings suggest that linear assessments of tumor shrinkage may have limitations in determining the effects of bevacizumab on long-term survival outcomes.

The 2-DR model combines parameters of tumor shrinkage with the effects of treatment over time. Of patients with high 2-DR values, approximately 20% showed minor responses with long-term stable disease and 60% showed major responses to treatment. These results indicate that 2-DR may reflect both the cytostatic effects of bevacizumab and the cytotoxic effects of chemotherapy and may act as a surrogate marker of long-term survival.

The 2-DR model also considered the contribution of individual parameters because each of these parameters showed different degrees of correlation with OS. Time to progression following best response was strongly correlated with OS, whereas TTR showed only a weak correlation. Early tumor shrinkage and DpR had similar moderate degrees of correlation with OS. These correlations were similar in two independent cohorts of patients treated with bevacizumab-containing regimens. Although the weight of each parameter on the cytotoxic and targeted agents may differ, the 2-DR model may be adapted to other regimens by adjusting the contribution rates.

This study has several limitations. First, tumor size and response according to RECIST were not evaluated by central review. Second, the treatment regimens in the learning and validation cohorts differed, although their baseline characteristics, treatment status including total dose and dose intensity of key drugs, and treatment outcomes were comparable. Furthermore, the degree of correlation between each parameter and OS showed a similar trend in both cohorts. Third, the relatively small sample size of this study necessitates confirmation of these results in a larger cohort study. Finally, this model of 2-DR is too complicated for use in the clinical setting. However, the aim of this report was to propose the concept of combining the parameters of tumor shrinkage with time factors for use primarily in evaluating treatment regimens in clinical trials. In the next phase, efforts will have to be made to establish a simpler surrogate marker for application in the clinical practice setting.

In conclusion, our exploratory analysis of 2-DR as a new surrogate marker for OS in a pooled data set from two independent cohorts reveals that 2-DR may predict long-term survival outcomes in patients with mCRC treated with bevacizumab-containing regimens.

Disclosure Statement

The authors have no conflict of interest.

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