Metastatic Bulk Independently Predicts Outcomes for EGFR Precision Targeting in Colorectal Cancer

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Abstract

Background: Molecular profiles guide the clinical management of metastatic colorectal cancer (mCRC), particularly related to the use of anti-epidermal growth factor receptor (EGFR) antibodies. Tumor sidedness has also been implicated in resistance to these therapies, but has largely been studied in the first-line setting. We examined the role of tumor sidedness and disease bulk in predicting clinical outcomes to anti-EGFR therapy in the treatment-refractory setting. **Methods:** We identified a retrospective cohort of 62 patients with *KRAS* wild-type mCRC who received anti-EGFR therapy in the late-line setting. Response was assessed per RECIST 1.1, with bulky disease defined as any single lesion >35 mm in longest cross-sectional diameter or nodal short axis. Primary sidedness was defined in relation to the splenic flexure. **Results:** Patients with right-sided primary tumors at time of late-line EGFR therapy presented with increased tumor bulk and worsened overall survival (OS) relative to left-sided primary tumors. Tumor bulk, defined as either a categorical or continuous variable, predicted worsened progression-free survival (PFS) and OS, which persisted when controlling for differences in the primary tumor location. Within the right-sided cohort, no objective responses were observed for bulky disease or during treatment with anti-EGFR monotherapy. The nonbulky cohort experienced clinical benefit with anti-EGFR monotherapy, showing similar PFS and an improved response rate compared with sequential chemotherapy. **Conclusions:** In an effort to expand understanding of the role of primary sidedness in clinical response to anti-EGFR therapy, we identified sidedness and tumor bulk as potential predictive biomarkers of clinical response in late-line mCRC. Future prospective studies of EGFR targeting should consider tumor bulk in addition to molecular profiling in the identification of populations most likely to achieve meaningful clinical benefit.

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Despite advances in both prevention and treatment, metastatic colorectal cancer (mCRC) remains the second-leading cause of cancer-related mortality in the United States.^{1,2} For mCRC, therapeutic options include traditional cytotoxic chemotherapy and targeted agents depending on distinct molecular profiles. Antibodies targeting epidermal growth factor receptor (EGFR), including cetuximab and panitumumab, have shown clinical utility in the late-line setting.^{3,4} Defin-

ing populations most likely to benefit from anti-EGFR targeting continues to be an area of great interest to optimize their clinical utility.

Mutations resulting in the constitutive activation of the Ras/Raf/MEK/ERK pathway predict resistance to anti-EGFR therapy. Numerous investigations have demonstrated a lack of clinical benefit of cetuximab and panitumumab for mCRC harboring mutations in *KRAS* (exons 2/3/4),^{5–10} *NRAS* (exons 2/3/4),^{7,8,10} and

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BRAF (V600E).^{7–12} These molecular alterations result in constitutive pathway activation independent of EGFR, with resultant therapeutic resistance. Primary tumor location, or sidedness, has also been implicated in anti-EGFR therapy resistance in the first-line setting based on the results of the CALGB/SWOG 80405 clinical trial.^{13,14}

Patients with right-sided primary tumors have worse overall survival (OS).^{15–18} Delayed presentation of right-sided tumors is associated with a lack of recognition secondary to delayed symptom onset compared with left-sided cancers, resulting in patients presenting with advanced anemia and greater primary tumor bulk.^{19,20} In the adjuvant setting, disease bulk has been shown to predict worsened OS, including in patients with tumors >50 mm.²¹ Additionally, disease burden, including sites of metastases combined with size of metastases, has predicted worsened OS.^{17,22}

This study investigated the impact of sidedness on the response to anti-EGFR therapy in the late-line setting, defined after initial disease progression during treatment with a non-EGFR-targeting regimen. We analyzed disease bulk as an independent predictor of clinical outcomes associated with anti-EGFR therapies to build on the impact of sidedness in the treatment-refractory setting. Using a single-institution retrospective analysis of patients with mCRC treated with anti-EGFR therapy, we examined the late-line impact of sidedness and tumor bulk on clinical outcomes of OS, progression-free survival (PFS), and response rate (RR).

Methods

After Institutional Review Board approval was obtained, a retrospective review was performed of all patients with mCRC treated with cetuximab or panitumumab from July 2006 through May 2017 at a single academic center. Inclusion criteria included histologically confirmed adenocarcinoma, KRAS wild-type status, and prior progression on chemotherapy containing 5-fluorouracil (5-FU), with cross-sectional imaging performed within 6 weeks of initiating therapy. A single patient with microsatellite instability was included in the analysis. Exclusion criteria included first-line anti-EGFR therapy, and known mutations in the case of extended spectrum RAS or BRAF testing. Sites that received locally directed therapy were excluded from the analysis. Sidedness was defined by location of primary cancer relative

to the splenic flexure: right-sided included cancer of the cecum, ascending colon, and transverse colon, and left-sided included cancer of the splenic flexure and in regions distal to the splenic flexure, including the rectum. Tumor bulk was analyzed at sites of metastases for longest diameter in parenchymal disease or short axis for nodal disease. Bulk was analyzed as both continuous and categorical variables, with diameter ≥35 mm used to define bulky disease, which is the median size of CRC liver metastases. Use of concurrent irinotecan and anti-EGFR therapy following progression on FOLFIRI was defined as a unique line. Use of bevacizumab was monitored but was not considered an independent line of therapy.

Statistical Analysis

We assessed clinical outcomes with CT or MRI using RECIST 1.1 per previously reported guidelines.²³ OS and PFS were calculated from initiation of anti-EGFR therapy, with death prior to radiographic progression included in PFS analysis. Median PFS and OS were reported with corresponding 95% CIs. Multivariate analyses for PFS and OS were performed using Cox regression models. Group comparison for categorical variables was based on chi-square tests with Yates correction, and group comparison for continuous variables was based on *t*-tests. Two-sided *P* values were reported and significance was defined as <0.05. Survival curves were prepared using Origin 2017 (OriginLab Corporation) and the Kaplan-Meier method, with group comparison using the Breslow method.

Results

Sidedness Predicts Outcomes to Anti-EGFR Therapy in the Treatment-Refractory Setting

A total of 62 patients were available for analysis, with baseline characteristics stratified by primary tumor sidedness: right-sided (*n*=15) versus left-sided (*n*=47) (Table 1). Right-sided cancers had increased disease bulk at the largest metastases sites, with mean diameters of 52.7 vs 28.5 mm for left-sided tumors (*P*=.03). Patients with right-sided primary tumors presented with advanced mean age (69 vs 59 years; *P*=.04), with a trend toward advanced histologic grade (38% vs 13%; *P*=.12). When stratified for sidedness, no significant differences were seen in ECOG performance status, sites of metastases, tumor grade, or baseline laboratory values.

Table 1. Baseline Characteristics

Characteristic	Location of Tumor			Largest Diameter of Tumor		
	Left (n=47)	Right (n=15)	P Value	Nonbulky, ≤3.5 cm (n=39)	Bulky, >3.5 cm (n=23)	P Value
Sidedness	NA	NA	NA	34L, 5R	13L, 10R	.016
Maximum tumor diameter, mean ± SD, mm	28.5 ± 20.4	52.7 ± 36.5	.03	18.8 ± 9.8	60.6 ± 26.6	<.001
Sex			.86			.85
Female	20	6		16	10	
Male	27	9		23	13	
Age, mean ± SD, y	59 ± 14	69 ± 14	.04	61 ± 14	63 ± 15	.50
Body mass index, mean ± SD, kg/m ²	26.7 ± 6.9	25.1 ± 4.2	.27	27.9 ± 7.1	23.7 ± 3.9	.005
ECOG performance status, ≥2 (n/N)	19% (9/47)	13% (2/15)	.90	12% (4/39)	30% (7/23)	.10
Metastatic sites, ≥2 (n/N)	72% (34/47)	73% (11/15)	.94	72% (28/39)	74% (17/23)	.86
Tumor grade, high (n/N)	13% (6/46)	38% (5/14)	.12	13% (5/39)	27% (6/21)	.25
Concurrent FOLFOX/FOLFIRI (n/N)	26% (12/47)	7% (1/15)	.23	28% (11/39)	9% (2/23)	.13
Prior bevacizumab (n/N)	64% (30/47)	67% (10/15)	.84	67% (26/39)	61% (14/23)	.85
Line of therapy			.97			.6
Second	18	5		13	10	
Third	29	10		26	13	
Hemoglobin, mean ± SD, g/dL (n)	12.1 ± 1.8 (46)	11.6 ± 1.5 (15)	.23	12.5 ± 1.8 (39)	11.1 ± 1.1 (22)	<.001
Alkaline phosphatase, mean ± SD, IU/L (n)	163 ± 156 (46)	154 ± 149 (15)	.85	135 ± 133 (39)	207 ± 177 (22)	.076
Creatinine, mean ± SD, mg/dL (n)	0.81 ± 0.18 (47)	0.91 ± 0.27 (15)	.16	0.85 ± 0.19 (39)	0.81 ± 0.24 (23)	.54
CEA, mean ± SD, ng/mL (n)	412 ± 1,781 (47)	64 ± 64 (14)	.19	85 ± 130 (39)	770 ± 2,582 (22)	.23
Albumin, mean ± SD, g/dL (n)	3.25 ± 0.69 (26)	3.35 ± 0.42 (6)	.67	3.42 ± 0.61 (23)	2.89 ± 0.58 (9)	.04
LDH, mean ± SD (n)	191 ± 25 (10)	189 ± 60 (6)	.91	190 ± 24 (7)	191 ± 50 (9)	.95

P values were calculated using Chi square tests for categorical data and 2-sided t-tests for measurement data. Bolded values denote $P < .05$. Abbreviations: L, left; NA, not applicable; R, right.

Right-sided primary tumors had no significant differences in concurrent treatment regimen or line of anti-EGFR therapy. When stratified for primary tumor location, a trend toward improvement in the objective RR (ORR) was observed for left-sided primary disease (31.6% vs 14.3%; $P = .37$) (Figure 1). A trend toward improved PFS was observed for left- versus right-sided primary tumors (5.7 vs 2.3 months; $P = .066$), and significant differences in median OS were observed (16.7 vs 6.8 months, respectively; $P = .047$). For anti-EGFR monotherapy ($n = 40$), right-sided disease trended toward worse clinical outcomes, including ORR (0% vs 20%; $P = .286$) and OS (6.0 vs 10.0 months; $P = .076$). No differences in median PFS were observed (2.3 vs 3.7 months; $P = .346$).

Metastatic Bulk Predicts Worsened Clinical Outcomes for Anti-EGFR Therapy

Baseline characteristics were compared in patients with bulky ($n = 23$) versus nonbulky disease ($n = 39$) (Table 1), with bulky disease defined as any one lesion ≥ 35 mm. Patients with bulky disease were more likely to have right-sided primary tumors (43% vs 13%; $P = .016$). Using logistic regression, the continuous variable of metastatic diameter was found to strongly predict primary tumor location ($P = .012$), with larger tumors associated with a right-sided pri-

mary. Patients with bulky disease had reduced baseline body mass index (23.7 vs 27.9 kg/m²; $P = .005$), lower hemoglobin (11.1 vs 12.5 g/dL; $P < .001$) and reduced albumin levels (2.89 vs 3.42 g/dL; $P = .04$).

When patients were stratified based on disease bulk, no significant differences were found in age, ECOG performance status, sites of metastases, or tumor grade, and no differences were seen in concurrent treatment regimen or line of anti-EGFR therapy. Compared with patients with bulky disease, those with nonbulky disease were found to have a 4-fold improvement in ORR (38.7% vs 9.5%; $P = .044$) (Figure 2) and showed significant improvement in clinical outcomes, including median PFS (7.2 vs 3.5 months; $P = .001$) and median OS (23.4 vs 6.0 months; $P < .001$). For anti-EGFR monotherapy, nonbulky disease trended toward improved clinical outcomes, including ORR (23.8% vs 5.2%), with significant differences in PFS (5.5 vs 3.4 months; $P = .022$) and OS (16.0 vs 6.0 months; $P = .006$) compared with bulky disease.

Bulky disease predicted clinical outcomes independent of primary sidedness. Analysis of tumor bulk as a continuous variable was shown to independently predict PFS, with a hazard ratio (HR) of 0.014 ± 0.004 ($P < .001$) for every unit increase in millimeters, and

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Figure 1. Clinical outcomes of anti-EGFR-treated patients stratified between L and R primary tumors, including waterfall plots shown for primary (A) L and (B) R. Kaplan-Meier survival plot of (C) PFS and (D) OS. Abbreviations: CR, complete response; L, left; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, right; SD, stable disease. *Disease progression at nontarget lesion.

OS, with an HR of 0.020 ± 0.005 ($P<.001$). Using multivariate analysis to control for categorical disease bulk, primary sidedness failed to predict PFS (HR, 0.003 ± 0.361 ; $P=.994$) or OS (HR, 0.138 ± 0.342 ; $P=.687$). On the other hand, the HR for the categorical disease bulk is 0.825 ± 0.331 ($P=.013$) for PFS and 1.247 ± 0.324 ($P<.001$) for OS. When controlling for disease bulk as a continuous variable, primary sidedness also failed to predict PFS (HR, -0.019 ± 0.371 ; $P=.959$) or OS (HR, 0.101 ± 0.365 ; $P=.783$).

Nonbulky Disease Confers Improved Outcomes for Anti-EGFR Therapy for the Left-Sided Cohort

Outcomes were compared to predict subgroups of patients most likely to obtain meaningful clinical benefit when stratifying for primary tumor location and disease bulk (Figure 3). Within the left-sided cohort, a trend for improvement in ORR was seen when comparing nonbulky and bulky disease (37.0% vs 18.2%). Patients with left-sided, nonbulky disease ($n=34$) had a significant improvement in clinical outcomes compared with those with left-sided, bulky disease ($n=13$), including median PFS (7.2 vs 3.5 months; $P<.001$)

and median OS (21.6 vs 6.0 months; $P<.001$). These differences persisted with anti-EGFR monotherapy alone, including improved clinical outcomes for nonbulky disease in the left-sided cohort with better ORR (26.3% vs 10.0%), PFS (5.7 vs 1.9 months; $P=.001$), and OS (16.9 vs 5.7 months; $P<.001$).

The left-sided, nonbulky disease cohort showed consistently improved clinical outcomes compared with alternative pairwise cohorts. Left-sided, nonbulky tumors were found to have an ORR of 37.0%, with a trend toward improvement, compared with 16.0% for all remaining cohorts ($P=.1627$) (Figure 3). Patients with left-sided, nonbulky disease ($n=34$) showed a trend towards PFS compared with those with right-sided, nonbulky disease ($n=5$) (7.2 vs 2.3 months, respectively; $P=.074$) and OS (21.6 vs 4.8 months, respectively; $P=.462$). Compared with patients with right-sided, bulky disease, those with left-sided, nonbulky disease ($n=10$) experienced improvement in PFS (7.2 vs 2.3 months, respectively; $P=.010$) and OS (21.6 vs 6.0 months, respectively; $P<.001$).

Figure 2. Clinical outcomes of anti-EGFR-treated patients stratified between (A) nonbulky and (B) bulky tumors. Kaplan-Meier survival plot of (C) PFS and (D) OS. Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, right; SD, stable disease. *Disease progression at nontarget lesion.

Responses Observed for Right-Sided Nonbulky Disease With Anti-EGFR Therapy

No objective responses were observed for patients with right-sided bulky tumors ($n=10$; Figure 3). Objective responses were observed in patients with right-sided nonbulky tumors ($n=5$); however, these responses were in the setting of concurrent chemotherapy. Clinical evaluation within the right-sided cohort was limited by sample size ($n=15$), and no differences were seen in median PFS ($P=.81$) and OS ($P=.95$) with pairwise comparison stratified by disease bulk.

Similar Outcomes in Nonbulky Disease for Late-Line Anti-EGFR Therapy and Chemotherapy

Because clinical improvement was observed for anti-EGFR therapy within the nonbulky cohort, a subgroup analysis was performed in the second-line setting to compare the use of combination chemotherapy (FOLFOX or FOLFIRI) versus anti-EGFR monotherapy. A population ($n=16$) was identified that received sequential therapy with order-independent chemotherapy versus anti-EGFR monotherapy, allowing for internal control starting in the second-

line setting (Figure 4). Despite most patients receiving second-line chemotherapy ($n=12$) followed by anti-EGFR therapy, no significant differences were observed in PFS between anti-EGFR therapy versus chemotherapy (3.6 vs 5.9 months, respectively; $P=.71$). A trend toward improvement in RR was observed for anti-EGFR therapy versus combination chemotherapy (33.3% vs 7.7%; $P=.23$).

Discussion

This study expands on previous data indicating that primary sidedness is important in determining the potential clinical response to anti-EGFR therapy. Our findings show that in the late-line setting, tumor sidedness affects clinical outcomes, including worsened PFS consistent with results of prior investigations.²⁴ In addition, we show the importance of disease bulk in predicting clinical outcomes associated with anti-EGFR therapy. Durable clinical benefit was seen in the left-sided, nonbulky disease cohort, in contrast to patients with right-sided disease in whom responses were only observed in combination with systemic cytotoxic therapy. Advances in preci-

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Figure 3. Clinical outcomes of anti-EGFR-treated patients stratified for both tumor bulk and primary sidedness, including waterfall plots shown for (A) left-sided and (B) right-sided disease. Kaplan-Meier survival plot of (C) PFS and (D) OS (95% CI, for both C and D). Abbreviations: CR, complete response; L, left; NS, not significant; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, right; SD, stable disease. *Disease progression at nontarget lesion.

sion medicine present new challenges in incorporating both clinical and molecular markers to tailor applications to select populations that would derive meaningful clinical benefit.

To expand on advances in molecular profiling for predicting outcomes with anti-EGFR therapy, we proposed a model to incorporate both sidedness and disease bulk. Advances in molecular profiling allow for standard-of-care testing to avoid use of anti-EGFR therapy in patients with tumors harboring *KRAS*, *NRAS*, and *BRAF* mutations, which are commonly enriched within the right-sided primary population.^{25–27} When stratified for sidedness, prospective targeted sequencing panels have revealed that right-sided tumors have increased oncogenic alterations at additional loci, including *PIK3CA*, *AKT1*, *RNF43*, and *SMAD4*.²⁷ The role of understanding mutational profiles that emerge over the course of therapy remains unclear, because the predictive significance and mechanisms of resistance to anti-EGFR therapy were largely validated in the first-line setting.^{14,28–34}

Consistent with previous findings,^{13,24} we report worsened OS for patients with right-sided primary tumors in a diverse cohort receiving anti-EGFR therapy after initial progression on cytotoxic therapy. A population-based cohort of anti-EGFR therapy in the third line showed that right-sided primary tumors were associated with shorter median OS compared with left-sided tumors (30.5 vs 39.3 months, respectively).²⁴ Subgroup analysis of second-line panitumumab in combination with FOLFIRI revealed worsened clinical outcomes for right-sided tumors, with an ORR of 13.3% versus 49.7% and PFS of 4.8 versus 8.0 months.³⁵

Further work is necessary to define the molecular profiles that drive resistance to anti-EGFR therapy.^{36,37} Known mechanisms of resistance include *Ras* activation³⁸ and clonal evolution over the course of anti-EGFR therapy.³⁹ Vertical inhibition by combination therapies, such as anti-EGFR therapy and MEK inhibition, have been investigated in the late-line setting.⁴⁰ However, adaptive resistance has prov-

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Figure 4. Clinical outcomes of patients treated with sequential second- and third-line (A) anti-EGFR therapy or (B) chemotherapy, with (C) Kaplan-Meier plot of PFS. Abbreviations: Chemo, chemotherapy; CR, complete response; EGFR, epidermal growth factor receptor; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

en to be a formable challenge to translate clinically. Mutations conferring resistance to anti-EGFR therapy have been reported at *ERBB2*, *EGFR*, *FGFR1*, *PDGFRA*, and *MAP2K1*.⁴¹ Translational work specific to the Ras/Raf/MEK/ERK pathway suggest that resistance to growth signal pathways develops rapidly, highlighting a need for further understanding of targeting mechanisms and resultant signal feedback.⁴² Novel approaches could include multisite horizontal targeting, such as ongoing investigations in targeting *BRAF* V600E.⁴³ Mechanistic understanding may be aided by biobanks to profile pathways of adaptive resistance.⁴⁴

Differences in clinical outcomes for bulky disease necessitate further investigations into the physical delivery of antibody-based targeted therapies. Despite enhanced antibody–antigen recognition, preclinical data had proposed that the tuning of high-affinity monoclonal antibodies impaired deep penetration of limited remaining free antibody molecules.⁴⁵ Models of antibody delivery to solid tumors have suggested that high-affinity ligands have a predilection to be localized to perivascular regions.⁴⁶ Specific to anti-EGFR therapy, preclinical models have shown that delivery of cetuximab decreases with increasing vascular distance, including minimal binding observed in central areas of hypoxic tumor.⁴⁷ Additionally, changes in hydrostatic pressure have been shown to enhance therapeutic delivery of cetuximab in patient-derived xenografts, with reduction in tumor volume observed with coadministration of albumin to overcome this osmotic barrier.⁴⁸ Within complex tissue architecture, other limitations can include heterogeneous blood supply, elevated interstitial pressures, and increased transport distances conferring poor therapeutic delivery.⁴⁹

Despite large phase III data showing benefit of second-line anti-EGFR therapy in combination with FOLFIRI,³⁵ the choice between combination and sequential therapy remains unclear. Clinical application of anti-EGFR therapy in earlier lines of therapy could be considered; however, limited prospective data are available to guide this decision. Because of the different toxicity profile between targeted agents and chemotherapy, these could have unique applications in the second-line setting as monotherapy, provided we can predict populations that would experience clinical benefit. Historical controls of second-line FOLFIRI include reports with PFS of 2.5 months and RR of 4%,⁵⁰ and more recent control arms in the EGFR-targeting population with PFS of 4.8 months and RR of 13.3%.³⁵ These findings compare with analysis of anti-EGFR monotherapy within this cohort, including PFS of 3.6 months and RR of 15%. Improved clinical outcomes with anti-EGFR monotherapy are enriched within the left-sided, nonbulky cohort, including PFS of 5.7 months and ORR of 26.3%.

Despite differences in primary sidedness, objective responses were seen for right-sided disease with anti-EGFR therapy in combination with chemotherapy. Challenges of late-line therapy were recent-

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ly highlighted in the placebo-controlled TAS-102 trial, with PFS of 2.0 months and ORR of 1.6%.⁵¹ Right-sided disease has had limited response to anti-EGFR monotherapy, consistent with only objective responses seen with concurrent cytotoxic therapy. The rare population of patients with right-sided tumors who experience response to the addition of anti-EGFR monotherapy remains of great interest when considering anti-EGFR salvage applications.

To further expand applications of anti-EGFR therapy in the nonbulky cohort, subgroup analysis was performed for patients receiving sequential chemotherapy and anti-EGFR therapy. Interestingly, no differences in PFS were observed despite most patients being treated with anti-EGFR therapy in the third-line setting. Additionally, a 4-fold improvement in RR was observed for anti-EGFR therapy versus chemotherapy, at 33.3% versus 7.7%, respectively. This offers preliminary support for prospective studies to consider second-line anti-EGFR monotherapy, provided there is appropriate patient selection for molecular profiling, primary sidedness, and tumor bulk.

Limitations of this study are inherent to the retrospective cohort design and sampling from a single center. However, our work provides an additional frame for future prospective trial design in the application of anti-EGFR targeted therapies. Although durable benefits were observed in the left-sided, nonbulky cohort, meaningful conclusions for right-sided disease were limited by sample size. Disease bulk was analyzed as both a categorical and continuous variable stratified with median diameter for hepatic metastases.²¹ Our study calls for rigorous investigation to further define response to targeted therapy to in-

corporate disease burden, including tumor volume, number of metastases, and sites of metastases. The longstanding history of disease bulk as a mechanism of phenotypic resistance has long been described⁵²; however, readdressing this question within novel applications of targeted therapy remains of great interest. Within the limitations of a retrospective cohort, the differences shown in our study suggest that disease bulk independently predicts clinical outcomes, as reported for surgical outcomes of resectable hepatic disease.²¹ This expands on prior knowledge regarding the association of increased tumor burden with poor prognosis. We identify the objective marker of disease bulk for future analysis in prospective analysis for stratifying clinical outcomes.

Conclusions

Results of our study expand on prior understanding of primary sidedness and molecular profiling in predicting clinical outcomes for anti-EGFR therapy and identifies disease bulk as a potential independent predictive biomarker of clinical outcomes in mCRC. Worsened outcomes for right-sided tumors were observed in the late-line setting, with objective responses observed only in combination with cytotoxic chemotherapy. We found that nonbulky mCRC, which was specifically enriched in left-sided disease, demonstrated durable outcomes with EGFR-targeted therapies. As the applications of precision oncology continue to expand, prospective trials should analyze tumor bulk to help guide differential application of both precision oncology and traditional chemotherapy.

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