Title: The Impact of Bevacizumab in Metastatic Colorectal Cancer with an Intact Primary Tumour: Results from a large prospective cohort study

Short running title: Bevacizumab impact in intact primary mCRC

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Abstract: (250 words)

Background: Debate continues regarding the benefits *versus* risks of initial resection of the primary tumour in metastatic colorectal cancer (mCRC) patients with an asymptomatic primary tumour. Whilst the benefit of the anti-VEGF agent bevacizumab alongside first-line chemotherapy in mCRC is established, the impact of bevacizumab on the intact primary tumour (IPT) is less well understood.

Methods: Data from an Australian mCRC registry was used to assess the impact of bevacizumab-based regimens in the presence of an IPT, to see if this differs from effects in resected primary tumour(RPT) patients and to understand the safety profile of bevacizumab in patients with IPT. Progression free survival (PFS), overall survival (OS) and safety endpoints were analysed.

Results: Of 1,204 mCRC patients, 826 (69%) were eligible for inclusion. Bevacizumab use was similar in both arms (IPT (64%) vs. RPT (70%)); compared with chemotherapy alone, bevacizumab use was associated with significantly longer PFS (IPT:8.5 vs. 4.7 months, p=0.017; RPT:10.8 vs. 5.8 months,p<0.001) and OS (IPT:20 vs. 14.8 months,p=0.005; RPT:24.4 vs. 17.3 months, p=0.004)).[1]

Bevacizumab use in an IPT was associated with more GI perforations (4.5% vs. 1.8%, p=0.210) but less frequent bleeding (1.5% vs. 5.3%, p=0.050) and thrombosis (1.5% vs. 2.7%, p=0.470), versus chemotherapy alone. Median survival was equivalent between patients that did or did not experience bevacizumab-related adverse events – 20.0 vs. 19.9 months, hazard ratio (HR) 0.98, p=0.623.[1]

Conclusions: The addition of bevacizumab significantly improved survival outcomes in mCRC with an IPT. The occurrence of bevacizumab-related adverse events did not significantly impact survival outcomes.

Key words:

Colorectal cancer

Anti-VEGF therapy

Primary tumour resection

Drug safety

GI perforation rate

Introduction

The vast majority (~80%) of patients presenting with synchronous metastatic colorectal cancer (mCRC), will have unresectable metastases,[2] and in turn in the majority of these patients, the primary tumour remains asymptomatic with only 10-20% experiencing complications of the intact primary lesion such as bowel obstruction, tumour perforation or bleeding.[2] In the setting of an asymptomatic primary tumour, debate surrounding the risks and benefits of an immediate *versus* deferred surgical strategy continues.[3] Meanwhile, advances in systemic therapy have substantially improved outcomes in patients with mCRC with reported responses rates of 50%, disease control rates of up to 85% and median OS of 24 months with combination regimens of chemotherapy and targeted agents.[4-10] The management of mCRC with a combination of bevacizumab, a humanized, monoclonal antibody against vascular endothelial growth factor A (VEGF-A), and fluoropyrimidine-containing chemotherapy is now well established in the first- and second- line settings.[5, 6, 11] In the setting of an asymptomatic intact primary tumour [12], what is the standard guidance on initial treatment of unresectable metastatic disease and the primary tumour? Is there still controversy or is there an accepted practice? The rationale for early primary tumour resection includes the potential survival benefit, eliminating a "source" of future metastases and the aim of avoiding future complications of the primary lesion. On the other hand, the potential for substantial post-operative morbidity and subsequent delay in administering systemic therapy for patients undergoing surgery are arguments for retaining an intact primary tumour.

The proportion of mCRC patients being managed with combined chemo-biological therapy continues to increase. Modern systemic therapy reportedly has substantial activity on the primary tumour, inducing up to 70% tumour regression. [13] However, there are limited published data available on the effects of bevacizumab in specific subgroups such as patients with an intact primary tumour where there is potential concern for increased VEGF specific local complications. Using data from a prospective Australian tumour registry of consecutive patients with mCRC, the present study is the first to assess the efficacy and safety profile of bevacizumab in a large cohort of patients with an IPT *versus* those with a resected primary tumour (RPT).

Patients & Methods

Study population

The TRACC (Treatment of Recurrent and Advanced Colorectal Cancer) registry is a prospective, multi-centre database of consecutive patients with mCRC from 23 centres across Australia enrolled between 2009 and 2015.[12] Key clinical data relating to patient and disease characteristics, treatments and outcomes are recorded at the point of care. This study included patients who received first-line systemic therapy with palliative intent. Patients were excluded if they received no active treatment or underwent resection or localised intervention of metastases.

Survival and key safety endpoints were determined for patients with an IPT compared with a RPT. Manual chart reviews were performed to obtain data relating to treatment-specific safety endpoints including GI perforation, bleeding and thrombosis. The primary endpoints, progression-free survival (PFS) and overall survival (OS) were defined as the time from commencement of first-line

chemotherapy to disease progression or death; and time from treatment initiation to death from any cause, respectively. Patients were followed until 25 May 2015.[1]

Statistical Methods

Statistical calculations were performed on STATA version 12. Survival estimates were calculated using Kaplan-Meier method with the log-rank test for survival comparisons. Patients who were lost to follow-up before death were censored at the date of last follow-up. Univariate and multivariate cox proportional hazard regression analyses were performed to evaluate the independent effects of clinical variables on PFS and OS. Variables were compared using the Chi square method or *t*-test. As there were two primary endpoints, a Bonferroni correction was applied to the two-tailed *p*-value, with p-values of less than 0.025 considered statistically significant. Hazard ratios (HR) were calculated. For the safety analysis, odds ratios (OR) and corresponding 95% CI were estimated using logistic regression modelling. Interaction testing was performed between primary tumour resection and bevacizumab use for PFS, OS and adverse events.

Results

Study population:

At the time of analysis, 1,204 patients with mCRC were registered within the TRACC database – of these 826 patients met the inclusion criteria. Patients were excluded if they received no active treatment or underwent resection or localised intervention of metastases. Median age at diagnosis of metastatic disease was 67 years (range: 18-92 years) with median follow-up of 34.8 months. There were no significant differences in gender distribution or primary tumour location across the population (Table 1).

Table 1 depicts baseline parameters, tumour features and treatment. There was no significant difference in the frequency of bevacizumab use in patients with an IPT versus RPT (64% vs. 70%, *p=0.110)*. However, a significantly greater proportion of younger, fitter patients (ECOG PS 0-1) with less co-morbidities (CCI score 0-2) received bevacizumab. The predominant first-line chemotherapy regimen in the IPT and RPT groups was combination oxaliplatin- (78% and 60%) or irinotecan-based (4% and 13%) regimens, respectively, while 17% of IPT and 26% of RPT groups received single-agent chemotherapy. Based on metastatic disease site, the use of bevacizumab with chemotherapy in patients with peritoneal metastases was significantly greater in the RPT group (80%) compared with the IPT group (54%) (*p*=0.001). Whilst the use of bevacizumab and chemotherapy was also higher in the RPT group compared to the IPT group in other metastatic disease sites, these differences were not statistically significant (liver: p=0.300, lung: p=0.135 and 'other' metastatic disease sites: p=0.347). (Table 1).

Efficacy:

In both groups the addition of bevacizumab to chemotherapy was associated with extended PFS and OS (Figure 1). Bevacizumab-treated patients with RPT exhibited the longest median PFS (10.8 vs 5.8

months; HR 0.67, *p*<0.001*)*, followed by bevacizumab-treated patients with IPT (8.5 vs 4.7 months; HR 0.73, *p*=0.017*)*.[1] The addition of bevacizumab to chemotherapy also produced significant gains in OS: IPT (20.0 vs 14.8 months, HR 0.66*, p*=0.005*)*; RPT (24.4 vs 17.3 months (HR 0.71*, p*=0.004*).*[1] Thus, the impact of bevacizumab demonstrated comparable survival gains in both groups. (Figure 1)

In multivariate analysis (Table 2), primary tumour resection (HR 0.75; 95% CI: 0.64-0.88) and the addition of bevacizumab to chemotherapy (HR 0.72; 95% CI: 0.61–0.86) were independent predictors of PFS, with primary tumour resection (HR 0.65; 95% CI: 0.54-0.77) and the addition of bevacizumab to chemotherapy (HR 0.78; 95% CI: 0.65–0.95) also found to be protective of mortality (OS). Additionally, ECOG PS and number of metastases were independent prognostic indictors of PFS and OS, with increasing age also an indicator of worse OS outcomes. No statistically significant interaction was observed between bevacizumab therapy and primary tumour resection for the survival outcomes of PFS or OS (*p*=0.213 and *p*=0.737 respectively).

Adverse events:

As shown in Table 3, compared with chemotherapy alone, concurrent administration of bevacizumab indicated a trend towards a higher frequency of GI perforations in patients with IPT (4.5% vs. 1.8%, *p*=0.210), but not RPT (1.7% vs. 1.9%, *p*=0.850), although both of these comparisons were not statistically significant. However, while not statistically significant lower rates of bleeding and thrombosis were noted in the IPT group receiving bevacizumab *vs*. chemotherapy alone (1.5% vs. 5.3%, *p=0.050* and 1.5% vs. 2.7%, *p=0.470* respectively).[1] The apparent lower rates of these adverse events in the IPT group receiving bevacizumab may reflect clinicians avoiding bevacizumab use in patients considered at increased risk of these complications. In contrast, among RPT patients, compared with chemotherapy alone, concurrent bevacizumab used was associated with higher rates of bleeding (3.4% vs. 0.6%, *p*=0.070) and thrombosis (5.9% vs. 0.6%, *p*=0.007).Median survival was not significantly different between the groups of patients who did or did not experience bevacizumab-related adverse events – 20.0 vs 19.9 months, HR 0.98, *p*=0.623.[1]

Bleeding and thrombosis were the only outcomes exhibiting significant interaction, which were maintained in multivariate analysis, between bevacizumab treatment and primary tumour resection, with the likelihood of bleeding and thrombosis being higher for those patients with bevacizumab treatment in the RPT group (OR 6.87; 95% CI: 1.661-29.20) after adjusting for potential confounding factors. No significant association was found in the IPT group. In contrast, there was no statistically significant interaction noted in multivariate analysis for the following adverse events: GI perforation, hypertension, pulmonary embolus, diarrhoea and thrombocytopenia.

When considering those patients receiving chemotherapy with bevacizumab, no potential risk factors (including age greater than 70 years, Charlson comorbidity index [14] score greater than 3, and prior vascular and cardiovascular related comorbidities) were significantly associated with an increased risk for bleeding or thrombosis in either the RPT group or the IPT group (Table 4).

Discussion

Patients with mCRC presenting with complications from the primary tumour such as obstruction perforation or haemorrhage, exhibit a clear indication for tumour resection. In contrast, there is continued debate regarding the optimal approach to managing patients with unresectable metastatic disease and a non-obstructed, asymptomatic IPT. In these cases, the risk-benefit profile of surgical palliation *versus* that of upfront systemic therapy has not been fully resolved. There is currently limited published randomised clinical trial data addressing this issue but studies including SYNCHRONOUS (ISRCTN30964555)[15] and GRECCAR8 (NCT02314182)[16] are underway. Access to targeted therapies such as the anti-VEGF agent bevacizumab has significantly altered the treatment landscape by producing clinical gains beyond that seen with chemotherapy alone when administered concurrently first line for mCRC, [4, 6, 11, 17] Additionally, evidence supporting a non-surgical management strategy continues to build, with a low (<10%) incidence of primary tumour-related complications reported in mCRC patients receiving systemic therapy.[18] Consequently, improving our understanding of the effects of bevacizumab in subgroups such as patients with IPT or RPT is increasingly important.

The present study used data from a large, prospective multi-centre Australian registry of mCRC patients, to assess the comparative efficacy and adverse event profile of bevacizumab in patients with IPT or RPT managed in routine clinical practice. Of the 826 patients eligible for inclusion, a substantial proportion (nearly 40%) had an IPT, highlighting the increasing adoption of a non-surgical management strategy in routine clinical practice. Additionally, while concerns regarding tumour perforations could hinder the use of bevacizumab in the setting of IPT, our data suggest clinicians are comfortable using bevacizumab in the presence of an IPT (63% received bevacizumab therapy; and 69% in the RPT group). Concurrent use of bevacizumab alongside chemotherapy was associated with improved PFS and OS outcomes (*versus* chemotherapy alone) in the IPT and RPT arms. Key factors associated with PFS and OS were age, ECOG performance status and comorbidities.

The NSABP trial C-10, a prospective, multicentre phase 2 single-arm study of 86 patients with asymptomatic mCRC and IPT treated first line with mFOLFOX6 and bevacizumab demonstrated the safety of bevacizumab therapy in the setting of IPT.[4] Our larger study with 826 patients, which also included a RPT comparator arm, concurred with these findings – we note the administration of bevacizumab alongside first-line systemic chemotherapy is associated with an acceptable adverse event profile in carefully selected asymptomatic patients with an IPT. The type and frequency of bevacizumab-related adverse events were consistent with previously published data.[7, 19, 20]

The GI perforation rates were low in both groups (4.5% vs 1.8% in IPT vs RPT respectively). A trend for more GI perforations but less thrombosis and bleeding with the use of bevacizumab in patients with an IPT was observed. However, the increased rate of GI perforation was not statistically significant. Similarly, the BRITE study indicated an overall 1.9% rate of GI perforation with an increased risk in IPT or prior radiation therapy. [21] Other factors postulated to influence the risk of GI perforation in mCRC patients include recent colonoscopy, toxicity from chemotherapy, peritoneal metastases, colonic stenting and anti-VEGF therapy-induced alterations in tumour vasculature.[21, 22] In a meta-analysis on the risk of GI perforation with all cancers treated with bevacizumab, a relative risk of 3.1 (95% CI 1.26-7.63; p=0.013) in mCRC was reported.[23] In this analysis, the OR for GI perforation in an IPT was 2.05 (1/0.49), taking the intact primary tumour group as the reference group for primary resection. It has been suggested in a meta-analysis of patients with multiple tumour types receiving bevacizumab that the risk of GI perforation may be dose-dependent, as the

relative risk was found to be greater at a dose of 5mg/kg/week compared with 2.5mg/kg/week; and may vary with tumour type[23] The overall low rate of bevacizumab-associated adverse events in our study may reflect clinicians avoiding the use of bevacizumab in patients considered at risk of these complications.

Our results and those of the NSABP C-10 trial suggest concerns that bevacizumab-associated adverse events in the IPT setting could compromise survival, are largely unfounded. When patients were grouped based on whether or not they experienced bevacizumab-related adverse events, we found no significant difference in median survival between the adverse events and no adverse events groups (20.0 vs 19.9 months, HR 0.98, *P*=0.623). These results concur with those of smaller studies by Poultsides *et al* and Suarez *et al*. [8, 24]

The present study's limitations include its non-randomised observational design and the possibility that patient selection may in part explain the improved survival outcomes seen in bevacizumab-treated patients (since those treated with bevacizumab were younger, fitter and had less co-morbidity). The likelihood of experiencing adverse events may also increase as the length of follow-up increases, however, our results are in line with pooled data from other smaller randomised studies, which also reported that the addition of bevacizumab to first-line chemotherapy resulted in statistically significant improvements in OS and PFS.[5-7, 17, 25, 26]

Conclusions

In routine clinical practice clinicians appear comfortable using bevacizumab in patients with an IPT. Patients selected for bevacizumab treatment experienced improved PFS and OS outcomes regardless of primary tumour resection status. A trend for a higher GI perforation rate was observed in bevacizumab-treated patients with IPT although this was not statistically significant. These findings add to the body of evidence demonstrating the acceptable safety profile of and clinically meaningful benefit conferred by combination chemotherapy and bevacizumab as a first-line treatment strategy in carefully-selected asymptomatic patients with mCRC and IPT.

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Conflict of interest
None

Role of the funding source

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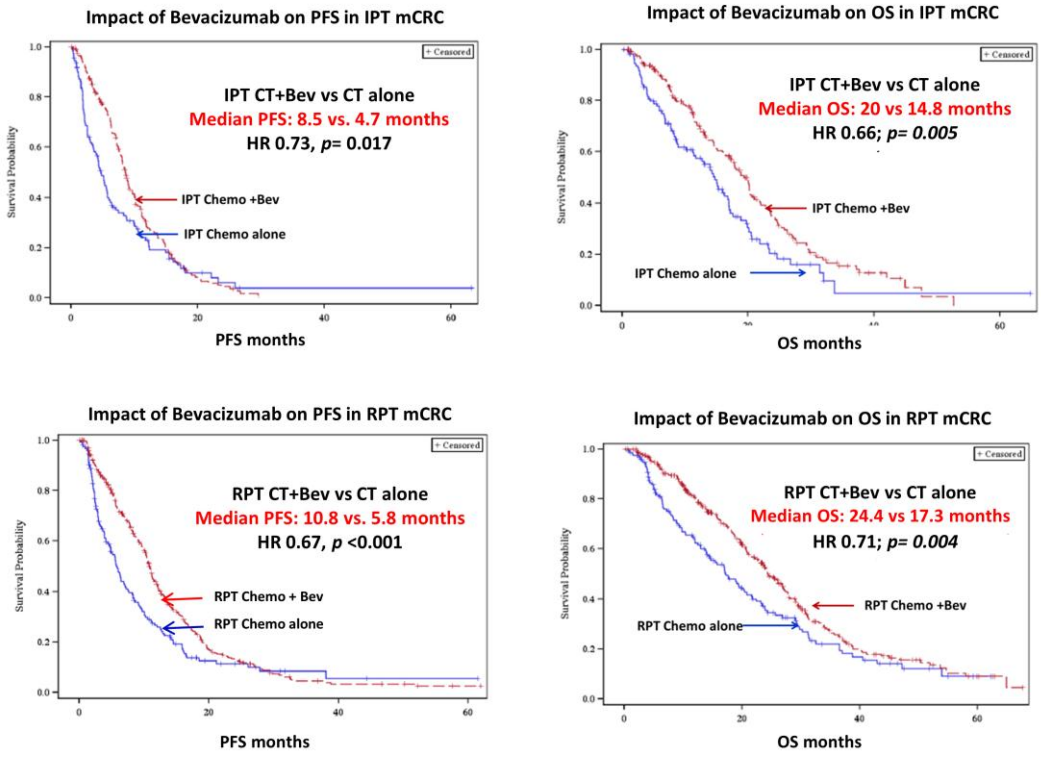

Table 1. Patients' characteristics and baseline parameters

Legend: CT= Chemotherapy; BEV= Bevacizumab; *p*= probability; ECOG= European Cooperative Oncology Group; PS= Performance status; CCI= Charlson Comorbidity Index

Characteristics	**Intact Primary (%) [*N*=313]**			**Resected Primary (%) [*N*=513]**		
	CT alone [*N*=113]	CT + Bev [*N*=200]	*p*	CT alone [*N*=156]	CT + Bev [*N*=357]	*p*
Median age (yrs.) [range]	69 [18 -92]	62 [27-89]	***<0.001***	74 [30-90]	66 [25-92]	***<0.001***
Gender Female Male	50 (44%) 63 (56%)	78 (39%) 122 (61%)	*0.360*	67 (43%) 89 (57%)	142 (40%) 215 (60%)	*0.500*
ECOG PS 0-1 PS ≥ 2	84 (75%) 29 (25%)	180 (90%) 20 (10%)	***<0.001***	119 (76%) 37 (24%)	327 (92%) 30 (8%)	***<0.001***
CCI score 0-2 ≥ 3	46 (41%) 67 (59%)	97 (48%) 103 (52%)	***0.006***	40 (26%) 116 (74%)	153 (43%) 204 (57%)	***<0.001***

Primary site			*0.800*			***0.010***
Right colon	22 (19%)	46 (23%)		53 (34%)	124 (35%)	
Left colon	37 (34%)	65 (33%)		44 (28%)	146 (41%)	
Rectum	45 (40%)	74 (37%)		50 (32%)	74 (21%)	
Not specified	6 (4%)	9 (4%)		9 (6%)	13 (3%)	
Occult	3 (3%)	6 (3%)		0 (0%)	0 (0%)	
Metastatic site						
Liver	76 (67%)	166 (83%)	***0.001***	82(53%)	218 (61%)	*0.070*
Peritoneum	21 (19%)	25(13%)	*0.140*	20 (13%)	25 (22%)	***0.010***
Lung	38 (34%)	61 (31%)	*0.570*	53 (34%)	61 (35%)	*0.770*
Other	46 (41%)	85 (43%)	*0.760*	85 (54%)	194 (54%)	*0.980*
Chemotherapy						
FOLFOXIRI	1 (1%)	3 (2%)		0 (0%)	1 (1%)	
Irinotecan-based	5 (4%)	6 (3%)		15 (10%)	51 (14%)	
Oxaliplatin-based	70 (62%)	174 (87%)		63 (40%)	244 (68%)	
Single agent	37 (33%)	16 (8%)		77 (50%)	60 (17%)	

Table 2. Multivariate contributors to PFS and OS

Legend: HR= hazard ratio; 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group Performance Status

	Multivariate		
	HR	95% CI	*P* value
Progression-free survival (PFS)			
Primary resection	0.75	0.64 - 0.88	<0.001
ECOG			
PS 0-1	1		
PS 2-4	1.36	1.09 – 1.70	0.006
Number of metastases			
1	1		
>1	1.23	1.05 – 1.43	0.009
Addition of bevacizumab to chemotherapy	0.72	0.61 – 0.86	<0.001
Overall Survival (OS)			
Age	1.01	1.00 – 1.02	0.027
Primary resection	0.65	0.54 – 0.77	<0.001
ECOG			
PS 0-1	1		
PS 2-4	1.95	1.54 - 2.47	<0.001
Number of metastases			
1	1		
>1	1.34	1.12 – 1.60	0.001
Addition of bevacizumab to chemotherapy	0.78	0.65- 0.95	0.012

Table 3. Univariate analysis comparing adverse events in IPT vs RPT receiving chemotherapy alone or chemotherapy with bevacizumab

NB: The Intact primary tumour group is the reference group in this analysis.

Adverse Events	**Intact Primary (%) [*N*=313]**			**Resected Primary (%) [*N*=513]**		
	CT alone [*N*=113]	CT + Bev [*N*=200]	*p*	CT alone [*N*=156]	CT + Bev [*N*=357]	*p*
GI perforation No perforation	2 (1.8%) 111 (98.2%)	9 (4.5%) 191 (95.5%)	0.210	3 (1.9%) 153 (98.1%)	6 (1.7%) 351 (98.3%)	0.850
Bleeding No bleeding	6 (5.3%) 107 (94.7%)	3 (1.5%) 197 (98.5%)	0.050	1 (0.6%) 155 (99.4%)	12 (3.4%) 345 (96.6%)	0.070
Thrombosis No thrombosis	3 (2.7%) 110 (97.3%)	3 (1.5%) 197 (98.5%)	0.470	1(0.6%) 155 (99.4%)	21 (5.9%) 336 (94.1%)	0.007

Table 4. Analysis of association between specific factors and the risk of thrombosis or bleeding with the use of bevacizumab therapy in the IPT and RPT groups

Legend:

CCI= Charlson Comorbidity Index score; prior vascular or cardiovascular-related co-morbidity including history of prior myocardial infarct, congestive cardiac failure, vascular disease, arterial ischaemic event, end-stage renal disease and diabetes with end-organ complications

Potential risk factor for bleeding or thrombosis	IPT receiving chemotherapy with bevacizumab		RPT receiving chemotherapy with bevacizumab	
	OR	*P*-value	OR	*P*-value
Prior vascular or cardiovascular-related co-morbidity	0.92	1.00	1.21	0.64
CCI score >3	1.12	1.00	1.03	1.00
Age >70 years	1.54	0.55	0.79	0.61