Chemotherapy and biologic use in the routine management of metastatic colorectal cancer in Australia: is clinical practice following the evidence?

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Background: Emerging evidence on the optimal use of chemotherapy and biologics in patients with metastatic colorectal cancer (mCRC) should impact management in routine care. Recent studies have demonstrated benefits for initial triplet chemotherapy (FOLFOXIRI) and for initial treatment with an epidermal growth factor receptor inhibitor (EGFRi) in patients with a RAS wild type tumour and a left-sided primary.

Aim: To explore evolving patterns of mCRC care over time in Australia.

Methods: We analysed data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry.

Results: From July 2009 to December 2017, 2552 mCRC patients were entered into the TRACC registry. Of 1585 patients who initially underwent chemotherapy, treatment was with a doublet in 76%. FOLFOXIRI was given to 22 patients (1.4%), mostly young patients and those with potentially resectable disease. Along with first-line chemotherapy, 61% received bevacizumab, while 3.3% received an EGFRi, predominantly over the last two years. Within the KRAS wild-type left-sided tumour cohort, EGFRi use increased from 9% in 2015 to 37% in 2017. Across treatment sites, there was wide variation in the utilization of FOLFOXIRI and EGFRi therapy; bevacizumab use was more consistent. A clear impact on survival outcomes from these regimens is not evident, potentially due to multiple confounders.

Conclusion: Doublet chemotherapy plus bevacizumab remains the dominant initial strategy, with limited uptake of triplet chemotherapy and of EGFRi. Potential explanations include uncertainty about the significance of post-hoc analyses for EGFRi and concerns regarding adverse events for both strategies.

Keywords: cetuximab, panitumumab, bevacizumab, metastatic colorectal cancer, real-world outcomes

I. Main Text

Introduction

Colorectal cancer is the third most common cancer in Australia, with an estimated 16,682 new cases diagnosed in 2017.[1] Survival outcomes for patients with advanced disease enrolled in clinical trials continue to improve.[2] For similar gains to be achieved in routine care, it is essential that medical oncologists continue to adapt their practice according to emerging clinical trial results showing improved outcomes. Over time, as new treatment strategies are tested and new prognostic and predictive biomarkers are defined, clinical practice should evolve with the evidence.

Over several decades, randomised controlled trials have continued to inform optimal chemotherapy for metastatic colorectal cancer (mCRC), with an initial move from single agent to combination chemotherapy.[3,4] Subsequent studies then showed a survival benefit with the addition of bevacizumab to irinotecan-based treatment, shifting the focus towards use of biologic agents.[5,6] Not long after, triplet chemotherapy with 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) was shown to improve survival outcomes versus doublet chemotherapy (FOLFIRI)[7]. Recently, FOLFOXIRI plus bevacizumab was found to prolong median overall survival by four months compared to doublet chemotherapy plus bevacizumab[8], providing another treatment option. In parallel studies, a survival benefit associated with adding an epidermal growth factor receptor inhibitor (EGFRi) to doublet chemotherapy versus chemotherapy alone[9, 10] or versus chemotherapy plus bevacizumab,[11,12,13] was demonstrated. These benefits appear to be limited to patients with an extended RAS wild-type tumour and a left-sided primary.[14,15]

These study results have variably been incorporated into treatment guidelines. FOLFOXIRI is now recommended in ESMO guidelines for patients appropriate for intensive therapy where cytoreduction is the goal, and for any fit patient with a BRAF mutated cancer where prognosis is

typically poorer.[16] The NCCN guidelines now recommend first line EGFRi (cetuximab or panitumumab) as the biologic of choice for patients with a left-sided and RAS wild-type tumour.[17]

In Australia, the Pharmaceutical Benefits Scheme (PBS) directs the use of subsidized medication, including chemotherapeutics. Bevacizumab was approved for first-line treatment of mCRC in July 2008.[18] Cetuximab was funded initially for second-line and third line mCRC treatment for KRAS wild-type patients in combination with irinotecan-based chemotherapy in July 2010[19], and was amended to include first-line use with any chemotherapy backbone in November 2014.[20] Panitumumab in turn was approved for first-line use in March 2015.[21] The Australian cancer guidelines resource, eviQ, endorsed the use of FOLFOXIRI +/- bevacizumab in June 2015 for mCRC patients less than 75 years old with WHO performance status 0-1, and for where the intention of treatment is rapid tumor shrinkage. It can also be considered for fit patients with BRAF mutations.[22]

There has not yet been an evaluation of how current practice has adapted these recommendations, and how clinical and patient factors impact utilization of these options. Here we present a comprehensive review of evolving patterns of care over time in Australia, describing in particular rates of bevacizumab and EGFRi use in the first-line setting; utilization of FOLFOXIRI; and differences in usage among different Australian treatment sites. We also explore how real-world survival outcomes for these therapies compare to those of landmark clinical trials.

Methods

This project utilized the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) database, which captures information regarding mCRC patients receiving care in major hospitals across Australia, and now also in Hong Kong. TRACC is a prospective, multicentre registry collating patient and disease characteristics, treatment strategies and outcomes for mCRC patients. Established in 2009, it is a collaboration between Biogrid Australia and public and private cancer centres in both metropolitan and regional Australia.[23] Data is stored at individual sites as property of the participating site; Biogrid integrates de-identified data from sites for access of individual researchers after application, and facilitates database upkeep. It is supported by a grant from Roche Australia for clinical and translational research projects.

All mCRC patients entered into the TRACC database from January 2009 to December 2017 were included in this review. Patient demographics, as well as histopathologic details and mutational profile were collated. Patients' comorbid conditions were captured using the Charlson Comorbidity Index.[24] Treatment details regarding biologic agent, chemotherapy backbone used, and survival outcomes were documented and analysed. We also explored variations in treatment choices among de-identified hospital sites for patients who commenced chemotherapy from 2015 onwards, when all treatment strategies were widely available.

Descriptive statistics were used, with proportions less than 10% reported to one decimal place. Chi-square analysis was undertaken to detect significant differences in patient demographics. Kaplan-Meier survival analysis was performed to determine overall survival (OS) of patients who had received FOLFOXIRI + bevacizumab, doublet chemotherapy + bevacizumab and doublet chemotherapy + EGFRi.

This study received approval from the Melbourne Health Ethics Review Board.

Results

From January 2009 to December 2017, 2552 mCRC patients were enrolled to the TRACC registry. The initial therapy was resection of metastases in 318 patients (Figure 1). These patients were excluded from further analysis along with the 458 patients who received no active therapy and another 182 patients who received other treatment modalities without systemic therapy. Nine patients who received immunotherapy, or a biologic agent not in combination with chemotherapy, were also excluded. The remaining 1585 patients, where the initial intervention was systemic chemotherapy, are the focus of our analysis.

I. Demographics

Of the 1585 mCRC patients treated with upfront chemotherapy, 967 (61%) received chemotherapy in combination with bevacizumab and 53 (3.3%) with an EGFR inhibitor (Figure 1). 565 patients (36%) did not receive a biologic during first line therapy. No patients received both biologics at the same time.

Age, ECOG performance status, comorbidities, primary tumour location, treatment intent, mutational status and chemotherapy backbone varied significantly among the treatment groups. Compared to patients who received chemotherapy alone or with bevacizumab, those who received chemotherapy plus an EGFRi in first line were more likely to have a younger age, fewer comorbidities, left-sided primary tumours and synchronous metastatic disease at diagnosis (Table 1). There was a significantly higher proportion of patients with potentially resectable

metastatic disease in the chemotherapy plus EGFRi group compared to chemotherapy plus bevacizumab or chemotherapy alone (42% vs. 18% vs. 33%, respectively; $P < 0.001$).

Doublet chemotherapy was most widely used, predominantly oxaliplatin-based. The majority of patients treated with single-agent fluoropyrimidine did not receive a concurrent biologic agent (227/363; 63%). Other clinicopathologic characteristics are further detailed in Table 1.

Table 2 shows the characteristics of the 22 patients (1.4%) who received FOLFOXIRI as initial therapy. Relative to the entire cohort, patients treated with triplet chemotherapy were younger (median age 51 years; range 28-65), had a mostly good performance status (86% ECOG 0-1) and fewer comorbidities (96% Charlson score 0-2). A slim majority of patients treated with FOLFOXIRI had resectable or potentially resectable metastatic disease (n=12; 55%). Only 2 (9%) were documented to have a BRAF mutation.

II. Patterns of Treatment Use

Figure 2a shows trends in the use of triplet chemotherapy over time. Overall, the proportion of patients treated with FOLFOXIRI was very small (<5%), but a steady increase in use was observed after 2014, coinciding with initial presentation of TRIBE data showing an overall survival advantage for FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab.[8]

Changes over time in the use of bevacizumab and EGFRi with chemotherapy are shown in Figures 2b and 2c, respectively. The use of bevacizumab in all patients appears stable from 2009 through 2015 at 50-70%. There is an evident drop in bevacizumab use in 2016, predominantly driven by a decrease in treatment of patients with a left-sided tumour. This coincided with a rise in use of EGFRi among patients with a left-sided tumour (Figure 2c). Specifically within the KRAS wild-type left-sided tumour cohort, the percentage of use was 9% (6/66) in 2015, then went up to 33% (21/64) in 2016 and 37% (15/41) in 2017. There are no clear trends over time in the use of bevacizumab in patients with a right-sided primary.

Variation in the use of FOLFOXIRI, bevacizumab and EGFRi (from 2015 onwards) across Australian sites is shown in Figure 3a. Data from the Prince of Wales Hospital in Hong Kong was excluded, as it is the only non-Australian site and thus could not be deidentified. FOLFOXIRI use was low across all sites, ranging from 0% to 11%. The overall use of bevacizumab or EGFRi with first-line chemotherapy varied across sites from 47% to 81%, and 0% to 16%, respectively. Sites with higher rates of EGFRi use had correspondingly lower use of bevacizumab; this is best illustrated in Figure 3b, which shows the use of first-line bevacizumab vs. EGFRi among patients with left-sided KRAS wild-type tumours. Here, the variation in use of EGFRi across sites is more evident, with zero to infrequent use at five sites (B, C, D, E and F), and a slight preference for EGFRi over bevacizumab at the remaining two sites (A and G).

III. Survival Outcomes

Overall survival (OS) outcomes are shown in Figure 4. Median OS for patients treated with FOLFOXIRI plus bevacizumab and doublet chemotherapy plus bevacizumab was 23.6 months and 25.1 months, respectively; median OS for those who received doublet chemotherapy with an

EGFRi was not reached. However, since possible confounding factors such as treatment intent have not been taken into account, no conclusions can be made regarding the benefit from specific chemotherapy regimens.

Discussion

Patients enrolled in the TRACC registry are representative of a real-world mCRC population, where a substantial proportion (18%) do not receive any active therapy, and chemotherapy-treated patients include the elderly (25% aged ≥ 75 years), those with borderline ECOG performance status (11% ECOG ≥ 2) and multiple comorbidities (53% Charlson ≥ 3).

The publication of data from the TRIBE study in 2015,[8] demonstrating a 4-month survival advantage for initial FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab, appears to have had a minimal impact on clinical practice. As shown in Figure 3a, use of FOLFOXIRI is low in all Australian centres contributing data to the TRACC registry. Where given, FOLFOXIRI is usually administered in younger and fitter patients, and those who have potentially resectable metastatic disease. This patient selection is considered likely due to a focus on quality of life and concerns regarding adverse effects in older patients. In younger patients improving response rates and increasing conversion to resection -- which data on triplet therapy does underscore – [7,25] are higher priorities.

Oxaliplatin-based doublet chemotherapy remains the dominant chemotherapy backbone; however, approximately one out of four patients in our cohort were initially treated with single agent chemotherapy. This approach is supported by multiple clinical trials[26-29] that failed to demonstrate prolonged survival with the use of initial combination chemotherapy in the pre-

biologic era. However, even in current times, when biologic use has been shown to improve outcomes, there will always be patients in real-life practice who will not be fit enough for combination treatment (whether doublet/triplet chemotherapy +/- biologic, or single agent chemotherapy + biologic) due to age, comorbidities, or functional status. This again brings into focus the importance of individualized therapy, weighing the risks and benefits for every treatment choice.

The use of bevacizumab remained reasonably steady over the first 6 years of the TRACC registry, coinciding with the time period when bevacizumab first became publicly funded in Australia and first line EGFRi were not available outside of clinical trials. In the last two years there has been an evident decrease in the use of bevacizumab in patients with a left side primary, which is occurring in parallel with the increase in use of EGFRi in this subgroup (Figure 2).

At the same time as first line EGFRi became available on the PBS, data began to emerge regarding the impact of extended RAS testing on treatment benefit and of primary tumour side on survival outcomes. This data was derived from first-line studies comparing chemotherapy plus EGFRi to chemotherapy alone,[9,10] and studies comparing chemotherapy combined with an EGFRi or bevacizumab.[11,12,13] Data in later lines of therapy also show clear side-based differences in EGFRi benefit.[30,31] While all these analyses of the impact of tumour sidedness are *post hoc*, the consistent data across studies and the strong hazard ratios create a compelling argument for side-based differences in survival outcomes and EGFRi treatment benefit, where patients with right-sided mCRCs are expected to derive little to no benefit from first-line EGFRi therapy. This conclusion appears to have been widely accepted by clinicians, with very few patients with right-sided primary tumours being treated with an EGFRi in the first-line setting.

In contrast, substantial variation in EGFRi use for patients with KRAS wild-type, left-sided tumours was observed, despite a meta-analysis of randomised trial data showing that this patient subset had approximately 30% longer survival when initially treated with an EGFRi compared to bevacizumab[32]. Patient factors that may contribute to the decision to give an EGFRi include the potential for conversion to resectable disease, as evidenced by the higher proportion of patients treated with potentially curative intent in the EGFRi group. Overall, however, the variable uptake of EGFRi is anecdotally explained by several factors. Concerns regarding the detrimental impact of skin toxicity on the patient`s quality of life – and balancing this with persistent uncertainty for many clinicians regarding the extent of benefit to be gained -- appear to be a major contributor.

The role of BRAF mutations in treatment choice also deserves consideration. A post hoc subset analysis of the TRIBE study[8] suggested a greater benefit from triplet chemotherapy in BRAF mutant cases, but the difference was not statistically significant. BRAF mutations are also known to be a significant negative prognostic factor and are only present in RAS wild type cases where EGFRI might be considered[33] The available data suggests EGFRi is relatively ineffective in BRAF mutant tumours[34], however these are predominantly seen in right colon cancers which is also associated with a lack of treatment benefit.[16] So the uncertainty regarding the benefit of triplet therapy and the benefit of EGFRi likely contribute to the negligible first-line use of these approaches in our cohort.

Overall survival is presented in this paper to illustrate how patients enrolled in the TRACC registry are faring, but any meaningful comparison between the different treatment strategies is

not possible due to the multiple confounding factors that impact treatment selection and impact survival outcomes.

Limitations of our data set include difficulty in capturing many of the factors that contribute to prognosis and to treatment selection. For example, beyond capturing the number of metastatic sites there are no standard measures to capture disease bulk, so patients with a few small lesions in both lobes of the liver cannot be distinguished from those with extensive bilobar disease. Likewise, it is not possible to fully capture patient frailty or the extent and severity of comorbidities (e.g. decompensated coronary artery disease vs. asymptomatic coronary artery disease). These limitations of registry data further highlight the importance and significance of prospective randomised studies, where any observed differences in outcomes between treatment arms in an appropriately powered study can be presumed to be driven by differences in treatment strategy. Major limitations of standard randomised studies however, include the high costs and the limited external validity, meaning that the relevance of results achieved in a highly selected study population may not necessarily translate well to the real world population. Overall, these considerations are driving interest in the novel concept of registry based randomised controlled trials.[35]

Conclusion

Registry data is a useful tool to analyse trends in treatment strategies over time. Our study has demonstrated the variable uptake of FOLFOXIRI, EGFRi and bevacizumab over time and across treatment sites. While the data on primary tumour side has clearly had an impact on the management of patients with a KRAS wild-type left side primary, and EGFRi use may continue to increase over time, currently first-line EGFRi is still only used in a minority of these patients at most centres. The data on triplet therapy has resulted in minimal change in clinical practice.

This may reflect pervading clinician opinions that for both triplet chemotherapy and EGFRi the available clinical trial data does not justify these approaches replacing the previous standard of doublet chemotherapy plus bevacizumab for the initial management of mCRC.

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III. Figure legends

Figure 1. CONSORT diagram describing treatment patterns for TRACC patients enrolled between 2009 and 2017.

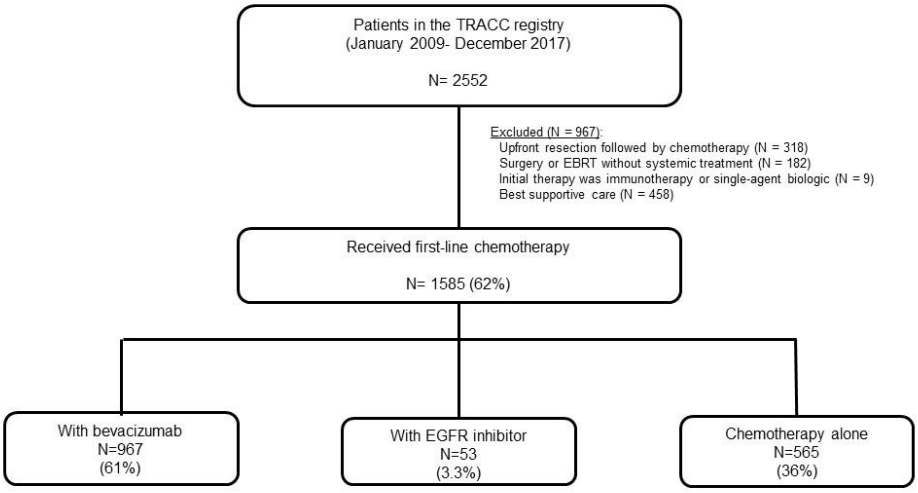
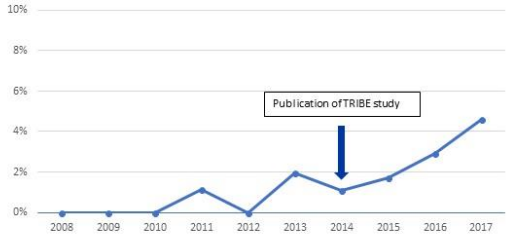
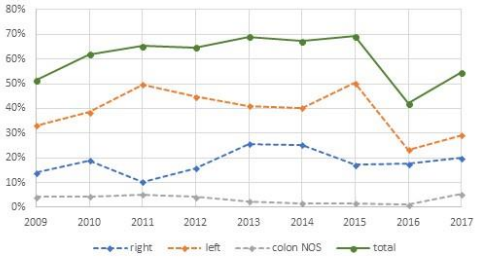


Figure 1. CONSORT diagram describing treatment patterns for TRACC patients enrolled between 2009 and 2017

Figure 2. Usage trends of triplet chemotherapy and biologic agents over time. **(2a)** Percentage of patients on triplet chemotherapy by year. **(2b)** Percentage of patients on first-line chemotherapy with bevacizumab by year. **(2c)** Percentage of patients on first-line chemotherapy with an epidermal growth factor inhibitor (EGFRi) by year.



(a)



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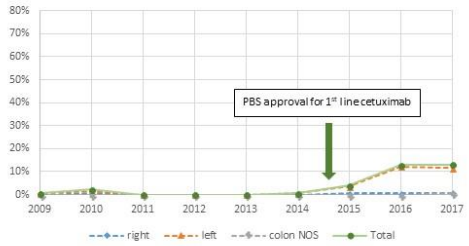

(c)

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Figure 3. Variation in the use of triplet chemotherapy and biologic agents from 2015 onwards across seven Australian sites. **(3a)** FOLFOXIRI, chemotherapy plus epidermal growth factor receptor (EGFRi), and chemotherapy plus bevacizumab (BEV) use in the whole patient cohort. **(3b)** Chemotherapy plus bevacizumab or EGFRi use among patients with left-sided KRAS wild-type tumours.

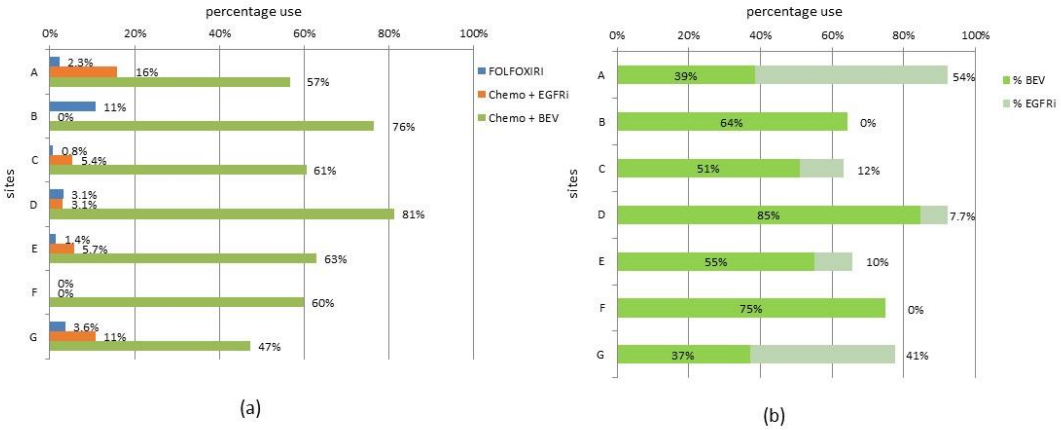

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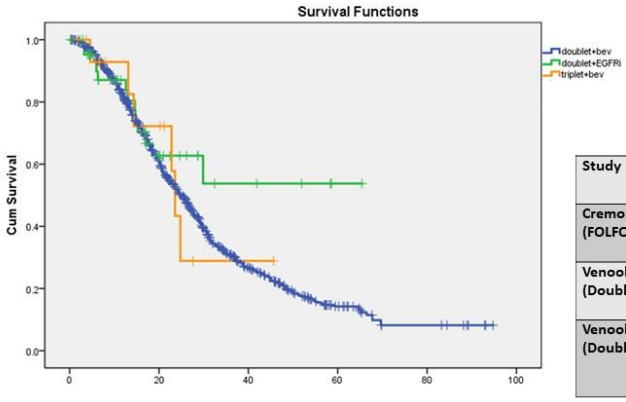
Figure 4. Comparison of TRACC survival outcomes with landmark clinical trials



Study	Sample size	Median OS (months)	TRACC cohort (n)	TRACC median OS (months)
Cremolini et al, 2015 (FOLFOXIRI + bev)	252	29.8	15	23.6
Venook et al, 2017 (Doublet + bev)	559	29.0	822	25.1
Venook et al, 2017 (Doublet + EGFRi)	578	30.0	46	not reached

Figure 4. Comparison of TRACC survival outcomes with landmark clinical trials

IV.Tables

Table 1. Clinicopathologic characteristics according to biologic agent received.

Patient Characteristics	Chemo plus Bevacizumab N=967	Chemo plus EGFRi N=53	Chemo alone N=565	Total 1585	p-value
Age					
Median (years) Range	64 (24-92)	60 (24-83)	67 (18-92)	65 (18-92)	<0.001
Age group >75	191 (19%)	5(9.4%)	195(34%)	391 (25%)	
Gender					0.2
Male	575 (59%)	25 (47%)	336 (59%)	936 (59%)	
Female	392 (41%)	28 (53%)	229 (41%)	649 (41%)	
ECOG					<0.001
0-1	892 (92%)	44 (83%)	460 (81%)	1396 (88%)	
≥2	71 (7.3%)	6 (11%)	105 (19%)	182 (11%)	
Missing	4 (0.4%)	3 (5.7%)	0	7 (0.04%)	
Charlson score					<0.001
0-2	475 (49%)	35 (66%)	234 (41%)	744 (47%)	
≥3	488 (50%)	15 (28%)	331 (58%)	834 (53%)	
Missing	4 (0.4%)	3 (5.6%)	0	7 (0.04%)	
Primary Site					<0.001
R colon	293 (30%)	4 (7.5%)	137 (24%)	434 (27%)	
L colon and rectum	622 (64%)	47 (89%)	397 (70%)	1066 (67%)	
Not specified	52 (5.4%)	2 (3.8%)	31 (5.5%)	85 (5.4%)	
Stage IV at diagnosis					0.14
Yes	672 (69%)	43 (81%)	376 (67%)	1091 (69%)	
No	295 (31%)	10 (19%)	188 (33%)	493 (31%)	
Missing	0	0	1 (0.2%)	1 (0.1%)	
Sites of Metastatic Disease					0.06
Liver only	373 (39%)	23 (43%)	217 (38%)	613 (39%)	
Lung only	65 (6.7%)	1 (1.8%)	50 (8.8%)	116 (7.3%)	
Peritoneum/Local only	85 (8.8%)	5 (9.4%)	79 (14%)	169 (11%)	
Other/Multiple sites	444 (46%)	24 (45%)	219 (39%)	687 (43%)	
Treatment Intent					<0.001
Potentially curative	170 (18%)	22 (42%)	186 (33%)	378 (24%)	
Palliative	794 (82%)	31 (58%)	377 (67%)	1202 (76%)	
Missing	3 (0.3%)	0	2 (0.4%)	5 (0.3%)	
Primary resected					0.19
No	322 (33%)	24 (45%)	194 (34%)	541 (34%)	
Yes	645 (67%)	29 (55%)	371 (66%)	1045 (66%)	
KRAS status†					<0.001

Wild-type	446 (46%)	51 (96%)	190 (34%)	686 (43%)	
Mutated	349 (36%)	1‡ (1.9%)	162 (29%)	512 (32%)	
Unknown	172 (18%)	1 (1.9%)	213 (38%)	387 (24%)	
BRAF †					<0.001
Wild-type	388 (39%)	34 (64%)	170 (30%)	592 (37%)	
Mutated	59 (6%)	1 (1.9%)	25 (4.4%)	85 (8.7%)	
Unknown	520(53%)	18 (34%)	370 (65%)	908 (57%)	
Chemotherapy backbone					<0.001
FOLFOXIRI	15 (1.5%)	1 (1.9%)	6 (1.1%)	22 (1.4%)	
Doublet -- oxaliplatin	715 (74%)	35 (66%)	301 (53%)	1051 (66%)	
Doublet -- irinotecan	107 (11%)	11 (21%)	31 (5.5%)	149 (9.4%)	
Single-agent fluoropyrimidine	130 (13%)	6 (11%)	227 (40%)	363 (23%)	

† at time of diagnosis/decision making for first-line chemotherapy
‡ One patient with a KRAS mutated tumour was initially treated with an EGFR inhibitor, which was ceased after subsequent pathology review.

Table 2. Clinicopathologic characteristics of patients who received triplet chemotherapy

Patient Characteristics	FOLFOXIRI (n=22)
Age	
Median (years) Range	51 (29-65)
Gender	
Male	12 (55%)
Female	10 (45%)
ECOG performance status	
0-1	19 (86%)
≥2	3 (14%)
Charlson score	
0-2	21 (96%)
≥3	1 (4%)
Primary Site	
R colon	8 (36%)
L colon and rectum	11 (50%)
Not specified	3 (14%)
Stage IV at diagnosis	
Yes	16 (73%)
No	6 (27%)
Treatment Intent	
Potentially curative	12 (55%)
Palliative	10 (45%)
Primary resected	
No	10 (45%)
Yes	12 (55%)
KRAS†	
Wild-type	8 (36%)
Mutated	10 (45%)
Unknown	4 (18%)
BRAF†	
Wild-type	11 (50%)
Mutated	2 (9%)
Unknown	9 (41%)

† at time of diagnosis/decision making for first-line chemotherapy