Uptake of first-line triplet chemotherapy and epidermal growth factor receptor inhibitors in metastatic colorectal cancer

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Introduction

The treatment paradigm for metastatic colorectal cancer (mCRC) has changed substantially over the past 10 years. Recent studies have demonstrated survival benefits for initial triplet chemotherapy with FOLFOXIRI in selected patients[1] and for initial treatment with epidermal growth factor receptor inhibitors (EGFRI) in patients with left sided RAS wild-type tumours[2]. These study results have variably been incorporated into treatment guidelines.

The rate and patterns of use of FOLFOXIRI and first-line EGFRI in Australia have not previously been evaluated to explore how current practice has adopted these recommendations, or how patient and disease factors impact utilisation of these therapies.

Aim

We aimed to analyse the use of FOLFOXIRI and EGFRI in the first-line treatment of mCRC in an Australian real-world population. Specific focus was given to:

- Patient and disease characteristics among those treated with FOLFOXIRI and EGFRI relative to all chemotherapy-treated patients
- Trends of use over time of FOLFOXIRI and EGFRI
- Treatment variation across different centres

Methods

This project utilised the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry, which captures information regarding patients with mCRC receiving care in centres across Australia.

This was a retrospective analysis of patients who received first-line chemotherapy, enrolled between January 2009 and December 2017.

Demographic, disease and treatment data were extracted for analysis. Overall survival was estimated using the Kaplan-Meier method.

Results

Among the 1585 mCRC patients who received first-line chemotherapy, 22 (1.4%) received FOLFOXIRI and 53 (3.3%) received an EGFRI with chemotherapy (**Figure 1**).

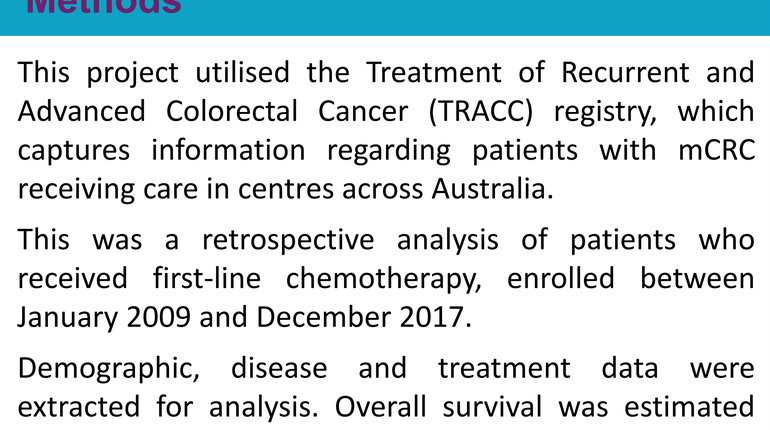


Figure 1. First-line treatment patterns for TRACC patients enrolled between 2009 and 2017

Relative to the overall treated cohort, patients who received first-line FOLFOXIRI or EGFRI were younger, had fewer comorbidities and more potentially resectable metastatic disease (**Table 1**). The vast majority of EGFRI-treated patients had left-sided primary tumours.

	FOLFOXIRI N = 22	Chemo + EGFRI N = 53	All chemo-treated patients N = 1585
Median age (range), years	51 (29-65)	60 (24-83)	65 (18-92)
Gender (%)			
Male	12 (55%)	25 (47%)	936 (59%)
Female	10 (45%)	28 (53%)	649 (41%)
ECOG (%)			
0-1	19 (86%)	44 (83%)	1396 (88%)
≥2	3 (14%)	6 (11%)	182 (11%)
Missing	-	3 (5.7%)	7 (0.04%)
Charlson score (%)			
0-2	21 (96%)	35 (66%)	744 (47%)
≥3	1 (4%)	15 (28%)	834 (53%)
Missing	-	3 (5.6%)	7 (0.04%)
Primary tumour site (%)			
Right colon	8 (36%)	4 (7.5%)	434 (27%)
Left colon and rectum	11 (50%)	47 (89%)	1066 (67%)
Not specified	3 (14%)	2 (3.8%)	85 (5.4%)
Treatment intent (%)			
Potentially curative	12 (55%)	22 (42%)	378 (24%)
Palliative	10 (45%)	31 (58%)	1202 (76%)
Missing	-	-	5 (0.3%)
KRAS status (%)			
Wild-type	8 (36%)	51 (96%)	686 (43%)
Mutated	10 (45%)	1 (1.9%)*	512 (32%)
Unknown	4 (18%)	1 (1.9%)	387 (24%)
BRAF status (%)			
Wild-type	11(50%)	34 (64%)	592 (37%)
Mutated	2 (9%)	1 (1.9%)	85 (8.7%)
Unknown	9 (41%)	18 (34%)	908 (57%)

Table 1: Clinicopathological characteristics of patients who received FOLFOXIRI or EGFRI
**One patient with a KRAS-mutated tumour was initially treated with an EGFRI, which was ceased after subsequent pathology review*

Increase in use of FOLFOXIRI and EGFRI was observed after 2014, coinciding with publication of TRIBE[1] data showing an overall survival (OS) advantage for FOLFOXIRI + bevacizumab versus FOLFIRI + bevacizumab, and PBS approval for first-line EGFRI use in RAS wild-type mCRC **(Figure 2)**.

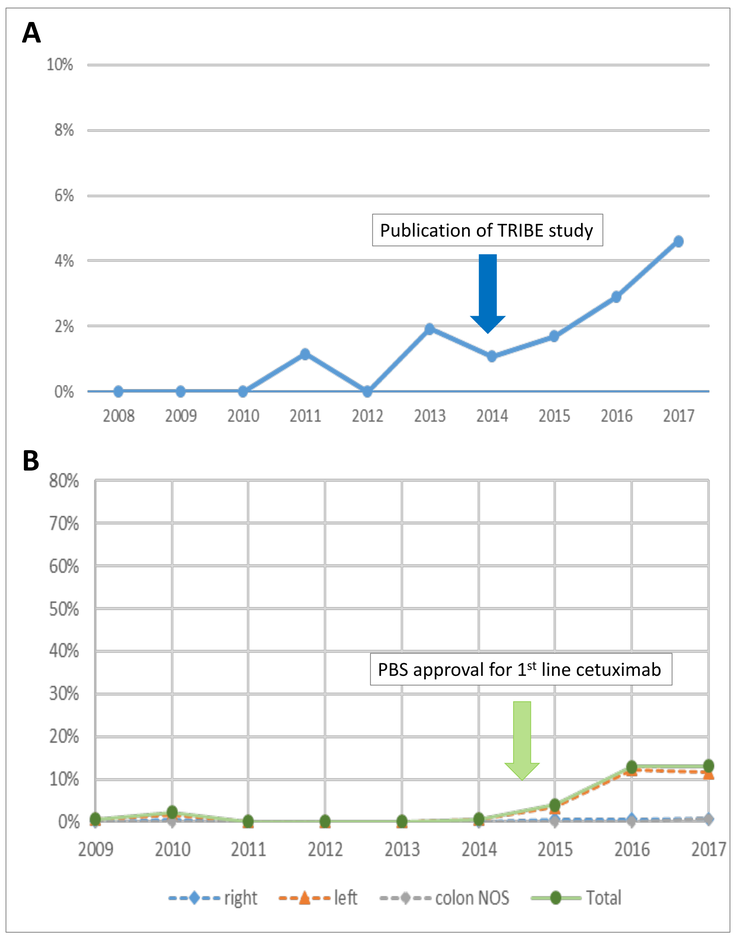


Figure 2. Percentage of patients by year treated with first-line (A) triplet chemotherapy, and **(B)** chemotherapy with an epidermal growth factor inhibitor (EGFRI)

Variation in the use of FOLFOXIRI and EGFRI (from 2015 onwards) is shown in **Figure 3**. FOLFOXIRI use was low across all sites, ranging from 0 to 11% (**Figure 3A**). Among patients with left-sided RAS wild-type tumours, the use of EGFRI ranged from 0% to 54%; <15% at the majority of centres (**Figure 3B**).

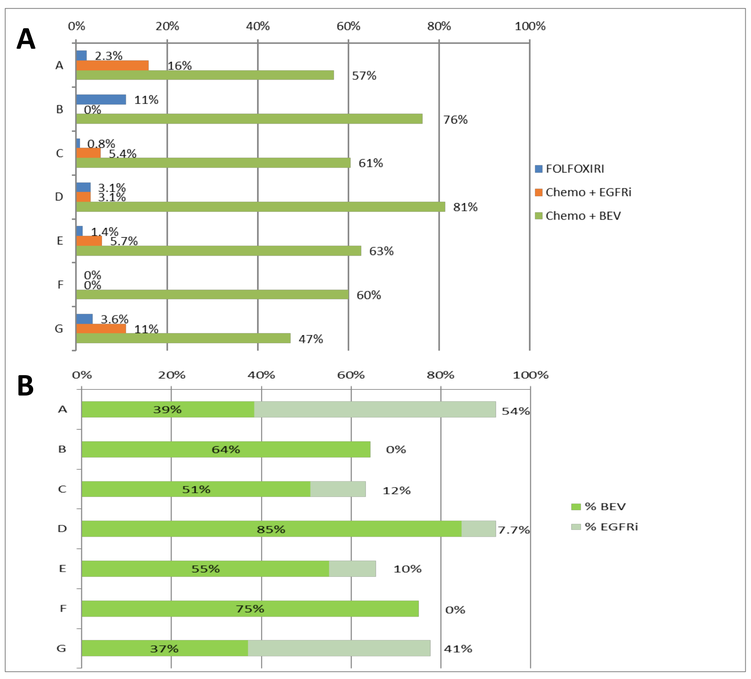
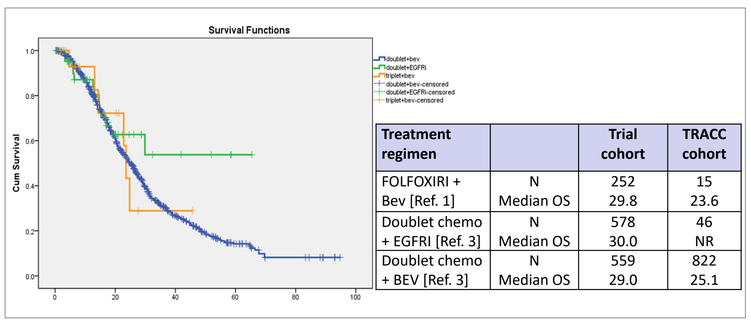


Figure 3. **(A)** FOLFOXIRI, chemotherapy plus epidermal growth factor receptor (EGFRI), and chemotherapy plus bevacizumab (BEV) use from 2015 onwards in the whole patient cohort. **(B)** Chemotherapy plus bevacizumab or EGFRI use among patients with left-sided RAS wild-type tumours.

OS by first-line treatment regimen is shown in **Figure 4**. Median OS from landmark clinical trials are shown for comparison.



Treatment regimen		Trial cohort	TRACC cohort
FOLFOXIRI + Bev [Ref. 1]	N Median OS	252 29.8	15 23.6
Doublet chemo + EGFRI [Ref. 3]	N Median OS	578 30.0	46 NR
Doublet chemo + BEV [Ref. 3]	N Median OS	559 29.0	822 25.1

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

Conclusion

Despite data supporting the first-line use of FOLFOXIRI, and of EGFRI in left-sided RAS wild-type mCRC, uptake of these therapies is low at most Australian centres and appears to be mostly reserved for younger patients with potentially resectable metastases. This may reflect pervading clinician opinions that triplet chemotherapy or EGFRI have not replaced the existing standard of doublet chemotherapy with bevacizumab for the initial management of mCRC.

References

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