Biomarker testing and biomarker-directed treatment utilisation for metastatic colorectal cancer in Australian practice

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BACKGROUND

In metastatic colorectal cancer (mCRC), tissue biomarkers such as *RAS* mutation and mismatch repair (MMR) status predict for response to epidermal growth factor inhibitors (EGFRI) and immune checkpoint inhibitors, respectively, whereas *BRAF* mutations portend a worse prognosis.

International guidelines recommend RAS testing for all patients who are candidates for EGFRI therapy. Universal testing of MMR status is increasingly being adopted for Lynch syndrome screening and for potential treatment selection.

Low testing rates (<50%) have been reported in the community setting[1-3], but have not been fully explored in the Australian context.

OBJECTIVES & ENDPOINTS

To explore the rates of biomarker testing and use of biomarker-directed therapies in real-world Australian practice.

Endpoints

1. Proportion of chemotherapy-treated mCRC patients who undergo *RAS*, *BRAF* and MMR testing
2. Clinical factors associated with *RAS* and MMR testing
3. Description of biomarker-directed therapy use among patients with *RAS* wild-type (wt), *BRAF* mutated (mt) and MMR deficient (dMMR) mCRC

METHODS

This was a retrospective analysis of data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry. TRACC was initiated in 2009 to collect data on patients with mCRC from multiple sites across Australia.

Criteria for this analysis were:

Patient eligibility: Started systemic therapy in Australia between January 2015 and December 2016

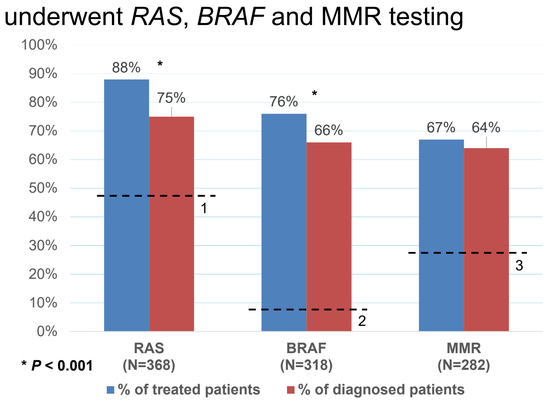
Biomarkers: *RAS* & *BRAF* mutation; MMR status

Treatments: EGFR inhibitors (EGFRI), BRAF-directed therapy (e.g. BRAF or downstream inhibitor), immune checkpoint inhibitors

RESULTS

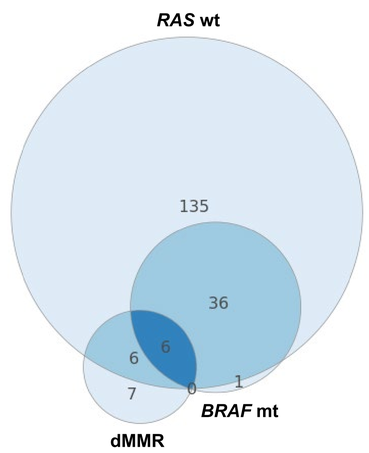
As of 19 June 2018, 2595 Australian patients with mCRC had been entered on the TRACC registry, of whom 419 (16%) started chemotherapy between 2015 and 2016. Median follow-up was 25 months.

Figure 1. Proportion of mCRC patients who underwent *RAS*, *BRAF* and MMR testing



[1]*RAS* testing rate reported by Carter *et al.* (all diagnosed mCRC, 2008-2011)
[2]*BRAF* testing rate reported by Price *et al.* (all diagnosed mCRC, 2006-2014)
[3]MMR testing rate reported by Shaikh *et al.*(all stages of CRC, 2010-2012)

Figure 2. Distribution of *RAS* wt, *BRAF* mt and dMMR mCRC cases



	N	%
RAS mt	181/368	49%
RAS wt *BRAF* wt/unknown	141/368	38%
RAS wt *BRAF* mt	42/368	11%
dMMR	19/282	6.7%

**One patient had both KRAS and BRAF mutations*

Figure 4. Rates and timing of EGFRI use among 141 *RAS* wt *BRAF* wt/unknown mCRC patients

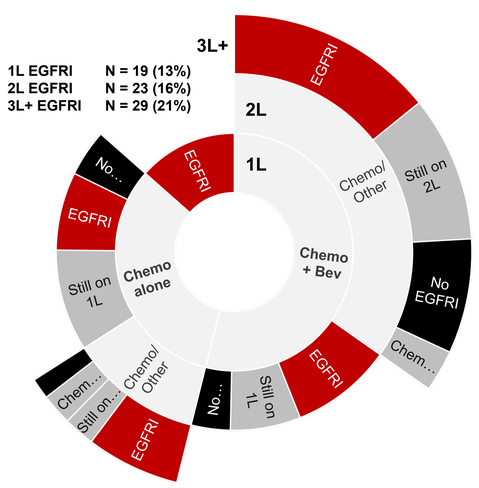
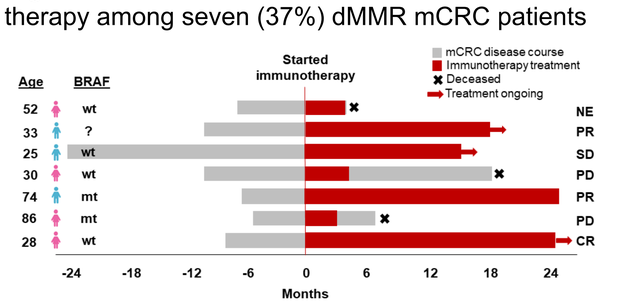


Table 2. EGFRI and BRAF-directed therapy among 43 *BRAF* mt mCRC patients

	EGFRI	BRAF-directed therapy
No. of patients treated	14 (33%)	7 (16%)
Median treatment duration (months) Range	2.0 (0.3 – 9.4)	6.0 (1.2 – 9.6)
Response rate (partial responses only)	3 (21%)	3 (43%)
Disease control rate (partial response & stable disease)	4 (29%)	4 (57%)

Figure 5. Duration of immune checkpoint inhibitor therapy among seven (37%) dMMR mCRC patients



CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable

Table 1. Multivariable logistic regression exploring factors associated with *RAS* and MMR testing

		RAS testing		MMR testing	
		%	OR	%	OR
Age	<75	90	**2.31**	71	**1.96**
	≥75 (Ref.)	80	(1.21-4.42)	54	(1.19-3.21)
Gender	Female	88	0.91	65	0.80
	Male (Ref.)	88	(0.49-1.68)	69	(0.52-1.23)
ECOG	PS 0-1	88	0.64	68	1.23
	PS ≥2 (Ref.)	91	(0.21-1.92)	61	(0.62-2.42)
Early stage CRC	Yes	88	1.15	73	**1.90**
	No (Ref.)	88	(0.62-2.14)	63	(1.22-2.98)
Primary site	Right	88	1.14	66	1.19
	Left/Other (Ref.)	88	(0.57-2.25)	68	(0.74-1.91)
Treatment location	Private	86	0.76	58	**0.47**
	Public (Ref.)	90	(0.41-1.41)	75	(0.30-0.72)

Figure 3. Relationship between age and dMMR in mCRC, where (A) is the % of cases in each age group that are dMMR and (B) is the contribution of each age group to the total number of dMMR cases

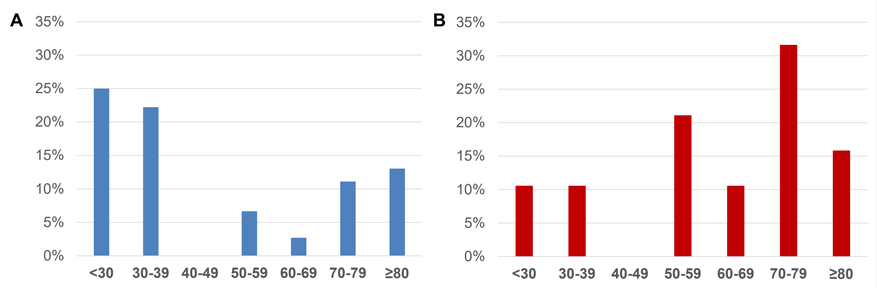
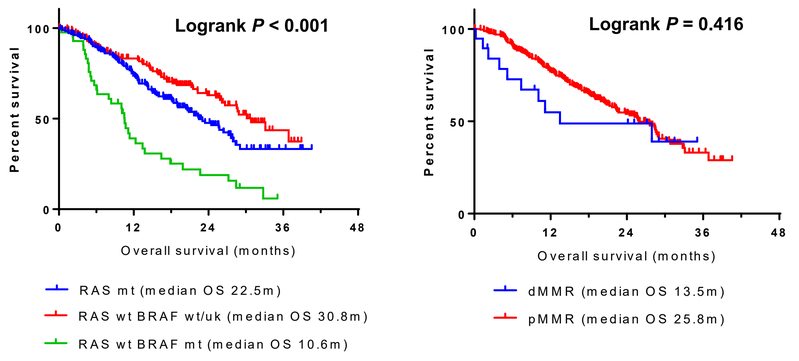


Figure 6. Overall survival by (A) *RAS*/*BRAF* and (B) MMR status



CONCLUSIONS

The majority of Australian chemotherapy-treated mCRC patients undergo *RAS* mutation testing, with at least 50% of *RAS* wild-type patients receiving an EGFRI during their treatment course.

Lower MMR compared to *RAS* testing rates may reflect lack of access to immunotherapy outside of clinical trials and cost share programs. MMR testing was more common in patients with younger age, initial early stage CRC and public treatment. The latter finding was unexpected, but an important caveat is that testing performed later in the disease course may not have been captured. Almost half of all dMMR cases occurred in patients aged ≥70 years.

A better understanding of the extent of benefit derived from biomarker-directed therapy in real-world mCRC patients may aid clinicians in optimising treatment selection.

REFERENCES & ACKNOWLEDGEMENTS

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