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Early onset metastatic colorectal cancer in Australia

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ABSTRACT

Background: Colorectal cancer (CRC) incidence and mortality rates have been increasing among young patients (YP), for uncertain reasons. It is unclear whether YP have a distinct tumor biology or merit a different treatment approach to older patients (OP).

Methods: We reviewed prospectively collected data from consecutive patients with metastatic CRC (MCRC) enrolled in the multi-site Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) Australian registry. Clinicopathological features, treatment and survival outcomes were compared between YP (<50 years) and OP (≥50 years).

Results: Of 3692 patients diagnosed August 2009 - March 2023, 14 % (513) were YP. YP were more likely than OP to be female (52% vs. 40 %, $P < 0.0001$), have ECOG performance status 0–1 (94% vs. 81 %, $P < 0.0001$), to have a left-sided primary (72% vs. 63 %, $P = 0.0008$) and to have fewer comorbidities (90% vs. 60 % Charleston score 0, $P < 0.0001$). There were no differences in the available molecular status, which was more complete in YP. YP were more likely to have de novo metastatic disease (71% vs. 57 %, $P < 0.0001$). YP were more likely to undergo curative hepatic resection (27% vs. 17 %, $P < 0.0001$), to receive any chemotherapy (93% vs. 78 % ($P < 0.0001$), and to receive 3+ lines of chemotherapy (30% vs. 24 % ($P < 0.0034$)). Median first-line progression free survival (10.2 versus 10.6 months) was similar for YP vs OP, but overall survival (32.1 versus 25.4 months, HR = 0.745, $P < 0.0001$) was longer in YP.

Conclusion: Known prognostic variables mostly favored YP versus OP with newly diagnosed mCRC, who were also more heavily treated. Consistent with this, overall survival outcomes were improved. This data does not support that CRC in YP represent a distinct subset of mCRC patients, or that a modified treatment approach is warranted.

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Introduction

Since the introduction of colorectal cancer (CRC) screening in many countries, such as the Australian National Bowel Screening Program[1] incidence and mortality rates have been declining in the screened population, typically those aged 50 years and above [2]. However, the incidence of early-onset CRC – widely defined as adults younger than 50 years of age – has been rising [3,4]. Incidence rates have increased by up to 41 % in Australia for this cohort since 1990[5] and symptomatic presentation occurs in up to 86 % of younger people [6,7]. Recently, the American Cancer Society and United States Preventive Services Task Force amended their recommendations for people at average risk to now start CRC screening from age 45 [8].

Young patients (YP) are more likely to present with advanced disease [9,10], likely in part due to delayed presentation. Patients are reported to wait up to 6.2 months before presenting for medical review [11]. When young patients do present, primary care physicians may be more likely to initially attribute gastrointestinal symptoms to benign anorectal pathology such as hemorrhoids, without doing additional workup [11]. Whether any differences in tumor biology lead to more advanced presentations in YP continues to be explored. Commonly documented is an increased proportion of left sided tumors [12–17], and these are more likely to present with symptoms. However, YP are more likely to have higher grade tumors (poorly differentiated or anaplastic), mucinous or signet ring features, and lymphovascular or perineural invasion, all features linked to worse disease-related survival [17–20]. Data on molecular markers in YP such as KRAS or BRAF mutations, and microsatellite instability (MSI) status have been variably reported, suggesting they are not clearly different to older patients (OP) and are not impacting treatment selection or outcomes [19].

Alongside an advanced presentation, YP patients are more likely to receive more intensive treatments because they have fewer comorbidities, and are more willing to undergo treatment [9]. Differences in individual treatment outcomes for YP versus OP have not been well demonstrated clinical trial cohorts and have not been well explored in large real world data sets. Our study aimed to provide an overview of patient and disease characteristics in YP with metastatic CRC and their treatment outcomes in a real-world population.

Methods

This was a retrospective analysis using data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry[21] which includes colorectal cancer patients from 30 Australian sites and 1 international site (Hong Kong). Inclusion criteria for our analysis were patients with metastatic or stage IV colorectal cancer, who were enrolled between August 2009 and March 2023. Patients were divided into YP and OP and compared, based on age less than 50 years old versus 50 years and over. The YP cohort was sub-divided further into under 30-year-olds, 30–39-year-olds and 40–49-year-olds to assess for differences in these smaller cohorts.

We analyzed prospectively collected data from these patients. The two main cohorts – YP and OP – were compared for patient characteristics (gender, functional status, comorbidities), clinico-pathologic features (familial cancer syndrome, family history, CEA, performance status, co-morbidity, synchronous versus metachronous disease, number and sites of metastatic sites, anatomical location of primary tumor) and molecular data (MMR/BRAF/RAS status), treatment patterns (lines of chemotherapy, metastatic resection), and survival (median progression free survival (PFS) and overall survival (OS).

Molecular data analysis was restricted to results reported from 2015 onwards. This was the year that the EGFR-monoclonal antibody cetuximab initially became available in the first-line setting in Australia, and thus prompted more routine molecular testing.

A familial cancer syndrome was adjudicated if there was a record of Lynch Syndrome or Familial Adenomatous Polyposis. A family history was recorded if there was at least one first degree relative diagnosed with colorectal cancer. A level of CEA greater than 5 was considered elevated. Co-morbidity data was calculated using the modified Charlson index [22]. Performance status was defined by the Eastern Cooperative Oncology Group (ECOG) scale [23]. A right-sided cancer was defined as one arising in the caecum, ascending colon, hepatic flexure or transverse colon. Tumors at and beyond the splenic flexure were considered a left-sided primary and included rectal cancers. Rectal cancer was defined as a tumor with the lower border within 12 cm of the anal verge. A line of therapy was defined as any treatment received before disease progression. PFS was calculated from date of diagnosis of metastatic disease until disease progression or death. OS was calculated from date of diagnosis of metastatic disease until death. Both were censored at last visit if no event had occurred.

Data analysis

Predicting variables were evaluated for their association with age group using a chi-squared test. A multivariate logistic regression model was applied to all variables with a p-value less than 0.05. Kaplan-Meier analysis was used to calculate the median OS and PFS and compared between the two groups using the log-rank test. If the proportion of missing data for a variable was >5 %, these missing values were coded in a separate category. Data were recorded in Microsoft Excel and statistical analyses were performed using SAS Enterprise Guide, version 8.1. $P < 0.05$ was considered statistically significant in this study. Ethics approval for this project was obtained from Melbourne Health Human Research Ethics Committee (HREC/18/MH/28, Project 2009.113).

Results

Between August 2009 and March 2023, there were 3692 patients with metastatic CRC that were enrolled in TRACC. 2156 (58.4 %) were male and median age was 66 years. There were 513 YP (13.9 %) and 3179 OP (86.1 %) in our analysis.

Patient characteristics are outlined in Table 1. The proportion of females was significantly higher in the YP group (51.7% vs. 40.0 %, $p < 0.0001$). There was a higher rate of YP with a performance status of ECOG 0–1 (93.8% vs. 80.6 %, $p < 0.0001$) and less patients with one or more comorbidities compared with the OP group (10.3% vs. 40.1 %, $p < 0.0001$).

Detailed clinicopathological features are shown in Table 1. YP had a higher frequency of familial syndromes (8% vs 1.5 %, $p < 0.0001$). A higher proportion of YP were diagnosed with de novo metastatic disease (71.2% vs 57.4 %, $p < 0.0001$) and had greater than 2 sites of metastatic disease (21.6% vs 17 %, $p = 0.0098$) compared with OP. YP were more likely to have a left-sided primary (72% vs. 63 %, $P = 0.0008$), and this included a rectal or left-colon primary site. Lung metastases were less common in YP (26.1% vs 32.0 %, $p = 0.0077$), with no significant difference in liver and bone metastases at diagnosis.

Sub-division of the YP cohort into under 30-year-olds ($n = 40$), 30–39-year-olds ($n = 141$) and 40–49-year-olds ($n = 332$) is demonstrated in Table 2. Gender, ECOG and comorbidity score were comparable between these three young groups. The youngest patients, under 30-years-olds, tended to have higher rates of metastatic disease at presentation (85.0% vs 67.2 % in 40–49-year-olds) and less left-sided tumors (60.0% vs 74.4 % in 40–49-year-olds). Under 30 year olds also had a higher incidence of deficient MMR (10.0% vs. 2.4 % in 40–49-year-olds) and BRAF mutation (17.5% vs. 4.4 % in 40–49-year-olds).

Statistical significance was assessed between the largest subgroup of YP (40–49-year-olds, $n = 332$) compared to OP (Table 3). There are significantly higher rates of women (50% vs. 40.0 %, $p = 0.0004$), greater rates of good ECOG 0–1 (95.8% vs 81.0 %, $p < 0.0001$) and low comorbidity score (11.5% vs. 40.3 %, $p < 0.0001$). More YP presented with metastatic disease at onset (67.2% vs 57.4 %, $p = 0.0006$). There are higher rates of left-sided tumor (74.4% vs 63.4 %, $p < 0.0001$) and

Table 1.
Patient and clinico-pathologic characteristics in the YP vs OP.

Variables		Young patients ($N = 513$)	Older patients ($N = 3179$)	P-value
Age	Median, years	43	69	-
	Mean	41.0	69.3	<0.001
Gender	Male, N (%)	248 (48.3)	1908 (60.0)	<0.0001
	Female, N (%)	265 (51.7)	1271 (40.0)	
ECOG PS	0–1, N (%)	481 (93.8)	2563 (80.6)	<0.0001
	Missing data, N	1	15	
Modified Charlson Index score	≥1, N (%)	53 (10.3)	1274 (40.1)	<0.0001
	Missing data, N	1	16	
Documented familial syndrome	*Yes, N (%)	21 (8.0)	22 (1.5)	<0.0001
	Missing data, N	251	1766	
CEA	≥ 5, N (%)	292 (56.9)	1826 (57.4)	0.5236
	Missing data, N	73	441	
Synchronous metastatic disease	Yes, N (%)	365 (71.2)	1824 (57.4)	<0.0001
Metastatic sites	≥3, N (%)	111 (21.6)	539 (17.0)	0.0098
Location of primary tumor	Left/ Rectum, N (%)	370 (72.3)	2017 (63.4)	0.0008
	Rectum, N (%)	166 (32.4)	910 (28.6)	0.0870
	NOS, multiple, N	16	156	
Site of metastases	Liver, N (%)	332 (64.7)	1963 (61.8)	0.1983
	Lung, N (%)	134 (26.1)	1017 (32.0)	0.0077
	Bone, N (%)	25 (4.9)	128 (4.0)	0.3718

Table 2
Patient and clinico-pathologic characteristics of young patients sub-divided into age categories: <30-year-old; 30–39 year-old and 40–49 year-old.

Variables		<30y/o $N = 40$	30–39y/o $N = 141$	40–49y/o $N = 332$
Gender	Male, N (%)	19 (47.5)	61 (43.3)	166 (50.0)
	Female, N (%)	21 (52.5)	80 (56.7)	166 (50.0)
ECOG PS	0–1, N (%)	36 (90.0)	128 (90.8)	317 (95.6)
Modified Charlson Index score	≥1, N (%)	4 (10.0)	11 (7.8)	38 (11.5)
Documented familial syndrome	*Yes, N (%)	3 (7.5)	5 (3.6)	13 (3.9)
CEA	≥ 5, N (%)	20 (50.0)	94 (66.7)	186 (56.0)
Synchronous metastatic disease	Yes, N (%)	34 (85.0)	108 (76.6)	223 (67.2)
Metastatic sites	≥3, N (%)	12 (30.0)	35 (24.8)	65 (19.6)
Location of primary tumor	Left/Rectum, N (%)	24 (60.0)	99 (70.2)	247 (74.4)
Site of metastases	Liver, N (%)	22 (55.0)	97 (68.8)	213 (64.2)
	Lung, N (%)	8 (20.0)	33 (23.4)	93 (28.0)
	Bone, N (%)	3 (7.5)	8 (5.7)	14 (4.2)
MSI status / MMR proficiency	MSI unstable/ dMMR, N (%)	4 (10.0)	9 (6.4)	8 (2.4)
BRAF V600E mutation	Mutant, N (%)	7 (17.5)	22 (15.6)	15 (4.4)
RAS mutation	Mutant, N (%)	12 (30.0)	49 (34.8)	148 (44.6)

Table 3
Demographic differences of the largest young cohort 40–49-year-olds compared to OP (>50-year-olds).

Variables		40–49y/o ($N = 332$)	Older patients >50y/o ($N = 3179$)	P-value
Gender	Male, N (%)	166 (50.0)	1908 (60.0)	0.0004
	Female, N (%)	166 (50.0)	1271 (40.0)	
ECOG PS	0–1, N (%)	317 (95.8)	2564 (81.0)	<0.0001
Modified Charlson Index score	≥1, N (%)	38 (11.5)	1274 (40.3)	<0.0001
Documented familial syndrome	Yes, N (%)	13 (7.5)	22 (1.6)	<0.0001
CEA	≥ 5, N (%)	186 (66.0)	1866 (68.2)	0.4521
Synchronous metastatic disease	Yes, N (%)	223 (67.2)	1825 (57.4)	0.0006
Metastatic sites	≥3, N (%)	65 (19.6)	549 (17.0)	0.2341
Location of primary tumor	Left/Rectum, N (%)	247 (74.4)	2016 (63.4)	<0.0001
Site of metastases	Liver, N (%)	213 (64.2)	1963 (61.8)	0.3898
	Lung, N (%)	93 (28.9)	1017 (32.0)	0.1379
	Bone, N (%)	14 (4.2)	128 (4.0)	0.8669
MSI status / MMR proficiency	MSI unstable/ dMMR, N (%)	8 (3.0)	113 (6.4)	0.0330
BRAFV600E mutation	Mutant, N (%)	15 (6.3)	203 (12.3)	0.0062
RAS mutation	Mutant, N (%)	148 (51.0)	1052 (47.7)	0.2836

lower rates of BRAF mutation (6.3% vs 12.3 %, $p = 0.0062$) and deficient MMR status (6.4% vs 3.0 %, $p = 0.0330$).

Molecular testing between our two main cohorts of YP and OP is outlined in Table 4. The proportion of YP who underwent testing for RAS (85.6% vs. 69.4 %), BRAF (71.8% vs 53.0 %) and MMR status (79.8% vs 56.0 %) were significantly higher than OP ($p < 0.0001$), but there were no differences in the rate of mutations of RAS, BRAFV600E or in MMR-deficiency in those tested. There was no difference in the proportion with an elevated CEA between the two groups.

Treatment data is summarized in Table 5. YP were more likely to undergo curative-intent liver resection than OP (26.8% vs 17.1 %, $p < 0.0001$). More YP received 3 or more lines of chemotherapy (30.3% vs 23.9 %, $p = 0.0034$) and a higher percentage of YP received triplet chemotherapy with both oxaliplatin and irinotecan in their first-line of chemotherapy (12.6% vs 1.2 %, $p < 0.0001$).

There was no significant difference in PFS rates (Fig. 1) but a longer median OS in YP was observed (32.1 vs. 25.4 months, $P < 0.001$) (Fig. 2). Gender was not significantly associated with survival outcomes in YP nor OP (Supplementary material, Figure 3). Compared with right-sided tumors, left-sided tumors were significantly associated with better survival outcomes for both groups: YP (36.1 vs. 21.0 months, $P =$

Table 4
Molecular data and testing rates in YP vs OP since 2015.

Variables		Young patients ($N = 364$)	Older patients ($N = 1646$)	p-value
MSI status / MMR proficiency	MSI unstable/ dMMR, N (%)	21 (5.1)	113 (6.4)	0.3490
BRAFV600E mutation	Mutant, N (%)	45 (12.4)	203 (12.3)	0.9876
RAS mutation	Mutant, N (%)	209 (47.7)	1052 (47.7)	0.9359
Rate of MMR testing	Performed, N (%)	410 (79.8)	1779 (56.0)	<0.0001
Rate of BRAF testing	Performed, N (%)	369 (71.8)	1683 (53.0)	<0.0001
Rate of RAS testing	Performed, N (%)	440 (85.6)	2205 (69.4)	<0.0001

Table 5
Treatment patterns in YP vs OP.

Variable		Young patients (*N* = 513)	Older patients (*N* = 3179)	p-value
Primary resection	Yes, N (%)	347 (67.6)	2284 (71.9)	0.0508
Lines of chemo	Any, N (%)	476 (92.8)	2464 (77.5)	<0.0001
	1–2, N (%)	332 (64.7)	1875 (59.0)	0.0034
	3+, N (%) (excl. patients receiving no treatment)	144 (30.3)	589 (23.9)	0.0034
First line of chemo	FOLFOXIRI, N (%) (excl. patients receiving no treatment)	59 (12.6)	28 (1.2)	<0.0001
	Missing data, N	44	810	
Liver metastases resection	Yes, N (%)	123 (26.8%)	500 (17.1%)	<0.0001
Any metastases resection	Yes, N (%)	217 (47.4)	949 (32.5)	<0.0001
	Missing data, N	55	259	

0.0041) and OP (28.7 vs. 19.8 months, $P < 0.0001$) (Supplementary material, Figure 4).

Survival outcomes of our YP sub-division is shown in Table 6. Patients in 40–49-year-old category had no difference in PFS but had improved OS (32.2 months vs 25.5 months, $p < 0.0001$) compared to OP. When assessing an alternative age cut-off of 40-years-old, statistically significant advantage was still demonstrated in younger patients with under-40-year-olds ($n = 181$) compared to greater-than-40-year-olds (32.1 months vs 26.2 months, $p = 0.0097$). PFS did not differ in the 40-year age cut-off.

Table 6
Survival outcomes of young patients further sub-divided into age categories: <40-year-old; 40–49-year-olds; and >50-year-olds.

	40–49 y/o *N* = 332	>50 y/o *N* = 3179	p-value
PFS	10.5 months	10.6 months	0.1978
OS	32.2 months	25.5 months	<0.0001
	<40y/o *N* = 181	>40y/o *N* = 3511	p-value
PFS	8.9 months	10.5 months	0.6609
OS	32.1 months	26.2 months	0.0097

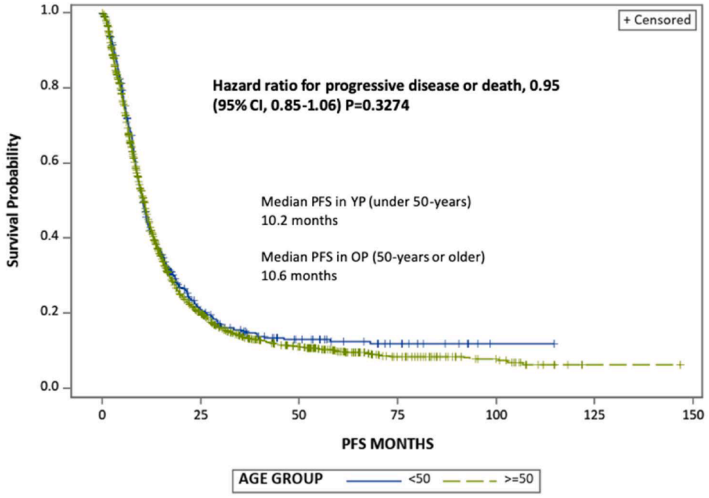

Fig. 1.. Kaplan-Meier curve comparing progression-free survival in YP vs OP, for all patients who received first-line therapy.

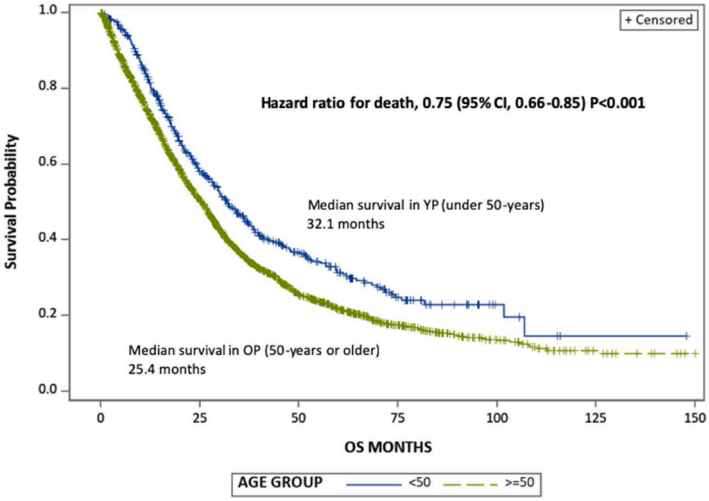

Fig. 2.. Kaplan-Meier curve comparing overall survival in YP vs OP, for all patients.

Discussion

The increasing global incidence of CRC in YPs[24] highlights the importance of better understanding what is driving this increase, and determining if there are any differences in CRC presentation, biology and treatment response that could inform clinical practice. Here we report findings from a large multi-site metastatic disease registry, finding significant differences in clinical presentation, but not standard molecular features. YP were more likely to undergo surgery for oligometastatic disease. We found no difference in progression free survival on first line treatment, however an improved overall survival was observed. The latter is likely due to the more aggressive and multidisciplinary approach to treatment.

In our Australian cohort, 13.9 % of patients with mCRC were under 50, consistent with other modern series [25]. As reported by others YP were more likely to have metastatic disease at initial presentation[9,10], which is typically associated with a poor survival outcome [26]. The increased rate of metastatic disease at diagnosis might be due to an absence of screening programs in this cohort or a delay in diagnosis due to a lower index of suspicion for CRC in younger patients. We found a higher proportion of YP females, in contrast to what is seen in OP. This has not been widely reported in other series [11,20]. Notably some previous series that included all age groups with mCRC reported a better outcome in female patients [27]. Our data suggests the possibility of a variable impact of gender dependent on age, though no differences were statistically significant. This is notable in the context of two previous reports of an influence of gender on early-onset CRC patient outcomes, where female gender had a variable impact on survival depending on age-cohort [28,29]. Potential explanations include age based hormonal differences [30].

As consistently reported in other series[12–17,31–33] YP have a greater incidence of left-side primary cancers, which is a known positive prognostic factor [34]. Some previous studies have reported that up to 80 % of CRC diagnosed in YP are left-sided cancers, with the most common site being the rectum. The absolute differences were modest however, as were the differences in sites of metastatic disease, and so while these factors are each known to impact prognosis, they are unlikely to substantially impact outcomes in our series, particularly as they are respectively positive[35,36] and negative[37] prognostic factors. In an exploratory analysis we found that primary tumor site had a consistent impact on survival in YP and OP. In both groups a right-sided tumor was associated with poor survival. Similarly, we found no reports that have established a significant interaction between age and primary site with respect to survival. The largest report is from a sub-group analysis of YP in SWOG-80,405, which found no age based difference in survival in association with tumor sidedness [38].

As expected YP had a better performance status and less comorbidities, making them better candidates for multiple active interventions. This included a higher proportion undergoing resection of oligometastatic disease, an intervention that may lead to long term survival. For patients treated with palliative intent there was a greater administration of chemotherapy. This is consistent with the findings of other series[39]. Notably initial triplet chemotherapy has been associated with improved PFS and OS in two recent meta-analyses of unselected CRC patients [40,41].

We found an improved overall survival in YP, consistent with multiple prior studies, including a large US cancer-registry analysis[42], Swedish[43] and Korean[25] data. In contrast other studies have reported no age based differences in survival outcomes [44,45]. Some series [9,38], after adjusting for patient-related and tumor-related factors, found no survival differences despite YP being more likely to receive chemotherapy. These variable findings may in part reflect the time periods studied, with these series respectively examining patients treated from 2003 to 2005 [9], an era with less active therapy, and a clinical trial cohort [38], which likely would have excluded many of the OP included in our analysis. The consistent findings that YP receive increased treatment intensity aligns with our interpretation, that we see an improved OS in YP due to increased treatment rather than any difference in underlying biology.

Our study found no significant difference between YP and OP in the results of testing of standard molecular markers, RAS, BRAFV600E and dMMR frequency. Others that have undertaken more extended testing have found YP had more MSI-H disease, more with CMS1, and more TP53 mutations while OP had a higher prevalence of BRAF, RAS and APC mutations [12,46,47]. Such data suggests the possibility of a different underlying biological process in YP[48,49] however a large genomic profiling study found no age based molecular differences [12]. Notably there are a small proportion of YP with familial-associated cancers, which are distinctly different [50,51], and these patients do need to be considered separately from sporadic cancers.

We also undertook a sub-division of our YP cohort to assess for any meaningful differences in the very young population. We demonstrated an improved OS in a younger age-cut off of 40-years (Table 6) which remained consistent with our findings using the standard YP definition of 50-years. The largest of our YP groups were 40–49-year-olds (n = 181) who had consistent differences to OP as for the entire YP cohort (n = 364) with the exception of BRAF mutation and dMMR status. In the 40–49-year-old group there were lower rates of both mutations compared to OP, which was not detected when assessing the YP cohort as a whole. It is unclear if the presentation of CRC in 40–49-year-olds differs from the very young population and does not alter our overall findings in our two main cohorts of YP vs OP. Although we had a large population, analysis of sub-groups in specific age-ranges were limited to smaller sample size.

There are several limitations to our study, including incomplete molecular profiling for the full cohort, even in the cohort examined from 2015 when first-line cetuximab became available in Australia and upfront RAS testing impacted initial treatment decisions. We found a higher uptake of molecular testing in YP compared to OP, consistent with a more aggressive diagnostic and therapeutic approach. The rate of RAS testing has progressively risen globally suggesting increasingly reflex testing[52] although a large US analysis found YP had unacceptably low rates between 32 and 42 % for of MSI/MMR, RAS and BRAF testing [53].

Our registry is now capturing genomic data in the context of multiple emerging treatment options and now standard use of bevacizumab, EGFR inhibitors, immune checkpoint inhibitors for dMMR cancers, BRAF inhibitors, and agents targeting cancers with HER2 overexpression. It will be important to understand the uptake of these agents and impact on YP, particularly any differences for patients with Lynch Syndrome versus the sporadic dMMR which dominates in older patients. The arbitrary but widespread definition of YP as patients diagnosed before age 50 may mean we are missing important differences in the very young, where the most concerning increases in incidence are being seen. Further studies to elucidate causes of mutational or genomic differences between age groups are required.

Conclusion

Our data has confirmed some of the findings of previous series of clinicopathological differences, but there are also some novel findings. Overall, the data supports a standard approach to patients with mCRC, regardless of age at diagnosis. Further and extended studies of molecular characteristics are warranted. A reduction in the screening age for colorectal cancer, as is being pursued in some jurisdictions, is an appropriate response to current trends.

CRediT authorship contribution statement

A. Jalali: Writing – review & editing, Project administration, Methodology, Conceptualization. **S. Smith:** Writing – review & editing, Writing – original draft, Project administration. **G. Kim:** Writing –

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Louise Nott reports consulting fees for advisory boards with BMS, Roche, Pfier, Servier, Ipsen, AstraZeneca and Novartis. Louise Nott reports speaker honorarium with MSD, Amgen, MS and Celgene. Louise Nott reports support for attending educational meetings with MSD and Novartis. There are no other interests declared by the authors which may be considered as potential competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2024.100827.

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