(i)Title

Utilisation of systemic therapy options in routine treatment of metastatic colorectal cancer in Australia

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Abstract

Background/Aim

In the treatment of metastatic colorectal cancer (mCRC), exposure to all three active cytotoxic agents; 5-fluorouracil/capecitabine, irinotecan and oxaliplatin improves overall survival. The addition of biologic agents (bevacizumab and cetuximab/panitumumab) further improves survival. The uptake of available systemic agents for mCRC in routine practice in Australia is poorly described.

Methods

The ACCORD database was interrogated to determine demographics, treatments and outcomes for patients diagnosed with mCRC between 1/01/2011 and 1/01/2016 at 6 Melbourne centres.

Results

1130 mCRC patients were identified: median age was 69 years (range 26-105), 61% had synchronous disease. *KRAS* status was known in 62%, of whom 49% were *KRAS* wild-type. At the time of analysis, 67% of all patients had commenced systemic treatment, 50% had received two or more lines of therapy and 19% of *KRAS* wild-type patients had received all five active drugs. Of *KRAS*-mutated patients, 35% had received all four PBS-reimbursed active drugs. Patients who had not received chemotherapy included 72 patients who underwent metastatectomy alone. At a median follow-up of 34 months, median overall survival was 25 months for all patients and 69 months for those who underwent metastatectomy.

Conclusion

In this community-based cohort 33% of patients had not received any systemic therapy for mCRC and few patients had received all available active systemic agents. As many patients remain alive these figures will likely increase over time. The overall survival of patients with mCRC in this community-based cohort was 25 months and not dissimilar to that achieved in recent clinical trials.

Key words

Cancer

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Metastatic

Treatment

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(i)Text

Background

Colorectal cancer incidence in Australia is one of the highest in the world. In 2018, an estimated 17000 new cases will be diagnosed, 40% of whom will present at an advanced stage or eventually develop metastases[1-3]. The survival of patients with metastatic colorectal cancer has continued to improve with the introduction of new agents. Introduced in the 1950's, 5-fluorouracil was initially used alone[4] and then in combination with leucovorin, resulting in an increase in median overall survival from 7.7 months to approximately 12 months[5]. The addition of oxaliplatin and irinotecan, led to a median overall survival of greater than 20 months[6-9]. More recently the optimal use of targeted therapies including bevacizumab, a vascular endothelial growth factor receptor inhibitor (VEGFi) and cetuximab/panitumumab, epidermal growth factor receptor inhibitors (EGFRi) has produced median overall survivals of greater than 30 months in defined subsets[10]. Triplet chemotherapy combined with a biologic is another approach with promising survival outcomes in randomised studies[11].

In Australia, bevacizumab has been PBS reimbursed for first-line treatment of metastatic colorectal cancer since 2009, with EGFRi available for second and subsequent line treatment of metastatic colorectal cancer since September 2011. Arguably, access to these therapeutic agents has shaped the management of colorectal cancer in Australia. First-line use of an EGFRi (+/- second-line bevacizumab) initially for KRAS and subsequently for all-RAS wild-type patients, has been PBS reimbursed since mid-2015. Thus, there are now several fully subsidised cytotoxic and targeted therapies available in the armamentarium of treatment of metastatic colorectal cancer in Australia.

Based on the combined evidence from pivotal phase 3 randomised controlled trials, consensus guidelines recommend chemotherapy combined with biological agents in patients with metastatic colorectal cancer deemed fit for systemic therapy[12]. An analysis of multiple randomised studies of chemotherapy alone found the best survival outcomes were achieved by patients who had been exposed to all active agents[13]. The current uptake of systemic treatment for metastatic colorectal cancer, including utilisation of all available cytotoxic and biological agents in a community setting in Australia is poorly described. Here we assess the real-world treatment patterns for metastatic colorectal cancer across Melbourne, including both the public and private sectors.

Methods

Established in 2003, the Australian Comprehensive Cancer Outcomes and Research Database (ACCORD) is a comprehensive, point of care database created to collect prospective data in patients diagnosed with colorectal cancer across Melbourne, Australia[14].

For this study, data was extracted on all patients diagnosed with metastatic colorectal cancer between January 1 2011 and January 1 2016 at six centers in Melbourne; three public and three private hospitals; distributed across geographical areas. Data collected included patient demographics, cancer diagnosis including histology and stage, molecular characteristics, treatment and outcomes. Of note, in line with testing recommendations at the time that the database was established, only *KRAS* status was collected and available for the purposes of this analysis.

Progression was determined by the clinician and could be based on clinical, biochemical or radiological findings. Overall survival was defined as the time from diagnosis of metastatic disease to death/censoring. The Kaplan Meier method was used to calculate overall survival. Descriptive statistics were conducted on the cohort with no comparison analysis. A P-value of less than 0.05 was used to indicate statistical significance.

Chemotherapy treatment was assigned via therapeutic lines; first, second, third-line and beyond (greater than or equal to fourth-line therapy). If a patient changed treatment due to progression or intolerance, this was regarded as a change from one line to the next.

Institutional Review Board Approval

This study has HREC approval for BioGrid linkage of the ACCORD databases from Melbourne Health (HREC 2005.198).

Results

From January 1 2011 through to January 1 2016, 1130 eligible patients were registered. Patient characteristics are outlined in Table 1. Of the identified patients, 71% (806/1130) were managed in the public sector and 29% (324/1130) in the private setting. Median age at presentation was 69 years (range 26-105). The majority of patients were male (59%), had presented with synchronous metastatic disease (61%) and (where recorded) had a good Eastern Cooperative Oncology Group performance status (ECOG PS), defined as ECOG PS 0-1 (81%). Notably 466 patients (41%) did not have an ECOG PS recorded in the database at the time of diagnosis of metastatic disease; predominately those with relapsed disease where ECOG PS had been captured at the time of diagnosis of early stage disease and had not been re-recorded. Forty-three percent of patients had disease limited to a single organ, either the liver or lung. At the time of analysis, 67% (753/1130) of all patients in this cohort had commenced at least one line of systemic therapy, similar for public and private patients (Table 1).

Compared to those who received systemic treatment, the 377 patients who had not commenced first-line chemotherapy were older, of poorer performance status and less likely to have had *KRAS*-testing performed (Table 1). The untreated cohort also included 72 patients who had undergone resection of metastatic disease and had not received chemotherapy before or after this surgery, with many of these remaining disease free at the time of analysis.

In line with guidelines at the time, *KRAS* testing of exon 2 was performed on 62% (696/1130) of patients. Although this may have expanded to include exons 3 and 4 and

NRAS exon 1,2,3,4, in the latter years, this was not well captured by the database. Of these 696 patients, 49% (341/696) were *KRAS* wild-type and 51% (355/696) were *KRAS*-mutated.

Of the 38% (434/1130) of the cohort who did not undergo *KRAS* testing, 271 (62%) received no systemic therapy. Of these patients, 11% (30/271) had undergone resection of metastatic disease as the only intervention whilst 89% (241/271) had received best supportive care only.

For the total treated population (n=753); 17% (131/753) had received one cytotoxic agent; 46% (348/753) had received either FP/oxaliplatin or FP/Irinotecan; and 36% (272/753) had received all three cytotoxic agents. Sixty-one percent (459/753) had received at least one biologic; 54% (406/753) had received bevacizumab, 16% (123/753) an EGFRi and 11% (80/753) received both bevacizumab and an EGFRi.

First-line chemotherapy was administered in 753 patients. Choice of regimen is outlined in Figure 1A. The most common first-line chemotherapy regimen was FP/Oxaliplatin used in 67% (502/753) of patients, followed by single agent FP, used in 22% (166/753). Few patients (9%) received first-line irinotecan-based treatment; FP/Irinotecan 8% (58/753) or irinotecan-monotherapy 1% (9/753). Additionally, only 2% (15/753) of patients received first-line FOLFOXIRI (FP/oxaliplatin/irinotecan). In total, 53% of patients who commenced treatment received a biologic agent as part of first-line therapy (Figure 1B). First-line concurrent bevacizumab was administered to 52% (390/753) of patients.

Compared to the overall cohort of patients, those who received first-line single agent FP were older, median age 74 years. Use of intravenous versus oral FP was similar: 55% 5-fluorouracil (92/166) and 45% (74/166) capecitabine. ECOG at time of initiation of first-line therapy was recorded in 51% (85/166) of patients. Eighty-one percent (69/85) were ECOG 0-1 and 19% (16/85) were ECOG ≥2. For combination regimens, there was a preference for 5-fluorouracil over capecitabine as the fluoropyrimidine backbone, with 74% (372/502) of patients receiving FOLFOX, 21% (103/502) CAPOX and 5% (27/205) both regimens. Similarly, 83% (48/58) received FOLFIRI, 10% (6/58) CAPIRI and 7% (4/58) both regimens.

At the time of analysis, 49% (368/753) of patients who received first-line therapy had gone on to receive second-line treatment, meaning second-line therapy had been received by 368 of all 1130 patients (33%). Choice of second-line chemotherapy regimen is outlined in Figure 1C. Irinotecan was the most common chemotherapy backbone administered; 63% (231/368), 50% (182/368) in combination with FP (94% FOLFIRI, 6% CAPIRI) and 13% (49/368) as a single agent. Over 35% (130/368) of patients received a biologic agent as part of their second-line regimen (Figure 1D). EGFRi use increased, used second-line in 16% (60/368) of all patients, including as a single agent in 8% (31/368) of patients.

At the time of analysis, 19% (144/743) of the total treated population had received third-line treatment (Figure 1E/1F).

For the treated population of patients with *KRAS* wild-type tumours (n=303): 11% (33/303) received one cytotoxic agent: FP - 27 patients, irinotecan - 6 patients; 45% (137/303) received FP and either oxaliplatin/irinotecan; and 44% (133/303) had received all three

chemotherapy agents. A biologic agent was administered to 75% (227/303) of patients; 62% (189/303) received bevacizumab, 38% (116/303) an EGFRi and 26% (78/303) received both bevacizumab and EGFRi. To date, 19% of patients (57/303) have received all five active PBS reimbursed drugs.

For the treated population of patients with *KRAS*-mutated tumours (n=287); 13% (36/279) received one cytotoxic agent: FP - 34 patients, irinotecan - 2 patients; 43% (122/287) received FP and either oxaliplatin/irinotecan; and 45% (129/287) received all three chemotherapy agents. 62% (179/289) of *KRAS*-mutated patients have received bevacizumab. Currently, 35% (100/287) of *KRAS*-mutated patient have received all four active PBS reimbursed drugs.

For the treated population where *KRAS* status was unknown (n=163): 38% (62/163) received one cytotoxic agent, 55% (89/163) had received FP and either oxaliplatin/irinotecan and 6% (10/163) all three agents. Twenty-nine percent (48/163) received bevacizumab and two patients received a biologic without chemotherapy (clinical trial). Three percent (4/163) of *KRAS*-status unknown patients received all four active PBS reimbursed drugs.

Metastatectomy was performed in 28% (317/1130) of patients of whom 147 had synchronous and 170 metachronous metastatic disease. To date, 23% (72/317) of patients who had metastatectomy have not required chemotherapy for metastatic disease. Of the 170 patients with metachronous metastatic disease who underwent metastatectomy, 109 had received adjuvant chemotherapy.

With a median follow-up of 34 months, 39% (438/1130) of patients remain alive, 57% (639/1130) are dead and 5% (53/1130) are lost to follow up. Of the patients who did not receive any systemic treatment 55% (209/377) have died, 9%(32/377) are lost to follow up and 36%(136/377) were alive at last follow up. The median overall survival for the whole cohort was 25 months (95% CI 22.8 - 27.0) (Figure 2). Patients who underwent metastatectomy had a survival of 69 months (95% CI 49.9 – not reached), compared to 17 months (95% CI 15.7 - 18.8) in those who did not (Figure 3). Overall survival of the *KRAS*-unknown patients was inferior to both the *KRAS* wild-type and *KRAS* mutated patients (15 months vs 29 and 27 months respectively, p <0.0001) (Figure 4). *BRAF* wild-type patients had a longer median overall survival compared to *BRAF* mutated patients (40 months vs 14 months, p-value is <0.0001).

Discussion

This analysis provides a snapshot of routine care for metastatic colorectal cancer in an Australian community setting. Overall 33% (377/1130) of patients had not yet received any systemic therapy. This included a mixed population including patients not fit for (or declining) therapy along with patients undergoing resection of metastatic disease. Where systemic treatment was given, the dominant chemotherapy strategy in first-line was oxaliplatin-based and in second-line irinotecan-based. Biologic use was dominated by bevacizumab, in part due to PBS restrictions and in part due to the evidence supporting EGFRi emerging over the time of this series. Given this is a real world population the survival outcomes were encouraging, particularly that long term survivors were seen among those undergoing resection of metastatic disease.

Included in the 33% (377/1130) of patients who did not receive any systemic therapy were 72 patients (19% of all untreated patients) who underwent metastatectomy without receiving any chemotherapy (6% of all 1130 patients) for metastatic disease. Therefore, in total, 27% (305/1130) of patients have not had active treatment (surgical or systemic) for metastatic colorectal cancer. As reported by others[15] this is reflective of real world practice, where patients may be old, frail or have a poor performance status, rendering them unfit for active therapy. The occasional patient may decline recommended active therapy and a proportion will be on an initial watch and wait strategy, with the intent to institute active therapy at a later date. When actively treated, these patients along with some relapsing after initial metastatectomy without systemic therapy may lead to a slight increase in the overall proportion that ultimately receive treatment.

At the time of analysis, around half of the patients who had received first-line treatment had gone on to second-line therapy. This is again consistent with other series describing routine care populations[16-18]. Overall, only 21% (16/753) of patients had ultimately received all three PBS-reimbursed cytotoxic agents. This is partially explained by a number of patients who are currently working their way through lines of treatment. There was no significant difference in the percentage of *KRAS* wild-type or *KRAS*-mutated patients who had received all three cytotoxic agents (44% vs 45%), however a higher proportion of *KRAS*-mutated patients have received all available PBS subsidised drugs (35% vs 19%, p=0.0001). *KRAS* wild-type patients were more likely than *KRAS*-mutated and KRAS-unknown patients to have received three or more lines of systemic therapy, reflecting the availability of EGFRi agents as a treatment line. A proportion (62%) of *KRAS* wild-type patients in our cohort are yet to receive an EGFRi. There was a low rate of systemic therapy administration in patients

where *KRAS* testing was not known/not performed; likely reflecting the fact that this included many poor prognosis patients where testing may not be performed when active therapy is not being considered.

In the first-line setting, doublet chemotherapy with FP/oxaliplatin was the preferred choice over FP/irinotecan. This is similar to US practice[15-17]whereas irinotecan based therapy is more often used first-line in some European countries[19]. While evidence demonstrating they are equally efficacious chemotherapy regimens[8,20] suggests use should be more balanced, Australian practice tends to follow US practice and all clinical trials over this time period had oxaliplatin as part of first-line therapy and irinotecan as second-line therapy. Anecdotally, physician preference when EGFRi were first approved, was to combine these agents in the second-line setting with an irinotecan chemotherapy backbone, given studies demonstrating the synergy of this approach[21]. Triplet therapy (FOLFOXIRI) was rarely used in our cohort, in part due to concerns of tolerability in a community based patient population[11]. More data supportive of triplet therapy has emerged over the course of the time period studied and subsequently, however recent reports suggest FOLFOXIRI use in Australia remains minimal[22].

With regard to choice of FP backbone, perhaps surprisingly given the convenience of oral over intravenous therapies, the use of 5-fluorouracil and capecitabine was similar for patients receiving FP monotherapy. For combination regimens, although data would suggested that FOLFOX and CAPOX are equivalent, there was a preference for Australian clinicians to use FOLFOX as the chemotherapy backbone over CAPOX[23].

The most common second-line regimen was FP/irinotecan. The percentage of patients who received second-line concurrent bevacizumab was higher than expected given the low use of EGFRi in the first-line setting. This result may be explained by a bevacizumab beyond progression access scheme supported by Roche Pharmaceuticals that was active during the period evaluated. The use of second-line bevacizumab is now restricted by the PBS to patients who received EGFRi in the first-line setting.

Sixty one percent (459/753) of patients have received a biologic agent during their course of therapy. This is partly reflective of drug availability, as only bevacizumab was available first-line for the entire study period. Other potential contributing factors are relative contraindications to bevacizumab (in particular impaired wound healing and risk of perforation), patient choice and, more recently, time required to process and receive RAS testing results. The toxicity of EGFRi, specifically skin toxicity, remains challenging to manage whereas bevacizumab is typically very well tolerated.

KRAS status was unknown in 38% (434/1130) of our patient population. Of the *KRAS*-unknown patients, 62% (271/434) have not received systemic therapy and 84% (137/163) of those treated, have received only one line of therapy. This suggests that in the community setting, during the period evaluated, *KRAS* testing was generally pursued only for patients being considered for active therapy. Another significant factor contributing to incomplete *KRAS* testing in this cohort is the timing of this study, with most patients diagnosed at a time when EGFRi were only PBS reimbursed in Australia for metastatic colorectal cancer patients treated in the second and subsequent line settings. The rate of *KRAS* testing in our study is in keeping with other community based cohort studies[17]. It is anticipated that the rate of RAS

testing will increase now that EGFRi are available in the first-line and subsequent line settings and this is suggested in a recent report[22].

Historically, interventional clinical trial inclusion/exclusion criteria have selected the fittest patients for active treatment. Invariably, these clinical trials inform PBS outcomes but how applicable these results are to a non-trial population remains unclear. Reassuringly the median survival for the metastatic colorectal cancer cohort was 25 months. On the plus side the inclusion of patients with resectable metastatic disease does improve the overall outcome compared to many first-line studies where these patients would be excluded, however the CALGB 80405 study which achieved a median survival of 30 months in a RAS wild-type cohort also included 12% patients who underwent resection[10]. However, we also included many patients not fit for active therapy where survival outcomes are very poor and these bring down the overall median survival. Consistent with many other studies[24,25] the *BRAF* mutated patients in our series did poorly, with a median survival of only 14 months.

To our knowledge, this is the largest study of the utilisation of systemic chemotherapy and biological agents for metastatic colorectal cancer in a community setting in Australia to date. The results in part are influenced by drug availability on the PBS and different patterns of care would likely have been observed if all active agents were freely available from the beginning of the time period studies. Limitations to this study include the variable availability and standards for RAS testing over the analysis period. Additionally, the database did not capture treatment beyond third-line systemic therapy. Enrollment in clinic trials was also not a mandatory field, meaning the impact of research studies on drug utilisation could not be further studied.

Conclusion

This analysis of over 1000 Australian metastatic colorectal cancer patients assessed the utilisation of systemic chemotherapy and biologic agents in a community setting, largely reproducing data from elsewhere in the world. These results reinforce the difference between clinical trial patient populations and real world practice, with a high proportion of this community-based cohort of patients not receiving any active therapy. Further longitudinal follow-up of this patient population will provide more robust information regarding the true uptake of available therapeutic agents, particularly as the treatment landscape changes, for instance TAS-102 being available on the PBS since December 1st 2018.

Acronyms

- ACCORD - Australian Comprehensive Cancer Outcomes and Research Database
- CAPIRI – capecitabine and irinotecan
- CAPOX – capecitabine and oxaliplatin
- EGFRi - epidermal growth factor receptor inhibitor
- FP – fluoropyrimidine
- FOLFIRI - folinic acid, 5-fluorouracil and irinotecan
- FOLFOX - folinic acid, 5-fluorouracil and oxaliplatin
- FOLFOXIRI - folinic acid, 5-fluorouracil, oxaliplatin and irinotecan
- PBS - Pharmaceutical Benefits Scheme
- TAS-102 – trifluridine, tipiracil hydrochloride

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(iii) Figure legends

Figure 1: Lines of therapy utilised. 1A: Systemic therapy options utilised in first line. 1B: Biologics agents used in first line. 2A: Systemic therapy options utilised in second line. 2B: Biologics agents used in second line. 3A: Systemic therapy options utilised in third line. 1B: Biologics agents used in third line.

Figure 2: Overall survival (whole cohort)

Figure 3: Overall survival (by metastatectomy status)

Figure 4: Overall survival (by *KRAS* status)

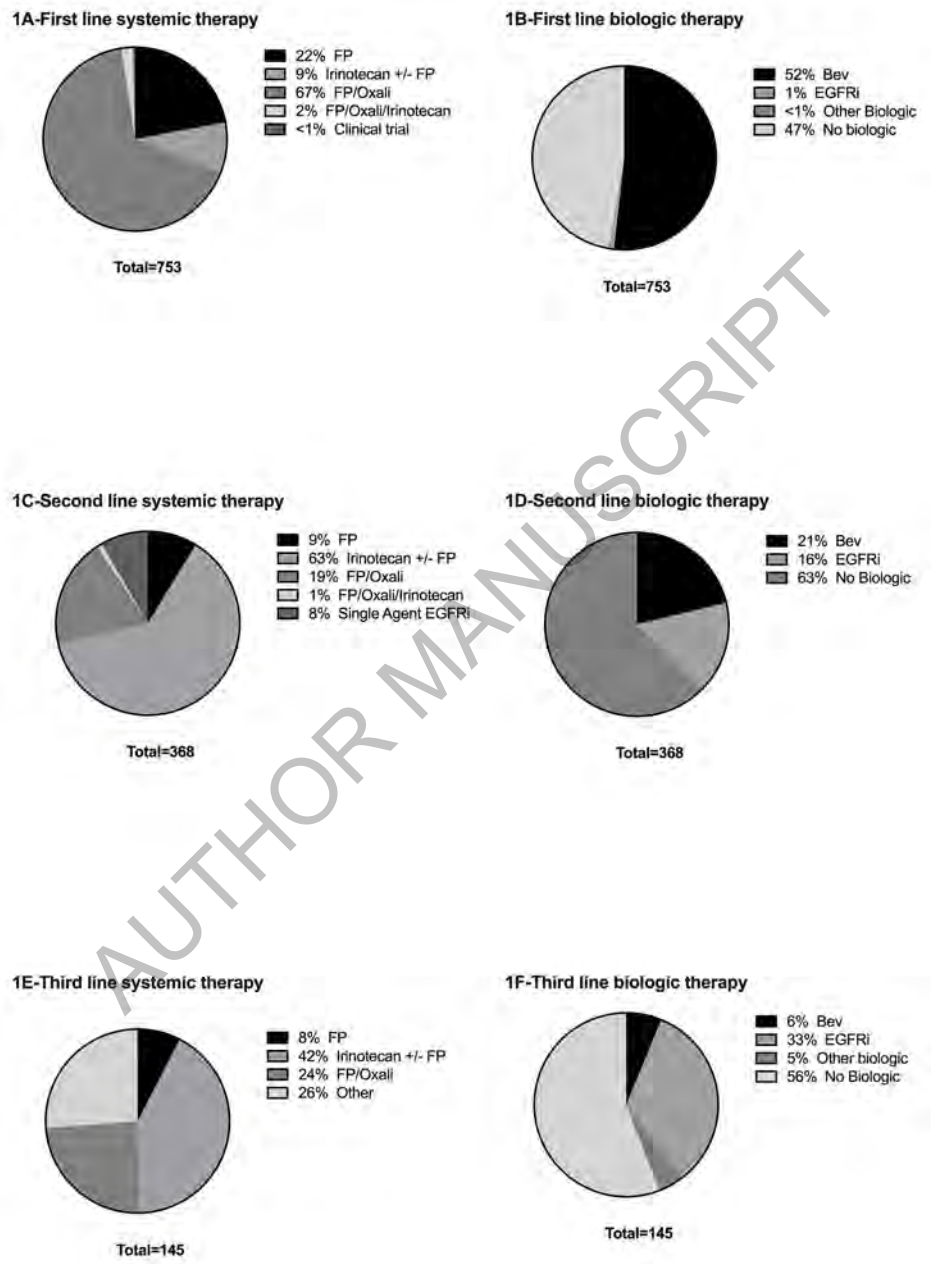
(iv)Table

Table 1: Patient and diseases characteristics

Description	All	%	Systemic therapy	%	No Systemic therapy	%
Number	1130		753	67	377	33
Age						
Median	69 years		64 years		74 years	
Range	26 - 105		26 - 89		31 - 105	
Sex						
Male	662	59	442	59	220	58
ECOG						
0-1	537	48	436	58	101	27
≥2	127	11	46	6	81	21
not documented	466	41	271	36	195	52
Sector						
Private	324	29	224	30	100	27
Public	806	71	529	70	277	73
Metastases						
Synchronous *	685	61	492	65	193	51
Liver only metastases	384	34	266	35	118	31
Lung only metastases	102	9	57	8	45	12
Other	644	57	430	57	214	57
Metastatectomy	317	28	245	33	72	19
KRAS mutation testing						
KRAS testing performed	696	62	590	78	106	28
KRAS Wild-Type	341	30	303	40	38	10
KRAS Mutated	355	31	287	38	68	18
KRAS Unknown	434	38	163	22	271	72
***BRAF* mutation testing**						
BRAF testing performed	353	27	280	37	73	19
BRAF Wild-Type	320	91	253	34	67	18

BRAF Mutated	33	9	27	4	6	2
BRAF Unknown	77	69	473	63	304	81

*Synchronous refers to the presentation of both primary and metastatic disease at diagnosis



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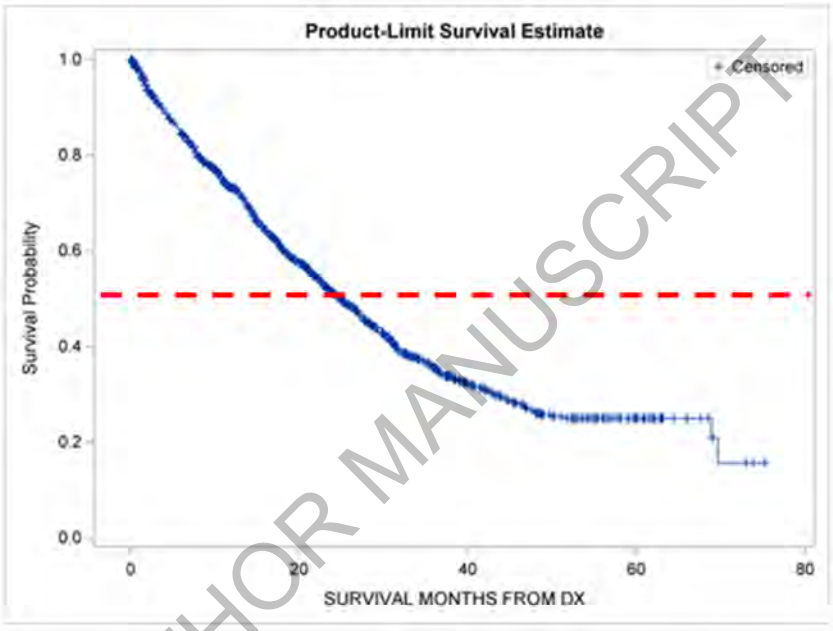

Cohort	Median overall survival
Whole	25 months

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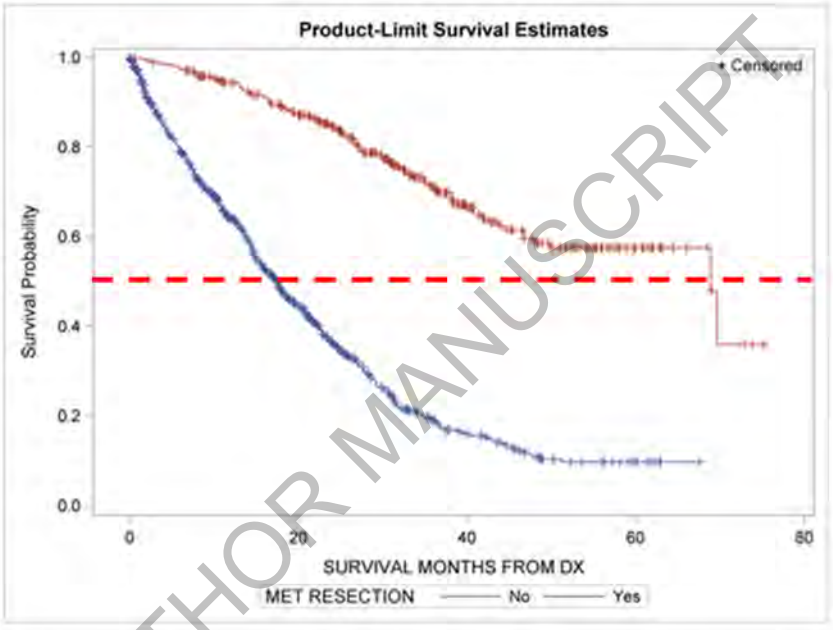
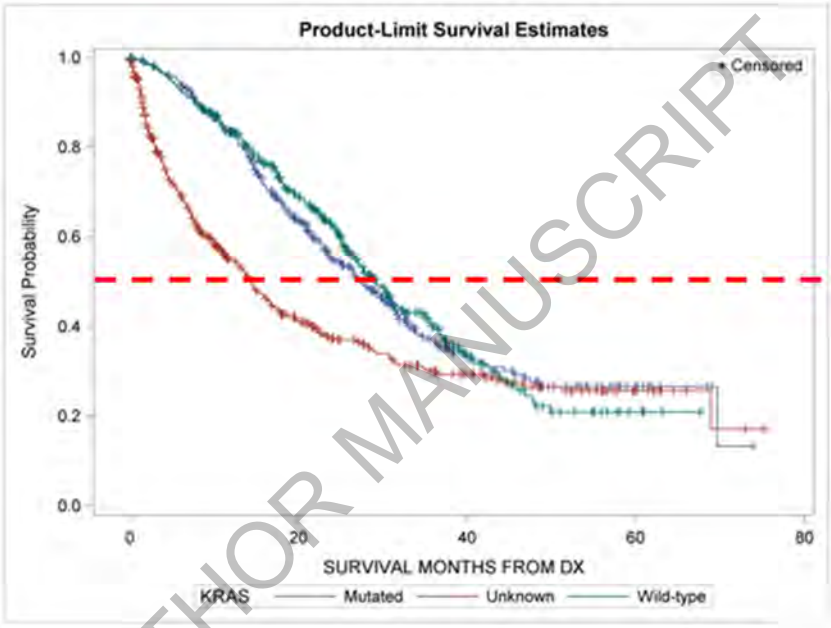


Cohort	Median overall survival
Metastatectomy performed	69 months
Nil resection	17months

IMJ_14288_Figure 3_Delahunty IMJ_2411 _Final.tif



***KRAS* status**	**Median overall survival**
Mutated	27 months
Wildtype	29 months
Unknown	15 months

IMJ_14288_Figure 4_Delahunty IMJ_2411 _Final.tif