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Metastasectomy and BRAF mutation; an analysis of survival outcome in metastatic colorectal cancer

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Abbreviations: BRAF, B-RAF mutation; dMMR, deficient mismatch repair; HR, hazard ratio; mCRC, metastatic colorectal cancer; MT, mutation; OS, overall survival; pMMR, proficient mismatch repair; RFS, recurrence-free survival; WT, wild type.

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A B S T R A C T

Background: Resection of oligometastases improves survival in metastatic colorectal cancer (mCRC). It is unclear whether the benefit is consistent for BRAF V600E mutant (MT) and wild type (WT) mCRC. This retrospective analysis explores the influence of BRAF MT on survival after metastasectomy. *Methods:* Overall survival (OS) and recurrence-free survival (RFS) for BRAF MT and WT mCRC were evaluated. Survival was also analyzed in the cohort of BRAF MT with or without metastasectomy. *Results:* Five hundred and thirteen patients who had undergone metastasectomy were identified, 6% were BRAF-MT. Median age 63. Median OS in BRAF MT vs WT: 25.7 vs 48.5 months (hazard ratio [HR] 1.95; 1.18-3.22). However, difference was not significant in a multivariate model. Right primary tumor, intact primary, >1 metastatic site, non-R0 resection, peritoneal metastasis, and synchronous metastasis were independent predictors of worse OS. Among 364 patients with RFS data there was no difference between BRAF MT and WT (16 vs 19 months, p=0.09). In another cohort of 158 BRAF-MT patients, OS was significantly better after metastasectomy compared to "no metastasectomy" (HR 0.34; 0.18-0.65, *P*= 0.001). Proficient mismatch repair status showed a trend toward worse survival after metastasectomy in BRAF MT (HR 1.71, *P*=0.08). *Conclusion:* OS did not differ after metastasectomy between BRAF MT and WT in a multivariate model. Median OS was >2 years in this study after metastasectomy among BRAFV600E MT patients suggesting a survival benefit of metastasectomy in this group where systemic therapeutic options are limited. Metastasectomy may be considered in carefully selected BRAF-MT patients.

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A R T I C L E I N F O

Keywords: Metastasectomy; Metastatic colorectal cancer; BRAF V600E mutation; Survival

Background

Metastasectomy increases the survival of patients with oligometastatic colorectal cancer. The 5-year survival rate in multiple surgical series after hepatic metastasectomy ranges from 27% to 58%.[1,2] Advances in surgical techniques and systemic therapies have improved the outcomes in the last two decades.[3] Even those who present with synchronous metastases, may be considered for curative combined resection at the same time or as a two staged procedure in conjunction with perioperative chemotherapy if suitable.[4,5] Although many patients benefit from metastasectomy, most will invariably relapse. Multiple liver metastases, extrahepatic disease, nodal status of primary tumor, elevated carcinoembryonic antigen >200 ng/ml, and positive resection margins are factors that increase the risk of recurrence.[6]

The role of metastasectomy in patients with BRAF mutation (MT) is controversial, considering the poor prognosis associated with BRAF MT and potential morbidity/mortality associated with the surgical procedures.[7,8] BRAF MT is present in about 10% of metastatic colorectal cancer (mCRC) and confer poor survival outcome. The reasons for the distinctly aggressive phenotype compared to BRAF wild type (WT) are unclear, however reports suggest they may be less responsive to traditional systemic therapy and there is a pattern of spread to poor prognostic metastatic sites like the peritoneum with less occurrence of liver-limited disease. Multi-agent combination chemotherapy such as FOLFOXIRI/bevacizumab has shown better efficacy compared to standard regimens in this subgroup.[9] Current investigations are focused on targeting driver mutations including EGFR, BRAF, and MEK.[10]

Such molecular markers play little or no role when decisions are made regarding metastasectomy with the sites of metastasis, volume of disease, performance status, and anatomical location being the critical determinants.[11] Studies looking into the impact of molecular markers are sparse, and are retrospective in nature with quite small sample size.[12] A handful of studies

report the potential benefit of metastasectomy in this cohort of patients, however, most studies report adverse outcomes (see supplementary Table A).[13-18] Increasingly providers are concerned whether metastasectomy should be avoided for BRAF mutant patients.

This study sought to explore the benefit of metastasectomy in patients with BRAF V600E MT.

Methods

This is a retrospective study of two different datasets extracted from two large Australian cancer registries. The South Australian Cancer Registry[19] is a state-wide population based registry which captures all incident cases, while the "Treatment of Recurrent and Advanced Colorectal Cancer" (TRACC) registry[20] is a federated national database with data collected from participating cancer centers in the Australian Capital Territory, Victoria and Tasmania. The latter includes patients referred to these participating cancer centers for treatment. Both data registries store data in a deidentified form and have approvals from the relevant Human Research Ethics Committees. (TRACC-201709/3, SA-20061004)

Patients with proven mCRC who were registered on either database from January 2005 to January 2017 were screened (SA-5047, TRACC-2487). The outcomes of interest were recurrence-free survival (RFS), defined as date of metastasectomy to first recurrence or progression after metastasectomy, and overall survival (OS) defined as date of first metastasectomy to the date of death. Patients who were alive and recurrence-free at the end of study were censored at last seen date.

Survival curves were constructed using the Kaplan-Meier method and the association of rate of progression with progression-free and OS was investigated using Cox proportional hazards models. The univariate association of multiple baseline characteristics were analyzed with a (2-sided) *P*value of <0.05 was considered significant. Multivariable analysis was conducted to adjust the effect those variables which were significant in the univariate analysis.

Two different analysis were undertaken on two cohorts of data

A. All patients undergone metastasectomy: Survival outcome was compared between BRAF MT and BRAF WT.
B. All patients with BRAF V600E MT: Survival outcome was compared between "metastasectomy" vs "no metastasectomy."

Results

Out of 7534 patients screened, a total of 513 patients who had undergone metastasectomy were identified. Median age was 63 and 58% were male. Six percent were BRAF MT (see Table 1). Site of primary CRC was strongly correlated with mutational status ($P=<0.001$), BRAF MT tumors were most prevalent in right side cancers, consistent with the literature. More than 50% of patients received perioperative chemotherapy. Four percent underwent metastasectomy at more than 1 organ site at diagnosis in BRAF WT compared to none in BRAF MT. Five percent of patients in BRAF WT underwent 3-4 metastasectomies during the period of follow up, while none in BRAF MT group underwent more than 2 metastasectomies. The incidence of liver metastases at diagnosis was lower in BRAF MT ($P=0.005$), while peritoneal metastases were present in 60% in BRAF MT group compared 31% in WT group ($P=0.002$). Peritonectomy was more common in BRAF MT group as well. Complete resection rate was similar in both groups.

All Patients Undergone Metastasectomy; Survival Outcome Between BRAF MT Vs BRAF WT

RFS data were only available for 364 patients from TRACC cohort. RFS was 19.4 months in BRAF WT compared to 16 months in MT which was not statistically not significant (hazard ra-

Table 1
Patient characteristics in the BRAF mutated and wild-type cohorts.

	Total N = 513 (%)	Wild type N = 483 (%)	Mutated N = 30 (%)	*P* value
Age (years)	63 (52 - 72)	63 (52 - 72)	65 (55 - 75)	0.35
Gender				0.021
Female	215(42)	196(41)	19(63)	
Male	298(58)	287(59)	11(37)	
Primary site				<0.001
Rectum	154(30)	151(31)	3(10)	
Right colon	157(31)	136(28)	21(70)	
Primary resected	438(85)	411(85)	27(90)	0.60
Metastasis				0.58
Metachronous	249(49)	236(49)	13(43)	
Synchronous	264(51)	247(51)	17(57)	
Liver metastasis	333(65)	321(66)	12(40)	0.005
Lung metastasis	128(25)	124(26)	4(13)	0.19
Peritoneal metastasis	166(32)	148(31)	18(60)	0.002
Number of organs involved				0.091
1	377(73)	359(74)	18(60)	
>1	136(27)	124(26)	12(40)	
Perioperative chemotherapy	295(58)	278(58)	17(57)	1.0

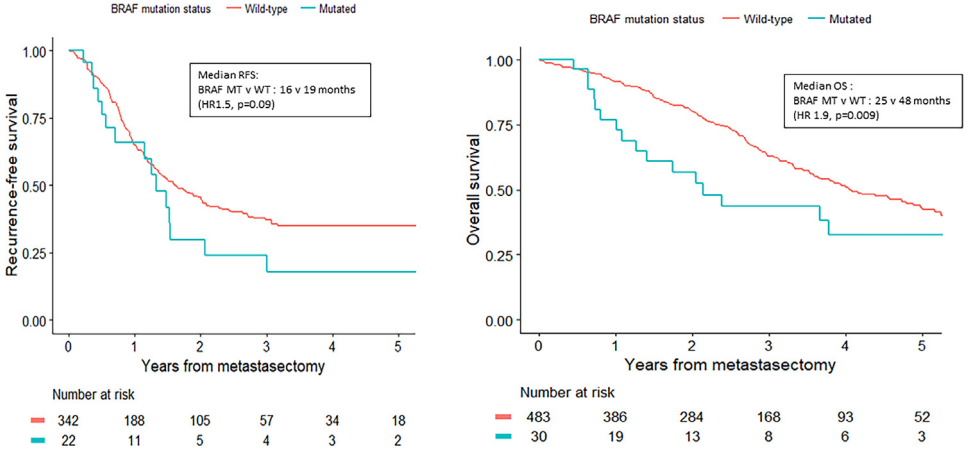

Fig. 1. Recurrence-free survival (RFS) and overall survival (OS) curves of BRAF MT and BRAF WT cohorts. RFS data were available for 346 patients. RFS difference was statistically not significant between BRAF mutant and wild-type groups. Overall survival difference was statistically significant on univariate analysis.

tio [HR] 1.541; 0.923-2.572, $P = 0.0980$; see Fig 1). On univariate analysis OS was significantly shorter in BRAF MT, 25.7 months vs 48.5 months in BRAF WT (HR 1.95; 1.18-3.22, $P = 0.009$; see Table 2).

In a multivariate model adjusting for variables which were significant on univariate analysis, OS difference was not statistically significant (HR 1.39; 0.80-2.43, $P = 0.24$). Right-sided primary tumor, rectal primary, intact primary, >1 metastatic site at diagnosis, non-R0 resection, peritoneal metastases, and synchronous metastases were independent predictors of worse OS (see Table 3). Rate of downsizing was higher with the use of triplet chemotherapy rather than doublet ± bevacizumab or doublet/anti-EGFR monoclonal (cetuximab or panitumumab) in BRAF WT (50% vs 30%) as well as MT (33% vs 11%).

Table 2
Univariate analysis of overall survival.

	No	HR	95% CI	*P* value
Primary site	513			0.013
Left colon		1.00		
Rectum		1.41	0.99 to 2.01	
Right colon		1.74	1.23 to 2.47	
Primary resected	513	0.54	0.35 to 0.81	0.003
Metastasis is synchronous/metachronous	513			0.027
Metachronous		1.00		
Synchronous		1.38	1.04 to 1.82	
Liver metastasis at metastatic diagnosis	513	0.77	0.57 to 1.03	0.077
Lung metastasis at metastatic diagnosis	513	1.28	0.94 to 1.73	0.117
Peritoneal metastasis at metastatic diagnosis	513	2.15	1.61 to 2.88	<0.001
Number of organs involved	513			<0.001
1		1.00		
>1		2.04	1.52 to 2.75	
MSI status	317			0.102
MSI-H		1.00		
MSS		2.31	0.85 to 6.29	
RAS mutation status	486			0.732
Wild type		1.00		
Mutated		1.05	0.79 to 1.40	
First metastasectomy - liver	513	0.57	0.43 to 0.75	<0.001
First metastasectomy- lung	513	0.76	0.52 to 1.13	0.182
First metastasectomy- peritoneum	513	2.67	1.96 to 3.63	<0.001
First metastasectomy number of sites	513			0.977
>1		1.00		
1		0.99	0.43 to 2.25	
Time from metastatic diagnosis to first metastasectomy (per month)	513	1.04	1.02 to 1.06	<0.001
First metastasectomy is R0	482	0.46	0.33 to 0.63	<0.001
Perioperative chemotherapy	513	0.86	0.64 to 1.14	0.282
Perioperative bevacizumab	513	1.58	1.13 to 2.21	0.007

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 3
Multivariate analysis for overall survival.

	HR	95% CI	*P* value
BRAF mutation status			0.247
Wild type	1.00		
Mutated	1.39	0.80 to 2.43	
Primary site			<0.001
Left colon	1.00		
Rectum	1.57	1.05 to 2.33	
Right colon	2.22	1.50 to 3.28	
Primary resected	0.54	0.33 to 0.88	0.014
Metastasis			0.031
Metachronous	1.00		
Synchronous	1.47	1.04 to 2.09	
Liver metastasis at metastatic diagnosis	1.29	0.87 to 1.90	0.210
Lung metastasis at metastatic diagnosis	1.38	0.94 to 2.03	0.100
Peritoneal metastasis at metastatic diagnosis	1.95	1.35 to 2.82	<0.001
Time from metastatic diagnosis to first metastasectomy (per month)	1.04	1.02 to 1.07	<0.001
First metastasectomy is R0	0.50	0.36 to 0.71	<0.001
Time from metastatic diagnosis to first metastasectomy (per month)	1.04	1.02 to 1.06	<0.001
First metastasectomy is R0	0.57	0.40 to 0.81	0.002
First metastasectomy – peritoneum	1.34	0.53 to 3.40	0.533

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4
Covariate analysis in BRAF MT population.

	Number	Median TTE	HR	95% CI	*P* value
Number of organs					0.010
>1	90	342	1.00		
1	67	690	0.57	0.38 to 0.87	
Primary resected					<0.001
No	49	303			
Yes	108	637	0.36	0.23 to 0.56	
MSI status					0.084
MSI-H	29	727	1.00		
MSS	88	516	1.71	0.93 to 3.14	
Peritoneal/Omental metastases					0.644
No	109	468			
Yes	48	384	1.10	0.72 to 1.69	

Abbreviations: CI, confidence interval; HR, hazard ratio; MT, mutation.

Patients With BRAF V600E Mutation; Survival Outcome Between "Metastasectomy" Vs "No Metastasectomy" (Among Patient With BRAF V600E)

One hundred and fifty-eight patients were identified with BRAF V600E MT, with 27 of them undergoing metastasectomy for mCRC out of which 56% had single organ involvement. Most of the metastasectomies occurred within 12 months of diagnosis (see supplementary Fig A). On a time-dependent covariate analysis, metastasectomy improved OS (HR 0.34; 0.18-0.65, $P = 0.001$). Resected primary was a significant variable associated with favorable prognosis on univariate analysis. However, when adjusted for "resected primary," the survival advantage from metastasectomy remained significant (HR 0.42, $P = 0.0002$). Due to the small numbers, it was impossible to conduct a proper multivariable analysis; hence important variables were selected and analyzed individually. When analysis was restricted to ">1 organ involvement," there was no survival advantage from metastasectomy (HR 0.86; $P = 0.7$). Similarly, survival advantage of metastasectomy was not significant (HR 0.64, $P = 0.36$) when analysis was restricted to "peritoneal/omental metastasis only" (see Table 4). MMR status was available for 117 patients with 25% showing MSI-H. Among BRAF mutant population, presence of MSS seems to be associated with poor survival outcome (HR 1.71; 0.93-3.14, $P = 0.08$), however this was not significant (see Fig 2).

Discussion

The presence of BRAF MT in metastatic CRC confers a poor prognosis, with lower responses to combination systemic anticancer therapies including EGFR inhibitors. The TRIBE study utilized a four-drug combination in the first-line setting which showed improved survival in BRAF MT cohort, however, median OS was still only 13 months in BRAF MT cohort.[9] A combination of three RAS pathway protein (BRAF, MEK, EGFR) inhibitors were used to treat BRAF MT mCRC patients in BEACON trial. Though survival improved with combined BRAF/MEK/EGFR inhibition (encorafenib, binimetinib, and cetuximab), median OS was only 9 months (second line).[10] The benefits of metastasectomy in the BRAF MT mCRC population are controversial and not well described in larger cohorts. Given the modest survival benefit despite aggressive, novel systemic therapeutic approaches, it is important to delineate the role of metastasectomy in this population. In our study, unadjusted median OS was 25.7 months in BRAF MT group which suggest a potential survival benefit of metastasectomy compared to other trials involving systemic therapy in this cohort.

The findings of our study support the aggressive biology of BRAF MT mCRC with a lower rate of metastasectomy, more than one organ involvement at diagnosis and these patients are

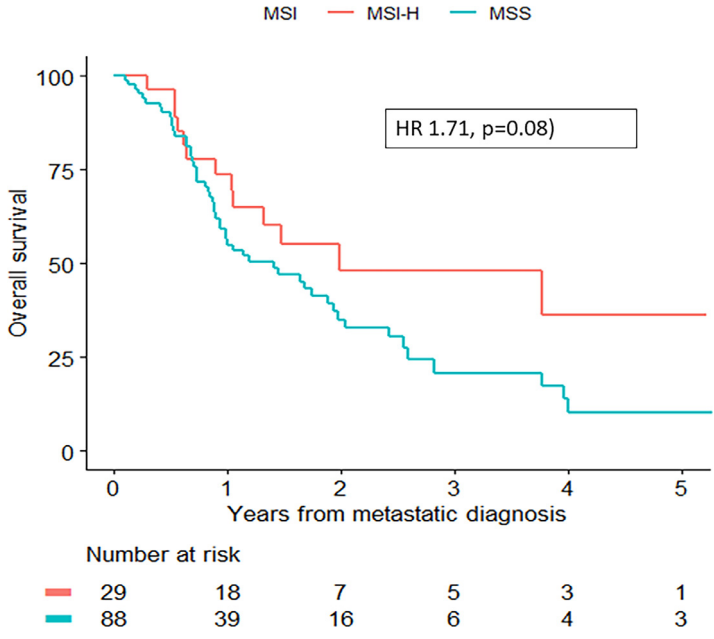

Fig. 2. Kaplan-Meier curve showing survival difference between MSI-H and MSS among patients with BRAF V600E mutation. Although, the differences were not statistically significant, there was a trend toward better survival in MSI-H group. MSI-H, microsatellite instability-high; MSS, microsatellite stable.

less likely to undergo more than 2 metastasectomies compared to BRAF WT. Survival was compared between BRAF MT and BRAF WT cohorts that had undergone metastasectomy and this demonstrated, after adjusting for key variables, that there was no difference in survival between BRAF MT and WT. Even though BRAF MT carries poor prognosis, additional factors are likely influence their survival and a subset of patients with oligometastatic disease may still benefit from metastasectomy. A cohort of patients who were classified as "potentially resectable" were identified. Triplet chemotherapy was associated with higher rates of downsizing the tumor, enabling (margin free/R0) surgical resection. Although perioperative chemotherapy did not affect the survival outcome, an early aggressive approach with triplet chemotherapy (with or without bevacizumab) may facilitate downsizing the tumor to enable resection.

Our understanding of the biology of mCRC has evolved significantly over the last decade. mCRC is no longer considered a single pathological entity. A number of studies have revealed distinct biological differences based on the site of primary and intact primary.[18,21,22] Furthermore, peritoneal metastasis, multi organ involvement and incomplete resection are reported as poor prognostic factors.[23,24] Hence, these confounding factors are likely to influence the results of many studies especially retrospective series. In this study, the documented poor prognostic factors and other factors that were significant on univariate analysis were adjusted in multivariate model, which gives more confidence in the results.

Survival was also explored among a cohort of BRAF MT patients, based on whether they underwent metastasectomy or not (method "B"). This again supported the above results (method "A") with metastasectomy improving OS (HR 0.34, $P = 0.001$). This is the largest published series of patients with BRAF MT mCRC who have undergone metastasectomy for oligometastatic disease to best of our knowledge. Another paper reported similar outcome in a small series with 52 patients.[25] Consistent with the above analysis, and literature[6,26] the number of organs involved, resected primary, and presence of peritoneal metastasis impacted survival.

Peritonectomy improves survival and is considered standard practice when feasible with the main determinant of eligibility being the peritoneal carcinoma index (PCI).[27] The peritoneum is a frequent site of metastasis in BRAF MT mCRC. In this study, survival was worse when peritoneum was involved at diagnosis (HR 2.15; $P = <0.001$) or peritoneum was the first site of metastasectomy (HR 2.67; $P = <0.001$). Despite loss of statistical significance in the multivariate model, HR was 1.34 favoring poor survival for those underwent peritonectomy. The second analysis also showed lack of survival benefit after peritonectomy in BRAF MT patients. Despite this, a subset of patients with dMMR cancer seems to derive modest benefit after peritonectomy, though this did not reach statistical significance in univariate analysis, possibly due to small numbers. A recent Norwegian study also suggested better survival after peritonectomy and hyperthermic intraperitoneal chemotherapy in those with BRAF MT/ dMMR.[28] Although our study shows a potential subgroup of BRAF MT patients who may benefit from metastasectomy, larger studies are needed to validate this result.

This study has several limitations. First, a small sample size makes it difficult to draw firm conclusions from the results. There are also biases that affect retrospective studies, particularly selection bias. The strength of this study was a relatively larger sample size from multiple institutions compared to most of the studies in the literature. Furthermore, statistical analysis was extensive and utilized number of important confounders in the multivariable model which provide more confidence in the results. However, there remains a risk of adjusting potential mediators that are responsible for the BRAF MT effect which could attenuate the differences between the two groups.

Overall, this study demonstrates, despite poor prognosis, a subset of patients with BRAF MT may derive survival benefit from metastasectomy. Left colon primary, resected primary, single organ involvement, metachronous metastasis, and absence of peritoneal metastases (and probably dMMR status) were associated with a favorable outcome. Given the lack of effective systemic therapeutic options, a multidisciplinary approach is recommended to identify patients who are likely to benefit from metastasectomy which may also avoid futile surgery which carries morbidity and mortality.

Authors' Contribution

TP, DY, CK, and PG: conceptualization. MS and TP: formal analysis. TP: writing-original draft. All other authors listed have made substantial, direct, and intellectual contribution in data curation, methodology, writing-review, and editing. All authors have viewed the final manuscript and agreed for submission.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100637.

References

1. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239:818–825 discussion 25-7.

2. Jamison RL, Donohue JH, Nagorney DM, Rosen CB, Harmsen WS, Ilstrup DM. Hepatic resection for metastatic colorectal cancer results in cure for some patients. *Arch Surg*. 1997;132:505–510 discussion 11.
3. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol*. 2009;27:3677–3683. doi:10.1200/JCO.2008.20.5278.
4. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol*. 2007;14:3481–3491. doi:10.1245/s10434-007-9522-5.
5. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg*.. 2010;210:934–941. doi:10.1016/j.jamcollsurg.2010.02.039.
6. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol*. 1997;15:938–946. doi:10.1200/JCO.1997.15.3.938.
7. Ubink I, Jongen JMJ, Nijkamp MW, et al. Surgical and oncologic outcomes after major liver surgery and extended hemihepatectomy for colorectal liver metastases. *Clin Colorectal Cancer*. 2016;15:e193–e198. doi:10.1016/j.clcc.2016.04.006.
8. Grat M, Holowko W, Lewandowski Z, et al. Early post-operative prediction of morbidity and mortality after a major liver resection for colorectal metastases. *HPB (Oxford)*. 2013;15:352–358. doi:10.1111/j.1477-2574.2012.00596.x.
9. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306–1315. doi:10.1016/S1470-2045(15)00122-9.
10. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N Engl J Med*. 2019;381:1632–1643. doi:10.1056/NEJMoa1908075.
11. Berri RN, Abdalla EK. Curable metastatic colorectal cancer: recommended paradigms. *Curr Oncol Rep*. 2009;11:200–208.
12. Tosi F, Magni E, Amatu A, et al. Effect of KRAS and BRAF mutations on survival of metastatic colorectal cancer after liver resection: a systematic review and meta-analysis. *Clin Colorectal Cancer*. 2017. doi:10.1016/j.clcc.2017.01.004.
13. Yaeger R, Cowell E, Chou JF, et al. RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer. *Cancer*. 2015;121:1195–1203. doi:10.1002/cncr.29196.
14. Teng H-W, Huang Y-C, Lin J-K, et al. BRAF mutation is a prognostic biomarker for colorectal liver metastasectomy. *J Surg Oncol*. 2012;106:123–129. doi:10.1002/jso.23063.
15. Umeda Y, Nagasaka T, Mori Y, et al. Poor prognosis of KRAS or BRAF mutant colorectal liver metastasis without microsatellite instability. *J Hepato-Biliary-Pancreatic Sci*. 2013;20:223–233. doi:10.1007/s00534-012-0531-9.
16. Karagkounis G, Torbenson MS, Daniel HD, et al. Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. *Cancer*. 2013;119:4137–4144. doi:10.1002/cncr.28347.
17. Bachet J-B, Moreno-Lopez N, Vigano L, et al. BRAF mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases. *BJS (Br J Surg)*. 2019;106:1237–1247. doi:10.1002/bjs.11180.
18. Prasanna T, Karapetis CS, Roder D, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. *Acta Oncol*. 2018;57:1438–1444. doi:10.1080/0284186X.2018.1487581.
19. Neo EL, Beeke C, Price T, et al. South Australian clinical registry for metastatic colorectal cancer. *ANZ J Surg*. 2011;81:352–357. doi:10.1111/j.1445-2197.2010.05589.x.
20. Field K, Wong HL, Shapiro J, et al. Developing a national database for metastatic colorectal cancer management: perspectives and challenges. *Intern Med J*. 2013;43:1224–1231. doi:10.1111/imj.12230.
21. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016. doi:10.1001/jamaoncol.2016.4227.
22. Venook AP. *ASCO Annual Meeting*. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance); 2016.
23. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2011;18:1380–1388. doi:10.1245/s10434-010-1459-4.
24. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. *Ann Surg*. 2006;243:212–222. doi:10.1097/01.sla.0000197702.46394.16.
25. Johnson B, Jin Z, Truty MJ, et al. Impact of metastasectomy in the multimodality approach for braf v600e metastatic colorectal cancer: the Mayo Clinic experience. *Oncologist*. 2018;23:128–134. doi:10.1634/theoncologist.2017-0230.
26. Schirripa M, Bergamo F, Cremolini C, et al. BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. *Br J Cancer*. 2015;112:1921–1928. doi:10.1038/bjc.2015.142.
27. Burnett A, Lecompte M-EA, Trabulsi N, et al. Peritoneal carcinomatosis index predicts survival in colorectal patients undergoing HIPEC using oxaliplatin: a retrospective single-arm cohort study. *World J Surg Oncol*. 2019;17:83. doi:10.1186/s12957-019-1618-4.
28. Larsen SG, Dueland S, Goscinski M, et al. Survival according to mutations in BRAF, KRAS, or microsatellite instability (MSI-H) after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases from colorectal cancer. *J Clin Oncol*. 2019;37(15_suppl):3565. doi:10.1200/JCO.2019.37.15_suppl.3565.