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Original Article

Prognostic impact of *KRAS* and *BRAF* mutations in patients who underwent simultaneous resection for initially resectable colorectal liver metastases

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Abstract: This study aimed to explore the prognostic impact of *KRAS* and *BRAF* mutations in patients who underwent simultaneous resection for synchronous colorectal liver metastases (SCRLMs) that were initially resectable. Clinicopathological and outcome data of 139 consecutive patients with SCRLMs who underwent resection between July 2003 and July 2013 was collected from our prospectively established SCRLM database. The *KRAS* and *BRAF* genotypes were evaluated in the primary cancer tissues by pyrosequencing. The prognostic value of *KRAS* and *BRAF* status was assessed by Kaplan-Meier and Cox regression analyses. *KRAS* and *BRAF* mutated in 28.8% and 7.2% of the patients with SCRLMs, respectively, but the genotypes did not significantly associate with any clinicopathologic characteristics. By Kaplan-Meier survival analysis, we found *KRAS* mutation was not significantly associated with short overall survival (OS) (P = 0.213), but was significantly correlated with short disease-free survival (DFS) (P = 0.041); *BRAF* mutation was significantly associated with both short OS and DFS (P = 0.001, P<0.001, respectively). Multivariate survival analysis showed *KRAS* mutation was an independent negative prognostic factor for DFS (P = 0.005) and *BRAF* mutation was an independent negative prognostic factor for OS and DFS (P = 0.001, P<0.001, respectively). *KRAS* and *BRAF* mutation similarly contributed to an adverse prognostic effect in patients who underwent simultaneous resection for SCRLMs that were initially resectable. These findings should suggest the use of *KRAS* and *BRAF* status in current practice as an important determinant for precision surgery for initially resectable SCRLMs.

Keywords: Synchronous colorectal liver metastases, simultaneous resection, *KRAS*, *BRAF*, prognosis

Introduction

Even in the United States of America, colorectal cancer (CRC) is the third highest incidence cancer diagnosed and the third leading cause of cancer mortality in both men and women [1]. Approximately 25% of CRC patients will present with synchronous colorectal liver metastases (SCRLMs) at the initial diagnosis, and 25~50% of CRC will progress with metachronous colorectal liver metastases (MCRLMs) when the disease has a recurrence [2]. Improvements in surgical and non-surgical techniques and skill have greatly increased the proportion of CRC patients eligible for curative resection of colorectal liver metastases (CRLMs) [3], and about 25~50% of CRC patients with surgically resected CRLMs have a survival 5 or more years [4-6]. However, more than 50% patients will endure rapid recurrence within 2 years and consequently may not acquire long survival from resection [7-9].

The high frequency of clinical and biological heterogeneity in metastatic CRC [10] highlights the necessity to accurately risk-stratify to contribute to surgery determination. The reported clinical risk scores (CRS) system applying standard pathologic and clinical characteristics comprising the number and size of CRLMs, disease-free interval until liver metastasis, carcinoembryonic antigen (CEA) level, primary tumor stage, SCRLMs or MCRLMs has failed to precisely predict the risk of recurrence and metastasis after resection, and ultimately aids in the selection of patients who may authentically benefit from surgery; also the CRS lacks prognostic precision in contemporary chemothera-

py [11-13]. To date, there are not any molecular predictors comprised in the clinical setting that can indicate such biological heterogeneity.

Presently, studies on metastatic CRC have intensively focused on mutations in two proto-oncogenes, *KRAS* and *BRAF*, that take effect downstream of the epidermal growth factor receptor (EGFR) signaling pathway, and function in the initiation and progression of CRC [14, 15]. *KRAS* isa member of the *RAS* family of genes (*KRAS*, *NRAS*, and *HRAS*) that encode guanosine-5'-triphosphate (GTP)-binding proteins. KRAS is a very important ligand binding to EGFR that acts primarily, but not exclusively, through the signal pathway of BRAF and the MAPK axis. KRAS can also activate PI3K by interaction with its catalytic subunit, directly. About 32~40% of metastatic CRC have a *KRAS* mutation and approximately 85~90% of these mutations take place in codons 12 or 13. The other mutations occur in codons 61 (5%) and 146 (5%) [14]. Mutated *KRAS* is concordantly considered to be a indicator of resistance to EGFR monoclonal antibodies [14-17]. Presently, *KRAS* mutation was found to be a predictor for worse morphologic and pathologic response to chemotherapy, or monoclonal antibodies [18].

BRAF, belongs to the *RAF* gene family (*BRAF*, *ARAF1*, and *RAF1*), encodes a serine-threonine protein kinase, and is a downstream effector of *KRAS* activation. *BRAF* mutations occur in V600E most frequently in more than 95% tumors within the kinase activation domain of the BRAF protein. The signaling path changes that result from the V600E mutation are still not clear. A study demonstrated an increase in MAPK1/3 activation that results from *KRAS* mutation, because BRAF acts as downstream of KRAS to MAP2K activation. The mutation of V600E might have additional functions [14]. Approximately 10~15% metastatic CRC harbor the mutations of *BRAF* [14, 19]. Some studies have demonstrated that *BRAF* mutation has a prognostic role rather than a predictive role, for patients with metastatic CRC who do not receive cetuximab also have a poor survival when their tumors harbor the mutation of *BRAF* [20, 21].

Recently, mutations in *KRAS* and *BRAF* genes have received some attention as the most promising mutations for prognostication in patients undergoing resection of CRLMs [11, 18, 22]. However, no studies have examined the factors that influence long-term outcome in patients exclusively undergoing simultaneous resection about SCRLMs. Furthermore, nearly all of the patients included in these studies were initially determined to be unresectable. The purpose of our study was to determine the incidence and prognostic impact of *KRAS* and *BRAF* mutations in patients with SCRLMs who underwent simultaneous R0 resection for tumors that were initially resectable.

Materials and methods

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. It was approved by the institutional review board of Zhongshan Hospital. Informed consent was obtained from all individual participants who were included in the study.

Study population

We reviewed our prospectively collected SCRLM database between July 2003 and July 2013. In our center, all the SCRLM patients are discussed by a multidisciplinary team (MDT) that includes colorectal and liver surgeons, oncologists, radiologists and physicians in the related fields. Patients were evaluated preoperatively applying hepatic B-ultrasound, contrast-enhanced chest, abdominal and pelvic computed tomography, and/or liver magnetic resonance imaging; positron emission tomography was utilized in selected cases. The ultimate decisions with regard to the decision of perioperative chemotherapy and type of liver resection were made by the MDT, patients, and the patient's relatives on a consensus. The criteria of selection established by the MDT for simultaneous resection have been published presently and are as follows [23]: the primary tumors are to be radically resected, liver metastases (LMs) are to be margin-negative resected (R0), and leave an adequate predicted volume of hepatic remnant post resection. Patients with extrahepatic metastases or who had targeted therapy at any time were excluded from this study. Patients who experienced perioperative death or had incomplete data were also excluded. All the patients included in the study underwent

Table 1. Correlation between the clinicopathological characteristics of the patients and the status of *KRAS* and *BRAF*

Variables	Patients		*KRAS* status			*BRAF* status		
	No.	%	Wild-type	Mutated	*P* value	Wild-type	Mutated	*P* value
	139	100	99	40		129	10	
Age (years)					0.351			0.495
≤60	89	64.0	61	28		84	5	
>60	50	36.0	38	12		45	5	
Gender					0.906			0.521
Male	81	58.3	58	23		74	7	
Female	58	41.7	41	17		55	3	
Tumor location					0.208			0.066
Colon	97	69.8	66	31		93	4	
Rectum	42	30.2	33	9		36	6	
Histological type					0.392			1.000
Adenocarcinoma	117	84.2	85	32		108	9	
Mucinous adenocarcinoma	22	15.8	14	8		21	1	
Tumor differentiation					0.310			0.515
Well, Moderate	74	53.2	50	24		70	4	
Poor and Others	65	46.8	49	16		59	6	
Primary tumor (T) stage					0.354			1.000
T1, T2	6	4.3	3	3		6	0	
T3, T4	133	95.7	96	37		123	10	
Primary nodal (N) stage					0.385			1.000
Absent	53	38.1	40	13		49	4	
Present	86	61.9	59	27		80	6	
Vascular invasion					0.925			0.690
Absent	114	82.0	81	33		105	9	
Present	25	18.0	18	7		24	1	
Nerve invasion					0.257			0.352
Absent	122	87.8	89	33		114	8	
Present	17	12.2	10	7		15	2	
No. of metastases					0.350			0.064
≤3	125	89.9	87	38		118	7	
≥4	14	10.1	12	2		11	3	
Largest metastasis					0.926			1.000
<5 cm	100	71.2	71	29		93	7	
≥5 cm	39	28.8	28	11		36	3	
CEA					0.252			0.501
≤5 ng/ml	44	31.7	34	10		42	2	
>5 ng/ml	93	68.3	63	30		85	8	

simultaneous radical resection for primary tumors and R0 resection for liver metastases, would be confirmed by the postoperative pathology.

Detection of mutations

We selected samples of the primary lesions carefully from the SCRLM patients that had been fixed with formalin and embedded in paraffin, before. Then extracted the DNA utilized a GT pure FFPE DNA Extraction Kit (®Gene Tech, Shanghai, China, Ltd). *KRAS* codons 12, 13, 61 and 146 and *BRAF* codon 600 were assessed together by the means of pyrosequencing, the details of the performance have been previously reported (Biotage Swedish AB company production) [15, 24].

Data collection

Clinicopathological data of these patients was collected from our prospectively established SCRLMs database. The timing of the perioperative chemotherapy regimen was also recorded. The follow-up surveillance including routine blood analysis, B-ultrasound, computed tomography of the chest, abdomen, and pelvis and regular colonoscopy were performed according the guidelines. Disease recurrence or metastasis was recorded on the findings of clinical, radiological and endoscopic results at the time of diagnosis. The time of the last follow-up, the vital status and recurrence or metastasis were recorded in detail for all patients. The overall survival (OS) was measured from the date of definite diagnosis until either the date of death because of CRC or until the ultimate follow-up time point. The disease-free survival (DFS) was calculated from the date of resection until the time of documented disease recurrence or metastasis.

Statistical analysis

All the summary statistics were acquired by established methods and were all presented as percentages or mean values with standard deviations. The categorical data was summarized as percentages and were analyzed by test of chi-squared analysis or Fisher's exact. The OS and DFS were analyzed with the method of Kaplan-Meier; survival curves were compared by the of log-rank. Univariate and multivariate analyses were performed by the model of Cox proportional hazards, and prognostic factors with $P<0.10$ in the univariate analysis were all entered into the Cox proportional hazards model utilizing stepwise selection for identifying independent predictors. All the statistical analyses was performed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Two-sided *P*-values were calculated, and $P<0.05$ was considered to be significant.

Results

Clinicopathological characteristics of the patients

From July 2003 to July 2013, we identified 139 patients who underwent simultaneous resection of SCRLMs. Detailed clinicopathological data of the 139 patients are shown in **Table 1**. We found majority of patients were male (58.3%) and younger than 60.0 years (64.0%). Most patients presented with a primary tumor in the colon (69.8%). The average number of metastases was 1.85 ± 1.14 (1.0-7.0), and the average size of the largest metastatic lesion was 3.79 ± 2.32 cm (range, 0.5 cm-15 cm).

Operative details and perioperative chemotherapy

With respect to resection for the primary tumors, 38.1% (53/139) of patients underwent right hemicolectomy, 33.1% (46/139) of patients underwent left hemicolectomy, and 28.8% (40/139) of patients underwent rectectomy. With respect to liver surgery, 79.1% (110/139) underwent wedge resection, 16.5% (23/139) underwent hemihepatectomy, 1.4% (2/139) underwent extended hepatectomy, and 2.9% (4/139) underwent a hepatic resection of unknown extent. In terms of complications, a total of 30.2% (42/139) patients experienced 54 total complications as follows: ascites (10), subphrenic fluid (8), pleural effusion (7), wound infection and fat liquefaction (6), small bowel obstruction (5), pneumonia and atelectasis (4), intra-abdominal infection (3), hemorrhage/hematoma (3), transient hepatic dysfunction (2), bile leakage (2), intestinal leakage (2) and others (2). All of the complications were non-surgical treated either medically or by the means of percutaneous drainage, successfully. With regard to adjuvant treatment, a total of 23.0% (32/139) patients accepted preoperative chemotherapy, and all the patients accepted postoperative chemotherapy. FOLFOX, FOLFIRI and XELOX were most routinely used chemotherapy regimens.

Mutations in KRAS and BRAF

Among the 139 tumor samples that were examined, *KRAS* mutations were observed in 40 (28.8%) samples via direct sequencing; 22.3% (31/139) of the mutations were detected at codon 12 and 6.5% (9/139) of the mutations were found at codon 13. Various clinicopathologic factors were evaluated together with the *KRAS* status, but no significant correlation was found between the clinicopathologic characteristics and the specific types of mutations (**Table 1**). The V600E mutation in *BRAF* was observed in 7.2% (10/139) of the patients. Various clinicopathologic characteristics were evaluated

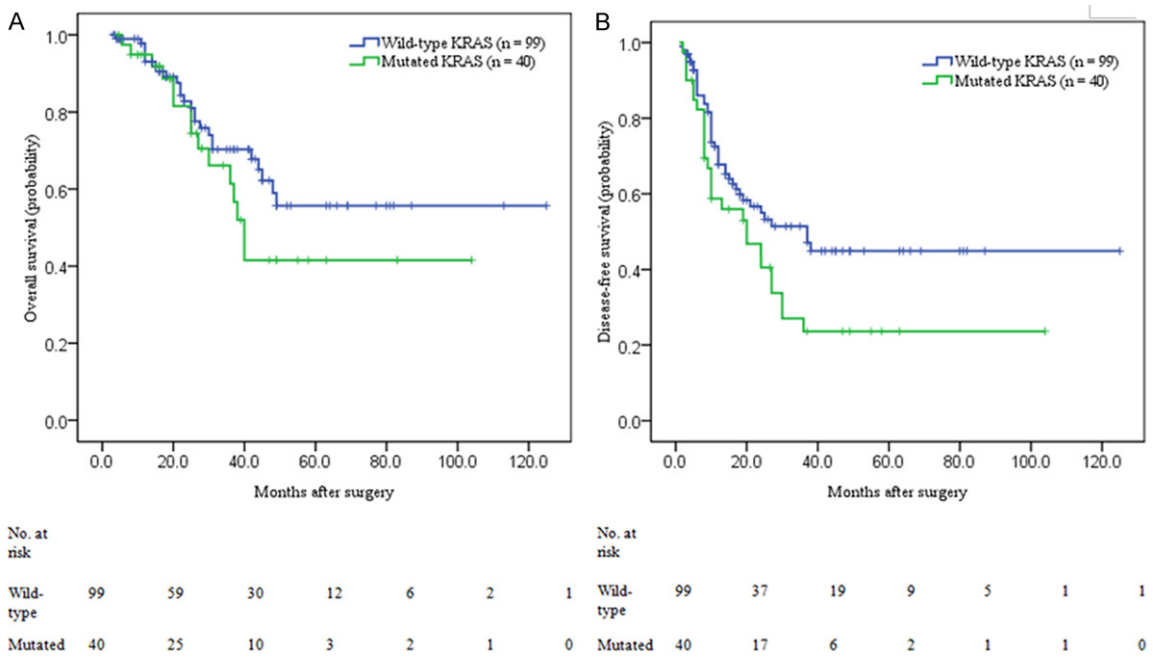

Figure 1. Analyses of overall survival and disease-free survival according to status of *KRAS* in patients with SCRLMs. A. Kaplan-Meier analyses of the overall survival of the patients with SCRLMs according to status of *KRAS* (n = 139; *P* = 0.213). B. Kaplan-Meier analyses of disease-free survival in patients with SCRLMs according to the status of *KRAS* (n = 139; *P* = 0.041).

together with the *BRAF* status, and no significant correlation was found between clinicopathologic characteristics and specific types of mutations (**Table 1**).

Overall survival analysis

The 5-year OS rate was 50.0%. The median follow-up period was 36.6 months. At the ultimate follow-up time point, 28.8% (40/139) patients had died, 49.6% (69/139) patients experienced tumor recurrence or metastasis, 35.3% (49/139) had recurrence in the liver only, 6.5% (9/139) had metastasis in the lung only and 8.6% (12/139) had recurrence in other sites.

To evaluate the prognostic value of *KRAS* and *BRAF* in patients with SCRLMs, we analyzed the OS relative to the status of *KRAS* and *BRAF* with a Kaplan-Meier survival analysis. The result of Kaplan-Meier survival analysis demonstrated that the OS of patients with SCRLMs who had a mutated *KRAS* was not significantly poorer than those with wild-type *KRAS* (P = 0.213; **Figure 1A**). However, the OS of patients with mutated *BRAF* was significantly poorer than those with wild-type *BRAF* (P = 0.001; **Figure 1B**).

To investigate the clinical significance of the various prognostic factors that might had an impact on survival in the study population, a univariate analysis was done for OS in 139 patients with CRC using the model of Cox proportional hazards. The following factors were significantly correlated with poorer OS: positive lymph node status, vascular invasion, nerve invasion, *BRAF* mutations in the primary tumor and the number of metastases (≥4) in the liver. The prognostic factors with P<0.10 in the univariate analysis were all entered into the Cox proportional hazards model utilizing stepwise selection to identify independent predictors. The results demonstrated that positive lymph node status (*P* = 0.001), vascular invasion (*P*<0.001), number of LMs (*P* = 0.047) and *BRAF* mutations (*P* = 0.001) were significantly correlated with poorer prognosis. The results of the univariate and multivariate analyses are shown in **Table 2**.

Disease-free survival analysis

The 5-year DFS of the 139 patients with CRLM was 36.0%. We also evaluated the DFS relative to the status of *KRAS* and *BRAF* by the means of Kaplan-Meier survival analysis. The result of

Table 2. Univariate and multivariate analyses of the associations between overall survival and the clinicopathologic characteristics of the patients who underwent simultaneous R0 resection of SCRLMs

Prognostic factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (>60:≤60)	0.652	0.331-1.282	0.215			
Sex (Female:Male)	1.525	0.819-2.841	0.184			
Primary tumor site (Rectum:Colon)	1.364	0.718-2.590	0.344			
Histological type (Mucinous adenocarcinoma:Adenocarcinoma)	0.847	0.331-2.165	0.729			
Tumor differentiation (Well, moderate:Poor and Others)	1.638	0.872-3.080	0.125			
Primary tumor (T) stage (T3, T4:T1, T2)	2.469	0.339-17.993	0.373			
Primary nodal (N) stage (N1, N2:N0)	3.468	1.532-7.854	0.003	4.359	1.890-10.050	0.001
Vascular invasion (Positive:Negative)	2.721	1.349-5.487	0.005	4.220	1.957-9.101	<0.001
Nerve invasion (Positive:Negative)	2.618	1.084-6.320	0.032	1.305	0.498-3.424	0.588
No. of LMs (≥4:≤3)	2.356	0.984-5.643	0.054	2.569	1.012-6.518	0.047
Size of LM (≥5 cm:<5 cm)	1.409	0.714-2.779	0.323			
CEA (>5 ng/ml:>5 ng/ml)	1.873	0.888-3.950	0.099	1.559	0.732-3.320	0.249
Chemotherapy (Postoperative:Perioperative)	1.145	0.569-2.304	0.704			
KRAS status (Mutated:Wild type)	1.495	0.788-2.838	0.219			
BRAF status (Mutated:Wild type)	3.782	1.657-8.631	0.002	4.244	1.772-10.165	0.001

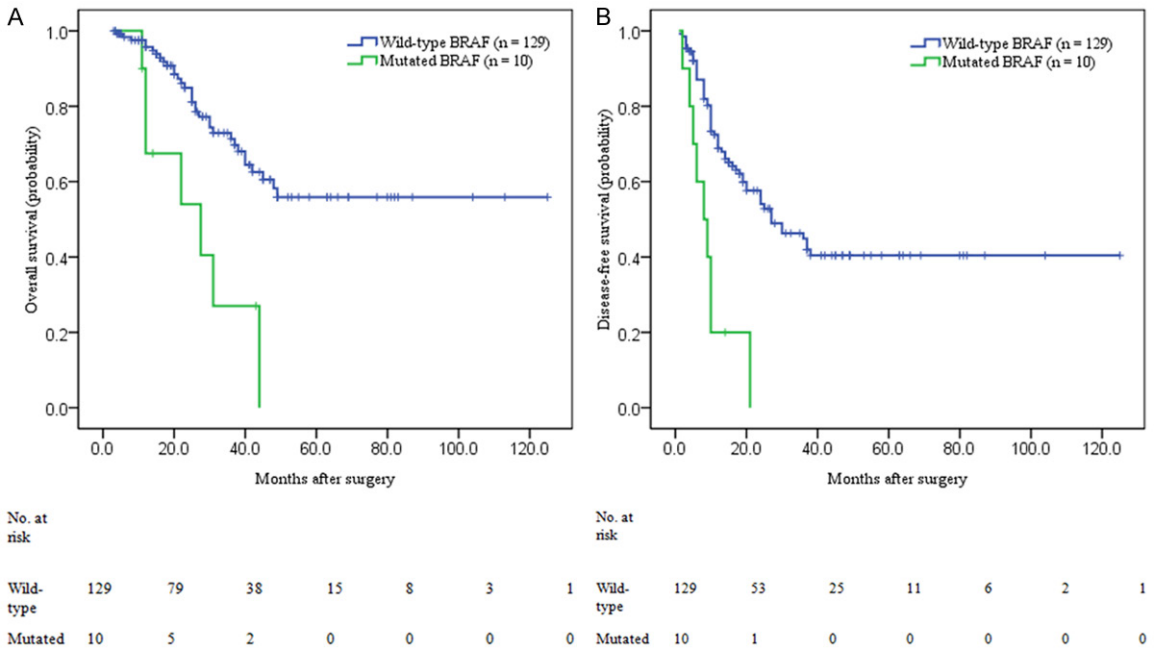

Figure 2. Analyses of overall survival and disease-free survival according to the status of *BRAF* in patients with SCRLMs. A. Kaplan-Meier analyses of overall survival of patients with SCRLMs according to the status of *BRAF* (n = 139; *P* = 0.001). B. Kaplan-Meier analyses of disease-free survival of the patients with SCRLMs according to status of *BRAF* (n = 139; P<0.001).

Kaplan-Meier survival analysis demonstrated that the DFS of patients with SCRLMs with mutated *KRAS* was significantly poorer than those with wild type *KRAS* (P = 0.041; **Figure 2A**); similarly, the DFS of patients with mutated *BRAF* was also significantly poorer than those with wild type *BRAF* (P<0.001; **Figure 2B**).

By univariate analysis, we found that the number of LMs (≥4) as well as mutated *KRAS* and *BRAF* were significantly correlated with a shorter DFS. Then, the prognostic factors with *P*<0.10 in the univariate analysis were all entered into the Cox proportional hazards model utilizing stepwise selection to identify

Table 3. Univariate and multivariate analyses of the associations between disease-free survival and clinicopathologic characteristics of patients who underwent simultaneous R0 resection of SCRLMs

Prognostic factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (>60:≤60)	0.711	0.429-1.178	0.186			
Sex (Female:Male)	1.573	0.983-2.519	0.059	1.226	0.737-2.040	0.432
Primary tumor site (Rectum:Colon)	1.369	0.839-2.232	0.208			
Histological type (Mucinous adenocarcinoma:Adenocarcinoma)	0.650	0.311-1.358	0.252			
Tumor differentiation (Well, moderate:Poor and Others)	1.525	0.947-2.456	0.083	1.424	0.871-2.327	0.158
Primary tumor (T) stage (T3, T4:T1, T2)	1.476	0.463-4.700	0.510			
Primary nodal (N) stage (N1, N2:N0)	1.596	0.962-2.647	0.070	1.727	1.037-2.877	0.036
Vascular invasion (Positive:Negative)	1.572	0.874-2.826	0.131			
Nerve invasion (Positive:Negative)	1.535	0.759-3.103	0.233			
No. of LMs (≥4:≤3)	2.109	1.075-4.139	0.030	2.172	1.030-4.578	0.042
Size of LM (≥5 cm:<5 cm)	1.361	0.820-2.260	0.233			
CEA (>5 ng/ml:>5 ng/ml)	1.380	0.827-2.304	0.218			
Chemotherapy (Postoperative:Perioperative)	1.128	0.656-1.937	0.664			
KRAS status (Mutated:Wild type)	1.628	1.005-2.636	0.048	2.094	1.249-3.510	0.005
BRAF status (Mutated:Wild type)	4.004	1.947-8.238	<0.001	4.525	2.053-9.976	<0.001

the independent predictors. The results demonstrated that positive lymph node status (P = 0.036), the number of LMs (≥4) (*P* = 0.042) and mutated *KRAS* (*P* = 0.005) and *BRAF* (*P*<0.001) were significantly correlated with a shorter DFS. The results of the univariate and multivariate analyses are shown in **Table 3** in detail.

Discussion

It has been demonstrated by many studies, including meta-analyses, that the timing of hepatectomy for patients with SCRLMs, simultaneous resections are not accompanied with increased rates of complications in the liver or colon compared with two-staged resection [25-27]. Furthermore, the long-term OS and DFS are not significantly different between the simultaneous and two-stage resection groups [4, 25]. Regardless of choice of the resection style, even the resection of LMs resulted in a possibility of cure, the majority of resected patients will unavoidable experience recurrence or metastasis within 5 years [28, 29]. The different outcomes were due to the heterogeneity of the tumor itself and the tumor environment [30-32]. The heterogeneity at genetic and molecular level presents different clinical courses, and so have different prognoses. Therefore, an investigation of the molecular mechanisms behind the metastatic CRC and identification of significant biomarkers, especially those with clinical prognostic value and early diagnosis may help oncologists select the optimal therapeutic regimen (including the style of resection) and appropriate surveillance program for patients with CRC.

KRAS and *BRAF* mutations have proven to be a very useful tool (maybe a gold standard) for the prediction of tumor response rate to targeted therapies in CRC [14-16, 20, 21, 33, 34]. In contrast, the prognostic implications of *KRAS* and *BRAF* mutations are less defined. Mutations are usually associated with a worse cell biology and a more aggressive metastatic behavior resulting in a propensity for early recurrences and metastasis after resection of metastatic tumors except their ability to predict sensitivity to monoclonal antibodies. Our study investigated these two biomarkers in patients with SCRLMs who underwent simultaneous R0 resection and whose tumors were initially resectable. The results demonstrated that *KRAS* mutations were observed in 28.8% of cases of SCRLMs, which was a little lower than the percentage found in previous studies of large sample cohorts; frequencies in the range of 29-45% were reported in those studies [11, 14, 15, 35, 36]. Our results showed that *BRAF* mutations were observed in 7.2% of patients with SCRLMs, and this observation was in agreement with previous studies of large sample cohorts that reported frequencies of mutation in the range of 1-15% [14-16, 34, 35, 37], and was higher than those recently reported in a systematic review and meta-analysis about 2-4% [36], likely due to the selection bias of

patients (all are SCRLMs included in our study). Indeed, owning to their peculiar metastatic spread, patients with *BRAF*-mutated tumors usually have advanced disease, rarely suitable candidates for liver surgery. None of the patients in our study harbored mutations in both *KRAS* and *BRAF*, which is a similar result to that in the above reports of metastatic CRC.

Some studies found that *RAS* (including *KRAS*) mutation was associated with right-side primary tumors [35, 38, 39], lung metastasis [38, 40], lymph node metastasis [41], positive hepatic margins [42] and radiologic and pathologic response rate in patients [18]. *BRAF* mutation was associated with right-side primary tumors [43], microsatellite instability (MSI)-high tumors [44], peritoneal involvement, and less frequently with liver-limited metastases [43]. Three studies simultaneously found that *BRAF* mutation was correlated with right-side primary tumors, poorly differentiated adenocarcinoma or mucinous carcinoma, and peritoneal metastasis [43-45]. Because such clinicopathological characteristics have been generally identified as poor prognostic factors in patients with CRC, this pattern of spread may be the explanation for the poor outcomes of patients with CRLMs whose tumors harbor the mutation of *BRAF*. However, consistent with other studies [46, 47], we did not found any significance between *KRAS* and *BRAF* mutation with any clinicopathological characteristics. Possible explanations for this discrepancy are tumor heterogeneity, selection bias or the small sample size in our study.

Some studies about patients with metastatic CRC have showed that patients with *KRAS* mutation have a poorer OS than those with wild-type tumors [15, 16, 48]. Some studies with patients with metastatic CRC have demonstrated that patients with mutated *BRAF* tumors have a poorer OS than patients with wild-type tumors [15, 34, 45]. Recently, few studies with patients with metastatic CRC who underwent curative resection have investigated the correlation between the presence of *KRAS* and *BRAF* mutations and the OS, as well as DFS. Some studies found that *RAS* (*KRAS/NRAS*) mutations predict a worse OS [18, 22, 37, 42, 44, 47, 49] and worse DFS [18, 22, 37, 39, 44, 47, 49] after curative resection in cases of CRLMs, and was also an independent poorer predictor of OS [18, 35, 42, 44, 46, 47, 49] and DFS [35, 39, 44, 49] after multivariate analysis. Some studies found *BRAF* mutation predicted a worse OS [22, 43, 49] and worse DFS [22, 49], and was also an independent poor predictor of OS [22, 44, 49] and DFS [22, 44, 49] after curative resection in cases of CRLMs. However, some studies failed to analyze the *BRAF* gene for a low mutation rate of 1-2% [35, 37]. It is possibly that patient selection or the different races of the patients played a role. In our study, although other clinicopathologic features including lymph node status and vascular invasion were also associated with poorer survival, *KRAS* status remained an independent predictor of poor DFS; similarly, *BRAF* status remained an independent predictor of poorer OS and DFS. Furthermore, the homogeneity of our study is better as, for all the patients included in our study are SCRLMs underwent simultaneous R0 resection; in addition, all of the patients had tumors that were initially resectable.

Conclusion

Despite the limitations of our study that result from the small sample size (although our sample is fairly representative), the current study has identified *KRAS* mutations as a predictor for increased risk of poor DFS. Similarly, our study has identified *BRAF* mutations as a predictor for increased risk of poor OS and DFS in patients with SCRLMs who underwent simultaneous R0 resection. These findings should encourage the use of *KRAS* and *BRAF* status in current practice as a primary determinant for precision surgery with resectable SCRLMs.

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Disclosure of conflict of interest

None.

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