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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Prognosis of Synchronous Colorectal Liver Metastases After Simultaneous Curative-Intent Surgery According to Primary Tumor Location and *KRAS* Mutational Status

Ho Seung Kim, MD[1], Jong Min Lee, MD[2], Han Sang Kim, MD, PhD[3], Seung Yoon Yang, MD[1], Yoon Dae Han, MD[1], Min Soo Cho, MD[1], Hyuk Hur, MD, PhD[2], Byung Soh Min, MD, PhD[1], Kang Young Lee, MD, PhD[1], and Nam Kyu Kim, MD, PhD, FACS, FRCS, FASCRS[1]

[1]Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Surgery, Yongin Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Background. Tumor location and *KRAS* mutational status have emerged as prognostic factors of colorectal cancer. We aimed to define the prognostic impact of primary tumor location and *KRAS* mutational status among synchronous colorectal liver metastases (CRLM) patients who underwent simultaneous curative-intent surgery (SCIS).

Methods. We compared the clinicopathologic characteristics and long-term outcomes of 227 patients who underwent SCIS for synchronous CRLM, according to tumor location and *KRAS* mutational status. We cross-classified tumor location and *KRAS* mutational status and compared survival outcomes between the four resulting patient groups.

Results. Forty-one patients (18.1%) had right-sided (RS) tumors and 186 (81.9%) had left-sided (LS) tumors. One-third of tumors (78/227) harbored *KRAS* mutations. The *KRAS* mutant-type (*KRAS*-mt) was more commonly observed among RS tumors than among LS tumors [21/41 (51.2%) vs. 57/186 (30.6%), $p = 0.012$]. Median follow-up time was 43.4 months. Patients with RS tumors had shorter survival times than those with LS tumors [median disease-free survival (DFS): RS, 9.9 months vs. LS, 12.1 months, $p = 0.003$; median overall survival (OS): RS, 49.7 months vs. LS, 88.8 months, $p = 0.039$]. RS tumors were a negative prognostic factor for DFS [hazard ratio (HR) 1.878, $p = 0.001$] and OS (HR 1.660, $p = 0.060$). RS *KRAS*-mt and LS *KRAS* wild-type (*KRAS*-wt) tumors had the worst and best oncological outcomes, respectively.

Conclusion. Tumor location has a prognostic impact in patients who underwent SCIS for CRLM, and RS *KRAS*-mt tumors yielded the worst oncological outcome. These results may allow for more tailored multimodality treatments.

Colorectal cancer (CRC) is the third most common malignancy worldwide. Moreover, approximately one-third of CRC patients exhibit systemic metastasis upon initial diagnosis,[1] with the liver as the most commonly metastasized organ.[2] According to authoritative guidelines, if R0 resection is possible, combined resection for the primary tumor and the liver metastases is the treatment of choice for patients with synchronous colorectal liver metastases (CRLM);[3–5] however, the National Comprehensive Cancer Network (NCCN) guidelines also recommend systemic chemotherapy, even for synchronous resectable CRLM. It is not yet clear which of these treatments is preferable.[3]

Recently, tumor location and *KRAS* mutational status have been identified as prognostic factors of CRC. Right-sided (RS) and left-sided (LS) tumors exhibit distinct clinicopathological characteristics and long-term

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N. K. Kim, MD, PhD, FACS, FRCS, FASCRS
e-mail: namkyuk@yuhs.ac

outcomes. Previously, differential tumor biology has been proposed as an explanation of this prognostic effect of tumor location.[6–8] Among biological markers, *KRAS* mutational status has also been suggested as a prognostic factor. RS tumors are frequently associated with driver gene mutations in *KRAS*.[9,10] These two factors have been extensively studied as prognostic markers in patients with CRC.

Tumor location and *KRAS* mutations have also been analyzed in patients with unresectable metastatic CRC (mCRC),[11,12] and their prognostic impacts have been investigated in CRLM patients undergoing resection.[13–15] The combined prognostic value of tumor location and *KRAS* mutational status has also been demonstrated in CRLM patients.[16,17] However, all of these studies included patients who underwent surgery for synchronous and metachronous liver metastases. To our knowledge, no similar study has been performed to specifically analyze patients with synchronous CRLM undergoing simultaneous curative-intent surgery (SCIS).

Therefore, the aim of the present study was to define the prognostic impact of primary tumor location and *KRAS* mutational status on patients who underwent SCIS for CRLM.

METHODS

Study Design

We included 227 stage IV CRLM patients who underwent SCIS for resection of synchronous lesions between January 2006 and December 2015 at Severance Hospital, Seoul. Patients with an unknown *KRAS* status, as well as patients who underwent palliative surgery (R2 resection), were excluded. The study was approved by the Institutional Review Board of Severance Hospital (4-2019-1147).

Detailed information was obtained on patient age, sex, primary tumor location (RS vs. LS), *KRAS* mutational status, and preoperative carcinoembryonic antigen (CEA) level. Tumors located in the cecum, ascending colon, and transverse colon were defined as RS tumors, and those located in the splenic flexure, descending colon, sigmoid colon, and rectum were defined as LS tumors. *KRAS* codons 12 and 13 were amplified using polymerase chain reaction and were analyzed for mutations. Primary tumor characteristics and CRLM tumor size and number were determined based on final pathological specimens. We identified primary tumor characteristics, including T stage and nodal status, according to the American Joint Committee on Cancer's cancer staging manual, 7th edition, as well as histology and lymphovascular invasion. Furthermore, liver metastases were classified according to the tumor with the largest size, bilobar involvement, and the number of tumors. Tumor size was defined as the maximal diameter of the tumor in the resected specimen; where multiple tumors existed, the largest lesion was used as the index lesion. We also obtained information on treatment-related variables such as R1 resection rate, preoperative treatment (chemotherapy or radiation therapy), intraoperative radiofrequency ablation (RFA), postoperative treatment (chemotherapy or radiation therapy), anti-epidermal growth factor receptor (EGFR) therapy, and anti-vascular endothelial growth factor (VEGF). R1 resection was defined as that where microscopic tumors remained in the surgical margins of either the primary tumor or the liver metastases. The use of anti-EGFR and anti-VEGF therapy was investigated regardless of preoperative or postoperative treatment. Long-term oncologic outcomes were analyzed in terms of overall survival (OS) and disease-free survival (DFS). OS was defined as the time from surgery to death from any cause, whereas DFS was defined as the time from surgery to either first colon cancer relapse or death. Recurrence was defined as the presence of a biopsy-proven tumor exhibiting colorectal adenocarcinoma cells, or a lesion deemed suspicious on follow-up imaging.

Detailed Information on Evaluation, Treatment, and Follow-Up

In our institution, baseline clinical staging was evaluated using abdomino-pelvic computed tomography (APCT) and chest CT. When there was primary CRC with liver metastases, positron emission tomography (PET) was performed for the evaluation of extrahepatic metastases. Liver magnetic resonance imaging (MRI) in contrast to gadoxetic acid was generally performed for patients who were found to have potentially resectable liver metastases on APCT, as well as for patients with an indeterminate lesion on APCT, at the discretion of surgeons and physicians. When systemic chemotherapy was administered first, APCT was used for the evaluation of tumor response. Liver MRI was conducted when resection could be performed to confirm the extent of liver metastases and surgery. PET was not used for routine follow-up in patients with no extrahepatic metastases.

For patients who underwent preoperative treatment, clinical response was reassessed every four cycles. The potential for R0 resection was assessed by specialized hepatobiliary and colorectal surgeons at a multidisciplinary team (MDT) meeting with medical oncologists and radiologists. If tumor response was good although extrahepatic metastases were suspected, surgery was performed according to the decision of the MDT meeting. If the patient's disease was considered unresectable, chemotherapy was performed and the case was re-evaluated.

Intraoperative RFA was performed to eradicate all of the multifocal tumors with resection. Most of the patients who underwent surgical resection were routinely assessed by intraoperative ultrasonogram (US). Separate multisite resection or resection plus RFA was performed for the multifocal tumors ineligible for en bloc resection due to bilobar involvement or when there was not enough hepatic function reserve after en bloc resection. Wedge resection was considered for superficial tumors, and RFA was performed for tumors < 3 cm in diameter that were located deep in the liver.

APCT and chest CT were performed 3–4 weeks after resection to assess the postoperative status of the cancer. Tumor relapse or systemic metastasis after completion of chemotherapy was assessed by abdominopelvic CT and chest CT every 2–3 months. There was no difference in follow-up protocol between the resection group and the RFA group.

Statistical Analysis

Summary statistics for continuous variables were reported as the mean ± standard deviation, while categorical variables were reported as frequency (percentage). The Student's *t* test was employed for comparing continuous variables, and the Chi square and Fisher's exact tests were employed for comparing categorical variables. The Kaplan–Meier method was utilized for univariate analyses of survival, and the log-rank test was utilized for statistical evaluation of differences in survival rates. Multivariate Cox regression models were implemented to assess the association between survival and clinicopathological factors. We cross-classified primary tumor location and *KRAS* mutational status in order to evaluate their simultaneous impact on survival. Survival outcomes among the four resulting groups [RS *KRAS*-mt, RS *KRAS*-wt, LS *KRAS*-mt, and LS *KRAS*-wt (reference group)] were evaluated using the Kaplan–Meier method combined with the log-rank test, as well as the Cox proportional hazards model. All data were analyzed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

We identified 227 patients who underwent SCIS for CRLM and for whom *KRAS* mutational status was known. Their clinicopathologic characteristics, stratified by primary tumor location and *KRAS* mutational status, are summarized in Table 1. Among 227 patients, 41 (18.1%) had an RS tumor, while 186 (81.9%) had an LS tumor. In terms of *KRAS*, 149 (65.6%) patients had the wild-type (*KRAS*-wt), while 78 (34.4%) patients had the mutant type (*KRAS*-mt). An RS location was more frequently observed among *KRAS*-mt tumors than among *KRAS*-wt tumors (26.9% vs. 13.4%, $p = 0.012$). Preoperative CEA levels were similar, regardless of primary tumor location and *KRAS* mutational status.

Primary tumor characteristics and extent of liver metastases were also similar, regardless of primary tumor location and *KRAS* mutational status. In terms of primary tumor characteristics, most patients had advanced CRC (T3-T4 tumors: $n = 209$, 92.1%; $>$ N1: $n = 167$, 73.6%). In terms of liver metastases, 118 (52.0%) patients had bilobar involvement and 124 (54.6%) had more than three metastases. In terms of treatment-related variables, R1 resection was performed in 46 (20.3%) patients, and was more frequently observed among *KRAS*-wt tumors than among *KRAS*-mt tumors (24.2% vs. 12.8%, $p = 0.044$). Intraoperative RFA was performed on 29 (12.8%) patients. Preoperative treatment was administered to 127 (55.9%) patients, more frequently among patients with LS tumors than among those with RS tumors (59.7% vs. 39.0%, $p = 0.016$). Postoperative treatment was administered to 208 (91.6%) patients, and anti-EGFR therapy was administered to 37 (16.3%) patients; the majority of the latter had LS *KRAS*-wt tumors.

Long-Term Survival Outcomes According to Tumor Location and KRAS Mutational Status

Median follow-up time was 43.4 months (interquartile range 23.2–60.1). Kaplan–Meier analysis revealed a lower DFS and OS among patients with RS tumors than among patients with LS tumors (median DFS: RS, 9.9 months vs. LS, 12.1 months, $p = 0.003$; median OS: RS, 49.7 months vs. LS, 88.8 months, $p = 0.039$) (Fig. 1a, b). We did not detect a difference in long-term survival outcomes based on *KRAS* mutational status (Fig. 1c, d).

Using multivariate analysis, we identified RS location of tumors as a prognostic factor associated with poor DFS [hazard ratio (HR) 1.878, 95% confidence interval (CI) 1.290–2.734, $p = 0.001$]. Preoperative CEA, primary tumor nodal metastases, histologic grade, lymphovascular invasion, amount of metastatic liver lesions, and preoperative treatment were also associated with DFS. Primary tumor nodal status and histologic grade were statistically significant independent prognostic factors of OS. RS location exhibited a clear tendency to significance as an independent prognostic factor of OS (HR 1.660, 95% CI 0.979–2.814, $p = 0.060$). *KRAS* mutational status was not identified as a prognostic factor of either DFS or OS (Table 2).

TABLE 1 Patient characteristics according to primary tumor location and *KRAS* status

Variables	Right-sided	Left-sided	*p*-Value	*KRAS*-wt	*KRAS*-mt	*p*-Value
No. of patients	41	186		149	78	
Age, years	59.8 ± 12.2	57.6 ± 10.3	0.233	57.6 ± 10.9	58.7 ± 10.3	0.481
Sex			0.155			0.953
Male	23 (56.1)	126 (67.7)		98 (65.8)	51 (65.4)	
Female	18 (43.9)	60 (32.3)		51 (34.2)	27 (34.6)	
Location						0.012
Right	–	–		20 (13.4)	21 (26.9)	
Left	–	–		129 (86.6)	57 (73.1)	
KRAS			0.012			
Wild	20 (48.8)	129 (69.4)		–	–	
Mutant	21 (51.2)	57 (30.6)		–	–	
CEA > 100, ng/mL	7 (17.1)	56 (30.1)	0.092	46 (30.9)	17 (21.8)	0.147
Primary tumor characteristics						
T stage			1.000			0.145
*T*1, 2	3 (7.3)	15 (8.1)		9 (6.0)	9 (11.5)	
*T*3, 4	38 (92.7)	171 (91.9)		140 (94.0)	69 (88.5)	
Node metastases	33 (80.5)	134 (72.0)	0.267	110 (73.8)	57 (73.1)	0.903
Histology			0.116			0.194
WD, MD	37 (90.2)	179 (96.2)		144 (96.6)	72 (92.3)	
PD, Muc	4 (9.8)	7 (3.8)		5 (3.4)	6 (7.7)	
LVI	20 (48.8)	73 (39.2)	0.261	63 (42.3)	30 (38.5)	0.578
Liver metastases characteristics						
Largest size ≥ 3, cm	12 (29.3)	58 (31.2)	0.810	50 (33.6)	20 (25.6)	0.220
Bilobar involvement	19 (46.3)	99 (53.2)	0.424	84 (56.4)	34 (43.6)	0.067
Number ≥ 3	20 (48.8)	104 (55.9)	0.406	87 (58.4)	37 (47.4)	0.115
Treatment						
R1 resection	6 (14.6)	40 (21.5)	0.322	36 (24.2)	10 (12.8)	0.044
Preoperative treatment	16 (39.0)	111 (59.7)	0.016	90 (60.4)	37 (47.4)	0.062
Intraoperative RFA	3 (7.3)	26 (14.0)	0.310	20 (13.4)	9 (11.5)	0.686
Postoperative treatment	35 (85.4)	173 (93.0)	0.122	138 (92.6)	70 (89.7)	0.458
Anti-EGFR	4 (9.8)	33 (17.7)	0.210	37 (24.8)	0 (0)	<0.001
Anti-VEGF	9 (22.0)	50 (26.9)	0.515	34 (22.8)	25 (32.1)	0.132

Data are expressed as *n* (%) unless otherwise specified

wt wild-type, *mt* mutant-type, *CEA* carcinoembryonic antigen, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *Muc* mucinous type, *LVI* lymphovascular invasion, *R1* microscopically positive surgical margin, *RFA* radiofrequency ablation, *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor

Long-Term Survival Outcomes of Four Categories of Colorectal Liver Metastases

RS *KRAS*-mt tumors demonstrated a poor DFS compared with LS tumors (RS *KRAS*-mt vs. LS *KRAS*-mt, $p < 0.001$; RS *KRAS*-mt vs. LS *KRAS*-wt, $p = 0.001$). In terms of OS, RS *KRAS*-mt tumors yielded worse oncological outcomes than LS *KRAS*-wt tumors (RS *KRAS*–mt vs. LS *KRAS*-wt, $p = 0.042$) (Fig. 2).

In multivariate analyses, we detected no statistically significant interaction between primary tumor location and *KRAS* mutational status. Our model predicted that patients with both risk factors (RS *KRAS*-mt tumors) would have a much worse DFS (HR 2.730, 95% CI 1.656–4.501, $p < 0.001$) and OS (HR 2.523, 95% CI 1.187–5.361, $p = 0.016$) than patients with neither risk factor (Table 3).

DISCUSSION

In this study, we found that primary tumor location had an independent prognostic impact on patients who underwent SCIS for CRLM. The location of the primary tumor

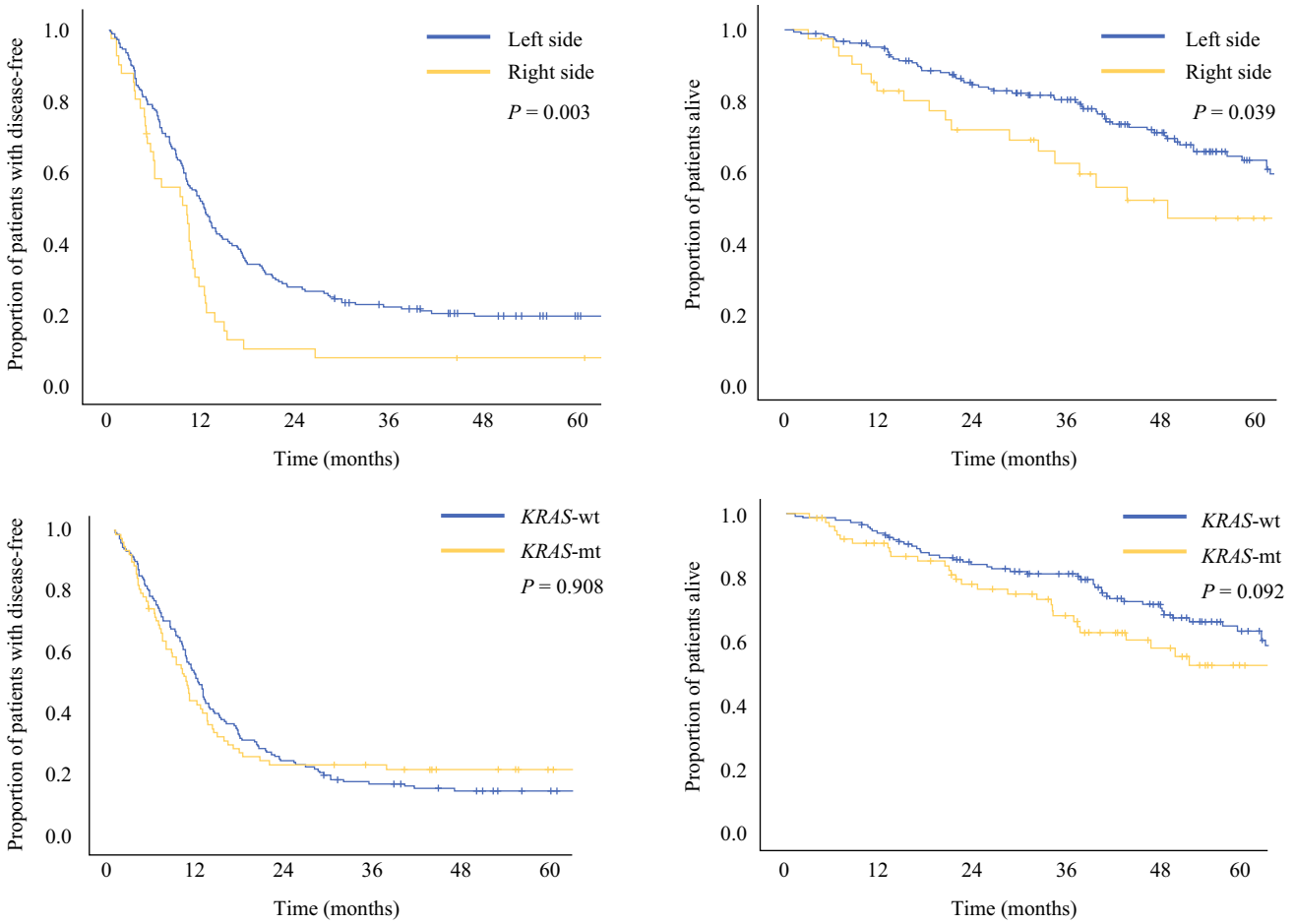

FIG. 1 Survival outcomes according to tumor location and *KRAS* mutational status. **a** DFS according to tumor location. **b** OS according to tumor location. **c** DFS according to *KRAS* mutational status. **d** OS according to *KRAS* mutational status. *DFS* disease-free survival, *OS* overall survival, *KRAS-mt KRAS* mutant-type, *KRAS-wt KRAS* wild-type

has been recognized as a prognostic factor in mCRC.[11,18] Recent prospective trials of patients with mCRC treated with palliative chemotherapy have demonstrated prolonged progression-free survival and OS for patients with LS primary tumors. *KRAS* mutational status has also been revealed as a potential molecular prognostic marker in mCRC.[12,19] The prognostic impact of these factors have been investigated in patients undergoing curative-intent resection of CRLM. Primary tumor location was independently associated with OS among such patients; LS primary tumors were associated with a better OS compared with RS primary tumors, although there was no association with relapse-free survival (RFS).[13,15] *KRAS* mutational status was also discovered to have a prognostic impact on OS, but not on RFS.[14]

However, to our knowledge, only two studies demonstrating a prognostic impact of both primary tumor location and *KRAS* mutational status have been published recently.[16,17] Sasaki et al.[16] evaluated the prognostic impact of *KRAS* mutational status on patients undergoing hepatic resection for CRLM, stratified by primary tumor location. Among patients with RS CRC, RFS and OS were not correlated with *KRAS* mutational status. In contrast, among patients with LS CRC, RFS and OS were shorter among patients with *KRAS*-mt than among those with *KRAS*-wt. Margonis et al.[17] demonstrated that the prognostic impact of primary tumor location differed according to *KRAS* mutational status. In *KRAS*-wt patients, a shorter OS was associated with RS location of tumors. In contrast, among patients with *KRAS*-mt, tumor location had no impact on OS. Margonis et al. also reported that RS tumors and *KRAS*-mt were independently associated with shorter OS in the entire cohort. In the present study, we discovered similar results, with poorer oncological outcomes in patients with RS tumors than in patients with LS tumors, although we did not identify *KRAS* mutational status as an independent prognostic factor.

However, our study population differed from that of previous studies in that we only included patients who underwent SCIS for synchronous lesions, and excluded

TABLE 2 Univariate and multivariate analysis for disease-free survival and overall survival

Variable	Disease-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age ≥ 60 years	0.871 (0.653–1.163)	0.349			0.841 (0.539–1.312)	0.445		
Female sex	1.031 (0.761–1.397)	0.842			0.818 (0.523–1.279)	0.378		
Right sidedness	1.734 (1.201–2.496)	0.003	1.878 (1.290–2.734)	0.001	1.725 (1.021–2.917)	0.042	1.660 (0.979–2.814)	0.060
KRAS mutation	1.018 (0.750–1.383)	0.908			1.466 (0.937–2.294)	0.094		
CEA > 100, ng/mL	1.434 (1.044–1.939)	0.026	1.408 (1.002–1.977)	0.048	1.170 (0.727–1.884)	0.517		
T3 or 4	1.318 (0.750–2.317)	0.337			1.899 (0.694–5.197)	0.212		
Nodal metastases	1.956 (1.372–2.789)	<0.001	1.938 (1.350–2.784)	<0.001	3.282 (1.642–6.561)	0.001	2.936 (1.462–5.896)	0.002
PD, muc	2.420 (1.313–4.462)	0.005	3.515 (1.823–6.776)	<0.001	5.291 (2.614–10.712)	<0.001	4.369 (2.146–8.895)	<0.001
Lymphovascular invasion	1.383 (1.035–1.848)	0.029	1.151 (0.833–1.590)	0.395	1.661 (1.077–2.562)	0.022	1.170 (0.738–1.855)	0.503
Largest size ≥ 3, cm	1.408 (1.037–1.910)	0.028	1.224 (0.888–1.688)	0.217	1.507 (0.966–2.349)	0.070		
Bilobar involvement	1.164 (0.873–1.552)	0.300			1.082 (0.701–1.672)	0.721		
Number ≥ 3	1.562 (1.167–2.092)	0.003	1.430 (1.036–1.973)	0.030	1.270 (0.817–1.976)	0.288		
R1 resection	1.327 (0.940–1.873)	0.108			1.281 (0.767–2.141)	0.344		
Preoperative treatment	1.503 (1.122–2.014)	0.006	1.550 (1.111–2.163)	0.010	1.010 (0.653–1.562)	0.965		
Intraoperative RFA	1.129 (0.745–1.709)	0.567			0.826 (0.425–1.603)	0.572		
Postoperative treatment	0.639 (0.382–1.068)	0.087			0.722 (0.332–1.569)	0.410		
Anti-EGFR	1.181 (0.806–1.729)	0.393			1.415 (0.806–2.485)	0.227		
Anti-VEGF	1.075 (0.776–1.075)	0.665			0.700 (0.405–1.210)	0.202		

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *PD* poorly differentiated, *Muc* mucinous type, *R1* microscopically positive surgical margin, *RFA* radiofrequency ablation, *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor

those with metachronous liver metastases. Patients with synchronous liver metastases have been revealed to have shorter DFS compared with those with metachronous liver metastases.[20] Where possible, SCIS remains the treatment of choice, according to authoritative guidelines.[3–5] As the primary tumor location and *KRAS* mutational status have been identified as potential prognostic factors in previous studies, our aim was to investigate whether these factors could assist us in identifying the patient groups that had poor survival outcomes after SCIS. Of the four patient groups in the present study, those with RS KRAS-mt tumors showed the worst oncological outcomes. These results suggest that patients with RS KRAS-mt tumors may not benefit from SCIS, and should first be considered for other treatment modalities, such as systemic chemotherapy. Moreover, further studies that compare the outcomes of

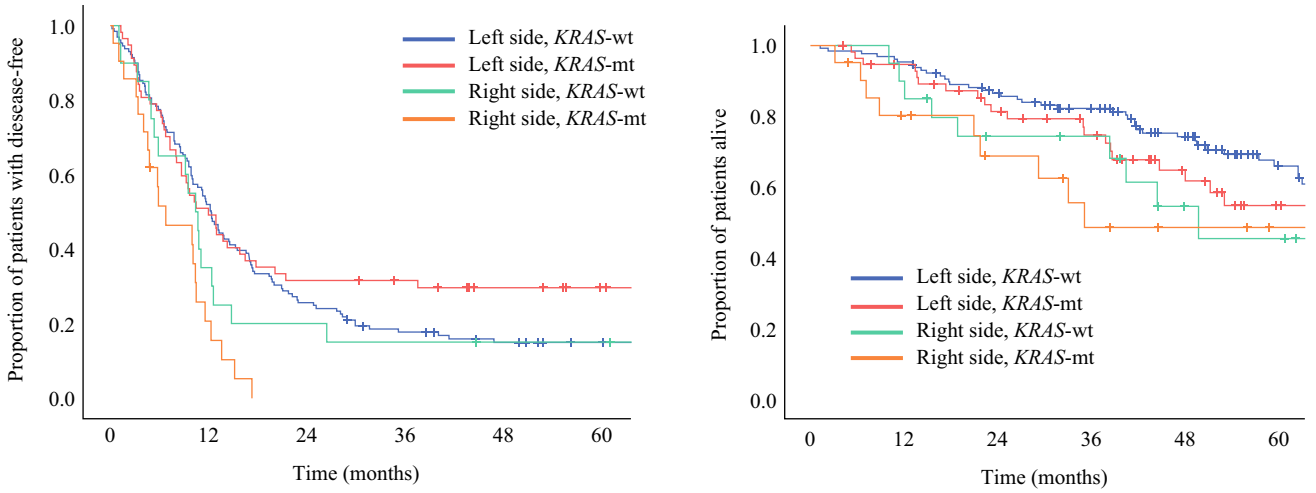

FIG. 2 Survival outcomes after cross-classifying tumor location and *KRAS* mutational status. **a** Disease-free survival (pooled $p < 0.001$). **b** Overall survival (pooled $p = 0.042$). *KRAS-mt KRAS* mutant-type, *KRAS-wt KRAS* wild-type

TABLE 3 Multivariate analysis for disease-free survival and overall survival

Variable	HR (95% CI)	
	Disease-free survival	Overall survival
Tumor location		
Right	1.878 (1.290–2.734)	1.660 (0.979–2.814)
Left	1 (Reference)	1 (Reference)
KRAS		
Mutant	1.137 (0.831–1.554)	1.420 (0.898–2.246)
Wild	1 (Reference)	1 (Reference)
Right-sided tumor and *KRAS*-mt		
Both	2.730 (1.656–4.501)	2.523 (1.187–5.361)
Neither	1 (Reference)	1 (Reference)

HR hazard ratio, *CI* confidence interval, *KRAS-mt KRAS* mutant-type

each treatment modality for patients with synchronous CRLM according to tumor location and KRAS mutational status are required.

In several studies, tumor location has been demonstrated to have a notable effect on the molecular and clinicopathologic characteristics of primary CRC.[6,21] For instance, *KRAS* mutations, *BRAF* mutations, and microsatellite instability (MSI) were more frequently observed in RS CRC than in LS CRC. Furthermore, RS CRC patients had worse long-term outcomes than LS CRC patients.[9,10] Similarly, in the present study, we demonstrated that *KRAS*-mt was more common in RS CRC tumors than in LS CRC tumors. In our analysis, the prognostic impact of the combination of primary tumor location and *KRAS* mutational status was more powerful than for each factor separately. Further research is necessary to explain the mechanisms leading to poor oncological outcomes in RS tumors.

In our study, histologic grade was the strongest prognostic factor among the clinicopathological variables that we assessed. Previous studies on the prognostic impact of tumor location and *KRAS* mutational status on curative-intent surgery for CRLM did not report on histologic grade.[13–17] RS tumors are generally more poorly differentiated than LS tumors.[9,10] Traditionally, the extent of liver metastases was a significant prognostic factor for CRLM;[22] however, medical and surgical treatment for liver metastases has improved and tumor biology has replaced it as the most significant prognostic factor for survival.

Among patients who enrolled in our study, the largest groups of patients who had received preoperative treatment were those with LS and *KRAS*-wt tumors; therefore, it is possible that preoperative treatment increased the viability of SCIS for patients with LS or *KRAS*-wt tumors. However, our study design was such that we did not compare the response to preoperative treatment among recipient patients. To our knowledge, there have been no studies on preoperative treatment response according to primary tumor location. In terms of *KRAS* mutational status, Chow et al.[23] reported that *KRAS*-mt tumors were associated with a lower pathologic complete response rate to neoadjuvant chemoradiation therapy in locally advanced rectal cancer. Therefore, preoperative treatment response according to primary tumor location and *KRAS* mutational status should be given consideration in CRLM in order to devise a proper treatment strategy, and further research in this area is necessary.

Our study had several limitations. As a retrospective analysis, our study was subject to inherent bias. Notably, in previous studies, patients receiving anti-EGFR therapy exhibited increased survival rates compared with patients not receiving anti-EGFR, particularly in patients with LS tumors and those with *KRAS*-wt tumors.[12,24] This was not observed in the present study, possibly due to the aforementioned bias. Second, the sample size was relatively small in the present study, which is a potential explanation for the lack of statistically significant results upon subgroup analysis, when stratifying based on primary tumor location and *KRAS* mutational status (electronic supplementary Fig. 1). Third, we included rectal cancer patients in the LS group, although this is different according to study design (electronic supplementary Figs. 2, 3).[16,17] Finally, we did not consider other molecular markers, such as *BRAF* and MSI mutations that have been demonstrated to differ between RS and LS tumors, as these results were available for only a limited number of patients. Therefore, further research will be necessary to investigate the prognostic importance of several factors on patients with synchronous CRLM. Nonetheless, to our knowledge, this is the first study to analyze the prognostic impact of primary tumor location and *KRAS* mutational status on patients who underwent SCIS for synchronous CRLM.

CONCLUSION

We demonstrated that primary tumor location has an independent prognostic impact on patients who underwent SCIS for CRLM. In contrast, *KRAS* mutational status was not identified as an independent prognostic factor. However, we identified patients with RS *KRAS*-mt tumors as those with the worst oncological outcome. For this group, even where R0 resection is possible, surgery may not be the best option. Therefore, prospective studies that compare the outcomes of each treatment modality for patients with synchronous CRLM are required. Stratifying patients based on primary tumor location and *KRAS* mutational status may allow for more tailored multimodality treatments.

DISCLOSURES Ho Seung Kim, Jong Min Lee, Han Sang Kim, Seung Yoon Yang, Yoon Dae Han, Min Soo Cho, Hyuk Hur, Byung Soh Min, Kang Young Lee, and Nam Kyu Kim have no conflicts of interest to declare.

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