ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2024.107.5.264
Annals of Surgical Treatment and Research

Primary tumor sidedness is not prognostic factor in resectable colorectal cancer liver metastasis: a retrospective observational cohort study

Sung Jun Jo*, Jongman Kim, Jung Kyong Shin, Jinsoo Rhu, Jung Wook Huh, Gyu-seong Choi, Jae-Won Joh

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Purpose: Right-sided tumors have been reported to have a poorer survival rate than left-sided tumors; however, there remains debate regarding whether sidedness is an independent prognostic factor in colorectal cancer liver metastasis (CRLM). This study aimed to assess the impact of sidedness on prognosis in resectable CRLM and to identify prognostic factors.

Methods: Patients who underwent liver resection for CRLM at Samsung Medical Center from January 2008 to December 2021 were included in the investigation. Overall survival (OS) and progression-free survival (PFS) were analyzed, and prognostic factors were identified.

Results: A total of 497 patients were included in the study, with 106 on the right side and 391 on the left side. The right-sided group had a higher percentage of synchronous tumors (90.6% *vs.* 80.3%, P = 0.020). In survival analysis, the right side showed lower 5-year OS (49.7% *vs.* 54.2, P = 0.305) and 5-year PFS (57.1% *vs.* 60.2%, P = 0.271), but the differences were not statistically significant. In the analysis of prognostic factors, synchronous tumor (odds ratio [OR], 5.01; P < 0.001), CEA (OR, 1.46; P = 0.016), and maximum tumor size of hepatic metastasis (OR, 1.09; P = 0.026) were associated with OS.

Conclusion: In resectable CRLM, there was no difference in prognosis based on sidedness. CEA level, synchronous tumor, and maximum tumor size of hepatic metastasis were identified as prognostic factors.

[Ann Surg Treat Res 2024;107(5):264-273]

Key Words: Colorectal cancer liver metastasis, Prognosis, Sidedness

INTRODUCTION

Colorectal cancer (CRC) is a common form of cancer, accounting for approximately 13% of newly diagnosed cases [1]. A significant concern is that 15%–25% of CRC cases are diagnosed at stage IV, often accompanied by hepatic metastasis [2]. In the treatment of colorectal cancer liver metastasis (CRLM), a combination of locoregional treatment (such as surgical resection, thermal ablation, and intra-arterial chemotherapy) and systemic therapy is typically employed [3,4]. Liver transplantation has also been attempted in select patients [5]. However, surgical resection remains a particularly noteworthy option, with reported 5-year and 10-year overall survival (OS) rates of 42% and 25%, respectively [6-9].

Several studies have consistently reported CRC sidedness, which has different embryologic origins depending on the primary tumor's location, resulting in genetic and histopathologic differences and differing prognoses [10-12]. Right-sided tumors in CRLM have been reported to have a worse survival rate than left-sided tumors, and liver transplant

Received July 25, 2024, **Revised** August 25, 2024,
Accepted September 9, 2024

Corresponding Author: Jongman Kim
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel/Fax: +82-2-3410-1176
E-mail: yjongman@naver.com
ORCID: https://orcid.org/0000-0002-1903-8354

*Sung Jun Jo's current affiliation is Department of Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea.

patients with CRLM have also shown a poor prognosis [13,14]. However, there is still debate as to whether sidedness is an independent prognostic factor in CRLM [14,15].

The aim of this study was to assess the effect of sidedness on both OS and progression-free survival (PFS) in resectable CRLM and to identify prognostic factors.

METHODS

Ethics statements

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. SMC 2024-02-063). The need for informed consent was waived by the IRB due to the retrospective nature of the study.

Patient selection

The study investigated patients who underwent liver resection for CRLM at Samsung Medical Center between January 2008 and December 2022. Exclusion criteria included unresectable CRLM, double primary colon cancer with different primary tumor locations, and R2 resection of liver lesion.

Medical records were reviewed to obtain data on sex, age, presence of synchronous cancer, hepatectomy timing in synchronous cancer, history of chemotherapy, history of concurrent ablation, and CEA levels. Pathology records were also reviewed to gather data on primary site, T stage of primary CRC, N stage of primary CRC, maximum tumor size of hepatic metastasis, and number of tumors. The extent of hepatectomy was determined from operation records and categorized into 2 groups: major and minor. Major liver resections are classified as the removal of more than 3 liver segments, while minor resections involve the removal of 3 or fewer segments. The hepatectomy method and resection status were also investigated based on the operation record, and the hepatectomy method was categorized into anatomical and non-anatomical resection.

Classification of sidedness

Sidedness was categorized into right side and left side based on the distal 2/3 of the transverse colon. For the OS analysis, apart from the right and left division, we also stratified the analysis into 3 groups: right, left, and rectum. The upper rectum was considered separately as rectum, while the rectosigmoid colon was grouped with the left colon.

History of chemotherapy

The history of chemotherapy was examined to determine the presence or absence of chemotherapy and the number of chemotherapy cycles administered before hepatectomy. Chemotherapy was defined as treatment administered after the detection of liver metastasis, and the number of cycles completed prior to surgery was recorded. Patients who did not receive chemotherapy were excluded from the analysis of calculating the distribution of the number of chemotherapy cycles. Neoadjuvant concomitant chemoradiation therapy for rectal cancer was not included in the chemotherapy count.

Classification of recurrence pattern

Recurrence patterns were categorized into local recurrence and distant metastasis. Local recurrence was defined as occurring at the surgical margin of the primary tumor. Patients with local recurrence accompanied by distant metastasis were classified into the distant metastasis group. Distant metastases were further classified into 5 categories: hepatic, pulmonary, peritoneal, distant lymph node, bone, and other. Recurrences were also classified as single- or multiple-organ based on whether a combination of the 5 categories was present.

Statistical analysis

The primary outcome measures were 5-year OS and PFS. For the survival analysis, the Kaplan-Meier estimates and the log-rank test were used. Both the OS and PFS were analyzed using time-to-event regression. The Cox proportional hazard model was used to evaluate prognostic variables, an estimated hazard ratio with a 95% confidence interval (CI) was presented, and $P < 0.05$ was considered statistically significant. Continuous variables with normal distribution are summarized with mean ± standard deviation, and non-normal continuous variables are expressed as the median (range). The Fisher exact test or Pearson chi-square test was applied to compare proportions between groups as appropriate. For the comparison of continuous variables, the Student t-test or Mann-Whitney U-test was used. All analyses were performed using R software ver. 4.2.1 (The R Foundation).

RESULTS

Among 499 patients who underwent liver resection for CRLM, 497 were eligible for the inclusion criteria after excluding double primary cancer (n = 2). Across the entire cohort, there were 106 patients on the right-sided group and 391 patients on the left-sided group.

Baseline characteristics

Comparisons of characteristics between the right-sided group and the left-sided group are summarized in Table 1. The right-sided group was older than the left-sided group (right *vs.* left, 62.6 ± 11.2 years *vs.* 58.3 ± 11.6 years; P = 0.001) and had a lower prehepatectomy chemotherapy rate (right *vs.* left, 17% *vs.* 28.9; P = 0.019). However, there were no differences in sex distribution, concurrent ablation, or CEA. Regarding primary

Table 1. Comparison of characteristics between right-side and left-side liver metastasis

Characteristic	Right side	Left side	P-value
No. of patients	106	391	
Age (yr)	62.6 ± 11.2	58.3 ± 11.6	0.001
Sex			
Male	59 (55.7)	236 (60.4)	0.446
Female	47 (44.3)	155 (39.6)	
Colorectal cancer TN stage			
T stage			
Tx	0 (0)	5 (1.3)	0.223
T1	2 (1.9)	12 (3.1)	
T2	5 (4.7)	17 (4.3)	
T3	67 (63.2)	264 (67.5)	
T4a	30 (28.3)	73 (18.7)	
T4b	2 (1.9)	20 (5.1)	
N stage			
Nx	33 (31.1)	82 (21.0)	0.138
N1a	17 (16.0)	65 (16.6)	
N1b	20 (18.9)	81 (20.7)	
N1c	0 (0)	11 (2.8)	
N2a	20 (18.9)	67 (17.1)	
N2b	16 (15.1)	85 (21.7)	
Synchronous metastasis			
No	10 (9.4)	77 (19.7)	0.020
Yes	96 (90.6)	314 (80.3)	
Hepatectomy timing in synchronous metastasis			
Simultaneous resection	95 (99.0)	305 (97.1)	0.464
Stage resection	1 (1.0)	9 (2.9)	
Prehepatectomy chemotherapy			
No	88 (83.0)	278 (71.1)	0.019
Yes	18 (17.0)	113 (28.9)	
No. of chemo-cycle	6 (3–10)	5 (3–9)	0.906
Concurrent ablation			
No	102 (96.2)	365 (93.4)	0.383
Yes	4 (3.8)	26 (6.6)	
Hepatectomy extent			
Minor	69 (65.1)	260 (66.5)	0.877
Major	37 (34.9)	131 (33.5)	
Hepatectomy method			
Anatomical resection	48 (45.3)	186 (47.6)	0.757
Non-anatomical resection	58 (54.7)	205 (52.4)	
Resection status			
R0/1	103 (97.2)	379 (96.9)	>0.999
R2	3 (2.8)	12 (3.1)	
No. of tumors			
1	61 (57.5)	217 (55.5)	0.901
2	21 (19.8)	85 (21.7)	
≥3	24 (22.6)	89 (22.8)	
Maximum tumor size of hepatic metastasis (cm)	2.2 (1.5–3.5)	2.1 (1.5–3.2)	0.438
Prehepatectomy CEA (ng/mL)			
≤3	44 (41.5)	139 (35.5)	0.310
>3	62 (58.5)	252 (64.5)	

Values are presented as number only, mean ± standard deviation, number (%), or median (interquartile range).

CRC characteristics, there were no differences in the T stage and N stage. In terms of liver metastasis characteristics, the proportion of synchronous metastasis was higher in the right-sided group (right *vs.* left, 90.6% *vs.* 80.3%; P = 0.020), but there were no differences in hepatectomy timing in synchronous metastasis, hepatectomy extent, hepatectomy method, resection status, number of tumors, or maximum tumor size of hepatic metastasis.

Survival outcomes according to sidedness

In the survival analysis, the right-sided group exhibited lower 5-year OS (right *vs.* left, 49.7% *vs.* 54.2; P = 0.305) and 5-year PFS (right *vs.* left, 57.1% *vs.* 60.2%; P = 0.271) compared to the left-sided group, although these differences were not statistically significant. Survival analyses in the 3 groups—right, left, and rectum—also indicated no difference in 5-year OS (right *vs.* left *vs.* rectum, 49.7% *vs.* 53.5% *vs.* 55.8%; P = 0.512) and 5-year PFS (right *vs.* left *vs.* rectum, 57.1% *vs.* 60.5% *vs.* 59.7%; P = 0.353) (Fig. 1). In subgroup analysis, there was no difference in 5-year OS (right *vs.* left, 47.8% *vs.* 50.4%; P = 0.521) and 5-year PFS (right *vs.* left, 61.1% *vs.* 61.9%; P = 0.344) based on sidedness in the synchronous tumor group. For metachronous cancer, 5-year survival analyses were not possible due to insufficient follow-up, thus 3-year survival analyses were conducted. The analysis revealed no difference in 3-year OS (right *vs.* left, 100% *vs.* 90.1%; P = 0.468), but PFS showed all recurrences in the right-sided group (P = 0.027) (Fig. 2).

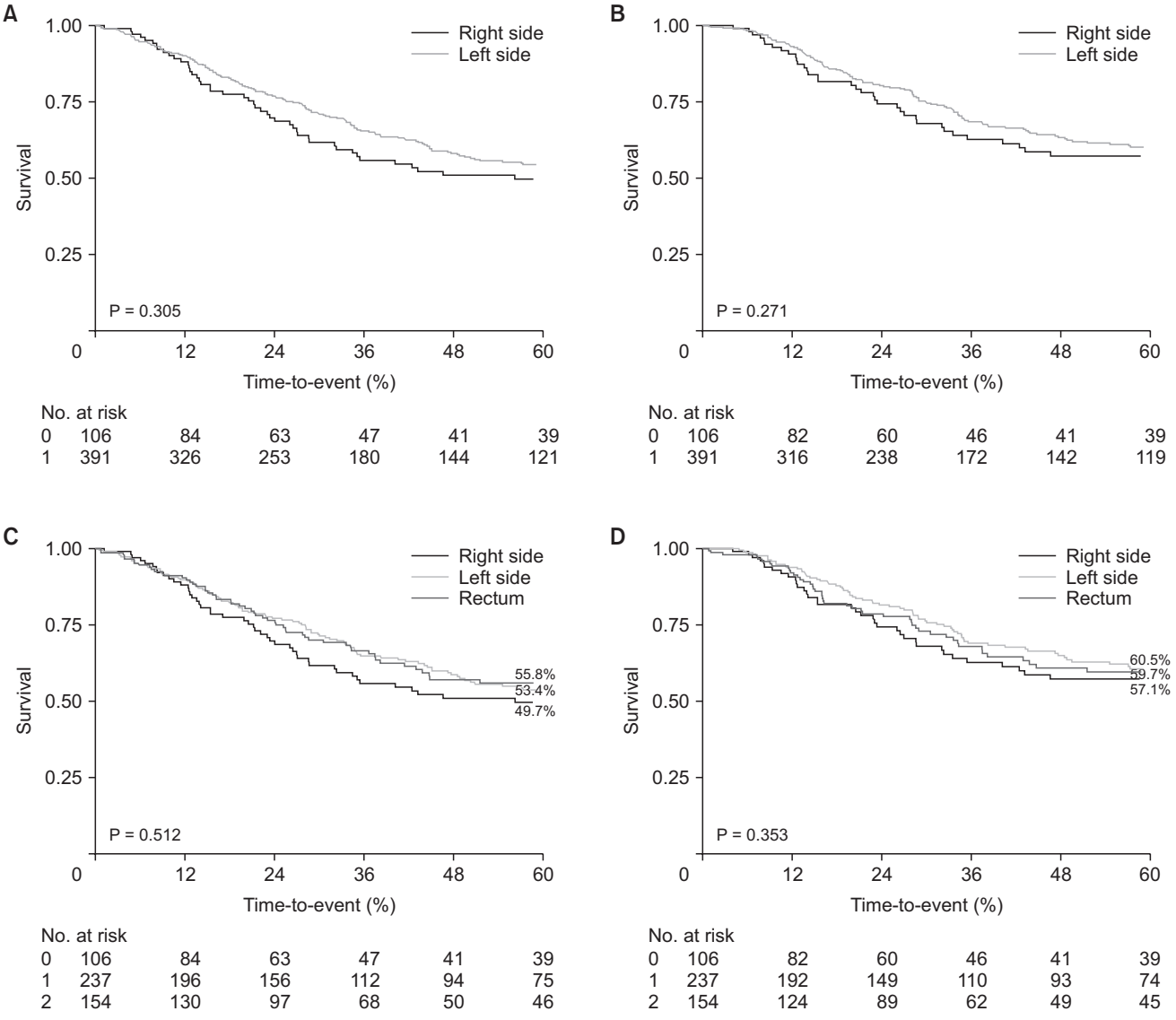

Fig. 1. Kaplan-Meier survival graph according to sidedness. (A) Overall survival. (B) Progression-free survival. (C) Overall survival categorized as right, left, and rectum. (D) Progression-free survival categorized as right, left, and rectum.

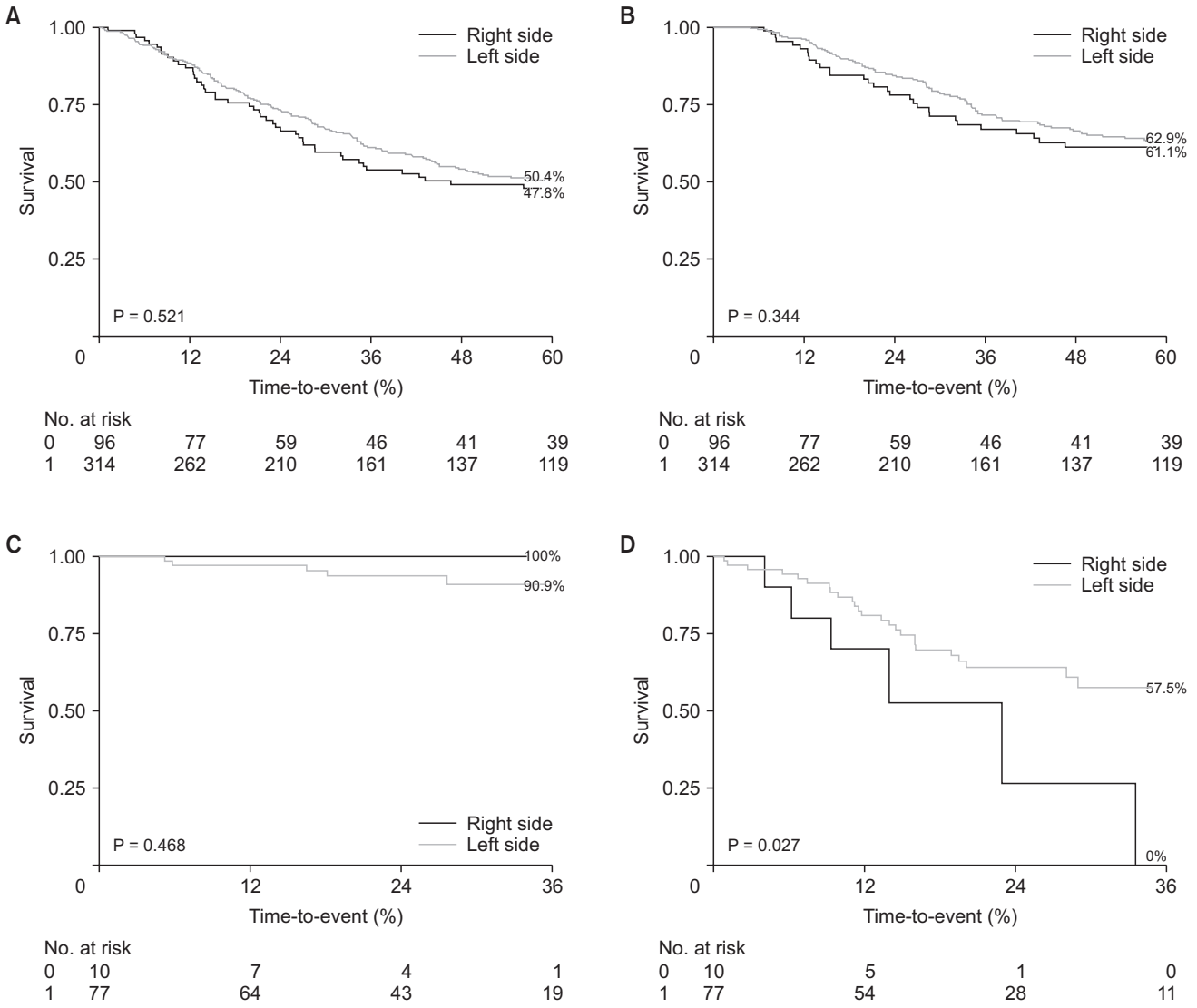

Fig. 2. Kaplan-Meier survival graph according to sidedness in synchronous and metachronous tumors. (A) Overall survival in synchronous tumors. (B) Progression-free survival in synchronous tumors. (C) Overall survival in metachronous tumors. (D) Progression-free survival in metachronous tumors.

Survival outcomes according to hepatectomy timing

The 5-year OS and 5-year PFS were subjected to further analysis in accordance with the timing of hepatectomy (staged *vs.* simultaneous) in the context of synchronous tumors. The findings indicated that the staged operation exhibited superior OS (staged *vs.* simultaneous, 87.5% *vs.* 49.3%; P = 0.465) and PFS (staged *vs.* simultaneous, 100% *vs.* 62.2%; P = 0.276) outcomes, although this difference was not statistically significant (Fig. 3).

Prognostic factor analyses

In the analysis of prognostic factors, synchronous tumor (odds ratio [OR], 5.01; P < 0.001), CEA (OR, 1.46; P = 0.016), and maximum tumor size of hepatic metastasis (OR, 1.09; P = 0.026) were associated with OS in multivariate analysis (Table 2). In the analysis of prognostic factors associated with PFS, synchronous tumor (OR, 0.43; P < 0.001), CEA (OR, 1.48; P = 0.014), and maximum tumor size of hepatic metastasis (OR, 1.06; P = 0.037) were significant in the univariate analysis, but only synchronous tumor (OR, 0.42; P < 0.001) and CEA (OR, 1.40; P = 0.042) remained statistically significant in the multivariate analysis (Table 3).

Recurrence pattern according to sidedness

Comparisons of recurrence pattern between the right-sided group and the left-sided group are summarized in Table 4. There was no difference in the proportion of local recurrence (right *vs.* left, 4.4% *vs.* 3.6%; P = 0.678) and distant metastasis (right *vs.* left, 95.6% *vs.* 96.4%) based on sidedness, and the types of distant metastasis were similar, with single-organ

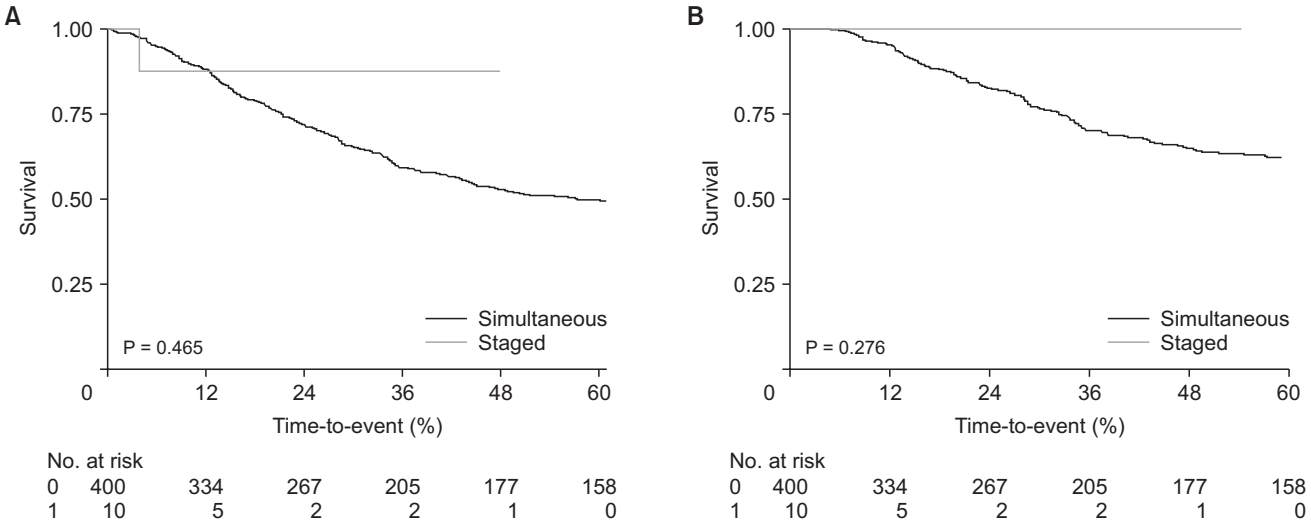

Fig. 3. Kaplan-Meier survival graph according to hepatectomy timing in synchronous tumors. (A) Overall survival. (B) Progression-free survival.

Table 2. Univariate and multivariate analyses of prognostic factors associated with overall survival

Variable	Univariate		Multivariate	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age	1.01 (1.00–1.02)	0.068		
Primary site sidedness, left *vs.* right	0.86 (0.63–1.17)	0.326		
T stage				
Tx	Reference			
T1	0.47 (0.11–2.11)	0.326		
T2	1.05 (0.29–3.83)	0.938		
T3	0.69 (0.22–2.16)	0.518		
T4a	1.22 (0.38–3.91)	0.734		
T4b	1.69 (0.49–5.82)	0.402		
N stage				
Nx	Reference			
N1a	0.87 (0.52–1.47)	0.61		
N1b	1.11 (0.71–1.72)	0.657		
N1c	0.73 (0.23–2.38)	0.607		
N2a	1.86 (1.22–2.84)	0.004		
N2b	2.22 (1.49–3.32)	<0.001		
Synchronous metastasis, yes *vs.* no	5.22 (2.14–12.72)	<0.001	5.01 (2.06–12.22)	<0.001
Prehepatectomy chemotherapy, yes *vs.* no	0.94 (0.68–1.3)	0.705		
No. of chemo-cycle	1.01 (0.97–1.04)	0.773		
Concurrent ablation, yes *vs.* no	0.89 (0.52–1.52)	0.662		
Hepatectomy extent, major *vs.* minor	1.17 (0.89–1.54)	0.268		
Hepatectomy method, anatomical *vs.* non-anatomical	0.87 (0.67–1.13)	0.304		
Resection status, R2 *vs.* R0/1	0.94 (0.44–1.99)	0.862		
No. of tumors				
1	Reference			
2	1.06 (0.76–1.47)	0.747		
≥3	1.04 (0.74–1.44)	0.837		
Maximum tumor size of hepatic metastasis	1.09 (1.04–1.14)	<0.001	1.09 (1.01–1.12)	0.026
Prehepatectomy CEA (ng/mL), 3> *vs.* ≤3	1.61 (1.20–2.16)	0.002	1.46 (1.07–1.97)	0.016

OR, odds ratio; CI, confidence interval.

Table 3. Univariate and multivariate analyses of prognostic factors associated with progression-free survival

Variable	Univariate		Multivariate	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age	1 (0.99–1.02)	0.761		
Primary site sidedness, left *vs.* right	0.83 (0.59–1.16)	0.272		
T stage				
Tx	Reference			
T1	0.39 (0.05–2.76)	0.344		
T2	1.11 (0.23–5.36)	0.896		
T3	0.87 (0.21–3.51)	0.840		
T4a	1.61 (0.39–6.62)	0.510		
T4b	2.11 (0.48–9.35)	0.326		
N stage				
Nx	Reference			
N1a	0.79 (0.45–1.36)	0.39		
N1b	0.95 (0.6–1.49)	0.808		
N1c	0.46 (0.11–1.91)	0.285		
N2a	1.65 (1.07–2.54)	0.025		
N2b	1.48 (0.96–2.29)	0.074		
Synchronous metastasis, yes *vs.* no	0.43 (0.29–0.64)	<0.001	0.42 (0.28–0.63)	<0.001
Prehepatectomy chemotherapy, yes *vs.* no	1.32 (0.95–1.83)	0.103		
No. of chemo-cycle	1.03 (0.99–1.06)	0.103		
Concurrent ablation, yes *vs.* no	1.02 (0.6–1.73)	0.95		
Hepatectomy extent, major *vs.* minor	1.08 (0.8–1.46)	0.604		
Hepatectomy method, anatomical *vs.* non-anatomical	0.94 (0.7–1.25)	0.661		
Resection status, R2 *vs.* R0/1	1.14 (0.54–2.43)	0.731		
No. of tumors				
1	Reference			
2	0.97 (0.68–1.4)	0.887		
≥3	1 (0.7–1.44)	0.996		
Maximum tumor size of hepatic metastasis	1.06 (1–1.13)	0.037	1.05 (0.98–1.12)	0.157
Prehepatectomy CEA (ng/mL), 3> *vs.* ≤3	1.48 (1.08–2.02)	0.014	1.40 (1.01–1.94)	0.042

OR, odds ratio; CI, confidence interval.

Table 4. Comparison of recurrence pattern between right-sided group and left-sided group

	Right side (n = 45)	Left side (n = 140)	P-value
Recurrence type			
Local	2 (4.4)	5 (3.6)	0.678
Distant metastasis	43 (95.6)	135 (96.4)	
Type of distant metastasis			
Single organ	31 (72.1)	95 (70.4)	0.981
Hepatic	15 (48.4)	35 (36.8)	0.868
Pulmonary	10 (32.3)	37 (38.9)	
Peritoneal	2 (6.5)	7 (7.4)	
Distant lymph node	2 (6.5)	6 (6.3)	
Bone	0 (0)	4 (4.2)	
Others	2 (6.5)	6 (6.3)	
Multiple organs	12 (27.9)	40 (29.6)	
Hepatic + pulmonary	8 (66.7)	21 (52.5)	0.982
Hepatic + intra-abdominal	2 (16.7)	8 (20.0)	
Hepatic + others	1 (8.3)	2 (5.0)	
Pulmonary + intra-abdominal	1 (8.3)	5 (12.5)	
Pulmonary + others	0 (0)	1 (2.5)	
Intra-abdominal	0 (0)	3 (7.5)	

metastasis accounting for about 70% in both groups (P = 0.981). The proportions of single-organ metastasis (hepatic; right *vs.* left, 48.4% *vs.* 36.8%; P = 0.868) also showed no difference in sidedness.

DISCUSSION

While numerous factors influenced survival in CRC, several studies have reported on the concept of 'sidedness', which refers to differences in survival based on the location of the primary tumor [16-19]. Survival outcomes according to sidedness suggest a worse prognosis for right-side colon cancer compared to left-side, and this discrepancy has been attributed to differences in embryonic origin, *RAS* status, and microsatellite instability [19].

Survival disparities based on the location of the primary tumor have also been observed in CRLM. In unresectable CRLM, right-sided colon cancer is associated with worse survival compared to left-sided colon cancer [20]. However, conflicting results have been reported in resectable CRLM. A meta-analysis of survival after hepatectomy showed that right-sided colon cancer was associated with a poorer prognosis compared to left-sided colon cancer, but Sasaki et al. [14] reported the opposite result. Furthermore, Zhang et al. [15] reported that patients with right-sided colon cancer had worse recurrence-free survival but similar OS.

In our study, we found no differences in OS or PFS based on sidedness. This result is consistent with the findings of Zhang et al. [15], who analyzed 611 patients using propensity score matching (PSM). The main difference between their study and ours is that we did not conduct PSM, and instead performed a subgroup analysis. In the subgroup analysis, synchronous tumors did not show a difference in prognosis based on sidedness. However, in the subgroup analysis of metachronous tumors, OS did not differ by sidedness, but PFS was worse in the right-sided group. Although various factors may have contributed to this outcome, we speculate that the higher proportion of single hepatic metastasis within the metachronous tumor (right *vs.* left, 30% *vs.* 67%) on the left side may have played a role.

The right-sided group exhibited a lower proportion of prehepatectomy chemotherapy. In the analysis of subgroups, prehepatectomy chemotherapy did not show any differences in the metachronous group, but the low proportion of prehepatectomy chemotherapy in synchronous tumors had an impact. It appears that this is due to selection bias that arose from our investigation of resectable CRLM rather than the entire CRLM population.

The prognostic factor analysis of our study revealed that resection status did not exert an influence on OS and PFS. Firstly, this result may be attributed to selection bias, whereby patients with a high probability of R2 resection are excluded from the initial selection process for hepatectomy. Furthermore, in the case of R2 resection, all but 3 patients had resections that were not detected and removed due to their small size. Consequently, we consider that the analysis demonstrated that resection status did not affect prognosis.

The postoperative recurrence rate of CRLM is reported to be around 70% [21], and intrahepatic metastasis has been identified as the most common recurrence pattern, although rates vary according to systemic therapy and clinical risk score (CRS) [22]. Recurrence patterns by sidedness also indicate that intrahepatic metastasis is the predominant pattern regardless of the primary tumor location [14]. However, in our study, pulmonary metastasis was identified as the most common single-organ distant metastasis in the left-sided group, although the difference was not statistically significant. Unlike previous studies, we differentiated between single-organ distant metastasis and multi-organ distant metastasis and found that the prevalence of at least one intrahepatic metastasis in multi-organ distant metastasis was more than 80%, regardless of the sidedness.

Various aggressive methods, including consideration of future remnant liver volume, are being explored in the management of CRLM, and liver transplantation is also under investigation [23-25]. When considering surgical resection, factors such as size, tumor location, and biological characteristics of the primary tumor should be taken into account to determine resectability [26-28]. However, in clinical practice, some patients may present with borderline resectability despite consideration of these factors. If the location of the primary tumor were an independent prognostic factor in these patients, the concept of sidedness could become a critical consideration in clinical decision-making. However, our results confirm that sidedness is not an independent prognostic factor in patients with CRLM.

This study has several limitations, including its retrospective nature and single-center study design. In addition, it did not consider various prognostic factors such as classification of CRS and genomic status (*RAS* or *BRAF* status). However, unlike other studies, we exclusively analyzed patients after 2008 onwards and also included patients after 2016, when less invasive liver resections such as laparoscopic liver surgery began to be actively performed [29,30].

In conclusion, sidedness was not identified as an independent prognostic factor in resectable CRLM. Instead, prognosis was associated with CEA levels, synchronous tumor, and maximum tumor size of hepatic metastasis. In addition, the patterns of recurrence after hepatectomy did not differ based on sidedness.

ACKNOWLEDGEMENTS

Fund/Grant Support

None.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID iD

Sung Jun Jo: https://orcid.org/0000-0003-4638-652X
Jongman Kim: https://orcid.org/0000-0002-1903-8354
Jung Kyong Shin: https://orcid.org/0000-0002-2298-8799
Jinsoo Rhu: https://orcid.org/0000-0001-9809-8525
Jung Wook Huh: https://orcid.org/0000-0002-4485-0184
Gyu-seong Choi: https://orcid.org/0000-0003-2545-3105
Jae-Won Joh: https://orcid.org/0000-0003-4823-6218

Author Contribution

Conceptualization, Methodology: SJJ, JK
Project Administration: JWJ, GC
Investigation: SJJ
Formal Analysis: SJJ, JK
Resources: JK, GC, JR, JKS, JWH
Writing – Original Draft: All authors
Writing – Review & Editing: All authors

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev 2015;41:729-41.
3. Prades J, Borras JM. Shifting sands: adapting the multidisciplinary team model to technological and organizational innovations in cancer care. Future Oncol 2014;10:1995-8.
4. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
5. Lanari J, Dueland S, Line PD. Liver transplantation for colorectal liver metastasis. Curr Transplant Rep 2020;7:311-6.
6. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
7. Carbone F, Chee Y, Rasheed S, Cunningham D, Bhogal RH, Jiao L, et al. Which surgical strategy for colorectal cancer with synchronous hepatic metastases provides the best outcome? A comparison between primary first, liver first and simultaneous approach. Updates Surg 2022;74:451-65.
8. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. Ann Gastroenterol Surg 2019;3:50-6.
9. Dekker E, Tanis PJ, Vleugels JL, Kasi PM, Wallace MB. Colorectal cancer. Lancet 2019;394:1467-80.
10. Hodges N, Mackenzie H, D'Souza N, Brown G, Miskovic D. Survival outcomes for right-versus left-sided colon cancer and rectal cancer in England: a propensity-score matched population-based cohort study. Eur J Surg Oncol 2022;48:841-9.
11. Brungs D, Aghmesheh M, de Souza P, Ng W, Chua W, Carolan M, et al. Sidedness is prognostic in locoregional colon cancer: an analysis of 9509 Australian patients. BMC Cancer 2017;17:251.
12. Joung JG, Oh BY, Hong HK, Al-Khalidi H, Al-Alem F, Lee HO, et al. Tumor heterogeneity predicts metastatic potential in colorectal cancer. Clin Cancer Res 2017;23:7209-16.
13. Smedman TM, Line PD, Hagness M, Syversveen T, Grut H, Dueland S. Liver transplantation for unresectable colorectal liver metastases in patients and donors with extended criteria (SECA-II arm D study). BJS Open 2020;4:467-77.
14. Sasaki K, Andreatos N, Margonis GA, He J, Weiss M, Johnston F, et al. The prognostic implications of primary colorectal tumor location on recurrence and overall survival in patients undergoing resection for colorectal liver metastasis. J Surg Oncol 2016;114:803-9.
15. Zhang Y, Wang Y, Yuan Y, Qiu J, Qiu Y, He W, et al. Primary tumor location affects recurrence-free survival for patients with colorectal liver metastases after hepatectomy: a propensity score matching analysis. World J Surg Oncol 2020;18:98.
16. Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107:dju427.
17. Yu J, Wu WK, Li X, He J, Li XX, Ng SS, et al. Novel recurrently mutated genes and a prognostic mutation signature in colorectal cancer. Gut 2015;64:636-45.
18. Waldstein S, Spengler M, Pinchuk IV, Yee NS. Impact of colorectal cancer sidedness and location on therapy and clinical outcomes: role of blood-based biopsy for personalized treatment. J Pers Med 2023;13:1114.
19. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. Gastroenterology Res

2018;11:264-73.
20. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017;3:194-201.
21. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.
22. Buisman FE, Galjart B, van der Stok EP, Balachandran VP, Boerner T, Drebin JA, et al. Recurrence patterns after resection of colorectal liver metastasis are modified by perioperative systemic chemotherapy. World J Surg 2020;44:876-86.
23. Calderon Novoa F, Ardiles V, de Santibañes E, Pekolj J, Goransky J, Mazza O, et al. Pushing the limits of surgical resection in colorectal liver metastasis: how far can we go? Cancers (Basel) 2023;15:2113.
24. Ros J, Salva F, Dopazo C, López D, Saoudi N, Baraibar I, et al. Liver transplantation in metastatic colorectal cancer: are we ready for it? Br J Cancer 2023;128:1797-806.
25. Ryu JH. Two stage hepatectomy (TSH) or associating liver partition and portal vein ligation for staged hepatectomy (ALLPS) for bilobar multiple colorectal liver metastasis. Ann Hepatobiliary Pancreat Surg 2021;25(Suppl 1):S19.
26. Dijkstra M, Nieuwenhuizen S, Puijk RS, Timmer FE, Geboers B, Schouten EA, et al. Primary tumor sidedness, RAS and BRAF mutations and MSI status as prognostic factors in patients with colorectal liver metastases treated with surgery and thermal ablation: results from the Amsterdam Colorectal Liver Met Registry (AmCORE). Biomedicines 2021;9:962.
27. Ivey GD, Johnston FM, Azad NS, Christenson ES, Lafaro KJ, Shubert CR. Current surgical management strategies for colorectal cancer liver metastases. Cancers (Basel) 2022;14:1063.
28. Choi M, Han DH, Choi JS, Choi GH. Can the presence of KRAS mutations guide the type of liver resection during simultaneous resection of colorectal liver metastasis? Ann Hepatobiliary Pancreat Surg 2022;26:125-32.
29. Jia C, Li H, Wen N, Chen J, Wei Y, Li B. Laparoscopic liver resection: a review of current indications and surgical techniques. Hepatobiliary Surg Nutr 2018;7:277-88.
30. Park JH, Suh S, Hong SK, Lee S, Hong SY, Choi Y, et al. Pure laparoscopic versus open right donor hepatectomy including the middle hepatic vein: a comparison of outcomes and safety. Ann Surg Treat Res 2022;103:40-6.