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ORIGINAL ARTICLE

Effect of Primary Tumor Location on Postmetastasectomy Survival in Patients with Colorectal Cancer Liver Metastasis

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Abstract

Background The effects of primary tumor location on colorectal liver metastasis (CRLM) and post-hepatic-metastasectomy overall survival (OS) are controversial. This study evaluated the difference in post-hepatic-metastasectomy OS among right-sided colon, left-sided colon, and rectal cancer groups.

Methods In total, 381 patients who underwent curative-intent CRLM resection were enrolled. Patients were grouped based on the primary tumor location (right-sided, left-sided, and rectum). The Kaplan–Meier analysis and log-rank test were performed for survival analysis. The univariate and multivariate analyses of clinical and pathological factors were performed using the Cox proportional hazards model.

Results Significant OS difference was noted among the three groups (log-rank, $p = 0.014$). The multivariate analysis revealed a 32% lower death risk in left-sided colon cancer compared with right-sided colon cancer (hazard ratio [HR] 0.68, $p = 0.042$), whereas no OS difference was noted between the rectal cancer and right-sided colon cancer groups. The left- versus right-sided OS advantage was noted only in the KRAS wild-type subgroup (HR 0.46, $p = 0.002$), and a rectal versus right-sided OS disadvantage was noted in the KRAS mutant subgroup (HR 1.78, $p = 0.03$).

Conclusions The CRLM post-hepatic-metastasectomy OS was superior in left-sided colon cancer than in right-sided colon cancer and was similar in rectal and right-sided colon cancer. The OS difference in different primary tumor locations is dependent on KRAS mutation status, with a decreased left- versus right-sided death risk noted only in KRAS wild-type colon cancer and an increased rectal versus right-sided death risk noted only in KRAS mutant colon cancer.

Keywords Colorectal neoplasms · Neoplasm metastasis · KRAS protein · BRAF protein

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Introduction

Colorectal cancer (CRC) is a composite of two distinct disease entities based on the tumor location side.[1,2] Right-sided CRC originates from the midgut, from the ileocecal valve to proximal two-thirds of the transverse colon, and left-sided CRC originates from the hindgut, from the distal one-third of the transverse colon to the rectum.[3] According to a large population study, higher frequencies of KRAS, BRAF, and PIK3CA mutation are observed in right-sided CRC than in left-sided CRC, suggesting different genetic backgrounds.[4] The prognosis of left-sided CRC is better than right-sided CRC,[5,6] and a difference in the survival rate is noted both after curative surgical resection and in metastatic disease.[7–10] The location of the primary tumor affected the efficacy of anti-EGFR agents

and had profound effects on systemic therapy choice and current treatment sequencing in CRC.[11–17]

Staged or simultaneous surgical resection of the primary tumor and liver metastasis in carefully selected cases improved the outcome in patients with CRC liver metastases (CRLM).[18,19] The 5-year post-hepatic-metastasectomy survival rate ranges from 20 to 50% and can reach 71% in patients with solitary liver metastasis.[20–23] Studies have indicated that independent factors are responsible for poor prognosis of post-hepatic-metastasectomy outcomes, which include positive resection margin of metastasis, multiple or large liver tumors, extrahepatic lesions, or positive lymph nodes of the primary tumor. However, evidence regarding the mechanism by which CRC location affects the post-hepatic-metastasectomy survival rate remains unknown. Three studies have revealed similar post-hepatic-metastasectomy survival rates for the right and left sides,[24–26] whereas three other studies have revealed better survival for left-sided primary tumor.[27–29] The significance of the location to post-hepatic-metastasectomy survival remains inconclusive and warrants further investigation. In this study, we investigated the effect of CRC location on post-hepatic-metastasectomy survival.

Material and Methods

Study Design and Patients

We identified patients who underwent curative-intent CRLM resection in Taipei Veterans General Hospital. All resected liver metastasis samples were pathologically confirmed as adenocarcinoma compatible to CRLM. Patients who underwent either simultaneous or sequential resection of primary CRC and CRLM were included. The exclusion criterion was either non-curative-intent surgical resection of CRLM or extrahepatic metastasis (diagnosed through an imaging study or biopsy) as noted during the pre-hepatic-metastasectomy survey. Our patients were classified into three groups: the right-sided colon group, including patients with tumor in the cecum, ascending colon, hepatic flexure, and proximal two-thirds of the transverse colon; left-sided colon group, including patients with tumor in the distal one-thirds of the transverse colon, splenic flexure, descending colon, and sigmoid; and rectal cancer group. The location of primary CRC was determined through imaging study and operative records. Overall survival (OS) was defined as the survival period from the date of hepatic metastasectomy to mortality or last follow-up. Patients alive at the end of study were censored. This study was approved by the Institutional Review Board and Ethics Committee of Taipei Veterans General Hospital.

Patient characteristics—age; sex; primary tumor location; synchronous or metachronous liver metastasis; number and size of CRLMs; lobar distribution of CRLMs; KRAS and BRAF mutation statuses; simultaneous or sequential resection of CRLM and primary tumor; resection margin; histology; initial T stage, nodal status, and metastasis status according to the American Joint Committee on Cancer seventh edition staging system; time to liver metastasis; and type of perioperative therapy—were documented.

Evaluation of OS after Hepatic Metastasectomy

All patients included in our study were followed up with a minimum frequency of once every 3 months at an outpatient clinic. The OS after hepatic metastasectomy was determined using the time from the date of hepatic metastasectomy to the date of death or last date of evaluation.

Statistical Analysis

Categorical and continuous variables were analyzed using the chi-square test and one-way analysis of variance, respectively, to determine the difference among three subgroups (right-sided colon, left-sided colon, and rectum). Continuous variables are presented as the median and 95% confidence interval. The Kaplan–Meier method and log-rank test were performed for survival analysis and to compare survival difference. The univariate Cox proportional hazard model was used to evaluate the mechanism by which different clinical and pathological factors or mutational statuses affected OS, and all clinicopathological factors with a p value < 0.100 were included in further multivariate analysis. In total, 336 patients with known KRAS status and 250 patients with known BRAF status were analyzed in the univariate analysis. Due to a lack of significance in OS (KRAS mutation, $p = 0.370$; BRAF mutation, $p = 0.450$), KRAS and BRAF statuses were not further analyzed in the multivariate analysis. Subgroup analysis evaluating OS difference in the left-sided and right-sided colon groups or the rectal cancer and right-sided colon groups was performed using the Cox proportional hazard model. The KRAS subgroup analysis included only patients with known KRAS mutation status, and the BRAF subgroup analysis included only patients with known BRAF mutation status. The results of univariate and multivariate analyses as well as subgroup analysis are presented as hazard ratios (HRs) and 95% confidence intervals. The HRs and confidence intervals were visualized using forest plots. Statistical

analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA).

Result

Patient Characteristics

In total, 381 patients who underwent curative-intent CRLM resection were included in this retrospective study and stratified by primary tumor location. A total of 75 patients had right-sided colon cancer, 161 patients had left-sided colon cancer, and 145 patients had rectal cancer. The baseline clinicopathological characteristics and mutational statuses of all patients are listed in Table 1. Using the data collected over the years, we examined KRAS mutation in 88% of cases and BRAF mutation in 66% of cases. Patients with different primary tumor locations had different frequencies of KRAS (right-sided colon 59%, left-sided colon 27%, and rectum 35%, $p < 0.001$) and BRAF (right-sided colon 8%, left-sided colon 4%, and rectum 0%, $p = 0.021$) mutation. Overall, 24% and 85% of patients had received induction and adjuvant systemic treatment, respectively. No significant difference in the proportion receiving induction or adjuvant therapy was noted between the three groups. We further analyzed the bioagent type (cetuximab, bevacizumab, or none) and chemotherapy backbone type (FOLFOX, FOLFIRI, FL, or tegafur/uracil) used in induction or adjuvant therapy. A small proportion (< 20%) of patients received bioagents as adjuvant therapy, and a difference in bioagent use in adjuvant therapy was noted between the three groups. The frequencies of chemotherapy backbone use in induction or adjuvant therapy and bioagent use in induction therapy were not significantly different. Other clinicopathological features—age; sex; synchronous or metachronous liver metastasis; number and maximal size of CRLM; lobar distribution of CRLM; simultaneous or sequential resection of CRLM and primary tumor; resection margin; histology; initial T stage, nodal status, and metastasis status according to the AJCC seventh edition staging system; and time to liver metastasis—were balanced among the three groups.

OS After CRLM Metastasectomy

The median follow-up time in our study was 39.5 months. The median OS after hepatic metastasectomy was significantly different among the three groups (right-sided colon 32.3 months, left-sided colon 56.2 months, and rectal cancer 41.4 months; log-rank $p = 0.014$; Fig. 1a). To evaluate the effect of primary tumor location and other potential clinicopathological factors on OS, further univariate analysis was performed(Fig. 2a, Table 2). The left-sided colon cancer had better OS than did right-sided colon cancer (HR 0.71, $p = 0.049$), whereas rectal cancer and right-sided colon cancer had similar OS (HR 1.05, $p = 0.80$). Several factors were found to be associated with a significant difference in OS, including liver metastasis number > 3 (Fig. 1b), bilobar liver metastasis (Fig. 1c), advanced T stage (T3 and T4, Fig. 1d), and advanced N stage (N1 and N2, Fig. 1e). Clinical factors with $p < 0.100$ were included in further multivariate analysis (Fig. 2b, Table 2). Longer OS was noted in the left-sided colon cancer than in right-sided colon cancer (HR 0.68, $p = 0.042$), whereas OS was similar in rectal cancer and right-sided colon cancer groups (HR 1.11, $p = 0.56$). Furthermore, liver metastasis number > 3 and advanced N stage were found to be associated with shorter OS in the multivariate analysis.

Comparison of Left-Sided Colon Cancer and Rectal Cancer with Right-Sided Colon Cancer Through Subgroup Analysis

OS of left-sided colon cancer and rectal cancer were compared with that of right-sided colon cancer in different subpopulations. OS was found to be longer in left-sided colon cancer than in right-sided colon cancer in the following subgroups: patients with age > 60 years, female gender, maximal size of liver metastasis ≦ 3 cm, unilobar liver metastasis, adenocarcinoma, advanced T stage (T3 and T4), advanced N stage (N1 and N2), and KRAS wild-type (HR 0.46, $p = 0.002$; Fig. 3). However, OS was poorer in the rectal cancer group than in the right-sided colon cancer group for the KRAS mutation subgroup (HR 1.78, $p = 0.031$). No significant difference was noted in all other subgroups (Fig. 4). Because of few cases, those with BRAF mutation ($n = 9$) and histology other than adenocarcinoma ($n = 8$) were not included in the subgroup analysis.

Subgroup Analysis by KRAS Gene

In the KRAS wild-type subgroup analysis, the median OS of the right-sided colon, left-sided colon, and rectal cancer groups was found to be 27.0, 61.2, and 41.6 months, respectively. A significant OS difference was noted among the three groups ($p = 0.003$, Fig. 5a). A significantly prolonged OS was noted in the left-sided colon cancer group than in the right-sided colon cancer group (HR 0.46, $p = 0.002$), and a similar OS was noted when the rectal cancer group was compared with the right-sided

Table 1 Patient characteristics

Patient characteristics	Right (%) ($n = 75$)	Left (%) ($n = 161$)	Rectum(%) ($n = 145$)	p value
Age y/o (95% CI)	63.9 (61.2–66.7)	60.9 (58.8–62.9)	61.6(59.6–63.6)	0.203
Sex				
Male	42 (56)	101 (63)	104 (72)	0.052
Female	33 (44)	60 (37)	41 (28)	
Liver metastatic tumor characteristics				
Synchronous metastasis				
Yes	51 (68)	100 (62)	90 (62)	0.636
No	24 (32)	61 (38)	55 (38)	
Number of liver metastasis				
≦ 3	62 (83)	136 (85)	121 (83)	0.957
> 3	13 (17)	25 (15)	24 (17)	
Maximal size of liver metastasis				
≦ 3 cm	64 (85)	140 (87)	131 (81)	0.492
> 3 cm	11 (15)	21 (13)	14 (19)	
Liver metastasis distribution				
Unilobar	63 (84)	118 (73)	106 (73)	0.151
Bilobar	12 (16)	43 (27)	39 (27)	
Primary tumor characteristics				
Histology				
Adenocarcinoma	71 (95)	159 (99)	142 (98)	0.124[b]
Mucinous adenocarcinoma	4 (5)	2 (1)	2 (1)	
Carcinoid	0 (0)	0 (0)	1 (1)	
T stage ($n = 355$)[a]				
T1, T2	4 (6)	5 (3)	13 (10)	0.078[b]
T3, T4	68 (94)	145 (97)	120 (90)	
N stage ($n = 342$)[a]				
N0	17 (25)	53 (37)	38 (30)	0.189[b]
N1–N2	52 (75)	92 (63)	90 (70)	
Stage (AJCC 7th)				
I, II, III	21 (28)	58 (36)	55 (38)	0.328
IV	54 (72)	103 (64)	90 (62)	
Time to liver metastasis				
≦ 18 months	12 (16)	27 (17)	38 (26)	0.066
> 18 months	9 (12)	31 (19)	17 (12)	
M1 at diagnosis	54 (72)	103 (64)	90 (62)	
Mutation profile				
KRAS mutation ($n = 336$)[a]				
Mutant	41 (59)	39 (27)	44 (35)	*< 0.001*
Wild	28 (41)	103 (73)	81 (65)	
BRAF mutation ($n = 250$)[a]				
Mutant	5 (8)	4 (4)	0 (0)	*0.021*[b]
Wild	54 (92)	98 (96)	89 (100)	
Hepatectomy characteristics				
Surgery sequence				
Combined resection	41 (55)	79 (49)	68 (47)	0.548
Sequential resection	34 (45)	82 (51)	77 (53)	
Resection margin ($n = 325$)[a]				
R0 resection	64 (99)	137 (99)	118 (97)	0.809[b]

Table 1 (continued)

Patient characteristics	Right (%) ($n = 75$)	Left (%) ($n = 161$)	Rectum(%) ($n = 145$)	p value
R1 resection	1 (1)	1 (1)	4 (3)	
Perioperative therapy				
Induction therapy				
Yes	14 (19)	40 (25)	36 (25)	0.530
No	61 (81)	121 (75)	109 (75)	
Induction bioagents				
Cetuximab	2 (3)	11 (9)	6 (4)	0.603[b]
Bevacizumab	4 (5)	7 (4)	5 (3)	
None	69 (92)	143 (87)	134 (93)	
Induction chemotherapy				
FOLFOX	12 (16)	31 (19)	22 (15)	0.467[b]
FOLFIRI	3 (4)	8 (5)	9 (6)	
FL or tegafur/uracil	0 (0)	4 (2)	6 (4)	
None	60 (80)	118 (74)	108 (75)	
Adjuvant therapy				
Yes	65 (87)	143 (89)	116 (80)	0.189
No	10 (13)	18 (11)	29 (20)	
Adjuvant bioagent				
Cetuximab	5 (7)	19 (12)	5 (3)	*0.021*
Bevacizumab	9 (12)	18 (11)	7 (5)	
None	61 (81)	124 (77)	133 (92)	
Adjuvant chemotherapy				
FOLFOX	29 (38)	77 (48)	60 (41)	0.136
FOLFIRI	30 (40)	49 (30)	36 (23)	
FL or tegafur/uracil	5 (7)	16 (10)	20 (14)	
None	11 (15)	19 (12)	29 (20)	

[a] The number of patients for whom data were available

[b] p value by Fisher's exact test

Italicized values, $p < 0.05$; *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *Max size*, maximum size; *FL*, fluorouracil plus leucovorin

colon cancer group (HR 0.71, $p = 0.178$; Fig. 3, Fig. 4). In KRAS mutation subgroup analysis, the median OS of the right-sided colon, left-sided colon, and rectal cancer groups was found to be 34.0, 52.0, and 28.2 months, respectively, with a significant OS difference ($p = 0.04$, Fig. 5b). In this subgroup analysis, OS was similar between left-sided and right-sided colon cancer groups, whereas a significantly shorter OS was noted in the rectal cancer group compared with that in the right-sided colon cancer group (Figs. 3 and 4).

Discussion

Although multiple studies have established that left-sided colon cancer has better prognosis than right-sided colon cancer,[5–10] the effect of sidedness on CRLM hepatic metastasectomy remains inconclusive. In our study, a decreased risk of death after CRLM hepatic metastasectomy was noted in the left-sided colon cancer group than that in the right-sided colon cancer group. Furthermore, we found similar OS after hepatic metastasectomy between the rectal cancer and right-sided colon cancer groups. Moreover, KRAS wild-type subgroup analysis revealed a lower death risk in left-sided colon cancer, whereas KRAS mutation subgroup analysis revealed a higher death risk in rectal cancer than in right-sided colon cancer.

In our study, 32% lower death risk was noted after hepatic metastasectomy in left-sided colon cancer compared with right-sided colon cancer. Multiple clinicopathological factors were balanced among the three groups, including age, sex, synchronous or metachronous metastasis, number and maximal size of liver metastases, lobar distribution, primary tumor size, nodal status, staging

Table 2 Summary of univariate and multivariate analyses

	Univariate		Multivariate	
Patient characteristics	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age				
> 60 y/o	1.09 (0.85–1.41)	0.488		
≦ 60 y/o	ref			
Sex				
Female	0.89 (0.68–1.16)	0.378		
Male	ref			
Primary tumor location				
Left	0.71 (0.50–0.99)	*0.049*	0.68 (0.47–0.98)	*0.042*
Rectum	1.05 (0.75–1.47)	0.795	1.11 (0.78–1.58)	0.561
Right	ref		ref	
Metachronous/synchronous				
Metachronous	1.10 (0.85–1.42)	0.484		
Synchronous	ref			
Number of liver metastasis				
> 3	1.79 (1.30–2.46)	*< 0.001*	1.46 (1.01–2.10)	*0.044*
≦ 3	ref		ref	
Maximal size of liver metastasis				
> 3 cm	1.05 (0.69–1.60)	0.831		
≦ 3 cm	ref			
Liver metastasis distribution				
Bilobar	1.54 (1.16–2.03)	*0.003*	1.34 (0.98–1.83)	0.067
Unilobar	ref		ref	
T stage ($n = 355$)[a]				
T3, T4	2.14 (1.10–4.18)	*0.025*	2.09 (0.98–4.46)	0.058
T1, T2	ref		ref	
N stage ($n = 342$)[a]				
N1–N2	1.59 (1.18–2.16)	*0.002*	1.46 (1.07–1.99)	*0.017*
N0	ref		ref	
Stage (AJCC 7th)				
M1	1.25 (0.96–1.63)	0.092	1.03 (0.77–1.39)	0.83
M0	ref			
KRAS mutation ($n = 336$)[a]				
Mutant	1.13 (0.86–1.49)	0.370		
Wild	ref			
BRAF mutation ($n = 250$)[a]				
Mutant	1.41 (0.58–3.45)	0.450		
Wild	ref			

[a] The number of patients for whom data were available

Italicized values, $p < 0.05$; *ref*, reference; *CI*, confidence interval

(AJCC seventh edition), surgery sequence, resection margin status, and the proportion receiving induction/adjuvant therapy. In this cohort study, only 88% and 66% of patients underwent KRAS and BRAF tests, respectively, due to technical limitation and diagnostic consensus during early years. Previous studies have noted an increased frequency of KRAS and BRAF mutation in right-sided colon cancer.[14–17,28,30–32] Similarly, an

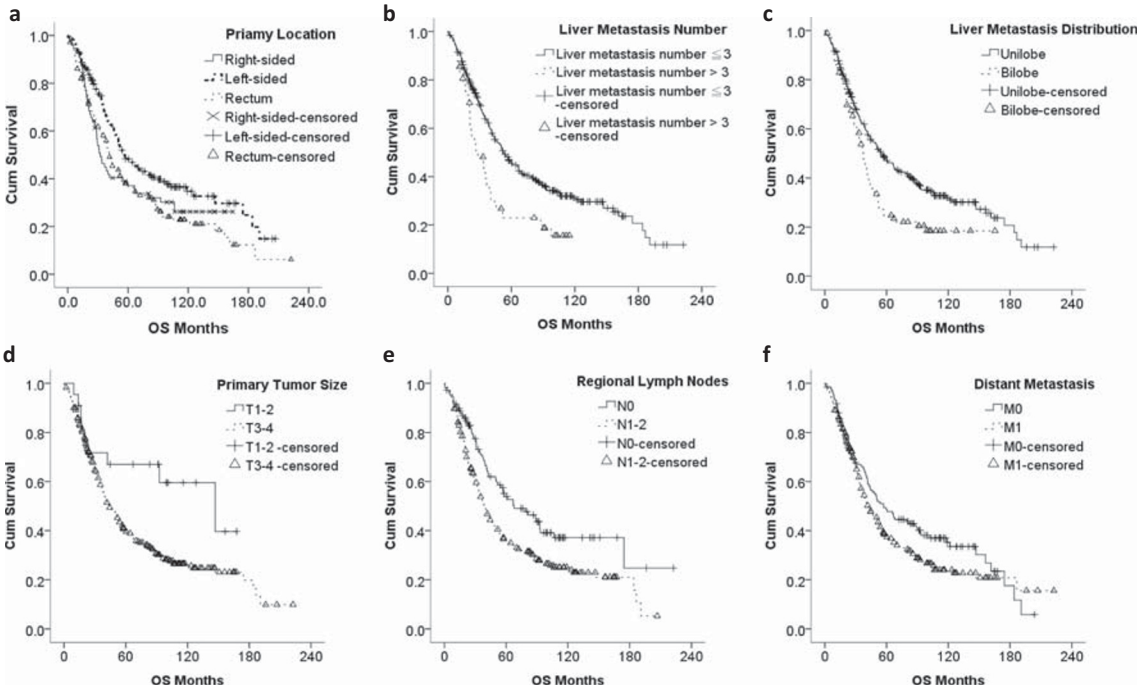

Fig. 1 The Kaplan–Meier curves for overall survival (OS). The median OS (mOS) in **a** right-sided colon cancer: 32.3 months; left-sided colon cancer: 56.2 months; rectal cancer: 41.4 months, $p = 0.014$. **b** Liver metastasis number ≦ 3: 52.4 months; liver metastasis number > 3: 26.6 months, $p < 0.001$. **c** Unilobar liver metastasis: 55.2 months; bilobar liver metastasis: 37.3 months, $p = 0.002$. **d** T1–T2: 146.8 months; T3–T4: 44.1 months, $p = 0.02$. **e** N0: 67.8 months; N1–N2: 39.1 months, $p = 0.002$. **f** M0: 57.0 months; M1: 42.3 months, $p = 0.09$

increased proportion of KRAS and BRAF mutation was noted in the right-sided colon group in our cohort study. Extrahepatic metastasis, previously identified as being a prognostic factor of poor post-hepatic-metastasectomy survival,[27,24,28] was excluded in this study to elucidate the prognosis of only CRLM and hepatic metastasectomy. Our findings correspond with those of three previous studies,[27–29] strengthening the concept of longer OS after hepatic metastasectomy in left-sided colon cancer compared with right-sided colon cancer.

Although both patients with left-sided colon and those with rectal cancer have been traditionally enrolled in the same group in large clinical trials, recent studies have implied substantial differences in both genetic and clinicopathological features between these two primary sites. These features have included increased KRAS mutation frequency, TOPO-1 expression, and HER2/neu amplification in rectal cancer compared with left-side colon cancer.[4,33] Furthermore, patients with left-sided primary tumor have significantly higher likelihood of liver metastasis, whereas patients with rectal cancer have significantly higher likelihood of lung metastasis and multiple-site metastasis.[33] The difference in clinical management should be considered in terms of using neoadjuvant radiation therapy or chemoradiation therapy in rectal cancer.[34] Indeed, in our study, similar OS after hepatic metastasectomy was noted between the right-sided and rectal cancer groups, whereas OS was significantly better in left-sided colon cancer.

Increased frequency of KRAS mutation was noted in right-sided colon cancer that contributed to poorer prognosis; thus, it is intriguing if the primary location of CRC affects OS after hepatic metastasectomy through mechanisms other than KRAS mutation. In this study, OS difference among the three groups was noted in both KRAS wild-type and mutation subgroup analysis. The superior outcome of left-sided colon cancer compared with right-sided colon cancer was observed only in the KRAS wild-type subgroup but not in the KRAS mutation subgroup. This implies that sidedness exerts an effect on colon cancer prognosis through a KRAS-independent mechanism, and this effect may be masked in the presence of KRAS mutation. Surprisingly, the KRAS mutation subgroup analysis revealed that rectal cancer had an increased risk of death compared with right-sided colon cancer. By contrast, no difference in OS was noted between rectal cancer and right-sided colon cancer in KRAS wild-type subgroup analysis. The difference in prognosis in the KRAS mutation subgroup may be related to more aggressive

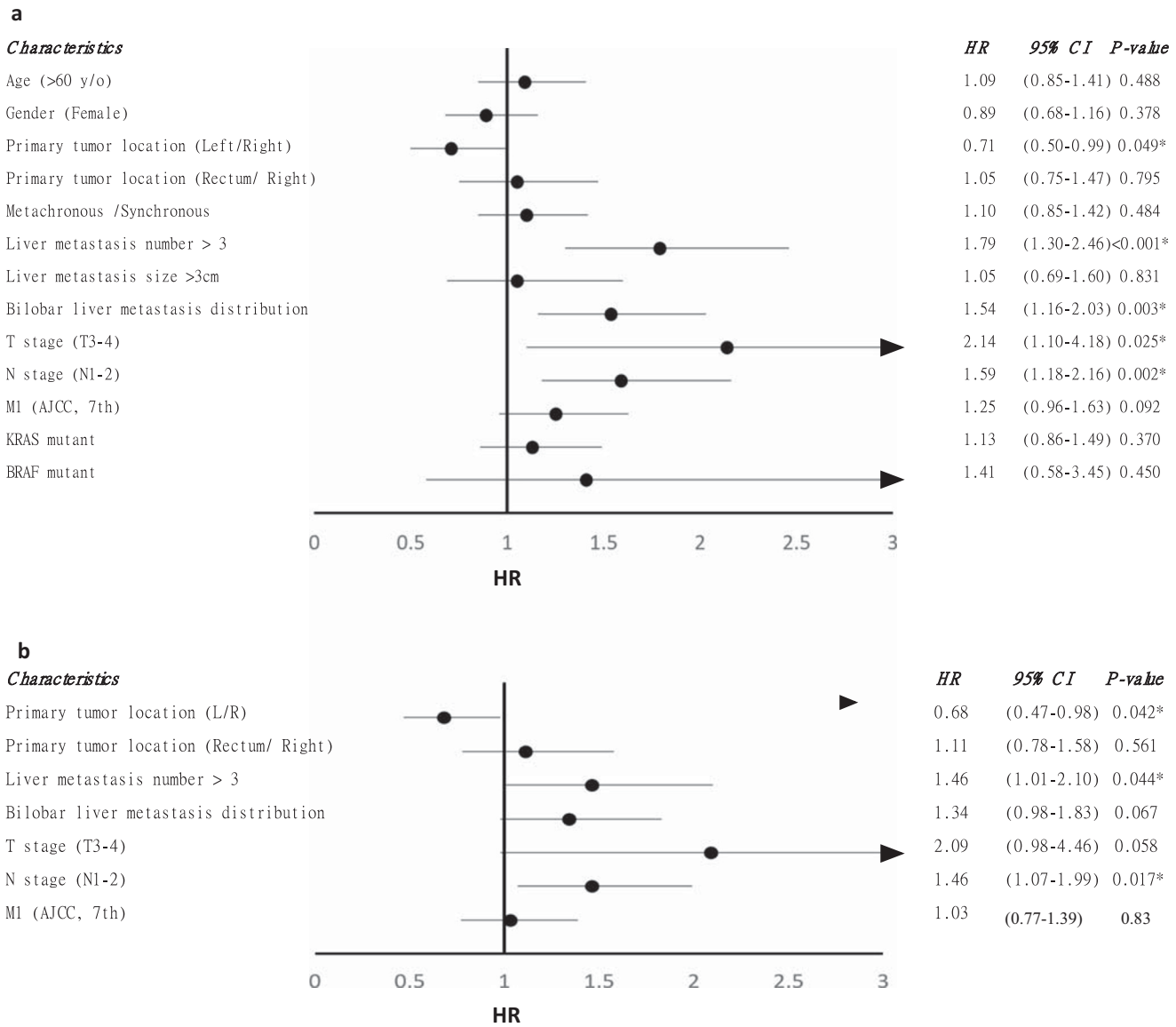

Fig. 2 **a** Significant prognostic factors of OS as revealed by univariate analysis: left-sidedness, liver metastasis number > 3, bilobar liver metastasis, advanced T stage, and advanced N stage. **b** Significant prognostic factors of OS as revealed by multivariate analysis: left-sidedness, liver metastasis number > 3, and advanced N stage. Asterisk: variable with a significant difference

biological characteristics or even resistance to radiation therapy. Further biological and molecular studies are required to uncover the underlying mechanism.

In this study, several factors predicting poor prognosis were identified through multivariate analysis: more than three liver metastases or bilobar distribution, increased primary tumor size, and lymph node involvement. Overall, an extensive primary tumor or CRLM involvement was associated with poorer post-hepatic-metastasectomy outcome. Subgroup analysis of various clinicopathological factors was performed to comprehensively determine how primary tumor location affects OS after hepatic metastasectomy. The left versus right-sided colon cancer OS benefits were noted in subgroups with limited disease status, including smaller maximal CRLM size, unilobar CRLM distribution, and no lymph node metastasis (pN0). A possible explanation is that with progression of colon cancer, successful curative surgery of primary tumor and CRLM become more difficult, and accumulation of mutations may perturb innate genetic characteristics. By contrast, when rectal cancer was compared with right-sided colon

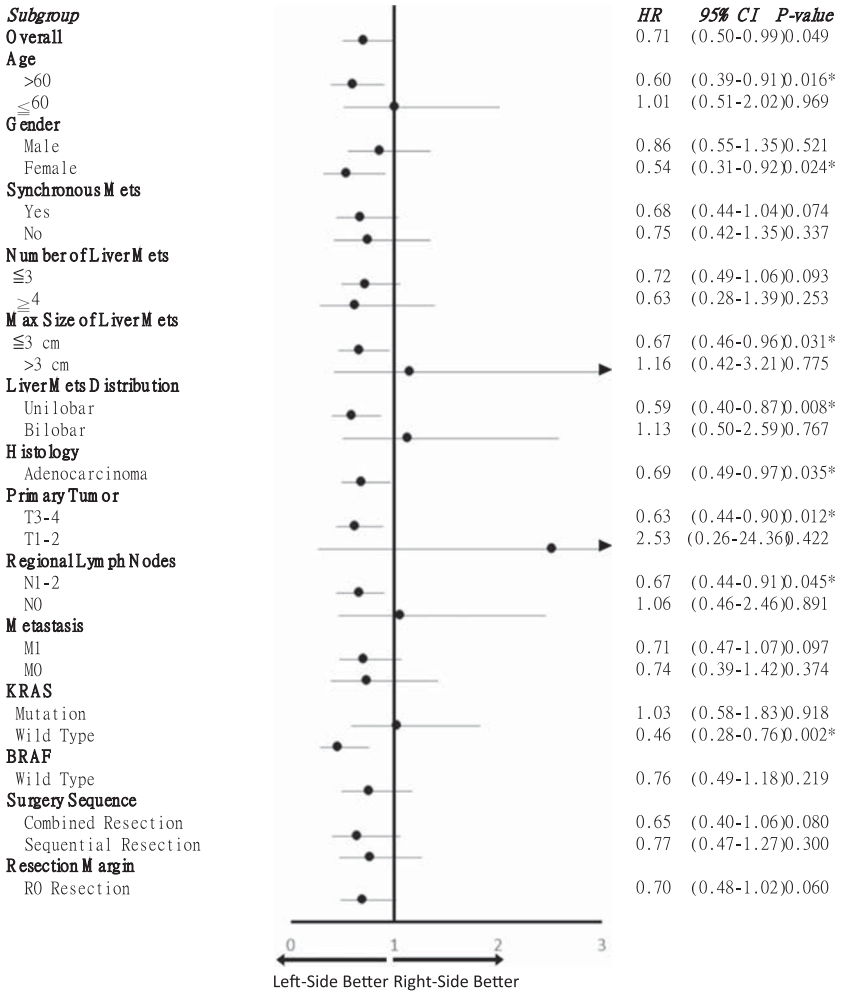

Fig. 3 Subgroup analysis: left-sided colon cancer group versus right-sided colon cancer group. Longer OS was noted in left-sided colon cancer than that in right-sided colon cancer in the following subgroups: age, > 60 years; female gender; maximal size of liver metastasis, > 3 cm; unilobar liver metastasis; adenocarcinoma; advanced T stage; advanced N stage; and KRAS wild-type

cancer, no difference in OS post-CRLM resection was noted in all subgroups except the KRAS mutation subgroups. Furthermore, this result strongly suggested that the KRAS mutation was a strong predictor of poor outcome in the rectal cancer group.

Interestingly, the left versus right-sided colon OS difference was noted only in the female subgroup. A possible explanation is the interplay between sex hormone and colon cancer. For instance, one large randomized trial, which enrolled postmenopausal women to receive estrogen plus progesterone or placebo, revealed a 44% decreased risk of colorectal cancer.[35] Another large-scale retrospective study reported a discrepancy in OS between premenopausal and postmenopausal women, which suggested that OS benefit was noted only in younger women (45 years old or younger).[36]

This study has several limitations. First, this is a retrospective study; thus, selection bias may exist. However, all patient characteristics were balanced among the three study groups, except for the proportion of KRAS and BRAF mutations. The imbalance in KRAS and BRAF mutations represented a naturally existing difference, which had been reported by multiple studies. Second, due to technical limitation and diagnostic consensus in early years, not all patients had received a KRAS or BRAF mutation test. Similarly, the NRAS mutation test was not requested at diagnosis. Third, although only a small proportion of patients received bioagents in adjuvant therapy, a difference regarding bioagent selection existed. However, the primary goal of our study was to evaluate OS after hepatic metastasectomy, and a lack of information regarding mutation status and minor differences in bioagent use in adjuvant therapy did not interfere with the analysis.

Conclusion

The CRLM post-hepatic-metastasectomy OS is dependent on the primary tumor location and KRAS mutation status. The post-hepatic-metastasectomy OS is longer in left-

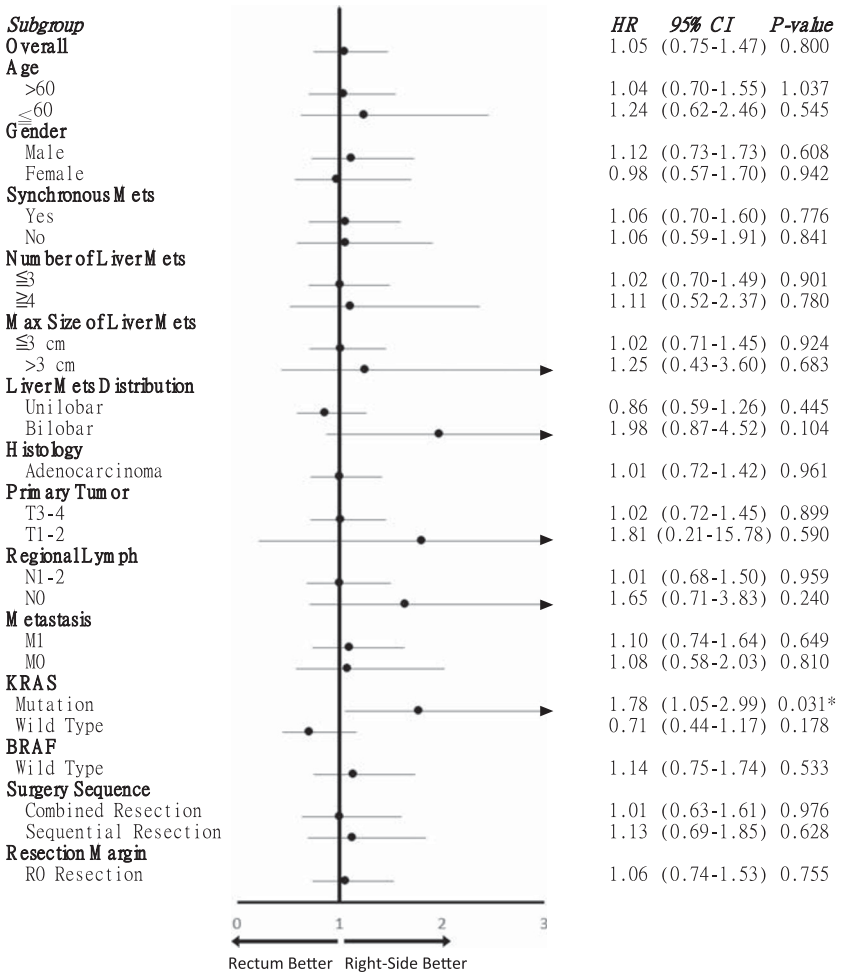

Fig. 4 Subgroup analysis: rectal cancer group versus right-sided colon cancer group. Shorter OS was noted in the rectal cancer group in the KRAS mutant subgroup analysis

sided rather than right-sided colon cancer and is similar in rectal cancer and right-sided colon cancer. The OS difference in different primary tumor location groups is dependent on KRAS mutation status. The decreased left- versus right-sided colon cancer death risk was noted only in the KRAS wild-type subgroup, and an increased rectum

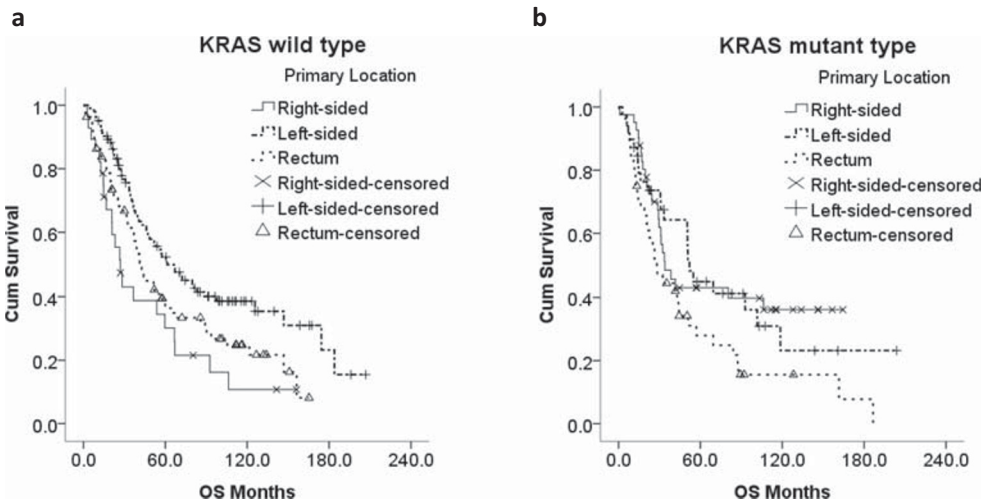

Fig. 5 The Kaplan–Meier curves for overall survival (OS). The median OS (mOS) based on **a** KRAS wild-type subgroup analysis: right-sided colon cancer: 27 months; left-sided colon cancer: 61.2 months; and rectal cancer: 41.6 months, $p = 0.003$. **b** KRAS mutant subgroup analysis: right-sided colon cancer: 34 months; left-sided colon cancer: 52.0 months; and rectal cancer: 28.2 months, $p = 0.04$. A crossover of the left-sided and right-sided colon cancer groups was noted

versus right-sided colon cancer death risk was noted only in the KRAS mutant subgroup.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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