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# Implication of primary tumor location for the indication of preoperative chemotherapy in patients with colorectal liver metastases

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## Abstract

**Background:** The benefit of preoperative chemotherapy for colorectal liver metastases (CRLM) remains uncertain. The aim was to clarify the effect of preoperative chemotherapy on CRLM according to the primary tumor location.

**Methods:** Among a total cohort of 163 patients who underwent curative hepatectomy for CRLM, 36 patients had a right-sided and 127 had a left-sided primary tumor. According to the performance of preoperative chemotherapy, survival analysis was conducted and prognostic factors were identified.

**Results:** Preoperative chemotherapy was administered to 17 patients (47.2%) with a right-sided and 74 (58.3%) with a left-sided primary tumor ($P$ = 0.24). Among the patients who received preoperative chemotherapy, overall survival (OS) and disease-free survival (DFS) were similar between patients with right- and left-sided primary tumors ($P$ = 0.36 and $P$ = 0.44, respectively). Among the patients who underwent upfront hepatectomy, the OS and DFS of patients with a right-sided primary tumor were worse than those with a left-sided primary tumor ($P$ = 0.02 and $P$ = 0.025, respectively). Among the patients who underwent upfront surgery, the right-sided primary tumor was identified as an independent poor prognostic factor for OS (hazard ratio 3.44, $P$ = 0.021).

**Conclusion:** The existence of a right-sided primary tumor may be an indication of preoperative chemotherapy for patients with CRLM.

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## Introduction

The liver is the most common organ for distant metastases from colorectal cancer, and approximately half of colorectal cancer patients will develop liver metastases at some point during the course of their disease.[1,2] Although hepatectomy remains the only treatment that can ensure prolonged survival, more than half of patients experience recurrence after hepatectomy.[3–6] The use of systemic chemotherapy in combination with surgery for patients with colorectal liver metastases (CRLM) is considered to be a tool to reduce relapse and improve long-term outcomes after hepatectomy. However, the benefit of perioperative chemotherapy remains controversial, especially for initially resectable CRLM.[7–12]

It is well known that colorectal cancer is a heterogeneous complex of disease. According to the location of the primary tumor, colorectal cancer can be divided into distinct disease entities from the viewpoint of its embryology, because the right-side colon (including the cecum, ascending colon, and transverse colon) develops from the midgut, while the left-side colon (including the descending colon, sigmoid colon, and rectum) develops from the hindgut.[13] Right-sided tumors are characterized by higher TNM-stage presentation, mucinous histology, high microsatellite instability (MSI) and CpG island methylator phenotype (CIMP), higher *BRAF* mutation, more active immune cell promoting immunogenicity, and less chromosomal instability.[13] Prognostic implications of primary tumor location have also been reported. Recent studies have found that patients with a right-sided primary tumor have worse survival rates than those with a left-sided primary tumor, in colorectal cancer patients

with or without metastatic diseases.[14–20] Although some studies demonstrated that the primary tumor location was associated with long-term outcome in patients with CRLM who underwent hepatectomy with curative intent,[21–24] the implication of primary tumor location for survival is still unclear.

The aim of this study was to investigate the prognostic implications of primary tumor location in patients with CRLM who underwent hepatectomy in combination with, or without, preoperative chemotherapy.

## Patients and methods

### Study population

From January 2005 to December 2016, a total cohort of 163 patients underwent initial hepatectomy with curative intent for CRLM at our institution and was enrolled in this study. A prospective maintained database was used to identify the patients and additional information was collected by reviewing each patient's medical record. This study was approved by the Human Ethics Review Committee of the Graduate School of Life Sciences, Kumamoto University (Kumamoto, Japan). Written informed consent was obtained from all of the patients prior to treatment.

### Preoperative workup

Preoperative chemotherapy was administered to patients with initially unresectable or marginally resectable disease, including those with concomitant extrahepatic disease in a conversion setting, or to patients with disease that was thought to be highly malignant (including those who were diagnosed synchronously, patients with a greater number of tumors, and patients with higher levels of tumor markers) in a neoadjuvant setting.[25] The response to preoperative chemotherapy was evaluated with computed tomography (CT) after every 4 cycles of treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST).[26]

Before hepatectomy, all patients underwent routine laboratory and liver function tests including the indocyanine retention rate at 15 min (ICG-R15) and $^{99m}$Tc-galactosyl human serum albumin (GSA) scintigraphy.[27–29] Thoracoabdominal and pelvic imaging including ultrasonography, CT, and magnetic resonance imaging were performed to determine disease stage.

### Surgical strategy

The objective of surgery was to remove all detectable lesions with a tumor-free margin. The type of hepatectomy was based on the preoperative imaging findings, intraoperative ultrasonography, and liver functional reserve, as described previously.[25] In brief, non-anatomical partial hepatectomy was preferred if the tumor location allowed. Portal vein embolization (PVE) was performed if the tumors were unilobar and the future remnant liver was too small. Radiofrequency ablation (RFA) in combination with hepatectomy was performed to treat unresectable tumors or tumors that were located deep within the remnant liver to spare the liver parenchyma. If complete tumor removal was impossible by one-stage hepatectomy, even when combined with PVE or RFA, two-stage hepatectomy was considered.

### Postoperative workup

Postoperative complications were graded according to the validated classification criteria described by Dindo *et al.*,[30] and major complications were defined as any complication of grade III or higher. After treatment, all patients received regular follow-up examinations with imaging studies and estimation of tumor markers such as serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9. When recurrence was observed, surgical treatment in combination with chemotherapy was preferred if the overall strategy was considered to be potentially curative.

**Table 1** Background characteristics of patients with right- and left-sided primary tumors

| | Right-sided primary (n = 36) | Left-sided primary (n = 127) | *P* |
|---|---|---|---|
| Age | 67.8 ± 11.0 | 62.1 ± 11.8 | 0.0034 |
| Sex (Male/Female) | 17/19 | 89/38 | 0.0126 |
| Body mass index | 22.5 ± 3.2 | 23.0 ± 3.3 | 0.228 |
| Primary T (1–2/3-4) | 4/32 | 13/110 | 0.927 |
| Primary N (0/1–2) | 14/22 | 46/77 | 0.871 |
| Bilobar distribution | 11 (30.6%) | 57 (45.2%) | 0.110 |
| Initially resectability (unresectable/borderline/resectable) | 4/4/9 | 30/10/34 | 0.343 |
| Tumor size at hepatectomy (mm) | 32.4 ± 21.0 | 32.1 ± 23.7 | 0.767 |
| Tumor number at hepatectomy | 2.6 ± 2.8 | 3.5 ± 3.3 | 0.115 |
| CEA (ng/ml) at hepatectomy | 4.3 (1.3–349) | 7.2 (0.5–2061) | 0.138 |
| CA19-9 (U/ml) at hepatectomy | 15.5 (1.2–1112) | 19.3 (0.1–1756) | 0.927 |
| Concomitant extrahepatic disease | 2 (5.6%) | 4 (3.2%) | 0.519 |
| ICG-R15 (%) | 13.9 ± 13.9 | 10.4 ± 5.8 | 0.825 |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; ICG-R15, indocyanine retention rate at 15 min.

### Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or median (range), and were compared using the Mann–Whitney *U* test. Categorical variables were compared using $\chi^2$ test or Fisher's exact test, as appropriate. Survival analyses were performed using the Kaplan–Meier method, with comparisons by means of the log rank test. Overall survival (OS) was calculated from the date of hepatectomy until death or last follow-up, and disease-free survival (DFS) was defined as the time between curative surgery and first recurrence or death. Variables in which the *P* value for the univariate analysis was <0.10 were subjected to a subsequent multivariate Cox hazard model by a stepwise backward elimination procedure with a threshold $P < 0.05$. All statistical analyses were performed using the JMP software program (SAS Institute, Cary, NC). Values of $P < 0.05$ were considered to be statistically significant.

## Results

### Patient characteristics

Among the 163 patients enrolled in this study, 36 had a right-sided primary tumor and the remaining 127 had a left-sided primary tumor. The demographic and clinical characteristics of the patients in these two groups are summarized in Table 1. Patients with a right-sided primary tumor were characterized primarily as older and female.

### Preoperative chemotherapy and surgical features

Chemotherapy and surgical features in the two groups are summarized in Table 2. Preoperative chemotherapy was administered to 17 patients (47.2%) with a right-sided primary tumor and 74 (58.3%) with a left-sided primary tumor, with a median number of six cycles and one line. Oxaliplatin-based chemotherapy was administered as first-line chemotherapy in most of the patients. Progression of disease during final-line chemotherapy was observed more frequently in the right-sided primary tumor group than in the left-sided primary tumor group.

### Survival analysis according to the primary tumor location and preoperative chemotherapy

Median follow-up after hepatectomy and after diagnosis of liver metastasis was 33.9 and 38.8 months, respectively. The OS after hepatectomy in the right-sided primary tumor group was not significantly different from that in the left-sided primary tumor group (5-year OS rate: 55.0 vs 52.3%, $P = 0.68$, Fig. 1a). DFS also did not differ between the two groups (21.3% vs 22.9%, $P = 0.089$, Fig. 1b).

**Table 2** Perioperative chemotherapy and surgical features in patients with right- and left-sided primary tumors

| | Right-sided primary (n = 36) | Left-sided primary (n = 127) | *P* |
|---|---|---|---|
| *Chemotherapy* | | | |
| Preoperative chemotherapy | 17 (47.2%) | 74 (58.3%) | 0.240 |
| Use of biological agents | 9 (52.9%) | 50 (67.8%) | 0.262 |
| Chemotherapy cycle | 6 (4–18) | 6 (2–38) | 0.331 |
| Chemotherapy line | 1 (1–3) | 1 (1–3) | 0.528 |
| Chemotherapy regimen | | | |
| First-line (Oxaliplatin/Irinotecan/both/other) | 15/1/0/1 | 69/2/1/1 | |
| Second-line (Oxaliplatin/Irinotecan/both/other) | 1/3/0/0 | 1/12/0/0 | |
| Response to first-line chemotherapy (CR or PR) | 10 (58.8%) | 48 (64.9%) | 0.643 |
| Response to final-line chemotherapy (CR or PR) | 11 (64.7%) | 55 (74.3%) | 0.432 |
| Adjuvant chemotherapy | 11 (30.6%) | 66 (52.0%) | 0.0214 |
| *Surgery* | | | |
| Major hepatectomy (≥3 segments) | 7 (19.4%) | 31 (24.4%) | 0.528 |
| Two-stage hepatectomy | 1 (2.8%) | 6 (4.8%) | 0.582 |
| Portal vein embolization | 4 (11.1%) | 10 (7.9%) | 0.552 |
| Concomitant use of RFA | 4 (11.1%) | 22 (17.3%) | 0.352 |
| Simultaneous resection of the primary | 13 (36.1%) | 22 (29.8%) | 0.117 |
| Operating time (min) | 431 (229–939) | 426 (90–986) | 0.998 |
| Blood loss (g) | 285 (0–2016) | 362 (0–4057) | 0.499 |
| Major complication | 7 (19.4%) | 27 (21.3%) | 0.812 |
| Blood transfusion | 5 (13.9%) | 8 (6.3%) | 0.163 |

CR, complete response; PR, partial response; SD, stable disease; RFA, radiofrequency ablation.

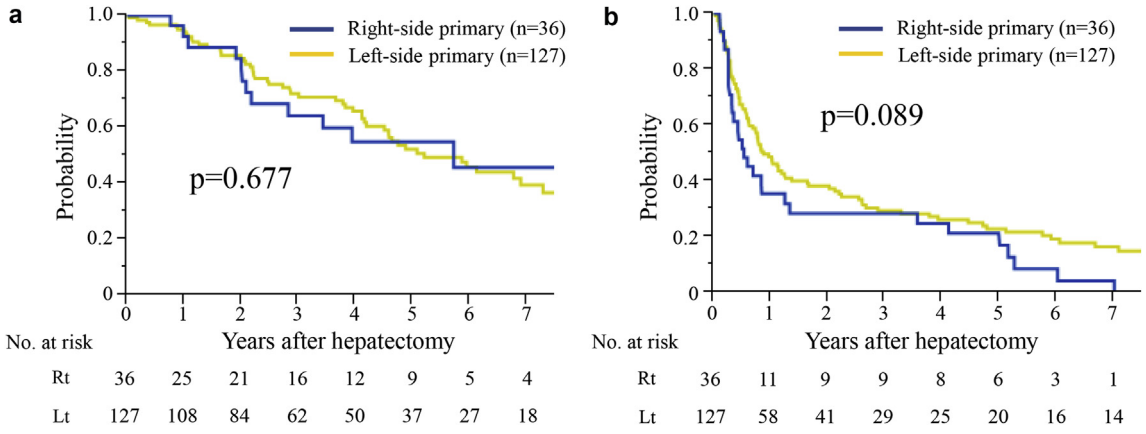


**Figure 1** Overall (**a**) and disease-free survival (**b**) in patients who underwent hepatectomy for colorectal liver metastases according to the primary tumor location (right vs left)

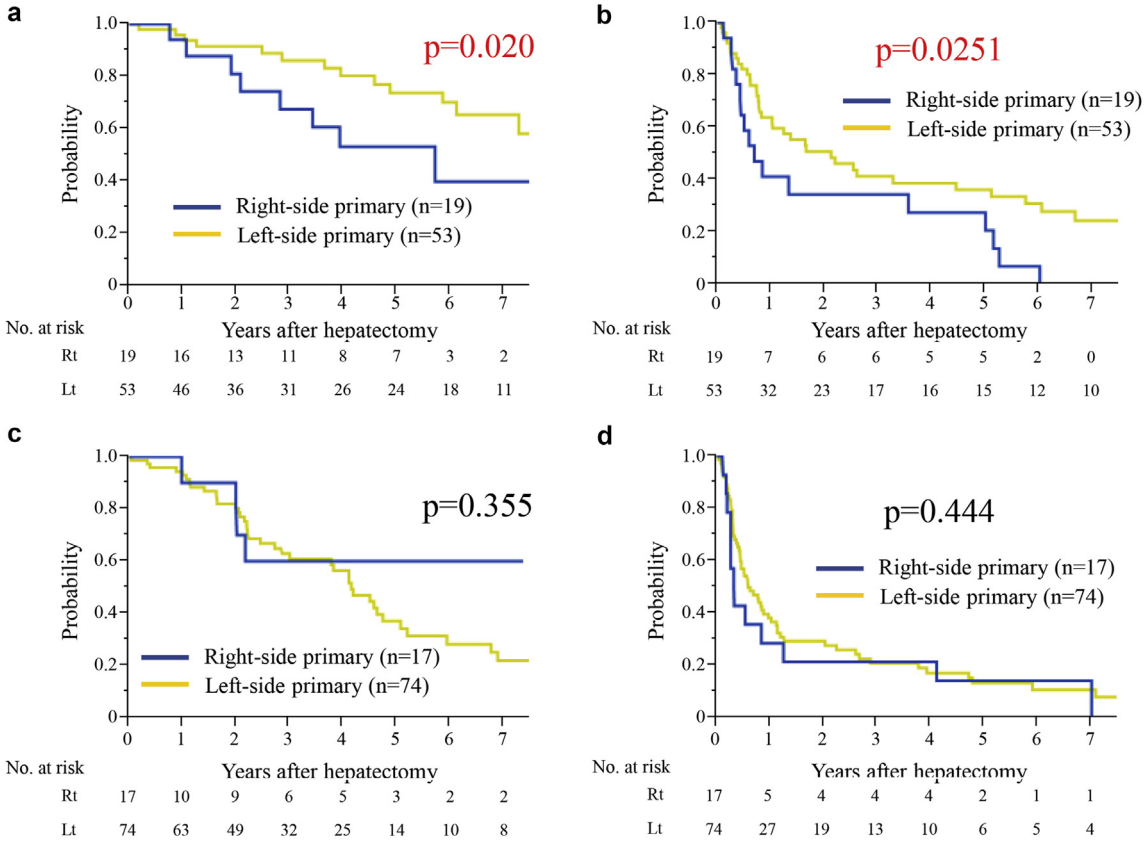


**Figure 2** **(a, b)** Overall (**a**) and disease-free survival (**b**) in patients who underwent upfront hepatectomy for colorectal liver metastases according to the primary tumor location (right vs left). **(c, d)** Overall (**c**) and disease-free survival (**d**) in patients who underwent preoperative chemotherapy followed by hepatectomy for colorectal liver metastases according to the primary tumor location (right vs left)

However, among the patients who underwent upfront hepatectomy without preoperative chemotherapy, the OS and DFS in the right-sided primary tumor group (n = 19) were significantly worse than those in the left-sided primary tumor group (n = 53) (5-year OS: 53.2 vs 73.9%, $P = 0.02$, Fig. 2a; 5-year DFS: 27.5 vs 36.1%, $P = 0.025$, Fig. 2b, respectively). On the contrary, among the patients who underwent preoperative chemotherapy followed by hepatectomy, the OS and DFS were similar between the right-sided primary tumor (n = 17) and left-sided primary tumor groups (n = 74) (5-year OS: 60.0 vs 37.2%, $P = 0.36$,

**Table 3** Univariate analysis of prognostic factors for survival stratified by preoperative chemotherapy

| | Preoperative chemotherapy (–) | | | Preoperative chemotherapy (+) | | |
|---|---|---|---|---|---|---|
| | n | 5-year OS | *P* | n | 5-year OS | *P* |
| Age | | | | | | |
| >65 | 38 | 66.1 | 0.972 | 36 | 46.0 | 0.092 |
| ≤65 | 34 | 69.5 | | 55 | 36.5 | |
| Sex | | | | | | |
| Male | 49 | 69.3 | 0.814 | 57 | 37.8 | 0.751 |
| Female | 23 | 65.3 | | 34 | 43.4 | |
| Primary tumor location | | | | | | |
| Right | 19 | 53.2 | 0.021 | 17 | 60.0 | 0.361 |
| Left | 53 | 73.8 | | 74 | 37.2 | |
| Primary T stage | | | | | | |
| T1-2 | 6 | 26.7 | 0.252 | 11 | 56.6 | 0.840 |
| T3-4 | 65 | 71.1 | | 77 | 40.7 | |
| Primary N stage | | | | | | |
| 0 | 28 | 61.8 | 0.460 | 32 | 40.6 | 0.750 |
| 1–2 | 43 | 71.9 | | 56 | 41.6 | |
| Timing of liver metastasis | | | | | | |
| Synchronous | 35 | 63.8 | 0.345 | 67 | 39.8 | 0.894 |
| Metachronous | 37 | 72.0 | | 24 | 39.9 | |
| Distribution of liver metastasis | | | | | | |
| Unilobar | 56 | 71.6 | 0.473 | 38 | 33.2 | 0.585 |
| Bilobar | 15 | 46.2 | | 53 | 44.6 | |
| Major hepatectomy | | | | | | |
| Yes | 12 | 73.3 | 0.765 | 26 | 40.9 | 0.879 |
| No | 60 | 66 | | 65 | 38.1 | |
| Concomitant use of RFA | | | | | | |
| Yes | 5 | 50 | 0.997 | 21 | 30.5 | 0.328 |
| No | 67 | 69.5 | | 70 | 43.6 | |
| Simultaneous resection of primary | | | | | | |
| Yes | 25 | 73.2 | 0.768 | 17 | 50.0 | 0.364 |
| No | 47 | 65.6 | | 74 | 38.2 | |
| Operating time (min) | | | | | | |
| >428 | 36 | 59.0 | 0.151 | 45 | 42.2 | 0.548 |
| ≤428 | 36 | 75.2 | | 46 | 37.9 | |
| Blood loss (g) | | | | | | |
| >360 | 31 | 64.0 | 0.841 | 48 | 35.1 | 0.0547 |
| ≤360 | 41 | 70.8 | | 43 | 46.6 | |
| Red blood cell transfusion | | | | | | |
| Yes | 5 | 37.5 | 0.067 | 8 | 64.3 | 0.553 |
| No | 67 | 69.8 | | 83 | 38.8 | |
| Major complication[a] | | | | | | |
| Yes | 11 | 40.9 | 0.020 | 23 | 32.5 | 0.038 |
| No | 61 | 74.5 | | 68 | 43.1 | |

(*continued on next page*)

Fig. 2c; 5-year DFS: 14.3 vs 13.4%, $P = 0.44$, Fig. 2d, respectively). Among the patients with initially resectable or borderline diseases, the OS and DFS in the right-sided primary tumor group was not significantly different from that in the left-sided primary tumor group (Supplementary Figure 1). In addition, as with the whole cohort, the OS and DFS of patients with a right-sided primary tumor were significantly worse than those with a left-sided primary tumor only in patients who did not receive preoperative chemotherapy (Supplementary Figure 2).

**Table 3** (*continued*)

| | Preoperative chemotherapy (–) | | | Preoperative chemotherapy (+) | | |
|---|---|---|---|---|---|---|
| | n | 5-year OS | *P* | n | 5-year OS | *P* |
| Tumor size (mm) | | | | | | |
| >30 | 31 | 63.0 | 0.294 | 37 | 35.6 | 0.327 |
| ≤30 | 41 | 71.4 | | 54 | 42.5 | |
| Tumor number | | | | | | |
| >3 | 9 | 37.0 | 0.0497 | 42 | 29.5 | 0.105 |
| ≤3 | 63 | 72.4 | | 49 | 48.0 | |
| CEA (ng/ml) | | | | | | |
| >5 | 44 | 63.6 | 0.363 | 54 | 21.1 | <0.0001 |
| ≤5 | 28 | 75.2 | | 37 | 64.6 | |
| CA19-9 (U/ml) | | | | | | |
| >37 | 22 | 49.8 | 0.017 | 24 | 42.3 | 0.469 |
| ≤37 | 50 | 75.0 | | 67 | 40.6 | |
| Chemotherapy cycle | | | | | | |
| >6 | – | – | – | 42 | 40.5 | 0.650 |
| ≤6 | – | – | – | 49 | 39.1 | |
| Chemotherapy line | | | | | | |
| >1 | – | – | – | 17 | 11.8 | 0.081 |
| ≤1 | – | – | – | 74 | 45.8 | |
| Use of biological agents | | | | | | |
| Yes | – | – | – | 59 | 44.2 | 0.674 |
| No | – | – | – | 32 | 38.6 | |
| Response to final-line chemotherapy | | | | | | |
| SD/PD | – | – | – | 25 | 17.8 | 0.0019 |
| CR/PR | – | – | – | 66 | 46.4 | |
| Adjuvant chemotherapy | | | | | | |
| Yes | 37 | 72.9 | 0.384 | 40 | 34.8 | 0.438 |
| No | 35 | 56.9 | | 51 | 43.4 | |
| Surgical treatment for first recurrence | | | | | | |
| Yes | 20 | 71.3 | 0.0001 | 27 | 49.6 | <0.0001 |
| No | 24 | 28.5 | | 37 | 8.6 | |

RFA, radiofrequency ablation; SD, stable disease; PD, progression disease; CR, complete response; PR, partial response; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; OS, overall survival.
[a] Clavien-Dindo classification ≥III.

Table 4 Multivariate analysis of independent prognostic factors for survival stratified by preoperative chemotherapy

| | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| Preoperative chemotherapy (–) | | | |
| Right-sided primary tumor | 3.44 | 1.21–10.03 | 0.021 |
| Major complication[a] | 5.61 | 1.76–18.04 | 0.0042 |
| Tumor number >3 | 12.41 | 2.77–65.61 | 0.0013 |
| No surgical treatment for first recurrence | 22.58 | 5.21–163.43 | <0.0001 |
| Preoperative chemotherapy (+) | | | |
| Response to final-line chemotherapy (SD/PD) | 3.00 | 1.40–6.23 | 0.0052 |
| No surgical treatment for first recurrence | 4.93 | 2.41–10.92 | <0.0001 |

SD, stable disease; PD, progression disease; CI, confidence interval.
[a] Clavien-Dindo classification ≥III.

### Prognostic factors of survival according to the primary tumor location

According to a univariate analysis, five variables (primary tumor location, major complication, tumor number, CA19-9, and surgical treatment for first recurrence) were related to OS after hepatectomy in patients who received upfront surgery, and four variables (major complication, CEA, response to final-line chemotherapy, and surgical treatment for first recurrence) were related to OS after hepatectomy in patients who received preoperative chemotherapy (Table 3). Multivariate analysis revealed that right-sided primary tumor, major complication, tumor number >3, and no surgical treatment for first recurrence were independent poor prognostic factors in patients who received upfront surgery, while response to final-line chemotherapy (stable disease or progression disease) and no surgical treatment for first recurrence were independent poor prognostic factors in patients who received preoperative chemotherapy (Table 4).

## Discussion

In the current study, sidedness of the primary tumor location was not associated with survival in patients with CRLM who underwent hepatectomy. However, among the patients who underwent upfront hepatectomy (i.e., without preoperative chemotherapy), those with a right-sided primary tumor showed a worse OS and DFS than those with a left-sided primary tumor, and the right-sided primary tumor was identified as an independent poor prognostic factor for OS.

Previous studies have reported several prognostic factors for long-term outcome after hepatectomy for CRLM, including not only patient- or liver tumor-related factors but also primary tumor-related factors. These factors included primary N stage,[31–36] tumor differentiation,[33] primary histology,[36,37] lymphovascular invasion,[32] and primary tumor location.[21–24] Because the right-side and left-side colon develop from embryologically distinct organs, these may be considered to be different diseases. Indeed, previous studies reported differences between these "two" diseases in terms of incidence, microbiomes, chromosomal and molecular characteristics (i.e., high MSI and CIMP, *KRAS* mutation, *BRAF* mutation, *PI3KCA* mutation in a right-sided primary tumor), immunological features, and outcome.[13,38]

In terms of liver metastases from colorectal cancer, the prognostic implication of primary tumor location remains unclear. An M.D. Anderson group analyzed data from 725 patients who underwent hepatectomy for CRLM and demonstrated that a right-sided primary tumor was significantly associated with worse recurrence-free survival (RFS) and OS after hepatectomy.[21] A Johns Hopkins group also showed that CRLM patients with a right-sided primary tumor had significantly worse OS after hepatectomy. Conversely, however, RFS in patients with a right-sided primary tumor was better than in those with a left-sided primary tumor.[24] Another group from the UK reported their analysis including 364 CRLM patients showing that a right-sided primary tumor was associated with worse OS, although it seemed to have no influence on RFS or on the pattern of recurrence.[23]

In the present study, OS and DFS showed no differences between patients with a right-sided tumor and a left-sided primary tumor after hepatectomy. Interestingly, however, among the patients who underwent upfront hepatectomy, DFS and OS were significantly worse for right-sided primary tumor than for left-sided primary tumor. In multivariate analysis, right-sided primary tumor was an independent poor prognostic factor in patients who underwent upfront hepatectomy. On the contrary, in patients who underwent preoperative chemotherapy, primary tumor location was not associated with long-term outcome. As reported previously, right-sided primary tumors are considered to show lower sensitivity to chemotherapy, perhaps due to multiple reasons such as a high rate of CIMP, *KRAS*, and *BRAF* mutation. Indeed, our results showed that disease control rate during final-line preoperative chemotherapy was significantly worse in patients with a right-sided primary tumor than in those with a left-sided primary tumor. Although it is unclear whether the patients with right-sided primary tumor had long-term outcomes comparable to those with left-sided primary tumor

in spite of its chemoresistance, our findings suggest that a right-sided primary tumor, in itself, is an indication of preoperative chemotherapy.

The retrospective data analysis and small sample size from a single institution over a period of 12 years are the main limitations of this study. Considering advances in surgical techniques and imaging modalities, improvement of perioperative management, and the advent of more effective chemotherapy, a historical bias may exist. Thus, we conducted this study from 2005, when oxaliplatin was approved by the Japanese social health insurance system for colorectal cancer treatment. Although targeted therapies were not available in the early stage of the study period, the main chemotherapy agents did not change over time. Another limitation was the fact that the study population enrolled in this study consisted of patients treated with hepatectomy. Therefore, the present study may suffer from some selection bias. Finally, a validation study using an external and larger cohort should be envisioned to confirm our results.

In conclusion, primary tumor location was not associated with OS or DFS in patients with CRLM who underwent hepatectomy in the whole cohort. However, patients with a right-sided primary tumor had significantly worse OS and DFS than those with a left-sided primary tumor in the setting of upfront hepatectomy, whereas no differences in terms of OS and DFS were observed between patients with right- and left-sided primary tumors in the setting of preoperative chemotherapy followed by hepatectomy. The existence of a right-sided primary tumor may in itself be an indication of preoperative chemotherapy for patients with CRLM treated with planned resection.

## Conflicts of interest

None declared.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.08.012.