Prognostic Role for Primary Tumor Location in Patients with Colorectal Liver Metastases: A Comparison of Right-sided Colon, Left-sided Colon, and Rectum

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ABSTRACT

Background: Although right-sided colon cancer is increasingly recognized as having a worse prognosis than left-sided colorectal cancer for colorectal liver metastases, little is known about the differences between the left-sided colon and rectum.

Objective: This study evaluated the prognostic value of primary tumor location in patients with colorectal liver metastases by examining the left-sided colon and rectum separately.

Design: This was a retrospective study from 2003 to 2017.

Settings: The study was conducted in a National Cancer Center Hospital.

Patients: The study cohort included 489 patients with colorectal liver metastases from right-sided colon cancer (n=119, 24%), left-sided colon cancer (n=251, 51%), or rectal cancer (n=119, 24%) who underwent hepatic resection.

Main Outcome Measures: Primary outcomes were relapse-free survival and overall survival.

Results: Five-year relapse-free survival rates for patients with right-sided colon cancer, left-sided colon cancer, and rectal cancer were 28.6%, 34.1%, and 26.4%, respectively, and 5-year overall survival rates were 53.9%, 70.3%, and 60.8%, respectively. Multivariable analysis revealed significant differences in relapse-free survival and overall

survival between left-sided colon cancer and rectal cancer (relapse-free survival: HR=1.37, p=0.03; overall survival: HR=1.49, p=0.03) and between left-sided colon cancer and right-sided colon cancer (relapse-free survival: HR=1.39, p=0.02; overall survival: HR=1.60, p=0.01), but not between right-sided colon cancer and rectal cancer. In patients with recurrence (n=325), left-sided colon cancer had the lowest multiple-site recurrence rate and the highest surgical resection rate for recurrence (left-sided colon cancer, 20%/46%; right-sided colon cancer, 32%/30%; rectal cancer, 26%/39%).

Limitations: This study was retrospective in design.

Conclusions: Rectal cancer was associated with worse relapse-free survival and overall survival compared with left-sided colon cancer in patients with colorectal liver metastases who underwent hepatic resection. Our findings suggest that the left-sided colon and rectum should be considered distinct entities in colorectal liver metastases.

Key words: Colorectal liver metastases; Right-sided colon cancer; Left-sided colon cancer; Rectal cancer; Primary tumor location; Sidedness

Introduction

Right-sided colon cancer (RSCC) is increasingly recognized as having a worse prognosis than left-sided colorectal cancer (LCRC) in metastatic colorectal cancer (mCRC).[1-3] RSCC and LCRC harbor distinct clinical and biological features, probably reflecting differences in embryonic origin, site-associated microbiota, exposure to nutrients and carcinogenic toxins, and gene expression.[4, 5] Previous studies have found that primary tumor location in colorectal liver metastases (CRLM) has prognostic value. For instance, in CRLM patients who underwent resection, RSCC was associated with worse overall survival (OS) compared with LCRC,[6] and also a worse pathologic response to chemotherapy.[7] Recent meta-analyses have suggested that RSCC is associated with a worse prognosis than LCRC for OS in CRLM patients.[8-10]

Clinical behaviors of the left-sided colon and rectum in colorectal cancer are known to differ. Although the left-sided colon and rectum are both derived from the hindgut, left-sided colon cancer (LSCC) and rectal cancer (RC) differ with respect to anatomical location, mutational behavior, and tumor development and progression.[11, 12] However, previous studies that examined the primary tumor location of CRLM have been limited to those which categorized RC as a left-sided cancer (i.e., RSCC vs. LCRC) [8-10, 13, 14] or those which excluded RC from the analysis (RSCC vs. LSCC).[7, 15, 16] To date,

prognostic differences between LSCC and RC have not been examined in CRLM patients.

Here we hypothesized that LSCC and RC have distinct prognostic value in CRLM patients undergoing hepatic resection. To this end, the present study aimed to evaluate the prognostic value of primary tumor location in CRLM patients for relapse-free survival (RFS) and OS by examining LSCC and RC separately.

Materials and Methods

Patients

Subjects were consecutive CRLM patients who underwent hepatic resection and who were referred to the National Cancer Center Hospital between January 2003 and December 2017. We excluded patients with missing clinicopathological data. We also excluded patients who received concomitant radiofrequency ablation because radiofrequency ablation has been reported to have a worse prognosis than hepatic resection in patients with resectable CRLM[17, 18]. Resectability was decided based on the possibility of achieving R0 resection with ≥30% of the liver remaining while preserving adequate vascular inflow or outflow after hepatic resection, regardless of the size or number of liver metastases. Patients with an unresectable primary tumor or unresectable extrahepatic metastases did not undergo hepatic resection, as described previously.[19]

Patients with synchronous CRLM typically underwent simultaneous surgical resection of colorectal and liver metastases. In accordance with Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines,[20] preoperative or postoperative chemotherapy was not typically performed before or after hepatic resection for either metachronous or synchronous liver metastases, and preoperative chemotherapy, radiotherapy, or chemoradiotherapy was not typically performed for rectal cancer patients. This retrospective study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code: 2017–437).

Data

The following information was extracted from medical records: sex, age, location of primary tumor (RSCC, LSCC, or RC, with right-sided colon defined as the cecum to the transverse colon, and left-sided colon defined as the splenic flexure to the rectosigmoid junction), T category and N category of primary tumor, timing of liver metastases (metachronous or synchronous, with synchronous defined as metastases diagnosed before or during primary tumor resection), extrahepatic metastases at hepatic resection, perioperative chemotherapy before and after hepatic resection, preoperative serum carcinoembryonic antigen (CEA) levels, size of largest liver metastasis, and number of

liver metastases.

Follow-up and treatment for first recurrence

After hepatic resection, follow-up consisted of tumor marker measurements and computed tomography (CT), as described previously.[21, 22] In patients with recurrence after hepatic resection, the pattern of first recurrence was classified as liver-only recurrence, lung-only recurrence, local recurrence, other recurrence (peritoneum, lymph node, brain, and pancreas), and multiple-site recurrence. Surgical resection for first recurrence was categorized as hepatic resection, pneumonectomy, or other surgery. Other surgery included resection for metastases of a single organ (e.g., surgical resection of peritoneum, lymph nodes, anastomotic site, or local recurrence) or multiple organs (e.g., hepatic resection plus pneumonectomy or hepatic resection plus lymph node dissection).

Statistical analysis

Wilcoxon's rank-sum test and Pearson's chi-square test were used to evaluate continuous variables and categorical variables, respectively. OS was defined as the interval between the date of hepatic resection and the date of all-cause death. RFS was defined as the interval between the date of hepatic resection and the date of recurrence or all-cause death.

The Kaplan-Meier method was used to calculate survival rates, and differences were evaluated with the log-rank test. Surviving patients were censored at the date of data cut-off (February 2020). In the multivariable analysis, Cox proportional hazards regression models were used to evaluate the prognostic value of factors for OS and RFS. Multivariable analyses included the following key clinical factors: sex (male or female), age (<65 or ≥65), T category of primary tumor (T1/T2/T3 or T4), N category of primary tumor (N0 or N1/N2), timing of liver metastases (metachronous or synchronous), extrahepatic metastases (yes or no), preoperative chemotherapy (yes or no), postoperative chemotherapy (yes or no), preoperative CEA level (≤200 ng/ml or >200 ng/ml),[9, 14, 15, 23] size of largest liver metastasis (≤5 cm or ≥5.1 cm), number of liver metastases (1, 2-4 or ≥5),[24] and primary tumor location (right-sided colon, left-sided colon, or rectum). Cut-off values were chosen based on previous studies.[9, 14, 15, 23, 24] P<0.05 was considered statistically significant. JMP14 software (SAS Institute Japan Ltd., Tokyo, Japan) was used for all statistical analyses.

Results

Study population

A total of 505 CRLM patients who underwent hepatic resection were enrolled. Patients

who received concomitant radiofrequency ablation (n=4) and those with missing clinicopathological data (n=12) were excluded. Therefore, the cohort of this study consisted of 489 CRLM patients, with a median follow-up time for survivors of 62.3 months (range, 1-204 months) (Fig. 1).

Clinical characteristics

Patient characteristics and associations between primary tumor location and clinicopathological findings are shown in Table 1. Among the 489 CRLM patients (median age, 63 years; range, 21-87 years) included in this study, 119 (24%) had RSCC, 251 (51%) had LSCC, and 119 (24%) had RC; 258 (53%) were diagnosed with metachronous metastases and 231 (47%) with synchronous metastases. Preoperative chemotherapy and postoperative chemotherapy were administered to 52 (11%) and 48 (10%) patients, respectively. Preoperative chemotherapy was administered mainly to those initially diagnosed with unresectable CRLM, and postoperative chemotherapy to those who participated in the JCOG 0603 study.[25] Five of the 119 patients with RC who were considered to be at high risk of local recurrence received chemoradiotherapy prior to the resection of RC. Significant differences by primary tumor location were noted for sex ($p<0.0001$) and age ($p=0.01$). Specifically, males more commonly had RC (80%) than

RSCC (55%) and LSCC (61%). RSCC was associated with an older median age (66.0 years) than LSCC (62.0 years) and RC (60.0 years).

Relapse-free survival after hepatic resection

Kaplan-Meier curves comparing RFS by primary tumor location are shown in Figure 2. Three- and 5-year RFS rates were 38.7% and 34.1%, respectively, for patients with LSCC, 29.7% and 26.4% for those with RC, and 28.6% and 28.6% for those with RSCC. Survival curves for RFS were worse for patients with RSCC than for those with LSCC (p=0.03), and tended to be worse (although not significantly) for patients with RC than for those with LSCC (p=0.15). In the first two years after hepatic resection, RFS curves fell sharply and began to plateau.

Overall survival after hepatic resection

Kaplan-Meier curves comparing OS by primary tumor location are shown in Figure 3. Three- and 5-year OS rates were 86.4% and 70.3%, respectively, for patients with LSCC, 83.3% and 60.8% for those with RC, and 68.7% and 53.9% for those with RSCC. Survival curves for OS were worse for patients with RSCC than for those with LSCC (p=0.02), and tended to be worse (although not significantly) for patients with RC than for those

with LSCC (p=0.08). The gap between OS curves for patients with RC and LSCC gradually increased with time, whereas the gap between OS curves for patients with RC and RSCC narrowed with time.

Clinical factors affecting prognosis

Variables tested in univariable and multivariable analyses for RFS are shown in Table 2. Multivariable analysis adjusted for key clinical factors revealed that N category of primary tumor (N1/N2: HR=1.40, p=0.006), timing of liver metastases (synchronous: HR=1.58, p=0.0001), postoperative chemotherapy (Yes: HR=0.47, p=0.0004), number of liver metastases (2-4: HR=1.75, p<0.0001, ≥5; HR=2.63, p<0.0001), and primary tumor location were independent predictors of recurrence. Significant differences in RFS were found between patients with LSCC and RC (HR=1.37, p=0.03) and between those with LSCC and RSCC (HR=1.39, p=0.02), but not between those with RSCC and RC (HR=1.01, p=0.94).

Variables tested in univariable and multivariable analyses for OS are shown in Table 3. Multivariable analysis adjusted for key clinical factors revealed that N category of primary tumor (N1/N2: HR=1.46, p=0.03), number of liver metastases (≥5: HR=1.90, p=0.01), and location of primary tumor were all independent predictors of OS. Significant

differences in OS were found between patients with LSCC and RC (HR=1.49, p=0.03) and between those with LSCC and RSCC (HR=1.60, p=0.01), but not between those with RCC and RC (HR=0.93, p=0.74).

Pattern of first recurrence

A total of 325 (66%) patients developed recurrence during the study period (primary tumor location: RSCC, 81 (25%); LSCC, 160 (49%); RC, 84 (26%). Recurrence sites differed by primary tumor location. Liver-only recurrence was most common in patients with LSCC (46% vs. 36% for RSCC and 31% for RC), and lung-only recurrence was most common in those with RC (27% vs. 15% for RSCC and 19% for LSCC). Multiple-site recurrence was least common in patients with LSCC (20% vs. 32% for RSCC and 26% for RC) (Figure 4a). After first recurrence, OS differed by recurrence site. Five-year OS rates after first recurrence were 46.6% for patients with liver-only recurrence, 49.8% for those with lung-only recurrence, 0% for those with local recurrence, 19.9% for those with other recurrence, and 12.3% for those with multiple-site recurrence ($p<0.0001$) (Figure 4b).

Surgical resection for first recurrence

After recurrence, surgical resection was performed in 24 patients (30%) with RSCC, 74 patients (46%) with LSCC, and 33 patients (39%) with RC. The surgical resection rate for first recurrence was highest for patients with LSCC (Figure 4c). Five-year OS rates after first recurrence were 59.0% in patients who underwent surgical resection for first recurrence and 18.6% in patients who did not undergo surgical resection for first recurrence ($p<0.0001$) (Figure 4d).

Discussion and Conclusion

LSCC and RC are typically classified into the same category (i.e., LCRC), and no study to date has evaluated the differences between the two [8-10, 13, 14]. Thus, in order to clarify clinical differences between these two types of cancers, we performed a prognostic evaluation of primary tumor location for CRLM by examining LSCC and RC separately. We found that RC was associated with worse RFS (HR=1.37, p=0.03) and OS (HR=1.49, p=0.03) after hepatic resection for CRLM compared with LSCC. Kaplan-Meier curves comparing RFS and OS clearly stratified the survival of patients with LSCC and RC, suggesting that LSCC and RC differ in their prognostic value for long-term survival in CRLM patients. To our knowledge, this study is the first to demonstrate prognostic

differences between LSCC and RC in CRLM patients who underwent hepatic resection. Our findings highlight the importance of considering LSCC and RC as distinct entities.

Interestingly, the HR of OS between LSCC and RC was higher than the HR of RFS in multivariable analysis (from RFS to OS, HR increased from 1.37 to 1.49), indicating that several factors affected survival between LSCC and RC other than recurrence. A similar gap in HR was observed between LSCC and RSCC (from RFS to OS, HR increased from 1.39 to 1.60). The pattern of first recurrence after hepatic resection for CRLM and surgical resection rate for first recurrence differed between patients with RSCC, LSCC, and RC. Differences in recurrence by primary tumor location could be caused by differences in gene expression, tumor microenvironment, and vascular drainage systems, and these differences may have affected the surgical resection rate for recurrence.[26-29] For instance, lung metastasis tends to be more common for RC because venous drainage from the rectum bypasses the portal vein and the first encountered organ is the lung.[30, 31] We also found that LSCC had the lowest rate of multiple-site recurrence and the highest surgical resection rate for first recurrence. Moreover, OS after first recurrence was significantly worse in patients with multiple-site recurrence ($p<0.0001$) and those who did not undergo resection for first recurrence ($p<0.0001$). These differences in recurrence spread and surgical resection rate by primary tumor location

may explain the gap in HRs of RFS and OS between LSCC and RSCC/RC.

Patients with RSCC were found to have significantly worse RFS and OS compared to those with LSCC among CRLM patients who underwent hepatic resection (RFS: HR=1.39, p=0.02; OS: HR=1.60, p=0.01). These results are compatible with those of a previous study which analyzed data from 725 CRLM patients (excluding patients with RC who underwent hepatic resection), which found that RSCC was an independent factor associated with worse RFS and OS (RFS: HR=1.71, p<0.0001; OS: HR=2.04, p<0.0001).[7] A recent meta-analysis reported that RSCC had worse OS than left-sided cancers, and also tended to have worse disease-free survival (DFS) in CRLM patients.[10] In contrast, another meta-analysis reported no difference between RSCC and left-sided cancer.[9] While these previous meta-analyses appear to be partially conflicting, it is important to note that they examined not only studies which excluded RC from the final analysis (RSCC vs. LSCC), but also studies which categorized RC as a left-sided cancer (RSCC vs. LCRC). It will be important for future meta-analyses to consider the colon and rectum as distinct entities when examining the impact of primary tumor location on prognosis.

The present study has several limitations. First, there may have been selection bias given the retrospective design and data from a single institution. Second, the proportion

of patients who underwent preoperative chemotherapy and postoperative chemotherapy differed from previous studies due to the small number of patients who underwent chemotherapy. The proportion of patients who received preoperative chemoradiotherapy for RC was also small, which also differed from previous studies. However, this allowed us to study trends in a population for which the effects of chemotherapy or radiotherapy have been minimized. Third, since many patients did not undergo chemotherapy, we did not have information on their RAS mutation status, an important prognostic factor for OS in CRLM.[7, 9, 13] Thus, we could not adjust for this confounder in the multivariable analysis. Fourth, we did not have information on detailed resection margins, a potential confounder in recurrence. Nevertheless, the present study was the first to show prognostic differences between LSCC and RC in CRLM patients who underwent hepatic resection.

In conclusion, RC and RSCC were associated with worse RFS and OS compared with LSCC in CRLM patients who underwent hepatic resection. First recurrence sites and surgical resection rates for first recurrence also differed by primary tumor location. Among patients with recurrence, LSCC had the lowest rate of multiple-site recurrence and the highest surgical resection rate for first recurrence, potentially resulting in better OS after recurrence relative to patients with RC and RSCC. Our results confirm that RSCC, LSCC, and RC should be considered distinct entities in CRLM, and that LSCC

and RC should be examined separately in future clinical trials for CRLM.

References

1. Price TJ, Beeke C, Ullah S, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? *Cancer.* 2015;121:830-835.

2. Tejpar S, Stintzing S, Ciardiello 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.

3. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol.* 2017;28:1713-1729.

4. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical Sequencing Defines the Genomic Landscape of Metastatic Colorectal Cancer. *Cancer Cell.* 2018;33:125-136.e3.

5. Lee MS, Menter DG, Kopetz S. Right Versus Left Colon Cancer Biology: Integrating the Consensus Molecular Subtypes. *J Natl Compr Canc Netw.* 2017;15:411-419.

6. Dupré A, Malik HZ, Jones RP, Diaz-Nieto R, Fenwick SW, Poston GJ. Influence of the primary tumour location in patients undergoing surgery for colorectal liver metastases. *Eur J Surg Oncol.* 2018;44:80-86.

7. Yamashita S, Brudvik KW, Kopetz SE, et al. Embryonic Origin of Primary Colon Cancer Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colon Cancer Liver Metastases. *Ann Surg.* 2018;267:514-520.

8. Buisman FE, Galjart B, Buettner S, Groot Koerkamp B, Grunhagen DJ, Verhoef C. Primary tumor location and the prognosis of patients after local treatment of colorectal liver metastases: a systematic review and meta-analysis. *HPB.* 2020;22:351-357.

9. Liu W, Wang H-W, Wang K, Xing B-C. The primary tumor location impacts survival outcome of colorectal liver metastases after hepatic resection: A systematic review and meta-analysis. *Eur J Surg Oncol.* 2019;45:1349-1356.

10. Wang XY, Zhang R, Wang Z, et al. Meta-analysis of the association between primary tumour location and prognosis after surgical resection of colorectal liver metastases. *Br J Surg.* 2019;106:1747-1760.

11. Imperial R, Ahmed Z, Toor OM, et al. Comparative proteogenomic analysis of right-sided colon cancer, left-sided colon cancer and rectal cancer reveals distinct mutational profiles. *Mol Cancer.* 2018;17:177.

12. Salem ME, Weinberg BA, Xiu J, et al. Comparative molecular analyses of left-sided colon, right-sided colon, and rectal cancers. *Oncotarget.* 2017;8:86356-86368.

13. Sasaki K, Margonis GA, Wilson A, et al. Prognostic Implication of KRAS Status after

Hepatectomy for Colorectal Liver Metastases Varies According to Primary Colorectal Tumor Location. *Ann Surg Oncol.* 2016;23:3736-3743.

14. Wang K, Xu D, Yan X-L, Poston G, Xing B-C. The impact of primary tumour location in patients undergoing hepatic resection for colorectal liver metastasis. *Eur J Surg Oncol.* 2018;44:771-777.

15. Creasy JM, Sadot E, Koerkamp BG, et al. The impact of primary tumor location on long-term survival in patients undergoing hepatic resection for metastatic colon cancer. *Ann Surg Oncol.* 2018;25:431-438.

16. Marques MC, C. Ribeiro HS, Costa Jr. WL, et al. Is primary sidedness a prognostic factor in patients with resected colon cancer liver metastases (CLM)? *J Surg Oncol.* 2018;117:858-863.

17. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am J Surg.* 2009;197:728-736.

18. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg.* 2009;250:440-448.

19. Fukuoka K, Nara S, Honma Y, Kishi Y, Esaki M, Shimada K. Hepatectomy for Colorectal Cancer Liver Metastases in the Era of Modern Preoperative Chemotherapy: Evaluation of Postoperative Complications. *World J Surg.* 2017;41:1073-1081.

20. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol.* 2018;23:1-34.

21. Shida D, Ahiko Y, Tanabe T, et al. Shorter survival in adolescent and young adult patients, compared to adult patients, with stage IV colorectal cancer in Japan. *BMC cancer.* 2018;18:334.

22. Shida D, Hamaguchi T, Ochiai H, et al. Prognostic Impact of Palliative Primary Tumor Resection for Unresectable Stage 4 Colorectal Cancer: Using a Propensity Score Analysis. *Ann Surg Oncol.* 2016;23:3602-3608.

23. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230:309-318.

24. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci.* 2012;19:72-84.

25. Kanemitsu Y, Kato T, Shimizu Y, et al. A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis

from colorectal cancer: Japan Clinical Oncology Group Study JCOG0603. *Jpn J Clin Oncol.* 2009;39:406-409.

26. Brouwer NPM, van der Kruijssen DEW, Hugen N, et al. The Impact of Primary Tumor Location in Synchronous Metastatic Colorectal Cancer: Differences in Metastatic Sites and Survival. *Ann Surg Oncol.* 2020;27:1580-1588.

27. Sun C, Zargham R, Shao Q, et al. Association of CD98, integrin β1, integrin β3 and Fak with the progression and liver metastases of colorectal cancer. *Pathol Res Pract.* 2014;210:668-674.

28. Stange DE, Engel F, Longerich T, et al. Expression of an ASCL2 related stem cell signature and IGF2 in colorectal cancer liver metastases with 11p15.5 gain. *Gut.* 2010;59:1236-1244.

29. Broman KK, Bailey CE, Parikh AA. Sidedness of Colorectal Cancer Impacts Risk of Second Primary Gastrointestinal Malignancy. *Ann Surg Oncol.* 2019;26:2037-2043.

30. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Sci Rep.* 2016;6:29765.

31. Robinson JR, Newcomb PA, Hardikar S, Cohen SA, Phipps AI. Stage IV colorectal cancer primary site and patterns of distant metastasis. *Cancer Epidemiol.* 2017;48:92-95.

FIGURE LEGENDS

Figure 1. Flow diagram for patient selection.

The final study cohort consisted of 489 patients who underwent hepatic resection for CRLM.

Figure 2. Relationship between primary tumor location and relapse-free survival in patients who underwent hepatic resection for CRLM.

Patients were divided into three groups: right-sided colon (n=119), left-sided colon (n=251), and rectum (n=119).

Figure 3. Relationship between primary tumor location and overall survival in patients who underwent hepatic resection for CRLM.

Patients were divided into three groups: right-sided colon (n=119), left-sided colon (n=251), and rectum (n=119).

Figure 4.

(a) Pattern of first recurrence by primary tumor location (n=325). In total, 81 patients, 160 patients, and 84 patients with right-sided colon cancer, left-sided colon cancer, and

rectal cancer, respectively, experienced recurrence. (b) Relationship between pattern of first recurrence and overall survival following first recurrence after hepatic resection ($p<0.0001$). The pattern of first recurrence was classified into liver-only recurrence (n=128), lung-only recurrence (n=65), local recurrence (n=12), other recurrence (n=39), and multiple-site recurrence (n=81). (c) Surgical resection rate for first recurrence by primary tumor location. Surgical resection was performed in 24 patients (30%), 74 patients (46%), and 33 patients (39%) with right-sided colon cancer, left-sided colon cancer, and rectal cancer, respectively. (d) Relationship between surgical resection for first recurrence and overall survival following first recurrence after hepatic resection ($p<0.0001$). In total, 131 patients underwent surgical resection for first recurrence and 194 patients did not.

TABLE LEGENDS and FOOTNOTES

TABLE 1. Clinical Characteristics by Primary Tumor Location

RSCC: right-sided colon cancer, LSCC: left-sided colon cancer, RC: rectal cancer, CEA: carcinoembryonic antigen

TABLE 2. Univariable and Multivariable Analyses for RFS

Data are presented as hazard ratios and 95% confidence intervals

HR: hazard ratio, CI: confidence interval, CEA: carcinoembryonic antigen, RSCC: right-sided colon cancer, LSCC: left-sided colon cancer, RC: rectal cancer

TABLE 3. Univariable and Multivariable Analyses for OS

Data are presented as hazard ratios and 95% confidence intervals

HR: hazard ratio, CI: confidence interval, CEA: carcinoembryonic antigen, RSCC: right-sided colon cancer, LSCC: left-sided colon cancer, RC: rectal cancer

TABLE 1. Clinical Characteristics by Primary Tumor Location

Characteristic	All cases	Primary Tumor Location			*p* value
		RSCC	LSCC	RC	
Cases	489	119 (24%)	251 (51%)	119 (24%)	
Sex					
Male	313 (64%)	65 (55%)	153 (61%)	95 (80%)	<0.0001
Female	176 (36%)	54 (45%)	98 (39%)	24 (20%)	
Age (years)					
Median (range)	63 (21-87)	66 (21-87)	62 (22-86)	60 (26-85)	
<65	289 (59%)	58 (49%)	151 (60%)	80 (67%)	0.01
≥65	200 (41%)	61 (51%)	100 (40%)	39 (33%)	
T category of primary tumor					
T1/T2/T3	401 (82%)	92 (77%)	205 (82%)	104 (87%)	0.13
T4	88 (18%)	27 (23%)	46 (18%)	15 (13%)	
N category of primary tumor					
N0	174 (36%)	40 (34%)	98 (39%)	36 (30%)	0.22
N1/N2	315 (64%)	79 (66%)	153 (61%)	83 (70%)	
Timing of liver metastases					
Metachronous	258 (53%)	56 (47%)	132 (53%)	70 (59%)	0.19
Synchronous	231 (47%)	63 (53%)	119 (47%)	49 (41%)	
Extrahepatic metastases					
Yes	20 (4%)	7 (6%)	9 (4%)	4 (3%)	0.52
No	469 (96%)	112 (94%)	242 (96%)	115 (97%)	
Preoperative chemotherapy					
Yes	52 (11%)	14 (12%)	24 (10%)	14 (12%)	0.73
No	437 (89%)	105 (88%)	227 (90%)	105 (88%)	
Postoperative chemotherapy					
Yes	48 (10%)	9 (8%)	29 (12%)	10 (8%)	0.41
No	441 (90%)	110 (92%)	222(88%)	109 (92%)	
Preoperative CEA level					
≤200 ng/ml	444 (91%)	107 (90%)	225 (90%)	112 (94%)	0.35
>200ng/ml	45 (9%)	12 (10%)	26 (10%)	7 (6%)	
Size of largest liver metastasis					
Median (range)	3 (0.1-23)	3 (0.5-15)	3 (0.1-23)	2.5 (0.3-10)	
≤5cm	400 (82%)	91 (76%)	207 (82%)	102 (86%)	0.17
>5.1cm	89 (18%)	28 (24%)	44 (18%)	17 (14%)	
Number of liver metastases					
Median (range)	2 (1-19)	1 (1-13)	2 (1-19)	1 (1-18)	
1	238 (49%)	61 (51%)	114 (45%)	63 (53%)	0.26
2-4	203 (42%)	51 (43%)	106 (42%)	46 (39%)	
5-	48 (10%)	7 (6%)	31 (12%)	10 (8%)	

RSCC: right-sided colon cancer, LSCC: left-sided colon cancer, RC: rectal cancer

CEA: carcinoembryonic antigen

TABLE 2. Univariable and Multivariable Analyses for RFS

Characteristic	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)				
<65	1.19 (0.96-1.49)	0.12	1.12 (0.90-1.41)	0.31
≥65	Reference		Reference	
Sex				
Male	Reference		Reference	
Female	1.11 (0.88-1.38)	0.38	1.06 (0.78-1.44)	0.71
T category of primary tumor				
T1/T2/T3	Reference		Reference	
T4	1.39 (1.06-1.82)	0.02	1.24 (0.93-1.65)	0.15
N category of primary tumor				
N0	Reference		Reference	
N1/N2	1.48 (1.17-1.87)	0.001	1.40 (1.10-1.77)	0.006
Timing of liver metastases				
Metachronous	Reference		Reference	
Synchronous	1.76 (1.42-2.19)	<0.0001	1.58 (1.25-1.99)	0.0001
Extrahepatic metastases				
Yes	1.59 (0.99-2.56)	0.06	1.16 (0.70-1.91)	0.57
No	Reference		Reference	
Preoperative chemotherapy				
Yes	1.60 (1.16-2.23)	0.005	1.00 (0.70-1.42)	0.98
No	Reference		Reference	
Postoperative chemotherapy				
Yes	0.63 (0.43-0.94)	0.02	0.47 (0.31-0.72)	0.0004
No	Reference		Reference	
Preoperative CEA level				
≤200 ng/ml	Reference		Reference	
>200 ng/ml	1.44 (1.01-2.04)	0.04	1.46 (0.89-2.41)	0.14
Number of liver metastases				
1	Reference		Reference	
2-4	1.83 (1.45-2.31)	<0.0001	1.75 (1.38-2.22)	<0.0001
≥5	2.67 (1.88-3.78)	<0.0001	2.63 (1.81-3.83)	<0.0001
Size of largest liver metastasis				
≤5 cm	Reference		Reference	
≥5.1 cm	1.41 (1.08-1.85)	0.01	1.21 (0.88-1.66)	0.23
Primary tumor location				
Right-sided colon	1.35 (1.03-1.75)	0.03	1.39 (1.05-1.82)	0.02
Left-sided colon	Reference		Reference	
Rectum	1.21 (0.93-1.57)	0.16	1.37 (1.04-1.80)	0.03

Data are presented as hazard ratios and 95% confidence intervals

HR: hazard ratio, CI: confidence interval

TABLE 3. Univariable and Multivariable Analyses for OS

Characteristic	Univariable		Multivariable	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Sex				
Male	Reference		Reference	
Female	1.05 (0.78-1.42)	0.73	1.06 (0.78-1.44)	0.71
Age (years)				
<65	1.08 (0.80-1.46)	0.60	1.00 (0.73-1.36)	0.98
≥65	Reference		Reference	
T category of primary tumor				
T1/T2/T3	Reference		Reference	
T4	1.45 (1.01-2.09)	0.04	1.38 (0.94-2.03)	0.10
N category of primary tumor				
N0	Reference		Reference	
N1/N2	1.57 (1.14-2.16)	0.006	1.46 (1.05-2.03)	0.03
Timing of liver metastases				
Metachronous	Reference		Reference	
Synchronous	1.40 (1.05-1.87)	0.02	1.16 (0.84-1.59)	0.36
Extrahepatic metastases				
Yes	Reference		Reference	
No	1.17 (0.48-2.84)	0.73	1.67 (0.67-4.21)	0.27
Preoperative chemotherapy				
Yes	1.74 (1.15-2.64)	0.009	1.36 (0.86-2.13)	0.19
No	Reference		Reference	
Postoperative chemotherapy				
Yes	0.71 (0.41-1.22)	0.21	0.68 (0.39-1.19)	0.18
No	Reference		Reference	
Preoperative CEA level				
≤200 ng/ml	Reference		Reference	
>200ng/ml	1.68 (1.09-2.58)	0.02	1.46 (0.89-2.41)	0.14
Size of largest liver metastasis				
≤5cm	Reference		Reference	
>5.1cm	1.52 (1.09-2.13)	0.01	1.19 (0.80-1.74)	0.41
Number of liver metastases				
1	Reference		Reference	
2-4	1.29 (0.95-1.75)	0.10	1.25 (0.91-1.72)	0.17
5-	1.88 (1.17-3.01)	0.009	1.90 (1.13-3.17)	0.01
Primary tumor location				
RSCC	1.52 (1.06-2.16)	0.02	1.60 (1.11-2.31)	0.01
LSCC	Reference		Reference	
RC	1.35 (0.96-1.91)	0.09	1.49 (1.04-2.14)	0.03

Data are presented as hazard ratios and 95% confidence intervals

HR: hazard ratio, CI: confidence interval, CEA: carcinoembryonic antigen

RSCC: right-sided colon cancer, LSCC: left-sided colon cancer, RC: rectal cancer

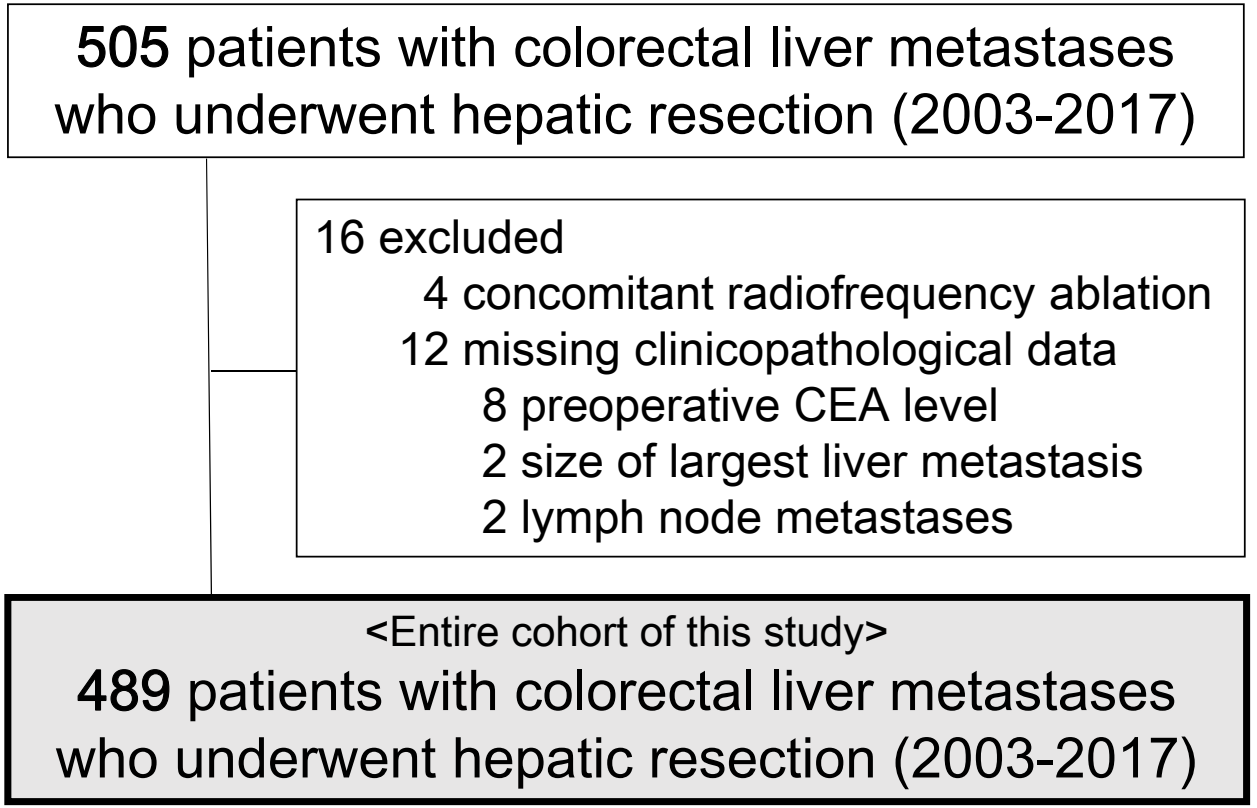
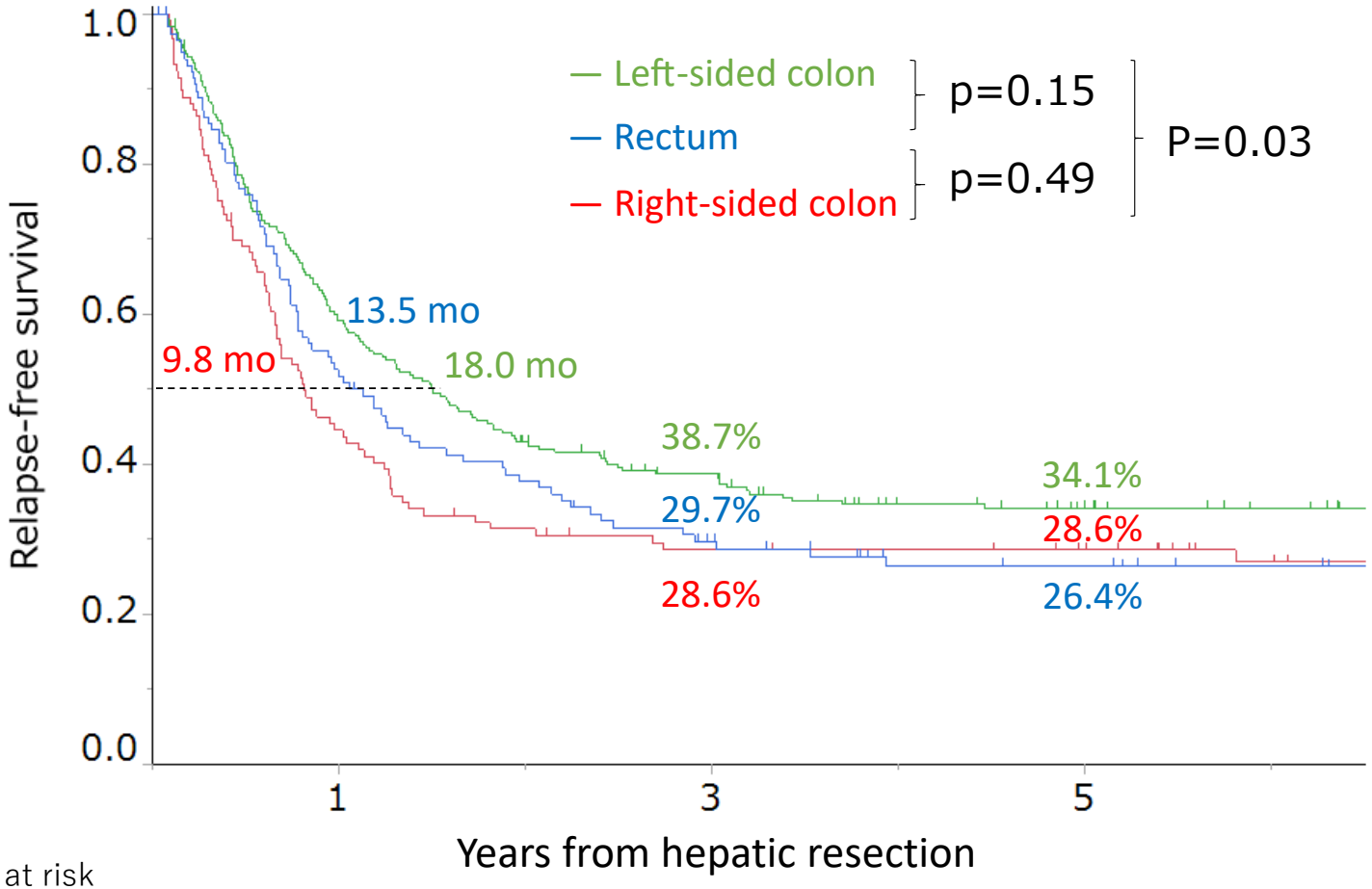

505 patients with colorectal liver metastases who underwent hepatic resection (2003-2017)
16 excluded
4 concomitant radiofrequency ablation
12 missing clinicopathological data
8 preoperative CEA level
2 size of largest liver metastasis
2 lymph node metastases
<Entire cohort of this study>
489 patients with colorectal liver metastases who underwent hepatic resection (2003-2017)

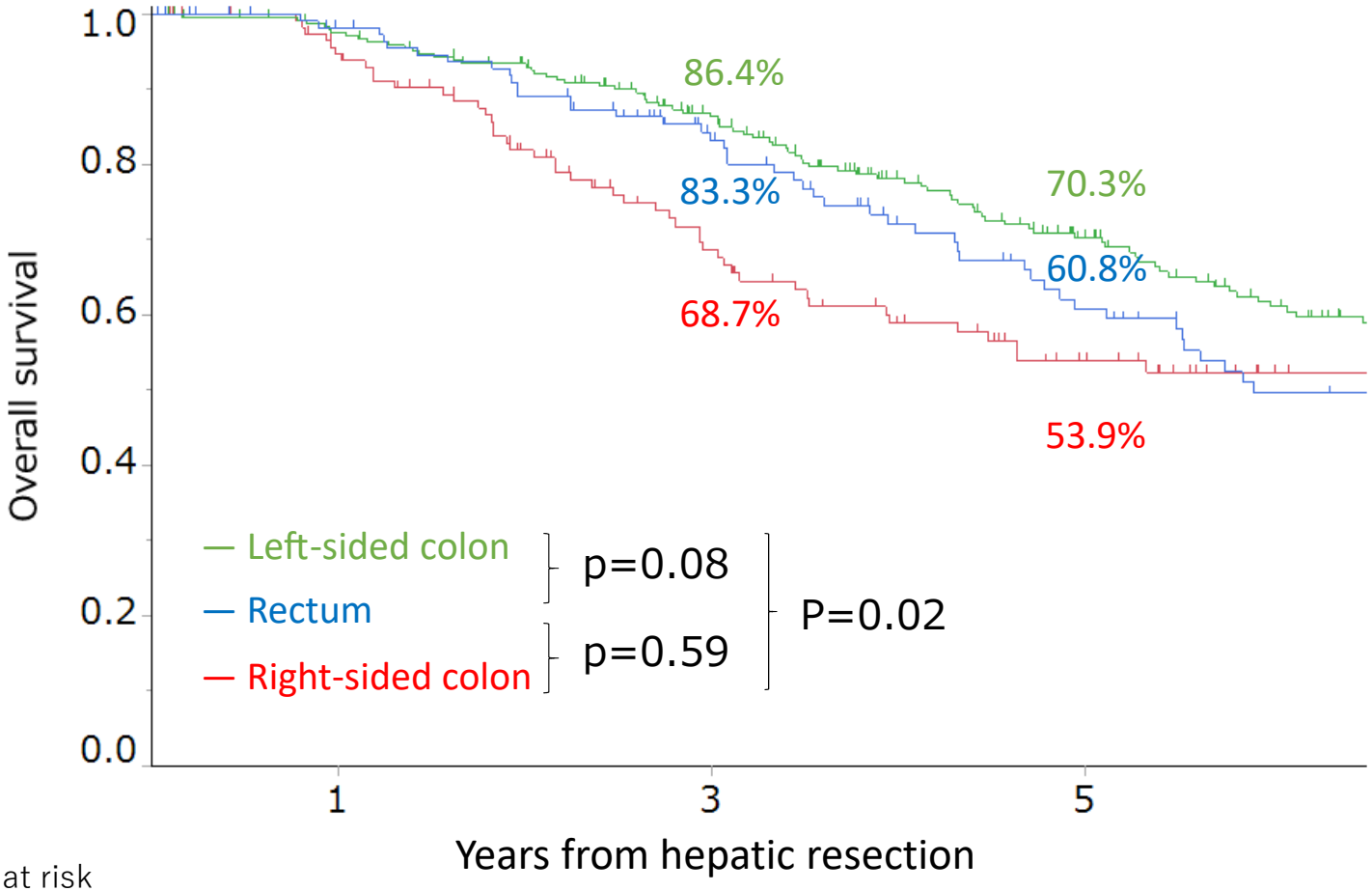
FIGURE 1



Number at risk

Left-sided	251	146	105	89	68	60	54
Rectum	119	61	44	32	22	21	17
Right-sided	119	52	36	31	30	26	18

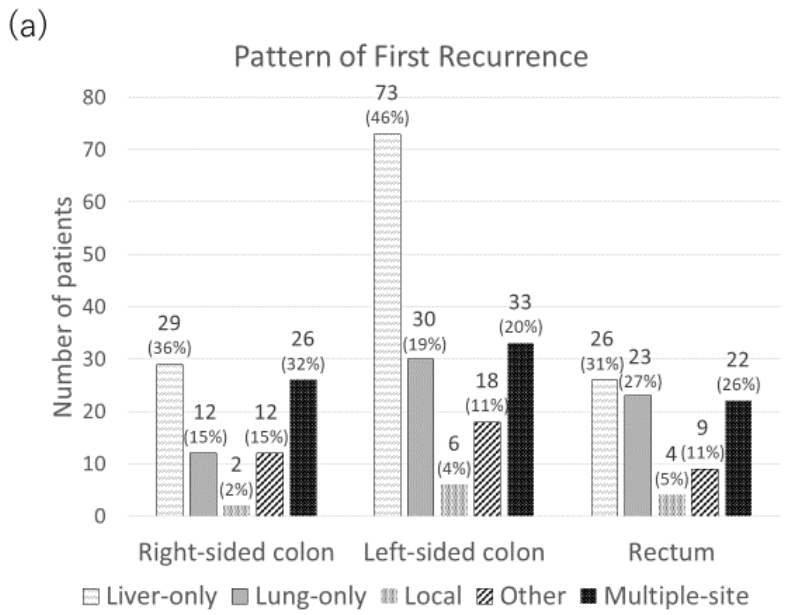
FIGURE 2

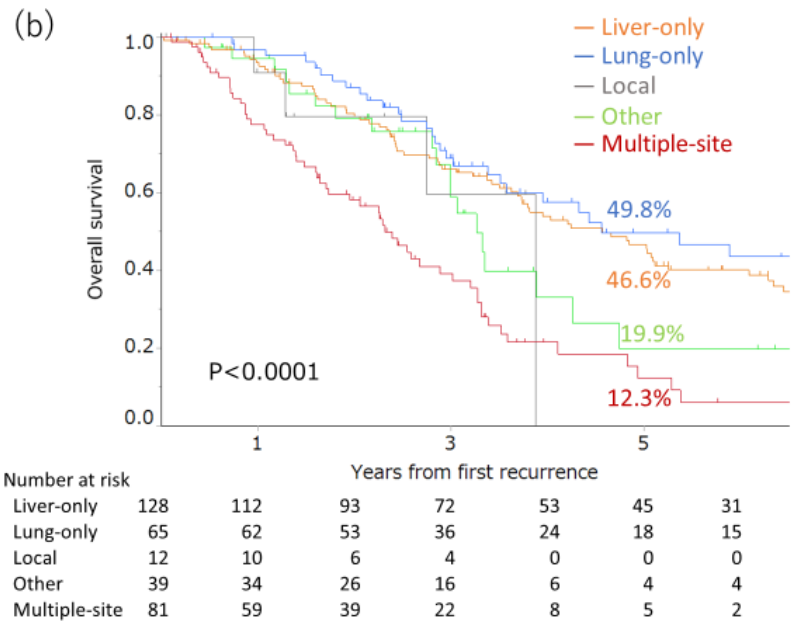


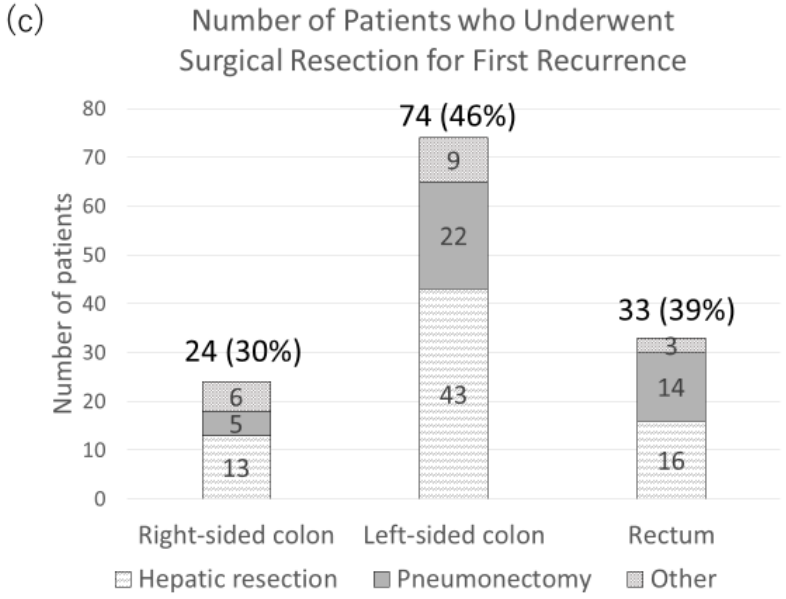
Number at risk

Left-sided	251	239	222	186	142	115	91
Rectum	119	110	100	81	60	48	36
Right-sided	119	108	86	67	52	39	26

FIGURE 3


(a)
Pattern of First Recurrence
Number of patients
80
70
60
50
40
30
20
10
0
29 (36%)
12 (15%)
2 (2%)
12 (15%)
26 (32%)
73 (46%)
30 (19%)
6 (4%)
18 (11%)
33 (20%)
26 (31%)
23 (27%)
4 (5%)
9 (11%)
22 (26%)
Right-sided colon
Left-sided colon
Rectum
Liver-only
Lung-only
Local
Other
Multiple-site


(b)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
Liver-only
Lung-only
Local
Other
Multiple-site
49.8%
46.6%
19.9%
12.3%
P<0.0001
1
3
5
Years from first recurrence
Number at risk
Liver-only 128 112 93 72 53 45 31
Lung-only 65 62 53 36 24 18 15
Local 12 10 6 4 0 0 0
Other 39 34 26 16 6 4 4
Multiple-site 81 59 39 22 8 5 2


(c)
Number of Patients who Underwent
Surgical Resection for First Recurrence
Number of patients
80
70
60
50
40
30
20
10
0
24 (30%)
6
5
13
74 (46%)
9
22
43
33 (39%)
3
14
16
Right-sided colon
Left-sided colon
Rectum
Hepatic resection
Pneumonectomy
Other

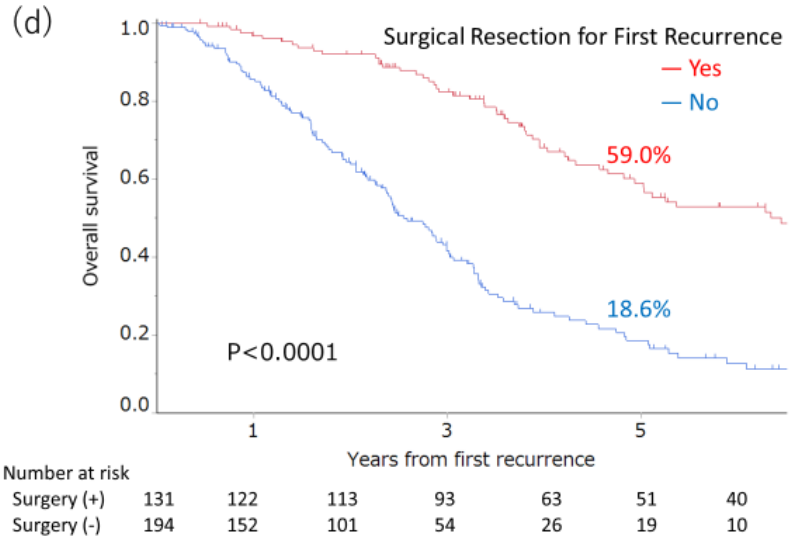

(d)
Surgical Resection for First Recurrence
Yes
No
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
59.0%
18.6%
P<0.0001
1
3
5
Years from first recurrence
Number at risk
Surgery (+) 131 122 113 93 63 51 40
Surgery (-) 194 152 101 54 26 19 10

FIGURE 4