The prognostic significance of a histological response to preoperative chemotherapy in patients with synchronous colorectal liver metastases

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Research

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Abstract

Background

Preoperative chemotherapy (PC) for colorectal liver metastasis (CRLM) is widely used to improve prognosis, but its clinical benefit has not been fully established. This study aimed to assess the effectiveness of PC for synchronous CRLMs, and to analyze the correlation between histological response to PC and survival.

Methods

We retrospectively analyzed the clinicopathological factors and outcomes of 69 patients who underwent initial hepatectomy for synchronous CRLM between 2004 and 2018 after receiving PC (PC group: n = 43) or who underwent upfront hepatectomy without PC (Non-PC group: n = 26).

In the PC group, the patients were divided into two groups, Grade 1 (n = 27) and Grade 2/3 (n = 16) groups according to their histological responses to PC.

Results

The median survival and 5-year overall survival (OS) rates were 80.9 months and 61.5%, respectively, in the PC group and 71.7 months and 61.5%, respectively, in the Non-PC group ($P = 0.867$). Regarding recurrence-free survival (RFS) and remnant liver-RFS, there were no significant differences between the two groups ($P = 0.087$ and 0.291). However, in a subgroup analysis according to the histological response to PC, the median 5-year OS, RFS, and remnant liver-RFS in the Grade 2/3 group were significantly longer than in the Grade 1 group (OS: 66 vs. 53 months; $P = 0.008$, RFS: 15 vs. 6.7 months; $P = 0.002$, remnant liver-RFS: 62 vs. 8.3 months; $P < 0.001$). Surgical margin positive status (< 1 mm) was associated with a high remnant liver recurrence rate (hazard ratio 2.597, $P = 0.008$).

Conclusion

PC should not be routinely administered to all patients with synchronous CRLMs. However, some patients benefit from PC, and the histological response to PC had prognostic significance for patients with synchronous CRLM.

Background

Liver metastasis is the most common distant metastasis of colorectal cancer (CRC), and approximately 15–25% of patients have synchronous colorectal liver metastases (CRLM) at initial treatment [1] [2]. Fifteen percent of patients with CRLM have resectable liver metastases [3] [4], and hepatectomy is

considered an optimal and potentially curative treatment for CRLM, with a reported 5-year postoperative survival rate of 45–61% [5] [6]. However, rates of postoperative recurrence and remnant liver recurrence are both reported to be approximately 60–70% [7] [8], and the outcomes of hepatectomy are not fully satisfactory.

On the other hand, chemotherapy with combinations of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus molecular targeted therapy have improved tumor responses and median survival times up to more than 30 months for unresectable CRLM [9]. Perioperative chemotherapy including preoperative chemotherapy (PC) for CRLM is widely used to improve prognosis [10]. Although the histological and radiological responses to PC have been reported to be useful predictors of outcomes [11] [12], the clinical benefit of PC has not been fully established. Some studies also reported a difference in prognosis between patients with synchronous and metachronous CRLM [13] and between patients with intrahepatic and extrahepatic metastasis [14]. Therefore, we focused on synchronous CRLM, and the aims of this study were the following: (i) to assess the effectiveness of PC for synchronous colorectal liver-limited metastases and (ii) to analyze the correlation between histological response to PC and postoperative survival.

Methods

Patients

Between June 2004 and December 2018, 168 consecutive patients underwent initial hepatectomy for CRLM at Gifu University Hospital in Gifu City, Japan. The exclusion criteria were as follows: (1) any other distant metastasis or peritoneal dissemination at the first treatment for CRLM, (2) R1/2 resection for primary tumor resection, and (3) R2 hepatectomy for CRLM. After excluding 45 patients who met the exclusion criteria, we excluded 54 patients with metachronous CRLM from the remaining 124 patients. This study thus included 69 patients with synchronous CRLM, and patients were divided into a PC group (n = 43) and an upfront hepatectomy without PC (Non-PC group, n = 26). Overall survival (OS), recurrence-free survival (RFS), and remnant liver-RFS were compared between the PC and Non-PC groups. In the PC group, according to the histological criteria for response to chemotherapy, survival outcomes were also compared between 16 patients who responded to PC (Grade 2/3), and 27 patients who did not (Grade 1).

All patients were fully informed of the study design according to the Ethics Committees of Gifu University Hospital (Approval number; 2020-231; February 8, 2021), and informed consent was obtained from all patients by the opt-out method, in accordance with the guidelines of the Japanese Ministry of Health, Labor and Welfare (Tokyo, Japan).

Pathological assessment of CRLM

The pathological liver resection specimens were fixed in formalin, embedded in paraffin and stained with haematoxylin-eosin (H&E). All specimens were sectioned into 5 mm-thick slices. The slice revisions were performed by experienced pathologists. Pathologic response was evaluated based on the histological

criteria for the assessment of response to chemotherapy in the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [15], and classified into five subgroups, as follows. Grade 0 (No effect) was categorized as no tumor cell necrosis or degeneration in response to treatment. Grade 1a (Minimal effect) was categorized as tumor cell necrosis or degeneration in less than one-third of the entire lesion. Grade 1b (Mild effect) was categorized as tumor cell necrosis or degeneration in more than one-third but less than two-thirds of the entire lesion. Grade 2 (Moderate effect) was categorized as prominent tumor cell necrosis, degeneration, lytic change, and/or disappearance present in more than two-thirds of the entire lesion, but remaining viable tumor cells. Grade 3 (Marked effect) was categorized as necrosis and/or lytic change throughout the entire lesion and replaced by fibrosis with or without granulomatous change, and no viable tumor cells. In this analysis, no patient was Grade 0, and patients in the PC group were divided into two subgroups, Grade 1 (1a/1b) and Grade 2/3. For patients with multiple CRLMs, all resected lesions were evaluated using this same procedure. The pathological characteristics of liver metastases were assessed based on patient-related analyses, and if the grades were different between metastases within a patient, the worst grade (lowest grade) was adopted.

Treatment strategies for CRLM

We reported previously that the tumor shrinkage effect reaches a plateau in about 100 days based on the radiological response of tumor shrinkage and drug-resistance mechanisms [16] [17]. Based on this evidence, including the findings of the past trials [18] [19] [20], following the approval of a multidisciplinary team, six cycles of oxaliplatin-based PC with molecular targeted drug therapy were administered to patients with borderline or unresectable CRLM that was in extensive contact with the root of the major hepatic veins or Glisson's capsules or who had insufficient residual liver volume. For patients with resectable CRLM, based on the results of the new EPOC trial [21], six cycles of oxaliplatin-based PC without molecular targeted drug therapy were administered. However, for patients referred from other hospitals and patients with a complicated medical history, such as renal dysfunction, the regimen, duration, and timing of chemotherapy were decided at the discretion of the attending surgeon and medical oncologist in each case.

Hepatectomies for CRLM were non-anatomic hepatectomies with a single-stage strategy, and were performed more than 4 weeks after the last cycle of oxaliplatin-based chemotherapy.

Preoperative chemotherapy

Chemotherapy regimens administered before hepatectomy were the following: FOLFOX (n = 9), FOLFOX with Bevacizumab (n = 9), FOLFOX with Cetuximab (n = 8), FOLFOX with Panitumumab (n = 5), capecitabine and oxaliplatin (CAPOX) with Bevacizumab (n = 2), 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) with Bevacizumab (n = 1), LV5FU2 with Bevacizumab (n = 1), CAPOX (n = 1), S-1 (n = 1). Some patients received 2 lines of chemotherapy: FOLFOX with Panitumumab followed by LV5FU2 with Bevacizumab (n = 1), FOLFOX with Bevacizumab followed by CAPOX with Bevacizumab (n = 1), S-1 and oxaliplatin (SOX) followed by FOLFOX with Bevacizumab (n = 1), FOLFOX with

Bevacizumab followed by FOLFIRI (n = 1), FOLFOX followed by FOLFIRI (n = 1), FOLFIRI followed by FOLFOX (n = 1), The median (range) duration and number of cycles of chemotherapy per patient were 3.5 (2–13) months and 6 (3–21) cycles.

Definitions

Liver metastases were classified into three subgroups, H1-H3, based on the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma [15]. H1 comprised patients with 1-4 metastatic tumors, all of which were 5 cm or less in maximum diameter. H3 comprised those with 5 or more metastatic tumors, at least one of which was more than 5 cm in maximum diameter. H2 comprised patients who were neither H1 nor H3. Lymphatic and venous invasion were also classified based on the Japanese criteria [15]. Radiological response of liver metastasis was assessed according to the revised Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 [22].

In this study, surgical margin status was defined by distance to the closest to the liver resection's surface, and surgical margin negative was defined as no microscopic evidence of the tumor in the liver resection margin with more than a 1-mm negative surgical margin. Postoperative complications were classified according to the Clavien-Dindo classification, with grade 3a or worse defined as a major complication. All complications that developed within 90 days after hepatectomy were included.

OS was defined as the interval between the date of the first treatment and the date of death from any cause or the last follow-up day. RFS and remnant liver-RFS were defined as the interval between the date of the initial hepatectomy for CRLM and the date of diagnosis of recurrence (RFS) or remnant liver after initial hepatectomy (remnant liver-RFS).

Statistical analysis

Categorial variables were expressed as proportions, and numerical variables were expressed as median and range. All *P*-values were two sided, and *P*-values of 0.05 or less were considered statistically significant. Univariate analysis results were compared with the Student's t-test, Chi-square test, Mann-Whitney's U test, or Fisher's exact test, as appropriate. Categorical variables were compared with the Chi-square test, and continuous variables with the independent sample Student's t-test. Survival curves were calculated with the Kaplan-Meier method and compared with the log-rank test (univariate analysis) or Cox proportional hazards regression (multivariate analysis). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [23].

Results

Patient characteristics

Between June 2004 and December 2018, 69 patients with synchronous CRLM underwent initial hepatectomy for CRLM at Gifu University Hospital in Gifu City, Japan. Patient characteristics are shown in Table 1. There was no difference between the PC and Non-PC groups in the side, histological type, tumor depth of T4, lymph node metastasis, and severe lymphatic and venous vessel invasion of the primary tumor. There were more patients with H1 liver metastasis in the Non-PC group (77%) than in the PC group (40%). More patients in the Non-PC group underwent synchronous resection with the primary tumor and received adjuvant chemotherapy after initial hepatectomy (Table 2).

Preoperative chemotherapy responses

According to the RECIST 1.1 criteria, 1 patient (2%) achieved a complete response (CR), 28 patients (67%) achieved partial responses (PR), 12 (29%) showed stable disease (SD), 1 (2%) showed disease progression (PD), and 1 patient was unable to be evaluated because of a lack of images.

Long-term survival

The median (range) follow-up period was 57 (8-193) months. The median survival and 5-year OS rates in the PC and non-PC groups were 80.9 months and 61.5%, respectively, in the PC group and 71.7 months and 61.5%, respectively, in the Non-PC group (P = 0.867; Fig. 2A). Univariate regression analysis identified severe lymphatic invasion (Ly1c) in the primary tumor (P = 0.005), H2/3 liver metastasis at pretreatment (P = 0.029), and surgical margin positive status (P = 0.004) as positively associated with poor prognosis, while PC was not associated with prognosis (P = 0.867; Table 3). Multivariate analysis revealed that severe lymphatic invasion (Ly1c) in the primary tumor (hazard ratio 4.185, P = 0.005) was independent predictive factor of poor OS.

As shown in Fig. 2, there were no significant differences between the PC and non-PC groups in RFS and remnant liver-RFS. The 5-year RFS rates in the PC and non-PC groups were 32.4% and 21.7%, respectively (P = 0.087; Fig. 2B). The 5-year remnant liver-RFS rates in the PC and non-PC groups were 44.0% and 36.3%, respectively (P = 0.291; Fig. 2C). Multivariate analysis revealed that tumor invasion to the serosa or adjacent structures (T4a/b) of the primary tumor (hazard ratio 1.897, P = 0.034) and surgical margin positive status (hazard ratio 2.453, P = 0.006) were associated with a high rate of recurrence (Table 4). Multivariate analysis also revealed that surgical margin positive status (hazard ratio 2.597, P = 0.008) was associated with a high rate of remnant liver recurrence (Table 5).

Analysis of OS, RFS, and remnant liver-RFS according to H subgroups

There was no difference between the PC and non-PC group with respect to OS in the H1 and H2/3 subgroups; therefore, we divided the patients into two groups, H1 (n = 37) and H2/3 (n = 32), and analyzed the OS, RFS, and remnant liver-RFS. As shown in Fig. 3, there were no differences in OS between the PC and non-PC groups in each of the H1 (P = 0.479) and H2/3 groups (P = 0.775). Moreover, RFS and remnant liver-RFS in the PC and non-PC groups were not significantly different in each of the H1 (P = 0.321, 0.842) and H2/3 groups (P = 0.912, 0.771).

Analysis of OS, RFS, and remnant liver-RFS according to histological response to chemotherapy in the PC group

We divided the PC group into two groups, the Grade 1 (n = 27) and Grade 2/3 (n = 16) groups, and compared their OS, RFS, and remnant liver-RFS. There was no significant difference in the characteristics of the primary tumor and liver metastasis between the Grade 1 and Grade 2/3 groups (Table 6). Regarding the PC regimen, the anti-EGFR (Cetuximab / Panitumumab) regimen tended to be more commonly administered in the Grade 2/3 group ($P = 0.09$). In the Grade 2/3 group, the CEA value at hepatectomy was lower than in the Grade 1 group ($P = 0.004$). Regarding radiological response (PR/CR) based on RECIST image evaluation and surgical margin, the Grade 2/3 group tended to have more CR/PR (88%) and less surgical margin positive status (13%). The median 5-year OS in the Grade 2/3 group (70 months, 86.7%) was significantly longer than that in the Grade 1 group (58 months, 45.9%, $P = 0.008$; Fig. 4A). Moreover, the median 5-year RFS in the Grade 1 and 2/3 groups was significantly different, at 6.7 months and 45 months, respectively ($P = 0.002$; Fig. 4B). In addition, the median 5-year remnant liver-RFS was significantly longer in the Grade 2/3 group (65 months) than in the Grade 1 group (8 months, $P < 0.001$; Fig. 4C).

Discussion

The present retrospective study demonstrated that PC in patients with synchronous CRLM did not prolong OS and RFS. In the subgroup analysis that separated the H1 and H2/3 group, there were also no significant differences in OS, RFS, and remnant liver-RFS between the PC and Non-PC groups. The results of this study are in accordance with those of recent studies. Following the phase III trial of the European Organization for Research and Treatment of Cancer Intergroup (EORTC) trial 40983 [24], the Guidelines of the National Comprehensive Cancer Network [25] and the European Society for Medical Oncology (ESMO) [26] recommended perioperative adjuvant chemotherapy for CRLM. However, there was no significant difference in survival in the intention-to-treat analysis of EORTC trial 40983, and it was later reported that OS in a preoperative FOLFOX group was not better than in a surgery-alone group (HR = 0.87, 95% CI 0.66–1.14, $P = 0.303$) at a subsequent 5-year follow-up. A systematic review also reported similar survival outcomes of PC [27]. The ESMO guidelines, revised in 2016, recommended surgery alone and postoperative chemotherapy in addition to perioperative chemotherapy for technically resectable CRLM [9]. As most studies were retrospective and included some biases, the debate as to whether PC or surgery alone is best is still ongoing. Only one prospective study is currently in progress [28], and the results of this study are awaited.

PC for CRLM is expected to have an effect of securing a cancer-free surgical margin due to tumor shrinkage (improvement of R0 resection rate), early treatment and suppression of micrometastases, and determination of the response to chemotherapy. On the basis of the findings of the present study, these expected effects of PC are limited, because there were no differences in survival and cancer-free surgical margin rate if chemotherapy was or was not administered before hepatectomy. Therefore, PC should not be administered routinely to all CRLM patients. However, in the subgroup analysis based on the

histological response to PC, the Grade 2/3 group (responders) achieved a higher cancer-free surgical margin rate, prolonged OS, RFS, and remnant liver-RFS than the Grade 1 group (nonresponders). This means that some patients derive a survival benefit from PC, and there is a prognostic significance of the histological response to PC in patients with synchronous CRLM. Similar to this result, many studies recently reported that responders to PC had a better prognosis after hepatectomy than non-responders [29] [30] [31].

Tanaka et al reported that 23 patients with 81 CRLMs presented with a complete pathologic response (Grade 3) to PC, and patients with at least one metastasis confirmed to achieve a complete pathologic response had a better survival than those with no complete pathologic response [32]. However, in this study, OS in 7 patients (16%) with at least one metastasis confirmed to achieve a complete pathologic response (Grade 3) was not significantly longer than in those with no complete pathologic response (P = 0.113). We speculate that the variations in CRLMs and their influences on survival are a possible reason for this. In this study, 2 patients with a Grade 3 response (29%) and 6 patients (16%) with multiple CRLMs had different grades of metastases within a patient. Cai et al. recently reported that tumor heterogeneity, manifesting as differences in metastatic tumor burden and chemotherapy sensitivity, exists among liver metastases and results in pronounced discrepancies in grade scores in the same patient after PC [11] [33]. They also reported that the worst metastasis (highest score of tumor regression grade) was considered as the reference in such cases. In this study, we used the same adoption method, and there was no significant difference in survival except for this study's classification that separated the Grade 1 and Grade 2/3 groups. Therefore, this study's histological criteria according to the residual tumor amount are considered to be appropriate for prognosis prediction.

Some studies recently reported that the radiological morphology of CRLM after PC also predicts postoperative outcomes [12] [34]. In this study, there was a correlation between histological response (Grade 2/3) and radiological response (PR/CR), but there was no significant difference in survival between the PR/CR and SD/PD groups according to the revised RECIST image evaluation (Fig. 6). For this reason, it is considered that the morphologic changes with bevacizumab were not sufficiently reflected in the RECIST image evaluation. On the basis of the findings of the present study, histological assessment is considered to be superior to radiological response for predicting prognosis.

We also showed that surgical margin positive status (< 1 mm) was associated with a high rate of remnant liver recurrence. However, contradictory outcomes in the literature are reported, in which OS and disease-free survival (DFS) are similar for patients with surgical margin negative or positive status [35]. The most likely reason for this is difficulty of accurate assessment of the resection margin in hepatic surgery, and current techniques of gross evaluation after formalin fixation may bias actual measurement of the surgical margin [36]. Moreover, the friability of the liver itself can cause the liver to crack, making assessment of the true resection margin difficult. However, recent large meta-analyses have strongly suggested that a tumor-free surgical margin of more than 1 mm is sufficient for achieving long-term DFS in patients with CRLMs, and 31% of CRLMs had micrometastases that were located from the metastatic tumor edge [37] [38] [39]. In our subgroup analysis of the PC group, surgical margin positive status (< 1

mm) was associated with a high rate of remnant liver recurrence. Therefore, we suggest that a cancer-free surgical resection margin of more than 1 mm should be achieved in all CRLM patients, irrespective of PC administration.

The present study had some limitations. First, because it was a single-center retrospective study, the number of patients was limited. Second, the greatest limitation is that the PC regimens were not uniform due to patient referrals from other hospitals and patient past medical histories. Moreover, the patients in the PC group had more advanced hepatic metastatic stages (H2/3) at pretreatment. More patients in the Non-PC group underwent synchronous resection with the primary tumor, possibly because of easier resectability. These differences in characteristics of resectability may have also affected the survival results of the present study.

To whom PC should be administered is unclear, but the Grade 2/3 group had a significantly lower carcinoembryonic antigen (CEA) value after NAC than the Grade 1 group. The reduced CEA value after NAC may predict a good histological response to PC. Neofytou et al. also reported that the CEA value following PC was correlated with prognosis [29]. Recent studies reported an association of circulating tumor DNA (ctDNA) with recurrence in patients with CRC, and a strategy based on ctDNA detection was recommended [40] [41]. We also reported previously that MYC up-regulation is a useful biomarker for selecting anti-EGFR combination therapy in PC for CRLMs [42], and evaluation of genomic information has become essential in planning CRC treatment.

Although the present study provides significant findings, a prospective study with uniform PC regimens and patient characteristics including sufficient genomic information is needed. In the near future, the development of individualized treatment strategies for CRLM based on evaluation of various types of genetic information is expected.

Conclusion

In conclusion, PC did not prolong survival in patients with synchronous liver-limited metastases. Therefore, PC should not be given routinely to all patients with synchronous CRLMs. However, some patients benefit from PC, and histological response to PC had prognostic significance for patients with CRLMs. In the future, it is predicted that genomic identification for individualized treatment will guide the administration of PC for resectable CRLMs.

Declarations

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Author Contributions

HT participated in the literature search, drafting of the manuscript, data interpretation, creation of the tables and performance of the statistical analysis. As NM, HI, KM, TT and KY conceived of the study and helped in the coordination and drafting of the manuscript. All authors have read and approved the final manuscript. The manuscript has not been submitted to another journal for simultaneous consideration.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study is exempt from ethical approval in our institution.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1, 2, 3, 4, 5, 6 is only available as a download in the Supplemental Files section.

Figures

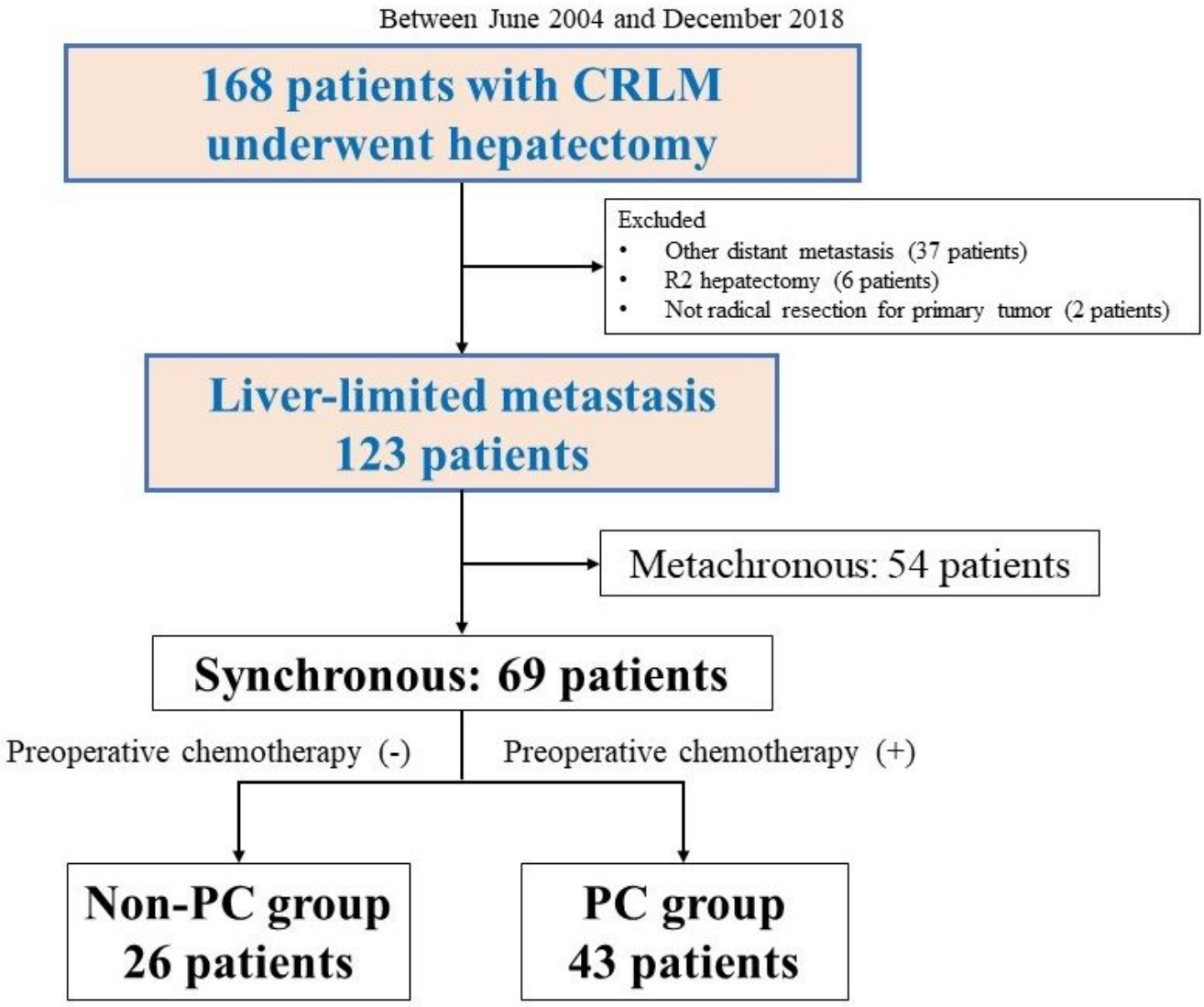
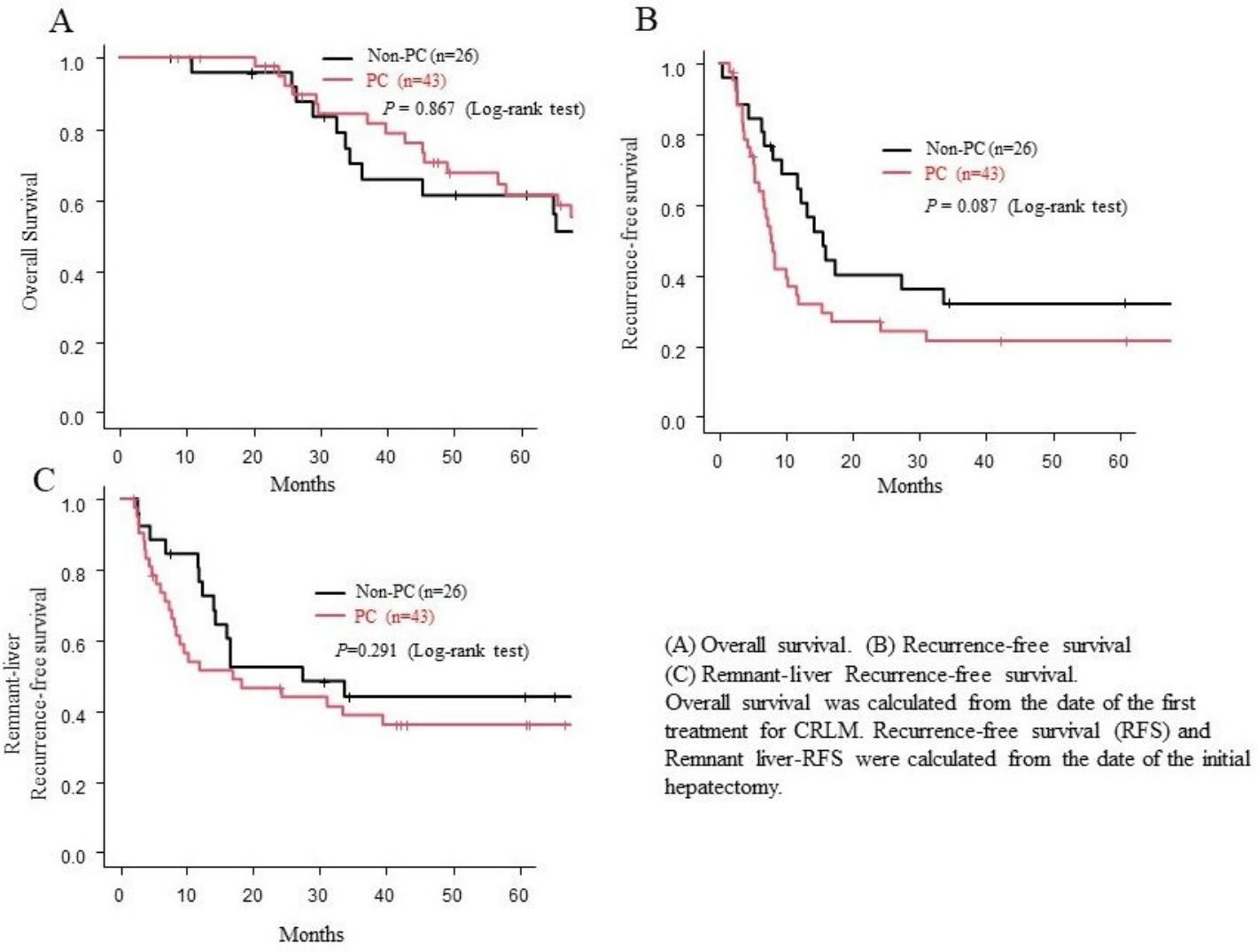


Figure 1

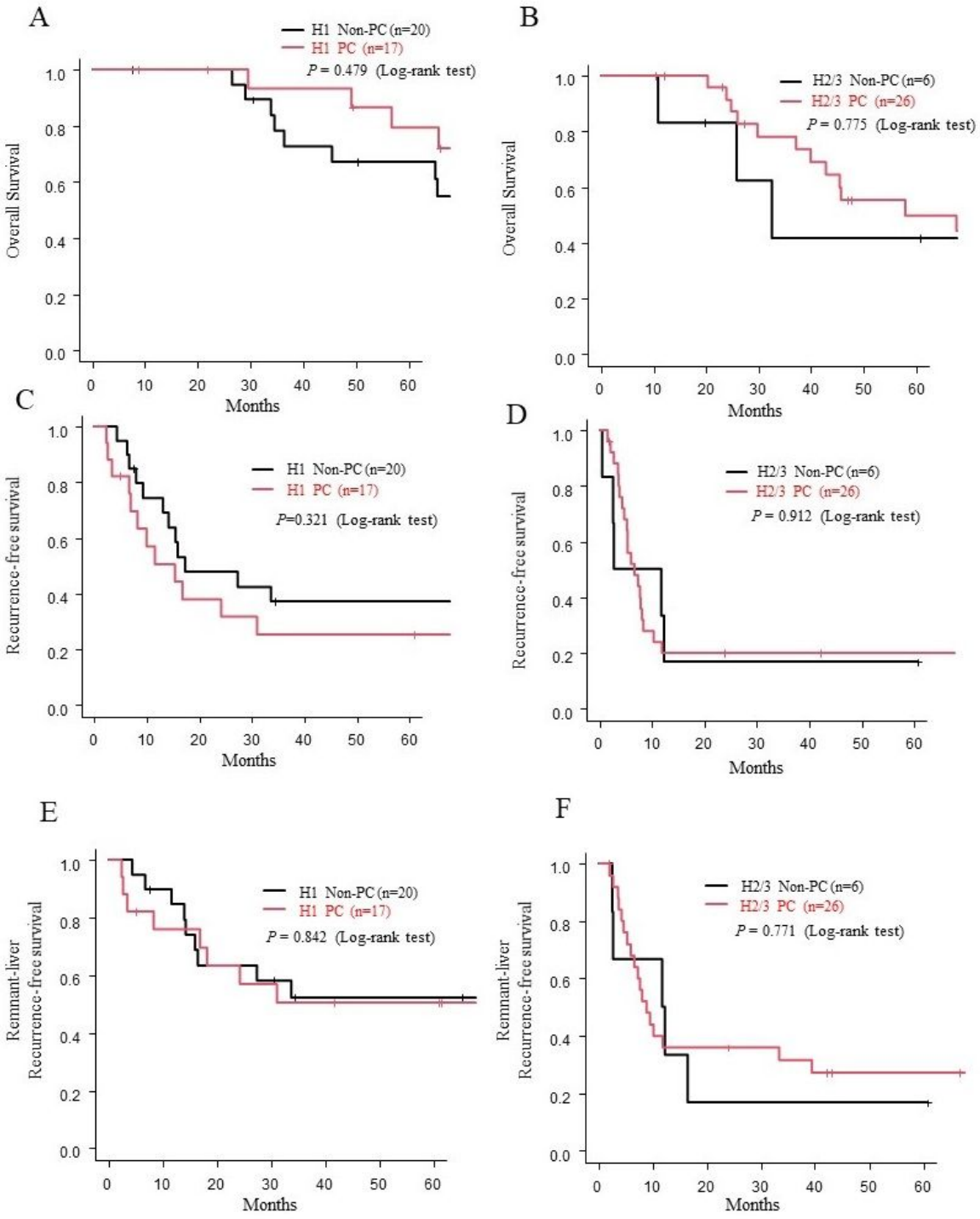
Flowchart of the patient selection process.



(A) Overall survival. (B) Recurrence-free survival (C) Remnant-liver Recurrence-free survival. Overall survival was calculated from the date of the first treatment for CRLM. Recurrence-free survival (RFS) and Remnant liver-RFS were calculated from the date of the initial hepatectomy.

Figure 2

Long-term survival in the Non-PC and PC groups.



(A) Overall survival in the H1 group. (B) Overall survival in the H2/3 group. (C) Recurrence-free survival in the H1 group. (D) Recurrence-free survival in the H2/3 group. (E) Remnant-liver Recurrence-free survival in the H1 group. (F) Remnant-liver Recurrence-free survival in the H2/3 group.

Figure 3

Long-term survival in the H1 and H2/3 groups.

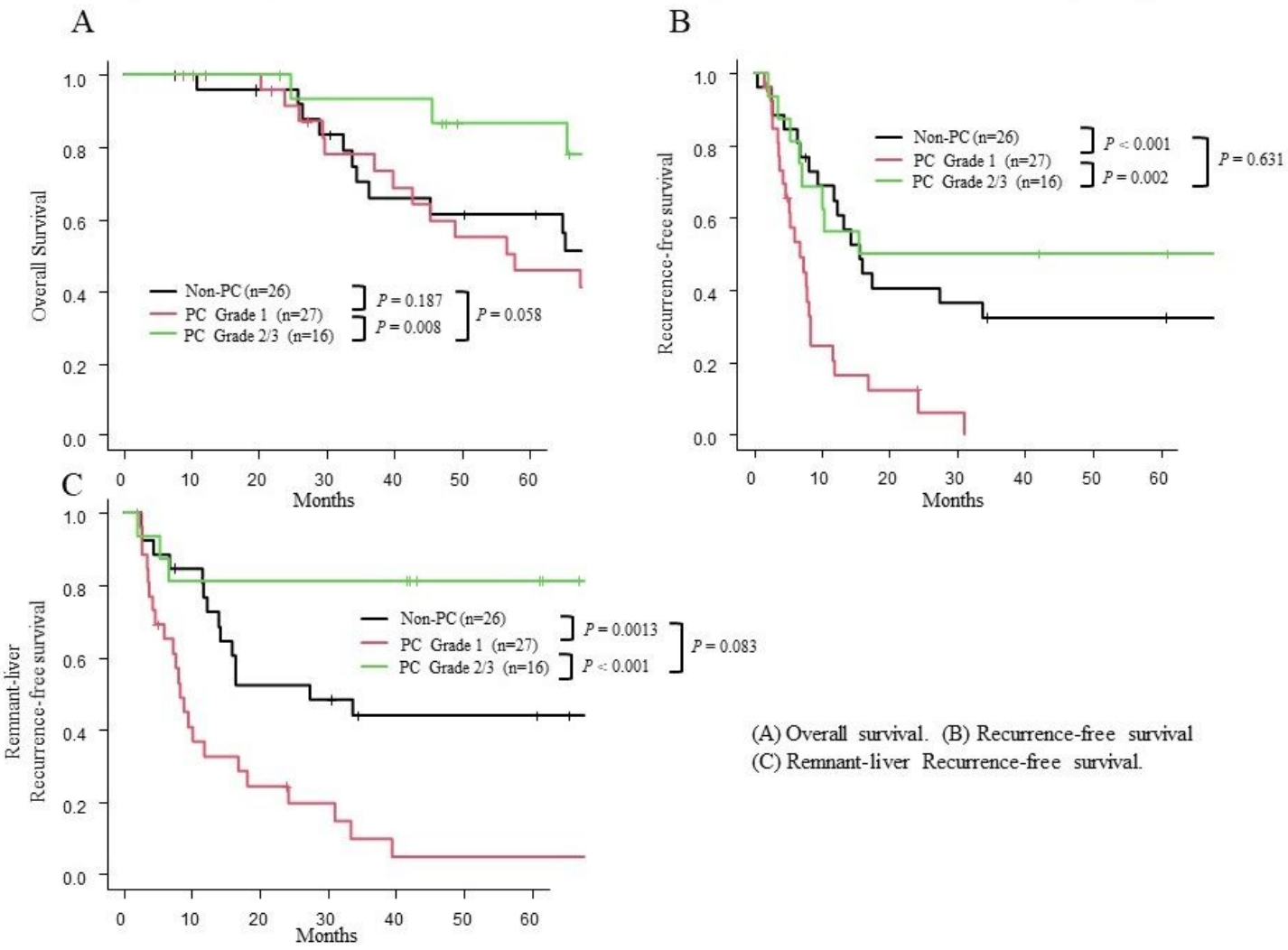


Figure 4

Long-term survival in the Non-PC, Grade 1 and Grade 2/3 groups.

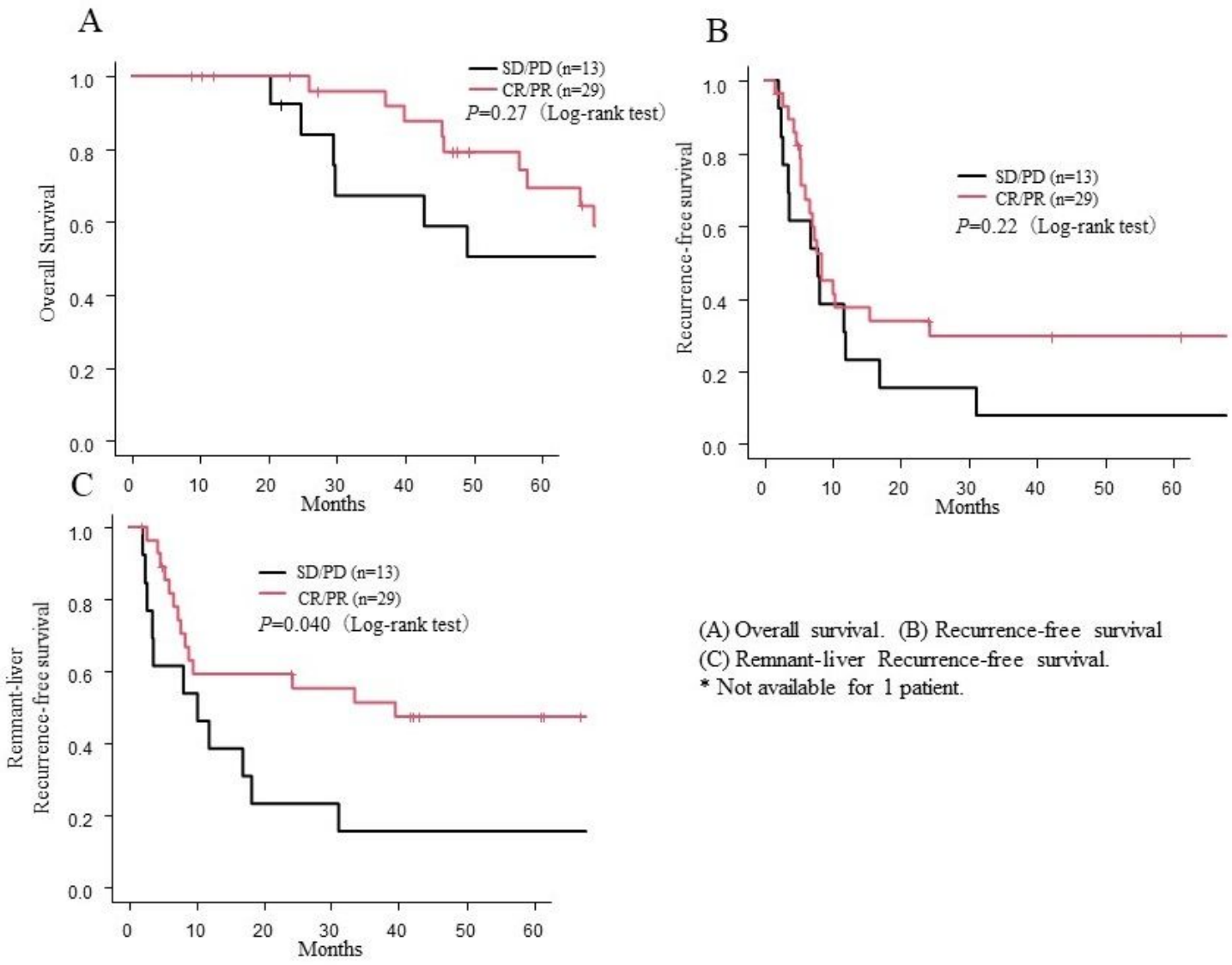


Figure 5

Long-term survival in the CR/PR and SD/PD groups.