# Development of an algorithm to predict recurrences after resection of liver metastases in patients with metastatic colorectal cancer

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## ABSTRACT

**[Background]**

Hepatic recurrences after resection of metastatic lesions in advanced colorectal cancer (CRC) have an enormous impact on patient prognosis. RECIST criteria or morphologic response on computed tomography (CT) have been reported as surrogate prognostication markers. In this study, we assessed a novel algorithm for the prognostication of liver metastasis treatment.

**[Patients and Methods]**

Forty-seven patients with liver metastases from CRC who underwent liver resection after systemic chemotherapy were included. The CT values examined before and after chemotherapy were collected. The velocity of CT values (CTv⊿) was calculated, and the subjects were divided into CTv⊿_high and _low groups. Clinicopathological variables, recurrence-free survival (RFS), and overall survival (OS) were statistically compared between the two groups. In addition, the effect of the combined evaluation of CTv⊿ and carcinoembryonic antigen (CEA) was evaluated.

**[Results]**

In univariate analyses, the hazard ratio (HR) for a recurrence after liver resection was relatively higher in the RECIST_stable disease (SD) or _progressive disease (PD) and the CTv⊿_low groups. In multivariate analysis, the HR was significantly higher in the CEA_high, the RECIST_SD or PD, and the CTv⊿_low groups.

The RFS was significantly longer in the CTv⊿_high group. Furthermore, the combination of CTv⊿ and CEA predicted significantly longer RFS and OS.

**[Conclusion]**

Our algorithm using CTv⊿ could be a useful tool to select patients suitable for

liver resection of hepatic CRC metastases.

## INTRODUCTION

### Therapeutic Trends in Liver Metastasis from Colorectal Cancer

Historically, the prognosis for patients with colorectal cancer (CRC) with liver metastases has been poor, with median survival ranging from 4.5 to 20 months (1, 2). The Clinical Recurrence Score (CRS) was used to determine the prognosis after liver resection (3, 4).

Systemic chemotherapy improved prognosis, and patients with metastatic disease who were considered to have a worse prognosis according to CRS criteria, achieved a survival comparable to that of patients with a good CRS (5). The current strategy is to recommend surgical intervention if the metastatic lesion has become resectable after chemotherapy (6).

### The Decision to Excise Colorectal Cancer Liver Metastases

In the CRS criteria, patients with the following factors are predicted to have a significantly worse prognosis: 1. positive surgical margin, 2. existence of extrahepatic metastatic lesions, 3. presence of regional lymph node metastasis, 4. recurrence within 12 months after metastatic lesion resection, and 6. Carcinoembryonic antigen (CEA) levels over 200 ng/mL (3).

However, these CRS criteria elements cannot be determined before the completion of chemotherapy and surgery. Therefore, a precise algorithm is needed to determine the appropriate timing for surgical intervention while the metastatic lesion changes morphologically during chemotherapy treatment.

### The Issue of RECIST and Morphologic Response Evaluation as Indicators for

## Surgical Strategy

The standard indicator of therapeutic responses in CRC is the Response Evaluation Criteria in Solid Tumors (RECIST) assessment (7). Furthermore, morphologic tumor response assessment (8) using enhanced computed tomography (CT) data has been advocated to strengthen RECIST assessment for determining whether surgical intervention is preferable in a patient.

Several post-surgical interventional prognostication assessments using RECIST or morphologic response have been reported (9–12). However, accurate assessment is not possible if the tumor size does not change. On the other hand, morphologic response evaluation needs to be performed by radiologic diagnostic specialists.

Due to these issues, both RECIST or morphologic response evaluations are still not sufficient to determine whether surgical intervention is necessary. As these maneuvers can only be performed after the completion of chemotherapy, the optimal therapeutic timing for the surgical intervention might be missed.

## The Purpose of This Study

In this study, we suggest a novel algorithm to evaluate the velocity of CT values (CTv⊿) before and after chemotherapy. We assessed how accurately CTv⊿, as well as RECIST and morphologic responses, predict the prognosis after hepatic resection of CRC metastases. In addition, we aimed to improve the prognostic predictive power of CTv⊿ by combining it with CEA, an element of CRS.

# PATIENTS and METHODS

## Patients

This study was conducted retrospectively. From 2000 to 2012, patients diagnosed with CRC liver metastasis who were treated at the departments of surgery

of Kurume University and Kurume Medical Center were included. A total of 47 patients undergoing surgical liver resection after systemic chemotherapy were enrolled in this study.

Data on clinicopathological factors, tumor markers, therapeutic response, and enhanced CT images were collected and used in subsequent analyses. The TNM classification of Malignant tumor (TNM) 8$^{th}$ edition (13) was used to determine clinical staging. For the evaluation of CRC liver metastasis status and grade, we referred to the Japanese guideline of CRC 2019 (14) and the liver metastasis grade scoring system documented by Nagashima *et al*. (15).

**Imaging Analysis**

Enhanced CT imaging of metastatic lesions was performed with the 67-column multi-slice CT scan (Discovery CT750HD: General Electric, Boston, Massachusetts, US). For the CT scan, non-ionized iodine (Iopromide: Byer, Leverkusen, Germany) was administered at a dose of 600 mg/Kg, at 2.0ml/sec, and after 70 seconds, the scan was performed. RECIST and morphologic response assessments were performed by two independent radiologists.

**RECIST Assessment**

Assessment of the therapeutic response of the metastatic lesion was performed according to RECIST 1.1 evaluation criteria (7). In short, if a metastatic lesion disappeared after chemotherapy, it was considered a complete response (CR); if tumor regression was over 30%, it was considered a partial response (PR); if tumor progression was more than 20%, it was considered progressive disease (PD), and if the assessments were between PR and PD, it was considered stable disease (SD).

**Morphologic Response Assessment**

Assessment of morphologic response was performed with reference to the morphologic response criteria first published by Chun *et al*. (10) and modified by Suzuki *et al*. (9). In general, an Optimal Response (OR) was defined as the boundary of the tumor changes into smooth edges, and this persists after chemotherapy; No Response (NR) was defined as a tumor that does not show any change on the image after chemotherapy; and Intermediate Response (IR) was defined as a change on the image that ranges between an OR and NR.

**CTv⊿**

CT value measurements were performed using the CT value measurement mode installed on the Picture Archiving Communication System software (HOPE LifeMark PACS: FUJITSU, Minato City, Tokyo, Japan). Measurements were taken at the inner lateral border of a tumor and in the normal liver parenchyma, while avoiding the main hepatic vessels. The CT value measurements were performed before and after chemotherapy.

Tumor CT values were standardized by dividing the measured tumor values by the corresponding normal liver parenchyma CT values. The change in ratios of the tumor CT values before and after chemotherapy was calculated by dividing the pre-chemotherapy standardized CT value by the post-chemotherapy standardized CT value. In addition, the tumor CT change ratio was divided by the period (in days) between the pre- and post-CT examinations to obtain the CTv⊿ (Supplementary Figure 1).

**Statistical analyses**

Enrolled cases were divided into CTv⊿_high and _low groups and clinicopathologic variables were statistically compared between these groups to

address the significance of CTv⊿ stratification.

The Chi-square test was used to evaluate characteristic variables and the Student's t-test was used to compare continuous variables. The Kaplan-Meier method was used to develop survival curves. Log-rank and Wilcoxon signed-rank tests were used to compare the survival between groups. RFS was defined from the date of the liver resection to the date of the diagnosis of liver recurrence, and OS was defined to the date of patient death. Univariate and multivariate analyses were performed using the proportional hazards model. P-values $<0.05$ were considered statistically significant.

All statistical analyses were performed with JMP pro ver.16.0 software (SAS Institute, Cary, NC, USA).

**Ethics**

This research was conducted with the approval of the Ethics Committee Board of Kurume University (Approval Number: 14179), obtained in June 2014.

## RESULTS

### Summary of Patient Clinicopathological Characteristics and Chemotherapy Treatment

The median age of the patients was 60 years, 70% were male, and 67% of primary tumors were left-sided. Seventy percent of patients with metastases had multiple metastases, and 61% of these were synchronously diagnosed. Overall, 37% of cases with liver metastases were of grade C (Supplementary Figure 1).

The median number of chemotherapy cycles patients received was nine, and the median observation time after metastatic liver resection was 27 months (data not shown). Most of the chemotherapy regimens that patients received were FOLFOX

(5-FU, leucovorin calcium, and oxaliplatin) or FOLFIRI (irinotecan hydrochloride instead of oxaliplatin), or combined with molecular targeting drugs (bevacizumab, cetuximab, or panitumumab). The remaining regimens were capecitabine, S-1, and a combination of these with molecular targeted agents (Supplementary Table 2).

According to RECIST and morphologic response assessment, 67% of cases achieved a PR, and 57% of cases had an optimal response (OR) (Supplementary Table 1).

**CTv⊿ and Clinicopathological Characteristics**

In the enrolled cases, 77% of patients showed down-regulation of CT values after chemotherapy as shown in Supplementary Figure 2. The velocity of CT ratio change (CTv⊿) was calculated, as shown in Supplementary Figure 1. The upper 75% quartile of the CTv⊿ value was set as a cut-off value, and based on this value, patients were divided into CTv⊿_high and _low groups.

There were no clinicopathological variables that indicated a significant difference between the two groups (Table 1). Metastasis-related factors, such as the number of metastases, synchronous or metachronous metastasis, liver metastasis grade, CEA level, RECIST, and RAS status, were not significantly different between the two groups. However, there were significantly fewer OR cases in the CTv⊿_high group than in the _low group (Table 1).

**Comparison of Individual Factors for RFS and OS**

Recurrence-free survival (RFS) and overall survival (OS) after metastatic liver resection were compared between groups based on the CTv⊿, RECIST, and morphologic response assessments. For the CTv⊿ evaluation, RFS, but not OS, was significantly longer in the CTv⊿_high group than in the CTv⊿_low group (Figure 1).

Similarly, for the RECIST evaluation, the partial response (PR) group had a significantly longer RFS, but not OS, than the non-response (NR) group (Supplementary Figure 3). However, there were no significant differences in survival between the OR and the non-OR groups based on the morphologic response assessment (Supplemental Figure 4).

**Prognostic Univariate and Multivariate Analyses**

Univariate and multivariate proportional hazard analyses were performed to determine the risk factors for liver recurrences after surgery. In the univariate analysis, we did not detect a significant risk factor for hepatic recurrence, but RECIST SD or PD and CTv⊿_low were associated with a relatively higher HR. The factors with a p-value <0.25 were analyzed in a multivariate analysis, and we detected that CEA_high, RECIST_SD or PD, and CTv⊿_low were independent risk factors for shorter RFS (Table 2).

The same analysis was performed for OS, and right-sided colon cancer and CEA were associated with a significantly higher HR in univariate analyses, and right-sided colon cancer was associated with a significantly higher HR in multivariate analyses (Supplementary Table 3).

**Combination Prognostic Effect with CTv⊿**

Combination prognostic effects were compared between the risk factors CEA, RECIST, and CTv⊿, because these factors were associated with a significantly higher HR for hepatic recurrences after liver tumor resection. We defined that the cases that showed CTv⊿_high concurrently with normalized CEA as rapidly normalized CT and CEA group (RN group) and defined the remaining cases as non-RN group. We also defined the cases with RECIST PR concurrently with normalized CEA as

RECIST PR including normalized CEA (RN group) and defined the remaining cases as non-RN group.

As shown in Figure 2, the RFS and OS of the RN group was significantly longer than that of the non-RN group. On the other hand, when groups were split based on the combination of RECIST criteria and CEA levels, there was no such effect that was observed with the combination of the CTv⊿ and CEA levels (Figure 3).

**DISCUSSION**

In this study, we suggest that CTv⊿, which represents the velocity of the CT values being observed before and after chemotherapy, can be used to predict outcomes. The postoperative prognosis of patients in the CTv⊿_high group was significantly better than that of the CTv⊿_low group in this study. Based on this, we selected CTv⊿_high as an independent prognostic factor for recurrence, together with CEA and RECIST outcome measures. The combination of CTv⊿ and CEA was shown to be a prognostic marker for RFS after liver tumor resection in patients with metastatic colorectal cancer.

The patients enrolled in this study were diagnosed with CRC between 2000 and 2012. The chemotherapy regimens administered to the patients are, therefore, less used strategies in the last few years. However, most of the treatments incorporated FOLFOX and FOLFIRI, which are still being used as a mainstay chemotherapy treatment for CRC.

Currently, there is no consensus on the optimal therapeutic strategy for the treatment of CRC liver metastases. Options include neoadjuvant chemotherapy followed by liver resection (16), or upfront liver resection (17). More evidence needs to be collected comparing the benefit of additional chemotherapy to justify its use.

CTv⊿ evaluates the characteristic change of the therapeutically modulated metastatic lesion from the perspective of velocity. Initially, we expected that the CTv⊿ would be associated with TNM factors or other clinical factors such as metastatic grade, CEA level, RECIST outcomes, and morphologic responses, which all are prognostic factors after surgical intervention for liver metastases. However, none of these factors were associated with CTv⊿, and moreover, the morphologic response had shown an association with CTv⊿_low, which was a contradictory result that we had expected before the analyses.

These prognostic factors other than CTv⊿ do not include chronological elements that change the characteristics of metastatic lesions after chemotherapy treatment. In addition, the relationship between patients' prognosis and cycles of chemotherapy is not well documented. The result of this study suggests it is important to consider the velocity of the changing characteristics in the metastatic lesion in the decision for surgical intervention.

According to our multivariate analysis, the CTv⊿_low group had the second-highest HR after RECIST grouping for recurrences after surgery. The advantage of evaluating the CTv⊿ is that the RECIST assessment is performed after the completion of chemotherapy, while the CTv⊿ can theoretically be determined even in the middle of treatment, as it calculates the velocity of CT values. The importance of timing of surgical intervention after the introduction of chemotherapy has been reported (18), and the CTv⊿ assessment has the potential to determine the right timing for this therapeutic decision.

The CTv⊿ can be interpreted without a radiologist and is highly objective. The multivariate analysis showed the difficulty of determining the morphologic response

assessment, which was not found to be an independent prognostic factor for recurrences, and also was shown to have a negative relationship with the CTv⊿. On the other hand, to acquire a consistent CTv⊿ in clinically standardization of the CT enhancement administration and timing of the image acquisition is necessary.

A limitation of this study is that this is a retrospective assessment, and to confirm the prognostic benefits found in this study, a prospective study is needed. The number of patients analyzed in this study was small, and larger studies should be conducted to confirm our results. As the chemotherapy regimens administered to the patients in this study were not the latest used regimens, assessments should be repeated with patients that received standard neoadjuvant chemotherapy in future analyses.

## CONCLUSION

The CTv⊿ value developed in this study may serve as a useful marker for determining patients eligible for liver resection in metastatic colorectal cancer, besides the already existing RECIST assessment. CTv⊿ combined with CEA values may serve as a tool to predict the prognosis of patients with liver metastasis CRC after surgical intervention.

## CONFLICTS of INTEREST

The authors have no conflicts of interest directly relevant to the content of this article to declare.

## AUTHOR CONTRIBUTIONS

**MT** planned all experiments and wrote the manuscript. **TT** and **TK** evaluated treatment response on CT scans. **TS** performed the statistical analysis. **SN**, **KT**, **SF**, **KY**, and **HM** collected and summarized the clinical data for the enrolled patients. **TS**, **AY**, **FF**, and **TH** were involved in drafting the manuscript or revising it critically for intellectual content and **YA** gave the final approval of the to-be-published version of

the manuscript. **TS** and **TH** provided important suggestions for the study. All authors read and approved the final version of the manuscript.

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Dr. Tetsushi Kinugasa: Data curation

## REFERENCES


1 Bengtsson G, Carlsson G, Hafström L and Jönsson PE: Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg *141*: 586–589, 1981. PMID: 7223955.

2 Ballantyne GH and Quin J: Surgical treatment of liver metastases in patients with colorectal cancer. Cancer *71*: 4252–4266, 1993. PMID: 8508388.

3 Fong Y, Fortner J, Sun RL, Brennan MF and Blumgart LH: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg *230*: 309–18; discussion 318–21, 1999. PMID: 10493478.

4 Saiura A, Yamamoto J, Hasegawa K, Koga R, Sakamoto Y, Hata S, Makuuchi M and Kokudo N: Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases. World J Surg *36*: 2171–2178, 2012. PMID: 22547015.

5 Ichida H, Mise Y, Ito H, Ishizawa T, Inoue Y, Takahashi Y, Shinozaki E, Yamaguchi K and Saiura A: Optimal indication criteria for neoadjuvant chemotherapy in patients with resectable colorectal liver metastases. World J Surg Oncol *17*: 100, 2019. PMID: 31196104.

6 Saiura A, Yamamoto J, Koga R, Takahashi Y, Takahashi M, Inoue Y, Ono Y and Kokudo N: Favorable outcome after repeat resection for colorectal liver metastases. Ann Surg Oncol *21*: 4293–4299, 2014. PMID: 24962942.

7 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228–247, 2009. PMID: 19097774.

8 Shindoh J, Loyer EM, Kopetz S, Boonsirikamchai P, Maru DM, Chun YS, Zimmitti G, Curley SA, Charnsangavej C, Aloia TA and Vauthey J-N: Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol *30*: 4566–4572, 2012. PMID: 23150701.

9 Suzuki K, Muto Y, Ichida K, Fukui T, Takayama Y, Kakizawa N, Kato T, Hasegawa F, Watanabe F, Kaneda Y and Others: Morphological response contributes to patient selection for rescue liver resection in chemotherapy patients with initially un-resectable colorectal liver metastasis. Oncol Lett *14*: 1491–1499, 2017.

10 Chun YS, Vauthey J-N, Boonsirikamchai P, Maru DM, Kopetz S, Palavecino M, Curley SA, Abdalla EK, Kaur H, Charnsangavej C and Loyer EM: Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA *302*: 2338–2344, 2009. PMID: 19952320.

11 Nishioka Y, Shindoh J, Yoshioka R, Gonoi W, Abe H, Okura N, Yoshida S, Oba M, Hashimoto M, Watanabe G, Hasegawa K and Kokudo N: Radiological Morphology of Colorectal Liver Metastases after Preoperative Chemotherapy Predicts Tumor Viability and Postoperative Outcomes. J Gastrointest Surg *19*:

1653–1661, 2015. PMID: 25917536.
12 Shindoh J, Chun YS, Loyer EM and Vauthey J-N: Non-size-based response criteria to preoperative chemotherapy in patients with colorectal liver metastases: the morphologic response criteria. Curr Colorectal Cancer Rep *9*: 198–202, 2013. PMID: 23710157.
13 Shida D, Kanemitsu Y, Hamaguchi T and Shimada Y: Introducing the eighth edition of the tumor-node-metastasis classification as relevant to colorectal cancer, anal cancer and appendiceal cancer: a comparison study with the seventh edition of the tumor-node-metastasis and the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma. Jpn J Clin Oncol *49*: 321–328, 2019. PMID: 30608547.
14 Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kinugasa Y, Murofushi K, Nakajima TE, Oka S, Tanaka T, Taniguchi H, Tsuji A, Uehara K, Ueno H, Yamanaka T, Yamazaki K, Yoshida M, Yoshino T, Itabashi M, Sakamaki K, Sano K, Shimada Y, Tanaka S, Uetake H, Yamaguchi S, Yamaguchi N, Kobayashi H, Matsuda K, Kotake K, Sugihara K and Japanese Society for Cancer of the Colon and Rectum: Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol *25*: 1–42, 2020. PMID: 31203527.
15 Nagashima I, Takada T, Matsuda K, Adachi M, Nagawa H, Muto T and Okinaga K: A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. J Hepatobiliary Pancreat Surg *11*: 79–83, 2004. PMID: 15127268.
16 Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T, EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), Australasian Gastro-Intestinal Trials Group (AGITG) and Fédération Francophone de Cancérologie Digestive (FFCD): Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol *14*: 1208–1215, 2013. PMID: 24120480.
17 Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard J-Y, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne C-H, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJG, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A and Arnold D: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol *27*: 1386–1422, 2016. PMID: 27380959.
18 Chen Q, Mao R, Zhao J, Bi X, Li Z, Huang Z, Zhang Y, Zhou J, Zhao H and Cai J: From the completion of neoadjuvant chemotherapy to surgery for

colorectal cancer liver metastasis: What is the optimal timing? Cancer Med *9*: 7849–7862, 2020. PMID: 32886456.

Table 1. Comparison of clinicopathological characteristics, liver metastatic status, therapeutic response, and RAS status between CTv⊿_high and _low groups.

| **Characteristics** | | **CTv⊿_high**<br>**N=12 (%)** | **CTv⊿_low**<br>**N= 35 (%)** | **P** |
|---|---|---|---|---|
| **Sex** | male / female | 9(75)/3(25) | 27(77.14)/8(22.86) | 1.00 |
| **Age** | <65 / ≧65 | 6(50) / 6(50) | 17(48.57)/18(51.43) | 1.00 |
| **Tumor location** | Right / Left | 3(25)/9(75) | 8(22.86)/27(77.14) | 1.00 |
| **depth** | T2-T3 / T4a | 5(41.67)/7(58.33) | 11(31.43)/24(68.57) | 0.73 |
| **histological type** | tub1-tub2 / others | 12(100)/0(0) | 32(91.43)/3(8.57) | 0.56 |
| **N** | N+ / N- | 8(66.67)/4(33.33) | 22(62.86)/13(37.14) | 0.74 |
| **V** | V+ / V- | 11(91.67)/1(8.33) | 33(94.29)/2(5.71) | 0.47 |

| | | | | |
|---|---|---|---|---|
| **Ly** | Ly+ / Ly- | 8(60.64)/4(33.33) | 27(77.14)/8(22.86) | 1.00 |
| **Liver metastasis** | single / multiple | 4(33.33)/8(66.67) | 10(28.57)/25(71.43) | 0.73 |
| | synchronous / metachronous | 7(58.33)/5(41.67) | 21(60)/14(40) | 1.00 |
| **Liver metastasis Grade** | A-B / C | 7(58.33)/5(41.67) | 13(37.14)/22(62.86) | 0.73 |
| **CEA** | normal / high | 2(16.67)/10(83.33) | 9(25.71)/26(74.29) | 1.00 |
| **RECIST** | PR/SD-PD | 6(60)/6(50) | 21(60)/14(40) | 0.55 |
| **morphologic response** | OR / IR or NR | 1(8.33)/11(91.67) | 24(68.57)/11(31.43) | 0.0004* |
| **RAS status** | Wildtype/Mutation/Unknown | 5(41.67)/4(33.33)/3(25) | 18(51.43)/8(22.86)/9(25.71) | 0.7617 |

tub1: well differentiated adenocarcinoma, tub2: moderately differentiated adenocarcinoma, others: poorly or undifferentiated adenocarcinoma, N: lymph node metastasis, V: vascular invasion, Ly: lymphatic invasion, Liver metastatic grade A: B: C:, PR: partial response, SD: stable disease, PD: progressive disease, OR: optimal response, IR: intermediate response, NR: no response, CEA: carcinoembryonic antigen. Asterisk indicates statistical significance.

Table 2. Univariate and multivariate Proportional Hazard Model analysis for recurrences after resection of metastatic region

| **Characteristics** | **N** | **Event** | **Univariate HR (95%CI)** | **P** | **Multivariate HR (95%CI)** | **P** |
|---|---|---|---|---|---|---|
| **Sex (N=47)** | | | | | | |
| **Female** | 11 | 5 | 1 | 0.48 | - | - |
| **Male** | 36 | 27 | 1.3(0.62-2.76) | | - | |
| **Age(N=47)** | | | | | | |
| **<65** | 23 | 11 | 1 | 0.88 | - | - |
| **≧65** | 24 | 21 | 1.05(0.56-1.96) | | - | |
| **Tumor Location(N=47)** | | | | | | |
| **Left** | 36 | 31 | 1 | 0.83 | - | - |
| **Right** | 11 | 9 | 1.08(0.51-2.29) | | - | |
| **Tumor Depth(N=47)** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **T2-3** | 16 | 14 | 1 | 0.39 | - | - |
| **T4** | 31 | 26 | 1.33(0.68-2.56) | | - | |
| **Histological type(N=47)** | | | | | | |
| **Well or Moderate** | 44 | 37 | 1 | 0.71 | - | - |
| **Others** | 3 | 3 | 1.25(0.38-4.09) | | - | |
| **Lymph Node Metastasis (N=47)** | | | | | | |
| **N-** | 18 | 14 | 1 | 0.27 | - | - |
| **N+** | 29 | 26 | 1.45((0.74-2.84) | | - | |
| **Lymphatic Invasion(n=47)** | | | | | | |
| **Ly-** | 12 | 9 | 1 | 0.64 | - | - |
| **Ly+** | 35 | 30 | 1.19(0.64-2.46) | | - | |
| **Vascular Invasion(N=47)** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **V-** | 3 | 3 | 1 | 0.99 | - | - |
| **V+** | 44 | 37 | 1.01(0.31-3.30) | | - | |
| **Metastatic Number(N=47)** | | | | | | |
| **Single** | 14 | 12 | 1 | 0.26 | - | - |
| **Multiple** | 33 | 28 | 1.48(0.75-2.94) | | - | |
| **Metastasis Diagnosis(N=47)** | | | | | | |
| **Synchronous** | 28 | 23 | 1 | 0.87 | - | - |
| **Metachronous** | 19 | 17 | 0.95(0.50-1.78) | | - | |
| **Liver Metastasis Grade (N=47)** | | | | | | |
| **A or B** | 30 | 25 | 1 | 0.23 | 1 | 0.054 |
| **C** | 17 | 15 | 1.49(0.78-2.85) | | 2.07(0.99-4.37) | |
| **CEA (N=47)** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Normal** | 14 | 11 | 1 | 0.18 | 1 | 0.011* |
| **High** | 33 | 29 | 1.62(0.80-3.27) | | 3.01(1.29-7.07) | |
| **RECIST (N=47)** | | | | | | |
| **PR** | 27 | 21 | 1 | 0.06 | 1 | 0.0002* |
| **SD or PD** | 20 | 19 | 1.83(0.97-3.45) | | 4.70(2.11-10.48) | |
| **Morphologic Response (N=47)** | | | | | | |
| **Optimal Response** | 25 | 21 | 1 | 0.86 | - | - |
| **Intermediate or No Response** | 22 | 19 | 0.95(0.50-1.78) | | - | |
| **RAS status (N=47)** | | | | | | |
| **Wildtype** | 23 | 21 | 1 | 0.70 | - | - |
| **Unknown** | 12 | 9 | 0.71(0.33-1.57) | | - | |
| **Mutation** | 12 | 10 | 0.86(0.41-1.83) | | - | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **CTv⊿(N=47)** | | | | | | |
| **High** | 12 | 8 | 1 | 0.06 | 1 | 0.0047* |
| **Low** | 35 | 32 | 2.09(0.96-4.55) | | 3.32(1.45-7.62) | |

Multi-proportional hazard model analysis includes following covariate Liver Metastasis Grade, CEA, RECIST, and CTv⊿. CI indicates confidence interval. "*" indicates statistical significance. CEA: carcinoembryonic antigen, PD: progressive disease, PR: partial response, SD: stable disease.

Supplementary Table 1. Clinicopathological overview of enrolled patients.

| Clinicopathological variables | | N=47 (%) |
|---|---|---|
| **Age** | 65 years old under/over | 23(50)/24(50) |
| **Sex** | male/female | 36(77)/11(23) |
| **tumor location** | right/left | 11(23)/36(67) |
| **depth** | T2,T3/ T4 | 16(34)/31(66) |
| **histological type** | tub1,tub2/others | 44(94)/3(6) |
| **N** | N+/ N- | 30(64)/17(36) |
| **V** | v+/ v- | 43(94)/4(6) |
| **Ly** | ly+/ ly- | 36(74)/11(26) |
| **Liver metastasis** | single/multiple | 14(30)/33(70) |
| **Liver metastasis Grade** | A,B/C | 30(64)/17(36) |
| **Liver metastasis** | synchronous/non-synchronous | 28(60)/19(40) |
| **RAS status** | Wildtype/Mutation/unknown | 23(48.9)/12(25.5)/12(25.5) |
| **CEA** | normal/high | 11(23)/36(77) |
| **RECIST** | PR/SD-PD | 24(57.1)/18(42.9) |
| **Morphologic response** | OR/IR-NR | 25(53)/22(47) |
| **CTv⊿** | high/low | 12(25.5)/35(74.5) |

tumor location right: location from caecum to transverse colon, left: from descending colon to rectum, depth T2:Tumor invades muscularis propria T3:Tumor invades subserosa or into non-peritonealized pericolic or perirectal tissues T4:Tumor directly invades other organ or structures and/or perforates

visceral peritoneum, histological type tub1: well-differentiated histological type tub2: moderately differentiated, histological type tub3: poorly differentiated, N: node metastasis, V: vascular invasion, Ly: lymph duct invasion, Liver metastasis grade A: B: C:, RECIST PR: partial response, RECIST SD: stable disease, RECIST PD: progressive disease, Morphologic response OR: optimal response, Morphologic response IR: intermediate response, Morphologic response NR: no response, CEA: carcinoembryonic antigen.

Supplementary Table 2. Overview of the chemotherapies patients received for liver metastasis

| Chemotherapy regimen | Number of patients |
|---|---|
| mFOLFOX6 | 4 |
| mFOLFOX6+BV | 16 |
| mFOLFOX+Pmab | 3 |
| FOLFIRI+BV | 4 |
| FOLFIRI+Pmab | 1 |
| FOLFIRI+Cmab | 1 |
| FIREFOX+BV | 10 |
| CapeOX+BV | 5 |
| CapeOX+Cmab | 1 |
| SOX+Cmab | 1 |
| UFT+UZEL | 1 |

FOLFOX: Fluorouracil, Leucovorin Calcium, and Oxaliplatin, BV: bevacizumab, Pmab: Panitumumab, Cmab: Cetuximab, FOLFIRI: Fluorouracil, Leucovorin Calcium, and Irinotecan hydrochloride, FIREFOX: Every four cycles sequential exchange of FOLFOX and FOLFIRI, CapeOX: Capecitabine and Oxaliplatin, SOX: S-1 and Oxaliplatin, UFT: tegafur-uracil, UZEL: folinate calcium

Supplemental Table 3. Univariate and multivariate proportional hazard model analysis for overall survival after resection of metastatic region

| Characteristics | N | Event | Univariate HR (95%CI) | P | Multivariate HR (95%CI) | P |
|---|---|---|---|---|---|---|
| Sex (N=47) | | | | | | |
| Female | 11 | 5 | 1 | 0.2 | | |
| Male | 36 | 27 | 1.86(0.71-4.86) | | | |
| Age(N=47) | | | | | | |
| <65 | 23 | 11 | 1 | 0.131 | | |
| ≧65 | 24 | 21 | 1.76(0.84-3.65) | | | |
| Tumor Location(N=47) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Left | 36 | 22 | 1 | 0.0342* | 1 | |
| Right | 11 | 9 | 2.41(1.07-5.43) | | 4.08(1.28-12.96) | 0.017* |
| Tumor Depth(N=47) | | | | | | |
| T2-3 | 16 | 10 | 1 | 0.21 | | |
| T4 | 31 | 21 | 1.6(0.76-3.39) | | | |
| Histological type(N=47) | | | | | | |
| Well or Moderate | 44 | 19 | 1 | 0.89 | | |
| Others | 3 | 3 | 0.92(0.28-3.08) | | | |
| Lymph Node Metastasis (N=47) | | | | | | |
| N- | 18 | 11 | 1 | 0.17 | | |
| N+ | 29 | 21 | 1.69((0.79-3.62) | | | |
| Lymphatic Invasion(n=47) | | | | | | |

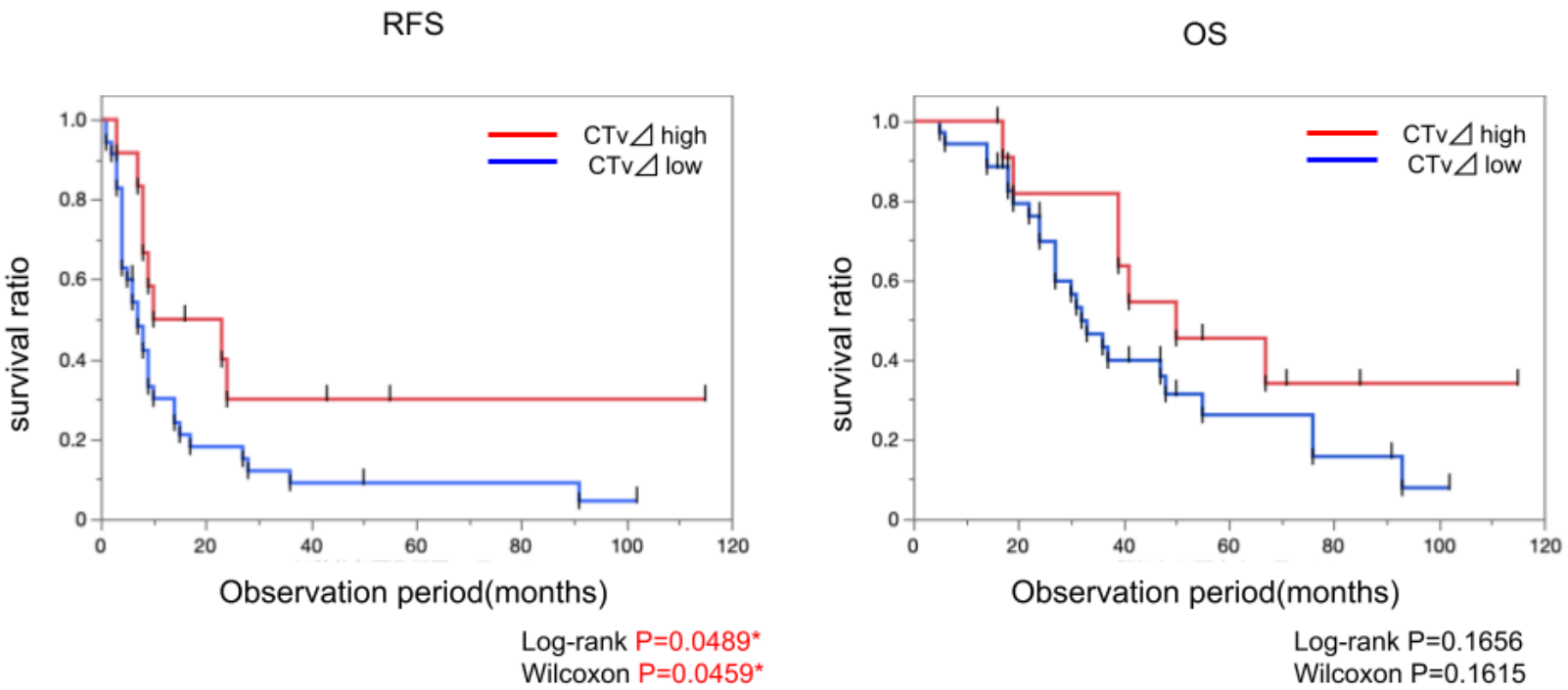
| | | | | | | |
|---|---|---|---|---|---|---|
| Ly- | 12 | 6 | 1 | 0.16 | | |
| Ly+ | 35 | 26 | 1.87(0.77-4.57) | | | |
| Vascular Invasion(N=47) | | | | | | |
| V- | 3 | 3 | 1 | 0.72 | | |
| V+ | 44 | 29 | 0.8(0.24-2.66 | | | |
| Metastatic Number(N=47) | | | | | | |
| Single | 14 | 9 | 1 | 0.15 | | |
| Multiple | 33 | 20 | 1.78(0.8-3.96) | | | |
| Metastasis Diagnosis(N=47) | | | | | | |
| Synchronous | 28 | 21 | 1 | 0.52 | | |
| Metachronous | 19 | 11 | 0.79(0.37-1.63) | | | |
| Liver Metastasis Grade (N=47) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| A or B | 30 | 19 | 1 | 0.19 | | |
| C | 17 | 13 | 1.6(0.79-3.29) | | | |
| CEA (N=47) | | | | | | |
| Normal | 14 | 7 | 1 | 0.046* | | |
| High | 33 | 25 | 2.41(1.02-5.72) | | | |
| RECIST (N=47) | | | | | | |
| PR | 27 | 18 | 1 | 0.33 | | |
| SD or PD | 20 | 15 | 1.42(0.33-1.43) | | | |
| Morphologic Response (N=47) | | | | | | |
| Optimal Response | 25 | 13 | 1 | 0.696 | | |
| Intermediate or No Response | 22 | 16 | 1.15(0.57-2.35) | | | |
| RAS status (N=47) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Wildtype | 23 | 16 | 1 | 0.95 | | |
| Unknown | 12 | 8 | 1.12(0.47-2.64) | | | |
| Mutation | 12 | 8 | 0.96(0.41-2.24) | | | |
| CTv⊿(N=47) | | | | | | |
| High | 12 | 7 | 1 | 0.17 | | |
| Low | 35 | 25 | 1.79(0.77-4.17) | | | |

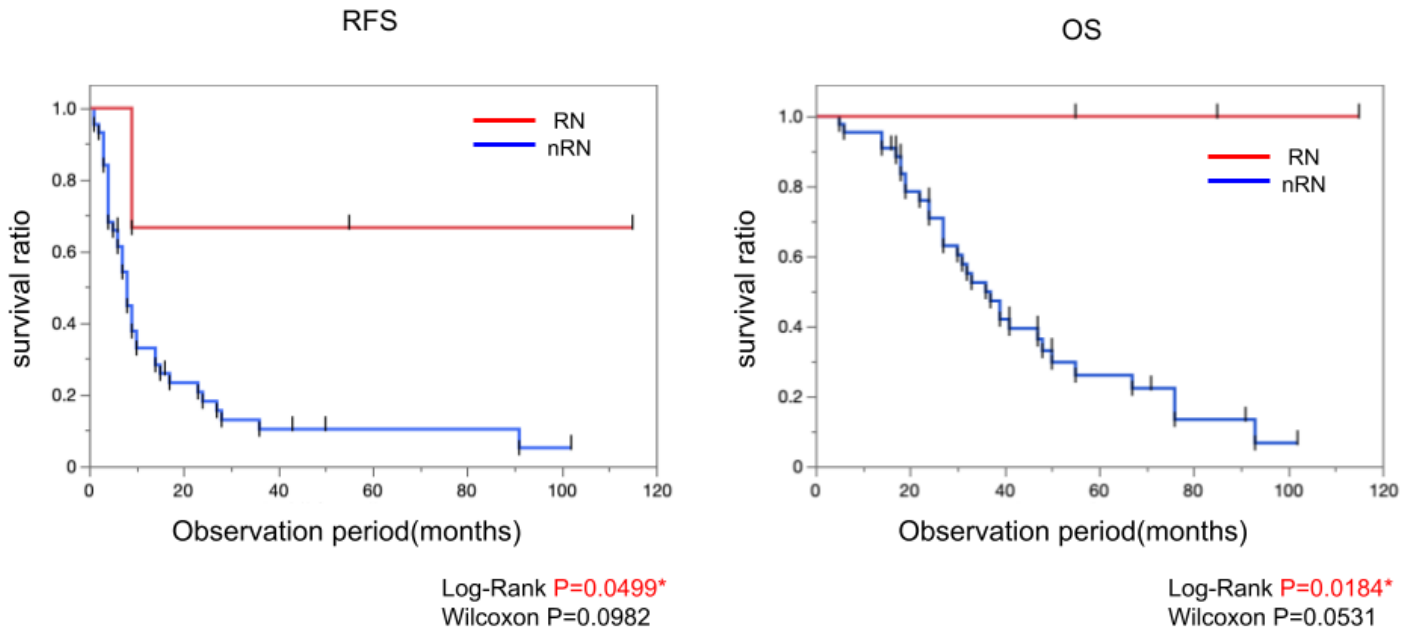
tumor location right: location from caecum to transverse colon, left: from descending colon to rectum, depth T2:Tumor invades muscularis propria T3:Tumor invades subserosa or into non-peritonealized pericolic or perirectal tissues T4:Tumor directly invades other organ or structures and/or perforates visceral peritoneum, histological type tub1: well-differentiated histological type tub2: moderately differentiated, histological type tub3: poorly differentiated, N: node metastasis, V: vascular invasion, Ly: lymph duct invasion, Liver metastasis grade A: B: C:, RECIST PR: partial response, RECIST SD: stable disease, RECIST PD: progressive disease, Morphologic response OR: optimal response, Morphologic response IR: intermediate response, Morphologic response NR: no response, CEA: carcinoembryonic antigen.

Figure 1.



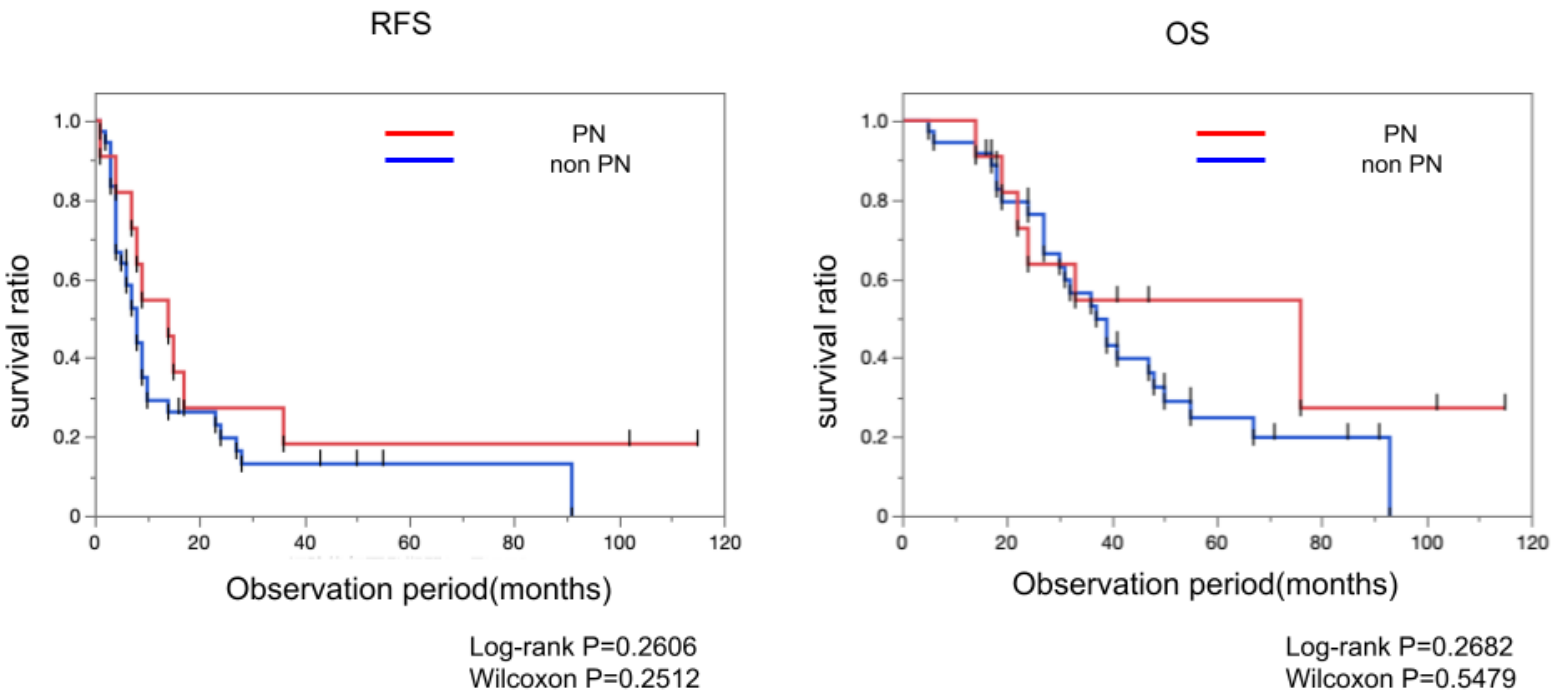

Comparison of recurrence free survival and overall survival between CTv⊿_high and _low group. The Red line indicates CTv⊿_high group and the blue line indicates CTv⊿_low group. Statistical significance was considered to be the P-value<0.05.

Figure 2.

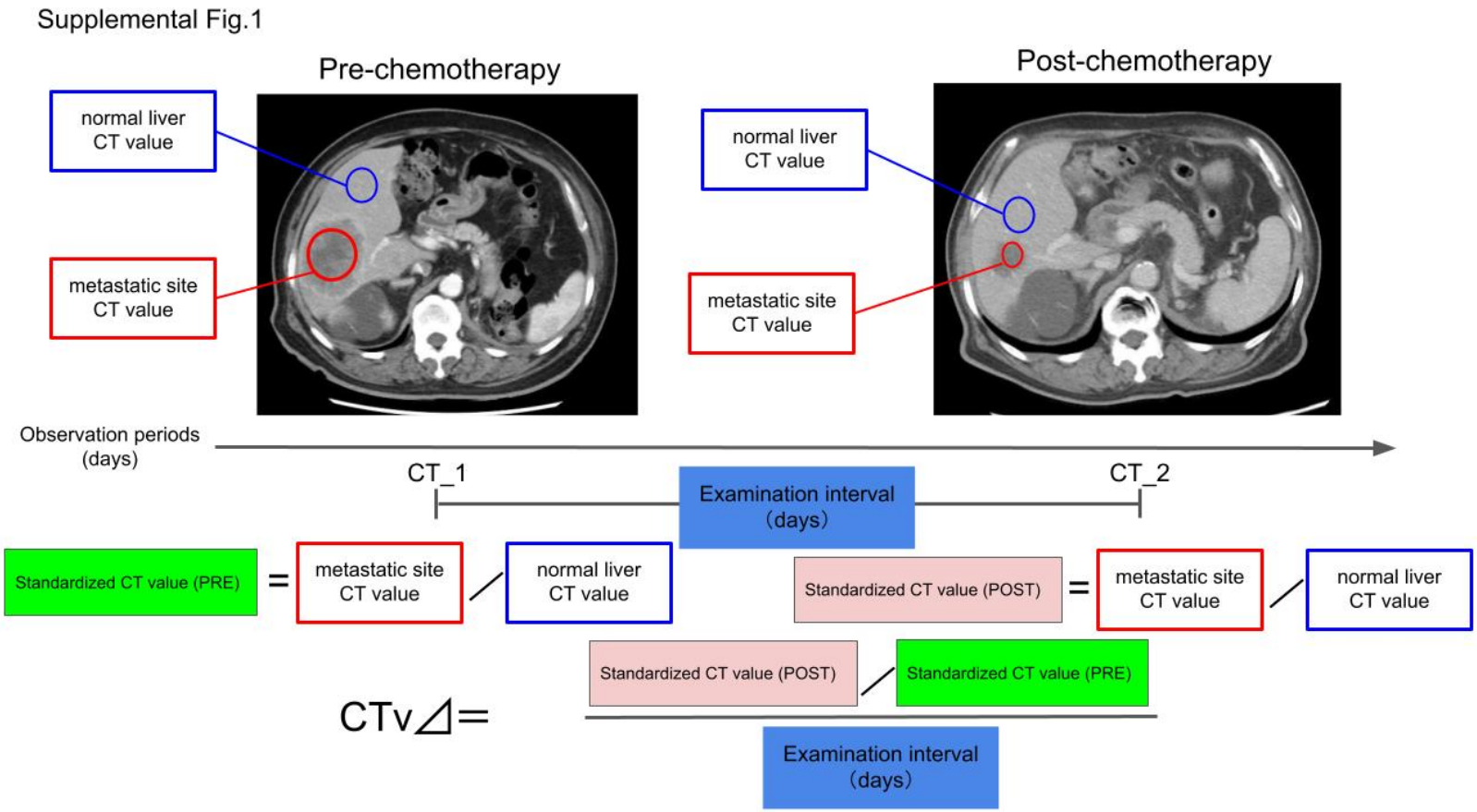



Comparison of recurrence free survival and overall survival between RN and non-RN (nRN) groups. The Red line indicates the RN group and the blue line indicates the nRN group. Statistical significance was considered to be the P-value<0.05. RN: CTv⊿_high concurrent with CEA normalized cases , nRN: the other cases.

Figure 3.

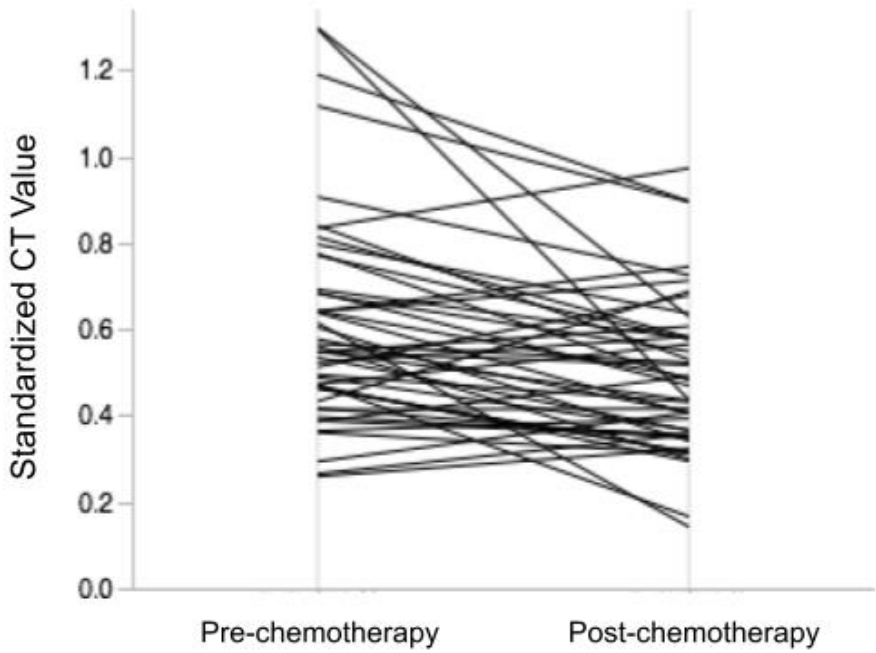



Comparison of recurrence free survival and overall survival between PN and non-PN (non PN) groups. The Red line indicates the PN group and the blue line indicates the non RN group. Statistical significance was considered to be the P-value<0.05. PN:



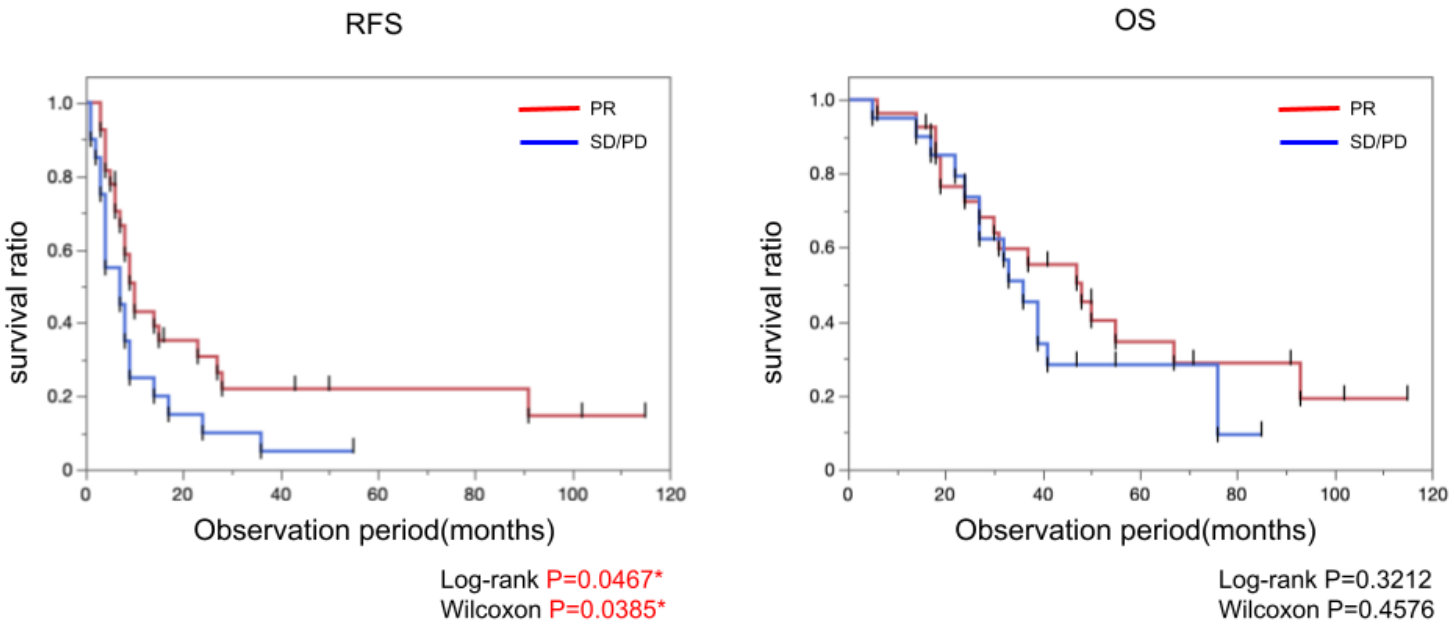

Overview of the methodology of the CTv⊿ calculation. The upper row CT scan figures showing the locations of the CT values analyses between normal and metastatic lesions. The lower row is equations to acquire the CTv⊿.

Supplemental Fig.2



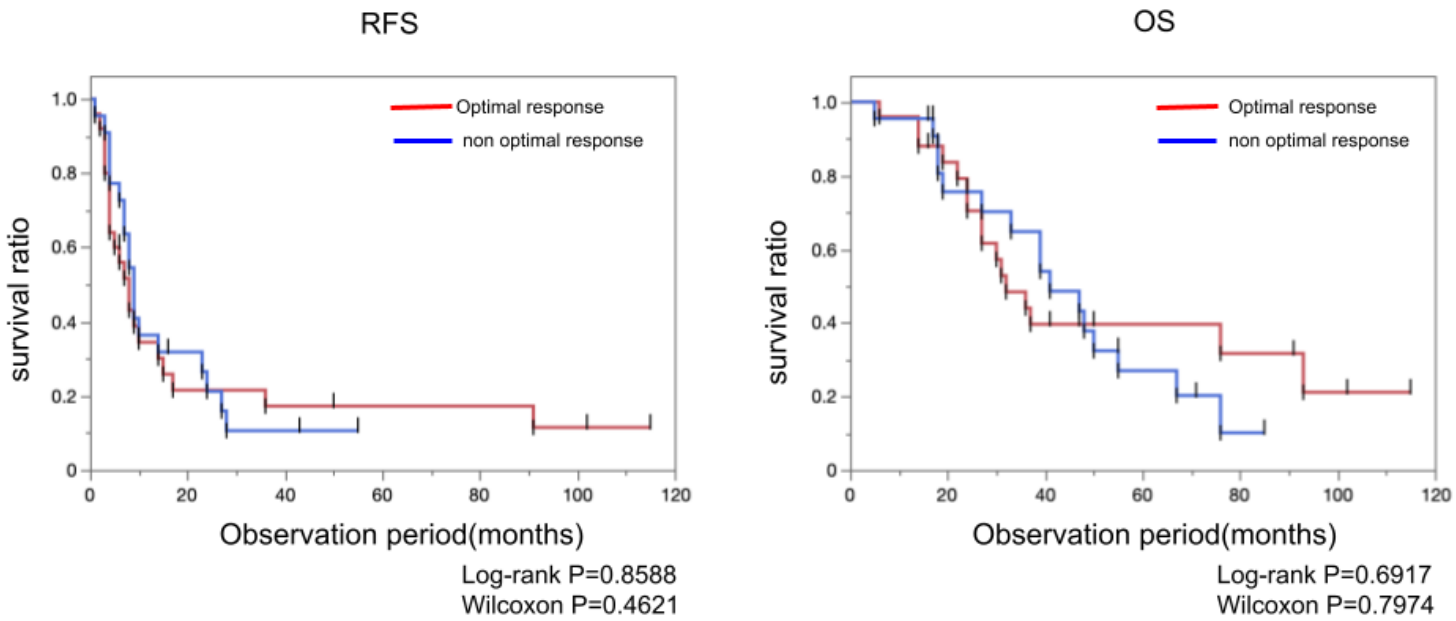

The overview of CT values change before and after the chemotherapies administered to the enrolled patients.

Supplemental Figure 3




Comparison of recurrence free survival and overall survival between RECIST PR and SD/PD groups. The Red line indicates the PR group and the blue line indicates the SD/PD group. Statistical significance was considered to be the P-value<0.05. PR: partial response, SD: stable disease, and PD: progressive disease

Supplemental Figure 4




Comparison of recurrence free survival and overall survival between morphologic response optimal group and non-optimal groups. The Red line indicates the optimal response group and the blue line indicates the non-optimal response group. Statistical significance was considered to be the P-value<0.05.