

# Compare of Sequential, Delayed and Simultaneous Resection Strategies for Synchronous Colorectal Liver Metastases

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## Research article

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# Abstract

**Background:** The present study aimed to compare perioperative safety and long-term survival of patients with synchronous colorectal liver metastases receiving sequential resection (SeR), delayed resection (DeR) and simultaneous resection (SiR). **Methods:** From January 2007 to December 2016, data of patients receiving surgery at Peking University Cancer Hospital for synchronous colorectal liver metastases were retrospectively collected. The above three different surgical strategies were compared. **Results:** A total of 233 cases were included, with 49 in the SeR group, 98 in the DeR group and 86 in the SiR group. The incidence of severe complications was 26.7% in the SiR group, higher than that in the DeR group (11.2%,  $p=0.007$ ) and the SeR group (16.3%,  $p=0.166$ ). Overall survival at 1-year and 3-year in the SeR group (93.9% and 50.1%) was lower than the DeR group (94.9% and 64.8%,  $p=0.019$ ), but not statistically different compared with the SiR group (93.0% and 55.2%,  $p=0.378$ ). Recurrence-free survival at 1-year and 3-year in the SeR group (22.4% and 18.4%) was lower than the DeR group (43.9% and 24.2%,  $p=0.033$ ), but not statistically different compared with the SiR group (31.4% and 19.6%,  $p=0.275$ ). Cox multivariate analysis indicated that T4, lymph node positive primary tumor, liver metastases >30mm and selective sequential resection (compared with delayed resection) were correlated with poor prognosis. **Conclusion:** Simultaneous resection has a relatively higher incidence of severe complication, and when staged resection strategy was made, the prognosis of delayed resection was better than that of sequential resection.

## Background

Liver is the most common target organ of metastases from colorectal cancer. Almost 50% of the colorectal patients will develop liver metastases during the course, and 15-25% of the patients already have liver metastases upon diagnosis of primary colorectal cancer (synchronous liver metastases) [1, 2]. Surgery is still the best treatment to achieve long-term survival or even cure in patients with colorectal liver metastases, and the 5-year survival after surgery is about 30-50%[3, 4].

Compared with metachronous liver metastases, synchronous liver metastases usually have poorer biological behaviors and the treatment is also more complicated. Moreover, surgery for synchronous liver metastases has to deal with both primary and metastatic lesions, and can be divided into two major categories, simultaneous and staged resection. Generally, a higher proportion of patients receive selective staged resection of colorectal cancer and liver metastases[5, 6]. Along with the progress in surgical technique, the proportion of patients receiving simultaneous resection increases over time[7, 8]. However, simultaneous resection causes surgical trauma at two sites at the same time, which may increase the risk (e.g., intraperitoneal infection, anastomotic fistula and hepatic insufficiency). As a result, the incidence of complications and mortality are higher for simultaneous resection than staged resection[9, 10]. So, not all patients are fit for simultaneous resection, and staged resection remains an important choice.

Conventionally, the primary colorectal cancer lesion is first resected, and then the liver metastases. Later the "liver first" surgical strategy appeared[11], that is, the liver metastasis is first resected, and then the primary colorectal cancer lesion. But whatever the strategy, chemotherapy between two surgeries is

selective and not mandatory[12-14], for fear of chemotherapy-associated liver injury and the missing of best timing for surgery due to post-chemotherapy progression. Nowadays, more and more patients start chemotherapy before the resection of primary colorectal cancer and liver metastases[15]. However, for selective staged resection, especially those who have received initial chemotherapy, no consensus has been reached as to whether first-stage surgery should be sequentially followed by second-stage surgery or by interval chemotherapy then second-stage surgery. Comparisons of the safety and long-term survival benefits between these two strategies and simultaneous resection are still unknown.

The purpose of the present study was to compare perioperative safety and long-term survival of three different strategies, namely, selective sequential resection, delayed resection or simultaneous resection in colorectal cancer with synchronous liver metastases.

## Methods

### Study design, selection of patients and grouping

From January 2007 to December 2016, patients receiving surgery at the department of hepatobiliary surgery at Peking University Cancer Hospital for colorectal cancer with synchronous liver metastases were retrospectively collected and reviewed. Synchronous liver metastasis was defined as the occurrence of liver metastases synchronous with or before the confirmed diagnosis of colorectal cancer. Inclusion criteria: resection of primary colorectal cancer and liver metastases was performed with curative intent, and the patients completed the treatment; the combined extrahepatic metastases were also resected. Combined lung metastases without resection was allowable if controllable under chemotherapy[16, 17]. Exclusion criteria: (1) Recurrence after resection of liver metastases; (2) Non-radical surgery; (3) Failing to finish the resection of both colorectal cancer and liver metastases; (4) Combined with other malignancies. Among patients with initially unresectable colorectal liver metastases, those who did not receive second-stage surgery due to failed conversional chemotherapy after the first-stage surgery were thus excluded.

The treatment strategy was determined based on multidisciplinary discussion attended by colorectal surgeons, hepatic surgeons, medical oncologists, radiation oncologist and radiologists. The informed consent was obtained from the patients before the treatment began. The patients were divided into three groups based on surgical treatment strategies: sequential resection (SeR, sequential staged resection of colorectal cancer and liver metastases, without interval chemotherapy); delayed resection (DeR, staged resection of colorectal cancer and liver metastases, with interval chemotherapy); simultaneous resection (SiR, one-stage resection of primary colorectal cancer and liver metastases simultaneously). Simultaneous resection is more often used in patients that the tumor disease burden is not heavy, or the primary lesion is located in the right colon with heavy tumor burden but can be resected through one incision. Staged resection is mainly used in patients with severe symptoms of the primary lesion, or with heavy tumor burden, or with tumors located in the rectum requiring preoperative radiochemotherapy. After the first surgery, patients with resectable liver metastases were treated with sequential resection or

neoadjuvant chemotherapy, and patients with unresectable liver metastases were treated with conversional chemotherapy, then evaluated for the next surgery.

The protocol was approved by the ethics committee of Peking University Cancer Hospital and confirmed to the Declaration of Helsinki. The informed consent was harvested from all patients.

### **Initial assessment**

Before initial treatment, all patients received contrast-enhanced MRI of the liver, contrast-enhanced CT of the abdominopelvic cavity or contrast-enhanced MRI of the pelvic cavity (only for rectal cancer patients) and plain CT scan of the chest. If the primary colorectal cancer had already been resected at other centers, the operation note, pathology report and postoperative complications were kept and recorded in details. Radiological assessment was performed to exclude any signs of residual lesions.

### **Surgery**

The tumor number and position were determined by preoperative imaging, intraoperative ultrasound and palpation. The resected scope of liver was determined based on the tumor number and position. For lesions that were located deep in the liver parenchyma and smaller than 2cm in diameter, combined radiofrequency ablation was selectively performed to avoid excessive loss of liver volume. The liver resection margin was usually larger than 5mm, and the margin of 1mm (R1 margin status) for some lesions was acceptable as long as the chemotherapy was effective. Major liver resection was defined as the resection of 3 hepatic segments and above.

### **Perioperative chemotherapy**

Based on the consensus, initial chemotherapy was usually recommended for patients with asymptomatic primary lesions in our center, except for patients' refusal. Systemic chemotherapy regimens were oxaliplatin and/or irinotecan based regimens in combination with fluorouracil and leucovorin (folfox/folfiri/folfoxiri). Combined molecular targeted agents were selectively used according to the resectability of liver metastases and clinical risk scores. Assessment was performed after 2 or 4 cycles of initial chemotherapy, and those fit for surgery received surgery as soon as possible. For advanced middle and low rectal cancer (T3/T4 and/or N+), combined radiotherapy was given based on local staging. For staged resection, the chemotherapy regimen given between two surgeries was usually the same as the initial chemotherapy, or folfox/capox/folfiri plus or not molecular targeted agents in the absence of initial chemotherapy. Adjuvant chemotherapy was recommended regularly if the patients' conditions allowed after surgery.

### **Perioperative safety**

Postoperative complications were assessed by Clavien-Dindo grading system[18]. For staged resection, overall incidence of complications was the sum of incidence of complications after two surgeries, and

the highest grade of complications after either surgery was taken as the final grade of complications. Severe complications were defined as those of Clavien-Dindo grade 3 or above.

### **Postoperative follow-up and survival analysis**

Radiological assessment was given within 1 month after resection of both colorectal cancer and liver metastases. Later the patients received reexaminations once every 3 months. Overall survival (OS) was defined as the interval from the start of the initial treatment (surgery or chemotherapy) to the last follow-up or death. Recurrence-free survival (RFS) was defined as the interval from resection of both colorectal cancer and liver metastases to the time of the first recurrence. The time of the last follow-up was December 2018 for all cases.

### **Statistical analysis**

Statistical analysis was performed using SPSS 22.0 software. Continuous variables were described by ranges, and intergroup comparisons were conducted using t-test or U test. Categorical variables were expressed as frequencies or percentages. Intragroup comparisons were performed by using chi-square test. Kaplan-Meier survival analysis was performed, and the survival curves were compared by using the log-rank test. Univariate and multivariate analyses were performed using Cox model to identify the prognostic factors.  $P < 0.05$  indicated significant difference.

## **Results**

### **1. Comparison of baseline data between the three groups**

A total of 233 consecutive cases conformed to the inclusion criteria, with 49 cases in the SeR group, 98 cases in the DeR group and 86 cases in the SiR group. The comparison of baseline data between the three groups is shown in Table 1. In the SeR group, the proportion of patients with primary lesions in the rectum was significantly higher than that of the other two groups ( $P < 0.05$ ). Moreover, the median number of liver metastases in the SiR group was lower than that in the SeR group ( $P = 0.011$ ). Besides, the three groups of patients showed no significant difference in gender, age, T stage and N stage of primary lesions, diameter of liver metastatic lesions, or distribution in single or double lobes. The proportion of combined extrahepatic metastases was low in all groups, and there was no significant difference among the three groups.

### **2. Comparison of chemotherapy regimen, surgical strategies and postoperative complications between the three groups**

The comparison of chemotherapy regimen and surgical strategies among the three groups is shown in Table 2. Compared with the DeR group, a higher proportion of patients received initial chemotherapy in the SeR and SiR groups ( $P < 0.05$ ). It was as high as 83.7% in the SeR group. In addition, the proportion of patients receiving initial chemotherapy with molecular targeted agents was also higher in the SeR group

( $P < 0.05$ ). In the DeR group, the median number of chemotherapy cycles between the two surgeries was 4 (1, 25), and the median interval was 20.7 (10.1, 77.2) week. In the SeR group, the median interval was 5.7 (3.4, 14) week between the two surgeries. There was no significant difference in the proportion of patients receiving adjuvant chemotherapy among the three groups. Except for the higher proportion of portal occlusion in the SeR group, the three groups showed no significant difference in the use of extensive liver resection and combined radiofrequency ablation, intraoperative blood loss and postoperative status of resection margin.

As to postoperative safety, the perioperative mortality was 0 in all groups. The incidence of overall complications was 48.8% in the SiR group, higher than that in the DeR group (31.6%,  $p = 0.017$ ) and the SeR group (40.8%,  $p = 0.369$ ). The incidence of severe postoperative complications was 26.7% in the SiR group, which was higher than that of the DeR group (11.2%,  $p = 0.007$ ), and also higher but not significantly than that of the SeR group (16.3%,  $p = 0.166$ ). The SeR group and DeR group showed no significant difference in the overall incidence of postoperative complications and incidence of severe complications.

### 3. Survival analysis

There was no significant difference in the median OS (45 vs. 43 months,  $p = 0.887$ ) and RFS (9 vs. 8 months,  $p = 0.714$ ) between patients receiving simultaneous resection and staged resection (Fig. 1). The 1-year and 3-year survival rates were 93.9% and 50.1% in the SeR group, 94.9% and 64.8% in the DeR group, and 93.0% and 55.2% in the SiR group, respectively. The median OS of patients in the SeR group was lower than that of the DeR group (37 vs. 48 months,  $p = 0.019$ ), but it was not significantly different from that of the SiR group (37 vs. 43 months,  $p = 0.378$ ). The 1-year and 3-year recurrence-free survival rates were 22.4% and 18.4% in the SeR group, 43.9% and 24.2% in the DeR group, and 31.4% and 19.6% in the SiR group, respectively. The RFS of the SeR group was also lower than that of the DeR group (6 vs. 10 months,  $p = 0.033$ ), but the difference was not statistically significant compared with the SiR group (6 vs. 8 months,  $p = 0.275$ ) (Fig. 2).

### 4. Univariate and multivariate analysis of overall survival

Univariate analysis was performed using Cox regression model to identify the influence factors of OS (Table 3). The results showed that T stage and N stage of primary lesions, diameter of liver metastatic lesions, resection strategies and adjuvant chemotherapy were correlated with OS. Other imbalanced factors in baseline and treatment such as position of primary lesions, number of liver metastases, whether receiving initial chemotherapy or not, or the use of molecular target drugs did not affect OS. Cox multivariate analysis indicated that T4, lymph node positive primary tumor, tumor size  $> 30$ mm and selective sequential resection (relative to delayed resection) were correlated with poor prognosis (Table 4).

## Discussion

Treatment of colorectal cancer with synchronous liver metastases requires resection of both colorectal cancer and liver metastases. Symptoms and position of primary lesions and the resectability of liver metastases must be taken into consideration. In addition, whether and when radiotherapy should be given are also needs to be considered for advanced middle and low rectal cancer. So, there is no uniform standard for clinical treatment of colorectal cancer with synchronous liver metastases.

Whether simultaneous resection is equally safe as staged resection is a topic of dispute[19]. Along with the progress in surgical technology, selective simultaneous resection is increasingly applied. It has been reported that simultaneous resection does not necessarily increase postoperative complications compared with staged resection[20]. However, it should be noted that most of the patients who underwent simultaneous resection were screened for the location of the primary lesion and/or the extent and difficulty of hepatic metastasis resection, especially for those requiring extensive liver resection and/or Miles surgery for rectal cancer[21, 22]. There are no prospective randomized controlled studies to answer this question definitely. Upon the first visit, the treatment center and expertise of physicians in the treatment of liver metastases vary and the coordination between colorectal and hepatic surgeons is usually needed for simultaneous resection. For this reason, not all patients will be chosen for simultaneous resection. In our retrospective study, patient screening was also performed to ensure postoperative safety and recovery, and selection bias did exist. However, the results showed that after screening, the overall incidence of postoperative complications and incidence of severe complications were still higher in patients receiving simultaneous resection than those receiving staged resection. Apparently, if all patients received simultaneous dissection without screening and discrimination, more severe complications or even perioperative death might have occurred. Therefore, the staged resection strategy does have the benefits of avoiding superimposition of complications and severe complications.

In this study, OS and RFS of patients receiving simultaneous resection and staged resection did not differ significantly, and OS was superior to that reported in those receiving palliative chemotherapy. This indicated that either strategy is reasonable and effective. As not all patients are fit for simultaneous resection, staged resection remains a favorable choice. Generally, in staged resection, the primary colorectal cancer is first resected, followed by 2-3 cycles of chemotherapy. Resection of liver metastases will be performed after liver metastases are stabilized. The "liver first" strategy also appears latter. But whatever the strategy, whether chemotherapy should be given between two surgeries is still debated. A published international expert consensus[15] pointed out that for colorectal cancer with synchronous liver metastases without acute symptoms related to the primary lesions, systemic chemotherapy is recommended as the preferred choice. At present, more and more patients receive chemotherapy before the resection of either primary colorectal cancer or liver metastases. For those who have already received chemotherapy and are scheduled for staged resection, whether chemotherapy should be given between the two surgeries is our major concern. In the present study, most of the patients in SeR (41/49) had received initial chemotherapy and some were even treated by molecular target agents. Patients who did not receive initial chemotherapy were those who had no heavy tumor burden and poor tolerance or refused initial chemotherapy. However, survival analysis indicated that the median OS of patients receiving sequential resection was lower compared to those receiving delayed resection. Much to our

surprise, according to multivariate survival analysis, whether receiving initial chemotherapy or not did not affect OS, while chemotherapy between the two surgeries was an independent risk factor. In baseline comparison, SeR group had the highest proportion of patients with rectal cancer. This is because middle and low rectal cancer usually needs to be treated by synchronous radiotherapy and the interval between the end of radiotherapy and rectal surgery is 6-8 weeks [23, 24]. For these patients, the strategy of first-stage resection of liver metastases and second-stage resection of primary rectal cancer can be adopted. If chemotherapy is given between the two surgeries, the waiting time may be too long for second-stage resection. Edema caused by radiotherapy may make the resection of rectal cancer very difficult, and sequential resection seems to be the only choice left. However, multivariate survival analysis using Cox model indicated that the position of primary tumors did not affect OS either. Although there were some imbalanced factors in baseline and treatment regimen between the two groups, the median OS of the SeR group was still lower than that of DeR group after the correction of biased factors. Another major worry is that whether the tumor will progress after the first-stage surgery as chemotherapy is given instead of immediate second-stage surgery, which makes further surgery impossible. In the present study, after excluding the patients with initially unresectable tumors and failed to conversion therapy, only 2 patients in the DeR group progressed during chemotherapy between the two surgeries, which made second-stage surgery impossible (2/100). Therefore, there is no need to be too worried about tumor progression. We believe that no matter whether initial chemotherapy is given or not, it is preferable to add chemotherapy after the first-stage surgery in selective staged resection. Although it may increase the risk of chemotherapy-associated liver injury, cautious evaluation indicates that the risk is controllable for the second-stage surgery and the incidence of postoperative complications does not increase.

The survival benefits of delayed resection were higher than those of sequential resection, probably because of the following advantages of chemotherapy between the two surgeries: (1) Inflammation caused by the first-stage surgery may promote the spread of tumor cells[25], and chemotherapy between the two surgeries can control potential micro-metastases; (2) chemotherapy can cause further shrinkage and necrosis of tumors, thus achieving tumor regression[26] and improving the prognosis; (3) The patients are screened based on biological behavior[27, 28] and observed for some time after chemotherapy to determine the best timing for second-stage surgery after the lesions are stabilized. This is conducive to avoid early postoperative recurrence. Poor prognosis of patient receiving sequential resection may be also attributed to the longer interval between the resection of primary colorectal cancer and liver metastases. The resection of either primary colorectal cancer or liver metastases is highly traumatic. It usually takes about 3 to 4 week before the patients' physical strength is improved for the next surgery. However, the patients may need to wait for the arrangement of the next surgery without chemotherapy protection.

Since the present study adopted a retrospective design, there was the problem of mismatch of baseline information. Given the difference in physical status, local symptoms of primary lesions, referral system and levels of the first visit center, not all patients can receive treatment based on high-level multidisciplinary team (MDT) decisions. Therefore, there is no uniform standard for the choice of initial

treatment. Moreover, a small sample size would also influence the results. In the future, prospective randomized controlled study will be performed to obtain more reliable conclusions.

## Conclusions

Simultaneous resection has a relatively higher incidence of severe complication, and when staged resection strategy was made, the prognosis of delayed resection was better than that of sequential resection.

## Abbreviations

CRLM: Colorectal liver metastases; SeR: sequential staged resection of colorectal cancer and liver metastases, without interval chemotherapy; DeR: staged resection of colorectal cancer and liver metastases, with interval chemotherapy); SiR: one-stage resection of primary colorectal cancer and liver metastases simultaneously; CI: Confidence interval; OS: Overall survival; RFS: Recurrence free survival; MDT: multidisciplinary team.

## Declarations

### Acknowledgements

Not applicable.

### Authors' contributions

BCX contributed to the conception and design. HWW, KMJ and JL are responsible for the provision of the study materials and data collection. LJW contributed to the data analysis, interpretation and draft writing. All authors read and approved the final manuscript.

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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 was approved by the Clinical Research Ethics Committee of the Peking University Cancer Hospital and was performed in compliance with the Helsinki Declaration. Written informed consent was obtained from all patients.

### **Consent for publication**

All the participants of the study consent to publish the study.

### **Competing interests:**

The authors declare that they have no conflicts of interest.

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## Tables

1. The patients' demographics and tumor characteristics

Characteristics	Sequential resection (n=49)	Delayed resection (n=98)	Simultaneous resection (n=86)	p <sup>†</sup>	p <sup>‡</sup>	p <sup>§</sup>
Age, years (range)	54 (21-78)	59 (32-77)	57 (33-82)	0.070	0.382	0.390
Sex (male/ female)	33/16	65/33	45/41	0.902	0.089	0.053
Primary tumor location Colon/ rectum	22/27	63/35	62/24	0.025	0.002	0.258
T stage (T1-3/T4)	38/11	65/33	67/19	0.161	0.962	0.082
N stage (N <sub>+</sub> /N0)	37/12	70/28	55/31	0.600	0.166	0.278
Number of metastases	4 (1-13)	3 (1-14)	2 (1-12)	0.097	0.011	0.277
Size of tumor diameter, mm (range)	25 (1-160)	28 (3-100)	25 (3-90)	0.776	0.758	0.454
Distribution Bilateral/ unilateral	29/20	56/42	42/44	0.813	0.247	0.260
Extrahepatic metastases No/yes	47/2	91/7	76/10	0.715	0.138	0.295

Values are presented as median and range.

†sequential resection group versus delayed resection group.

‡sequential resection group versus simultaneous resection group.

§ delayed resection group versus simultaneous resection group.

## 2. Treatment details and postoperative outcomes among the three groups

Characteristics	Sequential resection (n=49)	Delayed resection (n=98)	Simultaneous resection (n=86)	p <sup>†</sup>	p <sup>‡</sup>	p <sup>§</sup>
Initial chemotherapy						
Yes/no	41/8	26/72	66/20	<0.001	0.340	<0.001
Biologic agents (yes/no)	17/32	10/88	30/56	<0.001	0.982	<0.001
Adjuvant chemotherapy	39/10	68/30	64/22	0.190	0.497	0.450
Yes/no						
Hepatectomy	21/28	31/67	29/57	0.180	0.290	0.763
Major/minor						
Combined with RFA	7/42	11/87	5/81	0.594	0.177	0.194
Yes/no						
Hilar vascular clamp	46/3	82/16	66/20	0.082	0.011	0.237
Yes/no						
Blood loss, ml (range)	200 (80-1400)	200 (70-1000)	200 (100-3200)	0.709	0.132	0.024
Margin status	39/10	81/17	74/12	0.651	0.329	0.528
R0/R1						
Overall morbidity, n (%)	20 (40.8)	31 (31.6)	42 (48.8)	0.270	0.369	0.017
Cumulative major complication, n (%)	8 (16.3)	11 (11.2)	23 (26.7)	0.385	0.166	0.007

Values are presented as median and range.

†sequential resection group versus delayed resection group.

‡sequential resection group versus simultaneous resection group.

§ delayed resection group versus simultaneous resection group.

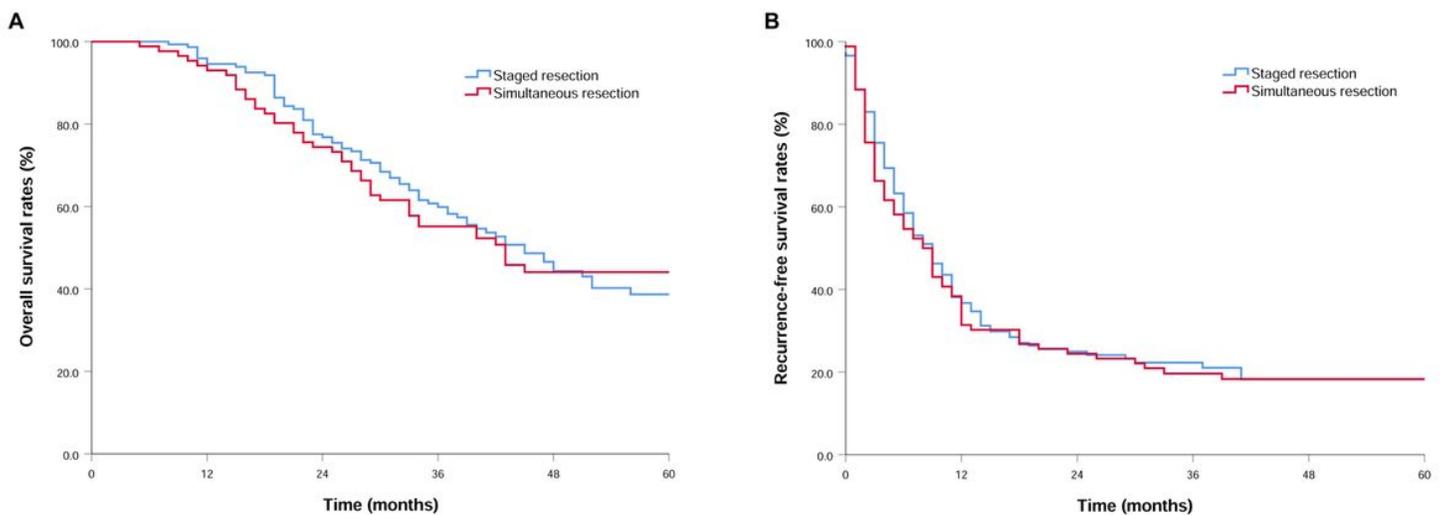
### 3. Factors affecting overall survival after resection in cox univariable analysis

	Number	Hazard ratio	P
Sex (male vs. female)	143/90	0.812 (0.568, 1.159)	0.251
Age $\geq$ 60 vs. $\leq$ 60	80/153	0.872 (0.597, 1.272)	0.476
Primary tumor location (rectum vs. colon)	86/147	0.886 (0.615, 1.276)	0.516
Primary tumor T stage (T4 vs. T1-3)	63/170	1.210 (1.072, 1.366)	0.002
Primary tumor node status (N <sub>+</sub> vs. N0)	162/71	1.596 (1.064, 2.395)	0.024
Number of liver metastases ( $>$ 4 vs. $\leq$ 4)	70/163	1.290 (0.888, 1.876)	0.181
Extent of liver metastases (bilobar vs. unilobar)	127/106	1.338 (0.936, 1.912)	0.110
Size of liver metastases ( $>$ 30 vs. $\leq$ 30 mm)	85/148	1.700 (1.196, 2.415)	0.003
Extent of hepatectomy (major vs. minor)	81/152	1.114 (0.775, 1.602)	0.559
Combined with RFA (yes vs. no)	23/210	0.588 (0.274, 1.261)	0.172
Margin status (R1 vs. R0)	39/194	1.321 (0.838, 2.082)	0.231
Initial chemotherapy (yes vs. no)	133/100	0.940 (0.661, 1.337)	0.731
Biologic agents used in initial chemotherapy (yes vs. no)	57/176	0.931 (0.752, 1.153)	0.511
Surgical strategy			
Sequential resection	49	1	
Delayed resection	98	0.612 (0.388, 0.967)	0.035
Simultaneous resection	86	0.735 (0.463, 1.168)	0.193
Adjuvant chemotherapy (yes vs. no)	171/62	0.683 (0.464, 1.005)	0.053

### 4. Factors affecting overall survival after resection in Cox multivariable analysis

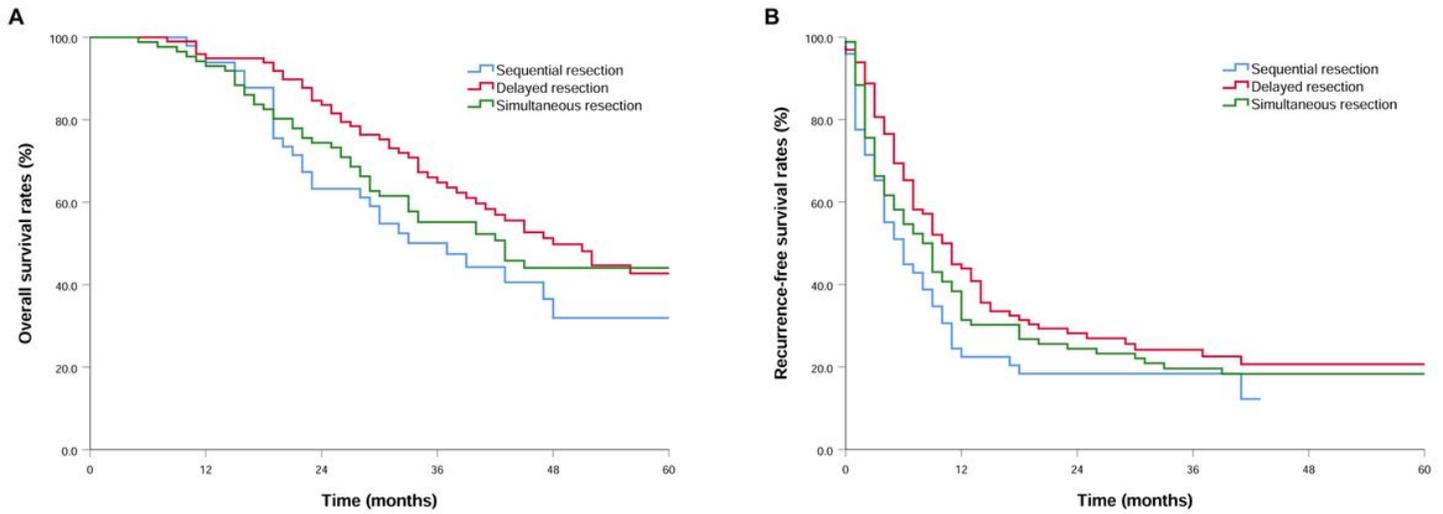
	Number	Hazard ratio	P
Primary tumor T stage (T4 vs. T1-3)	63/170	1.930 (1.318, 2.825)	0.001
Primary tumor node status (N <sub>+</sub> vs. N0)	162/71	1.585 (1.050, 2.393)	0.028
Size of liver metastases (>30 vs. ≤30 mm)	85/148	1.537 (1.077, 2.194)	0.018
Surgical strategy			
Sequential resection	49	1	
Delayed resection	98	0.534 (0.335, 0.850)	0.008
Simultaneous resection	86	0.813 (0.510, 1.295)	0.383
Adjuvant chemotherapy (yes vs. no)	171/62	0.735 (0.494, 1.091)	0.127

## Figures



**Figure 1**

(A) Overall survival of patients who underwent staged resection or simultaneous resection.  $p=0.887$ . (B) Recurrence free survival of patients who underwent staged resection or simultaneous resection.  $p=0.774$ .



**Figure 2**

(A) Overall survival of patients who underwent sequential resection, delayed resection or simultaneous resection.  $p = 0.019$  (SeR vs. DeR),  $p = 0.254$  (SeR vs. SiR),  $p = 0.378$  (DeR vs. SiR). (B) Recurrence free survival of patients who underwent sequential resection, delayed resection or simultaneous resection.  $p = 0.033$  (SeR vs. DeR),  $p = 0.275$  (SeR vs. SiR),  $p = 0.269$  (DeR vs. SiR).