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Original Article

Comparison of the effects and prognosis of concurrent and staged resections for the treatment of resectable colorectal cancer liver metastasis

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Abstract: Objective: To compare the effects and prognosis of concurrent and staged resections for the treatment of resectable colorectal cancer liver metastasis (CRLM). Methods: A prospective study was conducted on 118 patients with CRLM. The 59 cases in the observation group received concurrent resections, while the 59 cases in the control group received staged resections. The operation time, intraoperative blood loss, length of hospital stay, hospital cost, postoperative complications, 5-year survival rate and 3-year progression-free survival rate were recorded for all patients. Factors that affect the prognosis of CRLM patients were analyzed. Results: The length of hospital stay, operation time, intraoperative blood loss, hospital cost were significantly lower in the observation group than in the control group ($P<0.001$). The two groups were equivalent with respect to postoperative complications, 5-year survival rate and 3-year progression-free survival rate ($P>0.05$). Independent risk factors affecting the prognosis of CRLM included the number of liver metastasis, whether resection is feasible after recurrence, and RAS genotype ($P<0.05$). Conclusion: Compared to staged resection for CRLM, concurrent resection has shorter operation time, less blood loss, and shorter length of hospital stay, while postoperative complications, long-term efficacy and survival benefits are comparable. Furthermore, the study has found that the number of liver metastasis, whether or not resection is feasible after recurrence, and RAS genotype are risk factors affecting the prognosis of CRLM.

Keywords: Colorectal cancer, liver metastasis, concurrent resection, staged resection, prognosis, risk factor

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in the digestive system, with its incidence ranking third and fatality rate ranking second among all cancers in the world. In 2018, there were more than 1.8 million new cases of CRC worldwide [1]. In 2015, the number of new cases of CRC in China was as high as 388,000, including 187,000 deaths. According to China's statistics, it was found that the incidence of CRC ranked third and the fatality rate ranked fifth in all maligancies [2].

The majority of the affected population is 50-64 years old and the annual incidence keep increasing [3, 4]. Research has found that about 50% of CRC patients have liver metastasis [5, 6]. According to clinical studies, radical surgery is the most effective treatment of colorectal cancer liver metastasis (CRLM) [7]. Studies have also shown that the 5-year survival rate of CRLM patients after radical surgery can reach 40-60%, while that of patients without radical surgery is less than 5% [8, 9].

The surgical method can be divided into concurrent and staged resections according to the timing of procedures. Concurrent resections are the resection of colorectal cancer and liver metastasis at the same time, while the staged resections is to operate colorectal cancer resection first and then to operate liver metastasis resection at a later time. The two resection strategies for CRLM treatment are still controversial [10, 11]. Previous studies have pointed out that concurrent resections are associated with shorter hospital stay compared

to staged resections, but may cause large damage to human body and thus easily lead to increased postoperative complications (39.98% VS. 22.47%) [10]. However, in recent years, thanks to the wider application of laparoscopic and other improved minimally invasive techniques in clinical practice, there is no difference in long-term survival and perioperative mortality between concurrent and staged resections [11]. This study focuses on the clinical efficacy and prognosis of patients with resectable CRLM treated with concurrent or staged resections, and thus providing clinical references.

Materials and methods

General information

A prospective study was conducted on 118 patients with CRLM admitted to the General Surgery Department of The Second Affiliated Hospital of Jiaxing University between August 2012 and August 2015. The patients were aged 29-74 years, with a mean age of 54.4±6.7 years. The patients were randomly divided into observation and control group with 59 patients in either group. The observation group received concurrent resections, with a mean age of 53.4±7.8 years. The control group received staged resections, with a mean age of 54.3±6.8 years. Long-term follow-up was conducted after the resections. All the above patients signed an informed consent form, which was approved by the Ethics Committee of The Second Affiliated Hospital of Jiaxing University.

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the criteria of CRLM diagnosis and resections according to the *Guideline for the diagnosis and comprehensive treatment of colorectal cancer liver metastasis* (2010 version) by Gastrointestinal Surgery Branch and Chinese Society of Colorectal Surgery of the Chinese Medical Association of Chinese Surgical Association [12]; aged 18-75 years old; had good liver reserve according to preoperative evaluation; had complete clinical data. Exclusion criteria: Patients who cannot tolerate surgery; with extrahepatic metastasis; with a history of hepatitis, liver function insufficiency or liver surgery; with severe coagulation disorders; difficult or inconvenient to conduct follow-up and were not suitable for surgery.

Resection methods

In the first diagnosis, if there were patients with unresectable CRLM in either group, they needed to be converted to patients with resectable CRLM before undergoing resection. All patients underwent neoadjuvant chemotherapy before the resections. Radical resections were conducted to treat the primary colorectal cancer, while liver resections were conducted with a margin of at least 1 mm to treat liver metastases. The observation group received concurrent resection, that is, radical resections of both colorectal cancer and liver metastases, and systemic chemotherapy was routinely given after the resections.

The control group received staged resections. Colorectal cancer resection was conducted first, followed by FOLFOX4 chemotherapy within 1 month. On the first day after the resection, 80 mg/m^2 of oxaliplatin (Nanjing Pharmaceutical Co., Ltd., China) was infused intravenously for more than 2 h, and 400 mg/m^2 of leucovorin (YaoPharma Co., Ltd., China) and 400 mg/m^2 of fluorouracil (Tianjin Kingyork Group Co., Ltd., China) were infused intravenously. On the next day, 2,400 mg/m^2 of fluorouracil was infused intravenously for 48 hours. After 4-6 cycles of chemotherapy, patients who could tolerate liver resection according to the evaluation received liver metastasis resection. Systemic chemotherapy was performed after the two resections.

Outcome measures

Main outcome measures: Intraoperative and postoperative related indicators: Operation time: operation time from the incision of the skin to the end of the suture; intraoperative blood loss: the total blood loss from the beginning to the end of the operation.

Hospital cost: the expenses spent by the patient from hospitalization to discharge.

Postoperative complications: incision infection, biliary fistula, abnormal liver function, intestinal obstruction, pleural effusion, abdominal infection, postoperative bleeding, etc.

Secondary outcome measures: Postoperative overall survival (OS) and progression-free survival (PFS) were followed up for the participant patients. Outpatient visit or phone call follow-ups were conducted every 3 months.

Table 1. Comparison of general data and baseline data of the two groups of patients (($\bar{x}$ ± sd), n)

Variable		Observation group (n=59)	Control group (n=59)	χ^2/t	P
Age (years)		52.9±7.1	53.8±6.7	0.708	0.480
Gender (male/female)		39/20	32/27	1.733	0.188
Body mass index (kg/m^2)		23.69±2.41	24.01±2.67	1.733	0.188
ASA classification	I	7	9	0.309	0.857
	II	35	33		
	III	17	17		
Primary cancer location	Left colon	24	21	0.325	0.850
	Right colon	14	15		
	Rectum	21	23		
Liver metastasis location	Left lobe	31	34	0.415	0.812
	Right lobe	19	18		
	Whole liver	9	7		
Liver metastasis size	≥3 cm	25	22	0.318	0.573
	<3 cm	34	37		
Number of liver metastases	1	27	29	0.137	0.934
	2-3	18	17		
	3 or more	14	13		
T stage	T2	9	7	0.289	0.591
	T3-T4	50	52		
N stage	N0	10	8	0.262	0.609
	N1-N2	49	51		
Primary differentiation	Poorly differentiated	9	7	0.307	0.858
	Moderately differentiated	34	36		
	Well differentiated	16	16		
Preoperative CEA level	≥200 ng/mL	41	43	0.165	0.684
	<200 ng/mL	18	16		
Initial resection status	Initially resectable	54	52	0.371	0.542
	Resectable after conversion	5	7		
RAS genotype	Wild type	34	30	0.546	0.460
	Mutant	25	29		

Note: CEA: carcinoembryonic antigen.

Postoperative OS: The time from the beginning of radiotherapy and chemotherapy to the death of the patient or time included in the observation of this study.

PFS: The time from after the resection were finished to the first time the patient was shown to have tumor progression.

Statistical analysis

Statistical analysis was conducted using SPSS 22.0 statistical software. Continuous variables were presented as mean ± standard deviation ($\bar{x}$ ± sd). According to Shapiro-Wilk normality test, data with normal distribution and the homogeneity of variance were analyzed using the t test, otherwise, analyzed using rank sum test. Counting data were analyzed using Pearson chi-square test and expressed as chi-square. Survival analysis was conducted using the Kaplan-Meier method. The prognosis univariate analysis was conducted using Log-rank test and provided variables with differences. In logistic regression analysis, the death of CRLM patient was the dependent variable, while liver metastasis location, liver metastasis lesion number, preoperative carcinoembryonic antigen (CEA) level, whether resection is feasible after recurrence, and RAS genotype were set as independent variables. Variables were selected

Table 2. Comparison of intraoperative and postoperative indexes between the two groups ($\bar{x} \pm sd$)

Variable	Observation group (n=59)	Control group (n=59)	t	P
Postoperative hospital stay (day)	17.5±8.6	28.4±11.7	5.766	<0.001
Operation time (min)	221.63±66.78	442.78±97.58	14.372	<0.001
Intraoperative blood loss (mL)	396.46±100.21	589.54±140.36	8.599	<0.001
Hospital costs (ten thousand yuan)	5.72±1.14	7.63±2.17	5.985	<0.001

Table 3. Comparison of postoperative complications between the two groups (n (%))

Postoperative complications	Observation group (n=59)	Control group (n=59)	χ^2	P
Incision infection	4 (6.78%)	7 (11.86%)	0.902	0.342
Biliary fistula	3 (5.08%)	4 (6.78%)	0.152	0.697
Abnormal liver function	2 (3.39%)	2 (3.39%)	0.000	1.000
Intestinal obstruction	2 (3.39%)	1 (1.69%)	0.342	0.559
Pleural effusion	1 (1.69%)	1 (1.69%)	0.000	1.000
Abdominal infection	1 (1.69%)	2 (2.39%)	0.342	0.559
Postoperative bleeding	3 (5.08%)	2 (2.39%)	0.209	0.648
Total number of cases	16 (27.12%)	19 (32.20%)	0.336	0.545

Table 4. Comparison of 5-year survival rate of the two groups after resection (n (%))

	1-year survival rate after resection	3-year survival rate after resection	5-year survival rate after operation
Observation group (n=59)	53 (89.83%)	30 (50.84%)	20 (33.90)
Control group (n=59)	55 (93.22%)	33 (55.93%)	24 (40.68)
χ^2	0.437	0.306	0.580
P	0.509	0.580	0.446

using stepwise forward (Ward) method with the significant level at P<0.05 and no significant level at P>0.1. The prognosis risk reduction of colorectal cancer was calibrated to odds ratio (OR). P<0.05 was considered statistically significant.

Results

Comparison of general information

The two groups of patients were comparable in terms of age, gender, body mass index, ASA classification, location of carcinoma in situ, location of liver metastases, size of liver metastases, number of liver metastases, T stage, N stage, primary focus differentiation, and preoperative CEA, initial resection status, and RAS genotype (P>0.05). See **Table 1**.

Comparison of intraoperative and postoperative conditions

There were statistically significant differences in length of hospital stay, operation time, intraoperative blood loss and hospital costs between the two groups (P<0.001). See **Table 2**.

Comparison of postoperative complications

The postoperative complications of the two groups included incision infection, biliary fistula, abnormal liver function, intestinal obstruction, pleural effusion, abdominal infection, and postoperative bleeding. The incidence of complications of the observation and control group were 27.12% and 32.20%, respectively. There was no significant difference (P>0.05). See **Table 3**.

Comparison of 5-year survival rate and 3-year progression-free survival rate

There was no difference in 5-year survival rate or 3-year progression-free survival rate between the two groups after resection (P<0.05). See **Tables 4** and **5**.

Comparison of postoperative overall survival and progression-free survival

The median overall survival (OS) of patients in the observation and control groups were 44.23 months (95% CI: 34.729-45.271) and 44.68 months (95% CI: 30.186-50.814), respectively. There was no significant difference. The pro-

Table 5. Comparison of 5-year progression-free survival rate of the two groups after resection (n (%))

	1-year progression-free survival rate after resection	2-year progression-free survival rate after resection	3-year progression-free survival rate after surgery
Observation group (n=59)	32 (54.24%)	13 (22.03%)	7 (11.86)
Control group (n=59)	34 (57.63%)	15 (25.42%)	8 (13.56)
χ^2	0.138	0.187	0.076
P	0.771	0.665	0.782

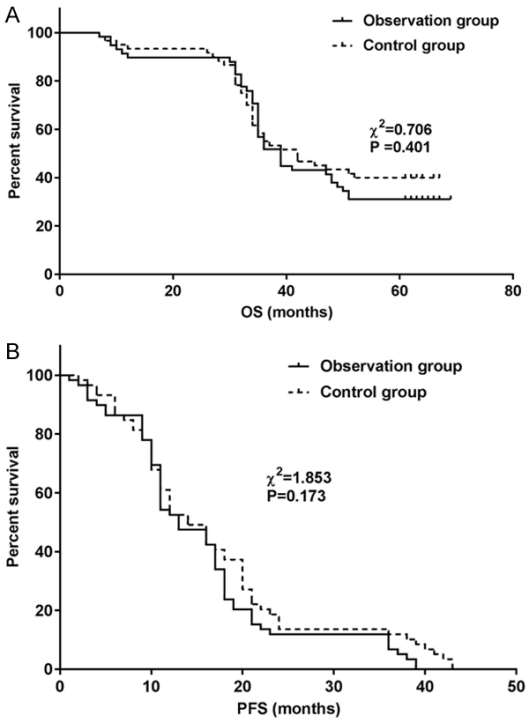

Figure 1. Comparison of OS and PFS between the two groups. A: The comparison of OS; B: The comparison of PFS. OS: overall survival; PFS: progression-free survival.

gression-free survival (PFS) of patients in the observation and control groups were 15.58 months (95% CI: 10.181-15.819) and 17.10 months (95% CI: 10.579-17.421), respectively. There was no significant difference (both P>0.05). See **Figure 1**.

Single factor comparison between the death and survival group within 5 years

According to the single factor comparison between the death group and the survival group, there were significant differences in location of liver metastases, number of liver metastases, preoperative CEA level, whether resection is feasible after recurrence, and RAS genotype (all P<0.05). See **Table 6**.

Multivariate logistic regression analysis of CRLM prognosis

Whether the patient with CRLM died was set as the dependent variable. Variables with differences in univariate analysis that included liver metastasis location, liver metastasis lesion number, preoperative CEA level, whether resection is feasible after recurrence, and RAS genotype were set as independent variables. According to the multivariate regression analysis, it is found that the number of liver metastases, whether resection is feasible after recurrence, and RAS genotype were independent risk factors for the prognosis of CRLM (all P<0.05). See **Tables 7** and **8**.

Discussion

Concurrent and staged resections are two commonly used procedures for CRLM treatment. However, the pros and cons of the two procedures are still controversial in clinical practice. In our study, CRLM patients undergoing concurrent resection had less intraoperative blood loss, shorter operation time, shorter postoperative hospital stay, and the incidence of postoperative complications did not increase. The results suggested that concurrent resection was safe and effective for CRLM patients. Staged resection has long been clinically applied to treat CRLM as the safest and most effective procedure. Compared to concurrent resection, staged resection has a lower fatality rate (9.1% vs. 4.9%) [13]. However, with the improvement of operative methods, more concurrent resections have been performed in CRLM patients. Studies have shown that the incidence of postoperative complications and 5-year overall survival of CRLM patients treated by current resections were comparable to those treated by staged resections, while the shorter length of hospital stay and the less hospital costs can be the advantage of concurrent resection [10]. Another study showed that the

Table 6. Single factor comparison between the death and survival group within 5 years

Variable		Survival group (n=44)	Death group (n=74)	χ^2/t	P
Age (years)		52.6±7.2	54.3±8.4	1.120	0.265
Gender (male/ female)		22/22	49/25	3.028	0.082
Body mass index (kg/m^2)		23.89±2.71	24.09±2.81	0.379	0.705
Resection method	Concurrent resection	24	35	0.580	0.446
	Staged resection	20	39		
Primary cancer location	Left colon	19	26	0.758	0.684
	Right colon	10	19		
	Rectum	15	29		
Location of liver metastases	Left lobe	28	37	7.695	0.021
	Right lobe	15	22		
	Whole liver	1	15		
Liver metastasis size	≥3 cm	18	29	0.034	0.854
	<3 cm	26	45		
Number of liver metastases	1	35	21	29.208	<0.001
	2-3	6	29		
	3 or more	3	24		
T stage	T2	7	9	0.331	0.565
	T3-T4	37	65		
N stage	N0	10	8	3.031	0.082
	N1-N2	34	66		
Primary differentiation	Poorly differentiated	7	9	0.834	0.659
	Moderately differentiated	27	43		
	Well differentiated	10	22		
Preoperative CEA level	≥200 ng/mL	20	64	22.469	<0.001
	<200 ng/mL	24	10		
Initial resection status	Initially resectable	39	67	0.110	0.741
	Resectable after conversion	5	7		
Whether resection is feasible after recurrence	Yes	34	32	12.964	<0.001
	No	10	42		
RAS genotype	Wild type	30	34	5.497	0.019
	Mutant	14	40		

Note: CEA: carcinoembryonic antigen.

Table 7. Influencing factors for the prognosis of CRLM

Factor	Independent variable	Assignment
Location of liver metastases	X1	Whole liver =1, half lobe =0
Number of liver metastases	X2	1 or more =1, 1=0
Preoperative CEA level	X4	≥200 ng/mL=1, <200 ng/mL=0
Whether resection is feasible after recurrence	X5	No =1, Yes =0
RAS genotype	X6	Mutant =1, wild type =0

Note: CRLM: colorectal cancer liver metastasis; CEA: carcinoembryonic antigen.

therapeutic effects of concurrent resection is associated with the location and size of liver metastases. For patients with small liver metastases, the complications and mortality after concurrent resection and staged resection are comparable. However, for patients with large liver metastases, the postoperative complication rate (17.6% vs. 36.1%) and fatality rate (10.5% vs. 14.1%) of concurrent resection are significantly lower compared to staged resection [14]. Another similar study also confirmed the efficacy of concurrent resection. The

Table 8. Multivariate logistic regression analysis of the prognosis of CRLM

Factor	β	SE	Wald value	OR (95% CI)	P
Location of liver metastases	0.674	0.849	0.579	1.841 (0.379-10.268)	0.423
Number of liver metastases	1.941	0.702	7.832	7.102 (1.726-27.369)	0.004
Preoperative CEA level	0.706	0.854	0.156	0.065 (0.023-0.223)	0.417
Whether resection is feasible after recurrence	1.016	0.279	3.123	3.792 (1.742-7.693)	0.002
RAS genotype	1.436	0.708	4.156	4.236 (1.057-16.879)	0.043

Note: CRLM: colorectal cancer liver metastasis; CEA: carcinoembryonic antigen; OR: odds ratio.

study found that concurrent resection caused the lower incidence of complications, and it was equally safe and effective for patients over 70 years old with no obvious complications [15].

The long-term curative effect after resection is a problem in CRLM treatment. Studies have shown that there is no difference in the 5-year survival rate and survival benefit between concurrent and staged resections [16]. A meta-analysis also pointed out that the perioperative mortalities of concurrent and staged resections are equivalent and there is no difference in the 5-year survival rate [11, 17]. Another study including elderly CRLM patients also showed no difference in overall survival rate or postoperative progression-free survival rate, suggesting that the concurrent resection is safe and effective [18]. What' more, concurrent resection can reduce the incidence of inoperable tumor progression due to the interval between operations [19]. In this study, after 5-year follow-up, no significant difference was found on 5-year overall survival or 3-year progression-free survival between the two groups, which was consistent with the results of the above studies.

This study further investigated the factors affecting the survival of CRLM patients and found that the number of liver metastatic lesions, whether or not resection is feasible after recurrence, RAS genotype were independent risk factors for the prognosis of CRLM. We also found that the patient's prognosis was not affected by whether or not the resection was staged or concurrent. Previous studies showed that poor prognosis of CRLM was correlated with positive primary tumor lymph node, the number of liver metastases >1, tumor size and CEA level [20]. Another study concluded that there was a correlation between RAS genotype and the postoperative prognosis of CRLM patients, as the 5-year survival rate and 3-year progression-free survival rate of RAS mutant were lower than those of wild genotype [21]. This study suggests that the number of liver metastases, whether resection is feasible after recurrence, and RAS genotype are independent risk factors that affect the prognosis of CRLM.

This study is a single-center study and can be further conducted as a multi-center study with a large number of samples and long-term follow-up, which is used to observe the effect of concurrent and staged resections on the prognosis of patients with CRLM.

In conclusion, compared with staged resection for CRLM, concurrent resection has shorter operation time, less blood loss, shorter hospital stay, but equivalent postoperative complications, long-term efficacy and survival benefits. Furthermore, the study has revealed that the number of liver metastases, whether or not resection is feasible after recurrence, RAS genotype are independent risk factors affecting the prognosis of CRLM.

Disclosure of conflict of interest

None.

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