Original Article

Prognostic Analysis of 102 Patients with Synchronous Colorectal Cancer and Liver Metastases Treated with Simultaneous Resection

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Abstract

Background: The liver is the most common site for colorectal cancer (CRC) metastases. Their removal is a critical and challenging aspect of CRC treatment. We investigated the prognosis and risk factors of patients with CRC and liver metastases (CRCLM) who underwent simultaneous resections for both lesions.

Methods: From January 2009 to August 2016, 102 patients with CRCLM received simultaneous resections of CRCLM at our hospital. We retrospectively analyzed their clinical data and analyzed their outcomes. Overall survival (OS) and disease-free survival (DFS) were examined by Kaplan-Meier and log-rank methods.

Results: Median follow-up time was 22.7 months; no perioperative death or serious complications were observed. Median OS was 55.5 months; postoperative OS rates were 1-year: 93.8%, 3-year: 60.7%, and 5-year: 46.4%. Median DFS was 9.0 months; postoperative DFS rates were 1-year: 43.1%, 3-year: 23.0%, and 5-year 21.1%. Independent risk factors found in multivariate analysis included carcinoembryonic antigen ≥100 ng/ml, no adjuvant chemotherapy, tumor thrombus in liver metastases, and bilobar liver metastases for OS; age ≥60 years, no adjuvant chemotherapy, multiple metastases, and largest diameter ≥3 cm for DFS.

Conclusions: Simultaneous surgical resection is a safe and effective treatment for patients with synchronous CRCLM. The main prognostic factors are pathological characteristics of liver metastases and whether standard adjuvant chemotherapy is performed.

Key words: Colorectal Cancer; Liver Metastases; Prognosis; Simultaneous Resection

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world. The incidence rate in China has increased in recent years; CRC is now the fifth most common malignancy in men, the fourth most common in women, and the fifth most common cause of death from cancer in China.[1] Liver is the most common site for CRC metastases, which are a major indicator of poor prognosis. Liver metastases can be found in 25% of patients with newly diagnosed CRC;[2] if these patients are not appropriately treated, their median survival time is only 6–9 months.[3] However, chemotherapy (CT) alone or hepatic arterial infusion CT are not favorable for the patients with synchronous CRC and liver metastases (CRCLM); only radical resection of the primary and metastatic lesions can apparently achieve good outcomes.[4,5] Our previous study[6] showed simultaneous resection of CRCLM to be a safe and effective treatment, compared with staged resections. However, few data are available regarding prognostic factors for this procedure. Therefore, this study

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retrospectively analyzed prognosis and risk factors of patients with CRCLM treated with simultaneous resection.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences.

Informed written consent was obtained from all patients prior to their enrollment in this study.

Patient selection

From January 1, 2009, to August 1, 2016, 102 patients with synchronous CRCLM underwent simultaneous resection of their primary lesions and liver metastases at National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and we retrospectively reviewed their data. All the patients had pathologically proven CRC with at least one liver metastasis and were followed up appropriately. There were 63 men and 39 women, whose median age was 57 years (range: 34–79 years). Their primary lesions included 46 rectal cancers and 56 colon cancers; among metastatic lesions, 45 patients had only one liver metastasis, 57 had 2–4 liver metastases, 44 had bilobar metastases, and 58 had metastases in only one lobe. Of the 102 patients, 67 underwent preoperative CT and 83 had postoperative CT; 75 patients had R0 (no cancerous cells seen microscopically) resection margins and 27 had R1 (cancerous cells can be seen microscopically) margins [Table 1].

Follow-up

All 102 patients were followed up regularly after their resections, with examinations in our outpatient service every 3 months in the first 2 years and every 6 months thereafter. Follow-up program included physical examination, liver and kidney function parameters, serum tumor markers, and imaging studies such as ultrasonography, CT, and magnetic resonance. Adjuvant CT was recommended routinely and if recurrence occurred, appropriate therapy (radiofrequency ablation, surgery, CT, and/or targeted therapy) would be performed based on consensus reached in Multiple Disciplinary Team meetings. The follow-up ended on December 31, 2016, or dates of death.

Statistical analysis

Data were analyzed using SPSS 11.5 for windows (SPSS Inc., Chicago, IL, USA). Patients' clinical data were compared using *t*-test and Chi-square test. Rates for overall survival (OS) and disease-free survival (DFS) were examined by Kaplan-Meier and log-rank methods, with OS calculated from surgery date to death date and DFS from surgery date to recurrence. A value of $P < 0.05$ was considered statistically significant.

Results

Perioperative care and follow-up

No perioperative death was observed in any of the 102 patients; 13 patients had moderate perioperative

Table 1: Clinicopathological features of 102 patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections

Parameters	*n* (%)
Gender	
Male	63 (61.8)
Female	39 (38.2)
Age (years)	
<60	66 (64.7)
≥60	36 (35.3)
Preoperative CEA (ng/ml)	
≥100	91 (89.2)
<100	11 (10.8)
Primary lesion	
Colon	56 (54.9)
Rectum	46 (45.1)
Differentiation	
High	4 (3.9)
Moderate	71 (69.6)
Low	27 (26.5)
T-stage	
1–2	5 (4.9)
3–4	97 (95.1)
N-stage	
N0	26 (25.5)
N+	76 (74.5)
Vascular thrombosis (gut)	
No	68 (66.7)
Yes	34 (33.3)
Nerve infiltration (gut)	
No	73 (71.6)
Yes	27 (28.4)
Infiltration of liver capsule	
No	44 (43.1)
Yes	58 (56.9)
Vascular thrombosis (liver)	
No	89 (87.3)
Yes	13 (12.7)
Distribution of liver lesions	
Bilobar	58 (56.9)
Unilobar	44 (43.1)
Preoperative chemotherapy	
Yes	67 (65.7)
No	35 (34.3)
Postoperative chemotherapy	
Yes	83 (81.4)
No	19 (18.6)
Margin	
R0	75 (73.5)
R1	27 (26.5)
Number of metastases	
1	45 (44.1)
2–4	57 (55.9)
KRAS	
Mutant	28 (27.5)
None mutant	21 (20.6)
Not clear	53 (51.9)

Contd...

Table 1: Contd...

Parameters	*n* (%)
Surgery	
Irregular resection	71 (69.6)
Hepatic segmentectomy	5 (4.9)
Left hemihepatectomy	5 (4.9)
Right hemihepatectomy	11 (10.8)
Left lateral lobectomy	10 (9.8)

CEA: Carcinoembryonic antigen; R0: No cancerous cells seen microscopically; R1: Cancerous cells seen microscopically; *KRAS*: Kirsten rat sarcoma viral oncogene.

complications (morbidity incidence: 2.7%), including four cases of fat liquefaction, four of abdominal infection, two of diarrhea, one of the coagulation dysfunctions, one of the chylous leakages, and one of the arrhythmias. Only one of the 13 patients, who suffered an abdominal infection, received secondary surgery; this patient recovered well and was discharged smoothly.

Patients were carefully followed up after their surgeries over a median period of 22.7 months. Seven patients were lost to follow-up (follow-up rate: 93.1%).

Survival outcomes

Median OS was 55.5 months, with OS rates of 1-year: 93.8%, 3-year: 60.7%, and 5-year: 46.4% [Figure 1]. Median DFS was 9.0 months, with DFS rates of 1-year: 43.1%, 3-year: 23%, and 5-year: 21.1% [Figure 2]. During the follow-up, 21 patients developed distant metastases, 56 developed intrahepatic recurrences, and 15 developed both.

Survival risk factors

We analyzed risk factors for OS and DFS based on patients' clinicopathological factors. In univariate analysis, age ≥60 years, carcinoembryonic antigen (CEA) ≥100 ng/ml, no preoperative CT, no postoperative CT, liver vascular thrombosis, multiple liver metastases, bilobar distribution, and tumor ≥3 cm were all adverse prognosis factors for OS. In multivariate analysis, independent risk factors for shorter OS included CEA ≥100 ng/ml, no postoperative CT, liver vascular thrombosis, and bilobar liver lesions [Table 2].

Univariate analysis showed that CEA ≥100 ng/ml, no preoperative CT, no postoperative CT, liver vascular thrombosis, multiple liver metastases, bilobar distribution, size ≥3 cm, R1 margin, and Kirsten rat sarcoma viral oncogene mutation were risk factors for shorter DFS, among which age ≥60 years, no postoperative CT, multiple liver metastases, and tumor ≥3 cm were shown in multivariate analysis to be independent risk factors for shorter DFS [Table 3].

Discussion

CRC is one of the most common malignancies in the world, and the liver is its most common site for CRC metastases. Therefore, liver metastases are a critical focus of CRC treatment. Complete resection of the primary tumor and

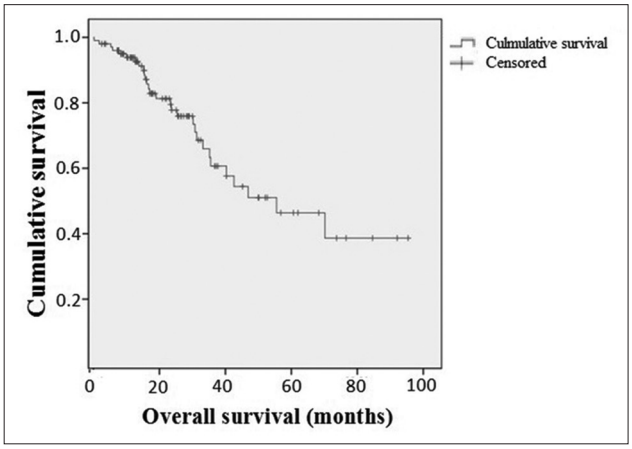

Figure 1: Overall survival of 102 patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections.

liver metastases is the only path to a good prognosis for patients with CRCLM. The 5-year OS for CRCLM patients who undergo CT alone is only 0–5%.[7] In contrast, if the primary lesion and metastases are radically resected, 5-year OS is 25–70%.[8-10] Although the optimal order of procedures is still in debate, accumulating recent studies have proven simultaneous resection of CRCLM to be a safe and effective therapy for these patients, for whom resulting OS and DFS are not inferior to those with staged resections.[6,11] However, the independent risk factors for the simultaneous resection had been unclear.

This study retrospectively analyzed the prognoses of 102 patients with synchronous CRCLM who underwent simultaneous resection of both lesions. We found the patients suffered no perioperative death or serious complications, with a secondary surgery ratio of only 1.0% (one patient, for abdominal infection) which indicates that simultaneous resection of CRCLM is a safe and effective method and is consistent with previous findings.[6] In the case of prognosis, this study showed that the median OS was 55.5 months, with OS rates of 1-year: 93.8%, 3-year: 60.7%, and 5-year: 46.4%, and median DFS was 9.0 months, with DFS rates of 1-year: 43.1%, 3-year: 23.0%, and 5-year: 21.1%. These results are similar to reported findings in China and abroad and indicate that simultaneous resection can provide a satisfactory prognosis for these patients.

In this study, multivariate analysis showed CEA ≥100 ng/ml, no postoperative CT, liver vascular thrombosis, and bilobar metastasis distribution to be independent risk factors for shorter OS; age ≥60 years, no postoperative CT, multiple metastases, and tumor ≥3 cm to be independent risk factors for shorter DFS. Interestingly, we did not find pathological features of the primary colorectal lesion (e.g., site, differentiation, lymph node metastasis, or margin) to be significantly associated with the outcome, which might be due to advances in local treatment and systemic CT that greatly improve patients' outcomes.[12] In contrast, we found the pathological features of liver lesions (including multiple tumors, tumors ≥3 cm, and bilobar distribution) to be the

Table 2: Effects of clinicopathological features on OS among patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections

Parameters	3-year OS (%)	5-year OS (%)	Univariate *P*	*HR*	95% *CI*	Multivariate *P*
Gender						
Male	53.2	41.9	0.926			
Female	68.4	47.9				
Age (years)						
<60	69.8	51.0	0.030			
≥60	41	30.7				
CEA (ng/ml)						
<100	64.8	48.6	<0.001			
≥100	16.2	–		3.05	1.06–8.73	0.038
Primary lesion						
Rectum	67.8	65.2	0.336			
Colon	51.5	36.8				
Preoperative chemotherapy						
No	71.7	58.4	0.031			
Yes	52.8	18.5				
Postoperative chemotherapy						
No	35.6	0	<0.001			
Yes	65.2	51.7		0.31	0.14–0.74	0.008
Vascular thrombosis (liver)						
No	64.8	48.5	<0.001			
Yes	18.5	–		4.74	1.72–13.1	0.003
Infiltration of liver capsule						
No	63.5	49.0	0.343			
Yes	57.1	42.3				
Lymph nodes metastases						
No	69.8	58.1	0.608			
Yes	56.3	41.1				
Distribution of liver metastases						
Unilobar	73.2	56.7	0.002			
Bilobar	35.2	23.4		2.73	1.17–6.35	0.020
Max diameter of liver lesion (cm)						
<3	71.4	47.7	0.017			
≥3	43.7	29.1				
Number of liver lesions						
Single	75.3	61.3	0.007			
Multiple	50.5	33.7				
T-stage						
1–2	–	–	0.184			
3–4	57.9	42.3				
Margin						
R1	50.4	–	0.116			
R0	63.2	45.5				
KRAS						
Mutant	44.2	29.4	0.101			
None mutant	58.1	–				
Vascular thrombosis (gut)						
No	65.8	46.5	0.378			
Yes	35.8	–				
Nerve infiltration (gut)						
No	64.3	48.2	0.120			
Yes	0	0				
Differentiation						
High	75.0	–	0.168			

Contd...

Table 2: Contd...

Parameters	3-year OS (%)	5-year OS (%)	Univariate *P*	*HR*	95% *CI*	Multivariate *P*
Moderate	63.1	45.7				
Low	57.8	57.8				

OS: Overall survival; CEA: Carcinoembryonic antigen; *HR*: Hazard ratio; *CI*: Confidence interval; R0: No cancerous cells seen microscopically; R1: Cancerous cells seen microscopically; *KRAS*: Kirsten rat sarcoma viral oncogene; –: No data.

Table 3: Effects of clinicopathological features on DFS among patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections

Parameters	3-year DFS (%)	5-year DFS (%)	Univariate *P*	*HR*	95% *CI*	Multivariate *P*
Gender						
Male	26.1	26.1	0.260			
Female	18.2	13.7				
Age (years)						
<60	24.9	24.9	0.089			
≥60	19.7	13.1		1.72	1.04–2.87	0.036
CEA (ng/ml)						
<100	25.4	23.3	<0.001			
≥100	0	0				
Primary lesion						
Rectum	20.1	20.1	0.417			
Colon	24.9	19.9				
Preoperative chemotherapy						
No	39.7	35.7	0.006			
Yes	13.0	–				
Postoperative chemotherapy						
No	7.0	–	0.002			
Yes	26.7	24.5		0.44	0.24–0.83	0.011
Vascular thrombosis (liver)						
No	25.0	22.9	0.033			
Yes	0	0				
Infiltration of liver capsule						
No	29.3	25.7	0.078			
Yes	18.0	–				
Lymph nodes metastases						
No	38.8	38.8	0.122			
Yes	17.8	15.2				
Distribution of liver metastases						
Unilobar	35.9	32.6	<0.001			
Bilobar	6.2	–				
Max diameter of liver lesion (cm)						
<3	32.7	28.1	0.002			
≥3	9.6	4.8		1.65	1.00–2.69	0.048
Number of liver lesions						
Single	50.1	44.5	<0.001			
Multiple	13.6	–		3.34	2.38–4.76	0.001
T-stage						
1–2	75.0	–	0.056			
3–4	20.4	18.3				
Margin						
R1	13.9	13.9	0.023			
R0	26.4	23.5				
KRAS						
Mutant	9.4	–	0.010			
None mutant	20.5	–				
Vascular thrombosis (gut)						
No	26.1	23.5	0.331			

Contd...

Table 3: Contd...

Parameters	3-year DFS (%)	5-year DFS (%)	Univariate *P*	*HR*	95% *CI*	Multivariate *P*
Yes	14.1	21.2				
Nerve infiltration (gut)						
No	26.3	26.3	0.326			
Yes	12.3	–				
Differentiation						
High	0	–	0.238			
Moderate	28.6	26.0				
Low	13.9	13.9				

DFS: Disease-free survival; CEA: Carcinoembryonic antigen; *HR*: Hazard ratio; *CI*: Confidence interval; R0: No cancerous cells seen microscopically; R1: Cancerous cells seen microscopically; *KRAS*: Kirsten rat sarcoma viral oncogene; –: No data.

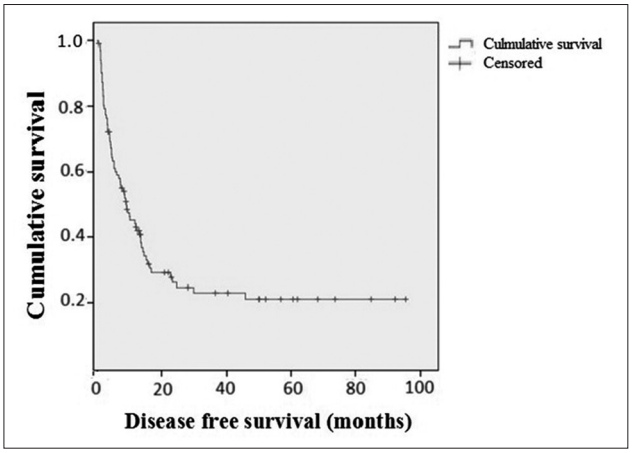

Figure 2: Disease-free survival of 102 patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections.

most important prognostic factors in this setting, which is consistent with a previous study.[13] These results indicate that patients with single liver lesions, limited to one lobe, and <3 cm might be more suited to surgical resection.

In addition to the pathological features, this study found that standard adjuvant CT was a highly favorable predictor for both OS and DFS. Actually, as the effectiveness of postoperative CT for CRCLM has been very clear, all the patients in this study were recommended to receive adjuvant CT in consideration of their advanced-stage disease. More than 80% of patients with CRCLM received standard adjuvant CT and achieved better OS and DFS. Recent research has established a stage system based on risk factors to guide use of perioperative CT, thereby optimizing prognoses as much as possible.[14]

This study has several limitations. Most patients had late-stage primary CRC (T1–T2: Five patients; T3–T4: 97 patients), which might have affected our survival analysis. The small sample size and the retrospective study design also limit our evidence level. Survival analysis with a larger sample size is needed to verify these prognostic factors in this setting.

In summary, this study shows that simultaneous resection of primary and metastatic lesions are a safe and effective therapy for patients with CRCLM, after which patients can obtain a satisfactory prognosis. Risk factors that influence outcomes for these patients are mainly the pathological features of the liver metastases (multiple, bilobar distribution, and ≥3 cm) and standard adjuvant CT. We believe that with appropriate selection and standard perioperative CT, simultaneous resection is a suitable choice for patients with synchronous CRC with liver metastases.

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Conflicts of interest

There are no conflicts of interest.

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