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

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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...
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...
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 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%. In contrast, if the primary lesion and metastases are radically resected, 5-year OS is 25–70%. 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. However, the independent risk factors for the simultaneous resection had been unclear.

This study retrospectively analyzed the prognoses of 102 patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections. This study retrospectively analyzed the prognoses of 102 patients with synchronous colorectal cancer liver metastases who underwent simultaneous resections. 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 DFS [Table 3]. 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. 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        |          |             |                |
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        |        |        |                |
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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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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.
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