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Original Article

Factors that influence survival in colorectal cancer with synchronous distant metastasis

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Abstract

Background: Treatments for the purposes of curing or more effectively managing metastatic colorectal cancer (CRC) are evolving. Our study focused on patients with primary CRC with synchronous distant metastasis, and we analyzed the factors influencing patient survival.
Methods: Data review was conducted retrospectively. Clinicopathological parameters included age, sex, site of primary cancer, tumor cell differentiation, number of liver metastasis, presence of extrahepatic metastasis, treatment of liver metastasis, pre-treatment carcinoembryonic antigen (CEA) level, status of treatment response, salvage treatment and survival.
Results: A total of 420 patients were identified and considered for our study. Of those, 275 patients (65.4%) had liver-only metastasis, 100 patients (23.8%) had concomitant lung metastasis, and 40 patients (9.5%) had other metastases. Additionally, 145 patients (34.5%) had liver-directed treatment including surgical resection (28.5%), radiofrequency ablation (RFA) (10.6%) and transcatheter arterial chemoembolization (TAE) (1.2%). There were 80 patients (19%) with CEA levels < 10, 135 patients (32.1%) with CEA 10–100, and 165 patients (39.2%) with CEA > 100. There were 200 patients (47.6%) who had received chemotherapy, 130 patients (30.9%) with target therapy, and 40 patients (9.5%) who had not undergone any salvage treatment. Three significant factors were identified, including treatment of liver metastasis ($p = 0.027$), pre-treatment CEA ($p = 0.04$), and salvage treatment ($p = 0.005$).
Conclusion: We demonstrated three factors influencing patient survival including treatment of liver metastasis, pre-treatment CEA level, and salvage treatment. Aggressive treatment of liver metastasis including surgical resection or RFA combined with chemotherapeutic agents appear to provide an increased rate of survival to patients.

Keywords: colorectal cancer; metastasis; survival

1. Introduction

Approximately 20% of patients with colorectal cancer (CRC) have synchronous liver metastasis at the time of diagnosis.[1] Although major advances in systemic chemotherapy have expanded the therapeutic options for these patients and improved median survival periods from less than 1 year to 20 months or longer, fewer than 10% of those treated with chemotherapy alone are still alive at 5 years.[2] Long-term survival of patients with metastatic CRC has only been achieved in those patients who could undergo primary surgical resection of metastases.[3] Unfortunately, such surgical treatments can only be offered to approximately 10% of the patients who present with metastases from CRC.[4]

Treatment choices for CRC with synchronous distant metastasis are evolving, especially those involving cases of liver metastasis. Given that three classes of chemotherapeutic agents and two classes of target therapy are currently available in Taiwan, treatment decision-making and management is more complicated as the optimum sequencing and dosing of the agents still remains to be determined. Clinicians are increasingly using

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and applying these new chemotherapeutic agents in the treatment of CRC with synchronous liver metastasis, which have demonstrated significant improvement in outcomes.[5,6]

It is important to identify prognostic factors that may help to determine the most effective CRC treatment response, thereby increasing patient survival periods. Such an approach could refine the decision-making and management of CRC with palliative chemotherapy according to the likelihood of clinical benefit.[7] In this study, we focused on patients with primary CRC with synchronous liver metastasis and analyzed the factors influencing survival.

2. Methods

This was a retrospective study conducted at Kaohsiung Veterans General Hospital, where we reviewed surgical and pathological records that included all patients treated for CRC with synchronous distant metastasis from 2002 to 2009. Patient data were collected into our electronic medical records database, which included all patient follow-up, including the latest follow-up or date of demise.

The clinicopathological parameters which we evaluated included age, sex, site of primary cancer, tumor cell differentiation, number of liver metastasis, presence of extrahepatic metastasis, treatment modality of liver metastasis, pre-treatment carcinoembryonic antigen (CEA) level (ng/mL), status of treatment response (according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, 1.1 version, 2009), salvage treatment (chemotherapy or target therapy) and survival period (months). The patient follow-up period ranged from 1 month to 60 months, and the survival period was calculated from the date that CRC with synchronous liver metastasis was detected until the latest follow-up date. Some parameters were excluded from further analysis due to limited case number, including patients without resection of the primary tumor ($n = 20$), and patients treated with radiation only ($n = 5$).

Chemotherapy regimens included conventional FOLFIRI (irinotecan 180 mg/m^2 plus 5-FU and leucovorin) and FOLFOX4 (oxaliplatin 85 mg/m^2 plus 5-FU and leucovorin). The target therapy regimen included cetuximab (initial dose 400 mg/m^2, weekly dose of 250 mg/m^2) plus FOLFIRI and bevacizumab (5 mg/kg IV over 90 minutes every 2 weeks) plus FOLFIRI or FOLFOX.

Survival curves were generated according to the Kaplan-Meier method, and the differences in patient survival periods were determined by employing the log-rank test. All data were analyzed by the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). To determine the prognostic factors for survival, all variables were tested from their relationship in the Cox-regression model and the Cox proportional hazards model. A p value < 0.05 was accepted as statistically significant.

3. Results

Among the 450 patients who underwent treatment for CRC with synchronous distant metastasis which were retrospectively analyzed, 20 patients had perioperative mortality, 10 patients had concomitant malignancies other than CRC, and 10 patients died of other disease and thus were excluded from this study. The clinicopathologic data of the 420 patients identified are summarized in Table 1. Since complete data on all factors were not available for each patient, the sample size in this study ranged from 396 to 420 in the further analysis.

Among these patients, 250 (59.2%) were males. The mean age was 60.7 ± 13.9 years (range, 29–88), and the median follow-up time was 20 ± 10.3 months (range, 1–60). Median overall survival in all patients was 18.5 ± 20 months (range, 1–60). Regarding treatment of the primary tumor, 395 patients (94%) had resection of the primary tumor, 20 patients (4.7%) without resection of the primary tumor, and five patients (1.2%) only underwent radiotherapy. Regarding the actual number of liver metastases, 215 patients (51.2%) had uncountable liver metastases, with the balance countable metastases (27.4% with one lesion, 7.1% with two lesions, 5.9% with three lesions, 3.5% with four lesions, 2.4% with five lesions, and 2.4% with six lesions). Furthermore, 275 patients (65.4%) had liver-only metastasis, 100 patients had concomitant lung metastasis, and 40 patients had other concomitant metastases including bone, ovary, brain, and carcinomatosis. Regarding the treatment of liver metastasis, 275 patients (65.4%) were without liver-directed treatment, 95 patients (22.6%) had liver resection metastasis, 20 patients (4.7%) underwent radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), 25 patients (5.9%) had resection and RFA, and five patients (1.2%) had transcatheter arterial chemoembolization (TAE).

CEA level was measured within 1 month of detection of the disease, with the results divided into three groups: < 10, 10–100, and > 100, and 80 patients (19%) with CEA < 10, 135 patients (32.1%) with CEA 10–100, 165 patients (39.2%) with CEA > 100. Regarding the salvage treatment, 200 patients (47.6%) had chemotherapy, 130 patients (30.9%) were treated with target therapy, and 40 patients (9.5%) did not have any salvage treatment. As for the status of treatment response, 315 patients (75%) had a progressive disease, 55 patients (13.1%) had a partial response, and 15 patients (3.5%) had a complete response.

Two-year and 3-year survival rates in patients with treatment of liver metastasis were 75% and 50%, respectively (Fig. 1B). There was no survival difference between patients with liver-only metastasis or extrahepatic metastasis ($p = 0.177$, Fig. 1B). In patients with treatment of liver metastasis, the 2-year survival rate was 75%, and the 3-year survival rate was 50%. Without any treatment of liver metastasis, survival rates decreased to 20% and 5%, respectively (Fig. 1C). There were significant differences in survival between patients with treatment of liver metastasis ($p < 0.001$, Fig. 1C, Hazard Ratio (HR): 5.15 in no treatment of liver metastasis), the number of liver metastasis ($p < 0.001$, Fig. 1D, HR: 4.4 in uncountable liver metastasis), pre-treatment CEA level ($p = 0.004$, Fig. 1E, HR: 2.4 in CEA: 10–100, HR: 8.0 in CEA > 100), and different

Table 1
Clinicopathologic data of patients with colorectal cancer with synchronous liver.

Demographic variables	No. of patients ($n = 420$)
Age (y)	60.7 ± 13.9 (29–88)
Sex	
Male	250 (59.2%)
Female	170 (40.8%)
Primary tumor site	
Right colon	90 (21.4%)
Left colon	215 (51.2%)
Rectum	110 (26.1%)
Tumor cell differentiation	
Well differentiation	9 (2.1%)
Moderate differentiation	381 (90.7%)
Poorly differentiation	30 (7.2%)
Primary tumor treatment	
Resection	395 (94%)
No resection	20 (4.7%)
Radiotherapy	5 (1.2%)
Number of liver metastasis	
Uncountable (≧7)	215 (51.2%)
1	115 (27.4%)
2	30 (7.1%)
3	25 (5.9%)
4	15 (3.5%)
5	10 (2.4%)
6	10 (2.4%)
Liver-only metastasis	
Yes	275 (65.4%)
No	140 (34.6%)
Concomitant other metastasis	
Lung	100 (23.8%)
Bone, ovary, brain, carcinomatosis	40 (9.5%)
Treatment of liver metastasis	
Nil	275 (65.4%)
Liver resection	95 (22.6%)
RFA or PEI	20 (4.7%)
Liver resection + RFA	25 (5.9%)
TAE	5 (1.2%)
Pre-treatment CEA (ng/ml)	
< 10	80 (19%)
10-100	135 (32.1%)
> 100	165 (39.2%)
Salvage treatment	
Chemotherapy	200 (47.6%)
Target therapy	130 (30.9%)
Nil	40 (9.5)
Status of treatment response	
Progressive disease	315 (75%)
Stable disease	55 (13.1%)
complete response	15 (3.5%)
Median survival (months)	18.5 ± 20 (1–60)

CEA = carcinoembryonic antigen; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TAE = transcatheter arterial chemoembolization.

salvage treatment ($p = 0.035$, Fig. 1F, HR: 0.39 in chemotherapy, HR: 0.29 in target therapy). Factors influencing survival in the Cox-regression model are shown in Table 2. There are three factors with significant differences, including treatment of liver metastasis ($p = 0.027$), pre-treatment CEA level ($p = 0.04$), and salvage treatment ($p = 0.005$).

4. Discussion

Various studies on survival factors for metastatic CRC have resulted in disparate results. These incongruent results probably depict differences in patient population and study design, thus making them difficult to evaluate. In 1983, Lahr et al[8] reported several factors predicting survival such as elevated alkaline phosphatase (ALP), elevated serum bilirubin level, the location of hepatic metastases (unilateral or bilateral), the number of metastatic nodes involved, depressed serum albumin, chemotherapy (given or withheld), and whether or not the primary colorectal tumor was resected. Schindl et al[9] reported in their 2005 study some prognostic factors in CRC with liver metastases including Dukes Stage, number of metastases, and serum concentrations of CEA, alkaline phosphatase, and albumin. In 2009, Luo et al[10] reported that poor differentiation of the tumor and high CEA level indicate an unfavorable prognosis. In 2010, Zacharakis et al[11] reported three factors that suggested improved survival in stage IV CRC: combination chemotherapy, improved performance status and dermatological complications. This study noted eight factors which indicated unfavorable survival: worsened performance status, C-reactive protein > 5 mg/dL, anemia, anorexia, weight loss > or = 10%, fatigue, hypoalbuminemia, and blood transfusions. Our study included consecutive non-selected CRC with synchronous distant metastasis cases from a single medical center. Based on these settings, we identify three factors that influence survival: treatment of liver metastasis, pre-treatment CEA level, and salvage treatment.

High preoperative serum CEA levels are associated with advanced tumor stage, elevated incidence of recurrence and reduced survival periods.[12] Carcinoembryonic antigen exists in the embryonic and fetal gut, liver, pancreas, and some adult organs.[13] It is elevated in approximately 40% of CRC[14] and was first mentioned as a factor in 1965.[15] In recent studies involving CRC with liver metastases, CEA is still an independent factor influencing survival.[10,16]

Resection of colorectal liver metastases in selected patients has evolved as the standard of care during the last 20 years. Five-year survival rates after resection range from 24% to 58%, averaging 40%, and surgical mortality rates are generally less than 5%. [17–21] Subgroups with advanced age, comorbid disease, and synchronous hepatic and colon resection may have higher procedure-related mortality and worse long-term outcomes.[22] Radiofrequency ablation has been widely applied to patients with metastatic liver tumors. The vast majority of published data on efficacy of RFA for CRC liver metastases come from retrospective series with limited follow-up (20 months or less); there are no published randomized trials.[23–26] A systematic review of the literature on RFA for CRC liver metastases reported a wide range of 5-year survival (14–55%), and local tumor recurrence rates (3.6–60%).[27] Given the evidence that resection improves overall survival, particularly in the absence of extrahepatic disease, a systematic review of the literature by an expert panel from American Society of Clinical Oncology (ASCO) concluded that there is not enough evidence to support the use of RFA over

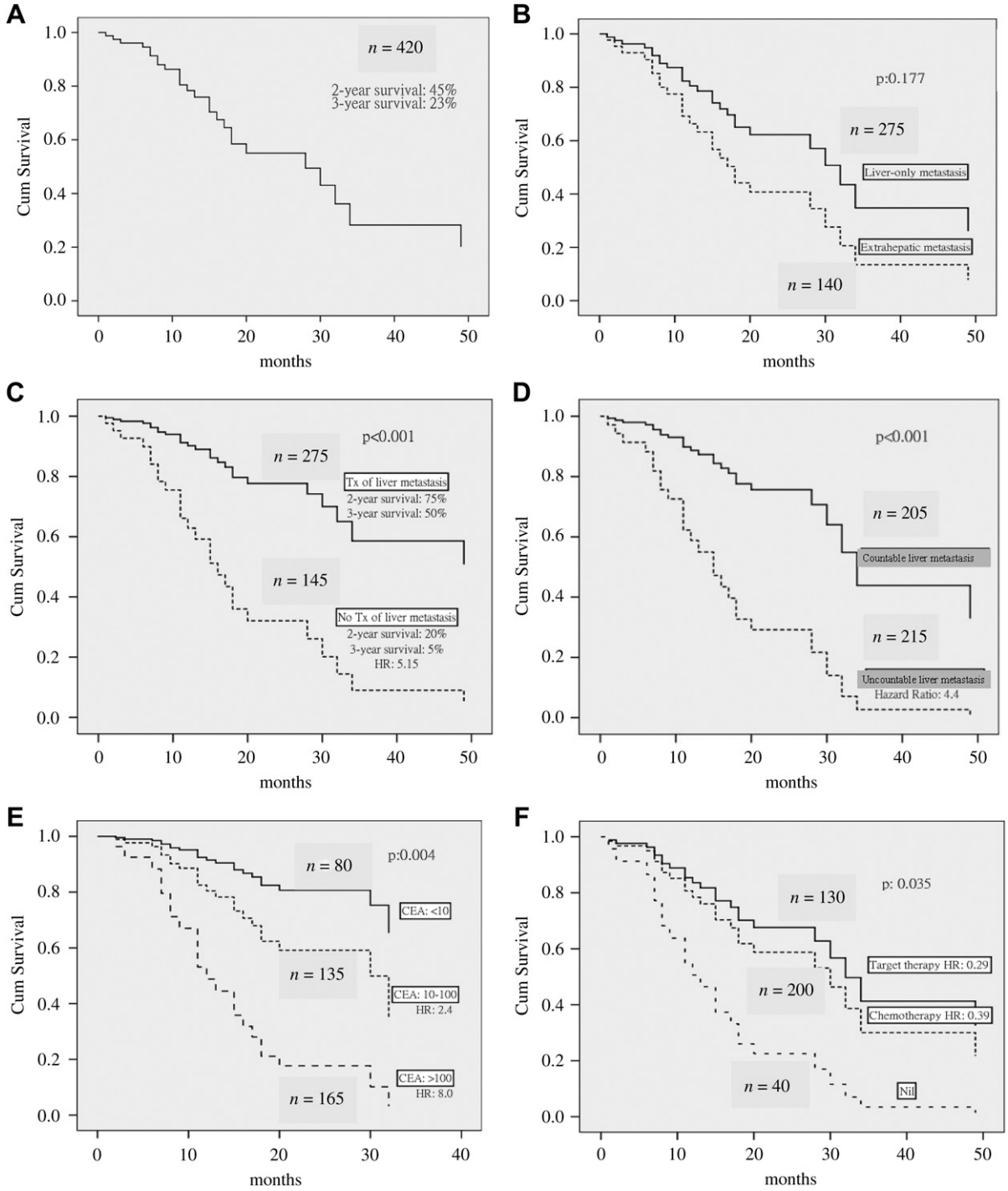

Fig. 1. (A) Overall survival curves; (B) survival curves according to liver-only metastasis and extrahepatic metastasis ($p = 0.177$); (C) survival curves according to treatment of liver metastasis ($p < 0.001$). 2-year and 3-year survival in patients with treatment of liver metastasis were 75% and 50% respectively; and 20% and 5%, respectively, if no treatment of liver metastasis was given (HR: 5.15); (D) survival curves according to number of liver metastasis ($p < 0.001$, HR: 4.4); (E) survival curves according to pre-treatment CEA level ($p = 0.004$, HR: 2.4 in CEA: 10–100, HR: 8.0 in CEA: > 100); (F) survival curves according to salvage treatment ($p = 0.035$, HR:0.29 in target therapy, HR: 0.39 in chemotherapy). HR = hazard ratio.

resection in patients with potentially resectable CRC liver metastases.[27]

Chemotherapy is a well-established salvage treatment strategy in CRC with synchronous liver metastasis and has been shown to independently predict survival.[28] Combination chemotherapy regimens including irinotecan and oxaliplatin in combination with 5-FU, with or without a biological agent, have improved response rates to as high as 50% and overall

Table 2
Factors influencing survival by multivariate Cox regression model.

	Standard error	p-value	95% CI	Hazard ratio	95% CI
Age	0.018	0.364	0.951-1.019		
Liver-only metastasis	0.462	0.579	0.313-1.915		
Number of liver metastasis	0.555	0.469	0.226-1.986		
Countable				Reference	−
Uncountable				4.4	1.818-10.707
Treatment of liver metastasis	0.725	0.027	0.048-0.829		
Yes				Reference	−
No				5.15	1.862-10.886
Pre-treatment CEA level	0.330	0.040	1.032-3.758		
<10				Reference	−
10-100				2.4	0.535-11.2
>100				8.0	1.744-37.228
Salvage treatment	0.400	0.005	0.148-0.714		
Nil				Reference	−
Chemotherapy				0.39	0.135-1.187
Target therapy				0.29	0.098-0.959

CI = confidence interval.

survival duration to 15−20 months.[29,30] Our analysis confirms the importance of combination chemotherapy as an independent predictor of survival for CRC with synchronous liver metastasis.

Resection of the primary tumor in CRC with unresectable metastases is still a matter of debate. In 2007, Costi et al[31] reported palliative resection of primary CRC should be pursued in patients with unresectable distant metastasis (without carcinomatosis), and, intraoperatively, whenever the primary tumor is technically resectable. In 2010, Scabini et al[32] also reported that an inability to perform cancer resection is associated with poor prognosis in symptomatic stage IV CRC, and also has reduced survival in the short term. However, all of these results come from retrospective data, so selection bias and other clinical factors that are not accounted for may explain this observation. Prospective, randomized surgical trials are needed to test the role of primary tumor resection in this setting.[33] In our study, most of the patients (94%) received resection of the primary tumor, including curative resection and palliative resection when the primary tumor is resectable.

There are some limitations to our study. First, this is a retrospective analysis of our experience. Second, there must be a selection bias in salvage treatment. It has to be assumed that, in general, enhanced patient survival was obtained when patients began treatment in better general physical condition, and then received more aggressive chemotherapeutic agents. However, this is very difficult to assess on a retrospective basis. These findings deserve further randomized-control trials and validation in large-scale studies.

In conclusion, management of CRC with synchronous distant metastasis is a medical challenge. In this retrospective study, we clearly demonstrated three factors that influence patient survival periods including treatment of liver metastasis, pre-treatment CEA level, and salvage treatment with chemotherapeutic agents. Aggressive treatment of liver metastasis, including surgical resection or RFA combined with chemotherapeutic agents, seems to present patients with a recognizeable survival benefit.

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