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Original Article

Prognostic significance of distant metastasis location in patients with metastatic colorectal cancers

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Abstract: Colorectal cancer is the fourth most frequently diagnosed cancer and the current TNM staging fails to take into account the different outcome among metastasis locations and the time of metastases. Here, we investigated the prognostic significance of different metastatic locations in patients with metastatic colorectal carcinoma (mCRC) in 496 patients diagnosed with synchronous mCRC and 559 patients diagnosed with metachronous mCRC between July 1984 and December 2003. The Cox proportional hazards regression showed that distant metastasis locations (liver and lung) were significantly associated with disease-specific survival in the univariate and multivariate analysis. Further survival analysis found that patients with metachronous liver and lung metastases had significantly shorter disease-specific survival than the other two patient groups with liver or lung metastases (P<0.001). However, there were no differences in disease-specific survival among three patient subgroups (liver metastases, lung metastases, and liver plus lung metastases) for patients with synchronous metastasis. Additional comparison analysis revealed that the disease-specific survival of patients with metachronous metastasis was significantly shorter than that of patients with synchronous metastasis. These results suggested that different distant metastases locations and different time of metastases have the different prognosis. Our study indicated that optimal TNM staging for mCRC should incorporate distant metastases locations and the time of metastases to provide a more effective and predictive model.

Keywords: Colorectal cancer, liver metastasis, lung metastasis, prognosis

Introduction

Currently, treatment for cancer is performed based on staging systems in which the degree of cancer development is defined objectively. The staging system for colorectal cancer (CRC) is the TNM staging system adopted by the National Cancer Institute [1] and the American Society of Colon and Rectal Surgeons [2], which remains the most important determinant of prognosis in CRC. Despite a continuous refinement of the T (tumor), N (node), and M (metastasis) staging system to express disease extent and define prognosis, and eventually to guide treatment [3], the outcome of patients with CRC may vary considerably even within the same tumor stage. Stage IV is the most advanced stage of the TNM system. It is no longer considered a monolithic entity [4], and several proposals have been raised for stratifying it [5-10]. For example, performance status of patients; the metastatic location; the size and resectability of hepatic and extrahepatic metastasis was all investigated as variables that would predict the prognosis of Stage IV CRC patients. Specifically, the current staging system does not take into account the impact of metastasis location on evaluating initially metastatic CRC (mCRC).

On the basis of the limited significance assigned to the effect of metastasis location among all prognostic factors that apply to mCRC patients, we decided to test and quantify the prognostic difference of this variable in patients with synchronous and metachronous lung metastases or liver metastases from CRC. Our hypothesis was that the inclusion of distant metastasis location could improve the accuracy of cancer-specific mortality predictions.

Table 1. Descriptive Characteristics of 496 Patients Diagnosed with Synchronous Colorectal cancer metastases

Variable	Overall	Liver metastasis	Lung metastasis	Liver + lung metastasis	*P* value
Total no. of patients	496	383	49	64	
Mean age, y (median), range	57.63 (58.00) 21~86	57.95 (60.00) 21~86	56.16 (58.00) 29~78	56.83 (55.00) 32~77	0.432
Sex					
Man	303 (61.1%)	242 (63.2%)	24 (49.0%)	37 (57.8%)	
Woman	193 (38.9%)	141 (36.8%)	25 (51.0%)	27 (42.2%)	0.134
Period of surgery					
1995-1999	66 (13.4%)	51 (13.3%)	9 (18.4%)	6 (18.4%)	<0.001
2000-2004	130 (26.3%)	119 (31.1%)	7 (14.3%)	6 (14.3%)	
2005-2008	298 (60.3%)	213 (55.9%)	33 (67.3%)	52 (81.3%)	
Location					
Colon	254 (51.2%)	190 (49.6%)	28 (57.1%)	36 (56.3%)	0.420
Rectum	242 (48.8%)	193 (50.4%)	21 (42.9%)	28 (43.8%)	
Resection for cure					
Yes	93 (18.8%)	87 (22.7%)	6 (12.2%)	0 (0%)	<0.001
No	403 (81.3%)	296 (77.3%)	43 (87.8%)	64 (100%)	
Gross type					
Noninfiltrating	165 (33.3%)	130 (33.9%)	16 (32.7%)	19 (29.7%)	0.796
Infiltrating	331 (66.7%)	253 (66.1%)	33 (67.3%)	45 (70.3%)	
Differentiation					
Well/moderate	312 (62.9%)	242 (63.2%)	36 (73.5%)	34 (53.1%)	0.083
Poor	184 (34.1%)	141 (36.8%)	13 (26.5%)	30 (46.9%)	
PT-stage					
T1-T3	128 (25.8%)	106 (27.7%)	12 (24.5%)	10 (15.6%)	0.122
T4	368 (74.2%)	277 (72.3%)	37 (75.5%)	54 (84.4%)	
PN-stage					0.026
N0	140 (28.2%)	105 (27.4%)	15 (30.6%)	20 (31.3%)	
N1	223 (45.0%)	185 (48.3%)	20 (40.8%)	18 (28.1%)	
N2	133 (26.8%)	93 (24.3%)	14 (28.6%)	26 (40.6%)	
Postoperative chemotherapy					0.001
Yes	194 (39.1%)	164 (42.8%)	8 (16.3%)	22(34.4%)	
No	302 (60.9%)	219 (57.2%)	41 (83.7%)	42 (65.6%)	
Mean follow-up Mo.(median), range	25.14 (20.28) 0.77~127.77	25.52 (20.27) 0.77~127.77	27.61 (24.13) 6.13~110.53	21.01 (18.23) 0.90~72.77	0.138

pT: primary tumor; pN: regional lymph node. Data were stratified according to the metastatic locations.

Table 2. Univariate Analysis Predicting the Probability of Cancer-Specific Mortality in Patients Diagnosed with Synchronous Colorectal cancer metastases

Variable	Univariate		
	Risk ratio	95% CI	*P* value
Age	1.005	0.995-1.014	0.339
Gender	0.825	0.681-0.998	0.048
Period of surgery	1.003	0.881-1.143	0.962
Location	0.958	0.797-1.153	0.651
Metastasis location	1.082	0.946-1.237	0.251
Resection for cure	1.649	1.297-2.095	<0.001
Gross type	1.182	0.970-1.441	0.182
Differentiation	1.282	1.058-1.554	0.011
PT-stage	1.242	1.004-1.537	0.046
PN-stage	1.600	1.403-1.824	<0.001
Postoperative chemotherapy	0.742	0.614-0.896	0.002

pT: primary tumor; pN: regional lymph node; CI: confidence interval.

Table 3. Multivariate Analysis Predicting the Probability of Cancer-Specific Mortality in Patients Diagnosed with Synchronous Colorectal cancer metastases

Variable	Multivariate		
	Risk ratio	95% CI	*P* value
Gender	0.792	0.652-0.963	0.019
Resection for cure	1.761	1.384-2.241	<0.001
Gross type	1.283	1.050-1.569	0.015
PN-stage	1.646	1.443-1.876	<0.001
Postoperative chemotherapy	0.743	0.614-0.899	0.002

pN: regional lymph node. CI: confidence interval.

Material and methods

Patients

Synchronous metastasis had to be diagnosed during the diagnostic work-up or within 12 months following the diagnosis of the CRC. Metachronous metastasis was defined as the metastasis occurring at least 12 months after the diagnosis of the CRC. Distant metastases were identified from clinicians' records on the occasion of iterative surveys conducted to identify metastasis. The last survey was conducted in January 2008 for patients diagnosed at the end of 2003. Only the first metastasis event was recruited.

Between July 1984 and December 2003, a total of 1055 consecutive patients with mCRC were included. Among them, the frequency of synchronous metastases locations were 383 for liver alone, 49 for lung alone and 64 for both liver and lung; the frequency of metachronous metastases locations were 237 for liver alone, 164 for lung alone and 158 for both lung and liver. Patients were divided into three groups according to metastasis location: liver group, lung group and both liver and lung group. Clinical and pathologic data of the primary tumor and follow-up information were analyzed. Resection for a cure was defined by the complete resection of both primary and metastatic tumors. Patients were prospectively followed after surgery or recurrent chemotherapy to a postoperative surveillance program.

Approval of the institutional review board was obtained to collect these patients' data in a secure database and report their outcomes. Patients who had received preoperative treatment were excluded from this study. Histologic type of the tumor was determined according to the World Health Organization classification. The staging was determined according to the international TNM staging system [2]. For staging, all patients underwent a physical examination, chest radiography, computed tomography of the thorax, brain, upper abdomen, bone scintigraphy, and bronchoscopy.

Statistical analysis

Descriptive statistics were calculated for all variables. Categorical variables were compared using Chi-square test and t-test. Disease-specific survival (DSS) was defined as the time from metastases until death from any cause. Survival differences in synchronous metastasis group and metachronous metastasis group were assessed by the Kaplan-Meier curves and compared using the log-rank test. Univariate and multivariate Cox proportional hazards model analyses were performed to evaluate the relationships of distant metastasis location and DSS. The significance was defined as *P* values being less than 0.05. All statistical analysis was done using SPSS software (version 13.0).

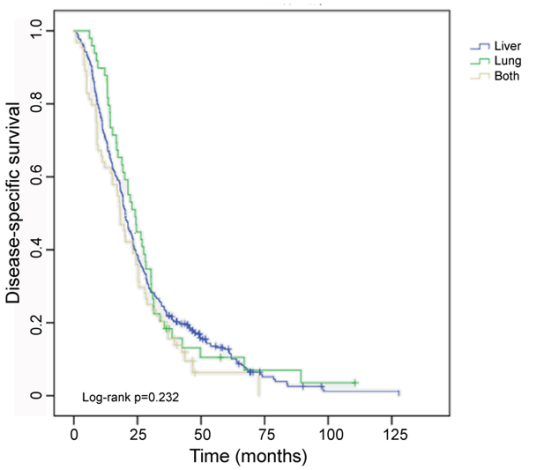

Figure 1. The Kaplan-Meier analysis demonstrates disease-specific survival and recurrence related survival in patients with mCRC in the synchronous metastases population (n=496).

Results

Characteristics of synchronous metastasis

Overall, 496 diagnosed mCRC (47.0%) had synchronous metastases. Among them, 383 (77.2%) were liver locations, 49 (9.9%) were lung locations, and 64 (12.9%) were both liver and lung locations. The characteristics of the patients who developed synchronous metastases were shown in **Table 1**. After stratification according to synchronous metastasis locations, statistically significant differences were identified among the 3 groups. Those differences were comprised of period of surgery (P<0.001), resection for cure (P<0.001), pN-stage (P=0.026) and the proportion of patients with postoperative chemotherapy (P=0.001).

Cox regression models were restricted to patients with pathologically confirmed distant metastasis locations (liver and lung). In univariate Cox regression models, gender (P=0.048), rate of resection for cure (P<0.001), differentiation (P=0.011), pT-stage (P=0.046), pN-stage (P<0.001) and postoperative chemotherapy (P=0.002) were found to be significantly associated with DSS (**Table 2**). The status of lymph node metastasis demonstrated a 1.65-fold higher rate of cancer-specific mortality, which was consistent with our previous findings (P<0.001). In addition, gender (P=0.019), rate of resection for cure (P<0.001), gross type of tumor (P=0.015), postoperative chemotherapy (P=0.002) revealed independent predictor status by multivariate Cox regression analysis (**Table 3**).

Kaplan-Meier survival analysis showed that there was a median DSS of 20.27 ± 0.78 months in the overall population (**Figure 1**). Stratified by the metastatic locations, median DSS was 20.27 ± 0.80 months in patients with simple liver metastasis, 24.13 ± 2.36 months in patients with simple lung metastasis, and 18.2 ± 1.55 months in patients with both liver and lung metastases. Thus, there was an obvious tendency that CRC patients with synchronous lung metastasis had the longest DSS, and then the simple liver metastasis, and the shortest was the CRC patients with both liver and lung metastasis. The five survival rate of CRC patients with synchronous lung metastasis is 12.7% which is higher than that of patients with liver metastasis (10.5%) or both liver and lung metastasis (6.3%), even if these differences were not statistically significant.

Characteristics of metachronous metastasis

Among patients diagnosed with metachronous metastasis (n=559), 237 (42.4%) were liver locations, 164 (29.3%) were lung locations, and 158 (28.3%) were both liver and lung locations. The characteristics of the patients who developed metachronous metastases were shown in **Table 4**. Those differences were comprised of the primary tumor site (P<0.001), the differentiation level of tumor (P=0.002), the pN-stage of the tumor (P=0.03), and AJCC stage of the tumor (P=0.001). The potential effect of those differences was adjusted for in multivariate Cox regression models.

Cox regression models were restricted to patients with pathologically confirmed distant metastasis locations (liver and lung). In univariate Cox regression models, differentiation level of primary tumor (P=0.012), pT-stage (P=0.002), postoperative chemotherapy (P=0.001), metastatic location (P<0.001) were found to achieve statistical significance (**Table 5**). In multivariate Cox regression models, The metastasis location significantly demonstrated a 1.23-fold higher rate of cancer-specific mortality (P< 0.001) and the pT-stage of the disease determined a 1.39-fold increase rate of cancer-specific mortality (P<0.001). In addition, year of surgery (P=0.048), differentiation level of

Table 4. Descriptive Characteristics of 559 Patients Diagnosed with Metachronous Colorectal cancer metastases

Variable	Overall	Liver metastasis	Lung metastasis	Liver + lung metastasis	*P* value
Total no. of patients	559	237	164	158	
Mean age, y (median),range	57.35 (57.00) 23-85	57.65 (57.00) 23-84	56.48 (56.00) 26-85	57.78 (58.00) 26-85	0.486
Sex					0.092
Man	337 (60.3%)	155 (65.4%)	95 (57.9%)	87 (55.1%)	
Woman	222 (39.7%)	82 (34.6%)	69 (42.1%)	71 (44.9%)	
Period of surgery					0.493
1995-1999	99 (17.7%)	34 (14.3%)	33 (20.1%)	32 (20.3%)	
2000-2004	221 (39.5%)	97 (40.9%)	65 (39.6%)	59 (37.3%)	
2005-2008	239 (42.8%)	106 (44.7%)	66 (40.2%)	67 (42.4%)	
Location					
Colon	219 (39.2%)	114 (48.1%)	47 (28.7%)	58 (36.7%)	<0.001
Rectum	340 (60.8%)	123 (51.9%)	117 (71.3%)	100 (63.3%)	
Gross type					
Noninfiltrating	438 (78.4%)	183 (77.2%)	131 (79.9%)	124 (78.5%)	0.816
Infiltrating	121 (21.6%)	54 (22.8%)	33 (20.1%)	34 (21.5%)	
Differentiation					
Well/moderate	392 (70.1%)	152 (64.1%)	132 (80.5%)	108 (68.4%)	0.002
Poor	167 (29.9%)	85 (35.9%)	32 (19.5%)	50 (31.6%)	
pT-stage					
T1-T3	191 (34.2%)	79 (33.3%)	59 (36.0%)	53 (33.5%)	0.844
T4	368 (65.8%)	158 (66.7%)	105 (64.0%)	105 (66.5%)	
pN-stage					
N0	247 (44.2%)	95 (40.1%)	92 (56.1%)	60 (38.0%)	0.03
N1	208 (37.2%)	91 (38.4%)	46 (28.0%)	72 (44.9%)	
N2	104 (18.6%)	51 (21.5%)	26 (15.9%)	27 (17.1%)	
AJCC stage					0.001
1-2	247 (44.3%)	95 (40.1%)	92 (56.4%)	60 (38.0%)	
3	311 (55.7%)	142 (59.9%)	71 (43.6%)	98 (62.0%)	
Postoperative chemotherapy					0.937
Yes	195 (34.9%)	82 (34.6%)	59 (36.0%)	54 (34.2%)	
No	364 (65.1%)	155 (65.4%)	105 (64.0%)	104 (65.8%)	
Recurrent chemotherapy					0.151
Yes	163 (29.2%)	79 (33.5%)	41 (25.0%)	43 (27.2%)	
No	395 (70.8%)	157 (66.5%)	123 (75.0%)	115 (72.8%)	
Mean follow-up Mo.(median),range	46.44 (39.6) 3.5-302.4	42.82 (35.80) 5.3-222.2	54.36 (51.28) 12.1-186.7	43.66 (35.18) 3.5-302.4	0.001

pT: primary tumor; pN: regional lymph node. Data were stratified according to the metastatic locations.

Table 5. Univariate Analysis Predicting the Probability of Cancer-Specific Mortality in Patients Diagnosed with Metachronous Colorectal cancer metastases

Variable	Univariate (Full Model)		
	Risk ratio	95% CI	*P* value
Gender	0.911	0.759-1.093	0.315
Age	0.995	0.987-1.004	0.287
Period of surgery	0.872	0.757-1.003	0.056
Location	0.874	0.726-1.052	0.154
Gross type	0.848	0.679-1.057	0.143
Differentiation	1.282	1.055-1.557	0.012
PT-stage	1.383	1.129-1.695	0.002
PN-stage	1.209	0.946-1.546	0.129
AJCC stage	1.201	0.823-1.755	0.342
Postoperative chemotherapy	0.713	0.586-0.867	0.001
Metastasis location	1.313	1.174-1.470	<0.001
Recurrent chemotherapy	0.868	0.709-1.063	0.17

pT: primary tumor; pN: regional lymph node; CI: confidence interval.

Table 6. Multivariate Analysis Predicting the Probability of Cancer-Specific Mortality in Patients Diagnosed with Metachronous Colorectal cancer metastases

Variable	Multivariate		
	Risk ratio	95% CI	*P* value
Period of surgery	0.877	0.770-0.999	0.048
Differentiation	1.276	1.051-1.549	0.014
PT-stage	1.394	1.141-1.701	0.001
PN-stage	1.351	1.199-1.521	<0.001
Postoperative chemotherapy	0.735	0.610-0.886	0.001
Metastasis location	1.232	1.104-1.374	<0.001

pT: primary tumor; pN: regional lymph node; CI: confidence interval.

tumor (P=0.014), pN-stage of the disease (P<0.001), and postoperative chemotherapy rate (P=0.001) achieved independent predictive status (**Table 6**).

Kaplan-Meier survival analysis showed that all patients diagnosed with metachronous metastasis have a median DSS of 18.20 ± 0.96 (**Figure 2**). Stratified by the metastatic locations, median DSS was 19.20 ± 1.197 months in patients with simple liver metastasis, 22.30 ± 1.12 months in patients with simple lung metastasis, and 12.20 ± 1.22 months in patients with both liver and lung metastases. It was well demonstrated that patients with metachronous liver and lung metastases had significantly shorter DSS than the other two groups (P<0.001).

Outcomes of synchronous vs. metachronous

Finally, we compared survival difference between synchronous metastasis group and metachronous metastasis group (**Figure 3**). It was shown that the DSS in metachronous metastasis group was significantly shorter than the DSS in synchronous metastasis group (18.20 ± 0.96 vs. 20.27 ± 0.78; P=0.003). The proportions of patients in the synchronous metastasis group and metachronous metastasis group were 18.4% and 11.7%, respectively, after five years.

Discussion

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2009, an estimated 106,100 new cases of colon cancer and approximately 40,870 cases of rectal cancer occurred [11]. Of these cases, 19% present with stage IV disease. CRC metastases are most commonly found in the liver; lung is the second most common site. Although significant improvements have been made in the TNM staging system for CRC, the current TNM staging fails to consider the different outcome among metastasis locations and the time of metastases. In the 7 th AJCC staging manual, M1 disease is now dichotomized into M1a and M1b according to whether metastasis is confined to one or more organ(s)/site(s). Thus, we hypothesized that the outcome of patients with mCRC may vary and should be further classified according to the different metastasis locations and the time of metastases.

Based on this idea, we analyzed the prognosis between colorectal liver metastases and colorectal lung metastases. First, in patients with synchronous metastasis, the site of first metastasis was the liver in 77.2% of patients, the lung in 9.9%, and both simultaneously in 12.9%. Multivariate analysis did not identify distant metastasis location was a statistically significant factor affecting survival but did iden-

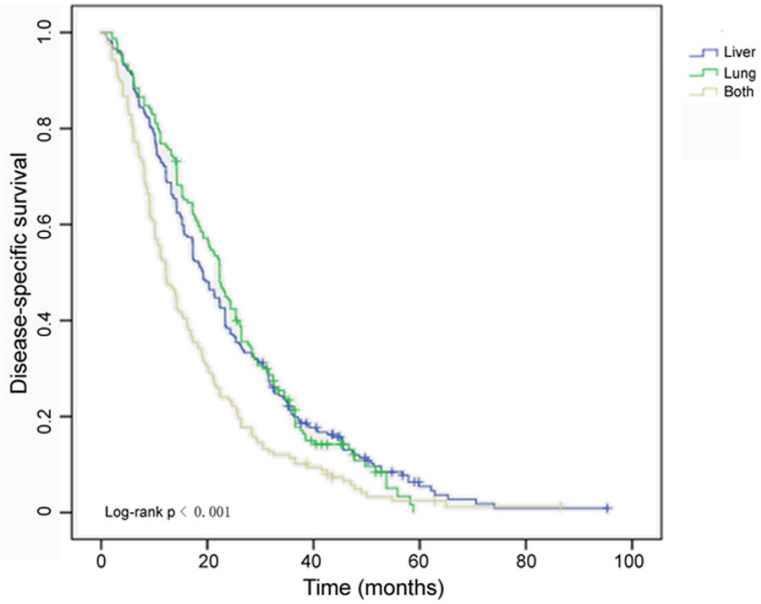

Figure 2. The Kaplan-Meier analysis demonstrates disease-specific survival and recurrence related survival in patients with mCRC in the metachronous metastases population (n=559).

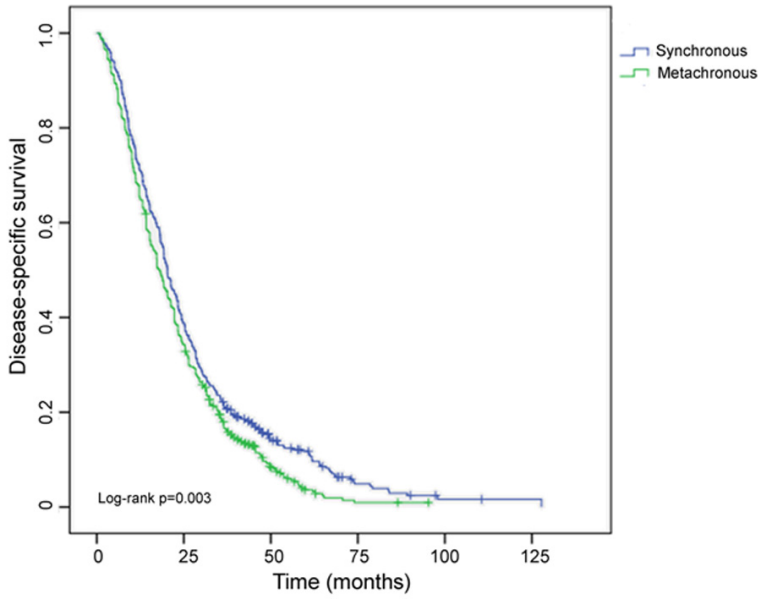

Figure 3. Subtype analysis was conducted between disease-specific survival in synchronous metastases and recurrence related survival in metachronous metastases.

tify the pN-stage was a significant prognostic factor determining the survival, which was consistent with our previous findings [12]. The survival difference among liver metastasis group, lung metastasis group and liver plus lung metastasis was not statistically significant, however, there was an obvious tendency that CRC patients with synchronous lung metastasis had the longest DSS and the CRC patients with both liver and lung metastasis had the shortest DSS. Second, in patients with metachronous metastasis, initial recurrence patterns included the following: liver only in 237 patients (42.4%), lung only in 164 (29.3%), and both sites in 158 (28.3%). On multivariate analysis distant metastasis was the strongest independent favorable prognostic factor ($P<0.001$). Furthermore, the outcomes were significantly better in patients with liver or lung metastasis than in those with liver and lung metastases. In this study, the difference between the simple liver and simple lung metachronous metastasis was not significantly different. But as we all know the prognosis of patients with liver metastasis worse than patients with lung metastasis in both metachronous and synchronous that has been confirmed in the previous articles. Finally, we analyzed the outcomes of synchronous and metachronous colorectal metastases. When comparing DSS of synchronous metastasis group with that of metachronous metastasis group, patients with synchronous metastasis had a better prognosis than those with metachronous metastasis. We regard that the comparison between DSS of synchronous metastasis group and DSS of metachronous metastasis group is a novel idea in our experiment for several reasons. First, obviously longer DSS in synchronous metastasis group than metachronous metastasis group might influence the surgical intervention for patients with metachronous metastasis. Second, the rela-

tively shorter DSS of metachronous metastasis group than DSS of synchronous metastasis group indicated that there was potential tumor growth in the disease-free interval as we believed that there was no difference of tumor growth velocity between synchronous and metachronous metastasis. Finally, comparison between DSS of metachronous metastasis group and DSS of synchronous metastasis group could help us further stratify the patients and have more precise prognostic information about mCRC patients.

Thus, we could show that distant location is a strong predictor of survival in patients with metachronous metastasis. Furthermore, patients with detected liver or lung metastases from a colorectal primary had better survival than the simultaneous detection of both metastases. However, in the two simple metastasis groups, the metastasis location did not have significantly predictive effects for the prognosis. Moreover, patients with synchronous metastasis had a better prognosis than those with metachronous metastasis, which might be partially attributed to differences in the rate of radical resection and the rate of chemotherapy between the two groups. There was another point we got from our study that the mean follow-up period and DSS were longer in patients with synchronous lung metastasis than synchronous liver metastasis but without statistical significance. The lack of statistical significance in the synchronous metastasis group might be partially attributed to the difference of the postoperative treatment. However, the exact cause should be further detected. To confirm our results, we reviewed the published reports about the outcomes of stage IV CRC patients. Few articles are focused on the prognostic impact of distant locations [13-15]. Kobayashi *et al.* used a prognostic scoring system to predict survival of stage IV CRC patients which including the different locations of metastasis. Our idea was similar to the article; however, we only focus on the metastasis location. Combined with the findings of the current studies, we regard that our findings have our own merits. First, recent consensus recommends that if the metastatic tumor is resectable no matter where it locates. Surgical resection is recommended for improving the overall survival [16]. However, guidelines for stage IV CRC recommend the use of chemotherapy or palliative care for this group without resection of an asymptomatic primary tumor [17, 18]. Facing the socioeconomic factors, refined classification of stage IV CRC patients that distinguish patients who would benefit from surgical intervention and who would not be important for planning a treatment strategy. Our study further stratified the mCRC patients according to the metastatic locations and would help a lot to classify the mCRC patients more detailedly. Second, TNM staging of mCRC, which classifies the patients only according to the M0, M1, and M2 stage, may be overly simplistic. The TNM-based staging of stage IV CRC should incorporate the specific organ involvement. In other words, we also consider that distant location could give an indication for the prognosis in stage IV colorectal cancer, which should be given more consideration in novel prognostic schemes devised for patients with mCRC. But, we must mention that one weakness in our material is the relatively small number of patients and that the study is retrospective. We believe this to be well compensated by the fact that the material is unselected and population based. Moreover, all patients were included, registered and treated using the same guidelines. We also admitted that we were not able to obtain detailed information on postoperative chemotherapy (drugs, dosages, time of application, etc.). Another weakness is our economic status restricts the regulatory and procedural treatment. The third weakness was the exclusion of patients who received neoadjuvant therapy. Neoadjuvant chemotherapy was used only for the recent years and the long time span of our study could not tolerate the influence of neoadjuvant therapy on the status of organ metastasis. In future studies, we may be able to choose all patients with neoadjuvant chemotherapy to study the prognostic significance of different organ metastasis.

In conclusion, the current study represented the complete analysis for prognostic significance of different metastatic organ locations in patients with synchronous or metachronous mCRC who are treated with primary tumor control. Our analysis of prognostic variables demonstrated that different metastatic organ locations (liver, lung vs. both liver and lung) and the time of metastases can discriminate between poor and favorable-risk mCRC patients. It is interesting to note that different metastatic

organ locations and the time of metastases increased the accuracy of pM grade to predict cancer-specific mortality. Unfortunately, virtually TNM staging scheme does not consider the role of different metastatic organ locations and the time of metastases for risk stratification of surgically managed mCRC patients. Consequently, different metastatic organ locations and the time of metastases warrant consideration in future prognostic schemes.

Disclosure of conflict of interest

None.

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