

Pattern of relapse after curative surgery for metastatic colorectal cancer

Jau-Jie You, MD, Hong-Chang Chen, MD, Hung-Jen Chen, MD, Ching-Shui Hsieh, MD, Mei-Chuan Chang, MD, Jui-Hung Yu, MD, Yao-Li Chen, MD, Cheng-Shyong Chang, MD.

ABSTRACT

الأهداف: دراسة نسبة انتكاس المرض بعد إجراء العملية الجراحية العلاجية للمرضى المصابين بالسرطان القولوني المستقيمي المنتشر، بالإضافة إلى معرفة إمكانية إيقاف العلاج الكيميائي نهائياً.

الطريقة: أُجريت هذه الدراسة في مستشفى شانغ هوا، شانغ هوا، تايوان حيث قمنا باسترجاع بيانات المرضى المصابين بالمرحلة الرابعة من السرطان القولوني المستقيمي المنتشر والذين خضعوا للعملية الجراحية العلاجية خلال الفترة من يناير 1999م إلى ديسمبر 2009م. لقد قمنا بتحليل العوامل المؤثرة على نسبة وأتماط انتكاس المرض باستخدام الانحدار اللوجستي، فيما حُللت العوامل المؤثرة على معدل النجاة العام باستخدام نسب الخطر المناسبة لكوكس. وقد لجئنا إلى اختياري كابلان مير ولوغ رانك من أجل تقييم العلاقة بين العوامل التي قمنا باستخراجها ومعدل النجاة العام.

النتائج: شملت الدراسة 132 مريضاً، وقد عانى منهم 94 مريضاً (71.2%) من انتكاس المرض. أشارت نتائج الدراسة إلى أن عدد الانتكاسات قد وصل إلى الذروة بين الشهر 3 إلى 6، ولقد أثر حدوث هذه الانتكاسات تأثيراً سلبياً على معدل النجاة العام حيث وصلت نسبة الخطر إلى 0.36 (95% CI: 0.01-0.26). وكانت نتائج المرض سيئة (العدد=25) عند انتكاسه بعد 6 أشهر من استئصال النقائل ($p<0.001$). وكان معدل النجاة العام أفضل عند عدم انتكاس المرض خلال 28 شهراً من إجراء العملية الجراحية ($p<0.001$).

خاتمة: أثبتت الدراسة بأن انتكاس المرض بعد إجراء العملية الجراحية بفترة قصيرة يؤثر سلباً على نتائج المرض وتشخيصه. ولقد تأكدنا من خلال بحثنا هذا بأن عدم انتكاس المرض خلال 28 شهراً بعد إجراء العملية يؤدي إلى تحسّن فرص المرضى في النجاة.

Objectives: To investigate patterns in the relapse frequency after curative surgical intervention, with the intention of determining the feasibility of a complete holiday from chemotherapy for metastatic colorectal cancer (mCRC) patients.

Methods: Patients with stage IV mCRC who received curative surgical intervention between January 1999

and December 2009 at Changhua Christian Hospital, Changhua, Taiwan were investigated retrospectively. Factors influencing the frequency and pattern of relapse were analyzed by logistic regression. Factors influencing overall survival (OS) were analyzed with Cox proportional hazard ratios. Significant factors were extracted and relationships to OS were evaluated by Kaplan-Meier with Log-Rank test.

Results: One hundred and thirty-two patients were included in the study in which 94 (71.2%) suffered from relapse. The number of relapses peaked between 3 and 6 months. The incidence of relapse and Disease-free survival had a negative influence on OS, with a hazard ratio (HR) of 0.36 (95% CI: 0.01-0.26) and 0.93 (95% CI: 0.90-0.95). The prognosis was significantly worse when the relapse (n=25) occurred within 6 months after metastectomy ($p<0.001$). Patients exhibited significantly better long-term OS if the relapse does not occur within 28 months after surgery ($p<0.001$).

Conclusions: Early relapse indicated a worse prognosis. We determined that if mCRC patients remain cancer-free for 28 months after curative surgery, their chance of long-term survival is significantly better.

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From the Division of Colorectal Surgery, Department of Surgery (You, Chen HC), Division of Trauma Surgery, Department of Emergency Medicine (Hsieh), Transplantation Center (Chen YL), Division of Hematology-Oncology, Department of Internal Medicine (Chang CS), Changhua Christian Hospital, Changhua, Division of Chest Medicine, Department of Internal Medicine (Chen HJ), China Medical University Hospital, Taichung, Department of Nursing (Chang MC), Tzuchi College of Technology, and the Department of Public Health (Yu), Tzuchi University, Hualien, Taiwan.

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Address correspondence and reprint request to: Dr. Cheng-Shyong Chang, Division of Hematology-Oncology, Department of Internal Medicine, Changhua Christian Hospital, 135 Nanshiao Street, Changhua 500, Taiwan. Tel. +886 47238595 Ext. 1940. Fax. +886 47200931. E-mail: 15120@cch.org.tw

Metastatic colorectal cancer (mCRC) is treated as a systemic disease, and the integration of effective systemic therapies has played a vital role in the management of metastatic colorectal cancer over the past decades.¹ Multi-modular surgical intervention coupled with modern chemotherapy has improved the survival of mCRC.¹⁻³ Survival rates of mCRC have dramatically increased since 1990. Currently, the median overall survival (OS) is 29.2 months, compared with only 14.2 months in 1990.⁴ Although OS has improved, most patients still suffer from relapse leading to death.⁵ Conversely, a number of patients remain disease-free for a long period of time after surgery, followed by chemotherapy and/or radiotherapy.⁶⁻⁸ The precise factors affecting relapse or long-term survival of the patients have yet been identified. This aims of the study was to, first, assess the predictive factors associated with the relapse and progression of the disease. Secondly, the period of time needed before safely discontinue treatment and refer patients as long-term survivors or cure cases is estimated.

Methods. Records of patients with colorectal adenocarcinoma from the Cancer Registry of Tumor Center, the Coding Division of the Medical Records Department, and the Information Systems Department were retrieved at Changhua Christian Hospital, Changhua, Taiwan. Patients with stage IV mCRC who received histological margin uninvolved en-bloc resection for distal metastatic site, with no residual tumors in other sites, or pathologically confirmed R0 resections between January 1999 and December 2009 were included. Patients with residual tumors noted after surgery were not included. Cases of pulmonary wedge-resection that had not been examined by positron emission tomography (PET) or bone scan before surgery was also excluded. Radio frequency ablation (RFA) was considered effective for tumorectomy in cases of a single metastasis in the liver.^{9,10}

This study was approved by the Institutional Review Board of Changhua Christian Hospital and conducted in compliance with the ethical principles for medical research involving human subjects of Helsinki Declaration. Written informed consent was waived due to the retrospective nature of the investigation. Relapse is defined as a local recurrence or new metastatic lesion. Disease-free survival (DFS) is defined as the time from curative surgery to first relapse. Overall survival (OS) was defined as the time from treatment to death of any cause. For patients who received repeated curative surgery, we limited our analysis to only include the outcome of the first surgery.

Data analyses were performed using SPSS® Version 13.0 and Excel® 2000. Descriptive statistics (frequency,

percentage, mean, and 95% confidence interval (CI)) were used to describe the distributions of demographic data. Logistic regression and Cox proportional hazard ratios were used to determine factors associated with relapse events and survival. The relationship to progression was analyzed, with a Chi-square test, the Student's-t test, and Kaplan-Meier with Log-Rank test. The differences were considered significant if the calculated probability value was less than 0.05.

Results. One hundred and thirty-two patients were selected (Table 1). During the follow-up period, 17 patients received 2 surgical interventions or RFA for the metastatic site, 4 patients received 3 interventions, and 2 patients received 4. The remaining patients received only one surgical intervention. In this study, we analyzed only the first relapse after the first surgery to avoid double-counting. The mean follow-up time counting from colorectal cancer diagnosis was 45.6 months (95% CI: 40.7-50.5). The median OS was 38.8 months (95% CI: 36.1-42.5). The median DFS was 13.6 months (95% CI: 11.0-16.1). Primary colorectal cancer totaled 79 (59.8%) in the colon, and 53 (40.2%) in the rectum. For procedures on metastatic site, 5 involved RFA, one port-site recurrent excision, 8 proctocolectomies concurrent with mesentery metastatic excision, 3 oophorectomies, 4 oophorectomies with proctocolectomies, 14 proctocolectomies with liver resection, 3 excision of intra-abdominal or pelvic tumor recurrent with bowel resection, one concurrent liver and lung resection, one combined lung, liver resection and abdominal-perineal resection, and 22 lung and 70 liver surgical procedures which included wedge resection or lobectomies. Among them, 23 (17.4%) patients received concurrent primary site and metastatic site resection. The average time for chemotherapy after first curative metastasectomy was 6.5 months (95% CI: 5.3-7.6) (Table 1). Most patients accepted first-line chemotherapy under National Comprehensive Cancer Network (NCCN) guidelines and institutional consensus. Twenty patients (15.15%) did not receive chemotherapy after first metastasectomy, and reviewing their medical records indicated that the reason for this was either patients' own refusal of treatment; surgical complications; or that they were suffering from co-morbidity.

Relapse pattern, long-term survival. Thirty-eight (28.8%) patients had no evidence of relapse during follow up (Table 1). Of the relapsed patients, 51 (38.6%) suffered from recurrent in the same organs, 25 (19%) noted new metastatic lesions without evidence of recurrence in the primary metastatic operative site, and 18 (13.6%) exhibited multiple distal metastasis. Our data showed 17 long-term surviving patients, 14 of whom were disease-free more than 5 years after curative

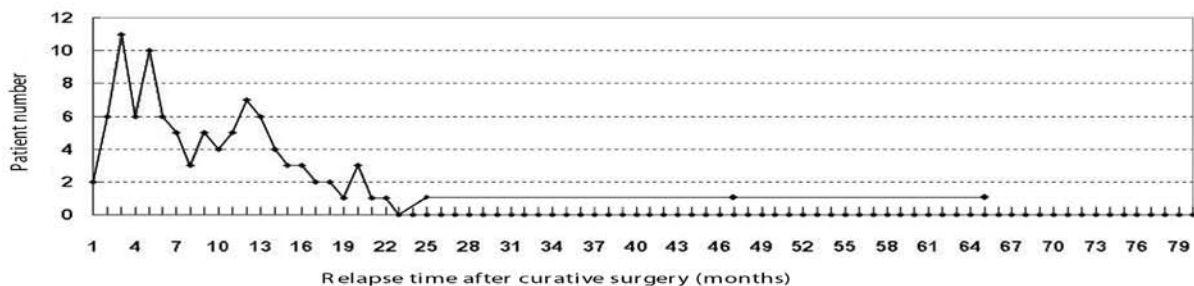
Table 1 - Patient characteristics.

Items	N	(%)	Mean (95% CI)
Gender			
Male	75	(56.8)	-
Female	57	(43.2)	-
Age (years old)			60.2 (57.9-62.5)
Follow-up time (months)			45.6 (40.7-50.5)
Primary tumor site			
Colon	79	(59.8)	-
Rectum	53	(40.2)	-
Initial diagnosis stage			
I-III	67	(50.8)	-
IV	65	(49.2)	-
Primary & metastatic site concurrent surgery			
Yes	23	(17.4)	-
No	109	(82.6)	-
Surgical site			
Lung	22	(16.7)	-
Lung+Liver	1	(0.8)	-
Lung+Liver+Colorectum	1	(0.8)	-
Radio frequency ablation	5	(3.8)	-
Liver	70	(53.1)	-
Live+Colorectum	14	(10.6)	-
Port-site (abdominal wall)	1	(0.8)	-
Intra-abdomen/Pelvis	3	(2.3)	-
Colorectum with peritoneum	8	(6.1)	-
Ovary	4	(3.0)	-
Ovary+Colorectum	3	(2.3)	-
Chemotherapy period, after first metastectomy and before 1 st relapse (months)	112	(84.8)	6.5 (5.3-7.6)
Relapse, after first metastectomy			
Yes, in the same organ	51	(38.6)	-
Yes, in others	43	(32.6)	-
No	38	(28.8)	-
Disease Free Survival (months, median (95% CI))			13.6 (11.0-16.1)
Times of curative metastectomy operations			
1 time	109	(82.6)	-
2 times	17	(12.9)	-
3 times	4	(3.0)	-
4 times	2	(1.5)	-
Total chemotherapy periods of stage IV treatment (months)			11.23 (9.41-13.05)
Overall Survival (months, median (95% CI))			38.8 (36.1-42.5)

surgery of mCRC. Three patients relapsed at 40, 55, and 72 months after curative surgery (Figure 1). During the same period, 18, 12, and 8 patients were followed, respectively. These 3 patients accepted segmentectomy for liver metastasis, at the ages of 25, 48, and 65 year-old. They received irinotecan-based and fluorouracil (5FU)-based chemotherapy after surgery, for one year or half a year. They were later diagnosed with distal metastasis of lung or peritoneal carcinomatosis.

Relapse risk. To measure the risk of relapse, univariate factor analysis with logistic regression was used. A serum carcino-embryonic antigen (CEA) concentration greater than 5 ng/ml correlated positively with relapse ($p=0.005$, odds ratio (OR) = 4.6 (95% CI 1.6-13.9); (Table 2). No other factors (including gender, age, initial colorectal cancer site and staging, tumor differentiation, extra-hepatic metastatic, concurrent surgery, and post-metastectomy chemotherapy) were statistically associated with relapse in our data set.

The factors influencing overall survival. To evaluate the factors influencing OS, the Cox regression model was used, and the results are shown in Table 3. Relapse and DFS had statistically significant negative influence on OS ($p<0.001$), with a hazard ratio (HR) of 0.36 (95% CI: 0.01-0.26) and 0.93 (95% CI: 0.90-0.95), respectively. As relapse events and DFS influenced OS, the time to relapse was used to differentiate those patients. We determined a long-term survival watershed of 28 months. If the relapse did not occur within 28 months after surgery, patients appeared to be long-term survivors ($p<0.001$; Figure 2). Reviewing the data of 17 patients, the treatment duration of first-line chemotherapy was 10.9 (95% CI: 4.6-17.3) months, and the total duration of chemotherapy treatment was 12.6 (95% CI: 5.7-19.5) months. The 13 female and 4 male included 16 liver and one ovary metastasis. Among them, 11 patients survived longer than 5 years, and all were liver metastasis cases. The DFS was 68.0 months (95% CI: 56.4-79.6). Because the peak relapse period occurred within 6 months of surgery, we compared OS of patients with relapses occurring more than 6

**Figure 1** - The numbers of patients and time until relapse, after first curative metastectomy. Briefly, the time to relapse is represented along the X-axis, and the number of patients is recorded along the Y-axis. Most relapses occurred within 28 months. The peak was between 3 and 6 months.

months with those of less than and equal to 6 months after curative surgery. The patients who relapsed early had a median OS of only 16.9 months (95% CI: 9.3-24.5), showing a poorer OS with significant difference ($p < 0.001$; Figure 3).

Discussion. Although approximately 1% of patients with mCRC can be cured with leucovorin and 5FU-based chemotherapy.^{7,8} Metastatic disease is generally considered “systemic, and impossible to cure”, despite advances such as multi-modular invasive treatment and modern chemotherapy.² Based on linear regression analysis from 39 clinical trials, Tang et al reported that progress-free survival (PFS) may be an appropriated surrogate for OS in first line chemotherapy.¹¹ Similarly, we found that relapse and DFS had statistically significant negative influence on OS (Table 3). Early failure in first line chemotherapy resulted in early relapse indicates rapid tumor regrowth, chemo-resistance, and poor prognosis.¹²⁻¹⁴

Table 2 - Univariate analysis with relapse as dependent variable.

Variables	Patients n (%)	P-value	Odds ratio
Gender		0.87	0.94 (0.44-2.00)
Female	57 (43.2)		
Male	75 (56.8)		
Age			
<40 yr	9 (6.8)	1.0	1.01 (0.4-2.55)
40-65 yr	76 (57.6)		
>65 yr	47 (35.6)	0.28	2.91 (0.23-2.53)
Initial cancer site		0.87	1.06 (0.5-2.23)
Colon	67 (50.8)		
Rectum	65 (49.2)		
Initial cancer staging		0.21	0.61 (0.29-2.31)
I-III	67 (50.8)		
IV	65 (49.2)		
Serum CEA (n=116)		0.005	4.60 (1.6-13.9)
5ng/ml	67 (57.8)		
>5ng/ml	49 (42.2)		
Tumor differentiation (n=120)			
Well	3 (2.5)	0.21	4.8 (0.42-54.97)
Moderate	109 (90.8)	0.11	14.0 (0.58-338.78)
Poor	8 (6.7)		
Metastatic operative site*			
Liver	89 (67.4)		
Lung	22 (16.7)	0.08	3.22 (0.88-11.75)
Other extra-hepatic	19 (14.4)	0.53	1.42 (0.47-4.33)
2 metastatic organs	2 (1.5)	1.00	
Concurrent surgery in stage IV (n=65)		0.08	0.39 (0.13-1.13)
No	42 (64.6)		
Yes	23 (35.4)		
Post-first metastectomy chemotherapy		0.58	0.74 (0.25-2.18)
No	20 (15.2)		
Yes	112 (84.8)		

CEA- Carcinoembryonic Antigen

Treatment regimens that are more aggressive have been recommended for patients suffering early relapse.¹¹ We compared OS of the 25 relapses within 6 months after metastasectomy with the rest, and the results indicated a statistically significant difference in OS ($p < 0.001$; Figure 3). First line chemotherapy for mCRC has shifted

Table 3 - Cox regression with overall survival.

Variable	Patient N (%)	P-value	Hazard ratio
Gender		0.594	1.15 (0.68-1.95)
Female	57 (43.2)		
Male	75 (56.8)		
Age (years)		0.287	1.91 (0.58-2.65)
<40	9 (6.8)	0.141	
40-65	76 (57.6)		
>65	47 (35.6)		2.48 (0.74-8.30)
Underlying disease			
Diabetes mellitus	15 (11.4)	0.216	1.65 (0.75-3.66)
Hypertension	24 (18.2)	0.83	1.10 (0.47-2.59)
Heart disease	4 (3.0)	0.72	0.70 (0.10-5.07)
Cerebral vascular disease	1 (0.8)	0.68	0.05 (-)
Lung disease	3 (2.3)	0.24	0.05 (0-7.53)
Liver cirrhosis	2 (1.5)	0.39	1.87 (0.45-7.71)
Uremia	2 (1.5)	0.09	5.81 (0.76-44.39)
Other cancers	4 (3.0)	0.84	1.23 (0.17-9.05)
Initial cancer site		0.22	1.39 (0.82-2.34)
Colon	67 (50.8)		
Rectum	65 (49.2)		
Initial cancer staging		0.72	1.10 (0.65-1.86)
I-III	67 (50.8)		
IV	65 (49.2)		
Tumor differentiation (n=120)			
Well	3 (2.5)		
Moderate	109 (90.8)	0.25	3.21 (0.44-23.42)
Poor	8 (6.7)	0.13	5.34 (0.62-46.32)
Metastatic operative site			
Liver	89 (67.4)	0.24	1.51 (0.76-2.98)
Lung	22 (16.7)	0.31	1.44 (0.71-2.93)
Other Extra-hepatic	19 (14.4)	0.69	1.50 (0.20-11.05)
2 organs	2 (1.5)		
Concurrent surgery (n=65)		0.56	0.80 (0.37-1.71)
No	42 (64.6)		
Yes	23 (35.4)		
Surgery after first metastectomy		0.52	0.81 (0.43-1.54)
No	109 (82.6)		
Yes	23 (17.4)		
Total chemotherapy time of stage IV treatment (months, mean (95%CI))	11.23 (9.41-13.05)	0.15	0.98 (0.96-1.01)
DFS after first metastectomy operation (months, median (95% CI))	13.6 (11.0-16.1)	0.001	0.93 (0.90-0.95)
Relapse		0.001	0.36 (0.01-0.26)
No	38 (28.8)		
Yes	94 (71.2)		

Concurrent surgery indicates concurrent primary colorectal cancer and metastectomy operation, CI - Confidence Interval, DFS - Disease-Free Survival

from fluorouracil alone to a combination of cytotoxic regimen and biologics during the past 10 years.¹⁵⁻¹⁷ Additionally, the previous second line or third line chemotherapy regimens were shifted to front line. Our data indicated that peak relapse period occurred within 6 months of surgery and these patients have significantly poor OS. Therefore, the role of first line chemotherapy is crucial in order to avoid early relapse.

Finally, the length of time needed to refer patients as cancer-free or cured cases was estimated. According to our observation, 28 months may be the watershed. If a relapse was not noted within 28 months following curative surgery, patients have a high chance of long-term survival (Figure 2).

The limitations of the present study, primarily related to its retrospective nature and the low number

of cases spanned through different treatments, initial and relapse metastatic sites made it difficult to identify differences in outcomes among the treatment regimens or metastatic sites. Further research along these lines performed in a larger sample size or a more defined and homogenized population, is needed to determine the feasibility of a complete holiday from chemotherapy for mCRC patients.

In summary, we first found that after curative surgery, the highest risk of relapse occurred within 6 months and the relapse correlated significantly with OS. Thus, first-line chemotherapy should contain more aggressive regimens for high-risk patients in order to avoid early relapse. Secondly, if the patients could remain disease-free for more than 28 months, they were more likely to be cancer-free and survive long-term. Thus, 28 months might be considered an optimal time-span for a chemotherapy holiday to avoid the inevitable side effects.

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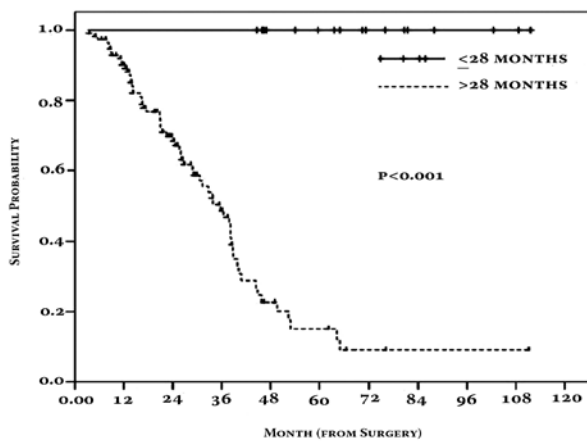


Figure 2 - The Kaplan-Meier plot for overall survival according to difference in relapse time over versus under 28 months after surgery.

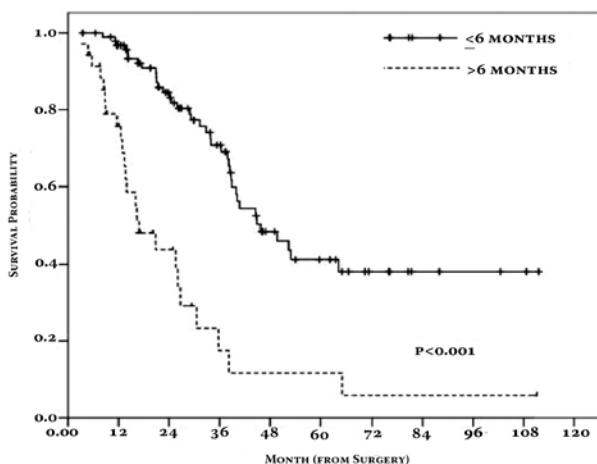


Figure 3 - The Kaplan-Meier plot for overall survival according to difference in relapse time over versus under 6 months after surgery.

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