Original Article

Prognostic Factors of Early Metastasis in Stage III Colorectal Cancer

Ren-Hao Chan
Po-Chuan Chen
Shao-Chieh Lin
Jenq-Chang Lee
Bo-Wen Lin
Division of Colorectal Surgery, Department of Surgery, National Cheng Kung University Hospital, College of Medicine, National ChengKung University, Tainan, Taiwan

Key Words
Metastasis;
Colorectal cancer;
Prognostic factor

Purpose. The metastasis rate of stage III colorectal cancer (CRC) was 30.8%. We noted that few patients had metastasis within 6 months postoperation. We investigatedthe possible prognostic factors and influencesonsurvival.
Methods. We searched the databank ofthe National Cheng Kung University Hospital Cancer Center from May 2004 to December 2011. Initial pathological stage III CRC was identified through a review of medical records. In the metastasis group, we analyzed the perioperative factors and the outcome.
Results. Forty-five patients with initial pathological stage III CRC who developed metastasis were recruited. The mean follow-up duration was 40.3 months. We did not find a significantdifference in the age, sex, primary lesion location, Unionfor International Cancer Control stage, *k-ras* mutant, metastatic lymph node number, lymph node ratio, oradjuvant chemotherapy. In the early metastasis group, patients had a higher postoperativecarcinoembryonic antigen (CEA) level and a smaller CEA reduction after operation. The overall survival and life span after metastasis did not differ significantly.
Conclusion. A higher postoperative serum CEA level and a smaller CEA reduction after operation were the prognostic factors of early metastasis.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2016;27:23-28*]

Colorectal cancer (CRC) is a common malignancy-leading to death in Western countries.[1,2] The same phenomenon was observed in Taiwan.[3] The standard treatment for CRC is radical colectomy. An accurate TNM stage after operation determines the prognosis. In approximately half of patients, metasta siseventually develops and resultsin poor outcomes.[4] We found a small group of patients with pathological stage CRC who had a short period of disease-free survival (i.e. they experienced metastasis early after primary tumor resection). Numerous prognostic factors for distant metastasis were surveyed in a previous study. Preoperative carcinoembryonic antigen (CEA), postoperative CEA, and lymph node ratio (LNR) are established prognostic factors according to a literaturereview.[4-7] The factor that influences the time of metastasis remains unclear. We reviewed the data bank of a single institution and investigated the possible prognostic factor.

Materials and Methods

We searched for initial pathological stage III CRC

Received: May 19, 2015. Accepted: September 16, 2015.
Correspondence to: Dr. Bo-Wen Lin, Division of Colorectal Surgery, Department of Surgery, National Cheng Kung University Hospital, College of Medicine, National ChengKung University, No. 138, Sheng-Li Road, Tainan 704, Taiwan. Tel: (886)-6-235-3535 ext. 5181; Fax: (886)-6-276-6676; E-mail: wen276@gmail.com

patients who developed metastasis from May 2004 to December 2011 inthe databank ofthe National Cheng Kung University Hospital Cancer Center. Among 604 stage III patients, 115 cases were metastatic; 45 patients were excluded because they underwent operations at other hospitals and were referred to our hospital for metastasis treatment, and therefore their perioperative data were missing. A total of 11 patients received emergent operation and lacked adequate preoperative study, and were thus also excluded. We excluded 8 patients who received preoperative neoadjuvant chemoradiation. Of the remaining 51 patients, 6 lacked follow-up data, and were thus also excluded. Finally, 45 patients were enrolled in this study with 17 (37.8%) cases of rectal cancer. Perioperative data included the preoperative CEA level, postoperative CEA level, number of lymph nodes harvested through operation, and number of metastatic lymph nodes. The postoperative CEA level was defined by blood sampling within 6 weeks after operation. All of the patients received preoperative survey including abdominal computed tomography with contrast and colonoscopy to accurately determine the clinical stage. None of them showed evidence of synchronous metastasis before surgery. Radical colectomy was performed and the pathological stage was based on the American Joint Committee on Cancer, 7th edition [8] and Unionfor International Cancer Control. The mean follow-up duration was 40.3 months (range, 7-131 months). All of the patients received postoperative follow-up: physical examination, chest X-ray, and serum CEA every 3 months; abdominal computed tomography with contrast every 6 months; and colonoscopy every year. We reviewed metastatic patients ata multidisciplinary team meeting to ensurethe accuracy of initial staging. The 45 patients were divided into subgroups. Early metastasis was defined as metastatic time less than 6 months after the initial diagnosis. If a patient developed metastasis more than 6 months after the initial diagnosis, we categorizedthe patient into the late metastasis group. Postoperative reduced CEA percentage was defined as the ratio of the postoperative reduced CEA value to the preoperative CEA value. LNR was defined as theratio of positive lymph nodes to the total number of harvested lymph nodes. The cut-off threshold of a high LNR was defined as 75%.

We analyzed the relationship between perioperative data and the time of metastasis. The overall survival and survival time from metastasis were collected and analyzed. We used Fisher's exact test for categorical variables and an independent *t* test for continuous variables. Kaplan-Meier analysis was used for survival curve analysis. All of the afore mentioned analyses were conducted using MedCalc Statistical Software Version 14.12.0 (MedCalc Software bvba, Ostend, Belgium).

Results

A total of 45 patients were enrolled with a mean follow-up duration of 40.3 months. Of these patients, 13 had early metastasis and 32 had late metastasis. There were 23 male patients and 22 female patients with a mean age of 63.8 ± 13.4 years. Of the patients, 9 had a primary lesion located at the right side of the colon, 19 had a primary lesion locatedat the left side, and 17 had rectal cancer. A total of 84.4% (38/45) of the patients received postoperative adjuvant chemotherapy witha main FOLFOX regimen (33/38) for pathological stage III CRC. A total of 7 patients refused adjuvant chemotherapy for personal reasons. The most common metastatic lesionswerein the liver (26/45) and lungs (11/45). No significant difference was observed in the age, sex, and primary tumor lesion between these 2 subgroups. The number of lymph nodes harvested through radical colectomy and the number of metastatic lymph nodesalso showed no significant difference. The LNR mean value also did not differ significantly ($p = 0.2001$). A high LNR was correlated with early metastasisbut no significant difference was observed ($p = 0.0788$). We found that postoperative serum CEA level and CEA change degree after operation differed significantly between the early and late metastasis groups. In the early metastasis group, patients had a higher postoperative serum CEA level and a smaller CEA reduction after operation. The postoperative reduced CEA percentage in the early metastasis group differed significantly compared with the late metastasis group (122.65% vs. -38.18%). All of these

data are summarizedin Table 1. Twenty-two patients had *k-ras* mutation data. No significantdifference in *k*-ras mutant was observed between the early metastatic group (4/7) and late metastatic group (8/15) (p = 1.0000).

A total of 13 patients received metastasectomy, but they did not differ significantlyin survival (p = 0.4666). A total of 34 patients (75.6%) died with a mean survival time of 19.6 months. The cause of death was reviewed and classified into 2 main causes. Disease-related death means a terminal case, and this patient received hospice care. Of these patients, 26 received hospice. The other patients (8/34) died from sepsis. The mean survival time of the early metastasis group was less than that of the late metastasis group (28.7 vs. 45.1 months). However, this datadid not have statistical significance (p = 0.1479). A similar result was found for the life span after metastasis (23.8 vs. 33.9 months, p = 0.359). The Kaplan-Meier survival analysis and survival curve areillustrated in Figs. 1 and 2.

Discussion

Stage III CRC had a 5-year survival rate of 65%. If metastasis occurred, stage IV patients had only a 15% 5-year survival rate, and the recurrence rate of stage III CRC was 30.8%.[9,10] Methods for the early detection of metastasis and for preventing metastasis were studied. Adjuvant chemotherapy plays a crucial role in reducing the risk of metastasis in stage III CRC.[9] Studies on identifying high-risk early metastasis patients are lacking in the literature. We used

Table 1. Characteristics ofthepatients

	Metastatic time ≦ 6 months		Metastatic time > 6 months		*p*-value
Number	13		32		
Gender	Male	7	Male	16	1.0000
	Female	6	Female	16	
Age (year-old)	66.6 ± 10.5		62.7 ± 14.4		0.1893
Primary lesion	Right side	4	Right side	5	0.3292
	Left side	6	Left side	13	
	Rectum	3	Rectum	14	
UICC stage	IIIA	1	IIIA	1	0.7508
	IIIB	5	IIIB	13	
	IIIC	7	IIIC	18	
Adjuvant chemotherapy	12		26		0.6539
Metastatic lesion	Liver	9	Liver	17	0.7401
	Lung	4	Lung	7	
	Para-aortic lymph node	2	Peritoneal seeding	4	
	Peritoneal seeding	1	Local recurrence	3	
	Brain	1	Para-aortic lymph node	3	
			Brain	3	
Lymph node harvest number	19 ± 9.5		18.8 ± 8.3		0.4696
LNR*	0.361 ± 0.280		0.299 ± 0.194		0.2001
Metastatic lymphnode number	6.3 ± 4.5		4.9 ± 3.1		0.1120
High LNR (> 75%)	2		0		0.0788
Pre-operative CEA** (ng/ml)	12.60 ± 12.75		11.92 ± 17.20		0.4489
Post-operative CEA (ng/ml)	20.68 ± 40.72		3.59 ± 4.95		0.0024
CEA decreased %***	122.65 ± 307.90		-38.18 ± 44.67		0.0027

* LNR: lymph node ratio.

** CEA: carcinoembryonic antigen.

*** CEA decreased = (postoperative CEA – preoperative CEA)/preoperative CEA * 100%.

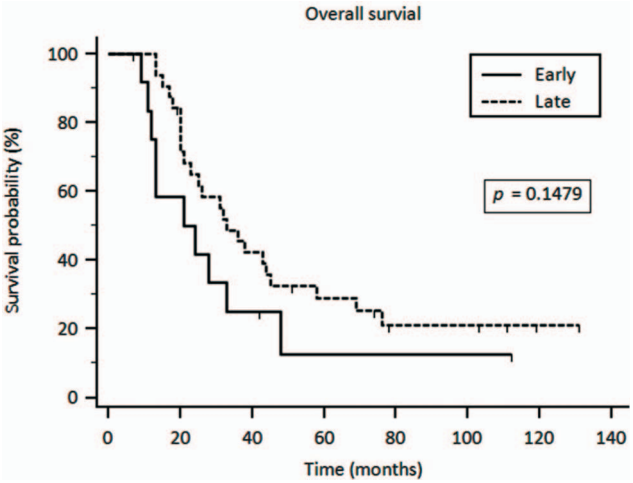

Fig. 1. Overall survival curve. No significant difference was observed between the early metastasis and late metastasis groups.

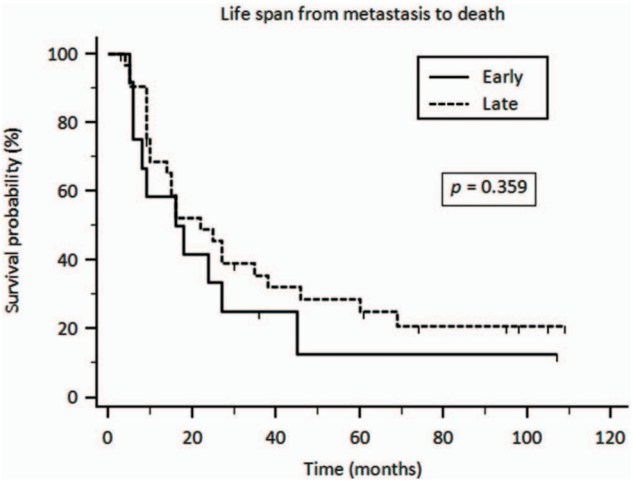

Fig. 2. Life span from metastasis to death did not exhibit a statistical difference between the early metastasisand late metastasis groups.

prognostic factors of stage III CRC to analyze the role of metastatic time.

Preoperative CEA examination is routine for CRC patients. CEA increases in smokers and patients with gastrointestinal tract malignancies. CEA plays a crucial role in the detection of CRC recurrence. The preoperative level was higher in the advanced stage but was less useful than the clinical TNM stage in predicting survival.[11] In 1978, Wanebo et al. found a linear correlation between preoperative CEA levels and the mean recurrence time.[12] Wiratkapun et al. reported a 5-year study in 2001. They found that patients with a preoperative CEA level less than 5 ng/mL had a significantly longer cumulative disease-freesurvival. If the preoperative CEA level was above 15 ng/mL, a higher risk of recurrence was suspected.[5] However, in our series, the preoperative CEA level did not differ significantly ($p = 0.4489$). Even when we used cut-off values of 5 ng/mL and 15 ng/mL, metastatic time did not differ significantly.

Postoperative CEA is typically used for follow-up and as an indicator of recurrence. CEA has a short half-life, and Park et al. hypothesizedthat it reflects the success of surgical treatment. They found that perioperative serum CEA change was a useful prognostic factor for systemic recurrence and survival in patients with stage III rectal cancer.[13] Lin et al. assessed the early postoperative CEA level within 3-4 weeks after surgery and found that a high CEA concentration was an independent prognostic factor for CRC.[4] If the postoperative CEA level was high, the 5-year disease-free survival was only 57.6%. In our series, we found that the early metastasis group hada higher postoperative CEA level. Perioperative CEA change also showed a significant difference between the early and late metastasis groups. Although 84.4% of the patients received postoperative adjuvant chemotherapy, the postoperative CEA played a role in predicting the recurrence time. If patients havea highpostoperative CEA level or a smalldecrease in perioperative CEA values, aggressive follow-up should be arranged to detect early recurrence.

Lymphadenectomy is crucial in curative CRC operation. At least 12 lymph nodes should be harvested for curative intent-to-treat surgery.[14] Adequate lymph node harvesting leads to an accurate N-stage, and it is a crucialprognostic factor. In our series, 86.7% (6/45) of the patients received lymphadenectomy for more than 12 nodes. Kenneth et al. found that the metastatic lymph node status was predictive ofpoor survivalin 256 patients in an 8-year follow-up period for pT1 and pT2 patients.[15] Lymph node harvesting and the metastatic lymph node number are crucial. Is the relationship between tumor-infiltrated nodesand resected lymph nodes (i.e. LNR) a prognostic factor? Berger et al. And Rosenberg et al. reported LNR as a

prognostic factor for CRC.[16,17] Chen et al. used 0.10, 0.25, 0.50, 0.99, and 1.0 as LNR thresholds and found that the metastatic LNR independently estimated survival in stage III CRC.[18] We only used a cut-off value of 0.75 because of the small sample size in the study. The result revealed a trend of correlation with early metastasis but no statistical significance.

We used a different end point: metastatic time. Few studies have had the same objective. Wanebo et al. reported a linear correlation between preoperative CEA levels and the mean recurrence time in 1978.[12] In our series, postoperative CEA level was correlated with metastatic time. A short metastatic time exhibited a trend of poor outcome. The mean life span in early and late metastasis groups was 23.8 and 33.9 months, respectively; however, the *p* value was 0.359. The relationship may be clarified after further data collection.

Limitation

This was a small-scale retrospective study. We excluded many cases because of the lack of data. Additional studies enrolling samples from multiple centers to obtain more cases can yield more accurate results.

Conclusion

Although this was a small-sized study, we still identifiedthe risk factors of early metastasis: postoperative serum CEA leveland a smaller CEA reduction after operation. The early metastasis group exhibited a trend of poor outcome but without statistical significance because of the small sample size.

References

1. Weinberg DS, Schoen RE. Colorectal cancer screening: America'snext top model? *Ann Intern Med* 2012;157:673-4.
2. Patel SS, Floyd A, Doorly MG, Ortega AE, Ault GT, Kaiser AM et al. Current controversies in the managementof colon cancer. *Curr Probl Surg* 2012;49:398-460.
3. Cancer registry annual report, Taiwan, R.O.C. The Department of Health, the Executive Yuan, R.O.C. December 2014.
4. Lin JK, Lin CC, Yang SH, Wang HS, Jiang JK, Lan YT, et al. Early postoperative CEA level is a better prognostic indicator than is preoperative CEA level in predicting prognosis of patients with curable colorectal cancer. *Int J Colorectal Dis* 2011;26:1135-41.
5. Wiratkapun S, Kraemer M, Seow-Choen F, Ho YH, Eu KW. High preoperative serum carcinoembryonic antigen predicts metastatic recurrence in potentially curative colonic cancer: results of a five-year study. *Dis Colon Rectum* 2001;44:231-5.
6. Ceelen W, Van Nieuwenhove Y, Pattyn P. Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. *Ann Surg Oncol* 2010;17:2847-55.
7. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000;124:979-94.
8. American Joint Committee on Cancer. AJCC cancer staging-manual. 7th ed. New York: Springer; 2010.
9. Sebastian Stintzing. Management of colorectal cancer. *F 1000 Prime Rep*. 2014;6:108.
10. Kobayashi H, Mochizuki H, Sugihara K, Morita T, Kotake K, Teramoto T, et al. Characteristics of recurrence and surveillance tools aftercurative resection for colorectal cancer: a multicenter study. *Surgery* 2007;141:67-75.
11. Chapman MA, Buckley D, Henson DB, Armitage NC. Preoperative carcinoembryonic antigen is related to tumorstage and long-term survival in colorectal cancer. *Br J Cancer* 1998; 78:1346-9.
12. Wanebo HJ, Rao B, Pinsky CM, Hoffman RG, Stearns M, Schwartz MK, et al. Preoperativecarcino-embryonic antigen level as a prognostic indicatorin colorectal cancer. *N Engl J Med* 1978;299:448-51.
13. Park YA, Lee KY, Kim NK, Baik SH, Sohn SK, Cho CW. Prognostic effect ofperioperative change of serum carcinoembryonic antigen level: auseful tool for detection of systemic recurrence in rectal cancer. *Ann Surg Oncol* 2006;13:645-50.
14. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colonand rectal cancer surgery. *J Natl Cancer Inst* 2001;93:583-96.
15. Chok, Kenneth SH, Law WL. Prognostic factors affecting survival and recurrence of patientswith pT1 and pT2 colorectalc Cancer. *World J Surg* 2007;31:1485-90.
16. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 2005;23:8706-12.
17. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single-center analysis of 3,026 patients over a 25-year time period. *Ann Surg* 2008; 248:968-78.
18. Chen SL, Steele SR, Eberhardt J, Zhu K, Bilchik A, Stojadinovic A. Lymph node ratio as a quality and prognostic indicator in stage III colon cancer. *Ann Surg* 2011;253:82-7.

原　著

第 III 期大腸直腸癌早期轉移預測因子分析

詹仁豪　陳柏全　林劭潔　李政昌　林博文

國立成功大學附設醫院　外科部　大腸直腸外科

目的　在第 3 期大腸直腸癌患者長期追蹤中，醫學文獻報導的轉移比率為 30.8%。臨床上有少數病人在手術後 6 個月內即發生遠端轉移的情況。我們試圖找出可能影響此現象的因素以及對之後預後的影響。

方法　由成大醫院癌症中心的數據庫中，我們找出一開始病理分期第三期並且手術之後有轉移的病人。分析他們的相關資料試圖找出預測因子。

結果　從 2004 年五月到 2011 年 12 月，在 604 個第 3 期患者當中有 45 例患者被收案，其平均術後追蹤時間為 40.3 個月。我們發現不管是年齡、性別、原發病灶的位置、UICC 分期、*k-ras* 基因突變、轉移淋巴結數目、轉移淋巴結比率或術後輔助化療都對轉移時間都沒有影響。但是在早期轉移的病人中，患者有較高的術後癌胚胎抗原 (CEA) 數值以及術後較少癌胚胎抗原下降幅度。是否早期轉移在存活期間和轉移後的生存時間並無統計上的差異。

結論　我們發現較高的術後癌胚胎抗原數值以及術後癌胚胎抗原較少降低幅度均是早期轉移的預測因子。

關鍵詞　轉移、大腸直腸癌、預測因子。