Original Article

Significant Clinicopathological Factors for Distant Metastasis of Stage II Colorectal Cancer Patients with Adequate Lymph Node Retrieval and Radical Resection

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Introduction. The aim of the present study was to determine which aspects of tumor histology and clinical features would influence postoperative distant metastasis after radical resection of stage II colorectal cancer (CRC) patients with adequate retrieval of lymph nodes.
Materials and Methods. Data was collected for 296 patients with stage II CRC who had radical resection at a single institution between January 2006 and October 2013. All the enrolled patients were followed up on until death or until December 2014. Clinicopathological factors affecting postoperative distant metastases were analyzed.
Results. Tumor location in the rectum ($p = 0.001$), vascular invasion ($p < 0.0001$), perineural invasion ($p = 0.004$), preoperative serum carcinoembryonic antigen (CEA) level ($p < 0.0001$), and postoperative serum CEA level ($p < 0.0001$) were significant for postoperative distant metastases by a univariate analysis. Using a multivariate analysis, tumor location ($p = 0.007$), vascular invasion ($p = 0.030$), perineural invasion ($p = 0.048$) and postoperative serum CEA level ($p < 0.0001$) were found to be independent predictors for postoperative distant metastases.
Discussion and Conclusions. This current study indicated that tumor location, vascular invasion, perineural invasion and postoperative serum CEA level significantly affected the postoperative distant metastasis of stage II CRC patients following adequate lymph-node retrieval and radical resection.
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Key Words
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Colorectal cancer (CRC) is the most common cancer and the third leading cause of cancer death in Taiwan.[1] Treatment decisions and estimates of patient prognosis are largely based on assessments of tumor stage according to the tumor-node-metastasis (TNM) system. Overall, between 30% and 40% of CRC cases are classified as stage II CRC.[2] However, patients with stage II CRC pose a significant therapeutic management problem. Considerable controversy exists regarding the role of adjuvant chemotherapy in such cases. At the same time, approximately 20-25% of stage II CRC patients who undergo radical resection will ultimately develop distant metastasis to the liver or lungs associated with a poor prognosis.[3] It is necessary to accurately stratify stage II CRC to identify those patients with high risk of distant metastases, and to prolong such patients' survival by intensive postoperative surveillance and adjuvant therapy.

Michael et al.[4] claimed that time from initial treatment to recurrence was strongly related to survival following recurrence in patients with recurrent colon cancer. Qiu et al.[5] demonstrated that knowledge of these differences in metastatic patterns may help to better guide pre-treatment evaluation of CRC patients, especially in making determinations regarding curative-intent interventions. Metastases, rather than primary tumors, are responsible for most cancer deaths.[6] Clinicopathological factors such as vascular invasion, perineural invasion, and postoperative serum CEA level and molecular markers (circulating tumor cells and vascular endothelial growth factor) are more significant in stage I-III CRC patients.[7-11] Particularly, for stage II CRC, how to identify the risk factors of developing distant metastasis is an important issue.[10,12]

The aim of this study was to determine the parameters that could be used to identify a group with higher risks of postoperative distant metastasis and worse clinical outcome among patients with stage II CRC undergoing radical resection and adequate retrieval of lymph nodes. To clarify this issue, we examined 13 demographic and histopathological characteristics of 296 stage II CRC patients with adequate retrieval of lymph nodes ($\geqq$ 12) to determine which parameters, if any, were predictors of postoperative distant metastasis and prognostic factors of clinical outcome.

Material and Methods

Patient selection and postoperative surveillance

We reviewed 1340 consecutive patients with Union for International Cancer Control (UICC) stage I-III CRC who underwent radical resection at one single institution from January 2006 to October 2013. We excluded patients receiving or who had received neoadjuvant chemotherapy treatment, radiotherapy or chemoradiotherapy, those with surgery-related death, and those lost to follow-up for over one year. A total of 1,167 stage I-III CRC patients were collected in our database. Among these 1,167 patients, 425 stage II CRC patients were surveyed in this study. Pathological lymph node number less than 12, preoperative acute obstruction, and perioperative tumor perforation were also excluded and the remaining 296 patients with adequate retrieval of lymph node ($\geqq$ 12) were enrolled in the study base. All 296 enrolled stage II patients received detailed studies, including laboratory data analyses, colonoscopy, image studies (i.e., abdominal computed tomography [CT], chest X-ray, magnetic resonance imaging [MRI], etc.) before surgery. The clinical stages of these enrolled patients were confirmed by radiologists via abdominal CT, chest X-ray, or MRI. All of the enrolled patients were also followed up on until death or until December 2014. All clinical data were obtained with informed consent from each subject, and the study protocol was approved by the hospital's Institutional Review Board (KMUHIRB-E-20150004).

Postoperative surveillance consisted of a medical history, physical examination, and laboratory studies, including a measurement of serum carcinoembryonic antigen (CEA) level every 3 months. Abdominal sonography was performed every 6 months, and chest radiography or chest CT scan and an abdominal CT scan were performed once a year or as the given patient's clinical condition indicated. The postoperative image diagnosis was also confirmed by radiologists. If the diagnosis of recurrence was controversial, another radiologist would be consulted. The enrolled patients were followed up at 3-month intervals for an initial 2 years and at 6-month intervals thereafter until 5 years. Adjuvant chemotherapy was administered to

patients having high-risk stage II CRC due to one or more of the following conditions: (1) colonic obstruction or perforation; (2) T4 invasive depth; (3) poorly differentiated carcinoma; and (4) vascular invasion.

Pathologic examination

Patients' medical records and original histopathological slides were independently re-evaluated by two investigators with special experience who were blinded to routine diagnoses and patient outcomes. Discrepancies were solved by simultaneous re-examination of the slides by both investigators.

Tumors located from the cecum to proximal of the rectosigmoid junction were defined as colon cancers. Tumors originating from the rectosigmoid junction to anal verge were defined as rectal cancers (International Classification of Disease for Oncology [ICD-O] code C19) and those originating from the rectum (ICD-O code 20) were also considered rectal cancers. Tumor stage was assessed according to the seventh edition of the AJCC/UICC tumor-lymph node-metastasis (TNM) classification.[13] Tumor grading was performed according to World Health Organization guidelines.[14]

Detection of serum CEA level

A 3 ml peripheral blood sample from each of the 296 stage II CRC patients was obtained less than 1 week prior to operation (preoperative) and 4 weeks after operation (postoperative). A previous study analyzed the prognosis after surgery for CRC patients associated with the post- and pre-operative serum CEA level, which obtained peripheral blood samples from patients for postoperative serum CEA measurement on the 30th day after surgery.[15] Serum CEA levels were determined by means of an enzyme immunoassay test kit (Beckman Coulter, Inc., Fullerton CA), with an upper limit of 5 ng/ml defined as normal according to the kit manufacturer.

Definitions of disease-free survival and overall survival

The definition of disease-free survival (DFS) was the length of time after primary surgery during which a patient survived with no sign of CRC. Overall survival (OS) was defined as the time relapsed between primary surgery and death from any cause or until the last follow-up.[16]

Clinicopathological features and postoperative distant metastasis

The clinicopathological features analyzed in this investigation included patient gender, patient age, tumor size, tumor location, tumor invasive depth, vascular invasion, perineural invasion, tumor differentiation grade, tumor histology, pre- and post-operative serum CEA levels, type of surgery and adjuvant chemotherapy. We used these 13 variables to compare the significant relationships between the two groups for distant metastasis versus non-distant metastasis.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 19.0 (SPSS, Inc., Chicago, IL). The clinicopathological characteristics of the two groups were compared using Pearson Chi-square tests, and the association between distant metastasis and clinicopathological variables was evaluated by multivariate analysis using Cox proportional hazard regression. Cox regression coefficients were used to estimate hazard ratios (HR) for each of the independent variables in the model. Patient survival was estimated by the Kaplan-Meier method, and the log rank test was used to determine the difference. A p value of less than 0.05 was considered statistically significant.

Results

Demographics of the enrolled 296 stage II CRC patients with adequate retrieval of lymph nodes ($\geqq$ 12)

The clinical and pathological data for the 296 stage II CRC patients are summarized in Table 1. Data

Table 1. The clinicopathologic features of 296 UICC stage II colorectal cancer patients with radical resection and adequate retrieval of lymph nodes (≧ 12)

Variables	Number (%)
Gender	
Male/Female	165 (55.7)/131 (44.3)
Age (y/o)	
≧ 65/< 65	157 (53.0)/139 (47.0)
Maximum size of tumor (cm)	
≧ 5/< 5	145 (49.0)/151 (51.0)
Tumor location	
Colon/Rectum	239 (80.7)/57 (19.3)
T stage	
T4/T3	14 (4.7)/282 (95.3)
Vascular invasion	
Yes/No	31 (10.5)/265 (89.5)
Perineural invasion	
Yes/No	66 (22.3)/230 (77.7)
Tumor grade	
PD/MD/WD[1]	22 (7.4)/261 (88.2)/13 (4.4)
Tumor histology	
M/A[2]	17 (5.7)/279 (94.3)
Preoperative CEA[3] (ng/ml)	
≧ 5/< 5	99 (33.4)/197 (66.6)
Postoperative CEA[3] (ng/ml)	
≧ 5/< 5	34 (11.5)/262 (88.5)
Type of surgery	
Open/Laparoscopy	252 (85.1)/44 (14.9)
Adjuvant chemotherapy	
No/Yes	167 (56.4)/129 (43.6)

[1]WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; [2]A: Adenocarcinoma; M: Mucinous carcinoma; [3]CEA: Carcinoembryonic antigen.

for 165 men (55.7%) and 131women (44.3%) were recorded. The age ≧ 65 years was 157 (53.0%) and < 65 years was 139 (47.0%). The maximum size of tumor ≧ 5 cm was 145 (49.0%) and < 5 cm was 151 (51.0%). Tumor location of the colon was 239 (80.7%) and for the rectum, was 57 (19.3%). Only 14 patients (4.7%) were classified as having T4 tumor invasion, and 282 as having T3 (95.3%). Thirty-one patients (10.5%) and 66 patients (22.3%) were found to have vascular invasion and perineural invasion respectively. With regard to the differentiation grades of the tumors, 13 (4.4%) were well-differentiated carcinomas, 261 (88.2%) were moderately differentiated carcinomas, and 22 (7.4%) were poorly differentiated carcinomas. The tumor histology showed 17 (5.7%) mucinous carcinomas and 279 (94.3%) adenocarcinomas. The abnormal preoperative serum CEA level was 99 (33.4%) and the abnormal serum postoperative CEA level was 34 (11.5%). Types of surgery were open for 252 (85.1%) and laparoscopy for 44 (14.9%) respectively. One hundred sixty-seven (56.4%) did not receive adjuvant chemotherapy. We followed up on the 296 enrolled patients until December 2014, with a median follow-up period of 42.0 months (range, 12-106 months).

Correlations between clinicopathological features and postoperative distant metastasis

By determining the correlations between postoperative distant metastasis and the clinicopathological features of stage II CRC patients by Chi-square test and Cox regression analysis, we found that there were five clinicopathological features including tumor in the rectum ($p = 0.001$), vascular invasion ($p < 0.0001$), perineural invasion ($p = 0.004$), preoperative serum CEA level ($p < 0.0001$), and postoperative serum CEA level ($p < 0.0001$) to be significant for postoperative distant metastases by univariate analysis. Using multivariate analysis, tumor in the rectum ($p = 0.007$), vascular invasion ($p = 0.030$), perineural invasion ($p = 0.048$) postoperative serum CEA level ($p < 0.0001$) were demonstrated to be independent predictors for postoperative distant metastasis; however, there were no significant differences in terms of gender, age, tumor size, depth of tumor invasion, tumor histology, tumor type, preoperative CEA level and operative method (Table 2).

Meanwhile, we analyzed DFS and OS between distant metastasis and non-distant metastasis groups. For stage II cases, both the DFS and OS were significantly better in the CRC patients without distant metastasis group (both $p < 0.0001$; Figs. 1 and 2).

Discussion

The principal aim of follow-up programs after curative resection of CRC is to improve survival. Distant

Table 2. Correlation between distant metastases and non-distant metastases in 296 UICC stage II colorectal cancer patients with radical resection and adequate retrieval of lymph nodes (≧ 12) as determined via univariate analysis and multivariate analysis

Variables	Distant metastases (n = 47) (%)	Non-distant metastases (n = 249) (%)	Univariate analysis *p*-value	Multivariate analysis	
				HR[1] (95% CI[2])	*p*-value
Gender (M/F[3])	28 (59.6)/19 (40.4)	137 (55.0)/112 (45.0)	0.564	1.413 (0.719-2.776)	0.315
Age (≧ 65/< 65) (years)	25 (53.2)/22 (46.8)	132 (53.0)/117 (47.0)	0.982	1.081 (0.584-2.000)	0.805
Size (≧ 5/< 5) (cm)	26 (55.3)/21 (44.7)	119 (47.8)/130 (52.2)	0.344	0.942 (0.497-1.787)	0.855
Depth (T4/T3)	4 (8.5)/43 (91.5)	10 (4.1)/239 (95.9)	0.183	2.692 (0.892-8.127)	0.079
Location					
Colon/Rectum	30 (63.8)/17 (36.2)	209 (83.9)/40 (16.1)	0.001	2.413 (1.270-4.586)	0.007
Vascular invasion					
Yes/No	13 (27.7)/34 (72.3)	18 (7.2)/231 (92.8)	< 0.0001	2.349 (1.087-5.077)	0.030
Perineural invasion					
Yes/No	18 (38.3)/29 (61.7)	48 (19.3)/201 (80.7)	0.004	2.105 (1.006-4.404)	0.048
Histology					
PD/WD + MD[4]	4 (8.5)/43 (91.5)	18 (7.2)/231 (92.8)	0.759	0.561 (0.096-3.274)	0.521
Type (M/A[5])	3 (6.4)/44 (93.6)	14 (5.6)/235 (94.4)	0.837	2.782 (0.347-22.284)	0.335
Preoperative CEA[6] (ng/ml)					
≧ 5/< 5	28 (59.6)/19 (40.4)	71 (28.5)/178 (71.5)	< 0.0001	1.743 (0.837-3.629)	0.137
Postperative CEA[6] (ng/ml)					
≧ 5/< 5	17 (36.2)/30 (63.8)	17 (6.8)/232 (93.2)	< 0.0001	4.059 (1.918-8.592)	< 0.0001
Type of surgery					
Open/Laparoscopy	37 (78.7)/10 (21.3)	215 (86.3)/34 (13.7)	0.178	0.521 (0.250-1.084)	0.081
Adjuvant chemotherapy					
No/Yes	29 (61.7)/18 (38.3)	138 (55.4)/111 (44.6)	0.426	1.140 (0.635-2.068)	0.650

[1]HR: Hazard ratio; [2]95% CI: 95% Confidence interval; [3]M: Male; F: Female; [4]PD: Poorly differentiated; MD: Moderately differentiated; WD: Well differentiated; [5]M: Mucinous carcinoma; A: Adenocarcinoma; [6]CEA: Carcinoembryonic antigen.

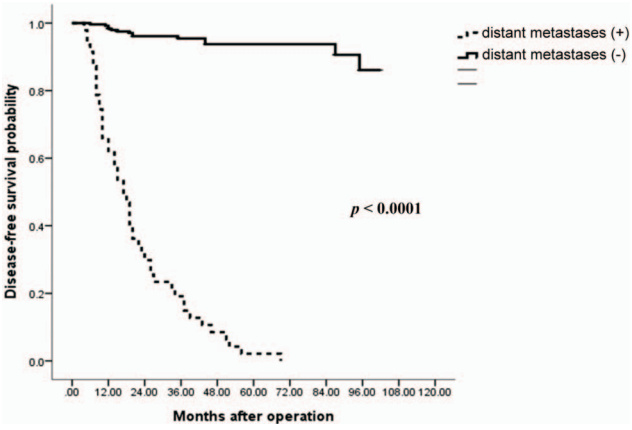

Fig. 1. Cumulative disease-free survival rates for the distant metastasis group and non-distant metastasis group were analyzed using the Kaplan-Meier method with differences compared by a log-rank test. There were no significant differences between the two groups ($p < 0.0001$).

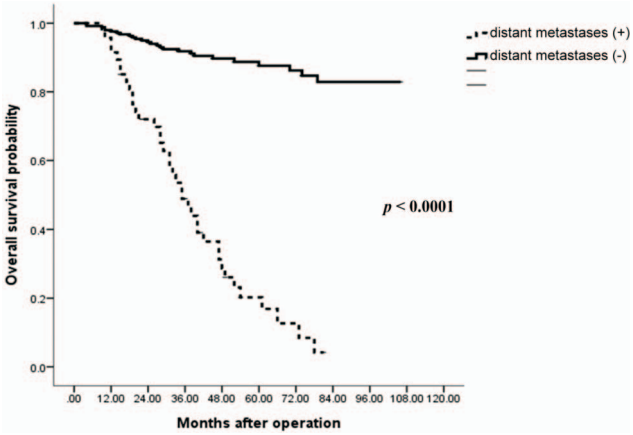

Fig. 2. Cumulative overall survival rates for the distant metastasis group and non-distant metastasis group were analyzed by the Kaplan-Meier method with differences compared by a log-rank test. Patients who exhibited postoperative distant metastasis had significantly worse overall survival rates than those who exhibited postoperative non-distant metastasis ($p < 0.0001$).

metastases from CRC are the leading cause of cancer-related morbidity and mortality.[16] To achieve this goal, patients are screened for distance metastasis. The reasons for our focus on stage II CRC disease are as follows: (1) stage II CRC deserves special attention, because the routine use of adjuvant chemotherapy is not recommended; and (2) stage II CRC poses considerable difficulties in terms of therapeutic strategy.[17] In this study, we only concentrated on stage II CRC patients with radical resection and adequate retrieval of lymph nodes ($\geqq$ 12) and further analyzed the independent factors and clinical outcomes of postoperative distant metastasis. The results of the present study have shown that tumor location, the presence of vascular invasion, the presence of perineural invasion, and a high postoperative serum CEA level were relevant factors of postoperative distant metastasis. Furthermore, we also demonstrated that stage II CRC patients with distant metastasis had poorer DFS and OS.

Räsänen et al.[18] reported that the rates of distant metastasis for rectal cancer patients treated with curative intent ranged between 20-50%. Akagi et al.[19] demonstrated that colon cancer patients with curative surgery had about 10% distant metastasis rates. In our study, the distant metastasis rates of colon cancer and rectal cancer were 12.5% and 29.8% respectively, which are similar to previous studies.[18,19]

Vascular invasion by the primary tumor has been used as a prognostic factor for predicting recurrence.[20-22] In our previous study, we also reported that the presence of vascular invasion might prominently affect the prognosis of stage II CRC patients after radical resection.[23] In the present study, our data show that vascular invasion is again a significant prognostic factor in predicting the postoperative distant metastasis of stage II CRC patients. Several investigators have shown that perineural invasion is a vital prognostic factor in patients with CRC.[24] Fujita et al.[25] reported that the perineural invasion status can be used to facilitate the selection of CRC patients for adjuvant chemotherapy and should be described in routine pathological reports. Our previous study demonstrated that the presence of perineural invasion might lead to postoperative early relapse in either colonic or rectal cancer.[20] In this present observation, perineural invasion was once again a significant factor for prediction of distant metastasis.

CEA is an important tumor marker in the management of CRC. An increased serum CEA level in the follow-up period suggests a probable relapse of the disease. A high preoperative serum CEA value is associated with advanced disease with either locally advanced or distant metastasis.[26,27] The time of postoperative blood sampling for CEA measurement was inconsistent in several previous studies, ranging from 1 to 4 weeks after surgery.[28-30] A previous study analyzed the prognosis after surgery for CRC patients associated with the post-preoperative serum CEA ratio, obtaining peripheral blood samples from patients for postoperative serum CEA measurement on the 30th day after surgery.[15] Yakabe et al. demonstrated that the CEA half-life time was approximately 3-7 days.[32] The adjuvant chemotherapy given in the current study started after one month. Therefore, the peripheral blood samples for postoperative serum CEA measurement were obtained on the 4th week after the surgery, taking into account the previous data, the CEA half-life, and the effects of adjuvant chemotherapy on the postoperative serum CEA concentration. McCall et al.[33] indicated that the diagnosis of recurrent disease for CRC patients may be made several months earlier by investigating the first abnormal serum CEA level.[34] In the present study, the elevated postoperative serum CEA level had a relative risk of 4.059 for distance metastases in comparison with patients without elevated postoperative serum CEA level in stage II CRC patients.

The limitations of this study are that it included a single institute and was also confined to enrolled patients. However, it would be mandatory to analyze clinical data from multiple institutions in order to develop simpler, more sensitive, and specific criteria for detecting patients with a high risk of postoperative distant metastasis and in turn, to improve clinical outcomes.

Conclusion

To the best of our knowledge, this is the first com-

prehensive report on the identification of significant prognostic factors in order to predict the postoperative distant metastasis in stage II CRC patients who underwent curative resection with adequate lymph-node retrieval. We have identified some crucial factors that may influence the postoperative distant metastasis of stage II CRC patients. Certainly, there is a need for large, high-quality, well-designed clinical trials to better define the significant predicting factors of postoperative distant metastasis in stage II CRC patients.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

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原　著

第二期結直腸癌患者經根治性切除及足夠之淋巴結清除後影響遠處轉移之臨床病理因子

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介紹　本研究是確定哪些組織病理與臨床因子會影響第 II 期大腸直腸癌經根治性切除及足夠的淋巴結清除術後的遠端轉移。

方法　我們收集了從 2006 年 1 月到 2013 年 10 月間在單一機構接受治療的 296 例第 II 期大腸直腸癌患者。所有參加試驗的患者皆追蹤至死亡或至 2014 年 12 月。並針對影響術後遠端轉移的臨床病理因子進行了分析。

結果　使用單變數分析發現 5 個病理與臨床因子，腫瘤部位 ($p = 0.001$)，血管侵犯 ($p < 0.0001$)，周邊神經侵犯 ($p = 0.004$) 術前血清癌胚抗原值 ($p < 0.0001$) 和術後血清癌胚抗原值 ($p < 0.0001$)，被認為是術後遠端轉移的獨立預測因子。使用多變量分析發現，腫瘤部位 ($p = 0.007$)，血管侵犯 ($p = 0.030$)，周邊神經侵犯 ($p = 0.048$) 和術後血清癌胚抗原值 ($p < 0.0001$)，被認為是術後遠端轉移的獨立預測因子。

討論與結論　本研究顯示，腫瘤部位、血管侵犯、周邊神經侵犯及術後血清癌胚胎抗原值，顯著影響有淋巴結數目截取足夠的第二期大腸直腸癌患者接受根治性切除手術後的遠端轉移。

關鍵詞　第二期大腸直腸癌、淋巴結數目截取足夠、臨床病理因子、遠處轉移。