Original Article

Risk Factors of Different Tumor Recurrence Pattern in Stage II Colorectal Cancer

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Key Words
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Stage II;
Risk factors of recurrence pattern

Background. Colorectal cancer (CRC) recurrence was estimated around 10%-22.2% in stage II patients. Several clinicopathological features were found to be associated with recurrence. In this study, we attempted to find the risk factors of different tumor recurrence pattern in stage II CRC.
Methods. A prospectively collected database contained 728 stage II CRC patients who underwent curative resection between January 2010 and December 2015. Using Cox's proportional hazards model, we examined the relationship between clinicopathological features and various recurrent patterns.
Results. Tumor recurrence occurred in 77 (10.6%) stage II CRC patients. Conversely, local recurrence only occurred in 9 (1.24%) patients, distant metastasis only occurred in 60 (8.24%), and both local and distant recurrences in 8 (1.10%) patients. In terms of distant metastasis, 17 (2.33%) patients had only lung metastasis and 18 (2.47%) had only liver metastasis. Elevated postoperative CA19-9 ($p = 0.018$), and perineural invasion ($p = 0.025$) were independent risk factors for tumor recurrence. Elevated postoperative CA19-9 ($p = 0.006$) and perineural invasion ($p = 0.004$) were found to be independent risk factors for distant metastasis. Meanwhile, rectal cancer ($p = 0.045$) and elevated postoperative CEA ($p = 0.009$) were found to be independent risk factors for only lung metastasis. Elevated postoperative CA19-9 ($p = 0.010$) and obstruction ($p < 0.001$) were independent risk factors for only liver metastasis.
Conclusions. Elevated postoperative tumor markers (both CA19-9 and CEA), tumor location, perineural invasion, and tumor obstruction are excellent predictors of prognosis in stage II CRC, and patients with these risks factors may benefit from intensive follow-up and adjuvant chemotherapy.

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Colorectal cancer (CRC) is the third most common cancer in the world, accounting for 10% of all cancer incidence.[1] In 2018, CRC was the most common cancer in Taiwan, accounting for 14.2% of total incidence.[2] Previous studies have found that the 5-year recurrence rate in stage I CRC is approximately 3.7%-5%, that in stage II CRC is approximately 10%-22.2%, and that in stage III CRC is approximately 30.8%-33%.[3-6] Moreover, the standard treatment for stage II CRC is surgical resection with lymph node dissection, with adjuvant chemotherapy recommended for patients at a high risk. According to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines, the

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risk factors for stage II CRC include pathological T4 stage, poorly differentiated histology, pathology showing lymphovascular invasion (LVI) or perineural invasion (PNI), inadequate lymph node harvesting (less than 12 lymph nodes), and preoperative bowel obstruction or perforation.[7] Other risk factors mentioned in the literature include tumor location, elevated tumor markers (carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)), infiltrative invasion patterns, mucinous adenocarcinoma, and round cell (lymphocyte) infiltration.[8,9] The risk factors for stage II CRC vary in different studies. The purpose of this study is to clarify the association between different risk factors and different tumor recurrence pattern.

Materials and Methods

Study design

From January 2010 to December 2015, stage II CRC patients who underwent curative resection with lymph node dissection were identified from a prospectively collected database of the Division of Colorectal Surgery, Taipei Veterans General Hospital. A total of 789 patients' medical records were analyzed retrospectively. Patients who received neoadjuvant concurrent chemoradiation therapy (nCCRT) for locally advanced rectal cancer were excluded (n = 61) because such preoperative treatments may have an impact on the analysis of the recurrence pattern.

Patient surveillance

According to Taipei Veterans General Hospital's recommendation, all patients were under surveillance. For the first 2 years, history and physical examination were taken every 3-6 months and then every 6 months for the next 3 years. Tumor markers were checked every 3 months for the first 2 years and then every 6 months for the next 3 years. A chest and abdominal CT scan will be performed every 6 months for 5 years. Colonoscopy should be performed 1 year after surgery or 3-6 months if a preoperative colonoscopy was not performed; it should be repeated every 3 years if no advanced adenoma was detected.

Data collection

Data on clinicopathological factors such as gender, age, elevated tumor marker levels (CEA > 5 ng/ mL and CA19-9 > 37 U/mL) before surgery and early after surgery (1 to 3 months after surgery), and adjuvant chemotherapy were collected. Pathological factors collected include tumor location, preoperative bowel obstruction or perforation, pathological T staging (pT4), differentiation histology, LVI, PNI, inadequate lymph node (LN) harvesting, round cell infiltration, tumor invasion pattern, and mucinous component. Recurrence was defined as a local or distant lesion discovered following curative surgery. Local recurrence was defined as a recurred lesion that was adjacent to the previously treated tumor. Distant recurrence was defined as a recurred lesion that was not the same as the original tumor. The time from surgery to evidence of recurrence from image modalities was defined as recurrence-free survival (RFS). Patients who received oxaliplatin- or fluorouracil-based regimens in oral form for more than 6 months or IV form for more than six courses were defined as having adjuvant chemotherapy.

Statistical analysis

As appropriate, data were expressed as means (± standard deviation) or medians (range). The chi-square test was used to determine statistical significance for categorical variables, and the independent t test was used for continuous variables. Conversely, the Kaplan-Meier method and a log-rank test were used to calculate RFS. The univariate and multivariate Cox's regression tests were used to assess predictors of RFS. If the p-value of risk factors was lower than 0.10 in univariate analysis, it would be analyzed in multivariate analysis. SPSS Ver. 25 (IBM, Chicago) was used to analyze all statistics. A p-value < 0.05 was considered significant.

Results

Initially, 789 patients were gathered, with 61 pa-

tients excluded because they received nCCRT. Finally, 728 patients were enrolled for further analysis (Fig. 1). The typical follow-up period is 54.36 months with a range from 52.23 to 56.49 months.

In a total of 728 patients, 77 (10.6%) patients experienced recurrence within 5 years. Across all clinical and pathological characteristics, only clinical presentation with tumor obstruction ($p = 0.011$) and pathology showing PNI ($p = 0.026$) were significantly associated with tumor recurrence (Table 1). Univariate analysis revealed that an elevated early postoperative CEA level ($p = 0.028$), an elevated early postoperative CA19-9 level ($p = 0.023$), tumor obstruction ($p = 0.012$), and PNI ($p = 0.014$) were significantly associated with 5-year RFS (Table 2). An elevated early postoperative CA19-9 level ($p = 0.018$), and PNI ($p = 0.025$) were found to be independent predictors of 5-year RFS in a multivariate analysis.

Of all patients, 598 (82.1%) had colon cancer and 59 (9.9%) had recurrence (6 local recurrence, 48 distant metastasis, and 5 with both local recurrence and distant metastasis) (Table 3). The remaining 130 patients (17.9%) had rectal cancer, with 18 patients (13.8%) experiencing recurrence (3 local recurrence, 12 distant metastasis, and 3 with both local recurrence and distant metastasis). There were 12 patients (2.01%) with only lung metastasis, and 15 patients (2.51%) with only liver metastasis in colon cancer patients with distant metastasis. In patients with rectal cancer who had distant metastasis, 5 (3.85%) had only lung metastasis, and 3 (2.31%) had only liver metastasis.

To identify the independent factors associated

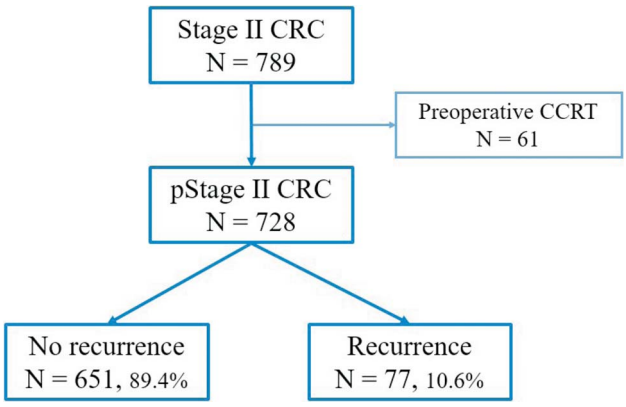

Fig. 1. Flowchart of patient enrollment.

Table 1. Patient demographics and clinicopathological characteristics

Clinicopathological characteristics	No recurrence N = 651	Recurrence N = 77	*p*-value
Age	68.93 (±13.49)	69.52 (±12.29)	0.693
Gender			0.767
Male	403 (61.9%)	49 (63.6%)	
Female	248 (38.1%)	28 (36.4%)	
Tumor location			0.285
Right colon	186 (28.6%)	17 (22.1%)	
Left colon	353 (54.2%)	42 (54.5%)	
Rectum	112 (17.2%)	18 (23.4%)	
CEA > 5 (ng/mL)			
Preoperation	203 (32.3%)	26 (35.1%)	0.626
Postoperation	40 (7.3%)	9 (12.9%)	0.106
CA19-9 > 37 (U/mL)			
Preoperation	89 (14.6%)	14 (18.9%)	0.329
Postoperation	24 (7.2%)	7 (15.9%)	0.106
Obstruction			0.011
No	604 (92.8%)	65 (84.4%)	
Yes	47 (7.2%)	12 (15.6%)	
Perforation			0.370
No	630 (96.8%)	73 (94.8%)	
Yes	21 (3.2%)	4 (5.2%)	
Tumor depth			0.058
T3	532 (81.7%)	56 (72.7%)	
T4	119 (18.3%)	21 (27.3%)	
Lymph node sampling			0.120
< 12	587 (90.2%)	65 (84.4%)	
> 12	64 (9.8%)	12 (15.6%)	
Differentiation			0.207
Good + moderately	611 (93.9%)	75 (97.4%)	
Poorly + undifferentiated	40 (6.1%)	2 (2.6%)	
Lymphovascular invasion			0.134
No	571 (87.7%)	72 (93.5%)	
Yes	80 (12.3%)	5 (6.5%)	
Perineural invasion			0.026
No	605 (92.9%)	66 (85.7%)	
Yes	46 (7.1%)	11 (14.3%)	
Round cell infiltration			0.320
No	482 (74%)	61 (79.2%)	
Yes	169 (26%)	16 (20.8%)	
Infiltrative invasion pattern			0.444
No	99 (15.2%)	9 (11.7%)	
Yes	552 (84.8%)	68 (88.3%)	
Mucinous component			0.947
<50	610 (93.7%)	72 (93.5%)	
>50	41 (6.3%)	5 (6.5%)	
Adjuvant chemotherapy			0.225
No	458 (70.4%)	49 (63.6%)	
Yes	193 (29.6%)	28 (36.4%)	

Table 2. Clinicopathological variables that affect 5-year recurrence-free survival

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor location (colon/rectum)	0.648	0.382-1.100	0.108			
High CEA level (> 5 ng/mL)						
Preoperation	1.228	0.762-1.978	0.400			
Early postoperation	2.189	1.087-4.409	0.028	1.455	0.597-3.549	0.410
High CA19-9 (> 37 U/mL)						
Preoperation	1.532	0.856-2.742	0.151			
Early postoperation	2.561	1.138-5.761	0.023	2.798	1.194-6.556	0.018
Obstruction	2.209	1.193-4.090	0.012	1.455	0.597-3.549	0.212
Perforation	1.465	0.535-4.008	0.457			
Tumor depth (T4/T3)	1.574	0.953-2.600	0.076	1.486	0.782-2.822	0.226
Inadequate lymph node sampling	1.702	0.919-3.152	0.091	1.280	0.451-3.633	0.643
Poor differentiation	0.553	0.136-2.252	0.408			
Lymphovascular invasion	0.496	0.200-1.228	0.130			
Perineural invasion	2.224	1.174-4.211	0.014	2.406	1.114-5.193	0.025
Round cell infiltration	0.729	0.420-1.264	0.260			
Infiltrative invasion pattern	1.155	0.576-2.315	0.685			
Mucinous component > 50%	1.001	0.404-2.478	0.998			
Adjuvant chemotherapy	0.982	0.617-1.563	0.938			

Table 3. Recurrence pattern of local recurrence or distant metastasis

Recurrence or metastasis (n = 77)	Colon cancer (n = 598)	Rectal cancer (n = 130)
Only local recurrence	6 (1.00%)	3 (2.31%)
Only distant metastasis	48 (8.03%)	12 (9.23%)
Only lung metastasis	12 (2.01%)	5 (3.85%)
Only liver metastasis	15 (2.51%)	3 (2.31%)
Only lung and liver metastasis	2 (0.33%)	1 (0.77%)
Liver, lung metastasis with other distant metastasis	6 (1.00%)	0
Other distant metastasis (tumor seeding, brain, bone, lymph nodes)	13 (2.17%)	3 (2.31%)
Local recurrence with distant metastasis	5 (0.84%)	3 (2.31%)
Local recurrence with liver and lung metastasis	1 (0.17%)	0
Local recurrence with lung metastasis	0	1 (0.77%)
Local recurrence with other distant metastasis	4 (0.67%)	2 (1.54%)

with the development of local recurrence and distant metastasis, all clinical and pathological variables were analyzed. There was no independent factor associated with local recurrence (Table 4). For distant metastasis, an elevated early postoperative CA19-9 level (95% CI: 1.430-8.510, $p = 0.006$) and PNI (95% CI: 1.464-7.710, $p = 0.004$) were independent factors (Table 5).

To specifically identify the independent factors of lung metastasis and liver metastasis, the patients with multiple metastases were excluded. Patient with only liver metastasis and patient with only lung metastasis were analyzed. Rectal cancer (95% CI: 0.146-1.014, $p = 0.045$) and an elevated postoperative CEA level (95% CI: 1.453-13.2233, $p = 0.009$) were found to be independent factors associated with only lung metastasis in the subgroup analysis (Table 6). An elevated postoperative CA19-9 level (95% CI: 1.394-12.023, $p = 0.010$) and tumor obstruction (95% CI: 2.378-20.822, $p < 0.001$) were independent factors associated with only liver metastasis (Table 7).

Discussion

The recurrence rate of stage II colorectal cancer varied between studies, ranging from 10% to 22.2%.[3,6]

Table 4. Risk factors of local recurrence

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor location (colon/rectum)	0.403	0.101-1.512	0.199			
High CEA level (> 5 ng/mL)						
Preoperation	2.828	0.759-10.532	0.121			
Early postoperation	1.849	0.231-14.787	0.562			
High CA19-9 (> 37 U/mL)						
Preoperation	1.868	0.388-8.997	0.436			
Early postoperation	22.526	0.00-82.693	0.686			
Obstruction	22.684	0.00-114.324	0.572			
Perforation	3.454	0.432-27.623	0.243			
Tumor depth (T4/T3)	1.217	0.253-0.586	0.806			
Inadequate lymph node sampling	2.611	0.542-12.573	0.232			
Poor differentiation	21.593	0.00-207.410	0.662			
Lymphovascular invasion	1.133	0.142-9.061	0.906			
Perineural invasion	22.430	0.00-184.385	0.590			
Round cell infiltration	1.256	0.261-6.046	0.776			
Infiltrative invasion pattern	1.207	0.151-9.654	0.859			
Mucinous component > 50%	1.837	0.230-14.692	0.566			

Table 5. Risk factors of distant metastasis

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor location (colon/rectum)	0.791	0.420-1.489	0.467			
High CEA level (> 5 ng/mL)						
Preoperation	1.040	0.590-1.834	0.893			
Early postoperation	2.519	1.190-5.332	0.016	1.461	0.534-3.997	0.461
High CA19-9 (> 37 U/mL)						
Preoperation	1.395	0.705-2.762	0.339			
Early postoperation	3.285	1.434-7.525	0.005	3.489	1.430-8.510	0.006
Obstruction	2.691	1.399-5.176	0.003	2.213	0.943-5.195	0.068
Perforation	1.086	0.265-4.445	0.909			
Tumor depth (T4/T3)	1.526	0.861-2.705	0.148			
Inadequate lymph node sampling	1.632	0.803-3.315	0.176			
Poor differentiation	1.396	0.341-5.716	0.643			
Lymphovascular invasion	2.658	0.832-8.486	0.099	3.077	0.725-13.048	0.127
Perineural invasion	2.669	1.353-5.263	0.005	3.360	1.464-7.710	0.004
Round cell infiltration	1.438	0.764-2.707	0.260			
Infiltrative invasion pattern	1.686	0.675-4.211	0.264			
Mucinous component > 50%	2.010	0.491-8.230	0.332			

In our study, the recurrence rate of stage II colorectal cancer was 10.58%, which was similar to that of previous studies. The recurrence rate of colon cancer was 9.87%, whereas the recurrence rate of rectal cancer was 13.85%. The percentage of only lung or only liver metastasis was similar in rectal cancer and colon cancer.

Lin et al. proposed that early postoperative CEA levels were a good predictor of prognosis in CRC.[10] In our study, it was an independent predictor of lung metastasis ($p = 0.005$, log-rank test). Our study also showed that an early postoperative CA19-9 level was a good prognostic indicator of tumor recurrence ($p = 0.018$, log-rank test), distant metastasis ($p = 0.006$,

Table 6. Risk factors of lung metastasis

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor location (colon/rectum)	0.411	0.156-1.083	0.072	0.385	0.146-1.014	0.045
High CEA level (> 5 ng/mL)						
Preoperation	1.476	0.572-3.807	0.421			
Early postoperation	4.234	1.405-12.763	0.010	4.383	1.453-13.223	0.009
High CA19-9 (> 37 U/mL)						
Preoperation	1.522	0.543-4.269	0.425			
Early postoperation	2.099	0.557-7.913	0.274			
Obstruction	2.171	0.633-7.452	0.218			
Perforation	21.004	0.001-112.714	0.617			
Tumor depth (T4/T3)	3.697	0.493-27.699	0.203			
Inadequate lymph node sampling	1.153	0.266-4.990	0.849			
Poor differentiation	21.650	0.002-127.789	0.517			
Lymphovascular invasion	2.545	0.340-19.063	0.363			
Perineural invasion	2.324	0.677-7.978	0.180			
Round cell infiltration	1.665	0.485-5.716	0.418			
Infiltrative invasion pattern	1.206	0.279-5.221	0.802			
Mucinous component > 50%	28.691	0.018-117.167	0.372			

Table 7. Risk factors for liver metastasis

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor location (colon/rectum)	1.157	0.392-3.420	0.792			
High CEA level (> 5 ng/mL)						
Preoperation	1.089	0.423-2.808	0.859			
Early postoperation	1.538	0.359-6.585	0.562			
High CA19-9 (> 37 U/mL)						
Preoperation	1.236	0.453-3.375	0.679			
Early postoperation	4.079	1.415-11.764	0.009	4.094	1.394-12.023	0.010
Obstruction	4.348	1.701-11.111	0.002	7.037	2.378-20.822	< 0.001
Perforation	21.022	0.001-169.326	0.587			
Tumor depth (T4/T3)	1.067	0.361-3.154	0.906			
Inadequate lymph node sampling	1.548	0.458-5.231	0.482			
Poor differentiation	21.658	0.004-362.375	0.485			
Lymphovascular invasion	2.937	0.395-21.833	0.293			
Perineural invasion	2.764	0.935-8.169	0.066	2.575	0.770-8.617	0.125
Round cell infiltration	1.995	0.590-6.742	0.266			
Infiltrative invasion pattern	24.737	0.103-366.330	0.252			
Mucinous component > 50%	28.912	0.003-344.992	0.476			

log-rank), and liver metastasis ($p = 0.010$, log-rank). Park et al. also proposed that an elevated postoperative CA19-9 level was related to peritoneal recurrence, which could provide additional information in predicting recurrence.[11]

In Hansdotter et al. study, they suggested that the independent risk factors for recurrence in colorectal cancer including lymph node positivity, T4 category, rectal cancer, cachexia, and diabetes mellitus.[12] They also suggested daily smoking as an independent risk factor when regarding lifestyle factors. In our study, we discovered elevated postoepration CA19-9 and perineural invasion as independent predictors for recurrence.

Previous studies found that the local recurrence rate in stage II rectal cancer was approximately 4% and the recurrence rate in stage II colon cancer was approximately 2%.[13,14] Rectal cancer had a higher rate of local recurrence than colon cancer. Stipa et al. suggested that tumor location below peritoneal reflection ($p = 0.019$), TNM stage ($p = 0.002$), and adjuvant radiotherapy ($p = 0.05$) were predicting factors for rectal cancer, and poorly differentiated histology ($p = 0.01$) was a predicting factor for colon cancer.[15] In our study, there was no independent predictor of local recurrence. We believe that this was because the majority of our patients had colon cancer (colon cancer, 598; rectal cancer, 130) and our local recurrence rate in stage II CRC was low (colon cancer, 1%; rectal cancer, 2.31%).

According to our findings, lung metastasis occurs more frequently in rectal cancer than in colon cancer (3.85% vs. 2.01%). A previous study suggested that it could be due to the vein flow from the middle and lower rectum directly draining into the systematic venous system, which could cause micrometastasis to the lung without passing through the portal vein system.[16] In the study by Tan et al., lung metastasis was found in 33% of the lower rectal cancer cases but only 17% of the upper rectal or colon cancer cases.[17] In addition, we discovered that rectal cancer and an elevated early postoperative CEA level were independent predictors of lung metastasis in our study.

Manfredi et al. suggested that the stage of diagnosis was the most important predictor of metachronous liver metastasis.[18] The odds ratio comparing stage II to stage I was 3.28, and that comparing stage III to stage I was 8.3. In the study by Ryuk et al. an elevated postoperative CA19-9 level was associated with a high risk of early recurrence. In their study, liver and peritoneal recurrence were significantly higher in the early recurrence group.[19] In our study, we found that elevated early postoperative CA19-9 and tumor obstruction were both independent predictors of liver metastasis.

The risk factors suggested in NCCN include pT4, poorly differentiated histology, pathology showing LVI or PNI, inadequate LN harvesting, and preoperative bowel obstruction or perforation. In our study, only PNI and bowel obstruction were found to be independent predictors of recurrence. The sample size in each risk factor could have been too small to achieve adequate power. For example, the case number of tumor perforation was only 25.

Our study has several limitations, including a small sample size, single center study, and retrospective design study. Our study lacked molecular markers such as BRAF mutation, KRAS, and MSI, which are important in determining future CRC treatment plans.

Conclusions

Elevated postoperative tumor markers (both CEA and CA19-9) were excellent predictors of prognosis for colorectal cancer. An elevated early postoperative CA19-9 level, and PNI were identified as independent predictors of recurrence. Elevated postoperative CA 19-9 level and PNI were found to be independent predictors of distant metastasis. Rectal cancer and an elevated postoperative CEA level were independent predictors of lung metastasis. Moreover, the independent predictors of liver metastasis include an elevated postoperative CA19-9 level and tumor obstruction. Intensive follow-up and adjuvant chemotherapy for patients with these risk factors may improve their outcome.

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References

1. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2021;

71(3):209-49.
2. Report CSA. *Taiwan Cancer Registry*. 2018.
3. Gunawardene A, et al. Disease recurrence following surgery for colorectal cancer: five-year follow-up. *NZ Med J* 2018; 131(1469):51-8.
4. Kobayashi H, et al. Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. *Surgery* 2007;141(1):67-75.
5. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. *Diseases of the Colon & Rectum* 2018;61(9):1016-25.
6. Tsikitis VL, et al. Predictors of recurrence free survival for patients with stage II and III colon cancer. *BMC Cancer* 2014; 14(1):336.
7. Benson AB, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network* 2021;19(3):329-59.
8. Guraya SY. Pattern, stage, and time of recurrent colorectal cancer after curative surgery. *Clinical Colorectal Cancer* 2019;18(2):e223-8.
9. Tokodai K, et al. Risk factors for recurrence in stage II/III colorectal cancer patients treated with curative surgery: the impact of postoperative tumor markers and an infiltrative growth pattern. *Journal of Surgical Oncology* 2016;114(3): 368-74.
10. Lin JK, 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. *International Journal of Colorectal Disease* 2011;26(9):1135-41.
11. Park IJ, Choi GS, Jun SH. Prognostic value of serum tumor antigen CA19-9 after curative resection of colorectal cancer. *Anticancer Research* 2009;29(10):4303-8.
12. Hansdotter P, et al. Patterns and resectability of colorectal cancer recurrences: outcome study within the COLOFOL trial. *BJS Open* 2021;5(4).
13. Cecil TD, et al. Total mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. *Diseases of the Colon & Rectum* 2004;47(7):1145-50.
14. Read TE, et al. Locoregional recurrence and survival after curative resection of adenocarcinoma of the colon. *Journal of the American College of Surgeons* 2002;195(1):33-40.
15. Stipa S, et al. Local recurrence after curative resection for colorectal cancer: frequency, risk factors and treatment. *Journal of Surgical Oncology* 1991;48(S2):155-60.
16. Lee H, et al. Recurrence pattern depends on the location of colon cancer in the patients with synchronous colorectal liver metastasis. *Annals of Surgical Oncology* 2014;21(5):1641-6.
17. Tan KK, Lopes GdL Jr, Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *Journal of Gastrointestinal Surgery* 2009;13(4):642-8.
18. Manfredi S, et al. Epidemiology and management of liver metastases from colorectal cancer. *Annals of Surgery* 2006; 244(2).
19. Ryuk JP, et al. Predictive factors and the prognosis of recurrence of colorectal cancer within 2 years after curative resection. *Annals of Surgical Treatment and Research* 2014;86(3): 143-51.

原　著

第二期大腸直腸癌不同復發位置的風險因子

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前言　第二期大腸直腸癌的病人約 10%-22.2% 復發。很多臨床病理因子被發現與復發有相關性。因此本篇要看看第二期大腸直腸癌不同復發模式的風險因子。

方法　回顧性分析資料庫中 2010 年至 2015 年間被診斷出第二期大腸直腸癌的病人。使用 Cox 比例危險模型來分析臨床病理因子與不同復發模式的關係。

結果　第二期大腸直腸癌的病人總共有 77 位復發，其中 9 位局部復發、60 位遠端轉移。在遠端轉移的病人中，有 17 位只有肺部轉移、18 位只有肝臟轉移。腫瘤復發的獨立風險因子包含了術後早期 CA19-9 上升與神經周邊侵犯。遠端轉移的獨立風險因子包含術後早期 CA19-9 上升與神經周邊侵犯。肺部轉移的獨立風險因子包含直腸癌與術後早期 CEA 上升。肝臟轉移的獨立風險因子包含術後早期 CA19-9 上升與腫瘤導致腸阻塞。

結論　術後早期腫瘤指標上升、腫瘤位置、神經周邊侵犯、腫瘤導致腸阻塞等是第二期大腸直腸癌的預後指標。有上述預後指標的病人，在密切追蹤和輔助性化療可能可以改善病人癒後。

關鍵詞　第二期、大腸直腸癌、復發模式的風險因子。