Original Article

Factors Predicting Local Recurrence in Rectal Cancer after Curative Surgery

Chun-Ting Chu
Jui-Ho Wang
Tai-Ming King
Chao-Wen Hsu

Division of Colon & Rectal Surgery,
Department of Surgery, Kaohsiung Veterans
General Hospital, Kaohsiung, Taiwan

Purpose. The aim of this study was to identify possible clinicopathological predictor of local recurrence (LR) of Stage I-III rectal cancer in patients undergoing curative resection without pre-operative neoadjuvant concurrent chemo-radiotherapy.

Methods. Between May 2005 and December 2008, a total of 178 patients with Stage I-III rectal cancer who had undergone curative resection and received regular follow-up were retrospectively analyzed. Possible clinicopathological risk factors of rectal cancer LR were analyzed using univariate and multivariate methods.

Results. Postoperative LR was found in 25 (14%) patients. Univariate analysis indicated LR to be significantly correlated with lesion location ($p = 0.046$), vascular invasion ($p = 0.001$), perineural invasion ($p = 0.001$), high pre-operative carcinoembryonic antigen (CEA) level ($p < 0.001$), depth of invasion ($p = 0.047$), nodal invasion ($p = 0.008$), distal resection margin < 1 cm ($p = 0.001$), and distal resection margin < 2 cm ($p = 0.025$). Multivariate analysis revealed LR to be significantly correlated with high pre-operative CEA levels ($p = 0.001$) and distal resection margin < 1 cm ($p = 0.030$).

Conclusions. The results of this study suggest that pre-operative CEA level and distal resection margin < 1 cm are important independent predicative factors for the development of the LR of rectal cancer after curative resection. Close follow up of these high-risk patients and intensive treatment after curative resection may be indicated.
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Colorectal cancer (CRC) represents a formidable health burden, with approximately one million new cases diagnosed annually in the western world.[1] In Taiwan, CRC became the most common cancer, exceeding Hepatocellular carcinma in 2010 and is now the third leading cause of cancer death in Taiwan, with over 10,000 new cases and 4,000 deaths per year.[2] Surgical intervention remains the most promising curative procedure, though local recurrence (LR) after curative surgery occurs at a constant rate, especially in cases of rectal cancer.[3] Although the pre-operative concurrent chemoradiotherapy (CCRT) and the introduction of total mesorectal excision have been found to decrease the risk of LR, recurrence continues to range from 6 to 15 percent.[4] LR is often catastrophic and carries an extremely poor prognosis, since it is difficult to cure and the associated symptoms are debilitating.[5] Previous studies report less distal resection margin, primary tumor involvement, regional lymph nodes involvement, vascular invasion and perineual

invasion to be prognostic factors.[6-10]

The purpose of this study was to review cases of local recurrence rate after curative resection for rectal cancer in recent years before 2009 at Kaohsiung Veterans General Hospital in Taiwan and identify the potential risk factors of LR. Such a study was made possible because at our hospital, Kaohsiung Veterans General Hospital, neoadjuvant CCRT for local advanced rectum cancer was not routinely performed until January 2009.

Patients and Methods

Between May 2005 and December 2008, a total of 275 consecutive patients with rectal adenocarcinoma were reviewed. Rectum was defined as any section, 15 cm or less from the anal verge.

Patients who had undergone curative surgery, including low anterior resection, abdominoperineal resection (APR) or Hartmann's procedure with standard total mesorectal excision were included. The dissection was begun using high ligation of the inferior mesenteric artery at its origin from the aorta. Anastomosis was performed by means of the double-stapling technique and rectal washout was performed routinely before transection when low anterior resection was performed.

Patients who had carcinoma in situ or distant metastasis, or who were not suitable for surgical intervention or who had just received diversion surgery, or who had the follow-up periods less than 2 years were excluded. (Those with LR occurring less than 2 years were included). Post-operative chemoradiotherapy and adjuvant chemotherapy may be given depending on final pathological staging and patient's clinical condition.

Postoperative surveillance consisted of maintaining medical history, physical examination, and laboratory studies. Serum carcinoembryonic antigen (CEA) levels were measured every 3 months. Abdominal ultrasonography or computed tomography, and chest radiography were performed every 6 months .Total colonoscopy or barium enema examination was performed once a year. Patients were followed up at 3- month intervals for 2 years and 6-month intervals thereafter.

Local recurrence was defined as tumor growth at the anastomotic site, perirectally, in the lesser pelvis (including vagina, bladder and lateral pelvic lymph nodes), perineum, or at rectal stump after Hartmann's procedure, at the top of the stoma after APR) or Hartmann's procedure as documented either by clinical, radiological or pathological examination or examination at surgery.[11]

Data on 13 clinicopathologic variables were collected to analyze the potential predictive risk factors for LR. They were gender, age, tumor location, pretreatment CEA level, tumor histology, tumor grade of differentiation, vascular invasion, perineural invasion, depth of tumor invasion, nodal invasion, tumor length, distal resection margin and circumferential resection margin.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 12.0 (SPSS, Inc., Chicago, IL). A p-value of 0.05 or less was considered significant. Chi-square test was used to compare individual variables between the two groups (local recurrence vs. no local recurrence). The Multivariate Cox proportional hazards model was used to identify those clinicopathologic factors that independently predicted LR of rectal cancer.

Results

A total of 275 consecutive patients with rectal adenocarcinoma diagnosed at Kaohsiung Veterans General Hospital were reviewed. Seventy of these patients had an initial diagnosis of adenocarcinoma of rectum with distant metastasis. Five patients received diversion surgery and two refused surgical intervention. Twelve patients were lost to follow up and eight expired during 2-year follow-up period. After exclusion, we were left with a total of 178 cases to include in this study. Among these patients, 153 cases received low anterior resection with or without loop colostomy or ileostomy, and 22 received abdominoperineal resection with permanent colostomy. One case received subtotal colectomy due to comorbid ascending colon cancer, and two

cases received Hartmann's procedure. LR occurred in 25 cases (14%) during the follow-up periods ranging between 14 and 71 months. The duration of local recurrence was 2-43 months (mean: 18.8 months). The clinical and pathologic features in patients with rectal cancer are summarized in Table 1. The mean age of these

patients was 64.56, slightly higher than the mean age in Taiwan. They were mostly male.

As can be seen in Table 2, which shows the correlation between distal resection margin and postoperative LR- 33% of patients had local recurrence if distal resection margin was less than 1 cm. Table 3, which summarizes the correlation between pathologic staging according to the AJCC version 7 and postoperative LR, shows that those with worse pathologic staging tend to have further LR. Fifty-five percent of patients with Stage IIIc lesions had further LR while only 2.3 percent of those with Stage I lesions had further LR.

Table 4 shows the correlation between predictive factors and postoperative LR. Univariate analysis found the following to be significantly correlated to postoperative LR, tumor location ($p = 0.046$), higher pre-operative CEA level ($p < 0.001$), the presence of vascular invasion ($p = 0.001$), the presence of perineural invasion ($p = 0.001$), depth of tumor invasion ($p = 0.047$), nodal invasion ($p = 0.008$), distal resection margin < 1 cm ($p = 0.001$) and distal resection margin < 2 cm ($p = 0.025$).

Multivariate analysis using the Cox proportional hazard model revealed the presence of higher CEA level and distal resection margin < 1 cm to be signifi-

Table 1. Clinicopathologic characteristics

Variables	Number (%)
Gender	
Male	111 (62.4)
Female	67 (37.6)
Age (y/o)	
< 65	86 (48.3)
≥ 65	92 (51.7)
Tumor location (cm)	
< 5	25 (14.0)
6-10	92 (51.7)
≥ 10	61 (34.3)
CEA (ng/ml)	
< 5	128 (71.9)
≥ 5	50 (28.1)
Histology	
Adenocarcinoma	162 (91.0)
Mucinous carcinoma	16 (9.0)
Grade of differentiation	
Well	1 (0.5)
moderate	160 (89.9)
poor	17 (9.6)
Vascular Invasion	
Yes	70 (39.3)
No	108 (60.7)
Perineural invasion	
Yes	32 (18.0)
No	146 (82.0)
Depth of invasion	
T1	14 (7.9)
T2	39 (21.9)
T3	118 (66.3)
T4	7 (3.9)
Nodal invasion	
N0	102 (57.3)
N1	49 (27.5)
N2	27 (15.2)
Distal resection margin (cm)	
< 1	33 (18.5)
1-2	50 (28.1)
≥ 2	95 (53.4)
Tumor length (cm)	
< 4	63 (35.4)
≥ 4	115 (64.6)
Circumferential resection margin	
Positive	5 (2.8)
Negative	173 (97.2)

Table 2. Correlation between distal resection margin and postoperative LR

Distal resection margin (cm)	Recurrence	No recurrence	Recurrence (%)
< 1	11	22	33
≥ 1~ < 2	6	44	12
≥ 2~ < 4	3	65	4.4
≥ 4	5	22	18.5

Table 3. Correlation between pathologic staging according to the AJCC version 7 and postoperative LR

Pathologic staging	Recurrence	No recurrence	Recurrence (%)
I	1	42	2.3
IIa	6	44	12
IIb	1	7	12.5
IIc	0	1	0
IIIa	1	7	12.5
IIIb	11	48	18.6
IIIc	5	4	55.6

Table 4. Correlation between local recurrence and clinicopathologic features using univariate analysis

	Recurrence	No recurrence	Hazard ratio	*p*-value	95% CI
Gender					
Male	18	93	1.661	0.287	0.654-4.219
Female	7	60			
Age (y/o)					
< 65	14	72	1.433	0.408	0.611-3.356
≧ 65	11	81			
Tumor location (cm)					
< 10	21	96	3.125	0.046	1.018-9.615
≧ 10	4	57			
CEA (ng/ml)					
< 5	9	119	0.154	< 0.001	0.062-0.382
≧ 5	16	34			
Histology					
Adenocarcinoma	21	141	0.447	0.196	0.132-1.515
Mucinous carcinoma	4	12			
Grade of differentiation					
Well + moderate	20	141	0.550	0.200	0.220-1.374
Poor	5	12			
Vascular Invasion					
Yes	18	52	4.995	0.001	1.961-12.721
No	7	101			
Perineural invasion					
Yes	11	21	4.939	0.001	1.980-12.320
No	14	132			
Depth of invasion					
T1 + T2	3	50	0.281	0.047	0.080-0.983
T3 + T4	22	103			
Nodal invasion					
N0	8	94	0.295	0.008	0.120-0.728
N+	17	59			
Distal resection margin (cm)					
< 1	11	22	4.695	0.001	1.887-11.628
≧ 1	14	131			
Distal resection margin (cm)					
< 2	17	66	2.809	0.025	1.140-6.897
≧ 2	8	87			
Length (cm)					
< 4	5	58	0.409	0.09	0.146-1.151
≧ 4	20	95			
Circumferential resection margin					
Positive	2	3	4.347	0.102	0.914-10.768
Negative	23	150			

cant and independent recurrent factors (*p* = 0.001 and *p* = 0.030, respectively) (Table 5).

Discussion

This study found the rate of LR for rectal cancer after curative surgery to be 14%, compatible with previous study,[4] and higher CEA level and distal resec-

tion margin < 1 cm to be predictors of LR.

CEA, a glycoprotein can be produced during fetal development. CEA can also be seen in several malignancies, including CRC, gastric carcinoma, pancreatic carcinoma and medullary thyroid carcinoma and in benign diseases, such as ulcerative colitis, pancreatitis, liver cirrhosis, and Crohn's disease as well as in heavy smokers.[12] Although CEA is not a specific tumor marker for CRC, it is an important tumor marker

Table 5. Correlation between local recurrence and clinicopathologic features using multivariate analysis

	Hazard ratio	*p*-value	95% CI
Tumor location (cm)			
< 10	2.439	0.173	0.678-8.772
≧ 10			
CEA (ng/ml)			
< 5	0.180	0.001	0.063-0.515
≧ 5			
Vascular Invasion			
Yes	2.390	0.175	0.679-8.410
No			
Perineural invasion			
Yes	3.047	0.075	0.894-10.374
No			
Depth of invasion			
T1 + T2	0.324	0.169	0.065-1.615
T3 + T4			
Nodal invasion			
N0	0.640	0.475	0.188-2.178
N+			
Distal resection margin (cm)			
< 1	4.975	0.030	1.172-20.964
≧ 1			

in the management of CRC. A preoperative high CEA value suggests advanced disease with either locally or distant metastases.[13] Increased preoperative CEA level should decrease to normal levels in 4-8 weeks and if they do not decrease to normal levels, then an incomplete resection of the primary tumor causing further LR or micrometastases should be suspected.[14] In our study, pre-operative higher CEA level was a significant risk factor ($p < 0.05$) and carried a 5.548 relative risk of post-operative LR. We tried to group the pre-operative higher CEA level to Group A (CEA > 5 during first follow up after operation) and Group B (CEA < 5 during first follow up after operation). The LR rate in Group A was 69.3% (9/13), while that for Group B was only 18.9% (7/37). ($p = 0.002$). These findings indicate that a higher post-operative CEA level may indicate to the surgeon the possibility of post-operative LR.

Distal resection margins are different in fresh specimens compared to those fixed in formalin. In most instances, a distal resection margin of 2 cm in fresh specimen or 1 cm in fixed specimen is safe.[15] In

this study, we collected the data from our pathology reports after formalin fixation. Univariate analysis showed significant correlations between distal resection margin < 1 cm ($p = 0.001$), and distal resection margin < 2 cm ($p = 0.025$) and postoperative LR. Multivariate Cox proportional hazards regression analysis found distal resections margin < 1 cm to be demonstrated to be independent predictors for LR. However, a colorectal surgeon cannot predict the length of distal resection margin after formalin fixation during the operation. The most popular recommended of distal safe resection margin is still > 2 cm. If the distal resection margin can be measured during the operation or the data can be collected between the distal resection margin during operation and after formalin fixation, the distal safe resection margin can be made more accurate.

The present study found circumferential resection margin (CRM) to be predictive of LR.[16] In this study, positive CRM occurred in five patients (2.8%), four of whom had lower or middle tumor locations. Two patients developed further local LR. Our univariate analysis did not indicate a significant correlation between CRM and postoperative LR ($p = 0.102$), possibly because of insufficient sample size.

Perineural invasion is a pathologic process characterized by tumor invasion of nervous structures and spread along nerve sheaths.[17] Perineural invasion is known to be a marker for a more aggressive tumor phenotype and poor prognosis. In the current study, perineural invasion was significantly correlated to postoperative LR by univariate analysis, though it was not found to be a significant factor by multivariate analysis ($p = 0.075$), possibly due to insufficient sample size. This trend, however, should not be neglected. Fujita et al. also has suggested that perineural invasion status can be used to facilitate the selection of CRC patients for adjuvant chemotherapy.[18]

In patients with pretreatment-staged T3/4 rectal cancer, the French Federation de Cancerologie Digestive (FFCD) 9203 trial and the European Organisation for Research and Treatment of Cancer (EORTC) Trial 22921 have reported LR rate to be significantly reduced when chemotherapy is administered in combination with pre-operative long-course radiotherapy com-

pared with administration of long-course radiotherapy alone.[19,20] The German Rectal Cancer Group also found an association between pre-operative chemoradiotherapy and reduction of relative risk for in LR of approximately fifty percents of patients with pretreatment stages of T3/4 compared to use of postoperative chemoradiotherapy.[21] Almost no patients with pretreatment stage T3/4 at our hospital received pre-operative chemoradiotherapy for rectal cancer until January 2009 because some post-radiation side effects including severe diarrhea which we were found in the first few cases. However, an increasing number of patients with pretreatment-staged T3/4 rectal cancer have received pre-operative chemoradiotherapy since 2009. Data can be collected for further comparisons in the future.

Conclusion

Pretreatment CEA level and distal resection margin were found to be significant predictive risk factors of LR after curative resection for rectal cancer. Physicians should follow up this these patients more carefully in order treat any recurrence as early as possible. Patients with these risk factors might benefit from more intensive treatment. Neoadjuvant preoperative CCRT might help reduce the LR rates in this disease.

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原　　著

影響直腸癌術後局部復發的因子

朱峻廷　　王瑞和　　金台明　　許詔文

高雄榮民總醫院　外科部　大腸直腸外科

目的　本篇研究的目的在找尋可能影響局部復發的相關臨床或病理因子對於第一期至第三期直腸癌術後的病人且術前並無接受化學放射治療。

方法　從 2005 年 5 月至 2008 年 12 月，178 位第一期至第三期直腸癌術後並有規則追蹤的病人被收錄與分析。利用單變項與多變項分析來找出可能影響直腸癌術後局部復發的相關臨床或病理因子。

結果　術後局部復發有 25 位 (14%) 病人。單變項分析發現，局部復發與腫瘤位置 (p = 0.046)、血管侵犯 (p = 0.001)、神經侵犯 (p = 0.001)、較高的術前癌胚抗原 (p < 0.001)、腫瘤侵犯的深度 (p = 0.047)、淋巴結侵犯 (p = 0.008)、遠端切除範圍小於 1 公分 (p = 0.001) 及遠端切除範圍小於 2 公分 (p = 0.025) 有明顯的相關性。在多變項分析中，局部復發與較高的術前癌胚抗原 (p = 0.001) 及遠端切除範圍小於 1 公分 (p = 0.030) 有直接相關。

討論　這個研究發現較高的術前癌胚抗原及遠端切除範圍小於 1 公分是直腸癌術後局部復發重要的危險因子。對於高危險的病人給予術後密切的追蹤及積極的治療是需要的。

關鍵詞　局部復發、直腸癌、預測因子、癌胚抗原。