Original Article

Clinical Relevance of Cabohydrate Antigen 19-9 Level after Chemoradiotherapy in Rectal Cancer Patients with Normal Carcinoembryonic Antigen Level

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Key Words
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CA 19-9

Purpose. This study aimed to investigate the role of carbohydrate antigen 19-9 (CA19-9) in rectal cancer patients with normal carcinoembryonic antigen (CEA).

Patients and Methods. From Jan 2001 to Dec 2010, 135 Patients who underwent preoperative chemoradiotherapy (CRT) followed by radical surgical resection were retrospectively enrolled from a prospectively constructed database. Characteristics of patients according to pre-CRT and post-CRT CA19-9 concentrations were analyzed.

Results. Patients with high post-CRT CA19-9 (≥ 37.0 u/ml) level were likely to have higher lymph node metastasis rate and tumor recurrence rate than those with normal post-CRT CA19-9 (< 37.0 ng/ml) level. Univariate and multivariate analysis showed that post-CRT CA19-9 level (HR = 8.474, 95% CI = 1.006~71.403) and ypN stage (HR = 2.422, 95% CI = 1.098~5.346) were independent prognostic factors for disease free survival rate. We also found that patients with high levels of post-CRT CA19-9 had a higher risk of lung metastasis (50.0% vs. 14.4%, $p = 0.013$).

Conclusions. Post-CRT CA19-9 level might be an independent prognostic factor for disease-free survival in rectal cancer patients with normal (< 5 ng/ml) pre-CRT CEA treated with preoperative CRT and radical surgery. An aggressive surveillance protocol for lung metastasis should be used for those patients with high post-CRT CA19-9 levels.

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Pre-operative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the gold standard of treatment for locally advanced rectal cancer. This procedure can produce tumor down staging, resulting in a reduced rate of postoperative local recurrence and a higher preservation rate of the anal sphincter.[1-4] The advantages of administering radiotherapy before as opposed to after surgery is that the tissues are better oxygenated; this is proposed to enhance the efficacy of radiotherapy.[5] Others include the treatment of less small bowel in the field (which can fall into the pelvis after surgery), avoidance of direc-

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tly irradiating the healing anastomosis (which could cause an anastomotic leak) and better ano-rectal function post-operatively.[1] Patient compliance with treatment is also greater when radiotherapy is given before surgery.[6]

Previous studies have suggested reduction of CEA levels after CRT may be an independent prognostic factor for disease-free survival following pre-operative CRT and surgery in rectal cancer patients.[7-10] However, the prognostic value of CEA reduction ratio remained in patients with rectal cancer and high CEA level. In addition, the 5-year recurrence rate remains as high as 20% in CRC patients with normal CEA levels.[11] In our previous studies, CA19-9 may be a prognostic factor for CRC patients with normal CEA levels. Patients with high CA19-9 levels also showed a higher incidence of lung metastasis (23.1%) than those with normal CA19-9 levels (7.2%).[12]

In this setting, the aim of this study was to clarify the predictive value of CA19-9 for rectal cancer patients with normal CEA levels.

Materials and Methods

Patient

From January 2000 to December 2010, 474 patients diagnosed with rectal adenocarcinoma received pre-operative CRT and surgical treatment at the Taipei Veterans General Hospital. Of these, 190 patients were excluded due to the presence of stage IV disease (n = 114), tumor located within the upper rectum (n = 5), transanal excision (n = 7), high CEA (> 5 ng/ml) level (n = 108), or a lack of complete data regarding CA19-9 (n = 105). Thus, 135 patients remained eligible for the study. The computerized database at Taipei Veterans General Hospital was constructed prospectively and updated constantly. The recording variables included patients' demographic data, major comorbidities, family history of cancers; location, number, gross and microscopic pathological characteristics and staging of the tumor; and status of the patient at their last follow-up visit. Tumor staging was classified using the TNM system published by the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC), 7th edition.[13]

Evaluation

All patients were evaluated with staging workups, including digital rectal examination, complete blood count, liver function test, serum CEA level, colonoscopy, chest radiography, computed tomography (CT) scan of the abdomen, and pelvic magnetic resonance imaging (MRI). In the context of an abdominal CT scan or MRI, lymph node involvement was regarded as positive when the lymph node was ≥ 5 mm in size in the short axis.

Response to CRT was evaluated by use of a tumor regression grade (TRG) system proposed by Dworak et al.[14] TRG definitions were as follows: TRG 0, no regression; TRG 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; TRG 2, dominant fibrotic changes with few tumor cells or groups (easy to find); TRG 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; and TRG 4, no tumor cells, only a fibrotic mass (total regression or response). TRG 4 was defined as "complete response", TRG 3 was defined as "good response" and TRG 1 or 2 were defined as "poor response." There was no TRG 0 in this study.

Treatment

The details of CRT in the protocol were described in our previous publication.[9] The prescription dose to the whole pelvis was 45 Gy in 20 fractions over 4 weeks. For primary T4 disease only, a boost of 5.4 Gy in 3 fractions to the gross rectal tumors with a margin of 1.5 cm was administrated following pelvic irradiation. The median RT duration was 26 days. Oral chemotherapy agents, tegafur-uracil (UFUR; TTY Biopharm, Taipei, Taiwan) 200 mg/m^2 day^{-1} and leucovorin (Wyeth Lederle Laboratories, Taipei, Taiwan) 45 mg/day, were concurrently administered with RT. The total daily doses of both drugs were divided into 3 doses per day. The oral chemotherapy was continued after RT with a dose of 250 mg/m^2 day^{-1} in another

28-day cycle on day 36-63. The patients were monitored with an interview, physical examination, and complete blood count every week.

Radical surgical resection by experienced colorectal surgeons was performed at 6-8 weeks after completion of RT. Pathological staging was available in these patients and was compared with the initial clinical stages.

Postoperative adjuvant chemotherapy was considered for those patients with pathologic stage III disease. Of these 71 patients, 11 did not receive adjuvant chemotherapy owing to patient refusal or poor performance status. 5-FU/leucovorin was administrated to 34 patients, FOLFOX (5-FU/leucovorin/oxaliplatin) to 18 patients, oral UFUR to 7 patients, and oral capecitabine to one patient. Postoperative adjuvant chemotherapy was also administrated to patients with pathologic stage II disease accompanied with other risk factors (including pathologic ypT3 to 4, lymphovascular invasion, perineural invasion and anastomosis leakage). Of these patients, oral UFUR was administrated to 41 patients, 5-FU/leucovorin to 3 patients, and FOLFOX (5-FU/leucovorin/oxaliplatin) to 6 patients.

CA19-9 group

Serum CA19-9 levels before CRT (pre-CRT CA19-9) were measured around one week before CRT, and serum CA19-9 levels after CRT (post-CRT CA19-9) were measured within one week prior to surgery. In addition, serum CA19-9 levels were record one month after surgery for those patients with high pre-CRT CA19-9 or post-CRT CA19-9. In this study, the normal limit of serum CEA measured by ELISA was set as < 37 u/ml.

Follow-up

All patients were followed up in the outpatient department every 3 months in the first 2 years, every 6 months in the third and fourth years, and annually thereafter. The follow-up examinations included chest radiography, serum CEA levels, abdominal sonography, abdominal/pelvis computed tomography (CT), and colonoscopy. Chest CT was arranged when a suspicious metastatic lesion was evident on a regular chest radiograph. It is our policy to perform the first follow-up colonoscopy 3 to 6 months after surgery for those patients in whom a complete colonoscopic study had not been or could not be performed before surgery. If the patient had received complete colonoscopy before surgery, the first colonoscopic surveillance was arranged 1 year after the surgery. The interval of surveillance was increased to 5 years if there were 2 consecutive negative colonoscopic surveillances.

Statistics

The data were analyzed using the Statistical Package for Social Science (SPSS V 16.0, SPSS, Inc., Chicago, IL, USA) statistical software. Ages of the patients were compared using independent t-test. We used chi-square or Fisher exact tests to reveal associations between categorical variables. The survival curve was plotted using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was defined as $p < 0.05$.

Results

Clinicopathological features of the patients

Of the 135 patients, 135 (62.9 %) were male. Median age was 64 years (range 27-93 years), and median pre- and post-CRT CA19-9 concentrations were 12.57 u/ml (range ≤ 1-1178 ng/ml) and 10.95 u/ml (≤ 1-944 ng/ml), respectively. Low anterior resection (LAR) was performed in 111 patients (82.2%), and free resection margin (< 1 mm) were found in all surgical specimens. Local recurrence occurred in 7 patients (5.1%) and distant recurrence occurred in 33 patients (24.4%). Sites of distant metastases were the lung (n = 23, 69.6%), liver (n = 10, 30.3%), brain (n = 3, 9.0%), bone (n = 2, 6.0%), and peritoneal carcinomatosis (n = 2, 6.0%) in descending order of frequency. Twenty-four patients (17.7%) achieved pathologic complete response after CRT. The median follow-up

interval was 42 months (range 4-149 months).

Characteristics of patients according to pre-CRT and post-CRT CA19-9 concentration

There was no statistically significance in all clinicopathological features between the normal (< 37.0 ng/ml) and high (≥ 37.0 u/ml) pre-CRT CA19-9 groups (Table 1). Patients with high post-CRT CA19-9 concentrations were likely to have higher lymph node positive rate and tumor recurrence rate than those with normal post-CRT CA19-9. Gender distribution, tumor location, histologic differentiation, clinical stage, down stage rate, lymphovascular and perineural invasion status did not differ significantly between the normal and high post-CRT CA19-9 groups (Table 1). In the normal pre-CRT CA19-9 group, only one patient had high post-CRT CA19-9 and then lung metastasis developed one year after radical surgery. There were 4 patients had normal post-CRT CA19-9

Table 1. Clinical characteristics according to pre-CRT and post-CRT CA19-9 level

	Pre-CRT CA19-9		*p*	Post-CRT CA19-9		*p*
	Normal	High		Normal	High	
Patients no.	122	13		125	10	
Gender						
Male	76 (62.3%)	9 (69.2%)	0.433	80 (64.0%)	5 (50.0%)	0.289
Female	46 (37.7%)	4 (30.8%)		45 (36.0%)	5 (50.0%)	
Mean age ± SD	63.1 ± 13.1	64.0 ± 13.7	0.871	63.1 ± 13.0	64.4 ± 15.8	0.871
Tumor location						
Mid rectum	64 (52.5%)	7 (53.8%)	0.579	65 (52.0%)	6 (60.0%)	0.440
Low rectum	58 (47.5%)	6 (46.2%)		60 (48.0%)	4 (40.0%)	
Surgery type						
LAR	100 (82.0%)	11 (84.6%)	0.583	102 (81.6%)	9 (90.0%)	0.439
APR	22 (18.0%)	2 (15.4%)		23 (18.4%)	1 (10.0%)	
cT#						
cT2	16 (13.1%)	2 (15.4%)	0.543	18 (14.4%)	0 (0.0%)	0.226
cT3~T4	106 (86.9%)	11 (84.6%)		107 (85.6%)	10 (100.0%)	
cN#						
cN0	29 (23.8%)	1 (7.7%)	0.166	30 (24.0%)	0 (0.0%)	0.073
cN1~2	93 (76.2%)	12 (92.3%)		95 (76.0%)	10 (100.0%)	
ypT^						
ypT0~2	56 (45.9%)	4 (30.8%)	0.228	58 (46.4%)	2 (20.0%)	0.097
ypT3~4	66 (54.1%)	9 (69.2%)		67 (53.6%)	8 (80.0%)	
ypN^						
ypN0	95 (77.9%)	7 (53.8%)	0.063	98 (78.4%)	4 (40.0%)	0.014
ypN1~2	27 (22.1%)	6 (46.2%)		27 (21.6%)	6 (60.0%)	
Down stage	93 (76.2%)	10 (76.9%)	0.630	95 (76.0%)	8 (80.0%)	0.563
Differenciation						
Well/Moderate	117 (95.9%)	11 (84.6%)	0.137	120 (96.0%)	8 (80.0%)	0.085
Poor	5 (4.1%)	2 (15.4%)		5 (4.0%)	2 (20.0%)	
LVi*	10 (8.2%)	1 (7.7%)	0.714	10 (8.0%)	1 (10.0%)	0.586
PNi+	4 (3.3%)	1 (7.7%)	0.402	4 (3.2%)	1 (10.0%)	0.324
Infiltration	9 (7.4%)	0 (0.0%)	0.390	9 (7.2%)	0 (0.0%)	0.489
Complete response	24 (19.7%)	0 (0.0%)	0.069	24 (19.2%)	0 (0.0%)	0.131
Recurrence	28 (23.0%)	6 (46.2%)	0.072	28 (22.4%)	6 (60.0%)	0.016
Local	6 (4.9%)	1 (7.7%)	0.516	6 (4.8%)	1 (10.0%)	0.424
Distant	28 (23.0%)	5 (38.5%)	0.182	28 (22.4%)	5 (50.0%)	0.064

c#: clinical stage; yp^: pathological stage after chemoradiation therapy; LVi*: lymphovascular invasion; PNi+: perineural invasion.

in the high pre-CRT CA19-9 group, and one of them had tumor recurrence in lung and brain 2 years after radical surgery.

Disease-free survival of patients with reference to factors

Univariate analysis showed that 8 clinicopathologic parameters (pre-CRT CA19-9 level, post-CRT CA19-9 level, ypT stage, ypN stage, complete response, tumor differentiation, lymphovascular invasion and perineural invasion status) were predictive of DFS (Table 2). Multivariate analysis showed that post-CRT CA19-9 level and ypN stage were independent, statistically significant prognostic factors for DFS (Table 3). We also found that patients with high levels of post-CRT CA19-9 also had a higher risk of lung metastasis. Of the 10 patients with high post-CRT CA19-9 levels, 5 cases developed lung metastases. In contrast, of the 125 patients with normal post-CRT CA19-9 levels, only 18 cases had lung metastases (50.0% vs. 14.4%, $p = 0.013$).

Discussion

CA19-9 is the carbohydrate determinant (sialylated lacto-N-fucopentaose II) of a circulating antigen that functions as an adhesion molecule and plays a role in tumor progression.[15]

This study demonstrates that CA19-9 level may be a prognostic marker for rectal cancer patients with normal CEA levels. Unlike CEA, which has been used as an independent prognostic factor for CRC in several consensus treatment guidelines, the value of CA19-9 has been overlooked, especially in patients with high CEA levels.[16-21] In our previous cohort study, the prognostic value of CEA was superior to that of CA19-9. Without stratification by CEA level, the 5-year DFS of CRC patients with high CA19-9 levels was 75.4%, which did not significantly differ from that of patients with normal CA19-9 levels (81.4%, $p = 0.103$).[12] Therefore, CA19-9 may not be a valuable prognostic marker for CRC patients with high CEA levels. Furthermore, of the rectal patients enrolled in our cohort, 38% had high CEA levels, but only 11% had elevated levels of CA19-9.[10] In addition, the specificity of CA 19-9 is limited due to CA 19-9 is frequently elevated in patients with various benign pancreaticobiliary disorders, including cholangitis, and

Table 2. Univariate analysis of prognostic factors for disease-free survival

Variable	No. of patients	5-year DSF rate	*p*
Gender			
Male	85	73.4%	0.187
Female	50	68.2%	
Age			
< 70	90	68.9%	0.149
≥ 70	45	77.4%	
Tumor location			
Mid rectum	64	71.1%	0.710
Low rectum	71	66.2%	
Surgery type			
LAR	111	77.9%	0.140
APR	24	52.2%	
Pre-CRT CA19-9			
< 37	122	74.8%	0.048
≥ 37	13	49.0%	
Post-CRT CA19-9			
< 37	125	75.2%	0.006
≥ 37	10	37.5%	
CA19-9 group			
Group 1	122	78.4%	0.095
Group 2	4	66.7%	
Group 3	9	41.7%	
ypT^			
ypT0~2	60	80.8%	0.014
ypT3~4	75	59.8%	
ypN^			
ypN0	102	80.8%	< 0.001
ypN1~2	33	38.1%	
Complete response			
Yes	24	87.8%	0.028
No	111	65.3%	
Differenciation			
Well/Moderate	128	74.1%	< 0.001
Poor	7	0.0%	
LVi*			
Yes	11	40.9%	0.021
No	124	79.7%	
PNi^+			
Yes	5	0.0%	0.001
No	130	72.8%	

yp^: pathological stage after chemoradiation therapy; LVi*: lymphovascular invasion; PNi^+: perineural invasion.

Table 3. Multivariate analysis of prognostic factors for disease-free survival

Variable	Hazard ratio	95% CI	*p*
Pre-CRT CA19-9			
< 37	1		0.225
≥ 37	2.032	0.885~4.662	
Post-CRT CA19-9			
< 37	1		0.049
≥ 37	8.474	1.006~71.403	
ypT			
ypT0~2	1		0.783
ypT3~4	1.138	0.454~2.854	
ypN			
ypN0	1		0.029
ypN1~2	2.422	1.098~5.346	
Complete response			
Yes	1		0.380
No	2.053	0.412~10.226	
Differenciation			
Well/Moderate	1		0.061
Poor	2.863	0.951~8.616	
LVi			
No	1		0.478
Yes	1.411	0.545~3.648	
PNi			
No	1		0.350
Yes	1.826	0.517~6.447	

other malignancies, including pancreatic cancer. Furthermore, CA 19-9 requires the presence of the Lewis blood group antigen to be expressed. Among individuals with a Lewis- negative phenotype, CA 19-9 levels are not a useful tumor marker since the antigenic determinant of CA19-9 is a sialylated derivative of the Lewisa antigen.[22-25] Since the sensitivity and the specificity of CA19-9 testing is low and since its prognostic value can be masked by CEA, CA19-9's utility as a prognostic factor is limited to patients with normal CEA levels.

In this study, only 9.6% of rectal cancer patients with normal CEA levels had high CA19-9 levels. Among these patients, post-CRT CA19-9 emerges as a prognostic predictor since high post-CRT CA19-9 levels were associated with advanced disease. Among patients with stage I and stage II disease, only 3.9% had high CA19-9 levels; this increased to 18.1% in those with stage III disease. In the univariate and multivariate analysis, post-CRT CA19-9 was as an independent prognostic factor. Moreover, patients with higher post-CRT CA19-9 levels had higher lymph nodes positive rate and tumor recurrence rate. These results are comparable to those of previous studies.[26-28]

We also found that patients with high levels of post-CRT CA19-9 also had a higher risk of lung metastasis, indicating that the prognostic value of post-CRT CA19-9 is not restricted to primary rectal cancer alone. Of the 10 patients with high post-CRT CA19-9 levels, 5 cases developed lung metastases (50.0%). In contrast, of the 125 patients with normal post-CRT CA19-9 levels, 18 cases had lung metastases (14.4%). These results suggest that post-CRT CA19-9 is a surrogate marker for hematogenous metastasis. Therefore, in patients with high levels of post-CRT CA19-9, aggressive screening for lung metastasis should be mandatory. Previous studies have shown that cancer cells expressing CA19-9 can adhere to endothelial cells through E-selectin. The attachment between cancer cells and endothelial cells is an important process in tumor metastasis.[29,30] In the patients with high pre-CRT CA19-9, CA19-9 levels became normal after CRT in only three patients in this study (23.0%). By the contrast, up to 69.4% patients with high pre-CRT CEA (75 of 108 cases) had normal post-CRT CEA levels in our previous cohort.[10] These findings indicated that CA19-9 level is relevant as a tumor marker for distant metastasis rather than local tumor response to irradiation.

In addition to post-CRT CA19-9 level, we found that ypN stage was an independent prognostic factor for DFS on multivariate analysis. Regional lymph node involvement is one of the strongest predictors of outcome following surgical resection of rectal cancers, second only to distant metastasis. Nodal spread is an indication for adjuvant therapy for rectal cancer in most guidelines.[31] Most studies suggest that ypN is an independent prognostic factor for DFS in patients with rectal cancers.[32,33]

The major limitation when performing comparative studies is the variability of adjuvant chemotherapy regimens. Considering the potential effects of different chemotherapy regimens, we analyzed several groups (5-FU/leucovorin, FOLFOX, oral UFUR and

oral capecitabine) and found there was no DFS difference between patients treated with these 4 regimens. Other limitations of this study included its retrospective design, relatively small cohorts, and short follow-up period in some patients. In the future, large prospective studies in which CA19-9 kinetics are analyzed through routine measurement of CA19-9 levels at follow-up are required.

Conclusion

In conclusion, post-CRT CA19-9 level might be an independent prognostic factor for disease-free survival in rectal cancer patients with normal (< 5 ng/ml) pre-CRT CEA treated with preoperative CRT and radical surgery. In addition, an aggressive surveillance protocol for lung metastasis should be used for those patients with high post-CRT CA19-9 levels.

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原　著

以 CA 19-9 值來評估，癌胚抗原 (CEA) 值正常的直腸癌病患在接受術前放射線化療 (CRT) 後的預後

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目的　癌胚抗原 (CEA) 是最廣泛使用的大腸直腸癌腫瘤指數。然而，對於 CEA 值正常的直腸癌病患，目前並沒有一個好的腫瘤標記來評估預後或者是追蹤病情。我們這個研究目的在探討直腸癌患者在接受術前放射線化療 (CRT) 後，其 CA19-9 值是否可以拿來作為病患的預後因子。

方法　自 2000 年 1 月至 2010 年 12 月，共有 474 名直腸癌患者在台北榮總大腸直腸外科接受完整的術前 CRT 合併手術治療。部分患者因為各種因素被排除，其中包含第四期患者 (n = 114)，腫瘤位於直腸上段 (n = 5)，經肛門切除 (n = 7)，CEA > 5 (n = 108)，缺乏完整 CA19-9 數據 (N = 105)。最後剩下 135 名患者進入研究。所有患者進行了完整的術前評估以及術後的追蹤，本實驗主要是要做病患分組間的生存分析以及其他臨床病理檢查結果的比較。

結果　本次研究的結果顯示出，post-CRT 19-9 以及 ypN 這兩個變項對於直腸癌病患的 5 年無疾病存活期 (disease free survival) 為獨立的預後因子。我們的研究另外發現 post-CRT 19-9 的上升也和腫瘤的肺部轉移有關連性。

結論　對於 post-CRT 19-9 上升的直腸癌病患，我們應該後續追蹤的部分得更加注意有無復發之情形，特別是肺部的部分。

關鍵詞　直腸癌、手術前放化療、CA19-9。