Original Article

Pre-operative Sensitivity of DR-70 in Colorectal Cancer Patients

Min-Hsuan Yen[1,2]
Tung-Cheng Chang[1,2]
Jin-Tung Liang[1]
[1]*Department of Surgery, National Taiwan University Hospital, Taipei,*
[2]*Department of Surgery, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan*

Key Words
DR-70;
CEA;
Colorectal cancer

Purpose. This study investigates the pre-operative sensitivity of a novel tumor marker for colorectal cancer (CRC).
Methods. A total of 83 patients with colorectal cancer from 2014 to 2016 were enrolled in this retrospective study. All patients received colectomy with at least D2 lymph node dissection. DR-70 and carcinoembryonic antigen (CEA) levels were tested and included in the preoperative evaluation. Hematological and biochemical tests, pathology, and demographic data from the patients were analyzed to evaluate the correlation of DR-70 and CEA with the distribution of colorectal cancer.
Results. Among the 83 patients, there were 12 (14.4 %) patients in pathological stage IV, 39 (46.9%) in stage III, 14 (16.8%) in stage II, and 18 (21.9%) in stage I. The sensitivity of DR-70 (> 1 mg/L) and CEA (> 5 μg/L) were 18.8% and 3.13% for the 32 patients in the early stages of colorectal cancer (stages I and II; *p* value = 0.04), while they were 23.5% and 49.0% for the 51 patients in the late stages (stages III and IV), respectively (*p* value = 0.19). However, for each of the four pathological stages, the sensitivity was not statistically significant. There was no correlation between CEA and DR-70 (*p* value = 0.661). There was no statistical significance in regard to the TNM staging. The perineural invasion was the only clinical characteristic that affected the sensitivity of DR-70.
Conclusions. The pre-operative sensitivity of DR70 in our patient with DR-70 was 21.7%, and there is no correlation between CEA and DR-70.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2017;28:171-176*]

Colorectal cancer (CRC) is the most commonly diagnosed cancer and the third leading cause of cancer death in Taiwan according to the Ministry of Health and Welfare. Screening for CRC is important because > 95% of cases of CRC would benefit from curative surgery if diagnosis can be made in an early stage. Screening methods include colonoscopy, flexible sigmoidoscopy, and fecal occult blood tests.[1] Tumor markers are also important for prognosis evaluation and follow up.

Before the DR-70 test was developed, CEA was the only tumor marker for CRC. CEA is a glycoprotein that may be elevated in gastrointestinal cancer, especially in CRC. However, CEA levels are not measurable in more than half of patients with CRC confirmed by biopsy (63%).[2] It is more difficult to detect recurrence or metastasis early in patients without elevated CEA levels by blood tests.

Received: March 28, 2017. Accepted: September 8, 2017.
Correspondence to: Dr. Jin-Tung Liang, Division of Colorectal Surgery, Department of Surgery, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. Tel: 886-2-2312-3456 ext. 65113; Fax: 886-2-3393-8506; E-mail: jintung@ntu.edu.tw

The DR-70 test measures both fibrin and fibrinogen degradation products (FDPs). Elevated FDPs were first documented in patients with malignancy in the 1970s.[3] The AMDL-ELISA DR-70 test (AMDL Diagnostics, Inc., Tustin, CA) is the newest test for in vitro cancer diagnosis to be cleared by the US FDA for monitoring CRC.[4] The detection of CRC using DR-70 is mainly based on the cancer-related coagulation cascade[5] and proteolysis within tumors.[6] Using a significant % change of > 15% of DR-70 to detect the progressive disease, the estimated specificity was determined as 67% with an estimated sensitivity of 65%.[4] However, there has been little discussion about the test for CRC since FDA approval was obtained in 2008.[4,7,8] This study reviews our experience with the DR-70 test to identify its clinical applicability.

Materials and Methods

In this retrospective study, we examined the medical records of patients with colorectal cancer who underwent surgery and pre-operative DR-70 tests between 2014 and 2016 at the National Taiwan University Hospital. There were 93 patients for whom pre-operative colonofiberscopic biopsies showed malignancy. Patients with concurrent pre-operative chemoradiotherapy (3, 3.2%), debulking surgery (5, 5.3%), or no CRC (2, 2.1%) were excluded (Fig. 1). A total of 83 patients with CRC received at least D2 lymph node dissection and colectomy. The serum DR-70 level was measured according to the manufacturer's protocol for the AMDL-ELISA DR-70 kit. The cut-off point of DR-70 was 1.0 μg/ml, and that of CEA was 5.0 ng/ml.

The correlation of DR-70 and CEA was analyzed by the chi-square test or Pearson correlation. Multivariable regression analysis was used to analyze the correlations between the DR-70 level and the TNM staging system, age, gender, tumor location, histological grade, lymphovascular invasion, and perineural invasion (PNI).

Results

In the 83 patients with CRC, the sensitivity of DR-70 and CEA according to the chi-square test were 21.68% (18/83) and 31.32% (26/83), respectively (p-value = 0.175; Table 1). The correlation of the serum values of DR-70 and CEA was not significant (Fig. 2; p-value = 0.661). The sensitivity of DR-70 (> 1 mg/L) and CEA (> 5 μg/L) were 18.8% and 3.13% for the 32 patients in the early stages of CRC (stages I and II) (p value = 0.04), while they were 23.5% and 49.0% for the 51 patients in the late stages (stages III and IV), respectively (p value = 0.19). For CRC stages

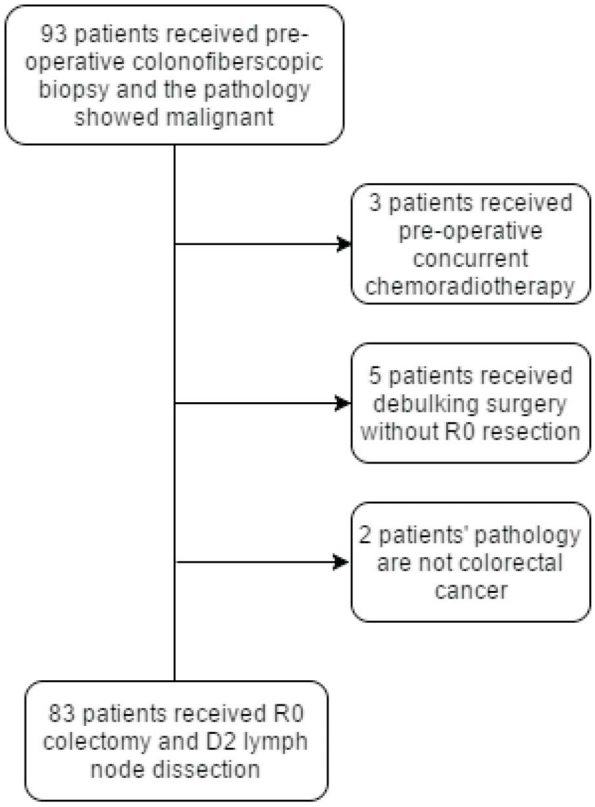

Fig. 1. Selection of patients in this study.

Table 1. Comparison of sensitivity of DR-70 and CEA according to colorectal cancer stage

	Sensitivity of DR-70	Sensitivity of CEA	p-value
Early stage (n = 32)	18.6% (6/32)	3.13% (1/32)	0.04
Stage I (n = 18)	16.7% (3/18)	5% (1/18)	0.645
Stage II (n = 14)	21.4% (3/14)	0% (0/14)	-
Lately stage (n = 51)	23.5% (12/51)	49.0% (25/51)	0.19
Stage III (n = 39)	23.1% (9/39)	35.9% (14/39)	0.315
Stage IV (n = 12)	25% (3/12)	91.7% (11/12)	0.546
All stages (n = 83)	21.7% (18/83)	31.3% (26/83)	0.175

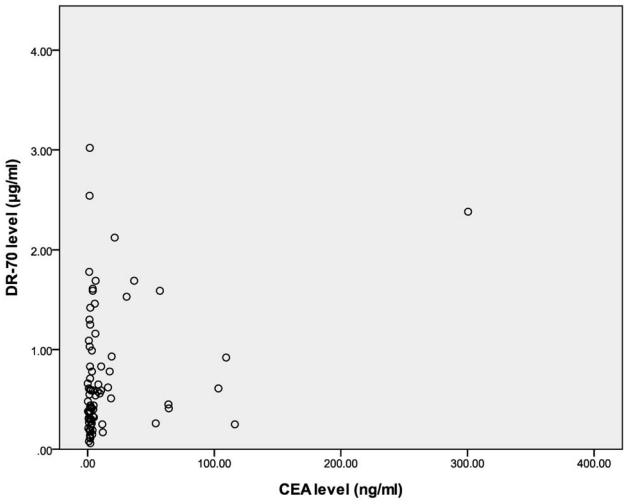

Fig. 2. Correlation of serum values of DR-70 and CEA.

I, II, III, and IV, the sensitivity were 16.7, 21.4, 23.1, and 25% for the DR-70 test, while they were 5, 0, 35.9, and 91.7% for the CEA test (Table 1). There was no statistical significance between DR-70 and CEA for each CRC stage.

According to tumor size or the direct extent of the primary tumor (T1, T2, T3, and T4), the sensitivities were 25, 15.4, 23.1, and 20% for the DR-70 test and 0, 7.7, 34.6, and 50% for the CEA test (Table 2). According to degree of spread to regional lymph nodes (N0, N1, and N2), the sensitivity were 18.2, 34.6, and 12.5% for the DR-70 test and 6.1, 42.3, and 54.1% for the CEA test (Table 2). According to the presence of distant metastasis (M0 and M1), the sensitivity were 21.1% and 25% for the DR-70 test and 21.1% and 91.6% for the CEA test, respectively (Table 2). There was no statistical significance between DR-70 and CEA in regard to the CRC TNM staging system.

The correlation of the patients' clinical characteristics with the DR-70 test was analyzed by multivariable regression analysis (Table 3). The mean age of all 83 CRC patients was 64.8 years (range: 33 to 86 years). When controlling for other variables, the odds ratio of the DR-70 sensitivity increases by 1.039 for a one year increase in age (p value = 0.121). The ratio of males to females was 48:35. When controlling for other variables, the odds ratio of the DR-70 sensitivity for males to females was 2.642 (p value = 0.168).

The mean tumor size was 4.4 cm (range: 0.8 cm to 11 cm). When controlling for other variables, a centi-

Table 2. Comparison of sensitivity of DR-70 and CEA according to TNM classification

	Sensitivity of DR-70	Sensitivity of CEA	p-value
T			
T1	25% (2/8)	0% (0/8)	-
T2	15.4% (2/13)	7.7% (1/13)	0.657
T3	23.1% (12/52)	34.6% (18/52)	0.352
T4	20% (2/10)	50% (5/10)	0.863
N			
N0	18.2% (6/33)	6.1% (2/33)	0.492
N1	34.6% (9/26)	42.3% (12/26)	0.563
N2	12.5% (3/24)	54.1% (13/24)	0.278
M			
M0	21.1% (15/71)	21.1% (15/71)	0.343
M1	25% (3/12)	91.6% (11/12)	0.546

Table 3. Clinical characteristics of 83 patients with colorectal cancer

Variable	Total (n = 83)	Exp (B) (95% CI)	p value
Age (years)			
Mean (range)	64.8 (33-86)	1.039 (0.990-1.089)	0.121
Gender (male/female)	48/35	2.642 (0.664-10.51)	0.168
Tumor size (cm)			
Mean (range)	4.4 (0.8-11)	1.179 (0.820-1.696)	0.374
Location (colon/rectum)	57/26	3.072 (0.543-17.38)	0.204
Histologic grade (well/poor)	80/3	0.630 (0.031-12.70)	0.763
Lymphovascular invasion (yes/no)	44/39	0.561 (0.113-2.780)	0.479
Perineural invasion (yes/no)	27/56	0.132 (0.020-0.865)	0.035
TNM stage			
Stage II/Stage I	14/18	0.689 (0.083-5.688)	0.729
Stage III/Stage I	38/18	2.515 (0.339-18.68)	0.367
Stage IV/Stage I	11/18	1.403 (0.072-27.47)	0.823

meter increase in tumor size corresponded to an increase of 1.179 in the odds ratios of the DR-70 sensitivity (p value = 0.374). There were 57 patients with colon cancer and 26 patients with rectal cancer. When controlling for other variables, the odds ratios of DR-70 sensitivity for colon cancer to rectal cancer was 3.072 (p value = 0.204). There were 80 patients with well-differentiated adenocarcinoma and 3 patients with poorly differentiated adenocarcinoma. When controlling for other variables, the odds ratios of DR-70 sensitivity for patients with well-differentiated adenocarcinoma to patients with poor-differentiated adenocarcinoma was 0.63 (p value = 0.763).

There were 44 patients with lymphovascular invasion and 39 patients without it. When controlling for other variables, the odds ratio of DR-70 sensitivity for patients with lymphovascular invasion to patients without it was 0.561 (p value = 0.479). There were 27 patients with PNI and 39 without it. When controlling for other variables, the odds ratio of DR-70 sensitivity for patients with perineural invasion to patients with no PNI was 0.132 (p value = 0.035). In regard to the TNM staging system, when controlling for other variables, the odds ratios of the DR-70 sensitivity of stage II, stage III, and stage IV to stage I were 0.689 (p value = 0.729), 2.515 (p value = 0.367), and 1.403 (p value = 0.823), respectively.

Discussion

Before the DR-70 test, the CEA test was the only lab test available for monitoring the result of treating CRC. The CEA test was used to detect recurrent CRC. In patients without CEA elevation, colonoscopy and computer tomography were the only monitoring methods. These methods have difficulty in detecting recurrent CRC early on without assistance from the CEA test. However, more than half of patients with CRC have no CEA elevation.[2] DR-70 is a new tumor marker for CRC that was approved by the FDA in 2008. The DR-70 test measures both fibrin and FDP in human serum samples.[4] The DR-70 test differs from the CEA test according to the different physical pathway. There was no correlation between the level of DR-70 and CEA in our study.

The sensitivity was only 3.1% for CEA in patients with stages I and II of CRC and 49% in patients with stages III and IV. In each CRC stage, the sensitivity of DR-70 were around 20%. CEA is highly elevated in advanced stages of cancer, and it is difficult to detect CRC in early stages.[9] Lee et al.[10] showed that CEA's sensitivity in stage I cancer was 7.4%. Su et al.[2] also found that the CEA test is more sensitive in more advanced stages. Currently, CEA is used to detect metastasis and evaluate prognoses.[11] For the early stages of CRC, the DR-70 test was more sensitive than the CEA test in our study. Although there were no statistically significant relationships between the two tests in each stage, the sensitivity of DR-70 were higher on average than those of CEA in early stage.

Atakan et al.[8] noted that DR-70 levels were higher in patients with high-grade dysplasia colon polyps than the healthy control group. The median DR-70 level of patients with high-grade dysplasia colon polyps, low-grade dysplasia colon polyps, and the healthy control group were 1.1, 0.6, and 0.5 μg/ml, respectively (p-value < 0.001). The high-grade dysplasia colon polyps were premalignant lesions in the adenoma-carcinoma sequence of CRC. This study also approved the clinical application of the test in early CRC patients.

The cut-off value of DR-70 was 1.0 μg/ml in our study, which is also recommended by the manufacturer. The DR-70 sensitivity of CRC was 21.7%. Kerber et al.[12] suggested a lower cut-off value of DR-70 of 0.7 μg/ml, which had good clinical performance with a sensitivity of 91% and specificity of 93%. They collected blood samples from 85 patients with CRC and from 100 healthy blood donors. However, there has been no large, randomized, controlled trial of DR-70, and a larger-scale study is still needed to clarify its clinical applicability.

In the present study, only pathological PNI affected the DR-70 sensitivity of CRC. The sensitivity of PNI-positive and PNI-negative patients were 11.1% (3/27) and 26.7% (15/56), respectively. DR-70-positive patients may have a lower chance of PNI, and PNI positivity was reported as a prognostic factor of CRC.[13-15] Yang et al.[14] showed that the PNI-positive rate ranges from 2.8 to 54.86% (median = 18.31%).

The postoperative survival of PNI-positive patients with stage II CRC was similar to those of stage III patients. In patients with stage II and III CRC, the five-year survival rates were higher for PNI-negative patients than PNI-positive patients.[13,15]

This still requires further investigation in relation to DR-70. Some limitations of our study deserve consideration. There was no DR-70 level of health patients as control group, but the median level of DR-70 about health patients was about 0.5 μg/ml.[8] There was also no long-term DR-70 follow up about those patients due to the high cost of this newly tumor marker. Further evaluation of DR-70 and prognosis may therefore be helpful.

Conclusions

The average pre-operative sensitivity of DR-70 and CEA in the our patients with CRC was 21.7% and 31.3%. The DR-70 level was not correlated with the CEA level.

Acknowledgements

There is no funding to declare. All authors have no conflicts of interest to report.

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原　著

DR-70 在大腸直腸癌病人的術前敏感度

顏珉玄 [1,2]　張東晟 [1,2]　梁金銅 [1]

[1] 台大醫院　外科部

[2] 雙和醫院　外科部

目的　探討 DR-70 此大腸直腸癌篩檢工具對協助臨床診斷之適用性。

方法　本研究採回溯性研究設計，在 2014 年至 2016 年間，共納入 83 位符合篩選標準之大腸直腸癌病患。此 83 位病患均接受至少有 D2 淋巴結廓清術的大腸直腸切除手術，並也在術前進行 DR-70 與 CEA 的檢測。將病患的血液與生化學檢查結果、病理報告和基本人口學資料納入統計分析，再評估與 DR-70 和 CEA 檢測數值之相關性。

結果　83 位大腸直腸癌病患中，第四期有 12 位 (佔 14.4%)，第三期有 39 位 (佔 46.9%)，第二期有 14 位 (佔 16.8%) 及第一期有 18 位 (佔 21.9%)。32 位的早期 (第一、二期) 大腸直腸癌病患其 DR-70 和 CEA 的敏感度分別是 18.8% 和 3.13% (*p* value 為 0.04)；而 51 位晚期 (第三、四期) 病者的 DR-70 和 CEA 的敏感度分別為 23.5% 和 49.0% (*p* value 為 0.19)；但以各別分期來看兩者的敏感度，均無統計顯著差異。而 DR-70 和 CEA 兩者的濃度值並無相關性。在 TNM 腫瘤分類，各別 T、N 及 M 的 DR-70 和 CEA 的敏感度也均無統計顯著差異。神經侵犯是唯一在臨床上會影響 DR-70 敏感度的因子。

結論　在大腸直腸癌病人，DR-70 的敏感度約為 21.7%，而 DR-70 和 CEA 兩者無相關性。

關鍵詞　DR-70、CEA、大腸直腸癌。