Serum CEA as a Predictor for Response to Preoperative Chemoradiation in Rectal Cancer

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The Master's Thesis submitted to the Department of Medicine the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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Finally, I would like to thank “God” for making this possible. Last, and most, I would like to dedicate this paper to my loving family.

Written by Yoon Ah Park

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Abstract

Serum CEA as a Predictor for Response to Preoperative Chemoradiation in Rectal cancer

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Recent data suggest that good responders to preoperative chemoradiation have favorable prognosis in rectal cancer patients. The aim of this study was to determine the predictive value of the selected clinicopathologic factor including serum carcinoembryonic antigen for response to preoperative chemoradiation.

Ninety five patients with rectal adenocarcinoma underwent preoperative radiation therapy and 5-FU based chemotherapy followed by curative resection. Pretreatment clinical stage was determined by endorectal ultrasound, abdominiopelvic computed tomography scan and/or magnetic resonance imaging. The outcome parameters were recurrences, 5-year cancer specific survival and 5-year disease free survival. Pretreatment clinicopathologic features including age, gender, location of tumor, cT classification, cN

classification, and serum CEA level were investigated as possible predictive factors for response to preoperative chemoradiation.

A pathologic complete and near complete response occurred in 10 (11%) and 8 patients (8%), respectively. Partial or no response occurred in the remaining 77 (81%). Twenty one patients had recurrent disease. All of these patients were included in partial or no response group (100%), while no patients with complete or near complete response showed recurrence (P = 0.012). Patients with complete or near complete response had higher 5-year cancer specific survival (100% vs. 68.3%, P = 0.0478) and disease free survival (100% vs. 60.0%, P = 0.0134) than those with partial or no response. Univariate analysis revealed that cN classification and pretreatment serum CEA can predict for response to preoperative chemoradiation. Using logistic regression analysis, pretreatment serum CEA (≤ 5ng/mL vs. ＞5ng/mL) was the only predictor for response (Odd ratio = 3.32, Confidence interval = 0.97-10.14, P = 0.04).

Patients with complete or near complete response to preoperative chemoradiation showed favorable prognosis compared with partial or no response. Pretreatment serum CEA was found to be a predictor for response to preoperative chemoradiation in rectal adenocarcinoma.

Key Words: Rectal adenocarcinoma, preoperative chemoradiation, serum CEA, predictor for treatment response

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I. INTRODUCTION

Although radical surgery followed by postoperative adjuvant chemoradiation (CRT) has been regarded as standard treatment strategy for stage II and III rectal cancer since the recommendation of National Institutes of Health consensus conference in 1990[1], there has been increasing number of studies on preoperative radiotherapy with or without chemotherapy. Several randomized studies have demonstrated an improvement of local control and overall survival following preoperative CRT compared with surgery alone[2-4]. In addition, the German Rectal Cancer Study Group compared preoperative and postoperative CRT in locally advanced rectal cancer, reporting lower rate of local recurrence in preoperative group[5].

Previous reports have correlated these successful results with downstaging of

tumor after preoperative radiotherapy[6-8]. However, the tumor response to radiotherapy varies with downstaging in 30 to 60% and complete pathologic response in 4 to 30%[7-11]. This variation come from dose and fractionation schedule of radiotherapy, time interval between completion of radiotherapy and surgery, concurrent chemotherapy and biologic characteristic of tumor.

To determine the radiosensitivity of individual tumor is important for predicting the patient prognosis and for modulating the treatment modalities. Many investigators have studied the biologic properties of tumor using numerous molecular markers related to tumor proliferation, apoptosis and angiogenesis[12-14]. However, they showed inconsistent results, which might be due to different detection techniques and reference ranges among the study groups. Moreover, the clinical application of these markers could not be widely available since the methods of detection are complicated, expensive, and not automated.

Carcinoembryonic antigen (CEA) is the most widely used tumor marker for the management of colorectal cancer and the method of measurement is standardized, readily available, and not costly. Elevated preoperative serum CEA levels are associated with an increased risk of relapse and poor patient outcome[15-17]. However, the predictive value of serum CEA for response to radiotherapy has not been fully evaluated.

The purpose of this study was to determine the predictive value of the selected clinicopathologic factor including serum carcinoembryonic antigen for response to preoperative chemoradiation.

II. MATERIALS AND METHODS

Between January 1989 and June 2004, 95 patients who underwent preoperative chemoradiation followed by potentially curative total mesorectal excision for rectal cancer in the Department of Surgery, Yonsei University College of Medicine were analyzed. Rectal cancer was defined as histologically-proven adenocarcinoma within 15cm from the anal verge.

Pretreatment evaluation included a physical examination, proctoscopy, colonoscopy or double-contrast barium enema, abdominopelvic magnetic resonance imaging (MRI) or endorectal ultrasound (ERUS) with abdominopelvic computed tomography (CT) scan, chest X-ray, complete blood cell count, liver function test and serum CEA level. Location of tumor was defined as the distance between the caudal margin of tumor and anal verge on proctoscopy.

On endorectal ultrasound, rectal wall penetration was determined according to Hildebrandt and Feifel. Circular or oval structure >5mm were considered malignant lymph nodes. Nodes <5mm with central hyperechogenicity were consiederd benign. Echogenicity was assessed based on the criteria of Beynon. Serum CEA levels were measured by use of CobasCore immunoassay (Boeringer-Manheim, Germany) from 1989 to 1994 and, thereafter, Elecsys

2010 electrochemilumine-scence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in which the reference range was below 5 ng/mL.

Pelvic radiation therapy was delivered with a 6-MV/10-MV dual photon linear accelerator. In most cases, the 3-port technique was used with 6-MV to the posterior port and 10MV to the lateral ports. When the target volume involved anterior pelvic structure such as uterus and bladder, the 4-field box technique was applied. The pelvic radiation volume was as follows: the superior border at the L5/S1 junction, the inferior border at the inferior margin of obturator foramen or 3cm below the lowest tumor border, the lateral border at 1.5cm lateral to the bony pelvic, the anterior border at 3cm anterior to the tumor mass, and the posterior border at 0.5cm to the sacrum surface. To exclude the small bowel from the radiation volume, patients were treated in a prone position with their bladders full of urine. Radiation therapy was administered 5 days a week with daily 1.8Gy fractionation. Total dose was 4500cGy to 5040cGy over 5 weeks.

Chemotherapy with intravenous or oral fluorouracil (FU) was given to all patients. Intravenous 5-FU (425mg/m2) plus leukovorin (20mg/m2) was administered for 5 days in continuous manner on first and fifth week of radiotherapy. Oral doxifluridine (900mg/m2, Furtulon®, Roche, Seoul, Korea) and leukovorin (30mg/day) was administered in 3 divided doses every

8 hours during the entire course of radiotherapy. Surgery was performed approximately 6 weeks after completion of radiation therapy.

Patients were followed up every 3 months for the first 2 years after the operation, every 6 months for the next 3 years and yearly thereafter. At each visit, patient history, physical examination, proctoscopy, chest X-ray, and measurement of serum CEA were performed. Annually and when the examinations and symptoms indicated recurrence, other examinations such as colonoscopy, computerized tomography scan, magnetic resonance imaging, bone scintigraphy were carried out.

Local recurrence was defined as recurrence within the pelvis and diagnosed by clinical and radiological examinations or by histologic confirmation. Systemic recurrence was defined as disease outside the pelvis and identified from clinical and radiologic examinations. The pattern of recurrence was characterized according to the first site of failure and, therefore, second and subsequent relapses were not included in this study.

The patients were followed up until death or the cutoff date (November 31, 2004). The median follow up duration for 74 patients alive at the cutoff date was 29 months (1-150 months).

Data analyses were performed using the statistical software 'Statistical Package for Social Science' (SPSS) version 11.0 for Windows (SPSS, Inc,

Chicago, IL). The inter-group comparisons of clinicopathological variables were made using two-tailed chi-square test for discrete variables. The multivariate analysis was performed using logistic regression analysis to identify the significant predictor for response to preoperative chemoradiation.. The pretreatment clinicopathologic features analyzed for the predictability of treatment response were age, gender, location of tumor, clinical tumor (cT) and nodal (cN) classification, and serum CEA level. The survival rate was estimated and compared according to the Kaplan-Meier method and log rank test, respectively. A P-value $<.05$ was considered statistically significant.

III. RESULTS

1. Patient and tumor characteristics

There was a male predominance comprising 70% (66/95) of patients. Clinical assessment based on ERUS, abdomino-pelvic CT scan and/or MRI revealed 8 cT2 (8%), 68 cT3 (72%) and 18 cT4 (19%) lesions. Fifty seven percent of patients (53/95) were suspected of lymph node involvement. In 47 patients (50%), pre-treatment serum CEA levels were above 5ng/mL. Patients and tumor characteristics at presentation were summarized in Table 1.

Table 1. Patient and tumor characteristics

Characteristics	n	%
Total number of patients	95	
Mean age in years (range)	53.8 (33-78)	
Gender		
Male	66	69.5
Female	29	30.5
Distance of tumor from the anal verge		
≥6cm	34	35.8
＜6cm	61	64.2
pre-RT cT *		
cT2	8	8.4
cT3	68	71.6
cT4	18	18.9
Undetermined	1	1.1
pre-RT cN *		
cN0	41	43.2
cN1	53	56.8
pre-RT serum CEA		
≤5ng/mL	48	50.5
＞5ng/mL	47	45.5

RT, radiation therapy

*cT and cN, determined by abdominopelvic MRI or endorectal ultrasound according to 6th AJCC staging system

2. Histopathologic staging of the resected tumor

Eleven percent of patients (10/95) showed a pathologic complete response.

Eight percent of the resected tumor (8/95) had focal residual cancer cells in the rectal wall. This group of patients were classified into TmicN0 and regarded as near complete pathologic response. The remaining 77 patients were categorized into partial or no response group as follows: thirteen percent of patients (12/95) had tumors confined to rectal wall (T1-2N0) and 32 percent (31/95) tumors infiltrating mesorectum or adjacent organ without lymph node metastasis (T3-4N0). Thirty six percent of patients (34/95) had lymph node positive disease regardless of T stage (TanyN1-3). Histopathologic staging of the resected tumor was shown in Table 2.

Table 2. Histopathologic stage

Histopathologic stage	n	%
pT0N0	10	10.5
pTmicN0	8	8.4
pT1-2N0	12	12.6
pT3-4N0	31	32.6
pTanyN1	34	35.8

3. Recurrence and survival according to tumor response to preoperative chemoradiation

Among total 95 patients, 21 had recurrences with 4 local, 14 distant and 3

combined diseases. All of these patients were included in partial or no response group (100%), while no patients with complete or near complete response showed recurrence (P = 0.012). The recurrence pattern according to the response to preoperative chemoradiation is listed in Table 3.

Table 3. Pattern of recurrence according to tumor response to preoperative chemoradiotherapy

Recurrence	Total or Near CR (n=18)	Partial or No response (n=77)	p value
Local	0	4 (100%)	NS
Distant	0	14 (100%)	0.05
Local and distant	0	3 (100%)	NS
Total	0	21 (100%)	0.012

CR, complete response; NS, not significant

Survival was analyzed according to response to preoperative chemoradiation (Fig. 1 and 2). There was significant difference for the 5-year cancer specific survival (100% vs 68.3%, P=0.0478) and disease free survival (100% vs 60.0%, P=0.0134) in favor of the patients who showed pathologic complete or near complete response.

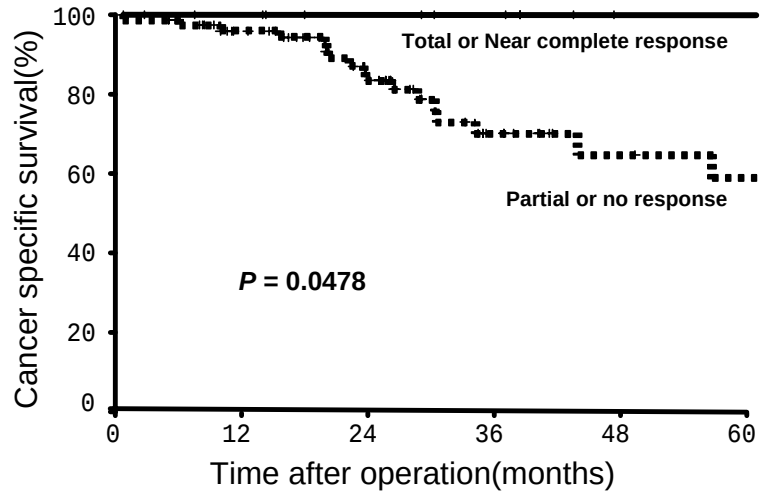

Fig.1 Cancer specific survival according to response to preoperative chemoradiation in rectal cancer.

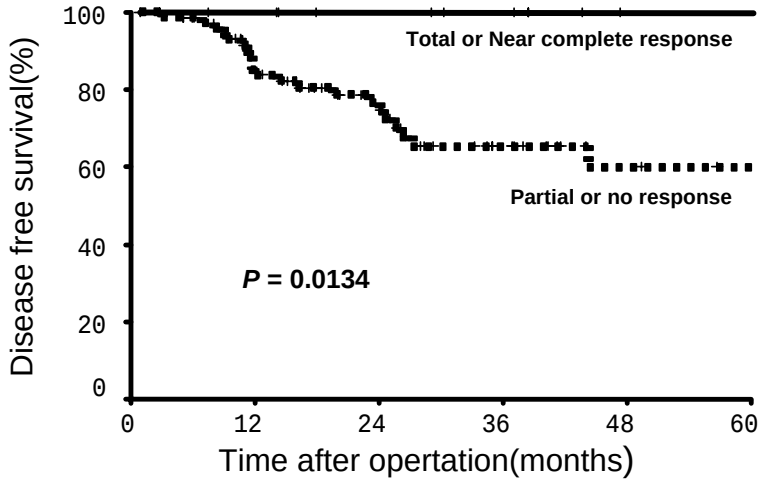

Fig2. Disease free survival according to response to preoperative chemoradiation in rectal cancer.

4. Predictors for response to preoperative chemoradiation in rectal cancer

Among the patient and tumor characteristics at presentation, pre-RT cN classification and pre-RT serum CEA were found to be predictive for response to preoperative chemoradiation by univariate analysis (Table 4). Logistic regression analysis using forward stepwise method revealed that pre-RT serum CEA was the only significant predictor for the response to preoperative chemoradiation (Table 5).

Table 4. Clinicopathologic feature as a predictor for total/near complete response

Clinicopatholigc features	Total or Near CR	Partial or No Response	p value
Age			NS
≥65 yrs	2 (13.3)	13 (86.7)	
＜65 yrs	16 (20.0)	64 (80.0)	
Gender			NS
Male	12 (18.2)	54 (81.8)	
Female	6 (20.7)	23 (79.3)	
Location			NS
≥6cm	6 (17.6)	28 (82.4)	
＜6cm	12(19.7)	49 (80.3)	
pre-RT cT*			NS
cT2	2 (25.0)	6 (75.0)	
cT3	13 (19.1)	55 (80.9)	
cT4	3 (16.7)	15 (83.3)	
Undetermined	0	1 (1.3)	
pre-RT cN*		0.025	
cN0	12 (29.3)	29 (70.7)	
cN1	6 (11.1)	48 (88.9)	
pre-RT serum CEA			0.041
≤5ng/mL	13 (27.1)	35 (72.9)	
＞5ng/mL	5 (10.6)	42 (89.4)	

CR, complete response; RT, radiation therapy; NS, not significant

*cT and cN, determined by abdominopelvic MRI or endorectal ultrasound according to 6th AJCC staging system

Table 5. Logistic regression analysis of predictor for total or near complete response

Covariate	Odd ratio	Confidence interval	p value
Pre-RT serum CEA (≤5ng/mL vs. ＞5ng/mL)	3.316	0.970-10.143	0.042

IV. DISCUSSION

The major findings of this study are 1) the responsiveness of tumor to preoperative chemoradiation has an impact on the prognosis of patients with rectal caner and 2) the pretreatment serum CEA is a predictor for treatment response.

The relationship between response to preoperative radiotherapy and clinical outcomes in rectal cancer patients has been previously investigated. However, the methods assessing treatment response were different among the study groups. Some investigators analyzed patient prognosis according to tumor downstaging determined by comparing the pretreatment endorectal ultrasound stage with the postoperative stage based on histologic examination of the pathologic specimen[10, 18]. In other studies, only the postoperative stage was considered to stratify the patient outcomes[7, 8, 19]. A grading scale was employed to record the tumor response from no evidence of treatment effect (0%) to complete response with no viable tumor (100%)[20]. The extent of tumor response was investigated as possible prognostic factor. Although there were the studies which had no conclusive results, most of them confirmed good responders have favorable outcomes. In the present study, we separated the patients into complete or near complete pathologic response group, in

which tumors showed no or microscopic foci of residual cancer cells, and partial or no response group of the remaining patients. Similar to prior studies, we observed that patients with complete or near complete pathologic response had an excellent prognosis showing marked difference from those with partial or no response.

The complete pathologic response rate is a parameter evaluated consistently in many series to be a relatively reliable end point. In this study, the patients who showed complete pathologic response comprised 11% of patients, which were comparable to the previous reports ranging from 4% to 30%[7-10]. The variation of radiotherapeutic effect can be attributed to treatment modalities. Several studies have focused on the optimal time interval between completion of radiotherapy and surgery, dosed and fractionation schedule, and concurrent chemotherapy to enhance the tumoricidal effect of radiotherapy[21-24]. The response also can vary as a consequence of biologic properties of individual tumors. The studies of molecular markers detected from the pretreatment tissue are under investigation to find their predictability of treatment response and prognosis[12-14]. However, they have shown inconsistent results and the clinical application of those markers is not widely available because the detection methods are complex, different among the researchers, time consuming and not automated.

In the present study, we evaluated the pretreatment clinicopathologic features as a predictor for response to preoperative chemoradiation which has been the topic of several studies. Some authors have identified no specific pretreatment clinicopathologic feature that would predict treatment response[7, 10, 11]. In contrast, others have presented histologic grade, clinical tumor size, clinical tumor staging, tumor mobility or circumference of the bowel wall involved by tumor as a predictor for response[6, 9, 18]. However, there has been no report investigating whether serum CEA can predict the response to preoperative chemoradiation or not. While the findings of endorectal ultrasonography or digital rectal examination can be dependent on the persons who perform the procedures, CEA is a reliable factor because of the standardization of measurement[25, 26]. Moreover, it is the most widely accepted worldwide and frequently used tumor marker in colorectal cancer management. In this respect, pretreatment serum CEA can serve as a readily available and objective predictor for treatment response in rectal cancer patients treated with preoperative chemoradiation followed by curative resection. Studies are also warranted to verify the relationships between serum CEA and molecular markers which are under investigation.

In conclusion, patients with complete or near complete response to preoperative chemoradiation have much better prognosis than those with

partial or no response in rectal cancer patients. Pretreatment serum CEA has a role as a predictor for treatment response.

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국문 요약

직장암 환자에서 술전 항암방사선 요법에 대한 반응 예측인자로서 혈청 CEA의 역할

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(지도교수 손승국)

최근 보고에 의하면 직장암 환자에서 술전 항암방사선 요법에 좋은 반응을 보인 환자들은 양호한 예후를 나타내는 것으로 알려져 있다. 본 연구의 목적은 직장암 환자에서 술전 항암 방서선 요법에 대한 종양의 반응도가 환자의 예후에 미치는 영향을 알아보고, 혈청 CEA 를 포함한 임상 병리적 특성 가운데 반응 예측인자로서 역할을 확인하고자 하였다.

95명의 직장암 환자가 술전 방사선 치료 및 5-FU 를 기본으로 한 항암치료를 시행받은 후 근치적 수술을 시행 받았다. 치료 전 임상적 병기는 경직장 초음파, 복부 컴퓨터 단층 촬영 및 자기 공명 영상으로 결정 되었다. 예후에 관한 변수는 재발, 5년 암 특이 생존률, 5년 무병 생존률을 고려하였다. 치료 전 임상 병리적 특성, 즉 나이, 성별, 종양의 위치, T 병기, N 병기, 혈청 CEA 가 술전 항암방사선 요법에 대한 반응 예측 인자로서 고려되었다.

조직학적 완전 반응 및 근완전 반응은 각각 10명(11%), 8명

(8%)에서 발생하였다. 부분 반응 혹은 무반응을 보였던 환자는 모두 77명 (81%)였다. 21명의 환자가 재발하였고, 재발은 모두 부분 반응 혹은 무반응군에서 발생하였다. 완전 반응 혹은 근완전 반응을 보인 환자에서는 재발이 없었다 (P=0.012). 완전 반응 혹은 근완전 반응을 보인 환자들은 부분 반응 혹은 무반응 환자들에 비하여 높은 암특이 생존률 (P=0.0478) 및 무병 생존률 (P=0.0134)을 나타내었다. 단변량 분석에서 임상적 N 병기 및 혈청 CEA 가 술전 항암 방사선 요법에 대한 반응 예측인자였고 다변량 분석에서 혈청 CEA (≤5ng/mL vs. >5ng/mL) 만이 의미있는 예측인자로 판명되었다 (Odd radio = 3.32, Confidence interval = 0.97−10.14, P = 0.042).

결론적으로, 직장암 환자에서 술전 항암 방사선 요법에 대하여 완전 혹은 근완전 반응을 보인 환자들은 부분 혹은 무반응 환자들에 비해 양호한 예후를 보였으며, 치료전 혈청 CEA는 술전 항암 방사선 요법에 종양 반응 예측인자로서 적용할 수 있다.

핵심 단어: 직장암, 술전 항암 방사선 요법, 혈청 CEA, 종양 반응 예측 인자