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Predictors of Pathologic Complete Response in Rectal Cancer Patients Undergoing Total Mesorectal Excision After Preoperative Chemoradiation

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Abstract: Preoperative chemoradiotherapy (CRT) is the standard of care for patients with stage II and III rectal cancer. This strategy leads to pathologic complete response (pCR) in a significant number of patients. Factors predictive of pCR are currently being extensively investigated. The aim of this study was to analyze clinical factors that might be predictive of pCR.

This study was a retrospective analysis of rectal cancer patients from January 2004 through December 2012. A total of 332 stage II and III patients with middle and low rectal cancer ($\leq$10 cm) who received CRT and underwent curative total mesorectal excision were eligible. The median radiation dose was 50.4 Gy, and 72.6% of patients received infusional 5-fluorouracil with leucovorin, whereas 19.6% of patients received TS-1 with irinotecan, and 7.8% of patients received xeloda only. Pathologic complete response was confirmed by using pathologic specimens and analyzed based on predictive clinical factors.

Among the 332 patients, 27.4% (n = 91) achieved pCR. Age, sex, body mass index, clinical T and N stages, tumor differentiation, the chemotherapy agent for CRT, and the time interval between CRT and surgery did not differ between the pCR and non-pCR groups. Carcinoembryogenic antigen (CEA) levels before CRT were 4.61 ± 7.38 ng/mL in the pCR group and 10.49 ± 23.83 ng/mL in the non-pCR group ($P = 0.035$). Post-CRT CEA levels were 1.4 ± 1.07 ng/mL in the pCR group and 2.16 ± 2.8 ng/mL in the non-pCR group ($P = 0.014$), and the proportion of middle rectal cancer patients was higher in pCR group (54.9%, $P = 0.028$). The results from multivariate logistic regression analysis indicated that higher tumor location (odds ratio 2.151; $P = 0.003$) and low post-CRT CEA level (odds ratio 0.789; $P = 0.04$) were independent predictive factors for pCR.

Tumor location and post-CRT CEA level were predictive factors in pCR for rectal cancer patients. Therefore, these factors may be important determinants in achieving pCR, and may also be used to predict oncologic outcomes.

Abbreviations: CEA = carcinoembryogenic antigen, CRT = chemoradiotherapy, pCR = pathologic complete response, TME = total mesorectal excision.

INTRODUCTION

Preoperative chemoradiotherapy (CRT) followed by surgery has become the standard treatment for patients with stage II and III rectal cancer, resulting in excellent local tumor control and possibly improved long-term survival.[1] Moreover, pathologic complete response(pCR) is often reported for specimens obtained after CRT followed by surgery. Pathologic complete response, defined as complete tumor regression with no viable cancer cells in both primary tumors and regional lymph nodes, is a remarkable finding, as it shows favorable results compared with patients without pCR.[2–5] It is also a critical issue for determining the optimal management of rectal cancer after CRT, in particular whether to perform surgery or not, as pCR is defined as having no cancer.[6] Several reports on breast cancer treatment showed that responsiveness to preoperative treatment is critical as it may predict clinical outcome and increase breast conservation.[7,8] Similarly, pCR can predict a good outcome in rectal cancer patients; however, surgery must be performed to confirm the presence of cancer, which can provide accurate and definite staging, although one should accept the risk of complications that may occur after surgery. If the patient chooses a "wait and see" policy, which involves declining surgery and relying on follow-up by observation, one might avoid the potential risk of surgery; however, accurate staging would not be available. Judging the tumor response before surgery is not a simple issue, but a complex problem. Although the disappearance of gross tumor after CRT has been found to be highly correlated with pCR, residual disease in the mesorectal lymph nodes has been reported in up to 17% of patients.[9] Therefore, the discovery of relevant clinical markers for predicting pCR is an important issue. The aim of this study was to determine any differences in clinical factors that might occur between pCR and non-pCR groups after CRT in order for physicians to better predict pCR.

METHODS

We performed a retrospective review of prospectively collected records from the database of the Department of Surgery, Yonsei University Health System, Seoul, South Korea from January 2004 to December 2012. This study included 332 patients with radiologic stage II or III rectal cancer as indicated by the National Comprehensive Cancer Network guidelines. These patients received CRT followed by total mesorectal excision

(TME). Strict selection criteria were tumor location ≤ 10 cm from the anal verge, no concurrent benign or malignant disease, and no history of familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer. Upper rectal cancer with a tumor location of more than 10 cm was excluded, as most of such patients underwent surgery without CRT in our hospital. In total, 91 of the 332 patients comprised the pCR group and the remaining 241 patients comprised the non-pCR group. Pathologic complete response was defined based on tumor regression and fibrotic changes of pathologic specimen after CRT followed by surgery, using a grading system adapted from Mandard et al.[10]

The initial clinical stage was based on digital rectal examination, colonoscopy, endorectal ultrasound abdominal computed tomography scan, and pelvic magnetic resonance imaging. Tumor location was defined as the distance from the caudal margin of the tumor to the anal verge, measured by digital rectal examination, rigid proctoscopy, and pelvic magnetic resonance imaging measurement. An anal verge of less than 6 cm was defined as low rectal cancer and that of 6– 10 cm was defined as middle rectal cancer. Chemoradiotherapy was administered to all patients with 3 types of chemotherapy options, 5-fluorouracil with leucovorin, TS-1 (tegafur, gimeracil, and oteracil potassium capsule) with irinotecan or xeloda only. 5-Fluorouracil was administered intravenously at a dose of 425 mg/m²/d and leucovorin was also administered intravenously at a dose of 20 mg/m²/d during the first and fifth weeks of radiotherapy. Five cycles of TS-1 and irinotecan were administered during the radiotherapy. Irinotecan was given intravenously at a dose of 40 mg/m²/d every once a week, and TS-1 was administered orally at a dose of 70 mg/m²/d for 25 days during the radiation therapy period. Xeloda was continuously administered orally at a dose of 1450 mg/m²/d twice daily during the radiation therapy period. Concurrent pelvic radiation treatment with a median radiation dose of 50.4 Gy (range 25–57.5 Gy) was administered; 45 Gy was applied to the whole pelvis in 25 fractions for 5 weeks, followed by 5.4 Gy boosts on the gross tumor area for 3 days. All patients underwent TME after the initial CRT. The time interval between CRT and surgery was recorded from the end date of radiotherapy to the day before surgery. Operations included low anterior resection (n = 167), low anterior resection with coloanal anastomosis (n = 107), and abdominoperineal resection (n = 58). The study was approved by the institutional review board of Severance Hospital (4-2015-0476).

Statistical Analysis

Data are summarized as frequencies and percentages for categorical variables, and medians and ranges are used for continuous variables. The χ^2 test was used to evaluate categorical variables and Student's *t*-test was used for continuous variables. Multivariate analysis was performed using a logistic regression model with factors shown to have an effect based on univariate analysis. All other results were considered statistically significant if $P < 0.05$. We calculated receiver-operating characteristic curves to validate the prediction power of the

TABLE 1. Patient, Tumor, and Treatment Characteristics

Variable	Statistic	Result (n = 332)
Sex	Male	228 (68.7%)
	Female	104 (31.3%)
Age, y	Median (range)	58 (27–85)
Body mass index, kg/m²	Mean (SD)	23.03 ± 3.07
American Society of Anesthesiologists	I	260 (78.3%)
	II	66 (19.9%)
	III and IV	6 (1.8%)
Pre-CRT carcinoembryogenic antigen, ng/mL	Mean (SD)	8.88 ± 20.82
Post-CRT carcinoembryogenic antigen, ng/mL	Mean (SD)	1.95 ± 2.47
Pretreatment clinical T stage	T2	16 (4.8%)
	T3	236 (71.1%)
	T4	80 (24.1%)
Pretreatment clinical N stage	N0	91 (27.4%)
	N1	188 (56.6%)
	N2	53 (16%)
Chemotherapy agent for CRT	5-Fluorouracil + leucovorin	241 (72.6%)
	Xeloda	26 (7.8%)
	TS-1 + irinotecan	65 (19.6%)
Initial tumor differentiation	Well	54 (16.3%)
	Moderate	246 (74.1%)
	Poor	11 (3.3%)
	Mucinous	21 (6.3%)
Tumor location (from anal verge)	Mean (SD)	5.735 ± 2.45
	Low (<6 cm)	182 (54.8%)
	Middle (6–10 cm)	150 (45.2%)
Radiation dose, Gy	Median (range)	50.4 (25–57.5)
Time interval between CRT and surgery, d	Mean (SD)	61 ± 13.16

CRT = chemoradiotherapy, SD = standard deviation.

TABLE 2. Univariate Pathologic Complete Response Analysis

Variable	Level	Pathologic Complete Response (n = 91)	Nonpathologic Complete Response (n = 241)	*P*
Sex	Male	60 (65.9%)	168 (69.7%)	0.508
	Female	31 (34.1%)	73 (30.3%)	
Age, y	Mean (SD)	58 ± 10.58	56.8 ± 11.74	0.406
Body mass index, kg/m^2	Mean (SD)	23.56 ± 3.03	22.82 ± 3.07	0.053
Pre-CRT carcinoembryogenic antigen, ng/mL	Mean (SD)	4.61 ± 7.38	10.49 ± 23.83	**0.035**
Post-CRT carcinoembryogenic antigen, ng/mL	Mean (SD)	1.4 ± 1.07	2.16 ± 2.8	**0.014**
Pretreatment clinical T stage	T2	7 (7.7%)	9 (3.7%)	0.108
	T3	68 (74.7%)	168 (69.7%)	
	T4	16 (17.6%)	64 (26.6%)	
Pretreatment clinical N stage	N0	27 (29.7%)	64 (26.6%)	0.624
	N1	50 (54.9%)	138 (57.3%)	
	N2	14 (15.4%)	39 (16.2%)	
Chemotherapy agent for CRT	5-Fluorouracil + leucovorin	61 (67.0%)	180 (74.7%)	0.157
	Xeloda	8 (8.8%)	18 (7.5%)	
	TS-1 + irinotecan	22 (24.2%)	43 (17.8%)	
Initial tumor differentiation	Well	18 (19.8%)	36 (14.9%)	0.112
	Moderate	67 (73.6%)	179 (74.3%)	
	Poor	3 (3.3%)	8 (3.3%)	
	Mucinous	3 (3.3%)	18 (7.5%)	
Tumor location (from anal verge)	Low (<6 cm)	41 (45.1%)	141 (58.5%)	**0.028**
	Middle (6–10 cm)	50 (54.9%)	100 (41.5%)	
Time interval between CRT and surgery, d	Mean (SD)	62.97 ± 11.56	60.25 ± 13.66	0.097

CRT = chemoradiotherapy, SD = standard deviation.

logistic regression model. Statistical Package for the Social Sciences for Windows (version 20.0, Chicago, IL) was used for statistical analyses.

RESULTS

Clinical and pathologic characteristics of the population are described in Table 1. The median age was 58 years (range 27–85) and the number of men was 228 (68.7%). Among the 322 patients, 91 (27.4%) were confirmed to have pCR on pathologic specimen analysis after surgery. In comparing the characteristics of patients in the pCR and non-pCR groups, no statistically significant differences were found in age (*P* = 0.407), sex (*P* = 0.508), and American Society of Anesthesiologists class score (*P* = 0.093). Body mass index, however, was slightly higher in the pCR group (*P* = 0.053).

Clinical factors predicting pCR by univariate analysis are presented in Table 2. Carcinoembryogenic antigen levels before CRT were 4.61 ± 7.38 ng/mL in the pCR group and 10.49 ± 23.83 ng/mL in the non-pCR group (*P* = 0.035). Post-CRT CEA levels were 1.4 ± 1.07 ng/mL in the pCR group and 2.16 ± 2.8 ng/mL in the non-pCR group (*P* = 0.014), and the proportion of middle rectal cancer patients was higher in the pCR group (54.9%, *P* = 0.028). Other variables (age, sex, body

mass index, pretreatment clinical T stage, initial tumor differentiation, pretreatment clinical N stage, time interval between CRT and surgery, and type of chemotherapy) showed no statistical differences between the two groups. Although statistically significant, pre-CRT CEA was to be excluded from multivariable analysis, as it had been obtained before CRT and was thus representative of the initial cancer rather than pCR. Multicollinearity between pre-CRT CEA and post-CRT CEA, however, indicated a low variance inflation factor (VIF = 1.449), thus, all factors were acceptable for inclusion in the multivariable analysis Table 3 shows tumor location (*P* = 0.003) and post-CRT CEA level (*P* = 0.04) as significant factors in multivariable logistic regression analysis, after applying effective variables with *P* value of less than 0.05 from univariable analysis. An acceptable receiver-operating characteristic curve was achieved after logistic regression model in Figure 1. The area under curve was 0.638, which indicated that the model was acceptable for predicting pCR.

DISCUSSION

Recently, there has been considerably more interest in devising a method to predict pCR before undertaking surgery,

TABLE 3. Multivariate Analysis of Variables Significant in Univariate Analysis for Pathologic Complete Response

| Variables | Multivariate | | |
	Odds Ratio	95% Confidence Interval	*P*
Postchemoradiotherapy carcinoembryogenic antigen	0.789	0.629–0.990	0.04
Tumor location	2.151	1.290–3.585	0.003
Prechemoradiotherapy carcinoembryogenic antigen			0.120

not only in the colorectal field but also in many other surgical fields. Physicians have investigated a variety of variables to find clinical factors that are predictive of pCR, such as tumor subtypes in breast cancer; biomarkers, serum CEA level, macroscopic ulceration status, and tumor circumference in rectal cancer; and smoking habits and tumor length in esophageal cancer.[11–14] A definite prediction of pCR is important, as a recent study showed that tumor regression of near-pCR with ypT3 or ypN1/2 in rectal cancer is associated with poor clinical outcome.[15] Moreover, performing surgery only to find a nonviable tumor creates unnecessary risk in terms of morbidity and mortality.

We found that post-CRT, CEA level and tumor location were significant factors associated with pCR. Carcinoembryogenic antigen is the most widely used serum marker for surveillance, particularly after colorectal cancer surgery, to monitor for recurrence. In addition, in rectal cancer, postoperative decrease in

FIGURE 1. Receiver-operating characteristic curve. Area under curve = 0.638 (95% confidence interval, 0.571–0.705), *P* < 0.001.

the CEA level has been found to be related to survival improvement.[16] Thus, several studies have used this simple tool to predict pCR, and low serum CEA level has been reported as a significant factor associated with pCR.[17–19] Based on the results of our study, a low post-CRT CEA level was associated with pCR. Pre-CRT CEA may therefore be more indicative of tumor biologic status than the response to CRT. Recently, Kleiman et al[20] similarly reported that normalization of CEA level after CRT showed predictive value for pCR. In addition, Perez et al[21] showed that CEA levels of less than 5 ng/dL were predictive for pCR as well as 5-year overall survival. There, however, is still some debate over whether pre-CRT CEA, post-CRT CEA, or even both, are predictive.[22,23] We did not analyze the change between post-CRT CEA and postoperative CEA; however, the pCR group had a lower post-CRT CEA level than the non-pCR group, which may account for the marked reduction in the CEA level of the non-pCR group after CRT.

Interestingly, our results indicated a middle tumor level as a predictor for pCR in multivariable analysis. Most previous reports do not report tumor height as a significant factor associated with pCR. There is no definite borderline for tumor height that divides rectal cancer between low and high. Some consider tumors 5 to 6 cm above the anal verge to be low rectal cancer, although classification remains arbitrary.[24,1] There is debate as to whether upper rectal cancer patients should undergo CRT before surgery or not, as they show lower local recurrence rates than those with middle or low rectal cancer, and certain reports also demonstrated no local recurrence differences between CRT and non-CRT groups in upper rectal cancer.[1,25,26] Accordingly, a low tumor location may increase the risk of local recurrence in postradiation status.[27] Kapiteijn et al[1] reported a 1% 2-year local recurrence rate in a radiotherapy with surgery group with tumor locations in the range of 5 to 10 cm, and a 10.1% recurrence rate in a surgery alone group with the same tumor locations; conversely a 5.8% 2-year local recurrence rate was found in the radiotherapy with surgery group with tumor locations at less than 5 cm, and a 10.0% recurrence rate was found in the surgery alone group with the same tumor locations. In addition, Das[28] et al reported that a tumor distance from the anal verge of more than 5 cm was independently predictive of tumor downstaging. From a Dutch rectal trial, middle rectal cancer showed lower local recurrence rate after short-course radiotherapy followed by TME than after TME alone.[25] Although these reports do not completely explain rectal cancer pCR in terms of tumor location, they are based on the expected effects of radiotherapy, such as tumor or lymph nodes sterilization; thus, a mid-level tumor location may be the most effective radiation field for rectal cancer. Further studies, however, are needed to confirm our findings.

CONCLUSIONS

Given its retrospective nature, our study had several limitations. First, there were no genetic data or biologic markers with relevant clinical variables. There were also several reports demonstrating that epidermal growth factor receptor and vascular endothelial growth factor expression predicted decreased pCR after CRT. The addition of such clinical data may have enriched our results when predicting pCR. Second, as these results were derived from a single institution, further prospective studies are necessary to fully evaluate the predictive factors for pCR in rectal cancer.
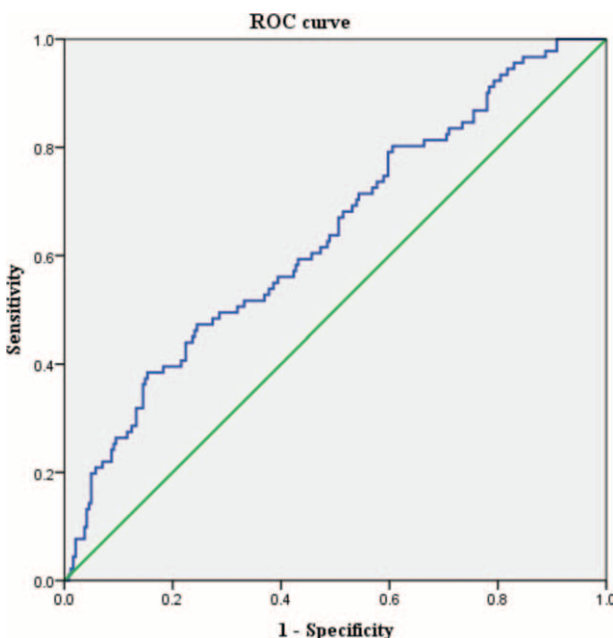
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