Prognostic Effect of Pretreatment Serum Carcinoembryonic Antigen Level

A Useful Tool for Prediction of Distant Metastasis in Locally Advanced Rectal Cancer Following Neoadjuvant Chemoradiotherapy and Total Mesorectal Excision

Chang Hyun Kim, MD, Soo Young Lee, MD, Hyeong Rok Kim, MD, PhD, and Young Jin Kim, MD, PhD

INTRODUCTION

Preoperative chemoradiotherapy (CRT)\textsuperscript{1–3} and total mesorectal excision (TME)\textsuperscript{4,5} are widely accepted as the treatment of choice for locally advanced distal rectal cancer, and this multidisciplinary approach has dramatically improved local control from an unacceptable local recurrence rate of 25% to 40% to <10%.\textsuperscript{1,2,4–6} However, 25% to 40% of patients still die of metastatic disease.\textsuperscript{2,3,7,8} Although survival depends primarily on distant metastasis, the treatment of advanced rectal cancer has focused on reducing local recurrence. Even neoadjuvant chemotherapy is intended as a radiosensitizer to reduce local recurrence rather than prevent systemic metastasis.

Therefore, to improve the survival of patients with advanced rectal cancer, reduction of distant metastasis is needed. An accurate predictor of distant metastasis could greatly benefit to select high-risk patients, especially before treatment initiation. The Union for International Cancer Control tumor–node–metastasis (TNM) classification is regarded as the best predictor of oncologic outcome. In addition to TNM staging, the College of American Pathologists identified 4 classes of colorectal prognostic markers; class I includes blood and lymphatic vessel invasion, residual tumor, and preoperative serum carcinoembryonic antigen (pre-CEA) level.\textsuperscript{9} Of these markers, reappraising the prognostic role of pre-CEA in rectal cancer treated with neoadjuvant CRT is important for several reasons. First, serum CEA is the only marker that yields presurgical information. Second, accurately assessing the anatomic extent of rectal cancer at the time of diagnosis is currently limited because of imprecise imaging tools,\textsuperscript{10,11} in particular, the assessment of nodal stage, the strongest predictor of outcome,\textsuperscript{11} is challenging. Finally, even the postneoadjuvant CRT pathologic stage (yp stage) cannot represent the initial metastatic burden because of variable downstaging, and subsequently, cannot provide differentiated adjuvant treatment strategies. The National Comprehensive Cancer Network guidelines suggest that adjuvant chemotherapy be administered for all patients treated with neoadjuvant CRT, regardless of pathologic stage, even following an apparent complete response.\textsuperscript{12}

Several studies have shown that elevated pre-CEA was an independent poor prognostic factor in colorectal cancer.\textsuperscript{13–17} Moreover, a recent large study suggested that CEA level (C-stage) be included in the conventional TNM staging of colon cancer.\textsuperscript{18} However, there are substantial clinical barriers to...
evaluating CEA as a prognostic factor, including the variable
definition of elevated CEA, heterogeneous study cohorts, and
factors associated with elevated CEA, such as other neoplastic
and nonneoplastic conditions. Therefore, in this study, we
determined pre-CEA cutoff values and evaluated the efficacy of
pre-CEA as a predictive factor for distant metastasis in patients
treated with neoadjuvant CRT.

METHODS

Patients

Between February 2005 and December 2012, 419 con-
secutive patients who received neoadjuvant CRT for locally
advanced (radiologic T3-T4 or N+ and/or clinically bulky) mid-
to-low rectal cancer were included in this prospective study.
Only patients who completed full-course neoadjuvant CRT were
included. Exclusion criteria included local excision after neoad-
juvant CRT, unavailable pre-CEA values, concurrent inflam-
matory bowel disease, hereditary colorectal cancer syndromes,
other malignancy, and newly developed distant metastasis
during neoadjuvant CRT. The smokers group was defined as
patients who smoked at the time of rectal cancer diagnosis. The
nonsmokers group included both ex-smokers (n = 40), who had
stopped smoking at least 6 months previously (n = 37) or before
the diagnosis of rectal cancer (n = 3), and patients who had
never smoked. Two patients who had stopped smoking after the
diagnosis of rectal cancer were included in the current smoker
group. This study was performed with approval of the institu-
tional review board of Chonnam National University Hwasun
Hospital, Gwangju, South Korea.

Staging and Treatment

Staging: The preoperative clinical stage of most patients
(396, 94.5%) was determined by rectal magnetic resonance
image (MRI). Abdominopelvic computed scan (CT) and
direct rectal ultrasound were used for staging in 16 (3.8%) and
7 (1.7%) patients, respectively.

Neoadjuvant CRT: All patients received 5-fluorouracil (5-
FU)-based chemotherapy with concomitant external beam radia-
tion using a 4-field box technique preoperatively. During
weeks 1 and 5 of radiotherapy, 5-FU (425 mg/m²/d) and leu-
covorin (20 mg/m²/d) were administered intravenously.

Surgery: At 6 to 8 weeks following completion of neo-
djuvant CRT, surgery was performed based on the same onco-
logic policy among surgeons.

Postoperative adjuvant chemotherapy: After recovery
from surgery, all patients who underwent radical surgery were
considered for postoperative chemotherapy.

Pathology and Follow-Up

All resected specimens were examined by 2 gastrointes-
tinal pathologists, and tumor regression induced by neoadjuvant
CRT was defined as the ratio of fibrosis to residual viable tumor.
The detailed tumor regression grade (TRG) scores were: TRG1
(<25% fibrosis), TRG2 (25%–50% fibrosis), TRG3 (50%–75% fibrosis), and TRG4 (>75% fibrosis). Pathologic complete
response (pCR) was defined as the absence of viable tumor cells
with no lymph node involvement.

Patients underwent standardized follow-up at 3-month intervals for 2 years and 6-month
intervals thereafter for a total of 5 years. Follow-up included
physical examination, complete blood count, blood chemistry
tests, and serum CEA assay. Distant metastasis was detected by abdominopelvic and chest CTs. Neither rectal MRI nor positron
emission tomography/CT scan was used routinely.

Statistical Analysis

The χ² test or Fisher exact test was used to analyze
categorical variables, and Student t test and the Wilcoxon
rank-sum test were used for continuous variables. Univariable
analysis was performed to evaluate the prognostic impact of

FIGURE 1. Cutoff value of pre-CEA. Nonsmoker group were ranked according to increased pre-CEA level and a maximum difference in
distant metastasis-free survival was determined with pre-CEA level = 6.6 ng/mL in nonsmoker group (A) and 11.4 ng/mL in smoker group
(B). pre-CEA = pretreatment serum carcinoembryonic antigen.
The maximal \( x^2 \) method was adapted to determine which pre-CEA value best separated patients into poor- and good-prognosis subgroup (in terms of the likelihood of surviving), and the log-rank test was used to measure the power of the grouping. The R MaxStat package (R Foundation for Statistical Computing, Vienna, Austria) was used for this analysis. Analysis according to smoking status was performed. The Kaplan–Meier method was used to establish the effects of each variable, and log-rank tests were used to compare survival curves. Multivariate analyses of survival were conducted using Cox proportional hazards models. Significant variables in univariate analysis (\( P < 0.1 \)) were entered into regression models with increasing complexity, and significance was assessed using analysis of variance analysis. The performance of predictive models was compared by the likelihood-ratio test, using the "coxph" and "anova" functions, which are included in the R "survival" package. Results with a \( P \) value \(< 0.05\) were considered significant. Statistical analysis was performed using R statistical software, version 3.1.1.

### RESULTS

**Patient Characteristics and Association Between Pre-CEA Level and Clinicopathologic Factors**

Of 419 patients, 307 (73.3%) were men. The mean age was 64.1 years (range, 27–87 years). A total of 364 (86.9%) patients...
underwent anterior resection, 51 (12.2%) underwent abdomino-perineal resection, and 4 (0.9%) underwent Hartmann procedure. The median pre-CEA level was 3.0 ng/mL (interquartile range, 1.9–4.9 ng/mL). The median pre-CEA level of smokers was 3.8 ng/mL, and that of nonsmokers was 2.8 ng/mL (P < 0.01). The pre-CEA levels of 6.6 ng/mL for nonsmokers and 11.4 ng/mL for smokers were determined to best separate patients on the basis of time to distant metastasis (Figure 1). Based on these cutoff values, 46 (12.2%) nonsmokers and 17 (17.9%) smokers were classified as the high-CEA group.

Clinical and pathologic features according to pre-CEA level are shown in Table 1. Patients in the high-CEA group were significantly more likely to have a more aggressive pathologic stage and poor prognosis. Higher pathologic tumor stage, larger pathologic tumor size, lymphovascular invasion, and perineural invasion were significantly higher in the high-CEA group than in the low-CEA group. Moreover, poor radiation response (TRG ≥ 3) was significantly more frequent in the high-CEA group (21.9% and 49.2% in the low and high pre-CEA groups, respectively). Indeed, the cumulative incidence of distant metastasis was 26.0% rather than local recurrence (9.3%), with isolated local recurrence (6.9%). These results question the current indiscriminate treatment strategy. Early systemic chemotherapy with newer biological agents is more likely to improve rates of distant metastasis and survival. Therefore, it is crucial to select high-risk patients who are more likely to experience systemic relapse and benefit from this treatment. In 1978, Wanebo et al.29 reported an inverse linear relationship between serum CEA and estimated mean time to relapse in Duke B and C colorectal cancer. Since then, many studies have reported the prognostic value of pre-CEA on colorectal cancer outcomes.13,15–18,26,27

When analyzing the prognostic role of pre-CEA in rectal cancer treated with neoadjuvant CRT, however, there has been controversy concerning the significance of elevated CEA level associated with low DFS.15,28–32 The inconsistent results could be explained by different cutoff values of pre-CEA levels. All of these studies used arbitrarily defined cutoff values of 2.5 to 10 ng/mL. No value was based directly on oncologic outcome. In contrast, we evaluated the prognostic significance of determined cutoff values that could define a subgroup with the greatest survival difference by using a maximal χ² method. In addition to the receiver operating characteristic, which assumes that all observations have occurred when the test is performed, maximally selected rank statistics allow for the evaluation of cutpoints with respect to a survival response. To our knowledge, this is the first study to use this method to determine the cutoff value of the pre-CEA level. Furthermore, most of the studies evaluated the correlation between pre-CEA and DFS and did not evaluate local or distant recurrence separately. In this study, pre-CEA level was only significantly associated with distant metastasis and not local recurrence, which is verified by previous studies.27,29 Park et al.27 showed that although perioperative CEA was a significant prognostic indicator for systemic recurrence, it was unable to predict locoregional recurrence in either stage II or III patients. Similarly, Wang et al.29 showed that the predictive value of pre-CEA on distant metastasis was more prominent in early systemic metastasis (within 6 months after surgery).

Another unique aspect to our study is the suggestion that current smoking history be considered in the evaluation of the clinical application of serum CEA. In the present study, the median pre-CEA level was significantly different according to smoking status. Using our calculated cutoff values of CEA for smokers and nonsmokers, the proportion of nonsmokers invasion, perineural invasion, ypT, ypN, CRM, and TRG. Similar results were obtained for DFS, with the exception of tumor location from the anal verge, which lacked prognostic significance.

Significant factors in univariate analysis were included in multivariate analysis (Table 3). Perineural invasion was the only prognostic factor associated with all outcomes (LRFS, DMFS, and DFS). In addition to perineural invasion, independent prognostic factors associated with DMFS included pre-CEA level, ypN, and ypT. In multivariate analysis, no other factor added significant prognostic information for the prediction of distant metastasis already considering perineural invasion, ypT, ypN, and pre-CEA level.

**DISCUSSION**

The cumulative distant metastasis rate of rectal cancer with neoadjuvant CRT, followed by TME, has been reported as 25% to 40%.2,3,7,8 In our study, the major treatment failure was distant metastasis (26.0%) rather than local recurrence (9.3%), with isolated local recurrence (6.9%). These results question the current indiscriminate treatment strategy. Early systemic chemotherapy with newer biological agents is more likely to improve rates of distant metastasis and survival. Therefore, it is crucial to select high-risk patients who are more likely to experience systemic relapse and benefit from this treatment. In 1978, Wanebo et al.29 reported an inverse linear relationship between serum CEA and estimated mean time to relapse in Duke B and C colorectal cancer. Since then, many studies have reported the prognostic value of pre-CEA on colorectal cancer outcomes.13,15–18,26,27

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However, if the same cutoff value is used for smokers and nonsmokers (ie, using the 6.6 ng/mL value of the nonsmoking group), the proportion of high-risk patients in the smoking group would increase to 34.3%, and is significantly different from nonsmoker group ($P = 0.02$).

We believe that prognostic effect of pre-CEA levels evaluated herein should be considered in future studies. First, the table is as follows:

| TABLE 2. Univariate Analysis of Predictors on the Percentage of 5-Year Local Recurrence, Distant Metastasis, and Disease-Free Survival |
|---|---|---|---|---|---|---|
| n | 5-y LRFS | $P$ | 5-y DMFS | $P$ | 5-y DFS | $P$ |
| Total | 419 | 89.5 | 69.7 | 62.5 | 0.38 |
| Age, y | | | | | | |
| <65 | 227 | 88.4 | 69.7 | 60.9 | 0.47 |
| ≥65 | 192 | 91.2 | 68.9 | 63.6 | 0.16 |
| Gender | | | | | | |
| Male | 307 | 89.4 | 70.6 | 62.6 | 0.44 |
| Female | 112 | 89.9 | 67.4 | 62.6 | |
| Body mass index, kg/m$^2$ | | | | | | |
| <25 | 321 | 89.0 | 68.4 | 60.6 | 0.53 |
| ≥25 | 98 | 91.2 | 73.3 | 68.2 | |
| Tumor location from anal verge, cm | | | | | | |
| <7 | 298 | 87.9 | 72.7 | 64.0 | 0.09 |
| ≥7 | 121 | 92.9 | 63.5 | 59.4 | |
| Preoperative T category | | | | | 0.05 | 0.1 |
| cT2 | 36 | 90.5 | 73.2 | 66.9 | |
| cT3 | 359 | 90.2 | 70.5 | 63.6 | |
| cT4 | 24 | 77.4 | 56.6 | 41.9 | |
| Preoperative N category | | | | | | |
| cN- | 125 | 91.7 | 79.6 | 73.4 | 0.32 |
| cN+ | 162 | 88.5 | 65.3 | 57.7 | |
| CEA before neoadjuvant treatment, ng/mL | | | | | | |
| Low | 356 | 90.3 | 75.5 | 67.6 | 0.27 |
| High | 63 | 85.7 | 42.7 | 38.3 | |
| Histologic differentiation | | | | | 0.19 | 0.01 |
| WD + MD | 386 | 90.3 | 70.7 | 64.0 | |
| PD | 33 | 80.9 | 66.5 | 54.1 | |
| Lymphovascular invasion | | | | | | |
| Yes | 28 | 72.3 | 31.0 | 19.9 | 0.01 |
| No | 391 | 90.7 | 72.1 | 65.9 | |
| Perineural invasion | | | | | | |
| Yes | 108 | 75.5 | 43.3 | 30.0 | <0.001 |
| No | 311 | 93.9 | 77.6 | 72.8 | |
| TRG | | | | | | |
| <50% | 122 | 81.4 | 64.4 | 52.4 | 0.01 |
| ≥50% | 248 | 91.2 | 69.1 | 62.7 | |
| pCR | 49 | 100.0 | 89.2 | 89.2 | |
| ypT category | | | | | | |
| ypT0 | 46 | 100.0 | 93.1 | 93.1 | 0.01 |
| ypT1 | 36 | 100.0 | 91.2 | 91.2 | |
| ypT2 | 94 | 89.7 | 77.8 | 69.2 | |
| ypT3 | 221 | 86.2 | 62.0 | 53.0 | |
| ypT4 | 22 | 78.4 | 25.3 | 18.0 | |
| ypN category | | | | | | |
| ypN0 | 307 | 92.2 | 77.6 | 71.5 | 0.01 |
| ypN1 | 86 | 81.8 | 51.4 | 41.5 | |
| ypN2 | 26 | 83.9 | 39.2 | 28.8 | |
| CRM | | | | | | |
| Negative | 389 | 90.7 | 71.0 | 64.3 | 0.01 |
| positive | 30 | 74.3 | 52.3 | 38.5 | |

CEA = carcinoembryonic antigen, CRM = circumferential resection margin, DFS = disease-free survival, DMFS = distant metastasis-free survival, LRFS = local recurrence-free survival, MD = moderately differentiated, pCR = pathologic complete response, PD = poorly differentiated, TRG = tumor regression grade, WD = well differentiated.
TABLE 3. Multivariate Analysis of Different Covariables on 5-Year Local Recurrence Free-Survival, Distant Metastasis Free-Survival, and Disease Free-Survival After Preoperative CRT

| Variable (Reference) | LRFS |             | DMFS |             | DFS |             |
|----------------------|------|-------------|------|-------------|-----|-------------|
|                      | HR   | 95% CI      | P    | HR          | 95% CI | P    | HR          | 95% CI | P |
| CEA (low vs high)    | –    | –           | –    | 1.743       | 1.129–2.690 | 0.01 | –           | –     | – |
| yp N category (N0 vs N+) | 1.688 | 0.859–3.314 | 0.12 | 1.867       | 1.246–2.797 | 0.01 | 1.863       | 1.292–2.687 | <0.001 |
| yp T category (T0–2 vs T3–4) | –       | –         | –    | 1.863       | 1.119–3.102 | 0.01 | 1.579       | 0.994–2.509 | 0.05 |
| Perineural invasion (negative vs positive) | 2.501 | 1.254–4.984 | 0.01 | 1.829       | 1.207–2.773 | 0.01 | 1.911       | 1.307–2.790 | <0.001 |
| Lymphovascular invasion (negative vs positive) | –    | –           | –    | –           | –     | –    | 1.711       | 1.040–2.816 | 0.03 |
| TRG (<50% vs ≥50%)  | 0.456 | 0.255–0.815 | 0.01 | –           | –     | –    | 1.302       | 0.562–1.048 | 0.09 |
| CRM (positive vs negative) | 0.509 | 0.217–1.190 | 0.11 | –           | –     | –    | 1.581       | 0.375–1.065 | 0.08 |
| Tumor location (<7 cm vs ≥7 cm) | 0.403 | 0.176–0.919 | 0.03 | –           | –     | –    | –           | –     | – |

CEA = carcinoembryonic antigen, CRM = circumferential resection margin, DFS = disease-free survival, DMFS = distant metastasis-free survival, LRFS = local recurrence-free survival, TRG = tumor regression grade.

According to the pre-CEA level, a more selective approach to neoadjuvant CRT should be considered for patients who are at a low risk of local recurrence, and systemic chemotherapy should be initiated as soon as possible.33,34 Williamson et al34 reported that the role of current neoadjuvant therapy could be diminished by performing surgery for highly selective patients. They suggested that the role of current neoadjuvant therapy could be diminished and moreover, could predict the response of neoadjuvant CRT.

In rectal cancer to some extent. Based on the observation made in this study, we recommend routine pre-CEA testing for all locally advanced rectal cancer patients. In addition, the cutoff value of pre-CEA should take into consideration the current smoking history of patients. The pre-CEA level appears to be a significant preoperative prognostic factor with a predictive role that is as valuable as any known pathologic factor. Future studies should consider pre-CEA when evaluating oncologic outcomes.

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