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ORIGINAL ARTICLE

Can serum dynamics of carcinoembryonic antigen level during neoadjuvant chemoradiotherapy in rectal cancer predict tumor response and recurrence? A multi-institutional retrospective study

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Abstract

Purpose We evaluate whether the change of carcinoembryonic antigen (CEA) level before and after preoperative chemoradiotherapy (CRT) in rectal cancer affects tumor response and recurrence or not.

Methods We retrospectively analyzed 1447 rectal cancer patients who underwent preoperative CRT followed by curative surgery. All patients received preoperative radiotherapy of 50.4 Gy in 28 fractions with 5-fluorouracil or capecitabine. Total mesorectal excision was performed 4 to 8 weeks after preoperative CRT. CEA levels were checked before and after CRT. Clinical and pathologic factors were analyzed for tumor response and recurrence.

Results Post-CRT CEA level (cutoff value, 2.5 ng/mL) was not a significant factor for tumor response on the multivariate analysis ($p = 0.095$). Patients were categorized according to the pre- and post-CRT CEA level (group A: pre-CRT CEA ≤5 ng/mL; group B: pre-CRT CEA >5 ng/mL and post-CRT CEA ≤2.5 ng/mL; group C: pre-CRT CEA >5 ng/mL and post-CRT CEA >2.5 ng/mL). The relapse-free survival (RFS) at 5 years was significantly higher in group A than in groups B and C (82.6 vs. 73.7 % vs. 72.2 %, $p < 0.001$). The overall survival (OS) at 5 years was significantly higher in group A than in groups B and C (90.1 vs. 84.4 % vs. 83.4 %, $p < 0.001$). However, there is no significant difference for RFS and OS between groups B and C (all, $p > 0.05$).

Conclusions Decline of elevated CEA level (>5 ng/mL) during preoperative chemoradiotherapy has no significant effect on tumor response and recurrence in rectal cancer.

Keywords CEA · Chemoradiotherapy · Rectal cancer · Recurrence · Response

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Introduction

Preoperative chemoradiotherapy (CRT) followed by curative resection is the standard treatment for patients with locally advanced rectal cancer [1, 2]. In several studies, good and complete pathologic response after preoperative CRT has led to good prognosis in rectal cancer [3–5].

Serum carcinoembryonic antigen (CEA) is the generally used tumor marker in patients with colorectal malignancy. Initially elevated CEA level before treatment is informative for predicting poor prognosis of a colorectal cancer patient, and serial checkups of post-treatment CEA level are performed to detect tumor recurrence after curative surgery [6–9]. Normalization of the postoperative CEA level after curative surgery has been associated with improved

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recurrence-free survival (RFS) and overall survival (OS) in rectal cancer [10–12]. Several recent studies reported that an elevation of pre-CRT CEA (> 5 ng/mL) level is a negative predictor of tumor downstaging and reduction of CEA level after preoperative CRT in rectal cancer could be a favorable prognostic factor [11–13]. However, the optimal cutoff value of post-CRT CEA level and clinical consequence of CEA change during CRT for tumor response and recurrence have not yet been clearly settled in rectal cancer. In a retrospective study, a decrease of CEA level after CRT was an independent predictor of good tumor regression [13]. However, the study had some limitations for short-term follow-up, small number of enrolled patients, and the retrospective and single-center design.

Thus, it is worthwhile to evaluate whether the change of the CEA level between before and after CRT is related to tumor response and recurrence. We performed a retrospective multicenter study to analyze the significance of post-CRT CEA level for pathologic complete response after CRT and RFS.

Materials and methods

Patients

The multicenter retrospective study assessed the association between post-CRT CEA level and tumor response and recurrence. The study was carried out by the Korean Radiation Oncology Group (KROG). Eligibility criteria included histopathologically confirmed adenocarcinoma within 10 cm of the anal verge, clinical T3-4N0-2M0, and no history of previous malignancy. We enrolled 1804 patients with rectal cancer who underwent preoperative CRT and curative surgery between March 2003 and June 2014 at eight institutions in Korea. In the data analysis, 336 patients had no record of post-CRT CEA level before radical surgery, one patient had previous malignancy history, and 20 patients had unavailable pathologic reports. Thus, they were excluded and the remaining 1447 patients were finally analyzed for this study. Institutional review board approvals of all participating centers were obtained, and the patient data were transferred to the KROG Data Management Center.

Evaluation

Staging workups included digital rectal examination, flexible sigmoidoscopy, chest and pelvic computed tomography (CT) scans, pelvic magnetic resonance (MR) scan, and CEA measurements. Preoperative CEA levels have been checked before and after CRT. Clinical and pathologic stages were determined according to the American Joint Committee on Cancer Staging, 7th edition. Colorectal pathologists who were highly specialized evaluated the pathologic specimens and assessed

the treatment response of preoperative CRT. A pathologic complete response (ypCR) definition was no viable tumor cells and only fibrotic mass in the pathologic specimen (ypT0N0).

Treatment

All patients received preoperative radiation of 50.4 Gy in 28 fractions. The radiotherapy consisted of whole pelvic radiotherapy dose of 45 Gy in 25 fractions and boost dose of 5.4 Gy in three fractions on the primary tumor. Concurrent chemotherapy consisting of bolus injection of 5-fluorouracil (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) for the first and last week of radiotherapy or continuous injection of 5-FU (225 mg/m^2/day) or oral capecitabine (825 mg/m^2, twice daily) was administered during radiotherapy. Total mesorectal excision (TME) was performed 4 to 8 weeks after preoperative CRT.

Statistical analysis

A receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of post-CRT CEA level for pathologic complete response after CRT. The threshold for maximum of (sensitivity + specificity) was calculated using ROC curve. The maximum value of the index (sensitivity + specificity) was represented as a criterion for selecting the optimal cutoff point [14]. Thus, post-CRT CEA point of 2.5 (area under curve, 0.593, $p < 0.001$) was adopted as the cutoff value in this study (Fig. 1). CEA level exhibited a
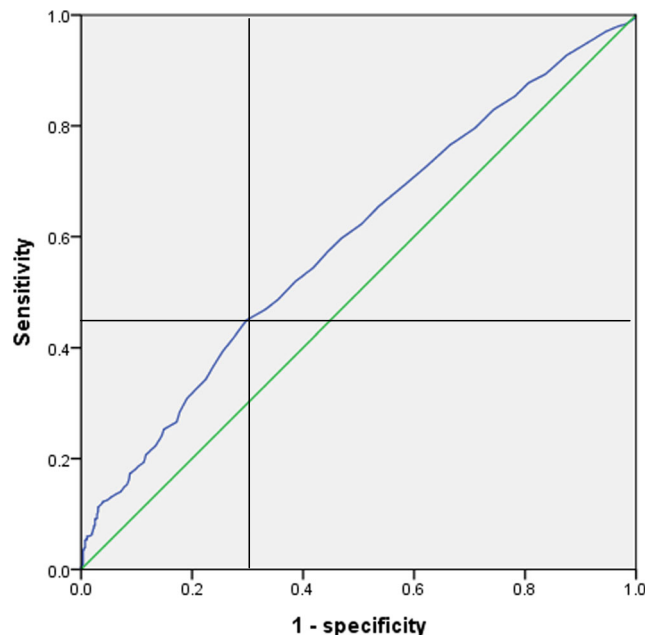

Fig. 1 Receiver-operating characteristic curve of post-chemoradiotherapy carcinoembryonic antigen (CEA) level with regard to pathologic complete response

maximum value of sensitivity (46.7 %) plus specificity (67.0 %) at 2.5 ng/mL. All predictive factors which were related to tumor response after CRT were analyzed by chi-square test. A logistic regression model was used in the multivariate analysis. RFS was defined as the time interval from the day of surgery to the day of any recurrence or death. OS was defined as the time interval from the day of surgery to the day of any death. The survival rate was estimated by the Kaplan-Meier method and compared by the log-rank test. A p value <0.05 by two-tailed tests was considered statistically significant. All statistical analyses were performed using SPSS version 12.0 (Chicago, IL, USA).

Results

Patient and tumor characteristics are summarized in Table 1. The study population was mostly male patients (69.0 %) with a median age of 62 years (range 27–84). The median distance between tumor margin and anal verge was 5 cm (range, 0–10). A total of 1360 (94.0 %) of 1447 patients had clinical T3 disease and 87 patients (6.0 %) had clinical T4 disease. 1144 (79.1 %) of 1447 patients had clinically positive node.

Table 1 Patient characteristics ($n = 1447$)

Characteristic	Number (%)
Age, year	
≤60	751 (51.9)
>60	696 (48.1)
Gender	
Male	999 (69.0)
Female	448 (31.0)
Distance of tumor from anal verge, cm	
≤5	761 (52.6)
>5	686 (47.4)
Tumor differentiation	
Well	226 (15.6)
Moderate	1187 (82.0)
Poor	34 (2.4)
Clinical T classification	
cT3	1360 (94.0)
cT4	87 (6.0)
Clinical N classification	
N0	303 (20.9)
N1	748 (51.7)
N2	396 (27.4)
Pretreatment CEA level, ng/mL	
≤5	954 (65.9)
>5	493 (34.1)

CEA carcinoembryonic antigen

Tumor response after chemoradiotherapy

One hundred and sixty (11.1 %) of 1447 patients had ypCR after preoperative CRT. Tumor downstaging was observed in 707 (48.9 %) of 1447 patients, and nodal downstaging was observed in 858 (59.3 %) of 1447 patients. Table 2 shows results of univariate and multivariate analyses of factors associated with ypCR after CRT. On the univariate analysis, pre-CRT CEA ($p = 0.001$), post-CRT CEA ($p = 0.036$), clinical T classification ($p = 0.007$), clinical N classification ($p < 0.001$), tumor location ($p = 0.001$), and tumor size ($p < 0.001$) were significantly associated with ypCR. Additional multivariate analysis revealed that pre-CRT CEA [odds ratio (OR), 0.507 and 95 % confidence interval (CI), 0.343–0.750; $p = 0.001$], clinical T classification (OR, 0.589 and 95 % CI, 0.419–0.826; $p = 0.021$), clinical N classification (OR, 0.642 and 95 % CI, 0.443–0.930; $p = 0.001$), tumor location (OR, 1.42 and 95 % CI, 1.10–1.84; $p = 0.006$), and tumor size (OR, 0.619 and 95 % CI, 0.439–0.872; $p = 0.002$) were independent predictors for ypCR of rectal tumors.

Recurrence and survival

After curative surgery, 1306 (90.2 %) of 1447 patients received 5-FU- or capecitabine-based adjuvant chemotherapy. After a median follow-up time of 51 months, the 5-year RFS rate was 79.3 % and the 5-year OS rate was 88.1 % for all patients. Locoregional recurrence occurred in 64 patients, and distant recurrence occurred in 224 patients during the follow-up period.

The 5-year RFS rate was significantly higher in the post-CRT CEA of ≤2.5 ng/mL group than in the post-CRT CEA of >2.5 ng/mL group (82.7 vs. 74.3 %, $p < 0.001$; Fig. 2a). Twenty-nine patients (3.4 %) in the post-CRT CEA of ≤2.5 ng/mL group and 35 patients (5.8 %) in the post-CRT CEA of >2.5 ng/mL group had local recurrences. The difference of locoregional recurrence rates between two groups was significant ($p = 0.037$). One hundred thirteen patients (13.3 %) in the post-CRT CEA of ≤2.5 ng/mL group and 111 patients (18.5 %) in the post-CRT CEA of >2.5 ng/mL group had distant recurrences. The difference of distant recurrence rates between two groups was significant ($p = 0.008$). The 5-year RFS rate was significantly higher in the ypCR group than in the non-ypCR group (97.3 vs. 76.9 %, $p < 0.001$; Fig. 2b). The 5-year OS rate was significantly higher in the post-CRT CEA of ≤2.5 ng/mL group than in the post-CRT CEA of >2.5 ng/mL group (89.1 vs. 86.6 %, $p = 0.003$; Fig. 2C). The 5-year OS rate was significantly higher in the ypCR group than in the non-ypCR group (96.5 vs. 87.0 %, $p < 0.001$; Fig. 2d).

Based on the pre- and post-CRT CEA level, we categorized patients into three groups. Group A comprised pre-CRT CEA ≤5 ng/mL. Group B comprised pre-CRT CEA >5 ng/mL and

Table 2 Analyses of factors associated with pathologic complete response after chemoradiotherapy

Factor	Univariate (*p*)	Adjusted odds ratio and 95 % confidence interval	Multivariate (*p*)
Age, year	0.554		0.908
≤60		1.00 (referent)	
>60		1.01 (0.78–1.31)	
Gender	0.341		0.882
Male		1.00 (referent)	
Female		0.98 (0.74–1.28)	
Pre-CRT CEA, ng/mL	0.001		0.001
≤5		1.00 (referent)	
>5		0.507 (0.343–0.750)	
Post-CRT CEA, ng/mL	0.036		0.095
≤2.5		1.00 (referent)	
>2.5		0.849 (0.587–1.228)	
Clinical T classification	0.007		0.021
cT3		1.00 (referent)	
cT4		0.589 (0.419–0.826)	
Clinical N classification	<0.001		0.001
cN−		1.00 (referent)	
cN+		0.642 (0.443–0.930)	
Histological tumor grade	0.091		0.149
Low		1.00 (referent)	
High		1.53 (0.85–2.75)	
Distance of tumor from anal verge, cm	0.001		0.006
≤5		1.00 (referent)	
>5		1.42 (1.10–1.84)	
Tumor size, cm	<0.001		0.002
≤4		1.00 (referent)	
>4		0.619 (0.439–0.872)	
Interval between radiation and operation, week	0.537		0.806
≤7		1.00 (referent)	
>7		0.96 (0.75–1.25)	
Concurrent chemotherapy	0.306		0.252
5-FU based regimen		1.00 (referent)	
Capecitabine		1.22 (0.86–1.73)	

CEA carcinoembryonic antigen, *FU* fluorouracil

post-CRT CEA ≤2.5 ng/mL. Group C comprised pre-CRT CEA >5 ng/mL and post-CRT CEA >2.5 ng/mL. All patients who had comprised pre-CRT CEA ≤5 ng/mL had post-CRT CEA ≤2.5 ng/mL. The 5-year RFS rate was significantly higher in group A than in group B and C (82.6 vs. 73.7 vs. 72.2 %, $p < 0.001$; Fig. 3a). The 5-year OS rate was significantly higher in group A than in groups B and C (90.1 vs. 84.4 vs. 83.4 %, $p < 0.001$; Fig. 3b). However, the differences of RFS and OS rate between groups A and B were significantly larger than between groups B and C (all, $p < 0.001$). The differences of RFS ($p = 0.326$) and OS ($p = 0.414$) rate between group B and C were not statistically significant.

Discussion

In our multi-institutional analyses, 160 (11.1 %) of 1447 patients achieved a ypCR after CRT. This is very similar to the results achieved by other series where 8–12 % of the patients in the preoperative CRT group had a ypCR [1–3]. Serum CEA is a valuable prognostic marker in colorectal cancer patients [15, 16]. In the present study, an elevated CEA level of >5 ng/mL was significantly associated with poor tumor response, and our results were in accordance with those of Yoon SM et al. [17], which suggest that a pretreatment CEA level of >5 ng/mL is a useful predictor of poor tumor regression. Post-treatment serial
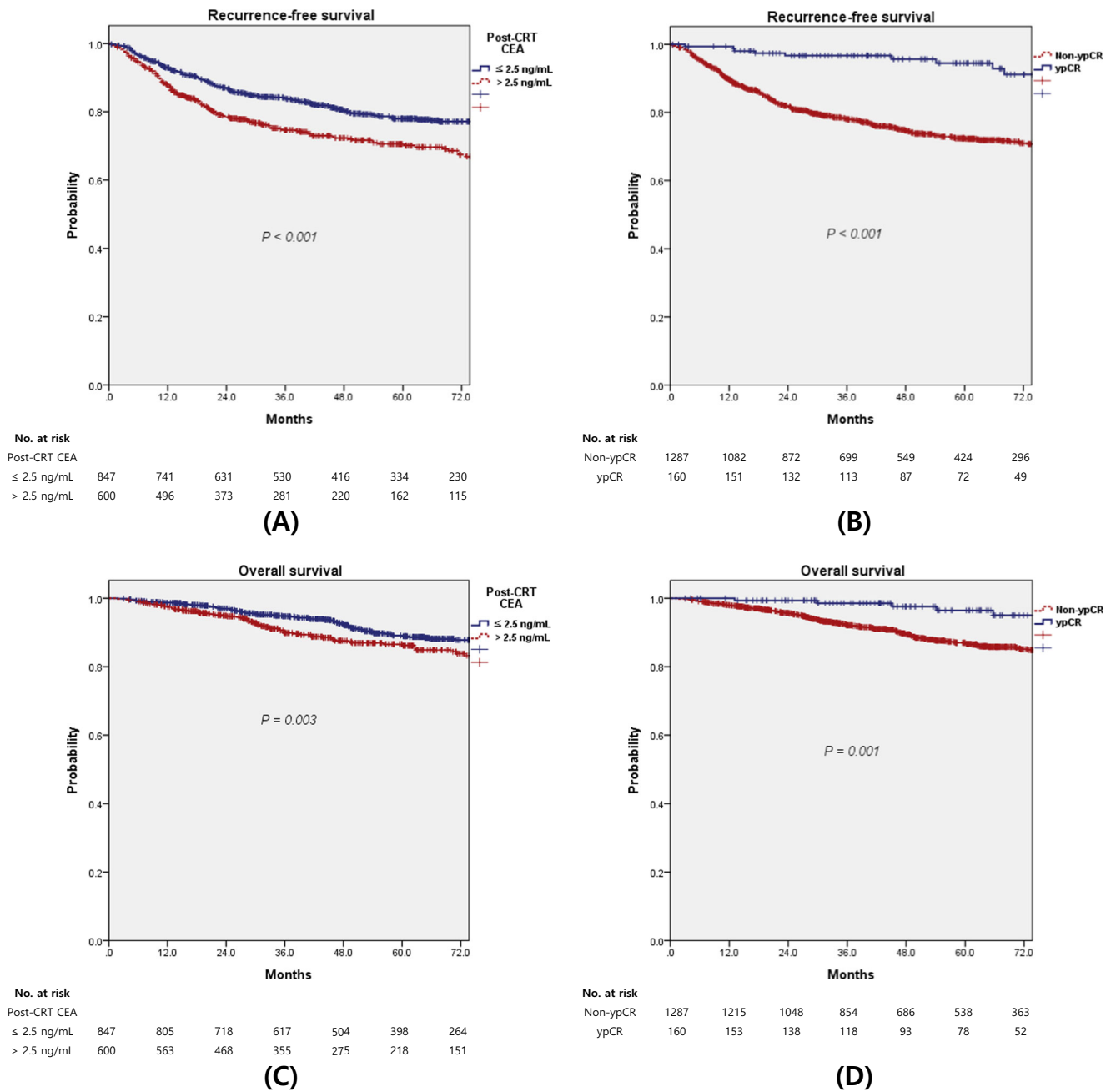
Fig. 2 Recurrence-free survival according to the post-CRT CEA level (**a**) and tumor response (**b**) and overall survival according to the post-CRT CEA level (**c**) and tumor response (**d**)

CEA can also provide an opportunity to detect the recurrent tumor [18, 19]. National Comprehensive Cancer Network guidelines suggest CEA as a tumor marker for following up colorectal cancer patients [20]. Several studies described the correlation between pretreatment CEA level and tumor response. Lee et al. reported that pre-CRT elevation of CEA level predicts poor tumor response and frequent distant recurrence in rectal cancer [21]. Park et al. described that an elevated pretreatment CEA level was an independent predictor for pathologic tumor response to CRT [22].

The prognostic significance of post-CRT CEA level in rectal cancer has been evaluated in only few series [13, 23]. In a recent retrospective study, the post-CRT CEA ≤2.7 ng/mL was identified as a good prognostic factor for disease-free survival [13]. In that study, post-CRT CEA level was also identified as a predictor of tumor regression and tumor down-staging. Our results suggest that post-CRT CEA <2.5 ng/mL could predict low locoregional ($p = 0.037$) and distant recurrence ($p = 0.008$) rate in rectal cancer patients who receive preoperative CRT and curative surgery. However, in the present study, post-CRT CEA ≤2.5 ng/mL
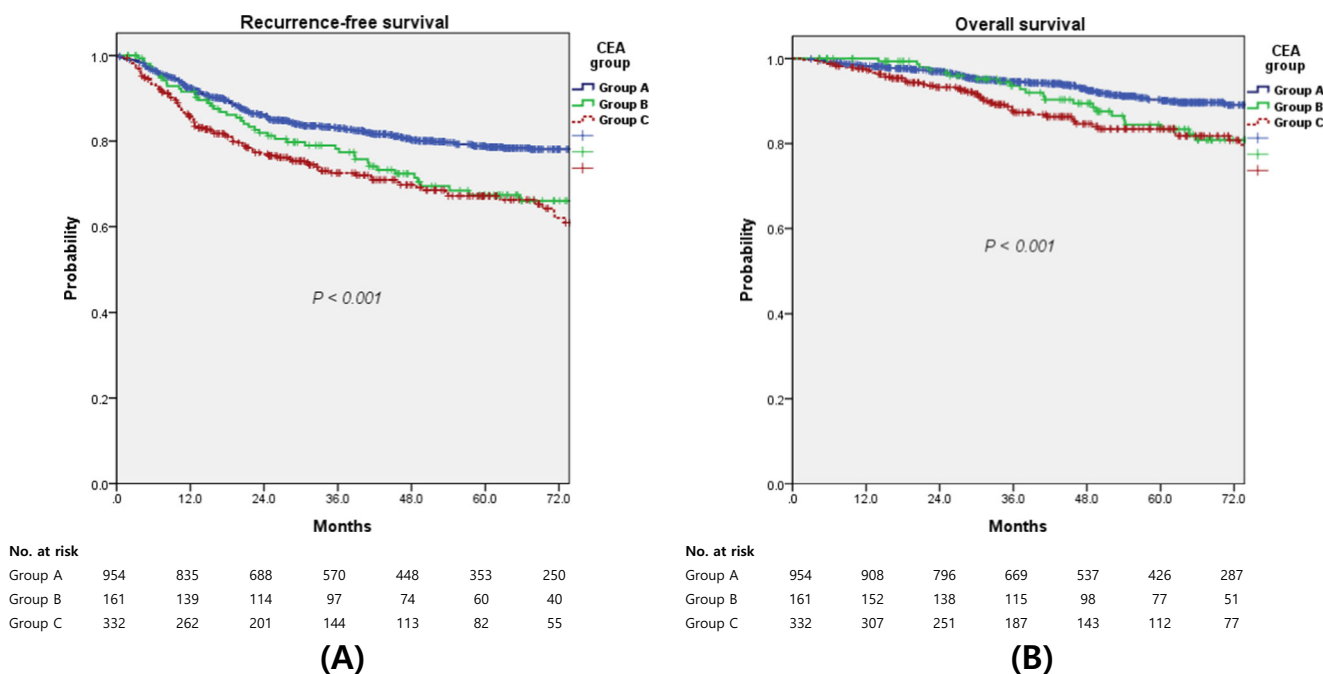
Fig. 3 Recurrence-free survival (**a**) and overall survival (**b**) according to the CEA grouping (group A: pre-CRT CEA ≤5 ng/mL, group B: pre-CRT CEA >5 ng/mL and post-CRT CEA ≤2.5 ng/mL, and group C: pre-CRT CEA >5 ng/mL and post-CRT CEA >2.5 ng/mL)

was not a significant predictor of ypCR after CRT on multivariate analysis. In our analyses, we assessed the ypCR after the CRT according to the clinical characteristics. On the multivariate analysis, the pre-CRT CEA level ($p = 0.001$), cT classification ($p = 0.021$), cN classification ($p = 0.001$), and tumor size ($p = 0.002$) were significant factors for ypCR. These results are similar to those of Yoon et al. [17] who reported that cT and cN classification, pretreatment CEA, and tumor volume were significantly associated with tumor downstaging after CRT in rectal cancer.

We evaluated the 5-year RFS rate according to combination of pre-CRT and post-CRT CEA levels (group A: pre-CRT CEA ≤5 ng/mL; group B: pre-CRT CEA >5 ng/mL and post-CRT CEA ≤2.5 ng/mL; and group C: pre-CRT CEA >5 ng/mL and post-CRT CEA >2.5 ng/mL). The RFS rates at 5 years were 82.6 % in group A, 73.7 % in group B, and 72.2 % in group C. The difference of RFS and OS rates between group A and B was significantly larger than between groups B and C (all, $p < 0.001$), and there was no significant difference of 5-year RFS and OS rate between group B and C (all, $p > 0.05$). In the multivariate analysis, pre-CRT CEA ($p = 0.001$) levels more significantly affected pathologic tumor response than post-CRT CEA levels ($p = 0.095$). In our study, we perform a ROC analysis to determine the optimal cutoff value of post-CRT CEA level for ypCR after CRT. Although we deduct a cutoff value of 2.5 ng/ml through the Youden index [maximum of (sensitivity + specificity)], the shape of ROC curve for post-CRT CEA level is regularly convex, not angled. Thus, not only AUC but

also sensitivity and specificity are relatively low at any point of post-CRT CEA level. Pre-CRT CEA level could have more significant impact on tumor response and RFS than post-CRT CEA levels.

This study had several limitations. First, our study should be understood in view of the inherent biases of a retrospective study design [24]. However, we conducted a multicenter retrospective study that enrolled 1447 patients in eight institutions, and all patients received a standard radiotherapy of 50.4 Gy in 28 fractions followed by total mesorectal excision. Thus, the evaluation of predictive factors seems reliable for those treated with this modality, which is the standard treatment of locally advanced rectal cancer. Second, concurrent chemotherapy was not delivered by the same regimen and schedule. Thus, we categorized chemotherapy regimens into three types (continuous 5-FU, bolus 5-FU and leucovorin, and oral capecitabine) and verified that the type of concurrent regimen had no significant effect on pathologic tumor response.

Conclusion

CEA change during preoperative CRT in rectal cancer has no significant effect on tumor response and recurrence-free survival. Pre-CRT CEA level rather than post-CRT CEA is an independent predictor for tumor response and recurrence-free survival in rectal cancer patients treated with preoperative CRT followed by curative resection.

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