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Value of Carcinoembryonic Antigen Levels After Chemoradiotherapy for Advanced Low Rectal Cancer

ATSUSHI TSURUTA[1], KAZUHIKO YOSHIMATSU[2] and TOMIO UENO[2]

[1]Department of Supportive and Palliative Medicine, Kurashiki Medical Center, Kurashiki, Japan;
[2]Department of Digestive Surgery, Kawasaki Medical School, Kurashiki, Japan

Abstract

Background/Aim: Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision is the standard treatment for advanced low rectal cancer; however, long-term oncological outcomes vary widely, and reliable prognostic biomarkers remain limited. Carcinoembryonic antigen (CEA) is commonly used in colorectal cancer management, but the prognostic value of post-CRT CEA levels has not been fully clarified. This study aimed to identify clinically relevant prognostic factors for recurrence and survival, with particular focus on pre- and post-CRT CEA levels.
Patients and Methods: A retrospective review was conducted of 41 consecutive patients with advanced low rectal cancer (Rb, cT3/4 or N1/2 and no lateral lymph node metastasis) who underwent long-course preoperative CRT followed by radical surgery. CRT consisted of 45 Gy in 25 fractions with concurrent tegafur/uracil, followed by total mesorectal excision 8-10 weeks after CRT completion. Clinicopathological factors were analyzed in relation to recurrence, disease-free survival (DFS), and overall survival (OS).
Results: With a median follow-up of 69.3 months, recurrence occurred in 16 patients. Five-year DFS and OS rates were 59.4% and 73.2%, respectively. Univariate analysis identified postoperative complications, pathological complete response, and pre- and post-CRT CEA levels as significant factors associated with recurrence. Multivariate analysis demonstrated that post-CRT CEA was the only independent prognostic factor. Receiver operating characteristic analysis identified a post-CRT CEA cut-off value of 3.9 ng/ml. Patients with lower post-CRT CEA showed significantly better DFS and OS.
Conclusion: Post-CRT CEA is a valuable prognostic biomarker for recurrence and survival in advanced low rectal cancer, and patients with elevated post-CRT CEA may benefit from additional consolidation chemotherapy.

Keywords: Low rectal cancer, chemoradiotherapy, carcinoembryonic antigen (CEA).

Atsushi Tsuruta, Department of Supportive and Palliative Medicine, Kurashiki Medical Center, 250, Bakuro-cho, Kurashiki, Okayama 710-8522, Japan. Tel: +81 864222111, Fax: +81 864224150, e-mail: tigarjava@icloud.com

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Introduction

Colorectal cancer (CRC) is responsible for approximately 10% of all diagnosed malignant tumors and cancer-related deaths worldwide. In 2020 approximately 1.9 million new cases were reported. Moreover thirty-nine percent of CRC cases are diagnosed as the rectal cancer (1). Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) had been the standard treatment for locally advanced rectal cancer patients in Western countries (2, 3). However, the long-term results of the CAO/ARO/AIO-94 trial showed that the benefit of preoperative CRT was limited on local control and there was no effect on disease-free survival (DFS) and overall survival (OS) (4). In recent years, a novel treatment strategy known as total neoadjuvant therapy (TNT) has emerged and is increasingly being adopted, particularly in Western countries. This strategy consists of systemic chemotherapy administered before and/or after preoperative radiotherapy or chemoradiotherapy (RT/CRT) for the purpose of enhancing local tumor control. It addresses a major limitation of preoperative RT/CRT, namely its insufficient efficacy in preventing distant metastases. TNT is generally categorized based on the timing of systemic chemotherapy relative to RT/CRT, comprising induction chemotherapy administered prior to RT/CRT and consolidation chemotherapy administered following RT/CRT. A multicenter, phase 2, non-randomized trial revealed that administration of mFOLFOX6 following chemoradiotherapy and prior to TME may expand the subset of patients suitable for less invasive therapeutic approaches (5).

Two phase 3 trials evaluating consolidation chemotherapy and one phase 3 trial investigating induction chemotherapy demonstrated that these TNT models were associated with high rates of pathological complete response (pCR) (6-8). By contrast, the Polish II trial showed that TNT incorporating short-course radiotherapy achieved pCR rates comparable to those obtained with long-course CRT. However, this strategy failed to confer a measurable oncological benefit (9).

In addition, the RAPIDO (consolidation) and PRODIGE 23 (induction) trials revealed that short- and long-term outcomes with TNT were superior to those with CRT (7, 8). The primary end point of the RAPIDO Trial was the 3-year disease-related treatment failure. In this trial, a significant improvement was obtained in the TNT group (short-course RT with CapeOX or FOLFOX) regarding both disease-related treatment failure and pCR rate compared with the CRT group (7). In the PRODIGE 23 trial, an intensified induction chemotherapy regimen using FOLFIRINOX was administered prior to long-course CRT in the TNT group. In the PRODIGE 23 trial, an intensified induction chemotherapy regimen using FOLFIRINOX was administered prior to long-course CRT in the TNT group. The completion rate of six cycles of FOLFIRINOX was high at 92%, while grade 3-4 adverse events occurred in 45% of patients. The trial also showed that the TNT group had a significant improvement in both 3-year DFS and pCR rate compared with the CRT group (8). Furthermore, subsequent reports with long-term follow-up demonstrated that the TNT group achieved superior outcomes compared with the CRT group, with higher 7-year DFS (67.6% *vs.* 60.7%) and OS rates (81.9% *vs.* 76.1%) (10).

The OPRA trial was the first large-scale prospective randomized study designed to evaluate the safety of nonoperative management (NOM) of patients who achieved a favorable tumor response following TNT. DFS was compared between induction or consolidation TNT strategies and historical controls treated with conventional CRT. The 3-year DFS rate was 76% in both treatment arms, which was comparable to the 75% observed in the historical control cohort (11).

Nevertheless, TNT expands the time that is required for the completion of treatment as compared with CRT. Moreover, TNT is mainly aimed to enhance oncologic radicality by reinforcing preoperative treatment for patients with high risk of recurrence. However, applying the same aggressive neoadjuvant approach to patients with a low risk of recurrence may represent overtreatment and impose an unnecessary treatment-related burden.

Therefore, adding neoadjuvant chemotherapy after or before CRT should not be necessary for all advanced rectal cancer patients.

In this study, we aimed to identify predictive markers of recurrence and survival, focusing on pre- and post-CRT CEA levels, which may help guide the selection of patients for TNT rather than CRT.

Patients and Methods

Between February 2008 and October 2019, forty-one consecutive patients with low rectal cancer (Rb, cT3/4 or N1/2 and no lateral lymph node metastasis) who underwent preoperative CRT followed by radical surgery at the Department of Digestive Surgery, Kawasaki Medical School, were studied. Patients in whom lateral pelvic lymph node metastasis was clinically suspected were excluded from the present study, because these patients were managed with preoperative systemic chemotherapy followed by curative surgery rather than CRT. The treatment consisted of long-course RT (25 fractions of 1.8 Gy) and concurrent tegafur/uracil (UFT), followed by radical surgery after 8-10 weeks. Oral uracil/tegafur was given for two consecutive weeks followed by a 1-week rest and then was given for two more weeks. The surgical procedure followed the TME that was the principal proposed by Heald *et al*. (12). The patients were retrospectively evaluated in this study, using those patients' medical records, which included information on patients, their tumors, surgeries and prognoses. Clinicopathological data, which included recurrence and survival, were reviewed by using medical records. TNM classifications were defined according to the criteria of the Japanese Classification of colorectal, appendiceal, and anal carcinoma (9th Japanese edition, 3rd English edition) (13).

Ethical approval. This study was approved by the Institutional Ethics Committee of Kawasaki Medical School (approval number: 3791-01) and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective nature of the study and the use of anonymized patient data.

Statistical analysis. Statistical analyses were performed with JMP ver. 14.0 (SAS Institute Inc., Cary, NC, USA). Data are presented as mean±standard deviation or median (range). Continuous variables were analyzed using Student's *t*-test and categorical variables were analyzed using the χ^2 test. Univariate and multivariate survival analysis were performed in order to identify independent predicting factors by using Cox regression analysis. The cut-off value was established by a receiver operating characteristic (ROC) curve. DFS was analyzed separately using the Kaplan-Meier method and log-rank tests. Statistical significance was determined by p values of less than 0.05.

Results

Patient characteristics. A total of forty-one patients who received preoperative CRT for locally advanced rectal cancer were included in this study. The median follow-up duration was 69.3 months (range=8.1-98.2 months). The mean age of the entire cohort was 65.4±10.2 years, and the mean body mass index (BMI) was 20.8±3.0 kg/m^2. Among the participants, 30 (73.2%) were male and 11 (26.8%) were female. The majority of patients were treated with abdominoperineal resection (APR), accounting for 68.3% of the cohort, while others received low anterior resection (LAR), intersphincteric resection (ISR), or Hartmann's procedure. Postoperative complications of Clavien–Dindo grade ≥II occurred in 11 patients (26.8%). The pCR rate was 12.2%. Downstaging was observed in 43.9% of cases for T classification, 43.9% for N classification and 58.5% for overall stage, respectively. Adjuvant chemotherapy was administered in sixteen patients, whereas twenty-five patients did not receive adjuvant chemotherapy (Table I).

Recurrence data. Patients were categorized based on the presence or absence of recurrence. During follow-up, disease relapse was observed in sixteen patients, involving eighteen recurrent lesions in total, while the remaining

Table I. *Clinicopathological characteristics of patients (n=41) with advanced low rectal cancer.*

Age (years), mean±SD	65.4±10.2
Sex (Male/Female), n	30/11
BMI (kg/m^2), mean±SD	20.8±3.0
Approach, n	
Lap/Open	19/22
Surgical procedure, n	
LAR	8
ISR	3
Hartmann	2
APR	28
Bleeding (ml), median (range)	58 (5-1300)
Duration (min), median (range)	427 (200-627)
cT (2/3/4a/4b) (pre-CRT) n	1/34/1/5
ypT (0/1a/2/3/4b) (post-surgery), n	5/1/11/20/4
T down stage (N/Y), n	23/18
cN (0/1/2), n	12/21/8
ypN (0/1a/1b/2), n	27/12/2
N down stage (N/Y), n	23/18
cStage(IIa/IIb/IIc/IIIa/IIIb/IIIc), n	9/1/2/1/25/3
ypStage(0/I/IIa/IIb/IIc/IIIa/IIIb/IIIc), n	5/9/10/0/2/3/10/2
Stage down stage (No/Yes), n	18/23
Pathological diagnosis, n	
Pap/Tub1/Tub2/Muc	1/17/21/2
Histology grade, n	
1a/1b/2/3	18/6/12/5
pCR rate (%)	12.2
Postoperative complications (Clavien-Dindo), n	
0/1/2/3a/3b	29/1/9/1/1
Adjuvant chemotherapy, n	
No	25
Yes (Capecitabine/UFT/LV/SOX)	10/5/1

BMI: Body mass index; SD: standard deviation; Lap: laparoscopic; LAR: low anterior resection; ISR: intersphincteric resection; APR: abdominoperineal resection; CRT: chemoradiotherapy; Pap: papillary; Tub1: well-differentiated tubular adenocarcinoma; Tub2: moderately differentiated tubular adenocarcinoma; Muc: mucinous; pCR: pathological complete response; UFT: tegafur uracil; LV: leucovorin; SOX: S-1+oxaliplatin.

twenty-five patients showed no evidence of recurrence throughout the study period. The lung was the most frequent site of relapse (n=7), followed by the liver (n=4), local recurrence (n=2), distant lymph nodes (n=2), bone (n=2), peritoneal dissemination (n=1) and brain (n=1).

Univariate and multivariate analyses of clinicopathological factors associated with recurrence. Clinicopathological characteristics of the study cohort, categorized by recurrence status, are presented in Table II. Baseline demographic and clinical variables were well balanced between the two groups, with no statistically meaningful differences. Specifically, the mean age was 65.1±10.9 years old in the non-recurrence group and 66.0±9.3 years old in the recurrence group (p=0.785). Likewise, BMI (21.0±2.4 *vs*. 20.7±3.9 kg/m^2, p=0.795) and sex distribution (men/women: 17/8 *vs*. 13/3, p=0.350) were comparable between two groups. The distribution of surgical approaches (laparoscopic *vs*. open surgery) did not significantly differ between patients with and without recurrence (p=0.790). Similarly, the frequency of each operative procedure – including low anterior resection (LAR), intersphincteric resection (ISR), Hartmann's procedure, and abdominoperineal resection (APR) – was comparable (p=0.201). Intraoperative blood loss and operative duration were analyzed, with operative time showing a trend toward longer durations in the recurrence group, although this difference did not reach statistical significance across all parameters. Postoperative complications, stratified by Clavien–Dindo grade, were evaluated. The recurrence group exhibited a higher rate of moderate-to-severe complications (grade II-IIIb) (p=0.007), which may reflect impaired perioperative physiological reserve or tumor biology associated with recurrence risk. In univariate analysis, both lower pre- and post-CRT serum carcinoembryonic antigen (CEA) levels were significantly associated with reduced recurrence risk (p=0.017, 0.0004). Moreover, the pCR rate and postoperative complications (0-I *vs*. II-IIIb) also showed a modest association with recurrence (p=0.020, 0.007). No meaningful associations were observed for other clinicopathological factors, including clinical or pathological T, N, and stage classifications with downstaging status, histopathological findings, pre- and post-treatment CA19-9 levels, tumor location, or the use of adjuvant chemotherapy. On multivariate logistic regression analysis, post-CRT CEA level emerged as an independent predictor of recurrence (odds ratio 0.457, 95% confidence interval=0.245-0.851, p=0.0008), indicating that patients with lower post-CRT CEA levels had a significantly lower likelihood of relapse. No other factors retained significance in the multivariate model.

Table II. *Univariate and multivariate analyses of factors associated with tumor recurrence in patients with advanced low rectal cancer.*

	Recurrence		Univariate	Multivariate (Recurrence)		
	–	+	*p*-Value	OR	95%CI	*p*-Value
Age (years), mean±SD	65.12±10.93	66±9.32	0.7846			
Sex (Male/Female), n	17/8	13/3	0.35			
BMI (kg/m^2), mean±SD	21.0±2.4	20.7±3.9	0.7945			
Approach Lap/Open, n	13/12	9/7	0.79			
Surgical procedure, n						
LAR	6	2	0.201			
ISR	3					
Hartmann	2					
APR	14	14				
Bleeding (ml), median	50	66	0.747			
Duration (min), median	395	448	0.333			
cT (2/3/4a/4b), n	1/23/0/1	0/11/1/4	0.095			
ypT (0/1/2/3/4b), n	5/1/8/10/1	0/0/3/10/3	0.105			
T down stage (No/Yes), n	12/13	11/5	0.192			
cN (0/1a/1b/2), n	8/12/1/4	4/8/0/4	0.749			
ypN (0/1a/1b/2), n	18/5/2/0	9/4/1/2	0.303			
N down stage (N/Y), n	14/11	9/7	0.987			
cStage, n			0.148			
(IIa/IIb/IIc/IIIa/IIIb/IIIc)	7/0/1/1/16/0	2/1/1/0/9/3				
ypStage, n			0.201			
(0/I/IIa/IIb/IIc/IIIa/IIIb/IIIc)	5/7/5/0/1/2/5/0	0/2/5/0/1/1/5/2				
Stage down stage (No/Yes), n	8/17	9/7	0.987			
Pathological diagnosis, n						
Pap/Tub1/Tub2/Muc	0/13/10/2	1/4/11/0	0.105			
Histology grade, n						
1a+1b/2+3	12/13	12/4	0.087			
pCR rate (%), mean±SD	20	0	0.020			0.094
CEA (ng/ml), mean±SD						
Pre-CRT	6.00±8.98	9.75±8.42	0.0169	1.07	0.932-1.229	0.248
Post-CRT	2.5±1.19	6.08±4.08	0.0004	0.457	0.245-0.851	0.0008
CA19-9 (U/ml), mean±SD						
Pre-CRT	35.20±84.23	1151.39±4424.97	0.8407			
Post-CRT	17.28±15.34	498.84±1925.80	0.8301			
Postoperative complication, n						
0-I/II-IIIb	22/3	8/8	0.007	3.617	0.453-28.877	0.344
Ra/Rb	6/19	2/14	0.365			
Adjuvant chemotherapy, n						
No/Yes	15/10	10/6	0.873			

BMI: Body mass index; SD: standard deviation; Lap: laparoscopic; LAR: low anterior resection; ISR: intersphincteric resection; APR: abdominoperineal resection; Pap: papillary adenocarcinoma; Tub1: well-differentiated tubular adenocarcinoma; Tub2: moderately differentiated tubular adenocarcinoma; Muc: mucinous carcinoma; pCR: pathological complete response; CEA: carcinoembryonic antigen; CRT: chemoradiotherapy; CA19-9: carbohydrate antigen 19-9; Bleeding and operative duration are presented as median.

Discriminatory ability of carcinoembryonic antigen for postoperative recurrence. Receiver operating characteristic curve analysis was applied to examine in detail the ability of CEA to discriminate patients who developed postoperative recurrence from those who did not. The analysis yielded an area under the curve (AUC) of 0.832, indicating excellent discriminative ability for identifying patients at risk of recurrence within five years after surgery (Figure 1). Taken together, these findings highlight the value of carcinoembryonic antigen as a noninvasive tool for postoperative monitoring, enabling the identification of disease recurrence at an earlier stage,

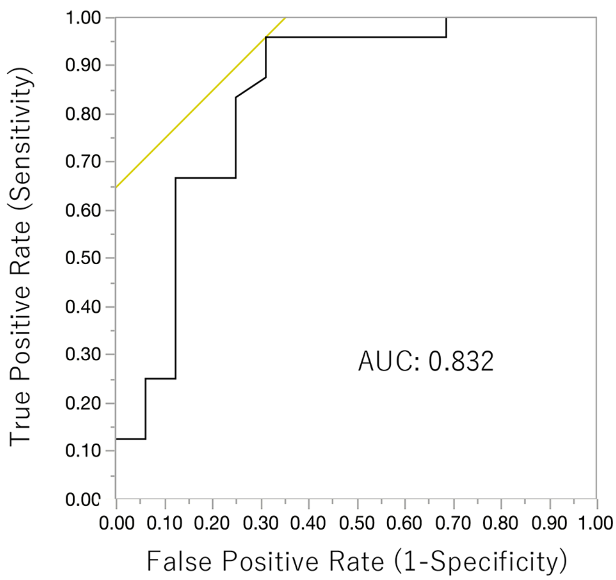

Figure 1. *Receiver operating characteristic (ROC) curve of post-chemoradiotherapy carcinoembryonic antigen (CEA) for recurrence (AUC=0.832). The area under the curve (AUC) was defined as the area under the ROC curve.*

when therapeutic intervention may be most beneficial. Using a cut-off value of 3.9 ng/ml, CEA demonstrated a sensitivity of 95.8%, correctly identifying all patients who experienced recurrence, and a specificity of 68.8%, indicating that the substantial proportion of patients without recurrence maintained CEA levels below this threshold.

Prognostic impact of post-CRT CEA on disease-free and overall survival. These observations support the relevance of post-treatment CEA as a prognostic marker in rectal cancer treated with CRT, potentially reflecting tumor control more reliably than pretreatment clinical and pathological features. Kaplan–Meier survival analyses were performed to evaluate the prognostic impact of post–CRT CEA levels, using a cutoff value of 3.9 ng/ml. Patients were stratified into two groups according to post-CRT CEA levels (<3.9 ng/ml *vs.* ≥3.9 ng/ml). DFS was significantly longer in patients with post-CRT CEA levels <3.9 ng/ml compared with those with CEA levels ≥3.9 ng/ml. The estimated 5-year DFS rate was 80.9% in the low-CEA group, whereas it was markedly reduced to 15.4% in the high-CEA group, demonstrating a clear separation between the survival curves (log-rank test, $p<0.0001$) (Figure 2A). Similarly, OS analysis revealed a significant survival advantage in patients with post-CRT CEA levels <3.9 ng/ml. The 5-year OS rate in the low-CEA group reached 85.7%, compared with 46.2% in the high-CEA group, indicating substantially poorer survival outcomes among patients with elevated post-CRT CEA levels ($p=0.004$) (Figure 2B).

These findings indicate that an elevated serum CEA level following CRT is strongly associated with inferior DFS and OS, underscoring the prognostic significance of post-CRT CEA as a biomarker for oncological outcomes in patients with rectal cancer.

Discussion

In the present study, we demonstrated that serum CEA levels measured after completion of preoperative CRT (post-CRT CEA) were a robust prognostic indicator for both recurrence and survival in patients with advanced low rectal cancer. In multivariate analysis, post-CRT CEA remained the only variable independently associated with both recurrence and OS, exceeding the prognostic value of established clinicopathological factors such as pathological complete response and postoperative morbidity.

Our observations support the view that CEA dynamics following treatment capture biologically relevant information regarding residual tumor burden and long-term disease behavior beyond that conveyed by baseline characteristics. CEA has been established as a tumor marker for colorectal cancer surveillance and recurrence detection after curative resection (14-16). However, its prognostic role in the neoadjuvant setting remains incompletely defined. Several studies have reported that elevated pretreatment CEA levels are associated with inferior oncologic outcomes in patients with rectal cancer undergoing CRT (17-19). Pretreatment CEA may reflect tumor volume, inflammatory status, or

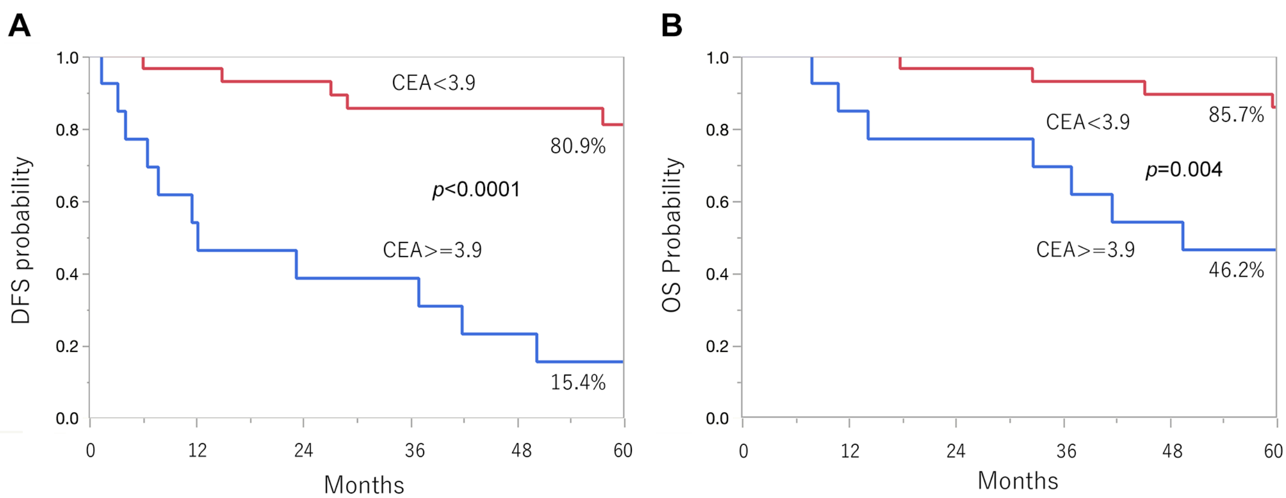

Figure 2. *Kaplan–Meier curves of disease-free survival (DFS) (A) and overall survival (OS) (B) stratified by post-chemoradiotherapy carcinoembryonic antigen (CEA) levels (cut-off: 3.9 ng/ml). Survival curves were compared using the log-rank test.*

host-related factors rather than intrinsic sensitivity to chemoradiation.

In contrast, post-CRT CEA represents a dynamic biomarker that integrates tumor biology and response to multimodal therapy. Persistently elevated CEA levels after CRT may indicate residual microscopic disease or an intrinsically aggressive tumor phenotype that is not fully eradicated by standard neoadjuvant treatment. This concept is consistent with recent molecular and clinicopathological studies demonstrating that specific biological features, including microRNA expression profiles and circulating tumor-related biomarkers, are associated with recurrence risk and survival in locally advanced rectal cancer (20, 21).

Moreover, patterns of local and distant recurrence after preoperative therapy have been shown to reflect underlying tumor biology rather than surgical factors alone (22, 23). The clinical relevance of CEA dynamics as a surrogate of tumor behavior has also been demonstrated in the metastatic setting. Kubota et al. reported a rapid decline in CEA levels and stabilization of metastatic lesions in an NRAS-mutant rectal cancer patient treated with FOLFIRI plus bevacizumab in combination with oral recombinant methioninase and a low-methionine diet, highlighting the close association between CEA kinetics and therapeutic response (24). Together with our findings, this evidence underscores the value of post-treatment CEA as a dynamic biomarker reflecting residual disease activity and treatment sensitivity across disease stages.

The importance of post-treatment CEA assessment becomes increasingly apparent when viewed against the backdrop of shifting therapeutic strategies for locally advanced rectal cancer. In this setting, total neoadjuvant therapy, which integrates induction or consolidation chemotherapy, has been shown to yield improved oncologic outcomes over standard CRT in multiple randomized phase III studies, including RAPIDO and PRODIGE 23 (7, 8). These trials showed improvements in pathological complete response rates and disease-related treatment failure or DFS. However, TNT inevitably prolongs treatment duration and increases treatment burden, which may not be appropriate for all patients. Therefore, biomarkers capable of identifying patients who would benefit most from treatment intensification are urgently needed. Our results suggest that patients with post-CRT CEA levels exceeding the ROC-derived cut-off value of 3.9 represent a high-risk subgroup for recurrence and may be appropriate candidates for consolidation chemotherapy following CRT. This approach aligns with emerging evidence supporting individualized neoadjuvant strategies based on recurrence patterns and biological risk profiles (22, 23, 25).

Postoperative complications were linked to an increased risk of recurrence and poorer survival on univariate analysis, which is in agreement with prior studies indicating a potential role of postoperative infectious or inflammatory responses in promoting tumor growth (26). Although postoperative complications were associated with outcomes in unadjusted analyses, their prognostic impact diminished after multivariate adjustment, in contrast to the persistent predictive value of post-CRT CEA. This finding suggests that biological tumor behavior exerts a greater influence on long-term outcomes than perioperative events in the setting of multimodal therapy.

Previous study reported that patients achieving pCR after chemoradiotherapy demonstrate superior long-term outcomes compared with those with residual disease (27, 28). The pCR likely reflects a biologically favorable tumor phenotype characterized by reduced metastatic potential and an associated improvement in survival. Although pCR is widely regarded as a favorable surrogate marker for oncologic outcomes, it did not emerge as an independent prognostic factor in our multivariate model. This may be attributable to the limited sample size and the heterogeneous biological behavior of non-pCR tumors. Importantly, post-CRT CEA may capture residual microscopic disease that escapes pathological detection, thereby providing complementary prognostic information beyond conventional histopathological assessment. This notion is supported by recent studies highlighting the prognostic relevance of circulating and molecular biomarkers in rectal cancer treated with neoadjuvant therapy (20, 21, 29).

In summary, the present study suggests that serum CEA levels measured after completion of preoperative CRT may provide useful prognostic information for patients with advanced low rectal cancer. Post-CRT CEA appears to reflect treatment response and residual disease activity, offering complementary insight beyond conventional clinicopathological parameters. While pathological response and postoperative factors remain important, our findings indicate that post-treatment CEA dynamics warrant consideration as part of postoperative risk assessment. Given the retrospective design and limited sample size of this study, these results should be interpreted with caution. Further large-scale prospective studies are required to validate the prognostic utility of post-CRT CEA and to determine its potential role within individualized neoadjuvant and adjuvant treatment strategies.

Limitations. First, this was a retrospective, single-institution study with a relatively small sample size, which may limit generalizability. Second, treatment strategies evolved during the long study period, potentially introducing heterogeneity. Nevertheless, the long median follow-up duration strengthens the reliability of survival analyses, and the consistent association between post-CRT CEA and oncologic outcomes supports its clinical relevance.

Conclusion

In conclusion, post-CRT CEA is a powerful and readily available prognostic biomarker in patients with advanced low rectal cancer undergoing preoperative CRT. Assessment of CEA levels after CRT treatment may aid in refining prognostic stratification and tailoring therapeutic decision-making, particularly by delineating a subset of patients who could derive benefit from further systemic therapy. Future investigations conducted across multiple institutions and in a prospective manner will be essential to confirm these observations and to define treatment frameworks incorporating post-CRT CEA in rectal cancer care.

Conflicts of Interest

All Authors declare that they have no conflicts of interest relevant to this study.

Authors' Contributions

Atsushi Tsuruta: Cancer treatment, Conceptualization, Methodology, Writing-original draft; Kazuhiko Yoshimatsu: Formal analysis; Tomio Ueno: Supervision.

Artificial Intelligence (AI) Disclosure

Artificial intelligence-based tools were used exclusively for assistance with linguistic refinement of the manuscript. These tools had no role in the study conception or design, data acquisition, analysis, or interpretation, or in the formulation of the study conclusions.

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