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Original Research Article

Prognostic Impact of the Postoperative Carcinoembryonic Antigen Level after Curative Resection of Locally Advanced Rectal Cancer

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Abstract

Objectives: This study was conducted to investigate whether preoperative or postoperative carcinoembryonic antigen (CEA) with a new cut-off value is more optimal for predicting long-term outcomes in patients with Stage II/III rectal cancer, and to investigate the effectiveness of postoperative adjuvant chemotherapy (POAC) based on the CEA values.

Methods: Serum CEA levels were measured preoperatively (pre-CEA) and postoperatively (post-CEA). The area under the receiver operating curve (AUROC) was used to determine a cut-off for CEA. The cut-off for CEA relative to recurrence-free survival (RFS) was established as that giving the highest AUROC. In comparison of superiority between pre- and post- CEA levels, Akaike's information criterion (AIC) was used in the Cox proportional-hazard regression model.

Results: The subjects were 323 patients who underwent curative surgical treatment for Stage II/III rectal cancer. AIC values indicated that RFS was better stratified by a post-CEA level with a cut-off of 2.3 ng/ml compared with other classifications of pre- or post- CEA. In Stage III or high-risk Stage II cases, there was no effect of POAC on RFS in those with post-CEA <2.3 ng/ml (p=0.39), but in those with post-CEA ≥2.3 ng/ml there was a trend for better RFS in patients who received POAC compared to those without POAC (p=0.06).

Conclusions: Patients with post-CEA ≥2.3 ng/ml had worse long-term outcomes compared with those with post-CEA <2.3 ng/ml. Post-CEA with a cut-off of 2.3 ng/ml may be useful in determining the indication for POAC for in Stage III or high-risk Stage II cases.

Keywords

locally advanced rectal cancer, carcinoembryonic antigen (CEA), minimal residual disease (MRD), recurrence-free survival, postoperative adjuvant chemotherapy (POAC)

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Introduction

Colorectal cancer is an increasingly common disease and a leading global cause of death[1,2]. About 30% of colorectal cancers are classified as rectal cancer[1], and these cases commonly have an aggressive course that results in poor recurrence-free survival (RFS) and cancer-specific survival in the long term[3]. Neoadjuvant treatment for locally advanced rectal cancer (LARC) has improved outcomes after surgery[4,5]. In Western countries, resectable LARC is often treated with neoadjuvant treatment followed by total mesorectal excision (TME)[3,6,7], whereas neoadjuvant treatment for LARC is not mainstream in Japan[8-10]. Even with these approaches, LARC has a high rate of local recur-

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rence of 5-10% after radical resection[11-15]. Distant metastases, which occur at a rate of 25-40%, are mainly responsible for treatment failure in cases of LARC[16,17].

Imaging markers {extramural venous invasion (EMVI), interrectal fascial involvement}, blood markers {carcinoembryonic antigen (CEA), neutrophil-lymphocyte ratio (NLR)}, pathological and molecular markers {tumor grade, tumor-infiltrating lymphocytes (TIL), circumferential resection margin (CRM)} have been reported as prognostic factors in LARC[18-20]. CEA is a glycoprotein with a molecular weight of about 200,000 that is related to cell adhesion factors. It was first extracted from human colon cancer tissue in 1965[21], and has long been used primarily as a marker of tumor activity, with many benefits to clinicians and patients. CEA is also used for screening of malignant disease[22,23], follow-up after surgery[24-26], and evaluation of the effects of chemotherapy[27,28].

Preoperative CEA (pre-CEA) levels are mainly used in disease evaluation, but the usefulness of postoperative CEA (post-CEA) has recently been suggested because a high post-CEA level may indicate minimal residual disease (MRD) after curative resection due to the characteristic short half-life of serum CEA[29]. Furthermore, a more optimal cut-off for the pre-CEA level (2.35 ng/ml), which is within the normal range, has been proposed for predicting prognosis in Stage I and II colon cancer[30]. Thus, this study was conducted to investigate whether pre- or post-CEA with a new cut-off value is more optimal for predicting long-term outcomes in patients with LARC, and to investigate the effectiveness of postoperative adjuvant chemotherapy (POAC) based on the CEA values.

Methods

Patient selection

A retrospective study was performed in patients with pathologically confirmed stage II/III rectal cancer who underwent surgery with curative intent at Juntendo University Hospital between January 1999 and March 2018. Patients with neoadjuvant treatment or with synchronous or recurrent cancer of other organs were excluded. Data were collected in a retrospective review of a database and medical records. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional review board of Juntendo University Hospital (No. 19-214). Due to the retrospective design, the requirement for formal informed consent was waived.

CEA measurements

Serum CEA was measured preoperatively (pre-CEA) and postoperatively (about four weeks after rectal cancer resection: post-CEA). CEA was analyzed using an immunoenzymatic assay (Elecsys CEA, Roche Diagnostics, Indianapolis, IN, USA) according to the manufacturer's instructions.

Surgical strategies for rectal cancer

Resection of rectal cancer with lymph node dissection at the root of the main vessels (inferior mesenteric arteries and veins) was performed with curative intent[31]. Radical surgery for rectal cancer is based on the principle of total mesorectal excision (TME)[32]. In LARC surgery, dissection is performed at least 2 cm distal to the cancer. A 2-cm mucosal margin above the dentate line makes it possible to preserve the sphincter[33]. Alternatively, abdominoperineal resection (APR) is used. Open or laparoscopic surgery was performed depending on tumor factors (tumor site, progression) and patient factors (obesity, history of abdominal surgery). There were some changes in these indications over the study period.

POAC

POAC was recommended for all eligible patients with Stage III or high-risk Stage II disease. A high-risk Stage II case was defined as one that met at least one of the following criteria: T4, perforation/penetration, poorly differentiated adenocarcinoma, mucinous carcinoma, and <12 examined lymph nodes[34]. Patients were considered ineligible if they had synchronous or metachronous multiple cancers, severe complications or were advanced in age. All eligible patients had an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. All patients were required to provide informed consent. The POAC regimens were not the same over the study period because this period was relatively long. Ultimately, the decision regarding this regimen was made for each case based on discussions between the physician and the patient. Basically, during the study period, patients received 5-FU orally or an oxaliplatin-based regimen intravenously for more than six months, starting 4 to 8 weeks after surgery.

Clinicopathological analysis

Clinicopathological factors of age, gender, presence of preoperative diabetes mellitus, location (upper rectum, above / below the peritoneal reflection / lower rectum), surgical method (open / laparoscopic), surgical procedure (APR / others), main macroscopic type (localized / diffuse)[31], maximum primary tumor diameter, main histological type of primary tumor (differentiated / undifferentiated), undifferentiated component in primary tumor (present / absent), T classification (T1, T2, T3 / T4)[35], N classification (N0 / N1, N2)[35], radial margin (RM) and survival were evaluated. An RM (+) case was defined as one in which the tumor was identified at the radial margin of the resection plane[31].

Follow-up

Clinical assessment and measurement of serum CEA every 3 months, and chest CT and abdominal ultrasonography or CT every 3-6 months were performed postoperatively. Cases with suspected recurrence underwent abdominal or pelvic magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) to detect the recurrence[32]. Local extraperitoneal tumor recurrence, tumor growth in local lymph nodes, intraluminal recurrence and peritoneal tumor growth below the promontory were defined as local recurrence[36]. Distant metastases were defined as recurrences outside the small pelvis, including in the lungs, liver, lymph nodes, peritoneum or another organ[36].

Statistical analysis

The area under the receiver operating curve (AUROC) was used to determine a cut-off for CEA. The cut-off for CEA relative to RFS was established as that giving the highest AUROC. Multivariate analysis was used to evaluate the effects of variables on RFS (time from surgery for rectal cancer until initial recurrence). In the multivariate analysis, a Cox proportional-hazard regression model was used with the hazard ratio (HR). In comparison of superiority between pre- and post-CEA levels, Akaike's information criterion (AIC) was used in the Cox proportional-hazard regression model to demonstrate the discriminatory ability of prognosis[37]. A lower AIC was regarded to indicate a more desirable model with both a better fit and lower complexity. Discrete variables were compared by Fisher exact test. Continuous variables were compared using a Mann-Whitney U-test for individual comparisons and a Wilcoxon signed rank test for paired comparisons. Clinicopathological factors for which there were significant differences in univariate analysis were used as co-variables in multivariate analysis. The multivariate analysis used a logistic regression model with a stepwise procedure. The odds ratio (OR) and 95% confidence intervals were calculated as a measure of association. JMP 14 was used for all analyses, with $p<0.05$ taken to indicate a significant difference. Data are shown as medians with the range in parentheses.

Results

RFS based on pre- and post-CEA values

A total of 323 patients were enrolled in the study. The median observation period was 69.8 months (range: 1.0-204.5 months) for RFS cases. AUROCs were calculated to establish cut-offs for pre- and post-CEA relative to RFS. For pre-CEA, the highest AUROC (0.606) was obtained at a pre-CEA level of 3.0 ng/ml. To compare this cut-off {pre-CEA (ob)} with the standard cut-off {5.0 ng/ml, pre-CEA(std)}, the patients were divided into low pre-CEA(ob) (<3.0 ng/ml, n=124) and high pre-CEA(ob) (≥3.0 ng/ml, n=199) categories, and low pre-CEA(std) (<5.0 ng/ml, n=201) and high pre-CEA(std) (≥5.0 ng/ml, n=122) categories. Similarly, for post-CEA, the highest AUROC (0.593) was obtained at a post-CEA level of 2.3 ng/ml, and to compare this cut-off {post-CEA(ob)} with the standard cut-off {5.0 ng/ml, post-CEA(std)}, the patients were divided into low post-CEA(ob) (<2.3 ng/ml, n=197) and high post-CEA(ob) (≥2.3 ng/ml, n=126) categories, and low post-CEA(std) (<5.0 ng/ml, n=302) and high pre-CEA(std) (≥5.0 ng/ml, n=21) categories.

Comparisons of clinicopathological factors according to pre-CEA(std) are shown in Table 1. In univariate analysis, surgical approach (open / laparoscopic), maximum primary tumor diameter and T classification (T1-3 / T4) were significantly different between the low pre-CEA(std) (<5.0 ng/ml, n=201) and high pre-CEA(std) (≥5.0 ng/ml, n=122) groups (Table 1A). Patients in the high pre-CEA(std) (≥5.0 ng/ml) group more frequently had open surgery (p=0.0008), larger maximum primary tumor diameter (p=0.0003) and a T4 tumor (p=0.0008) compared with those with low pre-CEA(std) (<5.0 ng/ml) group (Table 1A). No other clinicopathological factors differed significantly between these groups. In multivariate analysis using the significant clinicopathological factors, excluding those associated with interventions such as operations because these factors were not the cause of the elevation or drop in preoperative CEA, the maximum primary tumor diameter (OR=1.02 (1.00-1.03), p=0.01) and T classification of T4 (OR=2.13 (1.18-3.84), p=0.01) were identified as significant independent predictive factors for high pre-CEA(std) (Table 1A).

Univariate analysis also indicated that patients in the high pre-CEA(ob) (≥3.0 ng/ml) group more frequently had open surgery (p<0.0001), APR (p=0.03), larger maximum primary tumor diameter (p=0.0004) and a T4 tumor (p=0.02) compared to the low pre-CEA(ob) (<3.0 ng/ml) group (Table 1 B). In multivariate analysis using these clinicopathological factors, again excluding those associated with interventions, the maximum primary tumor diameter (OR=1.01 (1.00-1.03), p=0.01) was found to be a significant independent predictive factor for high pre-CEA(ob) (Table 1B).

Comparisons of clinicopathological factors according to post-CEA values are shown in Table 2. In univariate analysis, POAC differed significantly between the low post-CEA (std) (<5.0 ng/ml, n=302) and high post-CEA(std) (≥5.0 ng/ml, n=21) groups (Table 2A). Patients in the high post-CEA (std) (≥5.0 ng/ml) group less frequently had POAC (p=0.046) compared with those in the low pre-CEA(std) (<5.0 ng/ml) group (Table 2A). Since there was no significant factor other than POAC, multivariate analysis was not performed (Table 2A). Univariate analysis indicated that patients in the high post-CEA(ob) (≥2.3 ng/ml) group were

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Table 1. Clinicopathological Factors according to Preoperative CEA Levels.

Clinicopathological factors	Variables	(A) Preoperative CEA (ng/ml)						(B) Preoperative CEA (ng/ml)					
		Low CEA (std) < 5.0 ng/ml (n=201)	High CEA (std) ≥ 5.0 ng/ml (n=122)	Univariate	Multivariate			Low CEA (ob) < 3.0 ng/ml (n=124)	High CEA (ob) ≥ 3.0 ng/ml (n=199)	Univariate	Multivariate		
				p-value	Odds ratio	95%CI[a]	p-value			p-value	Odds ratio	95%CI[a]	p-value
Age	Years[b]	64 (32 - 91)	64 (36 - 97)	0.44	-	-	-	63 (32 - 81)	65 (32 - 97)	0.07	-	-	-
Gender	Male	128 (63.7%)	85 (69.7%)	0.28	-	-	-	78 (62.9%)	135 (67.8%)	0.40	-	-	-
	Female	73 (36.3%)	37 (30.3%)					46 (37.1%)	64 (32.2%)				
Preoperative morbidity: Diabetes Mellitus	Absent	180 (89.6%)	109 (89.3%)	1.00	-	-	-	114 (91.9%)	175 (87.9%)	0.35	-	-	-
	Present	21 (10.5%)	13 (10.7%)					10 (8.1%)	24 (12.1%)				
Location	Upper	137 (68.2%)	84 (68.9%)	1.00	-	-	-	87 (70.2%)	134 (67.3%)	0.62	-	-	-
	Lower	64 (31.8%)	38 (31.2%)					37 (29.8%)	65 (32.7%)				
Surgical approach	Open	96 (47.8%)	82 (67.2%)	0.0008	N/A[f]	N/A	N/A	49 (39.5%)	129 (64.8%)	<0.0001	N/A	N/A	N/A
	Laparoscopic	105 (52.2%)	40 (32.8%)					75 (60.5%)	70 (35.2%)				
Surgical procedures	APR[c]	30 (14.9%)	20 (16.4%)	0.75	-	-	-	12 (9.7%)	38 (19.1%)	0.03	N/A	N/A	N/A
	Others[d]	171 (85.1%)	102 (83.6%)					112 (90.3%)	161 (80.9%)				
Macroscopic type	Localized	180 (89.6%)	108 (88.5%)	0.85	-	-	-	113 (91.1%)	175 (87.9%)	0.46	-	-	-
	Diffuse	21 (10.5%)	14 (11.5%)					11 (8.9%)	24 (12.1%)				
Maximum primary tumor diameter	mm[b]	41 (2 - 140)	48.5 (7.5 - 120)	0.0003	1.02	1.00 - 1.03	0.01	40 (11 - 140)	45 (2 - 120)	0.0004	1.01	1.00 - 1.03	0.01
Predominant histological type of primary tumor	Differentiated	190 (94.5%)	117 (95.9%)	0.79	-	-	-	117 (94.4%)	190 (95.5%)	0.79	-	-	-
	Undifferentiated	11 (5.5%)	5 (4.1%)					7 (5.7%)	9 (4.5%)				
Undifferentiated component in primary tumor	Absent	167 (83.1%)	102 (83.6%)	1.00	-	-	-	102 (82.3%)	167 (83.9%)	0.76	-	-	-
	Present	34 (16.9%)	20 (16.4%)					22 (17.7%)	32 (16.1%)				
T classification	T1-3	174 (86.6%)	86 (70.5%)	0.0008	2.13	1.18 - 3.84	0.01	108 (87.1%)	152 (76.4%)	0.02	1.62	0.84 - 3.09	0.15
	T4	27 (13.4%)	36 (29.5%)					16 (12.9%)	47 (23.6%)				
N classification	N0	89 (44.3%)	50 (41.0%)	0.64	-	-	-	53 (42.7%)	86 (43.2%)	1.00	-	-	-
	N1, 2	112 (55.7%)	72 (59.0%)					71 (57.3%)	113 (56.8%)				
Radial margin (RM)	Absent	194 (96.5%)	119 (97.5%)	0.75	-	-	-	120 (96.8%)	193 (97.0%)	1.00	-	-	-
	Present	7 (3.5%)	3 (2.5%)					4 (3.2%)	6 (3.0%)				
Postoperative adjuvant chemo-therapy (POAC)[e]	Absent	42 (27.6%)	34 (36.2%)	0.20	-	-	-	25 (26.9%)	51 (33.3%)	0.32	-	-	-
	Present	110 (72.4%)	60 (63.8%)					68 (73.1%)	102 (66.7%)				

[a] 95% confidential interval

[b] Median (minimum-maximum)

[c] Abdominoperineal resection

[d] Low anterior resection (LAR), intersphincteric resection (ISR), Hartmann's operation

[e] Administered in Stage III or high-risk Stage II (n=246)

[f] Not applicable

Table 2. Clinicopathological Factors according to Postoperative CEA Levels.

Clinicopathological factors	Variables	(A) Postoperative CEA (ng/ml)						(B) Postoperative CEA (ng/ml)					
		Low CEA (std) < 5.0 ng/ml (n=302)	High CEA (std) ≥ 5.0 ng/ml (n=21)	Univariate	Multivariate			Low CEA (ob) < 2.3 ng/ml (n=197)	High CEA (ob) ≥ 2.3 ng/ml (n=126)	Univariate	Multivariate		
				p-value	Odds ratio	95%CI[a]	p-value			p-value	Odds ratio	95%CI[a]	p-value
Age	Years[b]	64 (32 - 97)	61 (36 - 84)	0.53	-	-	-	63 (32 - 97)	65.5 (36 - 91)	0.01	-	-	-
Gender	Male	199 (65.9%)	14 (66.7%)	1.00	-	-	-	123 (62.4%)	90 (71.4%)	0.12	-	-	-
	Female	103 (34.1%)	7 (33.3%)					74 (37.6%)	36 (28.6%)				
Preoperative morbidity: Diabetes Mellitus	Absent	269 (89.1%)	20 (95.2%)	0.71	-	-	-	178 (90.4%)	111 (88.1%)	0.58	-	-	-
	Present	33 (10.9%)	1 (4.8%)					19 (9.6%)	15 (11.9%)				
Location	Upper	208 (68.9%)	13 (61.9%)	0.48	-	-	-	133 (67.5%)	88 (69.8%)	0.71	-	-	-
	Lower	94 (31.1%)	8 (38.1%)					64 (32.5%)	38 (30.2%)				
Surgical approach	Open	168 (55.6%)	10 (47.6%)	0.50	-	-	-	110 (55.8%)	68 (54.0%)	0.82	-	-	-
	Laparoscopic	134 (44.4%)	11 (52.4%)					87 (44.2%)	58 (46.0%)				
Surgical procedures	APR[c]	46 (15.2%)	4 (19.1%)	0.55	-	-	-	31 (15.7%)	19 (15.1%)	1.00	-	-	-
	Others[d]	256 (84.8%)	17 (81.0%)					166 (84.3%)	107 (84.9%)				
Macroscopic type	Localized	271 (89.7%)	17 (81.0%)	0.26	-	-	-	175 (88.8%)	113 (89.7%)	0.86	-	-	-
	Diffuse	31 (10.3%)	4 (19.1%)					22 (11.2%)	13 (10.3%)				
Maximum primary tumor diameter	mm[b]	45 (2 - 140)	45 (9 - 90)	0.78	-	-	-	43 (2 - 140)	45.5 (7.5 - 100)	0.12	-	-	-
Predominant histological type of primary tumor	Differentiated	286 (94.7%)	21 (100%)	0.61	-	-	-	189 (95.9%)	118 (93.7%)	0.43	-	-	-
	Undifferentiated	16 (5.3%)	0 (0%)					8 (4.1%)	8 (6.4%)				
Undifferentiated component in primary tumor	Absent	253 (83.8%)	16 (76.2%)	0.37	-	-	-	167 (84.8%)	102 (81.0%)	0.44	-	-	-
	Present	49 (16.2%)	5 (23.8%)					30 (15.2%)	24 (19.1%)				
T classification	T1-3	245 (81.1%)	15 (71.4%)	0.26	-	-	-	162 (82.2%)	98 (77.8%)	0.39	-	-	-
	T4	57 (18.9%)	6 (28.6%)					35 (17.8%)	28 (22.2%)				
N classification	N0	130 (43.1%)	9 (42.9%)	1.00	-	-	-	84 (42.6%)	55 (43.7%)	0.91	-	-	-
	N1, 2	172 (57.0%)	12 (57.1%)					113 (57.4%)	71 (56.4%)				
Radial margin (RM)	Absent	293 (97.0%)	20 (95.2%)	0.49	-	-	-	191 (97.0%)	122 (96.8%)	1.00	-	-	-
	Present	9 (3.0%)	1 (4.8%)					6 (3.0%)	4 (3.2%)				
Postoperative adjuvant chemo-therapy (POAC)[e]	Absent	67 (29.1%)	9 (56.3%)	0.046	-	-	-	32 (21.1%)	44 (46.8%)	<0.0001	N/A[f]	N/A	N/A
	Present	163 (70.9%)	7 (43.8%)					120 (79.0%)	50 (53.2%)				

[a] 95% confidential interval

[b] Median (minimum-maximum)

[c] Abdominoperineal resection

[d] Low anterior resection (LAR), intersphincteric resection (ISR), Hartmann's operation

[e] Administered in Stage III or high-risk Stage II (n=246)

[f] Not applicable

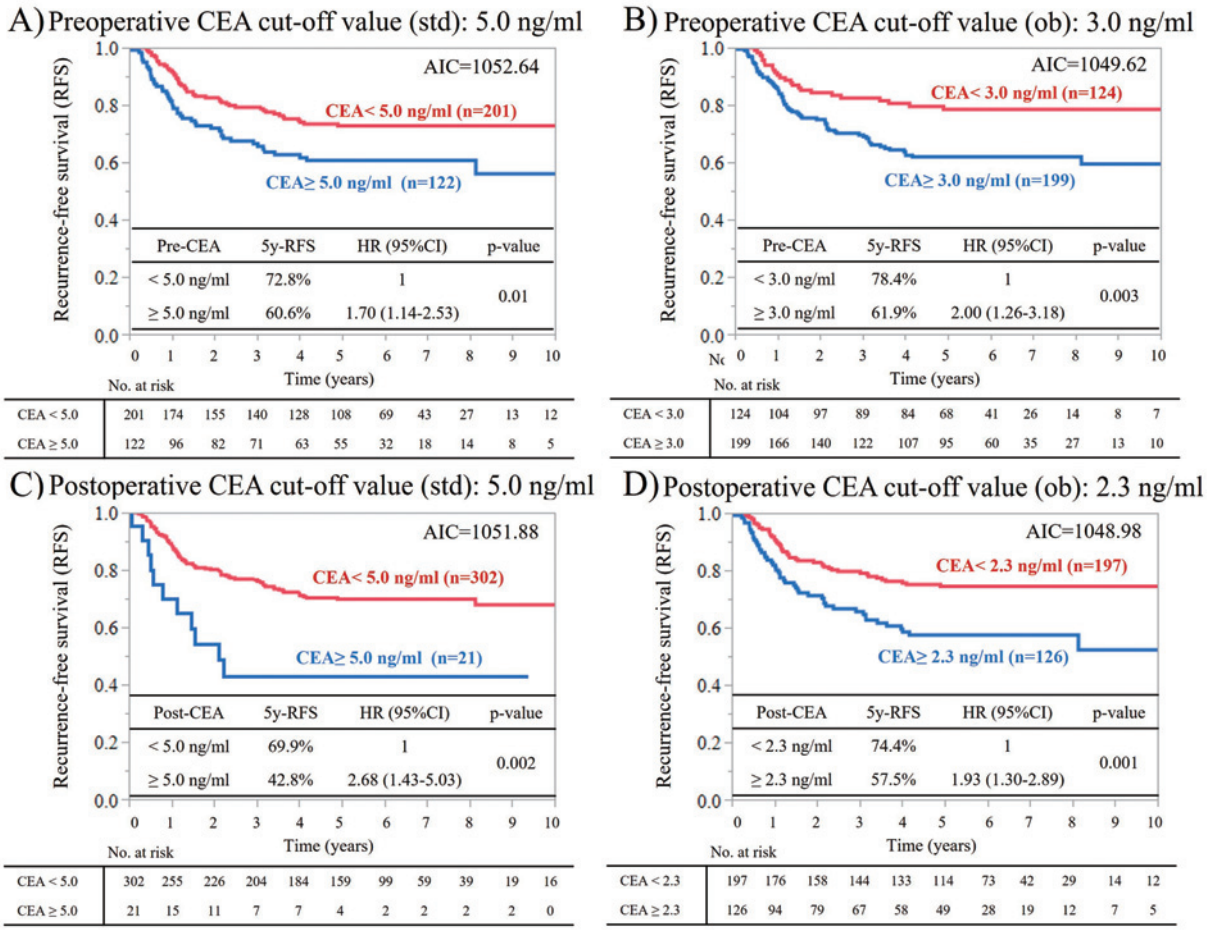

Figure 1. RFS based on preoperative (pre-) and postoperative (post-) CEA values.
RFS was well stratified in all four groups (low pre-CEA (std) (<5.0 ng/ml)/high pre-CEA (std) (≥5.0 ng/ml): HR=1.70 (1.14-2.53), p=0.01; low pre-CEA (ob) (<3.0 ng/ml)/high pre-CEA (ob) (≥3.0 ng/ml): HR=2.00 (1.26-3.18), p=0.003; low post-CEA (std) (<5.0 ng/ml)/high post-CEA (std) (≥5.0 ng/ml): HR=2.68 (1.43-5.03), p=0.002; low post-CEA (ob) (<2.3 ng/ml)/high post-CEA (ob) (≥2.3 ng/ml): HR=1.93 (1.30-2.89), p=0.001) (A-D). However, AIC (1048.98) was the lowest in classifications with post-CEA (ob) of 2.3 ng/ml compared with other classifications of pre- or post-CEA (D).

older (p=0.01) and less frequently had POAC (p<0.0001) compared with the low post-CEA(ob) (≥2.3 ng/ml) group (Table 2B). No other clinicopathological factors differed significantly in the two groups. Since only age, other than POAC, was significant in univariate analysis, multivariate analysis was not performed (Table 2B).

RFS was well stratified in all four groups (low pre-CEA (std) (<5.0 ng/ml) / high pre-CEA(std) (≥5.0 ng/ml): HR= 1.70 (1.14-2.53), p=0.01; low pre-CEA(ob) (<3.0 ng/ml) / high pre-CEA(ob) (≥3.0 ng/ml): HR=2.00 (1.26-3.18), p= 0.003; low post-CEA(std) (<5.0 ng/ml) / high post-CEA(std) (≥5.0 ng/ml): HR=2.68 (1.43-5.03), p=0.002; low post-CEA (ob) (<2.3 ng/ml) / high post-CEA(ob) (≥2.3 ng/ml): HR= 1.93 (1.30-2.89), p=0.001) (Figure 1A-D). However, AIC (1048.98) was the lowest in classifications with post-CEA (ob) of 2.3 ng/ml compared with other classifications of pre- or post-CEA (Figure 1D). This indicates that prognostic discrimination using post-CEA with a cut-off of 2.3 ng/ml was superior to those with other classifications of pre- or post-CEA, giving both a better fit and lower complexity.

Effectiveness of POAC according to the post-CEA value

Detailed information for POAC was obtained in 293 patients, and was unknown in 30 patients. Among all Stage III or high-risk Stage II cases (n=246), 170 patients received POAC, including 145 (85.3%) with oral 5-FU and 25 (14.7%) with an intravenous oxaliplatin-based regimen. Among the 145 patients treated with 5-FU, 134 (92.4%) and 11 (7.6%) received 5-FU for >6 and <6 months, respectively. All 25 patients with an oxaliplatin-based regimen received this treatment for >6 months. In Stage III or high-risk Stage II cases, RFS was better in patients with POAC than without POAC, but the difference was not significant (HR=0.74 (0.47-1.16), p=0.18) (Figure 2A). There was no effect of POAC on RFS in those with post-CEA <2.3 ng/ml (HR=1.42 (0.63-3.19), p=0.39) (Figure 2B), but in those

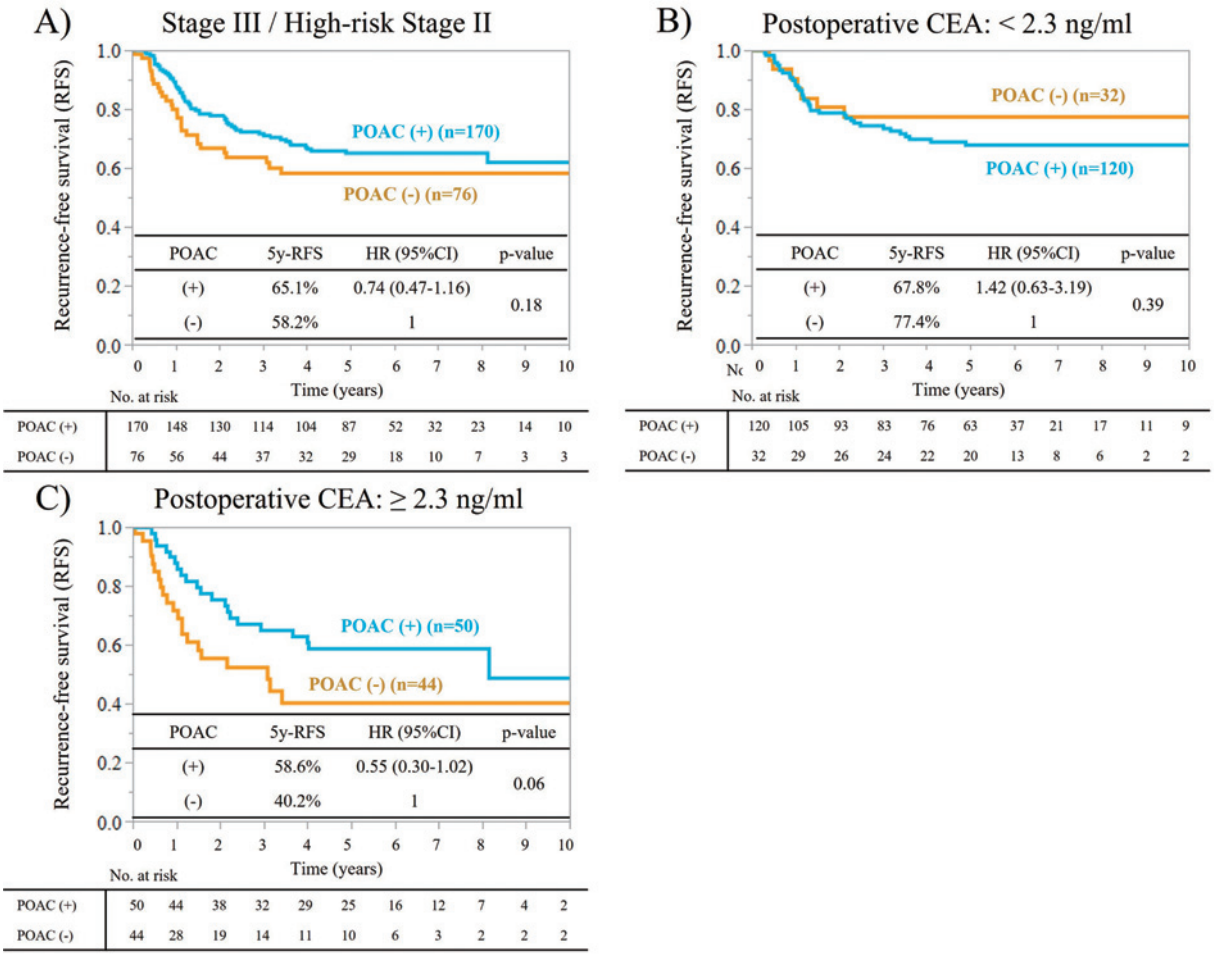

Figure 2. Effectiveness of POAC according to the post-CEA value.
Among all Stage III or high-risk Stage II cases (n=246), RFS was better in patients with POAC than without POAC, but the difference was not significant (HR=0.74 (0.47-1.16), p=0.18) (A). In Stage III or high-risk Stage II cases, there was no effect of POAC on RFS in those with post-CEA <2.3 ng/ml (HR=1.42 (0.63-3.19), p=0.39) (B), but in those with post-CEA ≥2.3 ng/ml there was a trend for better RFS in patients who received POAC compared to those without POAC (HR=0.55 (0.30-1.02), p=0.06) (C).

with post-CEA ≥2.3 ng/ml there was a trend for better RFS in patients who received POAC compared to those without POAC (HR=0.55 (0.30-1.02), p=0.06) (Figure 2C).

Discussion

Many studies have examined the value of CEA as a tumor marker for colorectal cancer[38-43]. Appropriate risk assessment can enhance postoperative surveillance and early detection of recurrence, and CEA has been shown to be particularly useful as a local recurrence marker[39] and for prediction of the effect of neoadjuvant chemoradiotherapy[38]. Therefore, in most previous reports, the usefulness of pre-CEA values has been evaluated[30]. However, in the present study, AIC values indicated that RFS was better stratified by a post-CEA level with a cut-off of 2.3 ng/ml compared with other classifications of pre- or post-CEA.

Patients with post-CEA >5 ng/ml have been reported to have a poor prognosis[41,42,44,45]. Therefore, in most studies, a post-CEA level of 5 ng/ml has been used as the cut-off to evaluate long-term outcomes. However, in this study, determination of the cut-off with recurrence as the endpoint resulted in a value lower than 5 ng/ml. As a result, risks for RFS were well stratified, and the difference in RFS in cases with post-CEA ≥2.3 ng/ml was especially clear. Patients with post-CEA ≥2.3 ng/ml also had worse long-term outcomes compared with those with post-CEA <2.3 ng/ml, despite CEA of 2.3 ng/ml being within the normal range. These results suggest that elevated CEA within the normal range may be correlated with MRD. MRD is defined as microscopic remaining materials after curative treatment that are not detectable clinically, and thus, have potential to predict disease recurrence[46,47]. Post-CEA has been found to be more sensitive in reflecting MRD and more useful than

pre-CEA for predicting recurrence in the surveillance period in metastatic CRC and non-metastatic CRC[43]. Our results also suggest that post-CEA levels may be associated with MRD, and AIC values indicated that post-CEA was superior to pre-CEA for stratification of RFS.

A previous study found that detection of MRD using post-CEA can be useful in clinical decision-making, such as for the intensity and duration of POAC and surveillance, which may improve long-outcomes[41]. Our study also indicates that post-CEA with a cut-off of 2.3 ng/ml may be useful in determining the indication for POAC in Stage III or high-risk Stage II cases. In particular, T1-T2N1 and T1N2a cases are classified as Stage IIIA in the TNM classification, and these Stage IIIA cases have a good prognosis[48]. Therefore, post-CEA with a cut-off of 2.3 ng/ml may be useful to identify Stage III cases in which POAC is unnecessary. In addition, pre-CEA is considered to be a high-risk factor in Stage II CRC and POAC should be administered for high-risk Stage II CRC based on ESMO Guidelines[49]. Therefore, in the future, the usefulness of post-CEA with a cut-off of 2.3 ng/ml should also be investigated for determining the indication for POAC in high-risk Stage II cases.

A randomized phase III trial comparing S-1 with UFT as POAC for stage II/III rectal cancer without prior radiotherapy or chemotherapy (ACTS-RC) has been conducted in Japan[50]. In this trial, one-year S-1 treatment was superior to UFT with respect to 5-year RFS (66.4% vs. 61.7%; p=0.02), and therefore, is now considered to be a standard POAC regimen for stage II/III rectal cancer following curative resection. After the trial, a prospective, multicenter, open-label, single-arm phase II study was conducted to investigate the efficacy of POAC with oxaliplatin plus capecitabine (CAPOX) for curatively resected high-risk stage II and stage III rectal cancer without preoperative chemoradiation[51]. In this trial, POAC with CAPOX gave an adequate 3-year disease-free survival of 70.1%. There has been no direct comparison of 5-FU and an oxaliplatin-based regimen to date, but both regimens seem to be effective for stage II/III rectal cancer without prior treatment, which was similar to the cohort in the current study. Approximately 90% of the patients in our cohort received POAC without an oxaliplatin-based regimen because the study referred to above[51] had not been published at this time. In this study, therefore, the usefulness of post-CEA with a cut-off of 2.3 ng/ml was clarified for determining the indication for POAC in a cohort in which almost all patients received POAC without an oxaliplatin-based regimen. In this context, the usefulness of post-CEA with a cut-off of 2.3 ng/ml requires clarification in limited patients who receive POAC with an oxaliplatin-based regimen. In our study, patients with high post-CEA (ob) (≥2.3 ng/ml) less frequently had POAC compared with those with low post-CEA(ob) (<2.3 ng/ml). This result was opposite to our expectation, but might reflect the significantly older age of the patients with high post-CEA(ob) (≥ 2.3 ng/ml) compared to those with low post-CEA(ob) (<2.3 ng/ml). A further prospective investigation is needed in more cases to obtain conclusive results.

We note that the study has several limitations. First, the results are based on a small number of cases at a single center, and patients who received neoadjuvant treatment were excluded. Second, the differences in AIC values between the pre- and post-CEA categories were relatively small. Although AIC can provide a relative evaluation[37], the results might change for a different cohort. In this respect, a further study with a different cohort is needed. We also had no data on smoking status, which can elevate CEA[52].

In conclusion, patients with post-CEA ≥2.3 ng/ml had worse long-term outcomes compared with those with post-CEA <2.3 ng/ml. Post-CEA with a cut-off of 2.3 ng/ml may be useful in determining the indication for POAC for in Stage III or high-risk Stage II cases.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

RT and Kiichi Sugimoto designed the study and provided overall guidance with the advice of Kazuhiro Sakamoto. RT analyzed the clinical data with the assistance and advice of YI, TI, Megumi Kawaguchi, AK, YT, KH, Masaya Kawai, SI and MT. Kiichi Sugimoto conducted the statistical data analyses, and RT prepared the tables and figures. RT and Kiichi Sugimoto wrote the manuscript, which was critically reviewed by Kazuhiro Sakamoto. All authors have read and approved the final version of the manuscript.

Approval by Institutional Review Board (IRB)

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