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ORIGINAL RESEARCH

Prognostic Value of Pretreatment Carcinoembryonic Antigen (CEA) in Rectal Cancer Treated with Preoperative Short-Course Radiotherapy with Delayed Surgery or Long-Course Radiotherapy

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Purpose: To investigate the prognostic value of the pretreatment serum carcinoembryonic antigen (CEA) level in patients with rectal cancer treated by preoperative short-course radiotherapy (SCRT) followed by chemotherapy and delayed surgery.

Patients and Methods: Two hundred and sixty-six consecutive patients with locally advanced rectal adenocarcinoma without distant metastasis receiving preoperative radiotherapy were enrolled. Group 1 patients (n=144) received long-course radiotherapy (LCRT) with 50.4 Gy in 28 fractions using photon radiotherapy (XRT). Group 2 patients (n=122) received SCRT with 25 Gy in 5 fractions using XRT or proton beam therapy (PBT) followed by chemotherapy and delayed surgery. Pathological complete response (pCR), near pathological complete response (npCR), locoregional recurrence (LRR), distant metastasis (DM), disease-specific survival (DSS) and overall survival (OS) rates were estimated and compared to scrutinize the prognostic significance of factors including CEA level.

Results: In group 1, higher CEA level (≥ 7 ng/mL) was a significant negative prognostic factor of pCR ($p = 0.003$, OR: 0.133), OS ($p = 0.011$, HR: 2.999), DM ($p = 0.008$, HR: 2.569), LRR ($p = 0.044$, HR: 3.160), and DSS ($p = 0.015$, HR: 3.273). In group 2, higher CEA level (≥ 7 ng/mL) was a significant negative prognostic factor of pCR ($p = 0.002$, OR: 0.038), OS ($p < 0.001$, HR: 44.658), DM ($p < 0.001$, HR: 8.926), LRR ($p = 0.028$, HR: 8.570), and DSS ($p = 0.001$, HR: 43.918). The npCR rates for clinical T4 patients were 6.5% and 22.0% ($p = 0.032$), in group 1 and group 2, respectively.

Conclusion: This study elucidates the prognostic merit of the pretreatment serum CEA level in patients with rectal cancer treated by either preoperative LCRT or SCRT followed by chemotherapy and delayed surgery.

Keywords: rectal cancer, carcinoembryonic antigen, short-course radiotherapy, proton therapy, prognosis

Introduction

Carcinoembryonic antigen (CEA), a set of highly related glycoproteins, which is secreted by a wide variety of solid tumors and could be easily and noninvasively assessed via blood test, has been well documented to have prognostic value in various types of malignancies,[1] including colorectal cancer of different stages.[2–4]

The standard treatment for locally advanced rectal cancer consists of radical surgery, radiotherapy, and chemotherapy.[5] There are two standard radiotherapy options, including short-course radiotherapy (SCRT) and long-course radiotherapy (LCRT). Some reports have demonstrated that CEA is significantly prognostic of treatment outcomes in different treatment combinations of LCRT in either preoperative or postoperative settings for locally advanced rectal

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cancer.[6–20] However, despite the fact that preoperative SCRT has also been established as the standard of care for locally advanced rectal cancer by several large randomized trials,[21–25] the prognostic role of CEA in rectal cancer patients receiving SCRT followed by chemotherapy and delayed surgery is yet unclear, since almost none of the previous studies have investigated its prognostic significance in this setting.

Accordingly, the present study aims to explore the prognostic value of the pretreatment serum CEA level in a homogenous cohort of locally advanced rectal cancer patients receiving either preoperative SCRT followed by chemotherapy and delayed surgery or preoperative LCRT followed by surgery.

Materials and Methods

Study Cohort

In this study, a total of 266 consecutive patients with non-distant metastatic, locally advanced, biopsy-proved rectal adenocarcinoma receiving preoperative radiotherapy with curative treatment intent at Kaohsiung Chang Gung Memorial Hospital between January 2014 and September 2023 were accrued based on the approval of Chang Gung Medical Foundation Institutional Review Board (202301515B0). These patients were classified into two groups. Group 1 included patients who underwent LCRT. Group 2 included patients who underwent SCRT with photon radiotherapy (XRT) or proton beam therapy (PBT).

The routine pretreatment evaluation for all patients included physical examination, colonoscopy, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the abdomen and pelvis, and plain film chest radiology and/or CT of the chest. The pretreatment serum CEA levels of all patients were obtained before any treatment initiates. The measurement of the pretreatment serum CEA levels was performed using electrochemiluminescence immunoassay. The patient charts were reviewed to determine the patient characteristics and tumor characteristics.

Radiotherapy

In our institution, patients with non-distant metastatic locally advanced rectal cancer having indication for preoperative radiotherapy were treated with either SCRT or LCRT. The decision to undergo SCRT or LCRT was made completely by the surgeons, who have their own personal preference for radiotherapy course such that some surgeons always designated LCRT while other surgeons always selected SCRT.

Each eligible subject underwent CT simulation in the supine position with molding of a personalized thermoplastic mask. The clinical target volume was delineated based on published consensus, adding an additional margin to generate the planning target volume (PTV). In group 1, the prescription dose to the PTVs was 50.4 Gy in 28 fractions at 1.8 Gy per fraction administered with the photon linear accelerator, with the exception of two patients receiving 54 Gy and 48.6 Gy respectively. In group 2, the prescription dose to the PTVs was 25 Gy (relative biological effectiveness) (Gy(RBE)) in 5 fractions at 5 Gy(RBE) per fraction administered with the photon linear accelerator or cyclotron-based PBT of intensity-modulated proton therapy (IMPT) plans. IMPT plans were generated by using two fields from two different directions of scanning beams.

Surgery and Chemotherapy

All patients underwent planned radical surgery after preoperative radiotherapy. Median intervals between preoperative radiotherapy and radical surgery were 15.5 weeks (range, 10.3 to 58.9 weeks) in group 1 and 16.2 weeks (range, 8.9 to 41.9 weeks) in group 2. Radical surgery was performed with total mesorectal excision. If indicated, abdominoperineal resection (APR) was performed at the surgeon's discretion. Pathological complete response (pCR) was defined as the disappearance of all invasive cancer in the specimen of rectal resection after completion of preoperative therapy. Near pathological complete response (npCR) was defined as having tumor size not more than 1mm in the specimen of rectal resection after completion of preoperative therapy.

Whether patients received the 5-fluorouracil (5-FU)-based systemic chemotherapy through either intravenous or oral route depended on the discretion of the clinicians. All LCRT patients received systemic chemotherapy during the course

of preoperative LCRT. One-hundred-and-seven, 15, 12, 5, 2, 2, and 1 LCRT patients received 5-FU, tegafur-uracil, xeloda, xeloda/oxaliplatin (XELOX), folinic acid/5-FU/oxaliplatin (FOLFOX), and folinic acid/5-FU/ irinotecan (FOLFIRI), and tegafur-uracil/leucovorin/oxaliplatin (TEGAFOX), respectively. All SCRT patients received systemic chemotherapy after the course of preoperative SCRT. Thirty-two, 24, 22, 16, 12, 11, and 5 SCRT patients received FOLFOX, XELOX, TEGAFOX, 5-FU, tegafur-uracil, FOLFIRI, and xeloda, respectively. After radical surgery, adjuvant chemotherapy was given for those with higher risk of recurrence.

Follow-Up

After the finalization of the treatment course, all participants were followed up every 3 months in the first 2 years, 4–6 months in the third to fifth years, and yearly subsequently. Colonoscopy, abdominopelvic CT or MRI, and chest radiology were done annually. CT of the chest, bone scan, or brain MRI were done if clinically indicated.

Statistical Analysis

For statistical processing, the Microsoft Statistical Package for Social Sciences version 22.0 software (SPSS, Chicago, IL) was utilized. To compile the data of patient characteristics and tumor characteristics, descriptive statistics were applied. The pCR/npCR rates and the survival outcomes considering locoregional recurrence (LRR), distant metastasis (DM), disease-specific survival (DSS), and overall survival (OS) were estimated and compared according to the Kaplan–Meier method and multivariate analysis to scrutinize the prognostic significance of different demographic, clinical, and treatment factors, including the pretreatment serum CEA level.

Results

Patient Characteristics and Tumor Characteristics

In Table 1, the age, T stage, N stage, and other characteristics of all subjects were displayed. As a whole, two-hundred and three (76.3%) patients were male and sixty-three (23.7%) were female. The clinical stages were T2, T3, T4 in 14 (5.3%), 156 (58.6%), 96 (36.1%) patients, and N0, N1, N2 in 31 (11.7%), 114 (42.9%), 121 (45.5%) patients, respectively, as per the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. For the surgical

Table 1 Characteristics of Patients (N= 266)

Parameters	Group 1	Group 2
Age (years)		
< 65	97 (67.4%)	76 (62.3%)
≥ 65	47 (32.6%)	46 (37.7%)
Gender		
Female	37 (25.7%)	26 (21.3%)
Male	107 (74.3%)	96 (78.7%)
Anal verge level (cm)		
<5	44 (30.6%)	45 (36.9%)
5–10	74 (51.4%)	62 (50.8%)
10–15	24 (16.7%)	14 (11.5%)
Unknown	2 (1.4%)	1 (0.8%)
CEA level (ng/mL)		
<5	83 (57.6%)	65 (53.3%)
5–10	20 (13.9%)	18 (14.8%)
10–15	41 (28.5%)	39 (32.0%)
Pre-OP tumor size (cm)		
< 5	58 (40.3%)	47 (38.5%)
≥ 5	61 (42.1%)	65 (53.3%)
Unknown	25 (17.4%)	10 (8.2%)

(*Continued*)

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Table 1 (Continued).

Parameters	Group 1	Group 2
cT Stage		
cT2	7 (4.9%)	7 (5.7%)
cT3	91 (63.2%)	65 (53.3%)
cT4	46 (31.9%)	50 (41.0%)
cN Stage		
cN0	16 (11.1%)	15 (12.3%)
cN1	70 (48.6%)	44 (36.1%)
cN2	58 (40.3%)	63 (51.6%)
pT Stage		
ypT0	31 (21.5%)	21 (17.2%)
ypT1	3 (2.1%)	5 (4.1%)
ypT2	32 (22.2%)	28 (23.0%)
ypT3	65 (45.1%)	52 (42.6%)
ypT4	13 (9.0%)	16 (13.1%)
pN stage		
ypN0	101 (70.1%)	83 (68.0%)
ypN1	31 (21.5%)	31 (25.4%)
ypN2	12 (8.3%)	8 (6.6%)
Pathological differentiation		
Well- or moderately-differentiated	140 (97.2%)	115 (94.3%)
Poorly-differentiated	4 (2.8%)	7 (5.7%)
Tumor regression grade		
0	28 (19.4%)	21 (17.2%)
1	27 (18.8%)	23 (18.9%)
2	59 (41.0%)	59 (48.4%)
3	7 (4.9%)	9 (7.4%)
Unknown	23 (16.0%)	10 (8.2%)
LVI		
No	120 (83.3%)	90 (73.8%)
Yes	24 (16.7%)	32 (26.2%)
PNI		
No	116 (80.6%)	95 (77.9%)
Yes	28 (19.4%)	27 (22.1%)
Proton beam therapy		
No	144 (100%)	104 (85.2%)
Yes	0 (0%)	18 (14.8%)
Surgery		
Non-APR	132 (91.7%)	109 (89.3%)
APR	12 (8.3%)	13 (10.7%)

Abbreviations: CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion.

outcomes, all patients achieved negative margins and completeness of total mesorectal excision. Twenty-five (9.4%) patients received APR. Following the radical surgery, 52 (19.5%) patients had ypT0 disease, and 184 (69.2%) patients had ypN0 disease. There were 48 patients with pCR (ypT0N0).

Prognostic Factors for Pathological Complete Response (pCR) and Near Pathological Complete Response (npCR)

The results of univariate and multivariate analysis for different demographic, clinical, and treatment factors for pCR and npCR are shown in Tables 2 and 3 separately.

Table 2 Univariate Analysis of pCR/npCR Among Different Groups

Parameters	Group 1	*p* value	Group 2	*p* value
Age		0.932/0.932		0.303/0.316
<65 years	18.6%/18.6%		14.5%/18.4%	
≥65 years	19.1%/19.1%		21.7%/26.1%	
Anal verge		0.866/0.866		0.554/0.127
< 5 cm	18.2%/18.2%		20.0%/28.9%	
≥ 5 cm	19.4%/19.4%		15.8%/17.1%	
CEA levels		0.006/0.006		<0.001/0.002
< 7 ng/mL	25.8%/25.8%		28.2%/31.0%	
≥ 7 ng/mL	7.3%/7.3%		2.0%/7.8%	
RT to OP interval		0.667/0.667		0.152/0.547
< 16 weeks	20.0%/20.0%		12.1%/19.0%	
≥ 16 weeks	17.2%/17.2%		21.9%/23.4%	

Abbreviations: pCR, pathological complete response; npCR, near pathological complete response.

Table 3 Multivariate Analysis of pCR in Group 1 and Group 2 Patients

Parameters	Group 1 OR (95% CI)	p-value	Group 2 OR (95% CI)	p-value
Age		0.687		0.533
<65 years	Reference		Reference	
≥65 years	1.242 (0.432–3.573)		1.416 (0.474–4.231)	
Anal verge		0.606		0.960
< 5 cm	Reference		Reference	
≥ 5 cm	0.750 (0.251–2.240)		1.030 (0.325–3.265)	
Pre-OP tumor size (cm)		0.797		0.681
< 5	Reference		Reference	
≥ 5	0.885 (0.351–2.235)		0.780 (0.239–2.549)	
cT Stage		0.142		0.249
cT2	Reference		Reference	
cT3	0.653 (0.136–3.148)		0.444 (0.049–4.006)	
cT4	1.518 (0.305–7.553)		1.168 (0.116–11.762)	
cN Stage		0.316		0.864
cN0	Reference		Reference	
cN1	3.940 (0.504–30.815)		0.725 (0.125–4.216)	
cN2	2.655 (0.320–22.056)		0.601 (0.094–3.861)	
CEA levels		0.003*		0.002*
< 7 ng/mL	Reference		Reference	
≥ 7 ng/mL	0.133 (0.035–0.509)		0.038 (0.005–0.312)	
RT to OP interval		0.280		0.124
< 16 weeks	Reference		Reference	
≥ 16 weeks	0.575 (0.211–1.569)		2.539 (0.774–8.323)	

Note: Symbol * indicates p<0.05.
Abbreviations: OR, odds ratio; CI, confidence interval.

In group 1, higher pretreatment CEA level (≥ 7 ng/mL) was the only significant negative prognostic factor of pCR ($p = 0.003$, OR: 0.133, 95% CI: 0.035–0.509). The pCR rates for patients with higher pretreatment CEA level (≥ 7 ng/mL) and lower pretreatment CEA level (< 7 ng/mL) were 7.3% and 25.8% ($p = 0.006$), respectively.

In group 2, higher pretreatment CEA level (≥ 7 ng/mL) was the only significant negative prognostic factor of pCR ($p = 0.002$, OR: 0.038, 95% CI: 0.005–0.312). The pCR rates for patients with higher pretreatment CEA level (≥ 7 ng/mL) and lower pretreatment CEA level (< 7 ng/mL) were 2.0% and 28.2% ($p < 0.001$), respectively.

The npCR rates for patients with lower pretreatment CEA level (< 7 ng/mL) were 25.8% and 31.0%, in group 1 and group 2, respectively; whereas the npCR rates for patients with higher pretreatment CEA level (≥ 7 ng/mL) were 7.3% and 7.8%, in group 1 and group 2, respectively. In multivariate analysis, CEA level (≥ 7 ng/mL) remained an independent factor of npCR in both group 1 ($p = 0.003$, OR: 0.133, 95% CI: 0.035–0.509) and group 2 ($p = 0.004$, OR: 0.166, 95% CI: 0.049–0.560) patients. Patients with PBT have a much higher npCR rates (40.0% and 30.8%) of having good treatment response for patients with higher and lower CEA level, respectively.

Although there are no significant differences regarding the effect of interval between radiotherapy and surgery, in group 1, patients with longer interval (≥ 16 weeks) have lower pCR/npCR rates compared to those with shorter interval (< 16 weeks). On the contrary, SCRT patients with longer interval (≥ 16 weeks) have higher pCR/npCR rates compared to those with shorter interval (< 16 weeks). This phenomenon is even more noticeable in the proton-SCRT patients, of which the pCR/npCR rates increased from 0%/25.0% to 30.0%/40.0% in patients with longer interval.

The bar chart of npCR rates among different groups is demonstrated in Figure 1. For clinical T2-3 patients, there was no statistical significance among npCR rates between different groups ($p = 0.575$). The npCR rates were 24.5% and 20.8% in group 1 and 2 patients, respectively. For clinical T4 patients, SCRT patients had statistically significantly higher npCR rates ($p = 0.032$). The npCR rates were 6.5% and 22.0% in group 1 and 2 patients, respectively.

Prognostic Factors for Survival Outcomes

The median follow-up time at the end of the study was 32.5 months (range 3.8 to 118.5) in alive patients. The results of multivariate analysis for different demographic, clinical, and treatment factors for OS, DM, LRR, and DSS are shown in Tables 4–7 separately.

In group 1, higher pretreatment CEA level (≥ 7 ng/mL) was a significant negative prognostic factor of OS ($p = 0.011$, HR: 2.999, 95% CI: 1.282–7.015), DM ($p = 0.008$, HR: 2.569, 95% CI: 1.280–5.155), LRR ($p = 0.044$, HR: 3.160, 95% CI: 1.030–9.692), and DSS ($p = 0.015$, HR: 3.273, 95% CI: 1.259–8.513). The comparison of OS, DM, LRR, and DSS rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) is displayed in Figures 2A, 3A, 4A, and 5A, respectively. As a whole, the resultant 3-year OS, DM, LRR, and DSS rates were 81.2%, 28.2%, 12.7%, 85.0%, respectively. The 3-year rates of OS, DM, LRR, and DSS for patients with higher CEA level (≥ 7 ng/mL) were 70.3%, 43.8%, 18.4%, and 76.2% respectively. The 3-year rates of OS, DM, LRR, and DSS for patients with lower CEA level (< 7 ng/mL) were 87.4%, 19.7%, and 9.8%, and 89.9%, respectively. Besides CEA level, older age (≥ 65 years old) was a significant negative prognosticator for OS ($p < 0.001$, HR: 5.192, 95% CI: 2.250–11.980), LRR ($p = 0.028$, HR: 3.882, 95% CI: 1.544–13.053), and DSS ($p < 0.001$, HR: 5.513, 95% CI: 2.130–14.269) but not DM.

In group 2, higher pretreatment CEA level (≥ 7 ng/mL) was a significant negative prognostic factor of OS ($p < 0.001$, HR: 44.658 95% CI: 5.807–343.454), DM ($p = < 0.001$, HR: 8.926, 95% CI: 2.627–30.330), LRR ($p = 0.028$, HR: 8.570, 95% CI: 1.263–58.157), and DSS ($p = 0.001$, HR: 43.918, 95% CI: 5.057–381.432). The comparison of OS, DM, LRR, and DSS rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) is displayed in Figures 2B, 3B, 4B, and 5B, respectively. As

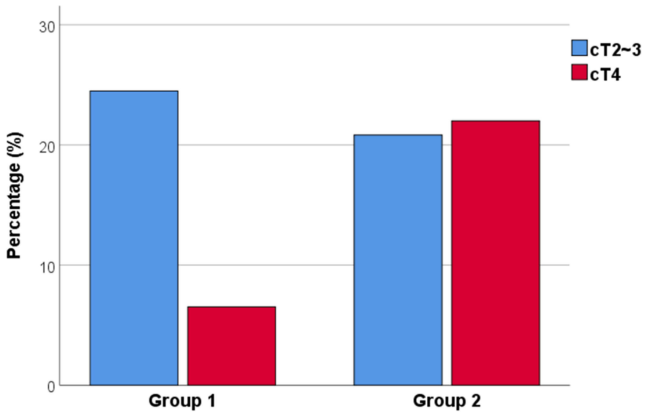

Figure 1 Comparison of npCR rates between cT2-3 and cT4 patients in group 1 and group 2 patients.

Table 4 Multivariate Analysis of OS in Group 1 and Group 2 Patients

Parameters	Group 1 HR (95% CI)	p-value	Group 2 HR (95% CI)	p-value
Age		<0.001*		0.011*
<65 years	Reference		Reference	
≥65 years	5.192 (2.250–11.980)		6.119 (1.646–22.743)	
Gender		0.708		0.284
Female	Reference		Reference	
Male	1.237 (0.407–3.759)		0.318 (0.074–1.371)	
Anal verge		0.724		0.392
< 5 cm	Reference		Reference	
≥ 5 cm	1.175 (0.480–2.876)		2.160 (0.371–12.583)	
Pre-OP tumor size (cm)		0.797		0.579
< 5	Reference		Reference	
≥ 5	0.885 (0.351–2.235)		0.688 (0.184–2.574)	
cT Stage		0.142		0.076
cT2	Reference		Reference	
cT3	0.653 (0.136–3.148)		4.912 (0.214–112.652)	
cT4	1.518 (0.305–7.553)		0.808 (0.032–20.410)	
cN Stage		0.316		0.053
cN0	Reference		Reference	
cN1	3.940 (0.504–30.815)		1.314 (0.151–11.431)	
cN2	2.655 (0.320–22.056)		0.129 (0.009–1.915)	
CEA levels		0.011*		<0.001*
< 7 ng/mL	Reference		Reference	
≥ 7 ng/mL	2.999 (1.282–7.015)		44.658 (5.807–343.454)	

Note: Symbol * indicates p<0.05.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 5 Multivariate Analysis of DM in Group 1 and Group 2 Patients

Parameters	Group 1 HR (95% CI)	p-value	Group 2 HR (95% CI)	p-value
Age		0.269		0.045*
<65 years	Reference		Reference	
≥65 years	1.520 (0.724–3.191)		2.759 (1.023–7.440)	
Gender		0.667		0.564
Female	Reference		Reference	
Male	1.204 (0.518–2.798)		1.423 (0.429–4.719)	
Anal verge		0.764		0.215
< 5 cm	Reference		Reference	
≥ 5 cm	0.897 (0.441–1.824)		2.026 (0.663–6.190)	
Pre-OP tumor size (cm)		0.217		0.041*
< 5	Reference		Reference	
≥ 5	0.612 (0.280–1.334)		0.324 (0.110–0.953)	
cT Stage		0.247		0.917
cT2	Reference		Reference	
cT3	0.766 (0.213–2.751)		0.963 (0.098–9.430)	
cT4	1.440 (0.380–5.458)		0.772 (0.065–9.158)	

(*Continued*)

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Table 5 (Continued).

Parameters	Group 1 HR (95% CI)	p-value	Group 2 HR (95% CI)	p-value
cN Stage		0.935		0.285
cN0	Reference		Reference	
cN1	1.094 (0.368–3.250)		2.196 (0.270–17.839)	
cN2	0.956 (0.301–3.036)		0.976 (0.111–8.581)	
CEA levels		0.008*		<0.001*
< 7 ng/mL	Reference		Reference	
≥ 7 ng/mL	2.569 (1.280–5.155)		8.926 (2.627–30.330)	

Note: Symbol * indicates p<0.05.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 6 Multivariate Analysis of LRR in Group 1 and Group 2 Patients

Parameters	Group 1 HR (95% CI)	p-value	Group 2 HR (95% CI)	p-value
Age		0.028*		0.382
<65 years	Reference		Reference	
≥65 years	3.882 (1.544–13.053)		2.057 (0.409–10.352)	
Gender		0.516		0.723
Female	Reference		Reference	
Male	1.679 (0.352–8.017)		0.716 (0.112–4.567)	
Anal verge		0.213		0.908
< 5 cm	Reference		Reference	
≥ 5 cm	0.506 (0.173–1.479)		0.905 (0.168–4.884)	
Pre-OP tumor size (cm)		0.563		0.709
< 5	Reference		Reference	
≥ 5	1.405 (0.445–4.441)		1.409 (0.233–8.508)	
cT Stage		0.190		0.874
cT2	Reference		14415 (0–2.615E+120)	
cT3	0.902 (0.094–8.694)		9413 (0–1.705E+120)	
cT4	2.487 (0.285–21.724)		Reference	
cN Stage		0.363		0.053
cN0	Reference		2.336 (0.189–28.933)	
cN1	1.698 (0.338–8.520)		0.160 (0.007–3.930)	
cN2	0.736 (0.128–4.225)		Reference	
CEA levels		0.044*		0.028*
< 7 ng/mL	Reference		Reference	
≥ 7 ng/mL	3.160 (1.030–9.692)		8.570 (1.263–58.157)	

Note: Symbol * indicate p<0.05.
Abbreviations: HR, hazard ratio; CI, confidence interval.

a whole, the resultant 3-year OS, DM, LRR, and DSS rates were 85.7%, 23.6%, 10.6%, and 86.6%, respectively. The 3-year rates of OS, DM, and LRR for patients with higher CEA level (≥ 7 ng/mL) were 69.8%, 47.1%, 20.5%, and 71.7%, respectively. The 3-year rates of OS, DM, LRR, and DSS for patients with lower CEA level (< 7 ng/mL) were 91.0%, 12.1%, and 4.2%, and 91.0%, respectively. Besides CEA level, older age (≥ 65 years old) was a significant negative prognosticator for OS (p = 0.011, HR: 6.119, 95% CI: 1.646–22.743), DM (p = 0.045, HR: 2.759, 95% CI: 1.023–7.440), and DSS (p = 0.007, HR: 12.593, 95% CI: 1.970–80.499) but not LRR.

Table 7 Multivariate Analysis of DSS in Group 1 and Group 2 Patients

Parameters	Group 1 HR (95% CI)	p-value	Group 2 HR (95% CI)	p-value
Age		<0.001*		0.007*
<65 years	Reference		Reference	
≥65 years	5.513 (2.130–14.269)		12.593 (1.970–80.499)	
Gender		0.726		0.582
Female	Reference		Reference	
Male	1.258 (0.348–4.545)		0.651 (0.141–2.997)	
Anal verge		0.789		0.374
< 5 cm	Reference		Reference	
≥ 5 cm	1.142 (0.431–3.025)		2.219 (0.382–12.890)	
Pre-OP tumor size (cm)		0.469		0.405
< 5	Reference		Reference	
≥ 5	0.696 (0.261–1.858)		0.558 (0.141–2.206)	
cT Stage		0.108		0.874
cT2	Reference		14415 (0–2.615E+120)	
cT3	0.608 (0.123–3.018)		9413 (0–1.705E+120)	
cT4	1.641 (0.325–8.271)		Reference	
cN Stage		0.309		0.100
cN0	Reference		0.962 (0.107–8.682)	
cN1	3.712 (0.468–29.457)		0.115 (0.008–1.678)	
cN2	2.236 (0.257–19.456)		Reference	
CEA levels		0.015*		0.001*
< 7 ng/mL	Reference		Reference	
≥ 7 ng/mL	3.273 (1.259–8.513)		43.918 (5.057–381.432)	

Note: Symbol * indicate p<0.05.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

The present preliminary study, to the best of our knowledge, is one of the first studies to highlight the prognostic merit of the pretreatment serum CEA level in patients with rectal cancer treated by either preoperative LCRT or SCRT followed by chemotherapy and delayed surgery. This might be useful for future risk-stratified guidance of more intensified treatment to improve the treatment outcome of these patients.

CEA is a family of related glycoproteins secreted by a wide variety of solid tumors, and could be recognized in the body fluids, particularly blood.[1] Previous researchers have found the prognostic value of the serum CEA level in various types of malignancies, including colorectal cancer of different stages.[2–4] The serum CEA level is easily accessible

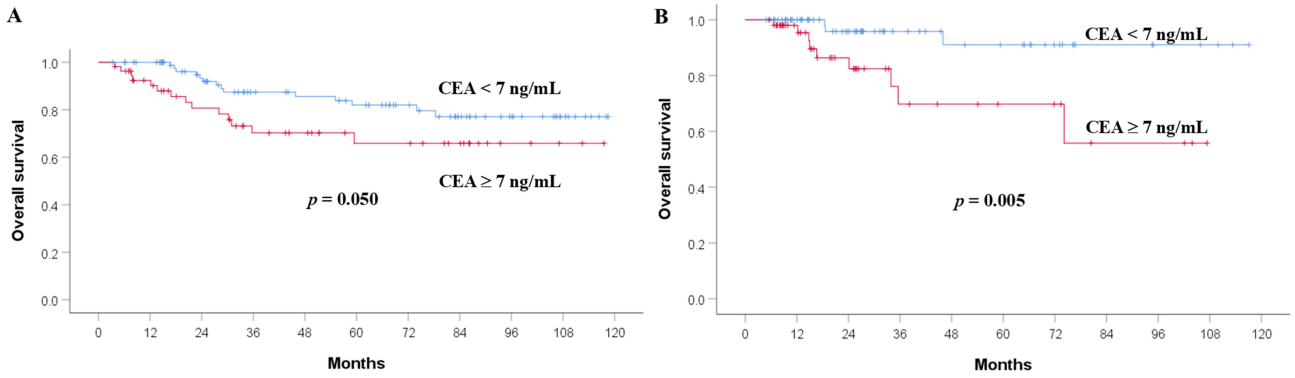

Figure 2 Comparison of OS rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) in (**A**) group 1 and (**B**) group 2 patients.

https://doi.org/10.2147/OTT.S474855

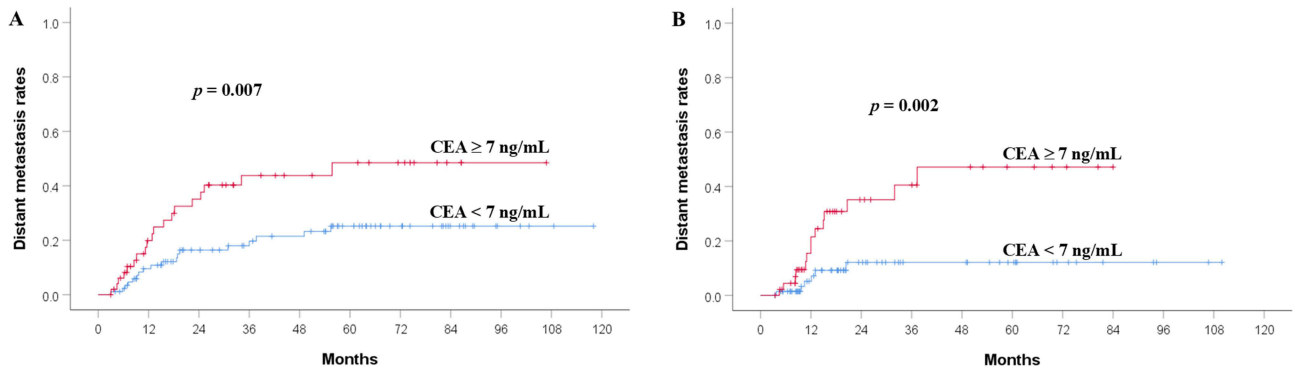

Figure 3 Comparison of DM rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) in (**A**) group 1 and (**B**) group 2 patients.

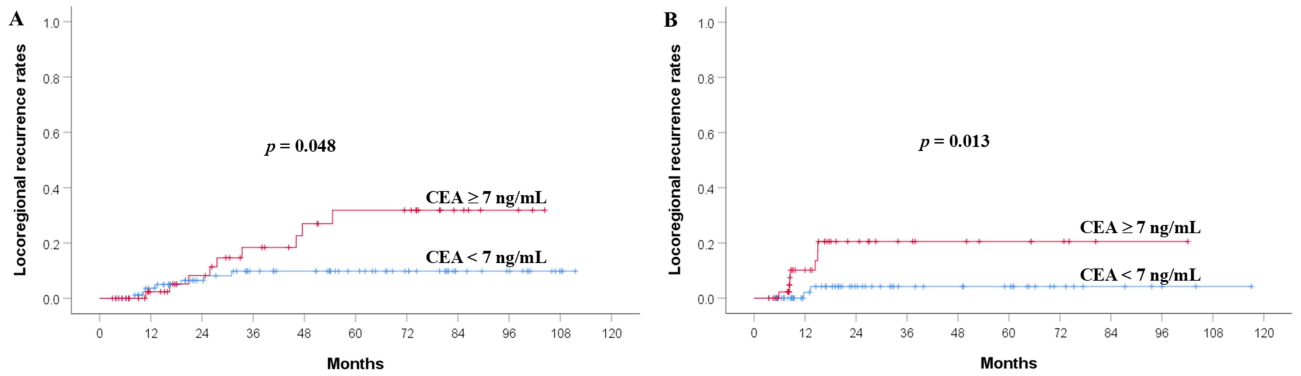

Figure 4 Comparison of LRR rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) in (**A**) group 1 and (**B**) group 2 patients.

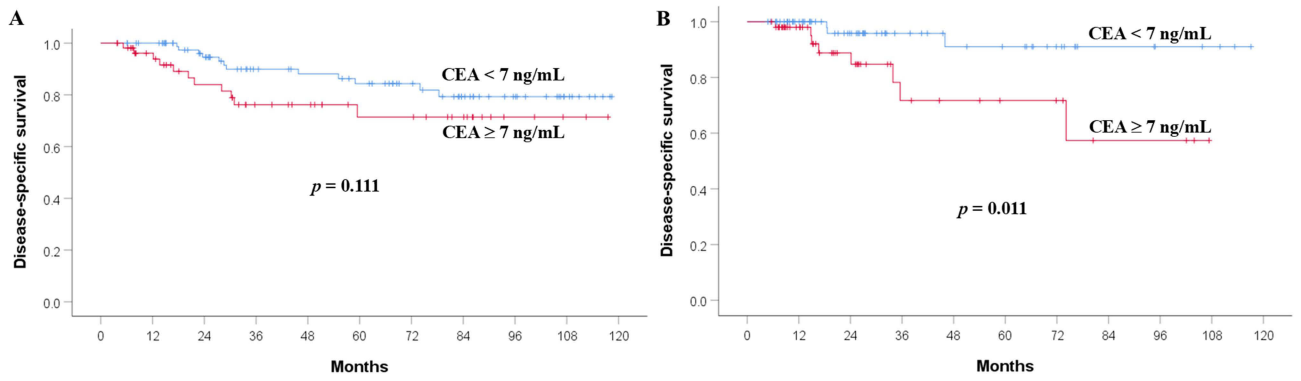

Figure 5 Comparison of DSS rates between CEA level (≥ 7 ng/mL) and lower CEA level (< 7 ng/mL) in (**A**) group 1 and (**B**) group 2 patients.

through blood draw, which is noninvasive for cancer patients and useful for oncologists to monitor the serial change of the disease status.

The current standard of care for locally advanced rectal cancer is a multimodal approach incorporating different combinations of surgery, systemic therapy, and radiotherapy.[5] Both LCRT and SCRT are acceptable radiotherapy dose regimens. Recently, the treatment strategy of a combination of preoperative SCRT and chemotherapy before total mesorectal excision has emerged as a more and more popular approach for locally advanced rectal cancer, as prospective clinical trials have demonstrated its benefit of decreasing the probability of disease-related treatment failure compared with the combination of LCRT.[26–28]

In the past few years, some investigators have evaluated the prognostic role of serum CEA, either pretreatment or posttreatment, in patients with rectal cancer treated by surgical resection plus mainly long-course (chemo)radiotherapy.[6–20] For instance: Park et al reported that elevated CEA level (> 5 ng/mL) predicted poor tumor response after preoperative long-course chemoradiation with 45 to 50.4 Gy in 1.8 Gy per fraction.[6] A study by Restivo et al illustrated that patients with increased CEA levels (> 5 ng/mL) were less likely to achieve pathological complete response (pCR) after preoperative long-course chemoradiation with predominantly 54 Gy in 1.8 Gy per fraction.[7] Wang et al observed that elevated CEA level (> 10 ng/mL) predicted poor downstaging and early occurring DM within 6 months postoperatively after preoperative chemoradiation with 30 Gy in 10 fractions, which was not a standard fractionation scheme for preoperative radiotherapy of rectal cancer.[11] Buijsen et al reported that CEA was a predictive marker for tumor response and pCR after preoperative long-course chemoradiation of 45 to 54.6 Gy in 1.8 Gy per fraction.[12] Kleiman et al reported that normalization of CEA levels (< 3.0 μg/L) was a highly significant predictor of pCR after preoperative chemoradiation with external beam radiotherapy of 25 to 60 Gy or brachytherapy of 26 Gy in 4 fractions.[13] Our previous study found that elevated CEA level (≥ 10 ng/mL) predicted local recurrence, DM, and OS after postoperative chemoradiation with 45 to 50.4 Gy in 5 to 6 weeks.[17] In the current study, higher pretreatment CEA level (≥ 7 ng/mL) also remained the prognostic factor of pCR ($p = 0.003$, OR: 0.133), OS ($p = 0.011$, HR: 2.999), DM ($p = 0.008$, HR: 2.569), LRR ($p = 0.044$, HR: 3.160), and DSS ($p = 0.015$, HR: 3.273), in the LCRT patients (group 1).

Nonetheless, although preoperative SCRT has also been established as a standard treatment for locally advanced rectal cancer by several large randomized trials,[21–25] none of the formerly mentioned studies have examined the prognostic role of CEA in the scenario of preoperative SCRT followed by chemotherapy and delayed surgery. Whether the results of the previous LCRT studies could be applied to different scenarios of preoperative SCRT followed by chemotherapy before total mesorectal excision is undetermined. In our homogenous cohort with all the participants treated by SCRT of 25 Gy in 5 fractions (group 2), a raised level of pretreatment CEA (≥ 7 ng/mL) was a significant negative prognostic factor of pCR ($p = 0.002$, OR: 0.038), OS ($p = < 0.001$, HR: 44.658), DM ($p = < 0.001$, HR: 8.926), LRR ($p = 0.028$, HR: 8.570), and DSS ($p = 0.001$, HR: 43.918). The results revealed by the current study, together with those of the previous studies, confirm that the pretreatment serum CEA level is useful as a noninvasive serum marker to not only predict the response after preoperative radiotherapy, but also the survival outcomes after both preoperative LCRT or SCRT. For future clinical trials, CEA could be considered as a stratification factor for better stratifying the patients. A more aggressive treatment approach, particularly total neoadjuvant therapy containing mainly SCRT and more intensified systemic therapy regimens, should be considered for these patients with elevated pretreatment serum CEA levels, to improve the tumor control outcome.

Recently, particle therapy, such as PBT, has emerged as a new promising radiotherapy treatment modality. Due to its physical advantage resulting from the Bragg peak, PBT generates better dose distribution, thus potentially reducing the treatment-related toxicity and improving the treatment outcomes.[29–31] In our study, the npCR rates for patients with higher pretreatment CEA level (≥ 7 ng/mL) were 4.3% and 40.0% in photon-SCRT and proton-SCRT patients, respectively. The npCR rate did not vary with different intervals between radiotherapy and surgery, but raised substantially from 25.0% to 40.0% with longer interval. Despite using the same SCRT dose regimen, the response after PBT is slower than XRT, and the biological effect of PBT seems better, particularly in more advanced patients having higher CEA level or clinical T4 disease. This is a commendable observation elucidating the distinct difference of biological effects between PBT and XRT, which is rather lacking in the literature. The encouraging combination of PBT and total neoadjuvant therapy to improve treatment outcomes warrants further investigation.

Chronological age appreciably impacts tolerance to the treatment, disease characteristics, and the prognostic outcome of cancer patients.[32–34] We found in our study that OS ($p < 0.001$ in group 1, $p = 0.011$ in group 2) was worse in elderly patients (≥ 65 years old). There were statistically significant differences between LRR of group 1 patients and DM of group 2 patients with older age (≥ 65 years old) or younger age (< 65 years old), which might be affected by the poorer compliance to the systemic therapy of the older age patients. To strike a balance between the cancer treatment outcome, treatment-related adverse effects, and long-term cancer survivorship, careful selection of the elderly patients for aggressive management and intense monitoring of the elderly patients during and after the treatment is important.[32,34]

There are some limitations in the study. The first limitation is the innate flaw existing with retrospective studies in which the information may not be accurately recorded. Second, the study subjects were exclusively from a single institution to ensure the homogeneity of the sample, hence, the results should be interpreted with caution when extrapolating to patients in different areas. Third, the follow-up period of proton-SCRT patients is limited. Thus, only the pCR/npCR rates, but not the survival outcomes, can be appropriately analyzed for proton-SCRT patients. A longer follow-up period might be needed to detect all the possible events. Despite these limitations, the current study is one of the only cohorts to date to investigate the prognostic value of serum CEA level in locally advanced rectal cancer treated by preoperative SCRT followed by chemotherapy and delayed surgery.

Conclusion

The pretreatment serum CEA level is demonstrated to be significantly prognostic of pCR, OS, DM, and LRR in patients with locally advanced rectal cancer treated by either preoperative LCRT or SCRT followed by chemotherapy and delayed surgery, which might be useful for future risk-stratified guidance of more intensified treatment to improve the outcome of these patients. Further investigations are warranted to scrutinize the prognostic value of CEA in different clinical scenarios as new treatment combinations for locally advanced rectal cancer have emerged.

Data Sharing Statement

The data are available from the corresponding author, E.Y. Huang, upon reasonable request.

Ethical Approval

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. This retrospective study was approved by the Institutional Review Board (IRB) of the Chang Gung Medical Foundation (IRB No. 202301515B0).

Informed Consent for Publication

The IRB approved the waiver of the participants' consent due to the retrospective nature of this chart review study. We confirmed the patient data was anonymized or maintained with confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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