

Predictive value of carcinoembryonic antigen and carbohydrate antigen 19-9 related to downstaging to stage 0–I after neoadjuvant chemoradiotherapy in locally advanced rectal cancer

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Objective: To explore the value of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) in predicting downstaging to stage 0–I cancer after neoadjuvant chemoradiotherapy (nCRT) in locally advanced rectal cancer.

Materials and methods: We respectively investigated pretreatment CEA, pretreatment CA19-9, posttreatment CEA, posttreatment CA19-9, pre–post-CA19-9 ratio, and pre–post-CEA ratio in 674 patients with locally advanced rectal cancer receiving nCRT and determined the patients' thresholds by using the receiver operating characteristic curve analysis. The association between downstaging (stage 0–I after nCRT), pathological complete response, and clinicopathological parameters was evaluated using the Pearson χ^2 test. The clinicopathological parameters which were found to be significantly associated with downstaging were analyzed by logistic regression models and were incorporated into a scoring system.

Results: Multivariate analysis showed that pretreatment CA19-9 level, posttreatment CEA level, pre–post-CEA ratio, and pre–post-CA19-9 ratio were significantly correlated with downstaging. Area under the curve of the scoring system was higher than that of parameters alone.

Conclusion: The 4-factor scoring system with CA19-9 level, posttreatment CEA level, pre–post-CEA ratio, and pre–post-CA19-9 ratio is of more value in predicting downstaging to stage 0–I patients with locally advanced rectal cancer after nCRT than using the parameters alone.

Keywords: CEA, CA19-9, neoadjuvant chemoradiotherapy, rectal cancer

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by radical surgery and adjuvant chemotherapy has become the standard treatment for locally advanced rectal cancer.^{1–4} After nCRT, 10%–30% patients could achieve pathological complete response (pCR) and 2%–50% patients could achieve complete clinical response.^{5–7} However, among the pCR or complete clinical response patients, outcomes of patients with a wait-and-see policy were similar to those who underwent surgery.^{6,8} According to previous studies, selective patients with stage ypT0–2N0 are considered eligible candidates for organ preservation.^{9–11} Accurate prediction of the response to nCRT is still under investigation. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are cancer antigens that might elevated in the serum of patients with colorectal cancer and has been routinely used in the staging of patients with rectal cancer.^{12–14} There have been some reports investigating whether pretreatment CEA and CA 19-9 level could predict pathological responses to nCRT in rectal cancer.^{15–17} However,

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the combination of or the changes in the level of CEA and CA19-9 have not been investigated among locally advanced rectal cancer patients with stage ypT0-2N0 after nCRT. The purpose of this study was to assess the predictive role of CEA and CA19-9 in tumor response of nCRT for individualized treatment strategy, especially for organ-sparing management after nCRT and for patients on a wait-and-see policy.

Materials and methods

Ethics statement

Although patients' consents were not specifically obtained for this analysis, all information was retrospectively extracted in the context of compliance with the ethical standards of the institutional and/or national research committees and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Patient medical records were analyzed retrospectively, with no individual patient identifiable information used. Therefore, The Fujian Medical University Union Hospital Ethic Review Board deemed patients' consents unnecessary.

Patients and clinical parameters

The retrospective study was approved by the Fujian Medical University Union Hospital Ethic Review Board. Clinicopathological parameters of 674 patients were obtained from our maintained database. These patients underwent nCRT followed by total mesorectal excision (TME) at our institution between September 2007 and April 2016. The clinicopathological parameters include age, gender, levels of CEA, levels of CA19-9, treatment modality, clinical tumor-node-metastasis staging (cTNM), pathological tumor-node-metastasis staging after the neoadjuvant treatment (ypTNM). The pretreatment parameters were collected one week before the nCRT began, and the post-treatment parameters were defined as changes in the levels of the preoperative parameters 6–8 weeks after nCRT. Patients were staged according to the seventh edition of the American Joint Committee on Cancer Staging Manual. Clinical T and N staging classification were determined according to magnetic resonance imaging and endoscopic ultrasonography.

Treatment

The definitions of gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) have been published previously.¹⁸ The GTV was calculated based on clinical information, including digital rectal examination, endoscopy ultrasound, and abdominopelvic magnetic resonance imaging. The CTV included a minimum of a 3 cm craniocaudal margin to the GTV in addition to the entire

mesorectum, presacral, and internal iliac lymph node drainage regions. The neoadjuvant radiotherapy regimen consists of 3-dimensional conformal radiotherapy and intensity-modulated radiation therapy. Forty-five Gy was delivered to PTV of CTV in 25 fractions. A dose of 50.4 Gy was delivered to PTV of GTV with 3-dimensional conformal radiotherapy in 28 fractions, while 50 Gy was delivered to PTV of GTV with intensity-modulated radiation therapy in 25 fractions. The chemotherapeutic regimens with dosages were as follows: 1) FOLFOX4: oxaliplatin 85 mg/m² intravenous (IV), Day 1, leucovorin 200 mg/m² IV ×2 days, 5-FU 400 mg/m² IV bolus ×2 days, then 600 mg/m²/d ×2 days continuous infusion. This was repeated every 2 weeks for a total of 6 months of perioperative therapy. 2) mFOLFOX6: oxaliplatin 85 mg/m² IV Day 1, leucovorin 400 mg/m² IV, 5-FU 400 mg/m² IV bolus on Day 1, then 1,200 mg/m²/d ×2 days continuous infusion. This was repeated every 2 weeks for a total of 6 months of perioperative therapy. 3) CapeOX: oxaliplatin 130 mg/m² IV, Day 1, capecitabine 1,000 mg/m² twice daily, Days 1–14 every 3 weeks. This was repeated every 3 weeks for a total of 6 months of perioperative therapy. The neoadjuvant 5-FU based or capecitabine-based chemotherapy was initiated on the first day of radiotherapy. Also, TME was performed 6–8 weeks after the end of nCRT.

Data analysis

In this study, we defined pre–post-CEA ratio as pretreatment CEA to posttreatment CEA ratio and pre–post-CA19-9 ratio as pretreatment CA19-9 to posttreatment CA19-9 ratio. Downstaging was defined as a transition from the pretreatment clinical stage II–III (cT3–4NanyM0) to the pathologic staging of surgical specimen ypStage 0–I (ypT0–2N0M0). pCR was defined as the absence of tumor cells. The receiver operating characteristic (ROC) curve was generated and Youden's index was calculated to evaluate the ideal cut-off values of pretreatment CEA, pretreatment CA19-9, posttreatment CEA, posttreatment CA19-9, pre–post-CA19-9 ratio, and pre–post-CEA ratio for tumor response prediction. Patients were assigned into 2 groups according to the cut-off value. The association between downstaging, pCR, and clinicopathological parameters was evaluated using the Pearson χ^2 test. A logistic regression analysis was used to identify significant independent parameters for downstaging. Significant independent parameters were incorporated into a scoring system. *P*-value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' general characteristics

Six hundred and seventy-four patients with locally advanced rectal cancer receiving nCRT were enrolled. Among the 674 patients, 444 patients were male, and 230 patients were female, with a median age of 56 at diagnosis. The median pretreatment CA 19-9 and CEA levels were 11.855 and 4.1 U/mL. Baseline characteristics are detailed in Table 1.

ROC curves of CEA and CA19-9 for downstaging and pCR

ROC curve analysis was used to evaluate cut-off values of CEA and CA19-9 for predicting downstaging and pCR. The optimum cut-off values defined by ROC curve for pretreatment CEA, pretreatment CA19-9, posttreatment CEA, posttreatment CEA, pre–post-CEA ratio, and pre–post-CA19-9

ratio to discriminate between patients' downstaging were 5.05 U/mL (area under the curve [AUC]: 0.637, 95% CI: [0.595–0.679], $P<0.0001$), 12.6 U/mL (AUC: 0.59, 95% CI: [0.547–0.633], $P<0.0001$), 2.45 U/mL (AUC: 0.604, 95% CI: [0.562–0.647], $P<0.0001$), 1.56 U/mL (AUC: 0.608, 95% CI: [0.565–0.651], $P<0.0001$), and 1.28 U/mL (AUC: 0.615, 95% CI: [0.572–0.657], $P<0.0001$), respectively. The posttreatment CA19-9 was not a predictive factor of downstaging (Figure 1). Meanwhile, the optimum cut-off value for pretreatment CEA, posttreatment CEA, pre–post-CEA ratio, and pre–post-CA19-9 ratio to discriminate between patients' pCR were 2.85 U/mL (AUC: 0.619, 95% CI: [0.568–0.670], $P<0.0001$), 2.45 U/mL (AUC: 0.628, 95% CI: [0.577–0.679], $P<0.0001$), 1.07 U/mL (AUC: 0.573, 95% CI: [0.518–0.627], $P=0.009$), and 0.92 U/mL (AUC: 0.615, 95% CI: [0.506–0.615], $P=0.029$), respectively, but pretreatment CA19-9 and posttreatment CA19-9 were not predictive factors of pCR (Figure 2).

Table 1 Characteristics of locally advanced rectal cancer patients

Characteristics values	Counts
Age (years, median [range])	56 (24–85)
Gender (male/female)	444/230
cT classification	
cT1	1
cT2	35
cT3	253
cT4	385
cN classification	
N0	61
N+	613
cStage	
II	55
III	619
Pretreatment CA19-9 (U/mL, median [range])	11.855 (0–1,000)
Pretreatment CEA (U/mL, median [range])	4.1 (0.2–1,000)
ypT classification	
ypT0	148
ypT1	38
ypT2	171
ypT3	270
ypT4	47
ypN classification	
ypN0	477
ypN1	149
ypN2	28
ypStage	
pCR	136
I	169
II	164
III	178
IV	27
Posttreatment CA19-9 (U/mL, median [range])	10.62 (0–173.2)
Posttreatment CEA (U/mL, median [range])	2.5 (0.2–308)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; pCR, .

Correlations of characteristic parameters with downstaging and pCR

Pearson χ^2 test was performed to investigate whether CEA and CA19-9 and other characteristic parameters were associated with downstaging. This revealed that pretreatment CEA, pretreatment CA19-9, posttreatment CEA, pre–post-CEA ratio, and pre–post-CA19-9 ratio were significantly associated with downstaging (Table 2). Meanwhile, pretreatment CEA, pretreatment CA19-9, pre–post-CEA ratio, and pre–post-CA19-9 ratio were significantly associated with pCR (Table 3).

ROC curves of a 4-factor scoring system for downstaging

The logistic analysis showed that pretreatment CA19-9, posttreatment CEA, pre–post-CEA ratio, and pre–post-CA19-9 ratio were significantly associated with downstaging (Table 4). A 4-factor scoring system which assigns points to various variables was constructed. According to the regression coefficient values in the logistic analysis, 5 points, 9 points, 6 points, and 5 points were added for pretreatment CA19-9 level lower than 12.6 U/mL, posttreatment CEA level lower than 2.45 U/mL, pre–post-CEA ratio lower than 1.56, and pre–post-CA19-9 ratio lower than 1.28, respectively. The cut-off value of the 4-factor scoring system calculated by ROC curve was 10.5 (AUC: 0.680, 95% CI: [0.64–0.721], $P<0.0001$, sensitivity 76.4%, specificity 53.7%) (Figure 3). AUC of the scoring system was higher than either of the parameters. These results implied that the scoring system

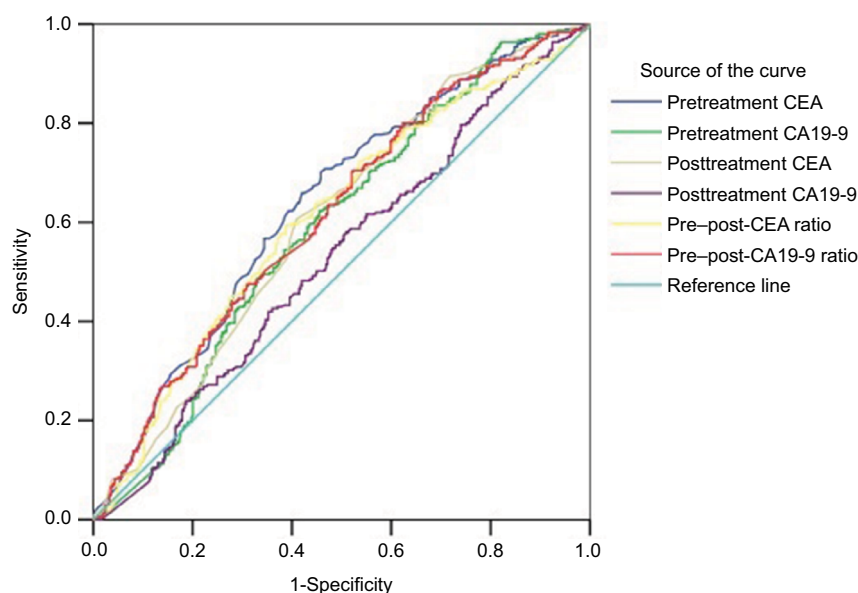


Figure 1 ROC curve analysis of CEA and CA19-9 for downstaging with locally advanced rectal cancer after nCRT.

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; nCRT, neoadjuvant chemoradiotherapy; ROC, receiver operating characteristic.

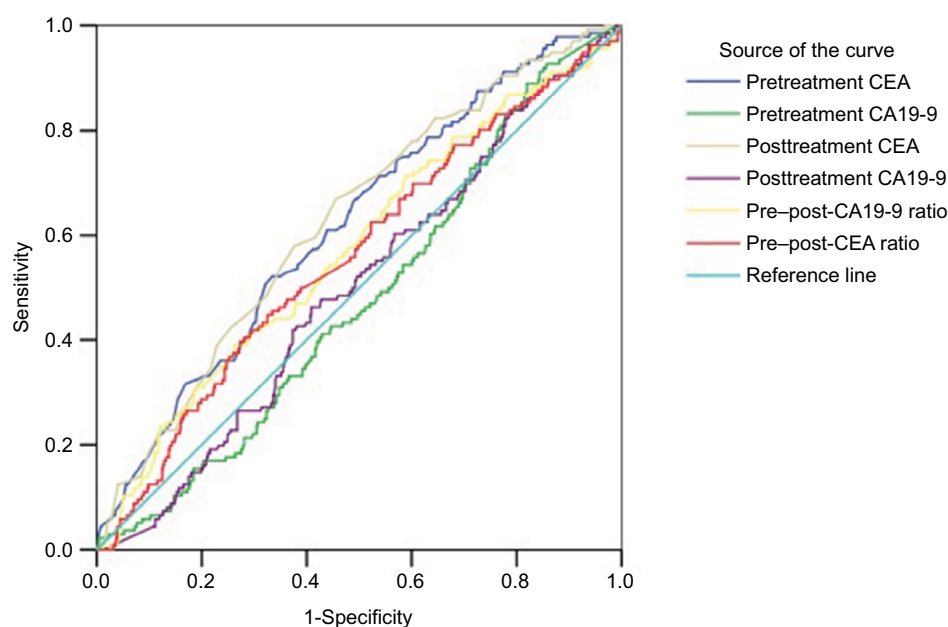


Figure 2 ROC curve analysis of CEA and CA19-9 for pCR with locally advanced rectal cancer after nCRT.

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; nCRT, neoadjuvant chemoradiotherapy; pCR, pathological complete response; ROC, receiver operating characteristic.

was a significant predictor that can be superior to the use of either CEA or CA19-9 alone.

Discussion

Local control and overall survival rate of rectal cancer has markedly improved after TME. However, TME is associated with poor functional outcome and decrease of the quality of life, especially among patients with distal rectal

cancer.^{8,19} nCRT reduced the rate of local recurrence and improved survival. The recurrence rate of ypT2 patients was not higher than the ypT1 or ypT0/Tis patients.^{11,20} Local excision after nCRT would be a simple and safe alternative to TME in selected patients with stage ypT0-2N0 while preserving the quality of life.^{11,20-23} Accurate prediction of the response to nCRT potentially assists in individualized treatment. However, there is a lack of an ideal model that

Table 2 Characteristics for downstaging with locally advanced rectal cancer after nCRT

Variables	Sum	Downstaging	Not downstaging	P-value
Age (years)				0.796
<65	534	243	291	
≥65	140	62	78	
Gender				0.634
Male	444	198	246	
Female	230	107	123	
cT classification				0.494
cT1	1	0	1	
cT2	35	18	17	
cT3	253	120	133	
cT4	385	167	218	
cN classification				0.146
N0	61	33	28	
N+	613	272	341	
cStage				0.379
I	55	28	27	
III	619	277	342	
ypT classification				<0.0001
ypT0	148	141	7	
ypT1	38	33	5	
ypT2	171	131	40	
ypT3	270	0	270	
ypT4	47	0	47	
ypN classification				<0.0001
ypN0	477	305	172	
ypN1	149	0	149	
ypN2	48	0	48	
ypStage				<0.0001
pCR	136	136	0	
I	169	169	0	
II	164	0	164	
III	178	0	178	
IV	27	0	27	
Pretreatment CEA (U/mL)				<0.0001
<5.05	383	214	169	
≥5.05	291	91	200	
Pretreatment CA19-9 (U/mL)				<0.0001
<12.6	357	189	168	
≥12.6	317	116	201	
Posttreatment CEA (U/mL)				<0.0001
<2.45	336	185	151	
≥2.45	338	120	218	
Posttreatment CA19-9 (U/mL)				0.066
<11.3	365	177	188	
≥11.3	309	128	181	
Pre-post-CEA ratio				<0.0001
<1.56	328	181	147	
≥1.56	346	124	222	
Pre-post- CA19-9 ratio				<0.0001
<1.28	438	223	215	
≥1.28	236	82	154	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; nCRT, neoadjuvant chemoradiotherapy; pCR, pathological complete response.

could accurately screen the stage ypT0-2N0 for organ-sparing management.

The serum CEA level is widely used as a tumor marker in rectal cancer patients. Some studies have evaluated the

value of CEA in predicting the response to nCRT in rectal cancer.^{24–29} However, the cut-off point was defined by the upper limit of normal value as 5 ng/mL rather than using the ROC curve analysis, as was done in the most previous

studies. Also, most of the previous studies analyzed the feasibility of pretreatment CEA level or posttreatment CEA level as the indicator for pCR, but few analyzed the combination of pretreatment CEA levels and posttreatment CEA level as the indicator of stage ypT0-2N0 cancer. Our study suggested that pretreatment CEA, posttreatment CEA and pre-post-CEA ratio was significantly associated with the stage ypT0-2N0, and pretreatment CEA and pre-post-CEA ratio was significantly associated with pCR.

Table 3 Characteristics for pCR with locally advanced rectal cancer after nCRT

Variables	Sum	pCR	Not pCR	P-value
Age (years)				0.442
<65	534	111	423	
≥65	140	25	115	
Gender				0.182
Male	444	83	361	
Female	230	53	177	
cT classification				0.136
cT1	1	0	1	
cT2	35	8	27	
cT3	253	62	191	
cT4	385	66	319	
cN classification				0.572
N0	61	14	47	
N+	613	122	491	
cStage				0.752
II	55	12	43	
III	619	124	495	
Pretreatment CEA (U/mL)				<0.0001
<2.85	251	71	180	
≥2.85	423	65	358	
Posttreatment CEA (U/mL)				<0.0001
<2.45	336	91	245	
≥2.45	338	45	293	
Pre-post-CEA ratio				0.006
<1.07	193	52	141	
≥1.07	481	84	397	
Pre-post-CA19-9 ratio				0.012
<0.92	240	61	179	
≥0.92	434	75	359	

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; nCRT, neoadjuvant chemoradiotherapy; pCR, pathological complete response.

Meanwhile, CA 19-9 is another widely used tumor marker in gastrointestinal tumor and is a significant predictor of survival for rectal cancer.³⁰⁻³² However, few studies analyzed the association between CA19-9 and nCRT response. Our study suggested that pretreatment CA19-9 and pre-post-CA19-9 ratio were significantly associated with stage ypT0-2N0 tumor, and pre-post-CA19-9 ratio was significantly associated with pCR. The result was similar to a previous study.¹⁷

Previous studies failed to build a scoring system for organsparing management among patients with stage ypT0-2N0 after nCRT. In the present study, multivariate analysis showed pretreatment CA19-9 level, posttreatment CEA level, pre-post-CEA ratio, and pre-post-CA19-9 ratio were significantly correlated with downstaging. A 4-factor scoring system which assigns points to various variables was constructed according to the regression coefficient values in the logistic analysis. The 4-factor scoring system with CA19-9 level, posttreatment CEA level, pre-post-CEA ratio,

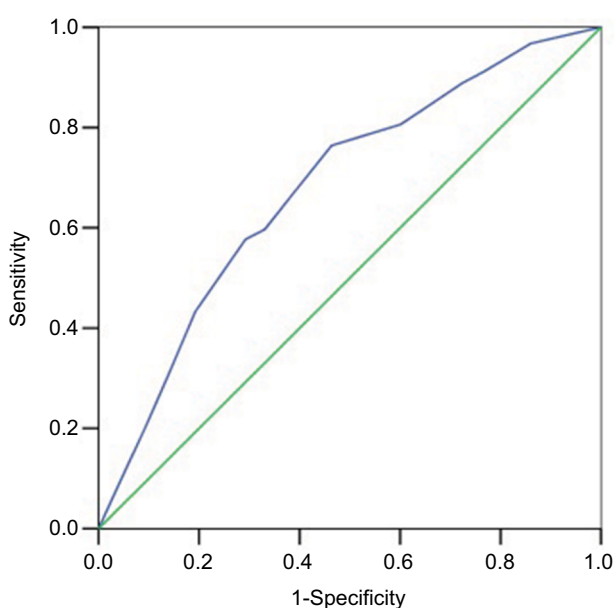


Figure 3 ROC curve analysis of 4-factor scoring system for downstaging with locally advanced rectal cancer after nCRT.

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; ROC, receiver operating characteristic.

Table 4 Multivariate analyses of predictors for downstaging with locally advanced rectal cancer after nCRT

Variables	Regression coefficient	SE	P-value	OR [95% CI]
Pretreatment CA19-9<12.6	0.379	0.177	0.33	1.46 (1.032–2.067)
Posttreatment CEA <2.45	0.696	0.184	<0.0001	2.007 (1.398–2.879)
Pre-post-CEA ratio <1.56	0.441	0.208	0.034	1.555 (1.034–2.34)
Pre-post-CA19-9 ratio <1.28	0.38	0.194	0.049	1.463 (1.001–2.137)
Constant	–1.436			

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; nCRT, neoadjuvant chemoradiotherapy.

and pre–post-CA19-9 ratio is a better predictive biomarker related to downstaging to stage 0–I tumor after nCRT in locally advanced rectal cancer patients than using any of the parameters alone.

There are still some limitations in this study. First, the study is subject to selection bias due to retrospective nature of the analysis. Second, the data were derived from a single institution. Last but not least, the discrimination threshold in this study was determined using ROC analysis. However, it should be validated in different cohorts of patients.

Conclusion

The 4-factor scoring system with CA19-9 level, posttreatment CEA level, pre–post-CEA ratio, and pre–post-CA19-9 ratio is a better predictive model related to downstaging to stage 0–I cancer after nCRT in locally advanced rectal cancer patients than using either CEA or CA19-9 alone. Further studies are needed to validate the result.

Author contribution

All authors contributed toward data analysis, drafting and revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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