BRIEF ARTICLE

Normal carcinoembryonic antigen indicates benefit from perioperative chemotherapy to gastric carcinoma patients

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Abstract

AIM: To evaluate pretreatment serum carcinoembryonic antigen (CEA) as a predictor of survival for patients with locally advanced gastric cancer receiving perioperative chemotherapy.

METHODS: We retrospectively studied a cohort of 228 gastric cancer patients who underwent D2 gastrectomy combined with chemotherapy at the Sun Yat-sen University Cancer Center between January 2005 and December 2009. Among them, 168 patients received 6-12 cycles of oxaliplatin-based adjuvant (post-operative) chemotherapy, while 60 received perioperative chemotherapy (2 cycles of FOLFOX6 or XELOX before surgery and 4-10 cycles after surgery). Serum CEA was measured using an enzyme immunoassay. The follow-up lasted until December 2010.

RESULTS: In the group that had elevated serum CEA, the difference in survival time between patients receiving perioperative chemotherapy and those receiving adjuvant chemotherapy had no statistical significance (*P* > 0.05). However, in the group that had normal serum CEA, patients receiving perioperative chemotherapy had a longer survival time. In multivariate analysis, T staging and lymph node metastatic rate were independent prognostic factors for the patients. Perioperative chemotherapy improved the overall survival of patients who had a normal pretreatment CEA level (*P* = 0.070).

CONCLUSION: Normal pretreatment serum CEA is a predictor of survival for patients receiving perioperative chemotherapy.

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. It is the second leading cause of cancer deaths in the world[1-3], and most of those patients are diagnosed at an advanced stage of disease[4,5]. Surgery is the main

treatment for gastric cancer. Many meta-analyses have demonstrated that adjuvant (post-operative) chemotherapy can improve the prognosis for gastric cancer patients[6-8], and in some prospective clinical trials, adjuvant chemotherapy has improved the prognosis of patients with locally advanced gastric cancer[9-11]. The Cunningham trial showed for the first time that perioperative chemotherapy (treatment both before and after surgery) is superior to surgery alone in treating gastric cancers. Further studies showed that preoperative chemotherapy combined with chemoradiotherapy provided substantial responses that improved the prognosis[12-14].

Carcinoembryonic antigen (CEA) was first identified in 1965 by Gold and Freedman in human colon cancer tissue extracts[15]. In the last two decades, CEA has been widely used as a tumor marker in the diagnosis and monitoring of some malignancies[16]. Since the 1990s, tumor markers including CEA, carbohydrate antigen 19-9, and others have been widely used to monitor gastric cancer progression and even to assess the prognosis of gastric cancer patients, although their specificities have not been satisfactory[17-20]. The controversial conclusions resulting from the use of these biomarkers are therefore understandable[21]. In the present study, we retrospectively evaluated the predictive value of pretreatment serum CEA in patients with late-stage gastric cancer in China.

MATERIALS AND METHODS

Patient inclusion and exclusion criteria

Inclusion criteria: (1) age: 20 to 75 years; World Health Organization performance status 0 to 1; (2) histologically proven adenocarcinoma of the stomach; T3 or T4 tumor based on endoscopic ultrasound; no evidence of distant metastases or of disease considered nonresectable by endoscopic ultrasonography, computed tomography (CT), or extended diagnostic laparoscopy; (3) no prior gastric surgery; (4) no previous radiotherapy or other treatments, including immunotherapy or Chinese traditional medicine; (5) no uncontrolled infectious or cardiac disease; adequate hepatic and renal functions; and (6) no synchronous or metachronous cancers.

Exclusion criteria: (1) age: older than 75 years or younger than 20 years; (2) hepatic, renal, pulmonary, or cardiac dysfunction; and (3) severe postoperative complications, such as anastomosis leakage or anastomosis stenosis, that may cause malnutrition or make the patients intolerant to postoperative chemotherapy.

Patient characteristics

We included 228 patients who underwent D2 gastrectomy at the Sun Yat-sen University Cancer Center between January 2005 and December 2009. Among them, 173 patients had a normal pretreatment serum CEA (≤ 5 ng/mL) and 55 patients had elevated pretreatment serum CEA (> 5 ng/mL). Sixty patients among both CEA groups (43 with normal serum CEA and 17 with

Table 1 Clinicopathologic characterization of patients with gastric adenocarcinoma treated by surgery in combination with chemotherapy

Data	Normal serum CEA (median 52 yr, range: 22-74 yr) n (%)	Elevated serum CEA (median 54 yr, range: 32-73 yr) n (%)	P
Sex			0.090
Male	116 (67.1)	44 (80.0)	
Female	57 (32.9)	11 (20.0)	
Tumor location			0.115
Upper	52 (30.0)	26 (47.3)	
Middle	42 (24.3)	12 (21.8)	
Lower	68 (39.3)	15 (27.3)	
Total	11 (6.4)	2 (3.6)	
Histological grade			0.128
G1	1 (0.6)	0 (0)	
G2	31 (17.9)	18 (32.7)	
G3	112 (64.7)	29 (52.7)	
G4	29 (16.8)	8 (14.6)	
Tumor size			0.053
≤ 2 cm	23 (13.3)	1 (1.8)	
2 cm < diameter ≤ 5 cm	98 (56.6)	36 (65.5)	
> 5 cm	52 (30.1)	18 (32.7)	
Boarrman type			0.093
I	3 (1.7)	0 (0)	
II	90 (52.0)	20 (36.4)	
III	69 (39.9)	28 (50.9)	
IV	11 (6.4)	7 (12.7)	
Pathological T staging[1]			0.664
T0	6 (3.5)	1 (1.8)	
T3	156 (90.2)	49 (89.1)	
T4	11 (6.4)	5 (9.1)	
Lymph node metastasis rate			0.951
0	12 (6.9)	3 (5.5)	
0 < r ≤ 0.1	29 (16.8)	8 (14.5)	
0.1 < r ≤ 0.3	50 (28.9)	17 (30.9)	
r > 0.3	82 (47.4)	27 (49.1)	
Surgery			0.313
Radical	165 (95.4)	50 (90.9)	
Palliative	8 (4.6)	5 (9.1)	
Chemotherapy			0.384
Adjuvant	130 (75.1)	38 (69.1)	
Perioperative	43 (24.9)	17 (30.9)	

[1]Pathological T staging was based on the 6th Union for International Cancer Control's staging systems for gastric cancer. CEA: Carcinoembryonic antigen.

elevated serum CEA) received oxaliplatin-based perioperative chemotherapy, with 2 cycles before surgery and 4-10 cycles of the same regimen after surgery. The exception was 6 patients suffering from progressive disease who received second-line chemotherapy for 4-6 cycles (see Treatment section). Among both CEA groups, 168 patients received only adjuvant chemotherapy (Figure 1). The clinicopathological characteristics of all patients are presented in Table 1.

Treatment

The two cycles of preoperative chemotherapy included the XELOX and FOLFOX regimes. All the chemotherapy regimens were used under standard protocols. The XELOX regimen consisted of oxaliplatin at 130 mg/m^2 (i.v. drip, day 1) and capecitabine at 1000 mg/m^2 (oral,
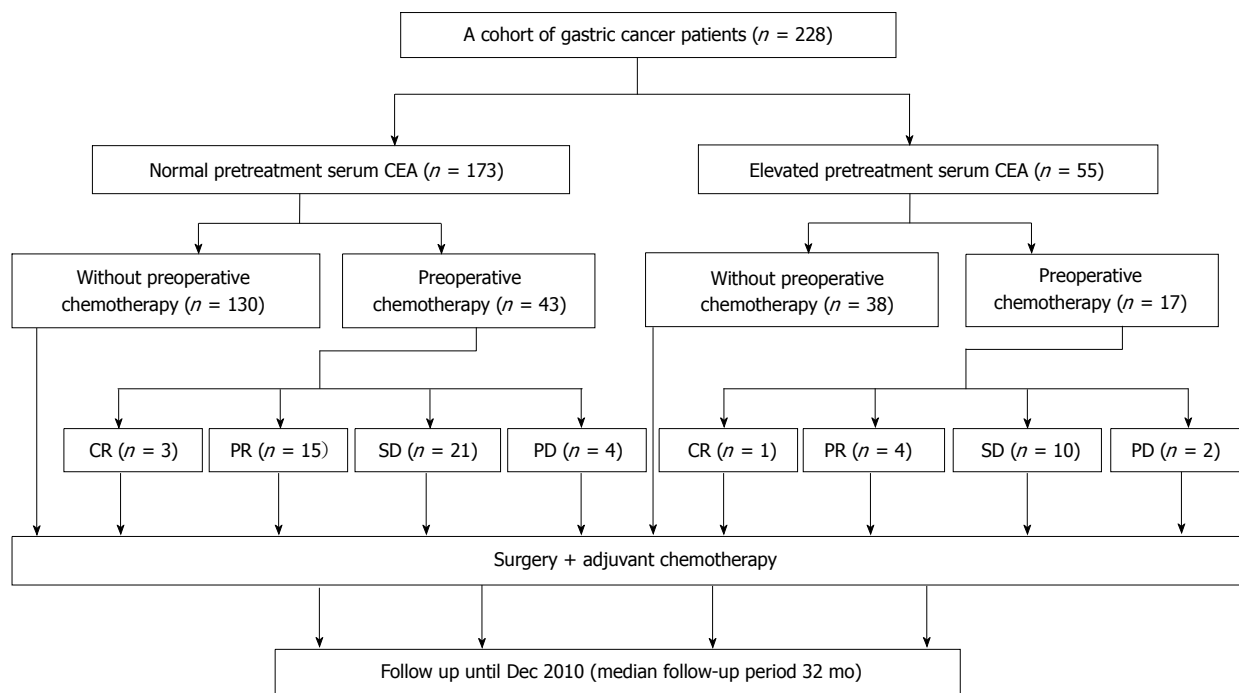
Figure 1 The treatment subgroups of the cohort of 228 patients in this retrospective study. CEA: Carcinoembryonic antigen; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

day 1-14), followed by one week of no treatment. Starting on day 22, the cycle was repeated, and surgery took place between day 43 and 47.

The FOLFOX6 regimen started on day 1 with oxaliplatin at 100 mg/m^2 (i.v. drip) with folic acid at 400 mg/m^2 (racemic) or 200 mg/m^2 (L-form), plus 5-fluorouracil (5-FU) as a 400 mg/m^2 bolus, followed by 2400 mg/m^2 of 5-FU as a continuous 46 h infusion. When the infusion was completed, there was no further treatment through day 14. On day 15, the cycle was repeated, with surgery taking place between day 30 and day 33.

After surgery, all of the patients received adjuvant chemotherapy starting within 2-4 wk. The median number of cycles for each regimen was 9 for FOLFOX6 (range: 7-12) and 7 for XELOX (range: 6-8). The six progressive disease patients received paclitaxel plus 5-FU (1 patient), docetaxel plus 5-FU (2 patients), or S-1 oral administration (3 patients) chemotherapy; these patients received a median of 5 cycles (range: 4-6).

Chemotherapy response evaluation
Assessment of the response to preoperative chemotherapy was based on the reduction of primary tumor size (as measured by endoscopic ultrasonography and CT scan) and the Response Evaluation Criteria in Solid Tumors criteria.

Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction of the short axis to less than 10 mm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as a reference the baseline sum of diameters.

Stable disease: Neither sufficient shrinkage to qualify as a partial response nor sufficient increase to qualify as progressive disease.

Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study (which may include the baseline sum). The sum must also show an absolute increase of at least 5 mm.

Patient follow-up
After treatment, the patients were monitored every 3 mo for the first 2 years, then every 6 mo thereafter. Telephone calls and letters were used to assess patients who could not be physically present. Complete data were collected from all 228 patients until December 2010. The follow-up period ranged from 8 mo to 59 mo (median, 32 mo). The total follow-up times are shown in Figure 2A.

Statistical analysis
The χ^2 test was used to compare categorical variables between the normal and elevated serum CEA groups. Univariate survival analysis was performed using the Kaplan-Meier method. Survival curves were compared with the log-rank test. Multivariate statistical survival analysis was performed using Cox regression. Analysis were performed with SPSS software version 16.0 for Windows
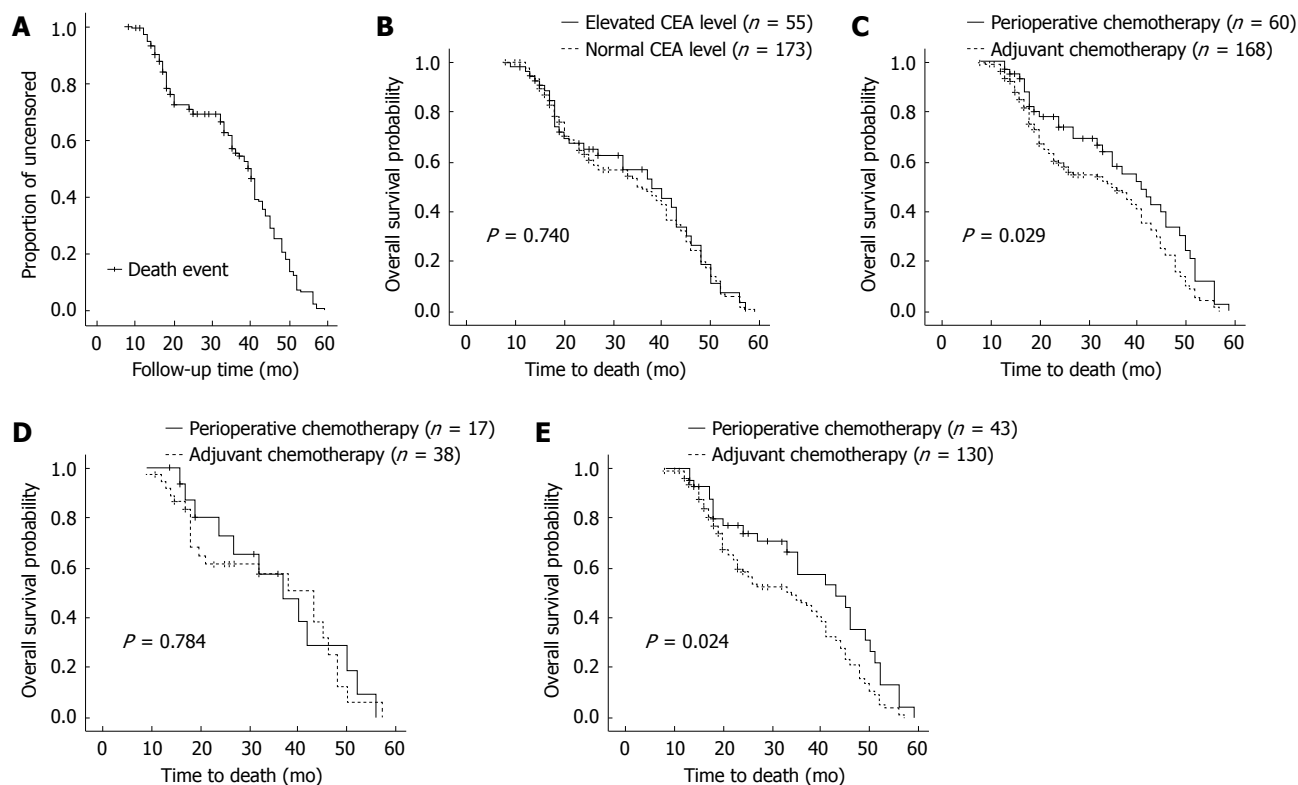
Figure 2 Survival curves for carcinoembryonic antigen patients with different treatments. A: The 228 patients in follow-up over this study; follow-up times ranged from 8 to 59 mo (median, 32 mo); B: Survival curves for the elevated carcinoembryonic antigen (CEA) patients and the normal CEA patients, with two-year survival rates of 57% and 51%, respectively, and no statistically significant difference between the groups (P = 0.740); C: Survival curves for patients receiving perioperative chemotherapy or adjuvant chemotherapy, with two-year survival rates of 58% and 50%, respectively. The difference is statistically significant (P = 0.029); D: Survival curves for the elevated CEA patients who received perioperative or adjuvant chemotherapy, with two-year survival rates of 58% and 58%, respectively, with no statistical significance (P = 0.784); E: Survival curves for normal CEA patients who received perioperative or adjuvant chemotherapy, with a two-year survival rate of 59% and 48%, respectively. The difference is statistically significant (P = 0.024).

(SPSS, Inc., Chicago, IL, United States). Statistical significance was defined as $P < 0.05$.

RESULTS

There was no statistically significant difference in overall survival between the normal CEA group (n = 173) and the elevated CEA group (n = 55). The survival curves are shown in Figure 2B.

The efficacy of preoperative chemotherapy was evaluated. Among these 60 patients, 4 (6.67%) had complete clinical response and 19 (31.7%) had partial clinical response, yielding an overall response rate of 40.0%. The response rates of the patients who had normal pretreatment serum CEA *vs* those who had elevated CEA were not significantly different, although patients with normal CEA had a higher response rate (complete response + partial response) (41.9% *vs* 29.4%). These results are shown in Table 2.

The 60 patients who received perioperative chemotherapy (*i.e.*, preoperative plus adjuvant) had a significantly better overall survival rate than the 168 who received only adjuvant chemotherapy, with median survival time of 41 mo for the perioperative group *vs* 35 mo for the adjuvant group (P = 0.029). The survival curves are shown in Figure 2C. For the patients with elevated se-

rum CEA, there was no significant difference in overall survival rate between perioperative chemotherapy (n = 17) and adjuvant chemotherapy (n = 38, P = 0.784, Figure 2D). For the patients with normal serum CEA, the overall survival rate was significantly better in the perioperative group (n = 43) and the median survival time was 43 mo *vs* 34 mo for the adjuvant group (n = 130, P = 0.024). The survival curves are shown in Figure 2E.

In univariate analyses, perioperative chemotherapy, T staging, and the lymph node metastasis rate significantly correlated with overall survival (Table 3). In multivariate analysis, T staging and the lymph node metastatic rate were independent prognostic factors. Perioperative chemotherapy improved the overall survival of patients who had normal pretreatment serum CEA (Table 4).

DISCUSSION

Perioperative chemotherapy, although it is a large physical and psychological burden, has been proven to be effective for some gastric cancer patients. The European Organization for Research and Treatment of Cancer Randomized Trial 40 954 showed no survival benefit from preoperative chemotherapy compared with surgery alone for locally advanced cancer[22]. However, this study had low statistical power; a high number of proximal

Table 2 The efficacy of preoperative chemotherapy on locally advanced gastric cancer patients *n* (%)

Pretreatment serum CEA	Response to preoperative chemotherapy			
	Complete response	Partial response	Stable disease	Progressive disease
Normal	3 (7.0)	15 (34.9)	21 (48.8)	4 (9.3)
Elevated	1 (5.9)	4 (23.5)	10 (58.8)	2 (11.8)

CEA: Carcinoembryonic antigen.

Table 3 Univariate analysis of overall survival in all patients and in patients with normal pretreatment serum carcinoembryonic antigen

Variable	No. of patients	2-yr survival rate (%)	Median survival (mo)	P value
All patients				
Pathological T staging				0.001
T0	7	86	52	
T3	205	52	37	
T4	16	36	27	
Lymph node metastasis				0.001
0	15	79	48	
0 < r ≤ 0.1	37	68	31	
0.1 < r ≤ 0.3	67	42	32	
r > 0.3	109	50	33	
Chemotherapy				0.029
Adjuvant	168	50	35	
Perioperative	60	58	41	
Normal-CEA patients				
Pathological T staging				0.001
T0	6	83	50	
T3	156	50	35	
T4	11	39	17	
Lymph node metastasis				0.002
0	12	74	44	
0 < r ≤ 0.1	29	70	45	
0.1 < r ≤ 0.3	50	38	26	
r > 0.3	82	49	33	
Chemotherapy				0.024
Adjuvant	130	48	34	
Perioperative	43	59	43	

CEA: Carcinoembryonic antigen.

Table 4 Multivariate analyses (Cox regression model) of overall survival of all patients and of patients having a normal pretreatment serum carcinoembryonic antigen

Variable	Hazard ratio	95% CI	P value
All patients			
Perioperative chemotherapy	0.723	0.501–1.044	0.084
T staging	1.422	1.067–1.896	0.016
Lymph node metastasis rate	1.302	1.101–1.539	0.002
Normal-CEA patients			
Perioperative chemotherapy	0.670	0.434–1.033	0.070
T staging	1.443	1.041–2.000	0.028
Lymph node metastasis rate	1.274	1.053–1.542	0.013

CEA: Carcinoembryonic antigen.

gastric cancers (which involved the gastroesophageal junction and were different from most of the cases in endemic areas); and an increased R0 resection rate, indicating a better outcome in those patients suffering from early-stage gastric cancer. In China, most gastric cancer patients are diagnosed as having locally advanced disease, suggesting that different treatments should be considered for increasing the survival of the patients. However, there is no reliable marker to determine which patients with advanced gastric cancer can benefit from perioperative chemotherapy. The goal of the present study was to determine whether the pretreatment serum CEA level could be used as a marker to select patients for this aggressive treatment.

Our study revealed that perioperative chemotherapy can improve overall survival in patients with advanced gastric cancer. Dividing the patients in two groups based on their pretreatment serum CEA, we found that perioperative chemotherapy improved the survival rate only for patients with a normal level of pretreatment serum CEA.

Although the biological functions of CEA are not fully known, the close correlation of CEA with cancer aggressiveness has been known for decades. Higher preoperative CEA correlates with more aggressive gastric cancer and a lower patient survival rate[23]. Our findings imply that patients with elevated CEA might have gastric cancers more resistant to chemotherapy, resulting in no survival benefit even from aggressive chemotherapy. CEA has been reported to have roles in homotypic adhesion and cellular aggregation[24], and it cooperates with Myc and Bcl-2 in cellular transformation[25]. In colon cancer, CEA is up-regulated in the microadenoma stage in the colon of patients with APC mutations[26], and CEA plays antiapoptotic and prometastatic roles in colon cancer cells[27]. Overexpression of CEA can protect tumor cells from apoptosis induced by loss of cell contact with the extracellular matrix (anoikis)[28].

Interestingly, those gastric cancer cells expressing alpha-fetoprotein (which is another oncofetal antigen) show P-glycoprotein overexpression and drug resistance in both animal models and human cancer[29,30]. In some case reports, drug-resistant patients always had elevated serum CEA[31,32], and CEA overexpression was observed in multidrug-resistant breast carcinoma cell lines[33]. The CEA promoter (AdCEAIacZ) can increase the IC50 of ganciclovir against gastric cancer cell lines by improving CEA production[34]. All of these pieces of evidence suggest that CEA may induce or promote drug resistance in cancer cells.

This study is retrospective, with its own weaknesses such as confounding factors and low persuasiveness. The cycles of adjuvant chemotherapy were different among the patients, and there were two main chemotherapy regimens: XELOX and FOLFOX6. We believe that the study would be more convincing if there had been a standard regimen, although most investigators report the efficacy of these two regimens as having no statistically significant difference in gastric cancer patients. Thus, more randomized controlled trials are needed to confirm

that pretreatment serum CEA can be used as a marker to select patients for the aggressive perioperative treatment or to find other markers for assigning patients to an appropriate treatment.

To our knowledge, there is no strong evidence that CEA is a marker of drug resistance in gastric cancer. More experiments and clinical trials are needed to validate whether CEA levels can predict such drug resistance. In summary, our study showed that only patients with normal pretreatment serum CEA obtained a survival benefit from cytotoxic perioperative chemotherapy. The role of CEA in the drug resistance of gastric cancers warrants further exploration.

ACKNOWLEDGMENTS

COMMENTS

Background

Perioperative chemotherapy has been proven to be effective for some gastric cancer patients. However, there is no reliable marker for determining which patients with advanced gastric cancer can benefit from perioperative chemotherapy.

Research frontiers

In the last two decades, carcinoembryonic antigen (CEA) has been widely used as a tumor marker in the diagnosis and monitoring of some malignancies. The research hotspot is to determine whether pretreatment serum CEA can be used as a marker to select patients for this aggressive perioperative treatment.

Innovations and breakthroughs

The study revealed that perioperative chemotherapy can improve overall survival in patients with advanced gastric cancer. After dividing the patients in two groups based on their pretreatment serum CEA, the authors found that perioperative chemotherapy improved the survival rate only for patients with a normal level of pretreatment serum CEA.

Applications

The study results suggest that normal pretreatment serum CEA is a predictor of survival benefit for the patients receiving perioperative chemotherapy.

Peer review

This is an interesting paper aimed to evaluate the role of pretreatment serum CEA level as a predictor of survival for patients with locally advanced gastric cancer receiving neoadjuvant chemotherapy. This retrospective study is well conducted and well written.

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