RESEARCH ARTICLE

# Changing patterns of Serum CEA and CA199 for Evaluating the Response to First-line Chemotherapy in Patients with Advanced Gastric Adenocarcinoma

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## Abstract

**Background: This study was designed to investigate the value of CEA and CA199 in predicting the treatment response to palliative chemotherapy for advanced gastric cancer. Materials and Methods: We studied 189 patients with advanced gastric cancer who received first-line chemotherapy, measured the serum CEA and CA199 levels, used RECIST1.1 as the gold standard and analyzed the value of CEA and CA199 levels changes in predicting the treatment efficacy of chemotherapy. Results: Among the 189 patients, 80 and 94 cases had increases of baseline CEA (≥5 ng/ml) and CA199 levels (≥ 27U/ml), respectively. After two cycles of chemotherapy, 42.9% patients showed partial remission, 33.3% stable disease, and 23.8% progressive disease. The area under the ROC curve (AUC) for CEA and CA199 reduction in predicting effective chemotherapy were 0.828 (95%CI 0.740-0.916) and 0.897 (95%CI 0.832-0.961). The AUCs for CEA and CA199 increase in predicting progression after chemotherapy were 0.923 (95%CI 0.865-0.980) and 0.896 (95%CI 0.834-0.959), respectively. Patients who exhibited a CEA decline ≥24% and a CA199 decline ≥29% had significantly longer PFS (log rank $p$=0.001, $p$<0.001). With the exception of patients who presented with abnormal levels after chemotherapy, changes of CEA and CA199 levels had limited value for evaluating the chemotherapy efficacy in patients with normal baseline tumor markers. Conclusions: Changes in serum CEA and CA199 levels can accurately predict the efficacy of first-line chemotherapy in advanced gastric cancer. Patients with levels decreasing beyond the optimal critical values after chemotherapy have longer PFS.**

**Keywords:** Tumor markers - gastric cancer - chemotherapy - response prediction

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## Introduction

As lifestyles have changed, the incidence of gastric cancer has exhibited a decreasing trend. However, authoritative data demonstrate that, in 2008, 738,000 patients worldwide died of gastric cancer, which is ranked second among all cancer-related causes of death (third among all cancer-related deaths in males and fifth among all cancer-related deaths in females) (Bertuccio et al., 2009; Jemal et al., 2011). Surgery is the only potential curative treatment for gastric cancer. However, more than 2/3 of patients are already at an advanced stage when diagnosed with gastric cancer, and radical resection cannot be performed at this stage (Macdonald, 2006). Furthermore, among patients who receive Ro resections, more than 25% exhibit recurrence or metastasis (Kim et al., 2013). Chemotherapy is one of the main treatments for advanced gastric cancer and, to a certain extent, can prolong patient survival and improve quality of life (Wagner et al., 2006). The effectiveness rate of chemotherapy for advanced gastric cancer is only 34.5%-47.3%, with a median survival time of 9.2-13.8 months (Van et al., 2006; Bang et al., 2010).

Currently, clinical research and practice mainly utilize imaging techniques, such as computed tomography and magnetic resonance imaging, to examine changes in the solid tumor lesion size before and after treatment and evaluate the treatment efficacy. These techniques may currently represent the most objective and accurate assessment method (Eisenhauer et al., 2009). However, not all patients have measurable lesions, and radiologists apply a certain degree of subjectivity when measuring lesion diameters. Therefore, it is necessary to identify other possible evaluation methods to complement imaging techniques. Serum tumor markers are detected automatically by machines and are often used for patient follow-up and prognosis determination. Recent studies have revealed that changes in the levels of serum markers have some value in predicting treatment efficacy for a variety of malignant tumors, especially ovarian cancer, colorectal cancer, and lung cancer(Hanke et al., 2001; Guppy and Rustin, 2007; Kim et al., 2010; Arrieta et al., 2013).

Serum CEA and CA199 are the tumor markers most

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widely used in gastric cancer, and their expression levels are closely related to the patient prognosis (Shimada et al., 2014). So far, limited numbers of reports have examined the ability of CEA and CA199 to predict chemotherapy efficacy in the treatment of gastric cancer. Yamao et al. (1999) enrolled 26 patients with advanced gastric cancer who were treated with systemic chemotherapy and found that the reduction of tumor markers was highly consistent with alleviation as shown by imaging studies. This study aimed to analyze the role of serum CEA and CA199 changes in predicting the effectiveness of chemotherapy and post-chemotherapy progression in patients with advanced gastric cancer, as well as the relationship to patients' progression-free survival (PFS).

## Materials and Methods

*Patient population and treatment*

We studied patients with advanced gastric cancer who were treated in the Jiangxi Cancer Hospital during the period from January 2010 to December 2012. The inclusion criteria were as follows: metastatic gastric adenocarcinoma diagnosed by histopathology and imaging examinations; serum CEA and CA199 levels measured before chemotherapy and after each chemotherapy cycle (the post-chemotherapy date refers to the 21st day of the current chemotherapy cycle); use of first-line chemotherapy; completion of at least two cycles of chemotherapy; identification of measurable lesions; an Eastern Cooperative Oncology Group (ECOG) score 0-2 points and an expected survival time ≥3 months; and existence of complete follow-up information for the patient. Patients with other malignancies were excluded. In total, 189 patients met the inclusion criteria. A chemiluminescence immunoassay was used to detect the serum CEA and CA199 levels; the critical values for CEA and CA199 were 5 ng/ml and 27 U/ml, respectively. The detection value before treatment was marked as BV0, and the values after the first and second cycles of chemotherapy were marked as BV1 and BV2, respectively. Based on whether the baseline CEA and CA199 levels before chemotherapy exceeded the critical values, the patients were assigned to the CEA (+) group or CEA (-) group and the CA199 (+) group or CA199 (-) group.

We collected the patient disease history, clinical data, and laboratory examinations, including the gender, age, smoking history, ECOG performance status, and chemotherapy regimen. The patients were followed up, and their PFS times were recorded. The patients received CT and ultrasound examinations before chemotherapy and after two cycles of chemotherapy to assess the tumor lesions. The Response Evaluation Criteria in Solid Tumors Revision (RECIST1.1)(Eisenhauer et al., 2009) was used as the gold standard to evaluate the chemotherapy efficacy. Based on the RECIST1.1 evaluation, the tumor responses were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Effective chemotherapy was defined as producing CR or PR.

*Statistical analyses*

Subgroup analyses were performed in patients with normal baseline CEA and CA199 levels and in patients with abnormal baseline CEA and CA199 levels. The ratio of the serum tumor marker declines after one or two chemotherapy cycles was expressed as Dec%, which was calculated as (BV0-BV1/2)/BV0 × 100%. The SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis, and the Kaplan-Meier method was used to calculate the survival rates and plot the survival curves. The receiver-operating characteristics (ROC) curve was used to evaluate the Dec% values of the two tumor markers for predicting the objective response to chemotherapy and to determine the optimum operating point (Greiner et al., 2000). A $p$ value < 0.05 was considered statistically significant.

## Results

In total, 189 patients met the inclusion criteria, including 132 males and 57 females, and the median age was 57 years (26-84 years). The median values of the baseline serum CEA and CA199 were 3.47 ng/ml (0.01-1827.8 ng/ml) and 26.93 U/ml (0.1-60749 U/ml), respectively. Elevated CEA (≥ 5 ng/ml) was observed in 42.3% (80/189) of all patients, which was slightly lower than the proportion of patients with abnormal CA199 levels (≥ 27 U/ml), at 49.7% (97/189). The simultaneous detection of CEA and CA199 increased the sensitivity to 64.6% (122/189), and abnormal levels of both CEA and CA199 were found in 22.2% (42/189) of all patients. The patients received a median of four chemotherapy cycles (range, 2-8), and the efficacy evaluation could be conducted for all 189 patients. No patients exhibited CR, 81 cases (42.9%) exhibited PR, 63 cases (33.3%) exhibited SD, and 45 cases (23.8%) exhibited PD. The median PFS time was 4.2 months (range, 1.0-31.1 months) (Table 1).

**Table 1. Baseline Patient Characteristics**

| Characteristics | | N=189 (%) |
|---|---|---|
| Age (years) | Median (range) | 57 (26-84) |
| Gender | Male | 132 (69.8) |
| | Female | 57 (30.2) |
| Smoking History | Positive | 128 (67.7) |
| | Negative | 61 (32.3) |
| ECOG | 0 | 50 (26.4) |
| | 1 | 95 (50.3) |
| | 2 | 44 (23.3) |
| CEA | Median (range) | 3.47 (0.01-1827.8) |
| (ng/ml) | ≥5 | 80 (42.3) |
| | <5 | 109 (57.7) |
| CA199 | Median (range) | 26.93 (0.1-60749) |
| (U/ml) | ≥27 | 94 (49.7) |
| | <27 | 95 (50.3) |
| Chemotherapy Scheme | Fluoropyrimidine-based | 121 (64.0) |
| | Platinum-based | 47 (24.9) |
| | Others | 21 (11.1) |
| Tumor Response | Partial remission | 81 (42.9) |
| Evaluation | Stable Disease | 63 (33.3) |
| | Progressive Disease | 45 (23.8) |
| PFS (months) | Median (range) | 4.2 (1-31.1) |

After two cycles of chemotherapy, the efficacy evaluation revealed that, among the 80 patients with abnormal baseline serum CEA levels, the partial remission, stable, and progressive patients accounted for 41.2%, 32.5%, and 26.3% of the cases, respectively. The patients who experienced effective chemotherapy (as indicated by the efficacy evaluation) presented a decline in CEA (Dec %) of 55.0%±36.9%. The area under the ROC curve (AUC) for changes in the CEA levels and PR was 0.828 (95%CI 0.740-0.916), and the diagnostic critical value was a 24% decline in the CEA level, with a sensitivity of 0.848 and a specificity of 0.702 (Figure 1A). There were 42 patients with a CEA decline ≥ 24% at the time of the efficacy evaluation, including 66.7% of the PR cases (28/42), 31.0% of the SD cases (13/42), and 2.4% of the PD cases (1/42). The AUC for changes in the CEA levels and PD was 0.923 (95%CI 0.865-0.980), and the diagnostic critical value was a 24% increase in CEA, with a sensitivity of 0.905 and a specificity of 0.831 (Figure 1B). There were 29 patients with a CEA increase ≥ 24%, of whom PD accounted for 65.5%; SD accounted for 31.0%; and PR accounted for 3.5%.

Ninety-four patients had abnormal baseline serum CA199 levels. After two cycles of systemic chemotherapy, the efficacy evaluation revealed that PR, SD, and PD were observed in 44.7%, 28.7%, and 26.7% of these patients,

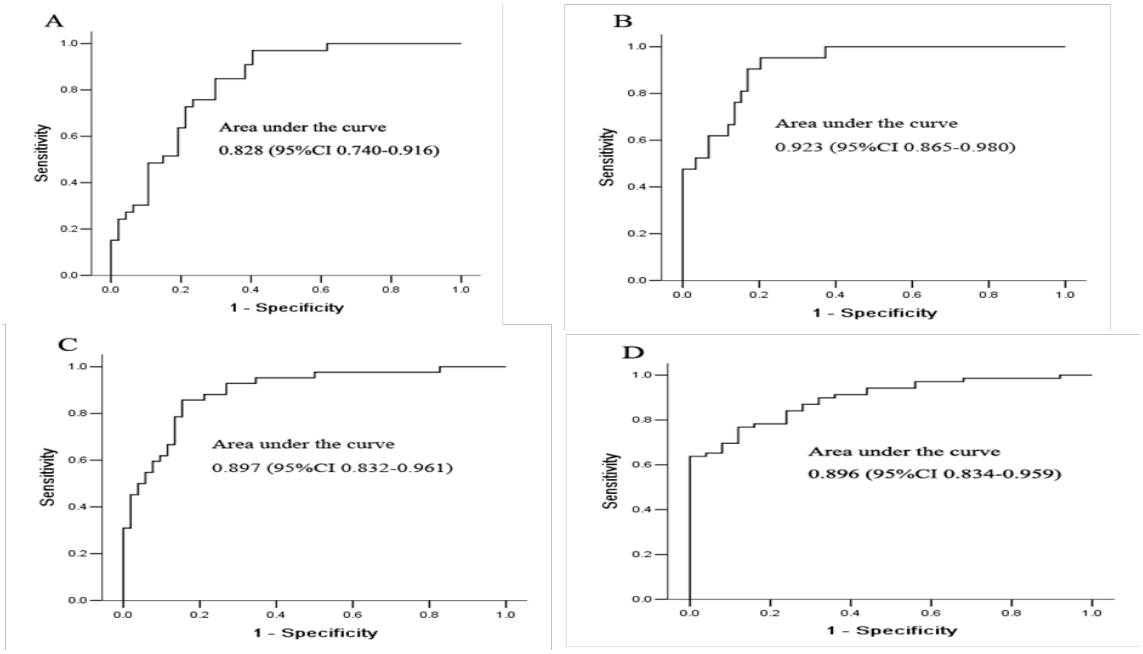


**Figure 1. Correlation between the Changes in Tumor Marker Levels and the Response.** A. ROC curve for the CEA levels and PR. B. ROC curve for the CEA levels and PD. C. ROC curve for the CA199 levels and PR. D. ROC curve for the CA199 levels and PD

**Table 2. Serum CEA/CA199 Changes for Evaluating the Response After two Cycles of Chemotherapy**

| Patients | Response evaluation | Area Under the Curve | (95% CI) | Std. Error |
|---|---|---|---|---|
| Baseline CEA level | Overall response | 0.498 | (0.387-0.609) | 0.057 |
| (< 5 ng/ml) | Progression | 0.606 | (0.474-0.738) | 0.067 |
| Baseline CA199 level | Overall response | 0.533 | (0.414-0.653) | 0.061 |
| (< 27 U/ml) | Progression | 0.71 | (0.587-0.833) | 0.063 |

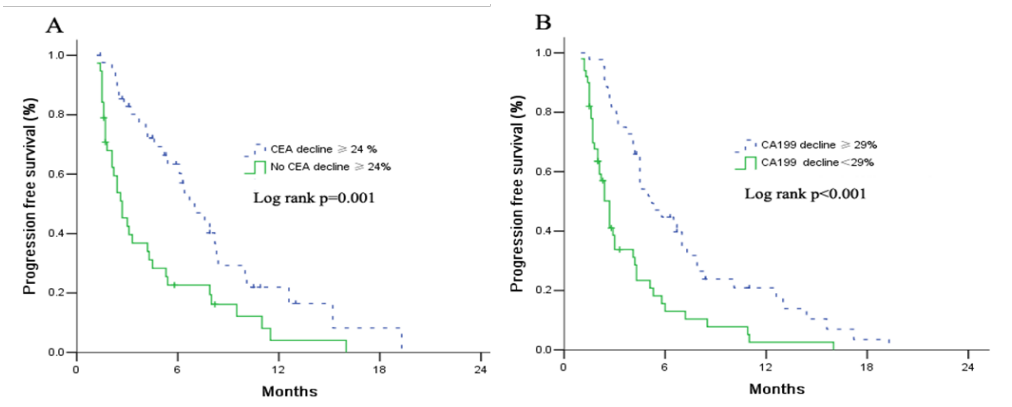


**Figure 2. The PFS in Patients Whose CEA and CA199 Decline Beyond the Cutoff Value and in Patients Whose CEA and CA199 Do Not.** A. Kaplan-Meier curve comparing the PFS times in patients with a ≥ 24% decline in CEA levels after two-cycle chemotherapy. B. Kaplan-Meier curve comparing the PFS times in patients with a ≥ 29% decline in CA199 levels

respectively. A ROC curve was used to analyze the value of the CA199 changes for predicting effective chemotherapy. The AUC was 0.897 (95%CI 0.832-0.961), and the optimal Dec% critical value was 29%, with a sensitivity of 0.857 and a specificity of 0.846 (Figure 1C). Twenty-four patients exhibited a CA199-level decline ≥ 29%, of whom PR accounted for 81.8% (36/44), SD accounted for 18.2% (8/44), and PD accounted for 0% (0/42). A ROC curve was used to analyze the value of changes in the CA199 levels for diagnosing PD. The AUC was 0.896 (95%CI 0.834-0.959), and the optimum critical value was a 30% increase in CA199, with a sensitivity of 0.68 and a specificity of 0.899 (Figure 1D). Twenty-four patients exhibited a CA199-level increase ≥ 30%, of whom PD accounted for 70.8%; SD accounted for 25.0%; and PR accounted for 4.2%.

We also analyzed the value of the CEA and CA199 changes after one cycle of chemotherapy for predicting the objective response to chemotherapy. The areas under the CEA- and CA199-level-decline ROC curve for predicting effective chemotherapy were 0.701 (95%CI 0.586-0.817) and 0.717 (95%CI 0.613-0.822), respectively. The areas under the CEA- and CA199-level-increase ROC curve for predicting PD were 0.833 (95%CI 0.732-0.933) and 0.778 (95%CI 0.670-0.886), respectively. It was worth noting that 20 patients exhibited a CEA or CA199-level increase ≥ 70.0%, of whom PD accounted for 90.0%.

For advanced gastric cancer patients with CEA (-) and CA199 (-) baseline levels, the serum CEA and CA199 changes did not yield a useful value for predicting effective chemotherapy and PD, and the areas under the ROC curve were within the range of 0.498-0.710 (Table 2). However, 77.8% (7/9) of the patients with abnormal CEA levels and 100% (4/4) of the patients with abnormal CA199 levels after two cycles of chemotherapy were PD.

Among the 189 patients, those undergoing effective chemotherapy (as evaluated by the RECIST1.1) had superior PFS times compared to patients with SD and PD (log rank $p < 0.001$). Similarly, among patients with CEA (+) baseline levels and patients with CA199 (+) baseline levels, the patients for whom the tumor markers decreased beyond the optimal critical values had a significantly longer PFS (Figure 2A, Figure 2B).

## Discussion

Serum CEA and CA199 are the most widely used tumor markers in studies focusing on gastric cancer (Shimada et al., 2014), and they may be abnormally expressed during the different stages of gastric cancer (Kim et al., 2011). The Japanese Gastric Cancer Association summarized 46 reports in the literature and statistically calculated that the CEA and CA199 positive expression rates in advanced gastric cancer were 39.5% and 44.7%, respectively (Shimada et al., 2014). Elevated CEA and CA199 levels often predict disease relapse or progression and are related to shorter survival times in patients with gastric cancer (Kochi et al., 2000; Takahashi et al., 2003). Therefore, serum CEA and CA199 levels are reliable indicators for gastric cancer patient follow-up and prognosis determination.

Currently, clinical practices mainly use imaging techniques to measure changes in tumor size based on RECIST, which was revised in 2008 (Eisenhauer et al., 2009). RECIST has good accuracy and objectivity and plays an important role in guiding clinical practice, and it is a common method in solid tumor clinical research (Bang et al., 2010). However, RECIST may be insufficient under certain circumstances, especially for patients who lack measurable lesions or who have lesions with edges that are difficult to confirm, such as malignant effusions, diffuse lymph node metastases, and bone metastases (Arrieta et al., 2013; Shimada et al., 2014). Erasmus et al. (2003) used spiral CT to detect the size of 40 tumor lesions in 33 patients with lung cancer and found that the measurement results were often inconsistent with each other, which was likely to cause decreased accuracy in determining the treatment efficacy. In addition, imaging examinations are expensive, time-intensive, and effort consuming. Some patients who are unable to walk easily cannot receive examinations in the radiology department. Therefore, it is necessary to seek a new efficacy evaluation method to complement imaging techniques.

The dynamic observation of changes in serum tumor markers may be an effective method. Arrieta Rodriguez et al. (2013) prospectively studied 180 advanced lung cancer patients who had never received previous chemotherapy and had elevated baseline serum CEA levels (>10 ng/ml). The patients received two chemotherapy cycles or took oral tyrosine kinase inhibitor agents. The RECIST standard was used to evaluate the treatment efficacy, and changes in the serum CEA levels were detected simultaneously. The results revealed that the CEA-level change had a higher value for assessing effective treatment and PD, for which the areas under the ROC curve were 0.945 (95%CI 0.91-0.99) and 0.911 (95%CI 0.86-0.961), respectively. Studies from Iwanicki-Caron et al. (Iwanicki et al., 2008) also demonstrated that the dynamic monitoring of changes in the serum CEA levels in patients with unresectable metastatic colorectal cancer before and after chemotherapy could accurately and efficiently identify patients with PD after chemotherapy.

Studies using serum tumor markers to assess the efficacy of chemotherapy for gastric cancer are rare. In elderly patients with advanced gastric cancer, changes in the serum CEA, CA199, and CA125 levels after chemotherapy had a significant correlation with the objective response (Caponetti et al., 2002). Yamao et al. (Yamao et al., 1999) enrolled 26 patients with advanced gastric cancer who received systemic chemotherapy and had at least one abnormal tumor marker (CEA, CA199, or CA125). Imaging examinations were conducted before chemotherapy and once every 4 weeks after chemotherapy. The objective response was evaluated according to the World Health Organization (WHO) criteria, and the determination of effective chemotherapy by tumor markers was defined by declines ≥50% in the serum levels, which were maintained for more than 4 weeks. The sensitivity and negative predictive value of decreasing tumor marker levels after chemotherapy for a partial response (as shown by imaging) were both 100%. When the patients were categorized as responders or

non-responders, a significant correlation was observed between the response assessment by the tumor markers and by the imaging studies.

We studied 189 advanced gastric cancer patients who received first-line chemotherapy; 80 cases had elevated serum CEA levels, accounting for 42.3%, and 94 cases had elevated serum CA199 levels, with a positive rate of 49.7%, which is consistent with the previous report (Shimada et al., 2014). RECIST1.1 was used as the standard to evaluate the chemotherapeutic efficacy in the patients, with none showing CR, 42.9% showing PR, 33.3% showing SD, and 23.8% showing PD. After two cycles of chemotherapy, the serum CEA and CA199 levels were measured to calculate the decline ratio relative to the baseline levels (Dec%). In addition, the areas under the ROC curve of CEA and CA199 for predicting effective chemotherapy were 0.828 and 0.897, respectively, and the areas under the CEA and CA199 ROC curves for predicting PD were as high as 0.923 and 0.896, respectively, all yielding good predictive values. The sensitivity of a 24% reduction in the serum CEA level for determining effective chemotherapy was 0.848, and the specificity was 0.702. The sensitivity of a 29% reduction in the serum CA199 level for determining effective chemotherapy was 0.857, and the specificity was 0.846. The sensitivity of a 24% increase in the serum CEA level for diagnosing PD was 0.905, and the specificity was 0.831. The sensitivity of a 30% increase in the CA199 level for diagnosing PD was 0.68, and the specificity was 0.899. Compared to previous reports (Yamao et al., 1999; Caponetti et al., 2002), we enrolled a larger group of patients, conducted a more in-depth study, analyzed both the prediction of effective chemotherapy and the prediction of progression after chemotherapy, and preliminarily established the critical values of serum tumor markers for determining the short-term efficacy of chemotherapy.

Efficacy evaluations based on imaging studies are often conducted after two cycles of chemotherapy. If there were a simple method to predict the efficacy at an earlier stage, patients not responding to the treatment could be identified earlier, allowing discontinuation of the drugs or switching to other treatment options as soon as possible. Holdenrieder et al.(Holdenrieder et al., 2009) reported that the detection of CYFRA 21-1 before the second chemotherapy cycle allowed the objective response to chemotherapy in advanced lung cancer to be assessed earlier than by imaging examinations. We performed subgroup analyses for patients with abnormally elevated baseline CEA or CA199 levels and calculated the serum CEA and CA199 changes after one chemotherapy cycle. The value of using the area under the ROC curve after one cycle was less than the value after the completion of two chemotherapy cycles in predicting either effective chemotherapy or PD. The analysis suggested that this finding might be related to the transient release of serum CEA and CA199 induced by chemotherapy, which interfered with the detection. It is reported in the literature that chemotherapy induces the apoptosis and necrosis of gastric cancer cells, which releases chemicals and causes abnormally elevated CEA and CA199 levels; that the median time points for the CEA and CA199 peaks are 2.8 weeks and 2.3 weeks, respectively; and that this release generally lasts approximately 7.1 to 9.1 weeks (Kim et al., 2009).

We analyzed the value of the post-chemotherapy changes in the tumor marker levels for predicting the objective response to chemotherapy in gastric cancer patients with normal baseline serum CEA and CA199 levels. The areas under the ROC curve were small and in the range of 0.498-0.710, suggesting low value for assessing the chemotherapy efficacy. Through research, we also discovered that the reduction in the CEA and CA199 tumor markers after chemotherapy was significantly correlated with the median PFS time of the patients ($p < 0.001$). Because the treatment methods utilized after the failure of first-line chemotherapy differed greatly in this group of patients, we did not analyze the effects of the tumor marker changes on the overall survival time of the patients.

In conclusion, the present study confirmed that, in advanced gastric cancer patients with abnormal baseline serum-tumor-marker levels, changes in the CEA and CA199 levels after two chemotherapy cycles may effectively predict the objective response to first-line chemotherapy and that patients who present a serum CEA-level reduction ≥ 24% and a CA199-level reduction ≥ 29% after chemotherapy have a significantly longer PFS. Therefore, we recommend the dynamic monitoring of serum CEA and CA199 levels in advanced gastric cancer patients before and after first-line chemotherapy. We also intend to pursue prospective studies with large sample sizes to determine the optimal critical values for the treatment efficacy assessment.

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## References

Arrieta OG, Villarreal GC, Martínez BL, et al (2013). Usefulness of Serum Carcinoembryonic Antigen (CEA) in evaluating response to chemotherapy in patients with advanced non small-cell lung cancer, a prospective cohort study. *BMC Cancer*, **13**, 254.

Bang YJ, Van CE, Feyereislova A, et al (2010). Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA), a phase 3, open-label, randomised controlled trial. *Lancet,* **376**, 687-97.

Bertuccio P, Chatenoud L, Levi F, et al (2009). Recent patterns in gastric cancer, a global overview. *Int J Cancer*, **125**, 666-73

Caponetti R, Caponetti T, Vici P (2002). Changes in tumor markers CEA, Ca 19-9 and Ca125 in monitoring of response to chemotherapy in elderly patients with advanced gastric cancer. *Clin Ter*, **153**, 373-5.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumors, revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

Erasmus JJ, Gladish GW, Broemeling L, et al (2003). Interobserver and intraobserver variability in measurement of non-small-cell carcinoma lung lesions, implications for

assessment of tumor response. *J Clin Oncol*, **21**, 2574-82.
Greiner M, Pfeiffer D, Smith RD (2000). Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med*, **45**, 23-41
Guppy AE, Rustin GJ (2007). CA125 response, can it replace the traditional response criteria in ovarian cancer? *Oncologist*, **7**, 437-43
Hanke B, Riedel C, Lampert S, et al (2001). CEA and CA 19-9 measurement as a monitoring parameter in metastatic colorectal cancer (CRC) under palliative first-line chemotherapy with weekly 24-hour infusion of high-dose 5-fluorouracil (5-FU) and folinic acid (FA). *Ann Oncol*, **12**, 221-6
Holdenrieder S, von PJ, Dankelmann E, et al (2009). Nucleosomes and CYFRA 21-1 indicate tumor response after one cycle of chemotherapy in recurrent non-small cell lung cancer. *Lung Cancer*, **63**, 128-35
Iwanicki-CI, Di FF, Roque I, et al (2008). Usefulness of the serum carcinoembryonic antigen kinetic for chemotherapy monitoring in patients with unresectable metastasis of colorectal cancer. *J Clin Oncol*, **26**, 3681-6.
Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.
Kim DH, Kim SM, Hyun JK, et al (2013). Changes in postoperative recurrence and prognostic risk factors for patients with gastric cancer who underwent curative gastric resection during different time periods. *Ann Surg Oncol*, **20**, 2317-27.
Kim DH, Oh SJ, Oh CA, et al (2011). The relationships between perioperative CEA, CA 19-9, and CA 72-4 and recurrence in gastric cancer patients after curative radical gastrectomy. *J Surg Oncol*, **104**, 585-91.
Kim G, Jung EJ, Ryu CG, et al (2010). Usefulness of carcinoembryonic antigen for monitoring tumor progression during palliative chemotherapy in metastatic colorectal cancer. *Yonsei Med J*, **54**, 116-22.
Kim HJ, Lee KW, Kim YJ, et al (2009). Chemotherapy-induced transient CEA and CA19-9 surges in patients with metastatic or recurrent gastric cancer. *Acta Oncol*, **48**, 385-90.
Kochi M, Fujii M, Kanamori N, et al (2000). Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer. *Gastric Cancer*, **3**, 177-86.
Macdonald JS (2006). Gastric cancer-new therapeutic options. *N Engl J Med*, **355**, 76-7.
Wagner AD, Grothe W, Haerting J, et al (2006). Chemotherapy in advanced gastric cancer, a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*, **24**, 2903-9
Shimada H, Noie T, Ohashi M, et al (2014). Clinical significance of serum tumor markers for gastric cancer, a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. *Gastric Cancer*, **17**, 26-33.
Takahashi Y, Takeuchi T, Sakamoto J, et al (2003). The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients, a prospective clinical study. *Gastric Cancer*, **6**, 142-5.
Van CE, Moiseyenko VM, Tjulandin S, et al (2006). Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer, a report of the V325 Study Group. *J Clin Oncol*, **24**, 4991-7.
Yamao T, Kai S, Kazami A, et al (1999). Tumor markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy in patients with advanced gastric cancer. *Jpn J Clin Oncol*, **29**, 550-5.