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Original Article

Role of CA19-9 in the prognostic evaluation of SOX neoadjuvant chemotherapy for gastric cancer

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Abstract: Objective: Neoadjuvant chemotherapy refers to systemic chemotherapy applied before local surgery or radiotherapy for malignant tumors. The level of certain tumor markers is an important indicator for assessing the efficacy of neoadjuvant chemotherapy. This study aimed to investigate the effect of serum CA19-9 levels on subsequent neoadjuvant chemotherapy in the treatment of gastric adenocarcinoma. Methods: We collected 86 advanced gastric adenocarcinoma patients from January 2016 to May 2018. Patients received at least 2 cycles neoadjuvant chemotherapy with SOX (Oxaliplatin, S-1) before surgery. Effective chemotherapy was defined as producing CR or PR andineffective was defined as SD or PD. We analyze the role of serum CA19-9 level in predicting the effectiveness of neoadjuvant chemotherapy in patients with advanced gastric cancer. Results: In total 86 patients, 28 patients had abnormal and 58 patients had normal serum CA19-9 levels. The positivity rate of pretreatment serum CA19-9 was higher when PR or CR was achieved (P=0.0005***). The area under the ROC curve (AUC) for CA19-9 levels was 0.720 (95% CI 0.610-0.829) (P=0.001**). Conclusions: Measurements of CA19-9 may be helpful in monitoring the efficacy of neoadjuvant chemotherapy in the treatment of patients with advanced gastric cancer and also may be able to effectively predict this effect, thereby reducing unnecessary chemotherapy.

Keywords: CA19-9, gastric adenocarcinoma, neoadjuvant chemotherapy, SOX

Introduction

Gastric cancer (GC) is the fourth most commonly diagnosed cancer in the world, and it ranks second in all cancer mortality rates, affecting about 1 million people each year. According to reports by the World Health Organization, almost one million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth (WHO) or fourth (GLOBOCAN) most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate. The high incidence of gastric cancer includes underdeveloped regions such as East Asia, South America, and Eastern Europe. This not only jeopardizes the survival and health of human beings, but also imposes a major burden on public health and the economy of each country [1]. More than 70% of GC cases occur in developing countries with half the world's total cases occurring in Eastern Asia [1-3]. In Asia, the mortality rate is higher in males than in females [4]. Similar to the incidence rate, GC mortality rate is the highest in Eastern Asia [5]. The early surface type of gastric cancer has a higher cure rate, and once it spreads, its survival rate will decrease rapidly. Research revealed that the global average five-year survival rate for postoperative advanced gastric cancer remains below 10%. At present, the treatment methods of gastric cancer mainly include: surgery, chemotherapy, radiation therapy and target treatment. Therefore, how to utilize these treatments to achieve optimal cancer treatment is an important challenge.

Neoadjuvant chemotherapy (NAC), also called preoperative chemotherapy, is a drug is given to the patient prior to cancer surgery or radical

radiotherapy, and it is mostly used in cases where surgery is planned in the future [6]. This chemotherapy method is not only used for advanced gastric cancer but is also increasingly used in the early stage of the disease [6, 7]. NAC could increase the rate of complete tumor resections, combat systemic metastasis, and prolong survival with tolerable and manageable toxicity, without increasing the mortality or morbidity of surgery in gastric cancer patients [6]. Compared to postoperative chemotherapy, NAC could reduce staging and increase the R0 resection rate. Since the progress of the disease is unavoidable for many people, it is crucial to monitor the responsiveness of NAC in treating patients with gastric cancer, which could improve quality of life of non-responders, reduce the time until surgery in non-responders, and reduce costs. Regrettably, limited numbers of reports have examined the ability of markers to predict chemotherapy efficacy in the treatment of gastric cancer.

CA19-9 is a tumor markerwidely used in Gastrointestinal Cancer, and its expression level is closely associated with development and progression of cancer [8]. Clinical studies evaluating the roles of CA19-9 in predicting of chemotherapy, especially in neoadjuvant chemotherapy are limited. Zheng [9] indicated that preoperative therapy harbored strong prognostic value for postoperative survival in intrahepatic cholangiocarcinoma patients. In this study, we analyzed the relationship between CA19-9 and the response to NAC in patients with advanced gastric cancer, to analyze the role of serum CA19-9 level in predicting the effectiveness of perioperative chemotherapy.

Patients and methods

Patient eligibility

We studied 86 advanced gastric cancer patients who received treatment in Zhejiang cancer hospital from January 2016 to May 2018. All patients were histologically confirmed gastric adenocarcinoma by surgical treatment after NAC, which were all at the gastric antrum or gastric body. All patients were excluded from the study if they demonstrated other organ insufficiencies, if they had experienced an acute event within the last three months (cerebral, coronary, and so forth), acute infection, or major trauma.

Neoadjuvant chemotherapy (NAC)

The decision to treat patients with NAC which is determined by the Multidisciplinary Oncology Committee, tumor histology and staging, patient tolerance therapy, and the national comprehensive oncology network (NCCN) guideline. Patients received at least 2 cycles neoadjuvant chemotherapy with SOX (Oxaliplatin, S-1) before surgery. In all cases, surgery was performed after neoadjuvant chemotherapy.

Clinical data

Patients' characteristics were obtained retrospectively from the patient database and were: age, gender, clinical stage, smoking history, drinking history, CA19-9, CA12-5 and CEA. The surgical and chemotherapy data were obtained from the patient records. The number and diameter of tumors were evaluated using computed tomography pre- and post-neoadjuvant chemotherapy. Serum tumor markers were divided into two groups based on the serum level being within normal limits or higher than normal limits.

Assessment of clinical response

The patients received CT scans before neoadjuvant chemotherapy and after 2 cycles of chemotherapy to assess the tumor lesions. The Response Evaluation Criteria in Solid Tumors Revision (RECIST1.1) was used to evaluate the chemotherapy efficacy. Two video doctors simultaneously analyzed and provided reports on CT images. If the judgment was found to be inconsistent, a consensus was obtained through negotiation. And the pathologist graded the chemotherapy according to postoperative histopathology and verified the above image evaluation. Tumor response is divided into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Effective chemotherapy is defined as the production of CR or PR, and invalidation is defined as SD or PD.

Statistical analyses

All statistical analyses were performed using SPSS 22.0. We applied the χ^2 test to analyze the association between efficacy of chemotherapy and clinicopathologic status. Accordingly,

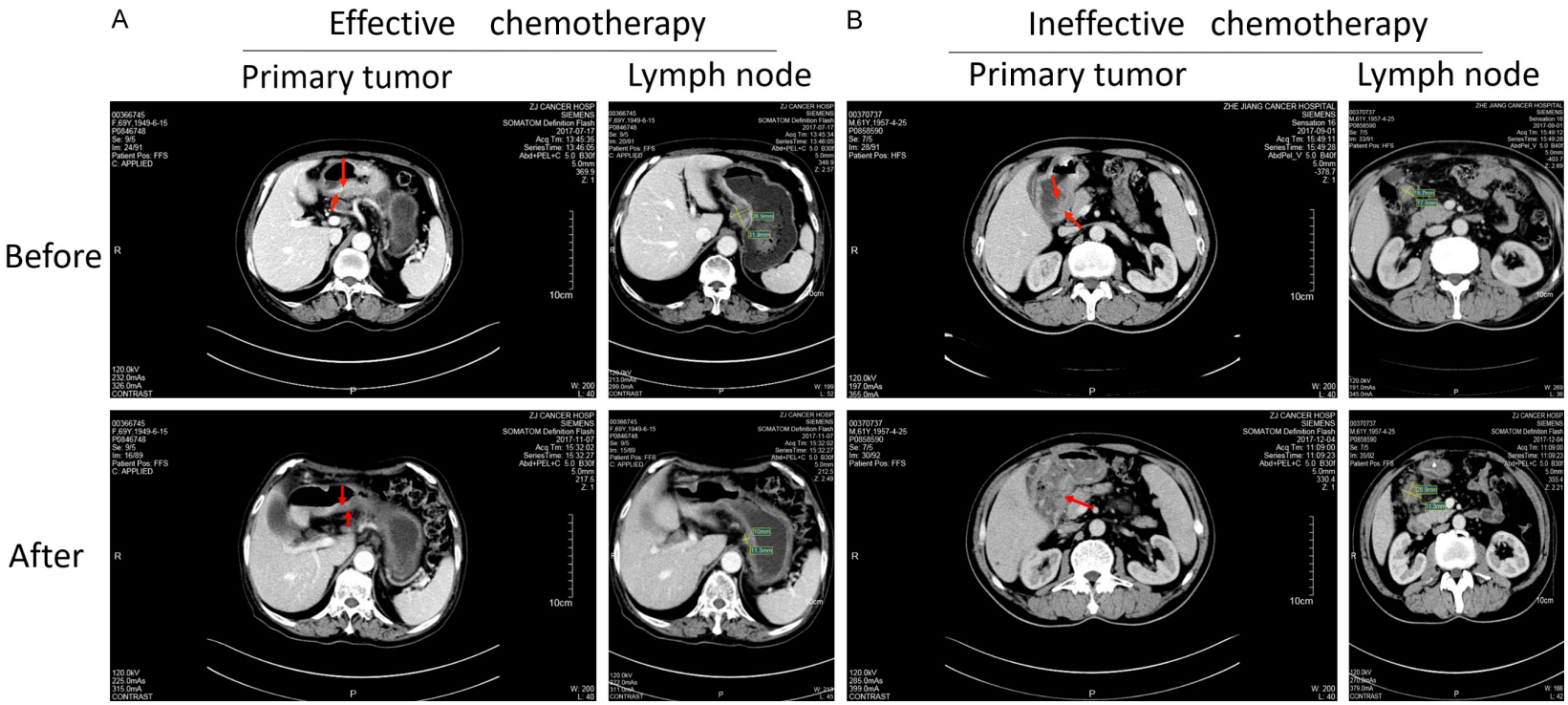

Figure 1. CT images of patients before and after neoadjuvant chemotherapy in (A) the effective group and (B) ineffective group.

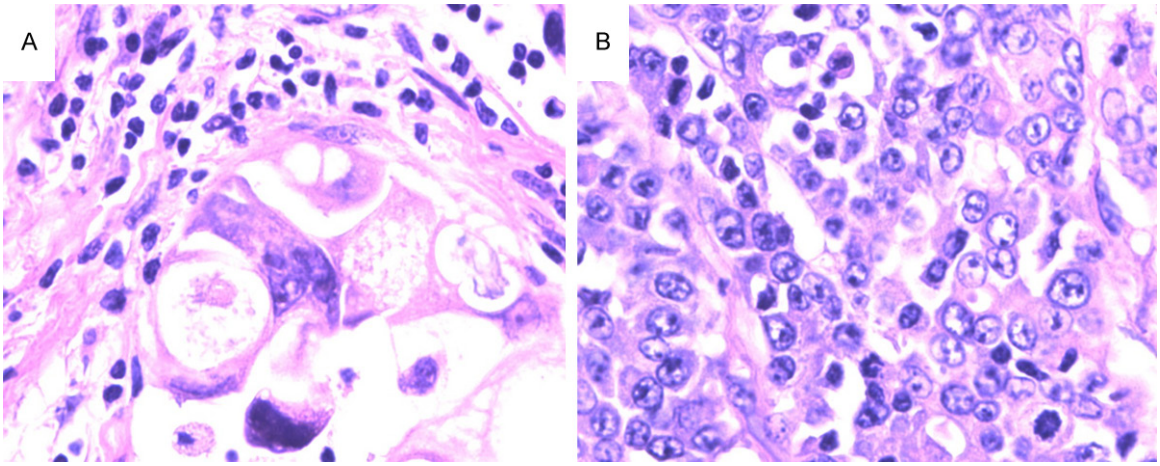

Figure 2. Specimen photomicrographs from patients after neoadjuvant chemotherapy of (A) an effective case and (B) an ineffective case.

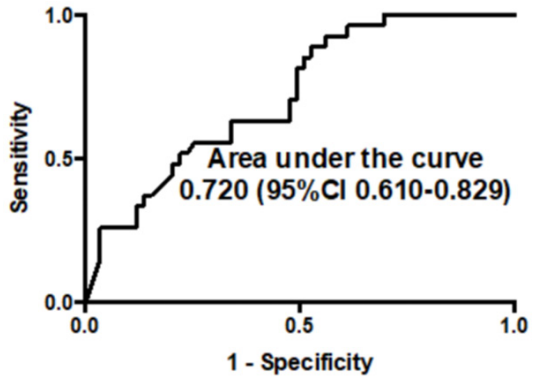

Figure 3. Correlation between the CA19-9 levels and-neoadjuvant chemotherapy curative effect.

the receiver-operating characteristics (ROC) curve was used to evaluate the Decile % values of CA19-9 for predicting the objective response to chemotherapy. All tests were 2-sided, and statistical significance was set at $P<0.05$.

Results

From January 2016 to May 2018, totally 86 gastric adenocarcinoma patients, 62 men, and 23 women were enrolled into this study, with the mean age of 59.9, and the median age was 61 years (31-75 years). All patients had been histologically confirmed with gastric adenocarcinoma obtained from the gastroscope. After two cycles neoadjuvant chemotherapy, 9 cases (10.5%) exhibited CR, 50 cases (58.1%) exhibited PR, 24 cases (27.9%) exhibited SD, and 3 cases (3.5%) exhibited PD. We defined CR and PR as an effective group and others as the ineffective group. As shown in **Figure 1**, the images illustrate the the primary tumor and lymph node size changes of the effective group and ineffective group before and after chemotherapy. In **Figure 1A**, portal vein phase contrast enhancement showed primary tumor located in gastric antrum with wall thickening (red arrow) before chemotherapy, and perigastric lymph node enlargement showed heterogeneous mild enhancement, size (31.9 mm*26.9 mm). After neoadjuvant chemotherapy, the contrast imaging of portal vein phase showed primary tumor shrank (red arrow) and the perigastric lymph node shrank (11.3 mm*10 mm). Therefore, the cases similar to the above were evaluated aseffective chemotherapy. In **Figure 1B**, portal vein phase contrast enhancement showed primary tumor located in gastric antrum with wall thickening (red arrow) before chemotherapy, and perigastric lymph node enlargement showed heterogeneous mild enhancement, size (18.7 mm*17.8 mm). After neoadjuvant chemotherapy, the thickening wall with no obvious shrinkage (red arrow), or even more seriously the perigastric lymph nodes showed enlargement (31.3 mm*28.9 mm). The cases similar to the above were considered ineffective chemotherapy. **Figure 2** shows the pathologic examination of postoperative specimens of the above two cases. Effective chemotherapy (**Figure 2A**) showed mucosal defects, ulcer formation in the posterior wall, and the formation of inflammatory granulation tissuebut no clear tumor residue (combined medical history, in line with chemotherapy response, treatment response assessment: level 0). The ineffective chemo-

Table 1. Relative clinical characteristics of patients

Characteristic		CR+PR (N=59)	SD+PD (N=27)	*P* value
Age (years)	≥61	31	16	0.5614
	<61	28	11	
Gender	Male	45	17	0.2979
	Female	14	9	
Smoking History	Positive	28	11	0.6438
	Negative	31	16	
Drinking History	Positive	18	11	0.4615
	Negative	41	16	
Clinical stage	I+II	16	8	0.8096
	III+IV	43	19	
CEA	≥5	24	9	0.6345
	<5	35	18	
CA19-9	≥37	26	2	0.0005
	<37	33	25	
CA12-5	≥35	7	3	0.9194
	<35	52	24	

therapy (**Figure 2B**) showed gastric sinus full-angle bulge type (tumor size 10*7*2 cm) with poorly differentiated adenocarcinoma, and infiltration into subserosal fibrous tissue, reciprocal nerve, visible vascular tumor thrombus (combined medical history, treatment response assessment: level 3). There was no statistically significant difference in age, gender, smoking history, drinking history and clinical stage between the two groups (P>0.05). It indicated that the two groups were comparable. In total 86 patients, 28 patients had abnormal and 58 had normal serum CA199 levels. After two cycles of SOX chemotherapy, CT evaluation revealed that CR, PR, and SD were observed in 25% (7), 67.9% (19), and 7.1% (2) of CA19-9 abnormal patients. Of CA19-9 normal ones, CR, PR, SD and PD were observed in 3.4% (2), 53.4% (31), 37.9% (22) and 5.2% (3) (**Table 1**). The positivity rate of pretreatment serum CA19-9 was higher when PR or CR was achieved (P=0.0005***) (**Table 1**). To evaluate whether pretreatment levels of CA19-9 could be used as a marker for predicting effective chemotherapy, a ROC curve was carried out (**Figure 3**). The area under the ROC curve (AUC) for CA-19-9 levels was 0.720 (95% CI 0.610-0.829) (P=0.001**), with a sensitivity of 0.929 and a specificity of 0.431 (**Figure 3**). The cutoff of this test was 37 U/ml.

Discussion

More than 677,100 cases of GC were diagnosed in Asia in 2012, accounting for 11.9% of all the cancers diagnosed [3]. It is the third most common cancer in Asia after breast and lung cancer [10]. Although surgical resection provides an opportunity for cure in early-stage disease, most patients are diagnosed at an advanced stage when therapy is directed primarily at disease control, prolongation of life, and symptom palliation [11]. Treatment modalities typically include systemic therapy with or without chemoradiation for locally advanced unresectable disease and systemic therapy alone for metastatic disease [12]. To improve survival in advanced patients, preoperative neoadjuvant chemotherapy is an available option, and several studies have certified that neoadjuvant chemotherapy can down-stage patients, improve curative respectability, and improve survival rates [13]. Neoadjuvant chemotherapy is one of the conventional treatment methods for gastric cancer, which could evaluate the curative effect after treatment and reduce the tumor size to reach a decreasing period [14]. Although scoring systems for tumor response in gastric cancer had not been uniformly adopted, in general, RECIST criteria area common method in solid tumor clinical research [15, 16]. Despite these advantages, some patients still have no effect to neoadjuvant chemotherapy [17]. To improve the quality of life of non-responders, the markers that can monitor the response to neoadjuvant chemotherapy are needed.

Ychou [18] indicated that perioperative chemotherapy significantly increased the curative resection rate. Li [19] showed significant differences in survival among gastric cancer patients at different post-neoadjuvant chemotherapy stages and reported that earlier staging after neoadjuvant chemotherapy predicted the better prognosis. Yet, invalid neoadjuvant chemotherapy might lead to disease progression or even lose the timing of surgery. Therefore, we had an urgent need to predict the clinical efficacy of chemotherapy indicators to guide the clinical treatment program. However, limited numbers of reports have examined the ability of markers to predict chemotherapy efficacy in the treatment of gastric cancer. Our study focuses on the clinical utility of tumor marker

CA19-9 in gastric cancer patients with neoadjuvant chemotherapy, and the aim of the study is to measure whether these tumor markers might be useful in monitoring response and in predicting the prognosis of patients.

He [20] indicated that patients who presented a serum CEA-level reduction ≥24% and a CA19-9-level reduction ≥29% after chemotherapy had a significantly longer PFS. But it had a low predictive value. Compared with their study, our research may preliminarily describe the effect of chemotherapy before systematic treatment. The advantage of this study was that the increased CA19-9 had a high sensitivity in predicting the efficacy of neoadjuvant chemotherapy for gastric adenocarcinoma, reaching 0.920. The disadvantage is that the specificity is low, only 0.421. Gastric adenocarcinoma patients with CA19-9 greater than 37 U/ml could have good chemotherapy efficacy. It was recommended that those patients undergo neoadjuvant chemotherapy, and the surgery should be performed after the primary tumor shrinks. Approximately 60% of patients with CA19-9 less than 37 U/ml are candidates for neoadjuvant chemotherapy, and for these patients, other predictors need to be sought.

In conclusion, the measurement of CA19-9 might be useful in the monitoring of response and in the prediction of neoadjuvant chemotherapy in patients with advanced gastric cancer treated with neoadjuvant chemotherapy. A higher CA19-9 could represent a more cost-effective tool for the evaluation of new therapies and guidance of clinical management in patients with gastric cancer. Further studies are required to confirm these findings.

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Disclosure of conflict of interest

None.

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