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Retrospective Study

Development of a clinical nomogram for prediction of response to neoadjuvant chemotherapy in patients with advanced gastric cancer

response to neoadjuvant chemotherapy

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Abstract

BACKGROUND

The efficacy of neoadjuvant chemotherapy (NAC) in advanced gastric cancer (GC) is still a controversial issue.

AIM

to find factors associated with chemosensitivity to NAC treatment, and provide the optimal therapeutic strategies for GC patients receiving NAC.

METHODS

The clinical information was collected from 230 GC patients who received NAC treatment at the Central South University Xiangya School of Medicine Affiliated Haikou Hospital from January 2016 to December 2020. LASSO logistic regression analysis was used to find the possible predictors. A nomogram model was employed to predict the response to NAC.

RESULTS

Totally 230 patients were finally included in this study, including 154 males (67.0%) and 76 females (33.0%). The mean age was (59.37±10.60) years, ranging from 24 to 80 years. According to the TRG standard, there were 95 cases in the obvious response group (grade 0 or grade 1) and 135 cases in the poor response group (grade 2 or grade 3). The obvious response rate was 41.3%. LASSO analysis showed that four risk factors significantly related to the efficacy of NAC were tumor location ($P<0.001$), histological differentiation ($P = 0.001$), clinical T stage ($P = 0.008$), and CA724 ($P = 0.008$). The C-index for the prediction nomogram was 0.806. The calibration curve revealed that the predicted value exhibited good agreement with the actual value. Decision curve analysis showed that the nomogram had a good value in clinical application.

CONCLUSION

The nomogram combining tumor location, histological differentiation, clinical T stage and CA724 shows satisfactory predictive power to the response of NAC, and can be used by gastrointestinal surgeons to determine the optimal treatment strategies for advanced GC patients.

Key Words: Advanced gastric cancer; predictor; neoadjuvant chemotherapy; nomogram; TRG

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Core Tip: Clinical information was collected from 230 gastric cancer patients who received NAC at the Central South University Xiangya School of Medicine Affiliated Haikou Hospital from January 2016 to December 2020. LASSO logistic regression analysis was performed to find the possible predictors which a nomogram model for prediction of response to NAC was based on. The conclusion is shown as, the nomogram which combined tumor location, histological differentiation , clinical T stage and CA724 showed satisfactory predictive power to response of NAC, and could be used by gastrointestinal surgeons to identify optimal treatment strategy for advanced gastric cancer patients.

INTRODUCTION

Gastric cancer (GC) is the fourth most common malignancy in terms of mortality, with approximately 770000 deaths in 2020 [1]. However, early GC does not show obvious symptoms, leading to the extremely low early diagnosis rate globally [2]. For advanced GC patients, their 5-year survival rate is as low as 25%-31% [3-6]. Although gastrectomy plus

D2 lymph node dissection and postoperative chemotherapy can improve the survival in advanced GC patients, their overall survival remains low. Recently, neoadjuvant chemotherapy (NAC) has been proposed by several national and international guidelines as a critical treatment to improve the therapeutic effect in patients with advanced GC [7-9]. NAC is used for the downstaging of the tumor and bringing likely R0 resection for advanced GC patients [10]. National Comprehensive Cancer Network (NCCN) guideline (version 2021.1) recommends that patients with clinical TNM stage ≥ T2N+ should receive NAC treatment [8]. The fifth edition of Japanese treatment guidelines recommends that patients with the stage from T2 to T4 and lymph node enlargement should receive NAC [9].

Although NAC can reduce tumor burden, decrease tumor stage, increase the radical resection rate and improve survival outcomes, there are still many controversial points including chemotherapy scheme, chemotherapy frequency, and indications [11]. It is previously reported that, NAC depends on chemotherapeutic response of tumor to achieve its survival advantage, indicating that patients with complete pathological response to NAC may show long overall survival and disease-free survival [12-14], while patients with low response to chemotherapy and no significant reduction of tumor after chemotherapy may indicate poor prognosis. For patients with low objective response rate to NAC, the treatment not only delays date of surgery, but also cause serious toxic side effects to patients. Therefore, it is very important to predict the sensitivity of NAC for patients with GC and further evaluate whether they are suitable for NAC. For those with poor sensitivity, surgery or other comprehensive treatment should be carried out immediately. Recently, many studies are conducted for identifying predicting factors for NAC response, and nomogram models have been used for the prediction of advanced GC prognosis after NAC [15-19]. Recently, researchers have built a deep learning radiomic nomogram which based on CT scan before treatment to solve this problem [20]. Compared with the traditional segmented models, these nomograms showed superior performance. However, most studies have only discussed the prognosis of patients and

postoperative complications after NAC. Only few studies identified some predictors that could predict the effect of NAC before chemotherapy.

Therefore, in this study, we retrospectively analyzed the tumor biological characteristics and clinical parameters that may affect the effect of NAC in patients with advanced GC, and established a nomogram model to predict the response of NAC, aiming to provide individualized treatment strategies and maximize the benefits for patients with advanced GC.

MATERIALS AND METHODS

Patients and data collection

This retrospective study was approved by the Research Ethics Committee of Haikou Hospital affiliated to Xiangya Medical College of Central South University. From January 2016 to December 2020, clinical information was extracted from the medical records of 259 patients with advanced GC who received NACT treatment in Haikou Hospital affiliated to Xiangya Medical College of Central South University. Then, the extracted information was analyzed retrospectively. Inclusion criteria were as follows: ①patients were diagnosed as GC through gastroscopy and biopsy; ②GC patients with clinical stage T2N + M0 or T3-4N0 / + M0; ③patients who had completed NAC; ④ GC patients received radical gastrectomy after neoadjuvant chemotherapy; ⑤the chemotherapy regimens were XELOX (Capecitabine plus oxaliplatin); and ⑥patients were aged between 18 and 80. The exclusion criteria included: ①preoperative chemotherapy was not completed as planned (<3 cycles); ②in addition to gastric cancer, the patient also suffers from other malignant tumors; ③patients with gastric stump cancer; ④patients have received radiotherapy, traditional Chinese medicine or other anti-tumor treatment; ⑤clinical data are incomplete; and ⑥postoperative pathology examination was not adenocarcinoma.

Treatment process

The patients whose clinical stage was T2N+M0 or T3-4N0 / +M0, were treated with laparoscopic exploration. If no distant metastasis such as intraperitoneal metastasis was

found during the operation, and the tumor could be resected, the chemotherapy would be given for 3 cycles on the first or second day after the laparoscopic exploration. Adjustments to dosage were made based on the effectiveness and patient tolerability. Two weeks after the completion of NAC, the resectability of the primary tumor site was confirmed again according to endoscopy and enhanced CT examination. Then, the surgery was performed. All of these patients who were enrolled received curative tumor resection (total or subtotal gastrectomy, open or laparoscopic surgery) with D2 Lymphadenectomy.

Data Collection

The clinical data collected before NAC in this study include age, gender, BMI, blood group, tumor markers (CEA, CA125, CA199, CA724), tumor location, tumor size, depth of invasion, lymph node metastasis, pathological classification, albumin, platelet count, lymphocytes, neutrophils, monocytes, and smoking history. Tumor size, depth of invasion and lymph node metastasis were evaluated on the basis of enhanced CT with laparoscopic exploration before NAC. The curative effect evaluation standard of NAC was based on TRG standard as proposed by National Comprehensive Cancer Network (NCCN) guidelines in 2021 [8]. Grade 0 (Complete response) is defined no viable cancer cells, including lymph cells; Grade 1 (Near complete response) is that single cells or rare small group of cancer cells; Grade 2 (Partial response) is interpreted as residual cancer cells with evident tumor regression but more than single cells or rare small groups of cancer cells; and Grade 3 (Poor or no response) is intermediate extensive residual cancer with no evident tumor regression. We classified grade 0 and grade 1 as obvious response. Grade 2 and grade 3 were classified as poor response. Postoperative complications were defined as events occurring within 30 days after surgery, which were assessed by the Clavien-Dindo classification system [21-22]. The adverse events of NAC were based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analysis

All statistical analyses were performed by SPSS software ver. 22.0 (IBM, Armonk, NY, United States) and R version 4.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria. www. r-project. org).

Univariate analysis: Parameters that were not normally distributed were expressed in the form of median (25% IQR to 75% IQR) and were analyzed by Mann-Whitney test, while normally distributed parameters were expressed in the form of mean±standard deviation and were analyzed by Student's T-test. Categorical variables were analyzed by chi-square test. The test level α= 0.05.

Multivariate analysis: The least absolute shrinkage and selection operator (LASSO) method was used to select the most useful predictive factors for outcomes of neoadjuvant chemotherapeutic response (P<0.05). The regression coefficient and odds ratio with 95% confidence intervals were estimated.

Nomogram construction: In order to predict the response of NAC, a nomogram including significant prognostic factors was constructed based on logistic regression analysis using glm R package (version 4.0.3). The consistency index was calculated. Decision curve analysis （DCA) and correction curve were drawn to evaluate the predictive efficiency of the nomogram.

RESULTS

Baseline and patient Characteristics

Patient information was listed in Table 1. Due to incomplete clinical data, receiving targeted therapy, pathological results for non-adenocarcinoma, 29 patients were excluded. A total of 230 patients entered the work, consisting of 154 men (67.0%) and 76 women (33.0%). All patients were 24-80 (average, 59.37 ± 10.60) years. In line with TRG standard, 95 patients were assigned into obvious response group (grades 0-1), whereas 135 into poor response group (grades 2-3), with the obvious response rate being 41.3%. The cases of depth of invasion T2 or T3 were 71, and T4 were 159.There were 83 patients (36.1%) whose tumors were at esophagogastric junction. Totally 180 patients showed positive lymph node metastasis, accounting for 78.3%.

Factors of NAC response

Table 1 displays univariable associations between the clinical parameters and response of NAC. Significant factors ($P < 0.05$) included tumor location, differentiation, clinical T stage, and CA724. The results showed that the tumor locating in the esophagogastric junction displayed better efficacy than that of non-esophagogastric junction. Greater differentiation level (well/moderate vs. poor differentiation), lower T stage (T2/T3 vs. T4 stage), and lower CA724 Level were associated with a better NAC efficacy.

To avoid the multicollinearity problem in regression analysis, the distribution coefficient was analyzed by LASSO regression with an elastic net penality. The results of LASSO regression analysis were the same with those of univariate analysis. Four independent predictors including tumor location, differentiation, clinical T stage and CA724 were included in the final model, as shown in Figure 1. The model incorporating the above independent predictors was developed and presented as the nomogram (Figure 2). The C-index for the prediction nomogram was 0.806, indicating that the prediction performance of this nomogram has good feasibility. The calibration curve of the NAC nomogram demonstrated a good consistence between prediction and actual observations in the primary cohort (Figure 3). The value of the nomogram and its use in the clinic was evaluated by the DCA, evaluating the value in terms of clinic application for the NAC nomogram (Figure 4).

Toxicity of NAC

Based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0, the overall incidence of NAC adverse events was 85.7%, and the rate of grade 3/4 toxicity was 33.48%. The main side effects were hematological toxicity and gastrointestinal reaction. Anemia (15.7%) was the most common grade 3/4 adverse event (Table 2). In addition, we found that in the Gastrointestinal, the hematological and the neurological system, the incidence of adverse reaction in the group with poor response was slightly higher than that in the group with obvious response, even though the differences were not statistically significant ($P>0.05$), as shown in Table 3.

Postoperative complications

In this study, 51 patients (22.2%) suffered from postoperative complications, and most of them were Clavien-Dindo grade 2 complication. The most common complications were pulmonary infection and pleural effusion (15.2%). One patient died of anastomotic leakage and abdominal hemorrhage. There was no statistical difference in the incidence of each complication between the obvious response group and the poor response group. Detailed information was listed in Table 4 and Table 5.

DISCUSSION

Surgery is the most vital treatment for GC. More than 60% of patients have reached the advanced stage at the time of diagnosis, which led to low radical resection rate; therefore, an efficient method for increasing the radical resection rate is urgently needed in the clinic [23].

Previous studies have indicated that surgery can induce tumor cells to transform into drug-resistant clones, and increase the production of tumor growth-stimulating factors which can promote tumor cell proliferation. In early stage, cell proliferation and DNA replication are active with the small number of tumor cells; at this time, tumor cells are more sensitive to chemotherapeutic drugs [24]. Therefore, giving chemotherapy drugs before tumor resection can not only kill the primary tumor, but also inhibit the growth-stimulating factors of cancer cells, which is also effective for micrometastases. It indicates the earlier chemotherapy, the fewer drug-resistant cell lines [25]. This highlights the importance of neoadjuvant chemotherapy.

At present, preoperative chemotherapy is receiving increasing attention. The role of NAC is to help surgeon decrease the primary tumor size and stage, eliminate micrometastasis, alleviate tumor related symptoms, improve curative resection rate and reduce postoperative recurrence rate. However, some patients who are not sensitive to chemotherapy drugs cannot be benefited from NAC, causing tumor progression and the time delay of surgical resection. Studies have shown that approximately 15% of patients receiving preoperative neoadjuvant therapy have the risk of tumor progression [26].

Moreover, patients often suffer from side effects of NAC including cardiotoxicity, hepatotoxic and nephrotoxicity, increasing the risk of complications and mortality during surgery. Therefore, it is particularly important to predict the efficacy of NAC. Thus, we performed an exploratory study to identify pre-treatment parameters that can predict NAC sensitivity, aiming to provide the basis for individualized treatment of gastric cancer patients. For patients with promising responsiveness to NAC, neoadjuvant chemotherapy should be considered. Otherwise, surgery or other comprehensive treatment should be performed as soon as possible.

Our data showed that the obvious response rate of NAC for advanced GC was 41.3%, which further indicated that only a portion of patients can benefit from NAC, thereby emphasizing the importance of predicting the responses to NAC. According to the results of the univariate and multivariate analysis, we found that tumor location, differentiation, depth of invasion, and CA724 were significant influencing factors for predicting the response of NAC. Using the four factors, we constructed a nomogram to predict the NAC response before performing gastrectomy with lymph node dissection.

A Germany retrospective cohort study including 410 patients indicated that tumor in the upper two-thirds of stomach tended to have a better response to NAT [27]. Study performed by Li *et al* also showed a similar finding [28]. This was consistent with our result that the obvious response rate of NAC in patients with tumor locating in esophagogastric junction (63.86%) was higher than that in patients without tumor locating in esophagogastric junction tumor (28.57%). The difference was statistically significant ($P<0.05$).

Many studies had explored that serum tumor markers were associated with diagnosis, prognosis, and therapeutic effect of preoperative or postoperative chemotherapy in GC [29,30]. Other studies had indicated that, CA724 was an independent factor for efficacy of NAC in GC [31]. Consistently, this work suggested that an increased CA724 level was related to the poor NAC response. Nonetheless, as reported in another study, CA724 just achieved a 45.0% sensitivity [32]. Additionally, CA724 was

related to environmental factors and H. pylori infection [33, 34]. Based on the above findings, a bias might exist in evaluating patient condition according to CA724 alone, and many studies are needed for solving the above problem.

Patients with well-differentiated had better survival than those with poor differentiation in GC [35, 36], and previous studies suggested that differentiation is a vial predictor of pathological response [37,38], conforming to our study. However, different from the previous studies [39], our results show that patients with lower T stage (T2, T3) had better response to neoadjuvant chemotherapy than advanced T stage (T4). The reason is that NAC regimens bring relatively serious toxic and side effects in patients, damaging hematological, digestive, and nervous systems [10]. In this study, the overall incidence of NAC adverse reactions was 85.7%, and the rate of grade 3/4 toxicity was 33.48%. Therefore, it is important to select the optimal treatment options for different patients. We suggest that for these patients who are not sensitive to NAC, one solution is to apply other regimens of NAC, such as FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel), resulting in superior OS compared with ECX [40]. The other is to implement surgery as soon as possible to avoid the useless time interval of chemotherapy and surgery when radical resection is available.

Additionally, numerous recent articles concentrate on the relation of tumor with serum inflammatory factors, suggesting that, lymphocytes, neutrophils and platelets within tumor microenvironment are associated with tumor metastasis and progression because inflammatory chemokines and cytokines are produced [41-46]. Typically, the increased neutrophil/platelet proportion whereas decreased lymphocyte proportion always suggest the damaged immune response and strong inflammatory response, thereby promoting cancer cell proliferation, distant organ metastasis, lymph node metastasis, and invasion. However, our study suggests that inflammatory factors such as platelets, neutrophils and lymphocytes are not independent predictors of chemosensitivity.

Although a nomogram predicting the response of NAC had been established with C index of 0.767 [10], our study achieved a C-

index of 0.806, indicating a better performance on prediction than a previously reported study. LASSO analysis was used to find significant clinical factors in this study, while other similar articles mostly use Logistic regression analysis. All patients were treated with XELOX (Capecitabine plus oxaliplatin), and thus the results are more reliable. Meanwhile, we also discussed the adverse reactions and postoperative complications of NAC, which further demonstrate the importance of predicting response to NAC.

However, this study has the following limitations. The results may be biased due to the retrospective design. In addition, because most patients enrolled in this study were in the recent two years, there were insufficient survival events to analyze the impact of the predictor and chemosensitivity on overall survival rate. Therefore, high-quality studies with a larger cohort of patients are warranted to address this issue.

CONCLUSION

To conclude, four risk factors significantly related to response of NAC included tumor location, differentiation, Clinical T stage, and CA724. The established nomogram exhibits favorable prediction performance in predicting NAC response, which can be applied in identifying the best therapeutic strategies in advanced GC patients by gastrointestinal surgeons.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant chemotherapy (NAC) has unclear therapeutic effect on advanced gastric cancer (GC).

Research motivation

This work focused on identifying factors related to chemosensitivity to NAC treatment, and offering the best treatments for GC patients receiving NAC.

Research objectives

This work focused on identifying factors related to chemosensitivity to NAC treatment, and offering the best treatments for GC patients receiving NAC.

Research methods

Predicting factors were identified by LASSO logistic regression. Additionally, a nomogram model was employed to predict the response to NAC.

Research results

Totally, we enrolled 230 patients, consisting of 154 men (67.0%) and 76 women (33.0%), in the present work. These patients aged 24-80 (average, 59.37±10.60) years. According to TRG standard, 95 patients were assigned into obvious response group (grades 0-1), whereas 135 into poor response group (grades 2-3), yielding the obvious response rate of 41.3%. As revealed by LASSO regression, tumor location ($P<0.001$), histological differentiation ($P = 0.001$), clinical T stage ($P = 0.008$), and CA724 ($P = 0.008$) were significant risk factors for NAC efficacy. With regard to the prediction nomogram, its C-index was 0.806. According to calibration curve analysis, the predicted value was highly consistent with real measurement. Moreover, decision curve analysis revealed the high application value of this nomogram clinically.

Research conclusions

Our nomogram combining tumor location, histological differentiation, clinical T stage and CA724 shows high performance in predicting NAC response, which can be applied in identifying the best therapeutic strategies for advanced GC patients by gastrointestinal surgeons.

Research perspectives

Candidate predicting factors were identified by LASSO logistic regression. The response to NAC was predicted by a nomogram model.

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