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Predictive Value of Pre- and Post-Neoadjuvant Therapy CT Features for Pathological Complete Response in Locally Advanced Gastric Adenocarcinoma: A Postprint Study

Authors: Li Min, Qin Hongtao, Liu Ao, Gao Lei, You Yang, Shi Jiabao, Li Yu, Cai Lijing, Yang Li, Yang Li

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Abstract

Background With the development of comprehensive therapy for gastric cancer, the demand for precise imaging evaluation in individualized diagnosis and treatment of advanced gastric cancer is increasingly growing. The accuracy of preoperative restaging after neoadjuvant therapy (NAT) declines, and it is difficult to accurately assess treatment efficacy based solely on post-treatment imaging.

Objective To investigate the predictive value of CT features before and after NAT for pathological complete response (pCR) in locally advanced gastric adenocarcinoma.

Methods A total of 180 gastric adenocarcinoma patients who underwent NAT at the Department of Gastrointestinal Surgery, Fourth Hospital of Hebei Medical University from April 2015 to April 2024 were retrospectively enrolled. Based on postoperative pathological results, they were divided into a pCR group (60 cases) and a non-pathological complete response (Non-pCR) group (120 cases). General patient data and CT features were compared between the two groups. Multivariate Logistic regression analysis was employed to screen independent predictors of pCR after NAT in advanced gastric adenocarcinoma, and a nomogram prediction model was established. Receiver operating characteristic (ROC) curves were plotted to predict pCR in locally advanced gastric cancer using the prediction model, and the area under the ROC curve (AUC) was calculated. The Delong test was utilized to compare differences in AUC. Hosmer-Lemeshow goodness-of-fit test and decision curve analysis (DCA) were adopted to evaluate the clinical predictive efficacy of the model.

Results Multivariate Logistic regression results demonstrated that post-NAT standardized thickness (OR=0.602, 95%CI=0.430~0.842), standardized thickness change rate (OR=0.985, 95%CI=0.971~0.999), post-NAT perigastric fat space (OR=0.193, 95%CI=0.089~0.422), and mucosal line enhancement (OR=5.882, 95%CI=2.123~16.393) were independent predictors of pCR in gastric cancer. The AUCs of the aforementioned four independent predictors and the nomogram model for predicting pCR after NAT in advanced gastric adenocarcinoma were 0.749 (95%CI=0.675~0.824), 0.726 (95%CI=0.645~0.807), 0.708 (95%CI=0.627~0.790), 0.617 (95%CI=0.525~0.708), and 0.856 (95%CI=0.796~0.917), respectively, with optimal cutoff values of 0.353, 0.409, 0.168, 0.270, and 0.360. Delong test results indicated that the nomogram model outperformed single predictors, with statistically significant differences ($P<0.05$). Hosmer-Lemeshow test results showed good model fit (2=6.802, P=0.558). DCA results revealed that when the threshold probability of the nomogram model was within the range of 0.1~0.75, the clinical benefit was superior to that of single predictors.

Conclusion Post-NAT standardized thickness, standardized thickness change rate, post-NAT perigastric fat space, and mucosal line enhancement are closely associated with the occurrence of pCR in gastric cancer and can serve as evaluation indicators for pCR in locally advanced gastric cancer. The nomogram model established based on these four independent factors can provide certain reference for clinical diagnosis and treatment of gastric cancer.

Full Text

Predictive Value of Pre- and Post-Neoadjuvant Therapy CT Features for Pathological Complete Response in Locally Advanced Gastric Adenocarcinoma

LI Min[1], QIN Hongtao[2], LIU Ao[1], GAO Lei[1], YOU Yang[1], SHI Jiabao[1], LI Yu[1], CAI Lijing[3], YANG Li[1]*

[1]Department of CT/MRI, the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China
[2]Department of Radiology and Nuclear Medicine, The First Hospital of Hebei Medical University, Shijiazhuang 050010, China
[3]Department of Pathology, the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China

Corresponding author: YANG Li, Professor; E-mail: 13582165802@163.com
LI Min and QIN Hongtao are co-first authors

Abstract

Background
With the advancement of comprehensive treatment strategies for gastric cancer,

there is an increasing demand for precise imaging assessment for individualized diagnosis and treatment of advanced gastric cancer. However, the accuracy of preoperative restaging after neoadjuvant therapy (NAT) is significantly reduced, making it challenging to reliably evaluate treatment efficacy based solely on post-therapeutic imaging findings.

Objective

To investigate the predictive value of CT features before and after neoadjuvant therapy (NAT) for pathologic complete response (pCR) in locally advanced gastric adenocarcinoma.

Methods

We retrospectively enrolled 180 patients with gastric adenocarcinoma who underwent NAT at the Department of Gastrointestinal Surgery, Fourth Hospital of Hebei Medical University, between April 2015 and April 2024. Based on postoperative pathological results, 60 patients were classified into the pathological complete response (pCR) group and 120 into the non-pathological complete response (non-pCR) group. General clinical data and CT features were compared between the two groups. Multivariate logistic regression analysis was performed to identify independent predictors of pCR after NAT in advanced gastric adenocarcinoma, and a prediction nomogram model was constructed. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive performance for pCR in locally advanced gastric cancer, and the area under the ROC curve (AUC) was calculated. AUC differences were compared using the Delong test. The Hosmer-Lemeshow goodness-of-fit test and decision curve analysis (DCA) were used to evaluate the clinical predictive efficacy of the model.

Results

Multivariate logistic regression analysis revealed that post-NAT standardized thickness (OR=0.602, 95%CI=0.430-0.842), rate of change in standardized thickness (OR=0.985, 95%CI=0.971-0.999), perigastric fat infiltration after NAT (OR=0.193, 95%CI=0.089-0.422), and mucosal line enhancement (OR=5.882, 95%CI=2.123-16.393) were independent predictors of pCR in gastric cancer. The individual AUC values for these four independent predictors and the nomogram model for predicting pCR after NAT in advanced gastric adenocarcinoma were 0.749 (95%CI=0.675-0.824), 0.726 (95%CI=0.645-0.807), 0.708 (95%CI=0.627-0.790), 0.617 (95%CI=0.525-0.708), and 0.856 (95%CI=0.796-0.917), respectively. The optimal cutoff values were 0.353, 0.409, 0.168, 0.270, and 0.360, respectively. Delong test results showed that the nomogram model demonstrated superior performance compared to single predictors, with statistically significant differences ($P<0.05$). The Hosmer-Lemeshow test indicated good model fit (^{2}=6.802, P=0.558). DCA results showed that the nomogram model provided greater clinical benefit than single predictors when the threshold probability ranged from 0.1 to 0.75.

Conclusion

Post-NAT standardized thickness, rate of change in standardized thickness, perigastric fat infiltration after NAT, and mucosal line enhancement are significantly associated with the occurrence of pCR in gastric cancer and can serve as reliable indicators for assessing pCR in locally advanced gastric cancer. The nomogram model developed based on these four independent predictors provides a valuable reference for clinical decision-making in the management of gastric cancer.

Keywords
Computed tomography; Gastric cancer; Neoadjuvant therapy; Pathologic complete response

Introduction

Gastric cancer ranks as the fifth most common malignancy and the third leading cause of cancer-related mortality in China [1]. Most patients present with locally advanced disease at diagnosis and have relatively low long-term survival rates. Neoadjuvant therapy (NAT) represents a crucial component of comprehensive treatment for locally advanced gastric cancer, offering benefits including tumor downsizing, stage reduction, improved R0 resection rates, and decreased postoperative recurrence and metastasis [2-4]. Patients who achieve pathological complete response (pCR), defined as ypT0N0M0, after NAT demonstrate significantly improved disease-free and overall survival rates [5-6]. However, pCR rates for locally advanced gastric cancer remain low, ranging from only 2.2% to 26.8% [7-8]. Furthermore, inflammatory reactions and fibrotic changes in the tumor bed following NAT reduce the accuracy of CT assessment [9], making it difficult to determine pCR based solely on post-treatment imaging.

This study analyzed CT features before and after NAT in patients with locally advanced gastric cancer to identify predictive factors and evaluate their value in predicting pCR, aiming to provide a reference for clinical treatment decision-making and prognostic risk assessment.

Methods

1.1 Study Subjects We retrospectively enrolled 180 patients with gastric adenocarcinoma who received NAT at the Department of Gastrointestinal Surgery, Fourth Hospital of Hebei Medical University, between April 2015 and April 2024. Based on postoperative pathological results, patients were divided into a pCR group (n=60) and a non-pCR group (n=120). Diagnostic criteria: pCR was defined as no residual tumor cells (including lymph nodes) visible under light microscopy [10]. Inclusion criteria: (1) endoscopic biopsy-confirmed adenocarcinoma with clinical stage cT2-4aN0-3M0; (2) completion of standardized NAT and radical surgical resection with complete clinical and pathological data; (3) contrast-enhanced CT examinations performed before NAT and within 2 weeks before surgery after NAT with complete imaging data. Exclusion criteria: (1) patients with other malignancies receiving concurrent anti-tumor treatment; (2) poor gastric distension or presence of respiratory or motion artifacts affecting lesion evaluation. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (approval number: 2021KY347), and all patients and their families provided informed consent.

1.2 General Data Collection We collected demographic information including sex, age, tumor location (cardia, body, antrum), NAT regimen (chemotherapy alone or combined with immunotherapy), and pre-NAT serum tumor marker levels including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 72-4 (CA72-4).

1.3 CT Examination Methods CT scans were performed using a GE Healthcare Revolution CT scanner or a Siemens Healthcare Somatom Definition Flash dual-source CT scanner. Patients fasted for 6 hours before examination. Ten minutes prior to scanning, 10 mg of anisodamine was administered intramuscularly, followed by oral ingestion of 800–1000 mL warm water or 6 g of effervescent powder to distend the gastric lumen. Patients were scanned in the supine position at end-inspiration breath-hold. The scanning range extended from the diaphragmatic dome to the upper margin of the pubic symphysis. After non-contrast scanning, non-ionic contrast agent iohexol (300 mg I/mL) was injected at 3.0 mL/s via the elbow vein at a dose of 2 mL/kg body weight. Dual-phase scanning was performed at 25–35 s and 70 s after injection. Enhanced scanning parameters: for Revolution CT, tube voltage was 120 kV with automatic tube current, collimation width 80 mm, pitch 0.992:1, slice thickness 5 mm, interval 5 mm, and reconstructed slice thickness 1.25 mm; for dual-source CT, tube voltages were 100 kV and Sn140 kV with reference tube currents of 230 mAs and 178 mAs, collimation width 32$×$0.6 mm, pitch 0.55, fusion coefficient 0.5, slice thickness 5 mm, interval 5 mm, and reconstructed slice thickness 1 mm.

1.4 CT Feature Analysis We collected pre- and post-NAT standardized tumor thickness and its change rate, venous phase standardized CT value and its change rate; pre- and post-NAT cT stage (cT4/non-cT4); pre- and post-NAT lymph node metastasis and ulcer characteristics (absent/present); pre- and post-NAT serosal surface (smooth/irregular), perigastric fat clearance (clear/obliterated), enhancement pattern (homogeneous/heterogeneous), and layered enhancement/mucosal line enhancement (absent/present).

1.4.1 Qualitative CT Feature Analysis

Two radiologists with 8 and 13 years of abdominal imaging experience independently analyzed pre- and post-NAT images without knowledge of postoperative pathology. Discrepancies were resolved by a senior radiologist with 18 years of experience. cT2-4a and N0-3 stages were determined according to the American Joint Committee on Cancer (AJCC) Gastric Cancer Staging Manual (8th edition) [11] and the Chinese Society of Clinical Oncology (CSCO) Gastric Cancer Diagnosis and Treatment Guidelines (2022 edition) [10]. Lymph nodes with short-axis diameter $ $10 mm were considered metastatic, while those <10 mm were considered non-metastatic, according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [12].

1.4.2 Quantitative CT Feature Measurement
A radiologist with 8 years of abdominal imaging experience measured tumor thickness on venous phase axial images at the maximal tumor dimension perpendicular to the gastric wall. Standardized thickness was calculated as maximal tumor thickness divided by adjacent normal gastric wall thickness. The rate of change in standardized thickness was calculated as: (post-NAT standardized thickness - pre-NAT standardized thickness) / pre-NAT standardized thickness $\times$ 100%. Circular regions of interest (ROI) of 8–25 mm were drawn on the maximal tumor layer, avoiding necrotic areas and perigastric tissue, to measure mean tumor CT value. The CT value of the abdominal aorta at the same level was measured for standardization. Standardized CT value was calculated as tumor CT value divided by aortic CT value. The rate of change in standardized CT value was calculated as: (post-NAT standardized CT value - pre-NAT standardized CT value) / pre-NAT standardized CT value $\times$ 100%. Post-NAT measurements were referenced to pre-NAT tumor location, with three measurements averaged.

1.5 Statistical Analysis Statistical analysis was performed using SPSS 27.0 and R 4.2.2 software. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x}\pm s$) and compared between groups using independent samples t-test. Non-normally distributed data were expressed as median (P25, P75) and compared using non-parametric tests. Categorical data were expressed as proportions and compared using ^{2} test. Multivariate logistic regression analysis was used to identify independent predictors of pCR in advanced gastric adenocarcinoma and construct a nomogram prediction model. ROC curves were plotted to evaluate predictive performance for pCR in locally advanced gastric cancer, and AUC values were calculated. AUC differences were compared using the Delong test. The Hosmer-Lemeshow goodness-of-fit test and decision curve analysis (DCA) were used to evaluate clinical predictive efficacy. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of Clinical Characteristics Between pCR and non-pCR Groups A total of 180 patients were enrolled, including 128 males (71.1%) and 52 females (28.9%), with a mean age of 57.57$±$9.38 years. There were statistically significant differences between the two groups in sex and NAT regimen ($P<0.05$). No significant differences were observed in age, tumor location, or pre-NAT CEA, AFP, CA19-9, or CA72-4 levels ($P>0.05$) .

Post-NAT standardized tumor thickness was lower in the pCR group compared to the non-pCR group, while the rate of change in standardized thickness and venous phase standardized CT value change rate were higher in the pCR group, with statistically significant differences ($P<0.05$). The proportion of patients with non-cT4 stage before and after NAT was higher in the pCR group than in the non-pCR group ($P<0.05$). Post-NAT ulcer presence, irregular serosal surface, and heterogeneous enhancement were less frequent in the pCR group, while clear perigastric fat clearance and mucosal line enhancement were more frequent, with all differences being statistically significant ($P<0.05$) .

2.2 Multivariate Logistic Regression Analysis of pCR Influencing Factors Using postoperative pathology results (pCR: yes=1, no=0) as the dependent variable, and sex (male=1, female=0), treatment regimen (chemoimmunotherapy=1, chemotherapy=0), pre- and post-NAT cT stage (cT4=1, non-cT4=0), post-NAT standardized tumor thickness, rate of change in standardized thickness, rate of change in venous phase standardized CT value (all as continuous variables), ulcer (present=1, absent=0), serosal surface (irregular=1, smooth=0), perigastric fat clearance (obliterated=1, clear=0), mucosal line enhancement (present=1, absent=0), and enhancement pattern (heterogeneous=1, homogeneous=0) as independent variables, multivariate logistic regression analysis identified post-NAT standardized tumor thickness (OR=0.602, 95%CI=0.430-0.842), rate of change in standardized thickness (OR=0.985, 95%CI=0.971-0.999), post-NAT perigastric fat clearance (OR=0.193, 95%CI=0.089-0.422), and mucosal line enhancement (OR=5.882, 95%CI=2.123-16.393) as independent predictors of pCR in locally advanced gastric adenocarcinoma .

2.3 Nomogram Model for pCR in Locally Advanced Gastric Adenocarcinoma Based on the multivariate logistic regression results, a nomogram model was constructed using post-NAT standardized tumor thickness, rate of change in standardized thickness, post-NAT perigastric fat clearance, and mucosal line enhancement as predictive factors. The total score was obtained by summing the points corresponding to each predictive factor, with the predicted probability representing the likelihood of pCR occurrence. When the predicted probability exceeded the cutoff value, pCR was predicted; when below the cutoff value, non-pCR was predicted [Figure 1: see original paper].

2.4 Predictive Efficacy of Independent Factors and Nomogram Model ROC curves were plotted for the independent predictors and nomogram model. The AUC values for post-NAT standardized tumor thickness, rate of change in standardized thickness, post-NAT perigastric fat clearance, mucosal line enhancement, and the nomogram model were 0.749 (95%CI=0.675-0.824), 0.726 (95%CI=0.645-0.807), 0.708 (95%CI=0.627-0.790), 0.617 (95%CI=0.525-0.708), and 0.856 (95%CI=0.796-0.917), respectively. The optimal cutoff values were 0.353, 0.409, 0.168, 0.270, and 0.360, respectively [Figure 2: see original paper] . Delong test results demonstrated that the nomogram model was superior to single independent predictors, with statistically significant differences ($P<0.05$) .

The Hosmer-Lemeshow test indicated good model fit (^{2}=6.802, P=0.558). The calibration curve showed good agreement between predicted and actual values, indicating satisfactory consistency between the model and clinical reality (^{2}=6.802, P=0.558) [Figure 3: see original paper]. DCA results demonstrated that the nomogram model provided greater clinical benefit than single independent predictors when the threshold probability ranged from 0.1 to 0.75 [Figure 4: see original paper].

2.5 Clinical Validation of the Nomogram Model A clinical case was included for validation: a 67-year-old male diagnosed with gastric adenocarcinoma. The nomogram yielded a predicted probability of 0.870, exceeding the cutoff value of 0.360, thus predicting pCR. Pre-NAT venous phase CT axial images showed wall thickening at the lesser curvature of the cardia with heterogeneous enhancement, irregular serosal surface, and obliterated perigastric fat clearance. Post-NAT images demonstrated decreased tumor thickness, smooth serosal surface, and clear perigastric fat clearance. Postoperative pathology revealed abundant acellular mucin infiltration in the submucosa and muscularis propria, with fibrosis and chronic inflammatory cell infiltration in the mucosal layer, confirming pCR—consistent with the nomogram model prediction [Figure 5: see original paper].

Discussion

With the development of comprehensive treatment for gastric cancer, the demand for precise imaging assessment in individualized management of advanced gastric cancer has increased. Due to the tortuous spatial course of the gastric wall, accurate measurement of tumor long-axis dimensions on two-dimensional images is challenging, and the application of RECIST criteria in gastric cancer remains problematic [13]. This study comprehensively analyzed clinical and imaging data from patients with locally advanced gastric adenocarcinoma to reveal associations between pCR and CT features before and after NAT, providing important scientific evidence for preoperative treatment response assessment and prognosis evaluation.

Our study demonstrated that post-NAT standardized tumor thickness and its change rate were independent predictors of pCR. Locally advanced gastric cancer infiltrates along the gastric wall, typically manifesting as wall thickening. Literature reports indicate that gastric cancer thickness reflects tumor infiltration depth and correlates closely with T stage [11,14]. Effective treatment reduces tumor infiltration and consequently decreases thickness. Our previous research found that post-NAT gastric tumor thickness is affected by the degree of gastric distension; therefore, we standardized tumor thickness measurements to avoid the impact of distension variability [15]. Studies by WANG et al. [16] and WEI et al. [17] demonstrated that post-chemotherapy thickness correlates with pCR, and the thickness change rate is an independent predictor of pCR, consistent with our findings and highlighting the importance of thickness change rate in predicting pathological complete response in gastric cancer.

We also identified post-NAT standardized thickness as an independent predictor of pCR, suggesting that standardized measurement methodology provides value for ensuring measurement accuracy and consistency. The pCR group exhibited lower post-NAT standardized thickness and higher standardized thickness change rates compared to the non-pCR group, indicating that greater thickness reduction and higher change rates correlate with more significant treatment response and higher likelihood of pCR.

When gastric cancer invades the serosa, local serosal damage can lead to tumor angiogenesis and increased local microcirculation in perigastric fat tissue, manifesting as increased fat density [18-20]. Clear perigastric fat clearance after NAT suggests downstaging of tumor T stage [21]. Our study found that the proportion of patients with clear perigastric fat clearance after NAT was significantly higher in the pCR group than in the non-pCR group (71.7% vs. 30.0%). However, 28.3% of patients in the pCR group still showed obliterated perigastric fat clearance, possibly due to post-treatment inflammatory changes or fibrous tissue proliferation. Therefore, clear perigastric fat clearance after NAT has substantial predictive value for pCR, but obliterated clearance does not exclude the possibility of pCR.

Mucosal line enhancement was another independent predictor of pCR. In our study, 33.3% (20/60) of patients in the pCR group exhibited mucosal line enhancement after NAT. WANG et al. [16] reported that 54.5% (6/11) of pCR patients showed mucosal line enhancement on CT after chemotherapy, a higher proportion than in our study, possibly related to tumor heterogeneity and sample size. Mucosal line enhancement is considered a CT feature of early gastric cancer [11,22]. In our study, this sign demonstrated high specificity (90.0%), and its appearance after complete tumor regression may result from inflammatory cell infiltration in the mucosal layer.

Currently, few domestic and international studies have investigated associations between conventional CT features and gastric cancer pCR. A recent nationwide retrospective study by CHEN et al. [23] found that earlier stage and chemoimmunotherapy combination were significantly associated with pCR in locally advanced gastric cancer. Our univariate analysis showed that the pCR group had higher proportions of non-cT4 stage before and after NAT (23.3% vs. 10.0%, 70.0% vs. 39.2%) and chemoimmunotherapy (31.7% vs. 10.8%) compared to the non-pCR group, confirming the important value of T stage and immunotherapy in comprehensive gastric cancer treatment [24-25]. GAO et al. [26] reported that total iodine uptake and its reduction rate in the venous phase correlated with response to neoadjuvant chemotherapy in gastric cancer primary lesions. However, MD et al. [27] found that higher CT attenuation change rates were associated with poor pathological response to chemotherapy regimens in gastric adenocarcinoma. Our univariate results showed that post-NAT ulcer presence was lower and venous phase standardized CT value change rate was higher in the pCR group compared to the non-pCR group (both $P<0.05$), consistent with GAO et al. [26]. As tumors regress after NAT, neovascularization with abundant blood supply and proliferating fibroblasts transform into scar and fibrous connective tissue with reduced vascularity, decreasing mucosal disruption and causing ulcers to become shallow or disappear. Changes in gastric cancer morphology and enhancement degree after NAT have reference value for treatment response assessment, though the clinical value of these features requires further investigation.

Although CT perfusion imaging, texture analysis, and radiomics have shown advantages in evaluating treatment response in advanced gastric cancer, factors such as radiation dose and software learning curves must be considered. Clinically, a simple and universally applicable predictive model is needed. Our study developed a model based on CT features before and after NAT, with all parameters obtainable from routine scans. The nomogram model demonstrated good performance superior to single independent predictors (AUC=0.856). Delong test confirmed that the nomogram model was statistically superior to single predictors (all P<0.05). The Hosmer-Lemeshow test (^{2}=6.802, P=0.558) indicated good model fit, and the calibration curve showed good agreement between predicted and actual values. Decision curve analysis demonstrated that the nomogram model provided significantly greater clinical benefit than single predictors when threshold probability ranged from 0.1 to 0.75. The nomogram enhanced clinical operability of the predictive model, enabling rapid individualized risk stratification through visualization of predictor scores and probability scales.

Study limitations: (1) This was a single-center retrospective study with potential selection bias; (2) The sample size was relatively small, and no test set was established for model validation. Future multi-center prospective validation will be conducted to optimize the model and improve its generalizability; (3) Imaging features from earlier time points after NAT may have higher clinical value, and we will continue to investigate their relationship with tumor regression grading to enable more timely and precise clinical guidance during early treatment.

In summary, we developed a clinical prediction model based on four independent predictors: post-NAT standardized tumor thickness, rate of change in standardized thickness, post-NAT perigastric fat clearance, and mucosal line enhancement. This model demonstrated high efficacy and accuracy in identifying pathological complete response after neoadjuvant therapy in locally advanced gastric cancer, providing imaging biomarkers for clinical assessment of treatment response and prognosis.

Author Contributions

LI Min and QIN Hongtao designed the study and drafted the manuscript; GAO Lei performed data analysis; LIU Ao, LI Yu, and SHI Jiabao collected data; LIU Ao and YOU Yang verified and entered data; CAI Lijing performed pathological analysis; LI Min, QIN Hongtao, YANG Li, and GAO Lei reviewed the manuscript; YANG Li revised the final version and took overall responsibility for the manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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