Risk Factors and Prognostic Impact of the Completion of Adjuvant Chemotherapy with Oxaliplatin Plus Oral Fluorouracil for AGC After D2 Gastrectomy

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1 **Risk factors and prognostic impact of the completion of**
2 **adjuvant chemotherapy with oxaliplatin plus oral**
3 **fluorouracil for AGC after D2 gastrectomy**

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Abstract

Background: To analyze the risk factors and prognostic impact of the completion of
adjuvant chemotherapy with oxaliplatin plus oral fluorouracil for advanced gastric
cancer (AGC) after D2 gastrectomy.

Methods: A total of 234 patients with AGC who underwent D2 gastrectomy and
received oxaliplatin plus oral fluorouracil adjuvant chemotherapy between January 1,
2012 to January 1, 2021 in the First Affiliated Hospital of Xiamen University were
identified (203 cases with SOX regime; 31 cases with XELOX regime) and their
clinicopathological information was retrospectively analyzed. The tolerability and
safety of oxaliplatin plus oral fluorouracil therapy were analyzed. Patients were divided
into high completion group ($n = 135$) and low completion group ($n = 99$) according to
whether they had completed 6 cycles of adjuvant combined chemotherapy. Relevant
risk factors and the prognostic impact of the completion rates of chemotherapy were
analyzed.

Results: 99 patients have completed more than 6 cycles of adjuvant chemotherapy with
oxaliplatin plus oral fluorouracil and the chemotherapy completion rate was 42.31%.
Chemotherapy completion was correlated with age ($P = 0.000$) and the extent of gastric
resection ($P = 0.039$). Age was independent risk factor of chemotherapy completion

(*OR*,2.487;95%*CI*,1.449-4.268; $P = 0.001$). As of January 1,2021, 124 patients were followed up for more than three years, the three-year survival rate (86.9% vs 68.8%; $P = 0.02$) were significantly different between two groups, and the differences of pN stage, pTNM stage and nerve invasion were also statistically significant ($P < 0.05$, respectively). Cox regression analysis showed that pN3 stage (*HR*,2.645; 95%*CI*,1.138-6.146; $P = 0.024$) was independent prognostic factor about poor survival.

Conclusions: Oxaliplatin plus fluorouracil oral adjuvant chemotherapy was safe and tolerable. Advanced age and total gastrectomy were risk factors for chemotherapy completion. The key to improve the prognosis of patients with AGC after D2 gastrectomy was to improve the completion rate of adjuvant chemotherapy.

Keywords: Advanced gastric cancer; Adjuvant chemotherapy; Completion rate of chemotherapy; Prognosis

Background

Gastric cancer was one of the most common malignant tumors in the world. In 2018, there were 1 million new cases of gastric cancer, and nearly 800 thousand people died of gastric cancer [1]. The incidence rate of gastric cancer has increased significantly in East Asia countries such as Japan, Korea and China [1, 2]. The detection rate of early asymptomatic gastric cancer was high in Japan and Korea [3-5]. However, more than 80% of Chinese patients with gastric cancer were diagnosed as advanced gastric cancer (AGC) for the first time[6, 7].

Radical resection was the only possible way to cure AGC [8], including standard gastrectomy and D2 lymphadenectomy [7-9]. But the recurrence rate of patients with AGC after radical resection was more than 60%, and more than 40% of patients relapsed within 2 years [10]. Postoperative adjuvant chemotherapy was widely used in Asia. The adjuvant chemotherapy based on fluorouracil can significantly improve the curative effect and reduce recurrence, and the 5-year survival rate can be increased by nearly 50% [11]. SOX regimen and XELOX regimen were the most commonly used adjuvant chemotherapy for AGC after D2 radical gastrectomy in China [7, 12-25].

The prognosis of patients with AGC was still not optimistic, even if they receive comprehensive treatment based on surgery [3]. The optimization of adjuvant chemotherapy was the key to delay tumor progression or recurrence and help patients maintain good quality of life and prolong survival time. IDEA study emphasizes the importance of sufficient duration of adjuvant chemotherapy for colon cancer [26]. JCOG1104 study showed that the 3-year RFS of patients with stage III AGC who received one-year S-1 single agent chemotherapy after radical resection was higher than that of patients receiving half a year of chemotherapy [27]. The second post hoc analysis of the classic study emphasized that patients with stage II - III advanced gastric cancer who received more than 6 cycles of XELOX postoperative adjuvant chemotherapy had a significantly better prognosis [23]. The ACTS-GC study showed that only 65.8% of patients completed one-year S-1 single agent adjuvant chemotherapy [12], and only 67% of patients in the CLASSIC study completed 8 cycles of XELOX adjuvant

chemotherapy[22]. It can be seen that the completion rate of adjuvant chemotherapy was relatively low in previous phase II or III clinical studies. Prolonging the time of adjuvant chemotherapy and improving the completion rate of postoperative chemotherapy were the key to improve the prognosis of patients with AGC after radical operation.

Methods

This study has been approved by ethics committee of The First Affiliated Hospital of Xiamen University. The clinicopathological information of patients with AGC who underwent D2 gastrectomy and received oxaliplatin plus oral fluorouracil adjuvant chemotherapy between January 1, 2012 to January 1, 2021 in the First Affiliated Hospital of Xiamen University were collected retrospectively. According to the inclusion criteria and exclusion criteria, 234 eligible cases were successfully included. Inclusion criteria: (1) No metastasis was found by preoperative examination and intraoperative abdominal exploration; (2) D2 radical resection was performed by the surgeon of our hospital under the assistance of laparotomy or laparoscopy. The postoperative pathological report confirmed that it was advanced gastric adenocarcinoma with negative upper and lower margins; (3) The patient received postoperative adjuvant chemotherapy in our hospital. Before the first chemotherapy, the patient's self-care skill, bone marrow and important organ function were basically normal; (4) The postoperative adjuvant chemotherapy regime was L-OHP plus oral

fluorouracil. Exclusion criteria: (1) Gastric stump cancer; (2) Patients received preoperative chemotherapy or preoperative radiotherapy; (3) D1 / D1 + lymph node dissection; (4) Chemotherapy particles were placed in the abdominal cavity during operation; (5) The postoperative pathological report could not confirm that the tumor was adenocarcinoma or combined with squamous cell carcinoma, or the upper and lower margins were positive; (6) The patient received postoperative radiotherapy; (7) The patients died within 30 days after operation.

Patients were followed up by outpatient, inpatient reexamination, or telephone to obtain relevant information. The life span started from the date of the first day after operation, ended in the dead day or the last follow-up date, and the deadline date of follow-up was January 1, 2021. Statistical analysis was performed using Stata13.0 software. Single factor analysis of counting data was used χ^2 test. Multivariate analysis used binary logistic regression model. The case (%) was used to perform binary classification data. The time-point survival rate and overall survival rate were calculated. The cumulative mortality was estimated using the Kaplan-Meier method and the survival curve was obtained. Univariate analyzed was performed by Log-rank test, statistically significant factors were selected and analyzed using a multivariate COX proportional hazards model to explore factors affecting the prognosis of patients with AGC. The hazard ratio (HR) was estimated using a 95% confidence interval (CI), $p < 0.05$ was considered statistically significant.

Results

Case data introduction

According to the inclusion and exclusion criteria, a total of 234 patients with AGC who underwent D2 gastrectomy and received oxaliplatin plus oral fluorouracil adjuvant chemotherapy were identified (203 cases with SOX regime; 31 cases with XELOX regime). Their clinicopathological information were shown in Table 1.

Tolerability and safety of adjuvant chemotherapy

Tolerability

99 patients have completed more than 6 cycles of adjuvant chemotherapy with L-OHP plus oral fluorouracil and the chemotherapy completion rate was 42.31%. 41 patients (30.37%) continued oral fluorouracil treatment after interrupting L-OHP treatment. The average interval between the first chemotherapy and operation was 33.98 days. 203 patients received SOX chemotherapy, the average dose intensity of L-OHP and S-1 were 117.13mg/m^2 and 35.31mg/m^2 respectively. 172 patients experienced delay, the average time interval two cycle of chemotherapy were 27.97 days. 31 patients received XELOX chemotherapy, the average dose intensity of L-OHP and CAPE were 119.37mg/m^2 and 923.88mg/m^2 respectively. 27 patients experienced delay, the average time interval two cycle of chemotherapy were 27.95 days.

Safety

192 patients (82.05%) suffered from adverse events. Grade 2 or higher adverse events occurred in 108 patients (46.15%) 17 patients developed obvious gastrointestinal adverse reactions, mainly nausea and vomiting. Serious peripheral neuritis and serious

oral ulcer was observed in one patient respectively. Hematological toxicities of all grades occurring in at least 10 patients were listed in Table 2. Anemia occurred in 160 patients (68.38%), it was the most common hematological toxicities of all grades, but grade 2 or higher events were observed in only 20 patients (8.55%). The most common hematological adverse reaction of grade 2 or higher was neutropenia, which occurred in 54 patients (23.08%), and grade 3 neutropenia occurred in 19 patients (8.12%). Grade 4 thrombocytopenia occurred in one patient.

Correlation analysis for chemotherapy completion

Univariate analysis of chemotherapy completion

The chemotherapy completion rate of L-OHP plus oral fluorouracil for more than 6 cycles was significantly correlated with the age ($P = 0.000$) and the extent of gastric resection ($P = 0.039$) (Table 3).

Multivariate analysis of chemotherapy completion

The significant items of univariate analysis were introduced into logistic regression model. In multivariable regression models, age was independent risk factor of chemotherapy completion ($OR, 2.487; 95\%CI, 1.449-4.268; P = 0.001$). Patients with distal gastrectomy were 1.623 times more likely to complete more than 6 cycles of adjuvant chemotherapy than patients with total gastrectomy ($P = 0.078, 95\% CI, 0.947-2.781$). (Table 4)

Survival analysis

Comparison of survival prognoses between high completed group and low completed group

124 patients with AGC who underwent D2 gastrectomy and received oxaliplatin plus oral fluorouracil adjuvant chemotherapy before January 1, 2018. Median follow-up time was 43.9 months. The survival rate was calculated by Kaplan-Meier method. The 1-year, 2-year and 3-year OS rate of patients were 96.6% ($S\bar{X}=0.017$), 83.9% ($S\bar{X}=0.035$) and 76.4% ($S\bar{X}=0.041$) respectively (Fig.1). As shown in Table 5, there was significant difference in OS rate between high completion group and low completion group (1-year OS rate, 100% vs 94.2%, $P = 0.04$; 2-year OS rate, 93.6% vs 76.9%, $P = 0.01$; 3-year OS rate, 86.9% vs 68.8%, $P = 0.02$). The Kaplan-Meier curves for the two groups were shown in Fig.2. A significant separation between the two groups was observed.

Univariate analysis of clinicopathological factors affecting three-year survival rate

The 3-year OS rate was calculated by Kaplan-Meier method, the survival curve was drawn, and the Log-rank test was performed. The differences of pN stage, pTNM stage and nerve invasion were also statistically significant ($P < 0.05$, respectively) (Fig.3-5). The above factors affected the prognosis of patients with AGC who underwent D2 gastrectomy and received L-OHP plus oral fluorouracil adjuvant chemotherapy (Table 6).

Multivariate analysis of prognostic factors

As shown in Table 7, Cox regression analysis showed that pN3 stage ($HR, 2.645$; $95\%CI, 1.138-6.146$; $P = 0.024$) was independent prognostic factor about poor survival. Nerve invasion was a risk factor affecting the prognosis of patients ($HR, 2.260$; $95\%CI, 0.266-1.092$; $P = 0.057$). Completion of more than 6 cycles of adjuvant chemotherapy was a favorable factor affecting the prognosis of patients ($HR, 0.539$; $95\%CI, 0.266-1.092$; $P = 0.086$).

Discussion

This study suggests that the completion of L-OHP plus oral fluorouracil adjuvant chemotherapy after D2 radical gastrectomy was closely related to the prognosis of patients. Improving the completion rate of adjuvant chemotherapy is the key to improve the prognosis of patients. In this study, the completion rate of combined chemotherapy for patients with more than 6 cycles was only 42.31%. The completion rate of SOX regimen and XELOX regimen was 42.36% (86/203) and 41.94% (13/31) respectively, which were lower than that of previous studies [16, 22]. However, the safety of chemotherapy was similar to previous studies and the adverse reactions of chemotherapy were also controllable. L-OHP plus oral fluorouracil adjuvant chemotherapy was safe and tolerable.

The results showed that the completion rate of chemotherapy in elderly patients was significantly reduced. Most patients with AGC in China were aged from 60 to 70[28]. The incidence of grade 3 or above adverse reactions in elderly patients

with AGC was significantly higher than that in young patients [29]. The key of treatment for elderly patients with AGC was to ensure that the expected benefit was higher than the expected risk. There were many basic diseases in elderly patients, so the individual drug treatment history of the elderly was relatively complex. Moreover, the elderly group has poor state of ability, and the immunity was reduced, and it was unable to withstand high-dose combined chemotherapy with multiple drugs. It can be considered to adjust the mode of chemotherapy administration [16, 30, 31], reduce the toxicity of chemotherapy [17-19, 32] and reduce the types of chemotherapy drugs [33, 34] for improving the completion rate of adjuvant chemotherapy in elderly patients with AGC after radical resection. Elderly patients need to formulate individualized treatment. In addition, in order to find more asymptomatic patients with early gastric cancer and improve their life quality, gastroscopy should be actively promoted in our country [35-37].

The results showed that the completion rate of chemotherapy in patients with AGC underwent total gastrectomy was significantly reduced. The standard surgical treatment of AGC was distal gastrectomy or total gastrectomy [7]. In this study, the tumors were located in the lower third of the stomach in 121 patients, of which 12.40% of patients underwent total gastrectomy. Total gastrectomy has many adverse factors, such as prolonging the postoperative hospital stay, prolonging the time of postoperative low calorie intake, increasing the long-term nutritional sequelae and reducing the quality of life of patients [38-42]. The results also showed that the nutritional status of patients who underwent total gastrectomy was poor. 58.41% of the patients lost more than 7%

of their weight after total gastrectomy, and 28.32% of patients even more than 10%. The time for patients with total gastrectomy to receive the first adjuvant chemotherapy was significantly delayed, and 15.04% of patients had an interval of more than 6 weeks. Distal gastrectomy was recommended for patients with lower third AGC when the proximal margin distance can be ensured. The choice of total gastrectomy or distal gastrectomy for the middle third of AGC has not yet been decided [43, 44]. For patients with AGC who cannot ensure the proximal margin distance and need total gastrectomy, perioperative chemotherapy can be considered to reduce the tumor stage, strive for partial gastrectomy, improve the completion rate of chemotherapy, improve the overall treatment effect and improve the life quality of patients [9, 25, 45-47].

The results showed that pN3 stage was independent prognostic factor about poor survival of patients with AGC who underwent D2 gastrectomy and received L-OHP plus oral fluorouracil adjuvant chemotherapy. High lymph node metastasis was an important predictor of poor prognosis in patients with AGC [48-51]. SP regimen preoperative chemotherapy was safe and effective for patients with high lymph node metastasis [52-55]. The results of FLOT4 study were better than the previous standard treatment [56-58]. The Chinese study confirmed that it was also safe and feasible for Chinese population to receive perioperative FLOT chemotherapy[59]. Patients with high lymph node metastasis can choose preoperative SP chemotherapy or perioperative FLOT chemotherapy, and randomized controlled clinical trials can be carried out to further improve the prognosis of patients with high lymph node metastasis.

259 **Conclusions**

260 L-OHP plus oral fluorouracil adjuvant chemotherapy was safe and tolerable.
261 Advanced age and total gastrectomy were risk factors for chemotherapy completion.
262 The key to improve the prognosis of patients with AGC after D2 gastrectomy was to
263 improve the completion rate of adjuvant chemotherapy.

264
265 **List of abbreviations**

266

Abbreviation	Full name
AGC	Advanced Gastric Cancer
AJCC/UICC	American Joint Committee on Cancer/ International Union Against Cancer
SOX	S-1 plus Oxaliplatin
XELOX	Capecitabine plus Oxaliplatin
DS	Docetaxel plus S-1
SP	S-1 plus Cisplatin
OS	Overall Survival
DFS	Disease Free Survival
RFS	Relapse Free Survival
CA724	Carbohydrate Antigen 724
CEA	Carcinoembryonic Antigen
D2	Dissection 2

HIMSS EMRAM Medical Record Adoption Model

AST aspartate aminotransferase

ALT alanine aminotransferase

TBIL total bilirubin,

ALP alkaline phosphatase

GGT γ -glutamyl transpeptidase

267

268 **Declarations**

269 **Ethics approval and consent to participate:** This study has been approved by
270 ethics committee of The First Affiliated Hospital of Xiamen University.

271 **Consent for publication:** All presentations of case reports must have consent for
272 publication.

273 **Availability of data and materials:** The datasets used and/or analysed
274 during the current study are available from the corresponding author on
275 reasonable request.

276 **Competing interests:** The authors have declared no conflicts of interest.

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Authors' contributions: Meng-Ting Pan and Yu-Qiang Huang collected and analyzed/interpreted data and drafted the manuscript. Zha-Xi Baima, Hui-Yao Lin and Yu-Fei Ji collected data and revised the manuscript. Ming-Xu Luo analyzed/interpreted data, performed statistical analyses, and revised the manuscript. Bo Chen designed the study, analyzed/interpreted data, and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

The Kaplan-Meier curves for overall survival curve in all patients

Figure 2

OS in the high completion group and low completion group

Figure 3

OS in patients with pN0-2 and pN3

Figure 4

OS in patients with pTNM II stage and pTNM III stage

Figure 5

OS in patients with nerve invasion and non-nerve invasion

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