Medicine®

OBSERVATIONAL STUDY

OPEN

The Efficacy of Taxanes- and Oxaliplatin-Based Chemotherapy in the Treatment of Gastric Cancer After D2 Gastrectomy for Different Lauren Types

Zhen Zheng, MS, Xiance Jin, PhD, Qiuxiang He, MD, Baochai Lin, MS, Huafang Su, MS, Hanbin Chen, MS, Shaoran Fei, MS, Zhenghua Fei, PhD, Guorong Chen, MD, Huangle Pan, BS, Xiaolei Chen, MD, and Congying Xie, PhD

Abstract: To investigate the efficacy of Taxanes- and Oxaliplatin-based chemotherapies (TC and OC) in the treatment of gastric cancer patients after D2 gastrectomy with different Lauren types. In this study, 299 patients of gastric adenocarcinoma with D2 lymph node dissection were reviewed between 2007 and 2014. Chemotherapies were classified as Oxaliplatin-based and Taxanes-based regimen. Treatment outcomes were analyzed according to different Lauren types, such as the intestinal type, diffuse type, and mixed type groups, respectively. The disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The log-rank test was used for univariate analysis, and Cox regression was used for multivariate analysis. In diffuse type gastric cancer, the Oxaliplatin-based arm had a longer median DFS and OS compared with Taxanes-based arm (DFS: 47.0 vs 28.6 months, $P = 0.04$; OS: 51.9 vs 34.5 months, $P = 0.048$). The chemotherapy regimen was an independent prognostic factor for DFS and OS of diffuse type gastric cancer patients by multivariate analysis ($P = 0.01$). In the intestinal type, although the DFS and OS of intestinal type patients in TC group were higher than those in OC group (DFS: 53.4 vs 42.4 months; OS: 69.7 vs 57.8 months), there was no statistical significance observed (both $P > 0.05$). For the mixed type, the 2 different chemotherapy regimens achieved similar median DFS and OS. In a conclusion, the patients of diffuse type were more sensitive to OC, and the intestinal type patients may be benefit from TC. Therefore, it will be of benefit for gastric patients by introducing Lauren classification clinically and to help the choice of chemotherapy regimen for gastric patients after D2 gastrectomy.

(*Medicine* 95(6):e2785)

Abbreviations: CT = computed tomography, DFS = disease-free survival, HFS = hand-foot syndrome, IRI-S = irinotecan plus S-1, OC = Oxaliplatin-based chemotherapy, OS = overall survival, pN-stage = pathological N-stage, pT-stage = pathological T-stage, RFS = relapse-free survival, TC = Taxanes-based chemotherapy, WHO = World Health Organization.

INTRODUCTION

Gastric cancer has become the second leading cause of cancer-related deaths worldwide, and it is particularly common in Eastern Asia.[1,2] In China, gastric cancer is the third most common malignant disease with 463,000 new cases and 352,000 deaths annually, which accounts for about 46.8% of the total new cases and about 47.8% of the total deaths, respectively. Meanwhile, the mortality rate of gastric cancer in China is in rising for the past 20 years.[3]

Surgical resection is accepted as the gold standard and the primary curative treatment modality for patients with early stage gastric cancer.[4,5] D2 lymphadenectomy is recommended for patients with resectable gastric cancer worldwide.[6] Studies from Japan and Korea demonstrated a low postoperative morbidity and mortality rate, as well as rare locoregional recurrence in the treatment of gastric cancer patients with D2 gastrectomy as a standard surgical procedure.[7] Although the diagnosis and treatment for gastric cancer has been improved over the past few decades, the disease still has a very poor prognosis and remains a major health problem. Partly due to lots of patients are diagnosed in an advanced stage.

During the past 2 decades, multiple randomized, controlled trials and meta-analyses had demonstrated a modest but significant survival benefit associated with postoperative adjuvant chemotherapy with various regimes.[8–13] As a third-generation platinum, Oxaliplatin and Taxanes have been suggested to decrease the risk of relapse and improve the survival and quality of life for patients with gastric cancer.[14–19]

Currently, the treatment choice and decision for gastric cancer patients are mainly based on tumor pathology according to the World Health Organization classification. Meanwhile, Lauren classification, which was established by the organizational structure and biological behavior of gastric cancer, plays a very important role in helping us understanding the pathogenesis and biological behaviors of gastric cancer.[20] To the best of our knowledge, few studies have evaluated the efficacy of different adjuvant chemotherapies for gastric cancer patients after D2 gastrectomy related to different Lauren types. The purpose of this study is to investigate the efficacy of Oxaliplatin- and Taxanes-based adjuvant chemotherapies in the treatment of gastric cancer after D2 gastrectomy according to different Lauren types.

Editor: Huitao Fan.
Received: October 8, 2015; revised: December 29, 2015; accepted: January 18, 2016.
From the Departments of Radiotherapy and Chemotherapy (ZZ, XJ, BL, HS, HC, SF, ZF, HP, CX), Pathology (QH, GC), and Gastrointestinal Surgery (XC), The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, P.R. China.
Correspondence: Xiaolei Chen, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, P.R. China (e-mail: chenxiaolei2@sina.com).
Congying Xie, Department of Radiotherapy and Chemotherapy, The First Affiliated Hospital of Wenzhou Medical College, Fuxue Road No. 2, Wenzhou, Zhejiang, P.R. China (e-mail: wzxiecongying@163.com).
ZZ and XJ have contributed equally.
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002785

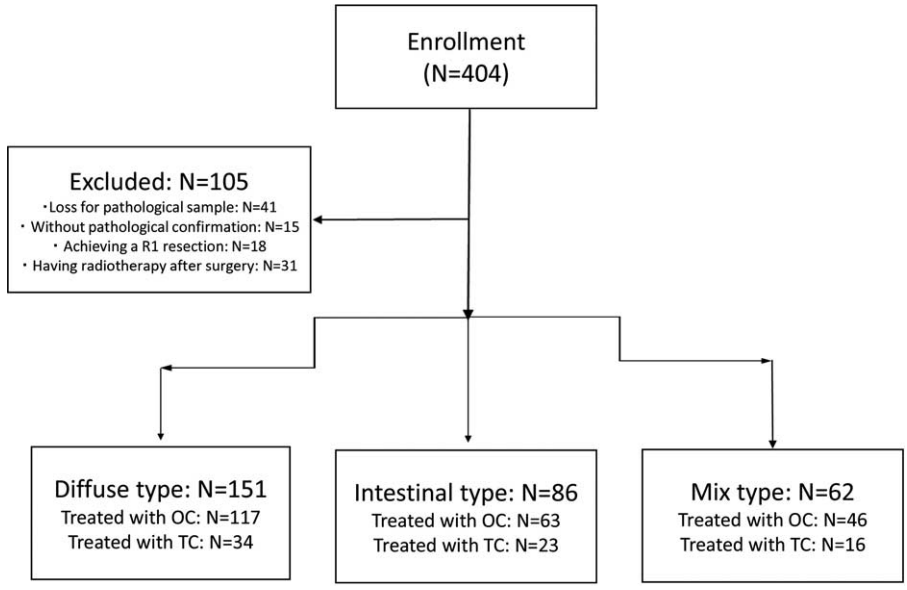

FIGURE 1. Inclusion and exclusion criteria flow diagram of all patients.

MATERIALS AND METHODS

Patients and Clinicopathological Characteristics

Over 400 gastric cancer patients underwent postoperative chemotherapies from July 2007 to May 2014 at the First Affiliated Hospital of Wenzhou Medical University were retrospectively reviewed in this study. The study design and the inclusion and exclusion criteria were presented by a flow diagram in Figure 1. The eligibility criteria of the patients for this study were as follows: histologically or cytologically confirmed gastric adenocarcinoma; underwent extensive (D2) lymph node dissection with no residual malignant disease and achieved R0 resection; adequate function of major organs (including cardiac, hepatic, and renal function) and hematologic function (absolute neutrophil $\geq 1.5 \times 10^9$/L or platelet count $\geq 100 \times 10^9$/L); had no uncontrolled morbidities (eg, myocardial infarction in the last 12 months); Eastern Cooperative Oncology Group performance status of 0 or 1.

TABLE 1. Characteristics of Diffuse Type Gastric Cancer Patients

Characteristics	Total (%)	OC (%)	TC (%)	*P*
All patients	151 (100)	117 (100)	34 (100)	
Gender				
Female	46 (30.5)	34 (63.1)	12 (60.1)	
Male	105 (69.5)	83 (36.9)	22 (39.9)	0.49
Age				
≤60	83 (55.0)	64 (54.7)	19 (55.9)	
>60	68 (45.0)	53 (45.3)	15 (44.1)	0.90
Tumor location				
Other sites	64 (42.4)	46 (39.3)	18 (52.9)	
Antrum	87 (57.6)	71 (60.7)	16 (47.1)	0.16
Differentiation				
Poorly differentiated	148 (98.0)	114 (97.4)	34 (100)	
Well differentiated	3 (2.0)	3 (2.6)	0 (0.0)	>0.99
pT-stage				
pT 1 + 2 + 3	79 (52.3)	62 (53.0)	17 (50)	
pT 4	72 (47.7)	55 (47.0)	17 (50)	0.76
pN-stage				
pN 1 + 2	98 (64.9)	77 (64.1)	21 (50.8)	
pN 3	53 (35.1)	40 (35.4)	13 (49.2)	0.66
TMN stage				
Stage IB + II	42 (27.8)	33 (28.2)	9 (26.5)	
Stage III + IV	109 (72.1)	84 (71.8)	25 (73.5)	0.84

OC = Oxaliplatin-based chemotherapies, pN = pathological N-stage, pT = pathological T-stage, TC = Taxanes-based chemotherapies.

The purpose of this study is to investigate the efficacy of Oxaliplatin- and Taxanes-based adjuvant chemotherapies in the treatment of gastric cancer after D2 gastrectomy. So, patients with stage IA or IB (T2aN0) disease (according to the American Joint Committee on Cancer 2002 staging system), positive resection margin, and involvement of M1 lymph node or distant metastases were excluded from the study. Patients with multimodal treatment before surgery, lost to follow-up, and died within 1 month after surgery were also excluded from the analysis. This study was approved by the Institutional Review Board and performed at the First Affiliated Hospital of Wenzhou Medical University.

Patients' gender, age at diagnosis, tumor location, tumor differentiation, pathological T-stage (pT-stage), pathological N-stage (pN-stage), stage of the disease (the TNM staging system of the International Union Against Cancer), and the type of chemotherapies administered in each group were recorded. The specimens for Lauren classification of each patient were obtained by either diagnostic or surgical procedures.

Lauran Classification and Chemotherapy

Patients were divided into 3 groups based on the Lauren classification such as the intestinal group, the diffuse group, and mixed group. Each case was independently reviewed by 2 pathologists called upon to confirm the diagnosis of intestinal or diffuse gastric cancer according to the Lauren classification. For each Lauran type classification, the patients were divided into 2 subgroups according to 2 chemotherapy schemes administered, which were Oxaliplatin-based chemotherapy (OC) and Taxanes-based chemotherapy (TC). The OC included XELOX (OXA: 130 mg/m^2 per d1 IV, Xeloda 1000 mg/m^2 PO Bid, d1–14 q3w), FOLFOX6 (OXA 85 mg/m^2 per d1, 5-Fu 400 mg/m^2 D1, 5-Fu 2400 mg/m^2 CIV 46 h, CF 400 mg/m^2 per d1 q2w), FLOFOX4 (OXA 85 mg/m^2 per d1, 5-Fu 400 mg/m^2 IV, D1–2, 5-Fu 600 mg/m^2 CIV 22 h, D1–2, CF 200 mg/m^2 per d1). The TC included Paclitaxel (135–175 mg/m^2 per d1 IV) plus DDP (25 mg/m^2 IV, D1–3) every 21 days, Paclitaxel (135–175 mg/m^2 per d1 IV) plus Xeloda (1000 mg/m^2 Bid d1–14) or S-1 (40–60 mg Bid PO, D1–14) every 21 days.

Matches were chosen based on age, sex, location of the tumor, tumor differentiation, pathological T-stage, pathological N-stage, and TNM stage for these 2 arms. Matching was done using a semiautomated method with Microsoft Access (Microsoft Corp., Redmond, WA) without knowledge of outcomes.

Follow-Up and Statistical Analysis

A blood test for toxicity was administered during the adjuvant chemotherapy. Re-evaluation during follow-up was done once per 3 months within the first 2 years, once per half year in the 3rd year and once per year from the 4th year after the treatment, which includes physical examination, a complete blood count measurement, liver function test, chest computed tomography (CT) scan, and abdominal CT scan. Toxicity was graded according to National Cancer Institute common terminology criteria for adverse events (CTCAE version 3.0).

The primary endpoint of our study was disease-free survival (DFS) and overall survival (OS). OS was measured from the date of diagnosis to death or the last follow-up visit. DFS was calculated from the date of surgery to the time of the first local or distant recurrence, or death from any cause. Local recurrence was defined as tumor regrowth in hilar, mediastinal, or supraclavicular lymph nodes, or at the bronchial margin of resection, as demonstrated on CT scan. Recurrences beyond those sites were defined as distant metastases.

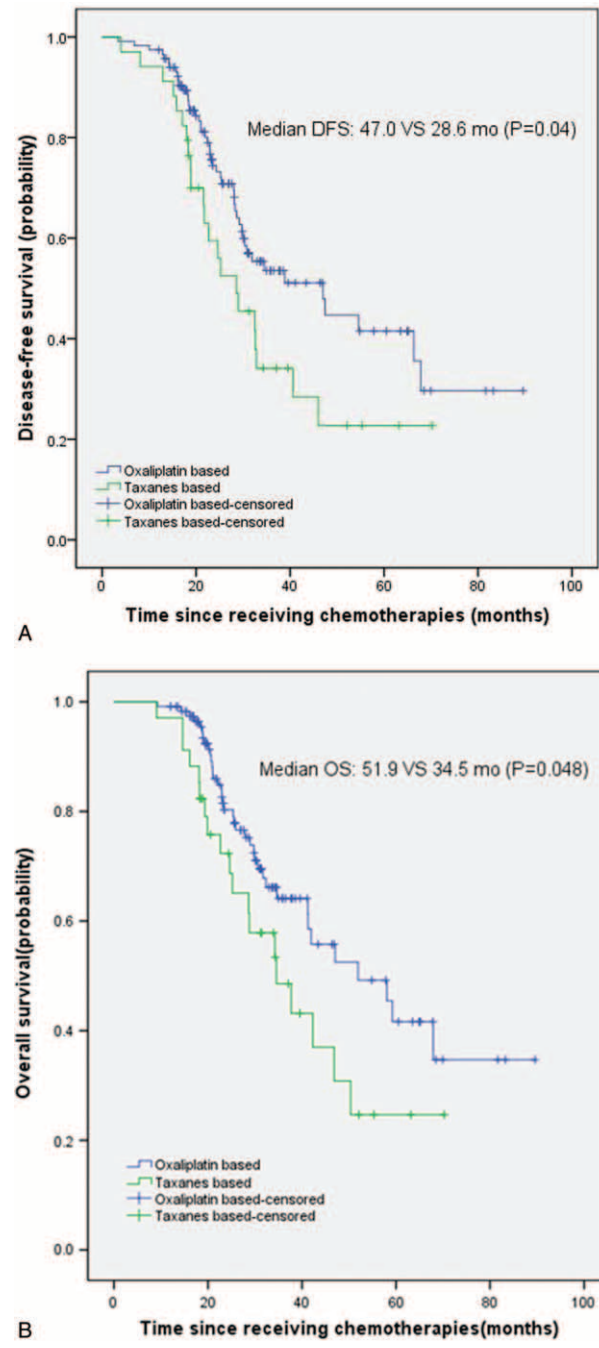

FIGURE 2. Progression-free survival (A) and overall survival (B) of diffuse type patients.

The chi-squared analysis was used for the patients' baseline and the potentially influential factors analysis. Kaplan–Meier method and log-rank test were applied to evaluate the DFS and OS.[21] Multivariate analysis on the factors influenced DFS and OS was carried out with Cox regression. All statistical analyses were conducted with the SPSS 17.0 software (SPSS Inc., Chicago, IL). Differences were considered statistically significant for $P < 0.05$.

TABLE 2. Univariate and Multivariate Analyses for DFS and OS of Diffuse Type Gastric Cancer Patients

	DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
Parameters	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Gender	0.09	1.43 (0.81–2.54)	0.22	0.11	1.45 (0.77–2.74)	0.25
Age	0.27	1.20 (0.72–2.00)	0.49	0.10	1.43 (0.82–2.50)	0.21
Tumor location	0.008	0.55 (0.34–0.90)	0.02	0.007	0.47 (0.27–0.82)	0.008
Differentiation	0.57	0.67 (0.09–4.91)	0.69	NA	0.78 (0.11–5.81)	0.81
pT-stage	<0.001	2.05 (1.18–3.54)	0.01	<0.001	1.91 (1.07–3.42)	0.03
pN-stage	<0.001	2.32 (1.32–4.07)	0.003	<0.001	2.37 (1.25–4.46)	0.008
TMN stage	<0.001	2.28 (1.00–5.18)	<0.05	<0.001	2.58 (1.03–6.42)	0.04
Chemotherapy regimen	0.04	0.48 (0.28–0.84)	0.009	0.048	0.48 (0.27–0.86)	0.01

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, NA = not available, OS = overall survival, pN = pathological N-stage, pT = pathological T-stage.

RESULTS

There were total of 404 patients of gastric adenocarcinoma had D2 gastrectomy between July 2007 and May 2014 in our hospital. There were 105 patients excluded from the study, in which, 56 patients were due to the loss of pathological samples or without pathological confirmation, 18 patients were because of R1 resection, and 31 patients were due to received radiotherapy after surgery. For the enrolled 299 patients, the number of patients in the diffuse type, intestinal type, and mixed type groups were 151 (50.5%), 86 (28.8%), and 62 (20.7%), respectively (Figure 1). A median of 5-cycle chemotherapy was administered (range 2–12).

Outcome of the Diffuse Type Gastric Adenocarcinoma

Detailed characteristics of 151 diffuse type patients were presented in Table 1 with a median age of 58 years (range 32–80) and a median of 5-cycle chemotherapy(range 2–12), in which 117 patients were in the OC group and 34 in the TC group. The median DFS and OS comparison were presented in Figure 2A and B with an average median DFS and OS for all the diffuse type gastric cancer patients of 32.8 months (95% confidence interval [CI] 23.6–42.0) and 46.8 months (95% CI 38.5–55.2), respectively. The OC group achieved a significantly longer DFS and OS compared with TC group

TABLE 3. Characteristics of Intestinal Type Patients

Characteristics	Total (%)	OC (%)	TC (%)	*P*
All patients	86 (100)	63 (100)	23 (100)	
Gender				
Female	19 (22.1)	14 (22.2)	5 (21.7)	
Male	67 (77.9)	49 (77.8)	18 (78.3)	0.96
Age				
≤60	36 (41.9)	25 (39.7)	11 (47.8)	
>60	50 (58.1)	38 (60.3)	12 (52.2)	0.50
Tumor location				
Other sites	40 (46.5)	28 (44.4)	12 (52.2)	
Antrum	46 (53.5)	35 (55.6)	11 (47.8)	0.53
Differentiation				
Poorly differentiated	43 (50.0)	30 (47.6)	13 (56.5)	
Well differentiated	43 (50.0)	33 (52.4)	10 (43.5)	0.47
pT-stage				
pT 1 + 2 + 3	46 (53.5)	34 (54.0)	12 (52.2)	
pT 4	40 (46.5)	29 (46.0)	11 (47.8)	0.88
pN-stage				
pN 1 + 2	65 (75.6)	47 (72.3)	18 (78.3)	
pN 3	21 (24.4)	16 (27.7)	5 (21.7)	0.73
TMN stage				
Stage IB + II	33 (38.4)	24 (27.9)	9 (39.1)	
Stage III + IV	53 (61.6)	39 (72.1)	14 (60.9)	0.93

OC = Oxaliplatin-based chemotherapies, pN = pathological N-stage, pT = pathological T-stage, TC = Taxanes-based chemotherapies.

(DFS: 47.0 vs 28.6 months, $P = 0.04$; OS: 51.9 vs 34.5 months, $P = 0.048$), respectively.

Table 2 shows the detailed univariate and multivariate analyses for the DFS and OS of diffuse type gastric cancer patients. Multivariate analysis revealed that tumor location ($P = 0.02$), pT-stage ($P = 0.01$), pN-stage ($P = 0.03$), TNM stage ($P < 0.05$), and chemotherapy regimen ($P = 0.009$) were independent predictors for the DFS. The tumor location ($P = 0.008$), pT-stage ($P = 0.03$), pN-stage ($P = 0.008$), TNM stage ($P = 0.04$), and chemotherapy regimen ($P = 0.01$) were correlated with OS.

Outcome of the Intestinal Type Gastric Adenocarcinoma

Table 3 shows the detailed characteristics for 86 intestinal type gastric cancer patients with a median of 5-cycle chemotherapy (range 2–9). The median age of these 86 patients was 62 years (range 33–80), in which 63 patients was in OC group and 23 patients in TC group. The DFS and OS of intestinal type patients were presented in Figure 3A and B with a median DFS of 39.2 months (95% CI 22.9–56.4) and a median OS of 64.2 months (95% CI 40.2–88.3), respectively. There was no significant difference on DFS (42.4 vs 53.3 months, $P = 0.33$) and OS (57.8 vs 69.7 months, $P = 0.44$) between OC and TC groups for intestinal type gastric patients.

Table 4 shows the univariate and multivariate analysis on DFS and OS for intestinal type gastric patients. Multivariate analysis indicated that gender ($P = 0.01$) and pN-stage ($P = 0.03$) were independent predictors for DFS. The gender ($P = 0.01$) and tumor differentiation state ($P = 0.008$) were correlated with OS.

Outcome of the Mixed Type Gastric Adenocarcinoma

The characteristics of 62 mixed type gastric cancer patients were shown in Table 5 with a median chemotherapy cycle of 5 (range 2–8). The median age of mixed type patients was 60 years (range 36–84 years), in which 46 was in OC group and 16 in TC group. Figure 4A and B presented the DFS and OS for mixed type gastric cancer patients with an average median DFS and OS of 45.1 months (95% CI 30.7–59.6) and 59.5 months (95% CI 29.3–89.7), respectively. The OC group achieved a higher DFS than TC group (57.5 vs 45.1 months, $P = 0.57$) but without statistical significance. The OS was similar for these 2 groups (59.5 vs 50.1 months, $P = 0.75$). Univariate and multivariate analyses on factors influence the DFS and OS for mixed type patients were presented in Table 6. Only TNM stage was indicated as an independent predictor for DFS ($P = 0.006$) and OS ($P = 0.04$) of mixed type gastric cancer patients.

Toxicity

The comparison of side efficacies between OC and TC groups in the treatment of different Lauren type gastric cancer patients after D2 gastrectomy was shown in Table 7. The most frequent hematologic side effects for all the gastric cancer patients were anemia (81.3%), neutropenia (74.6%), and thrombocytopenia (18.1%). The most common nonhematologic toxicities were nausea (88.6%), hand-foot syndrome (HFS; 47.8%), and vomiting (42.8%). Neutropenia had the highest rate of Grade III/IV toxicity (30.4%).

In the diffuse type gastric cancer patients, the patients in OC group had a higher rate of Grade III/IV neutropenia (41.9% vs 26.5%) and Grade II/III HFS (20.5% vs 0%) compared with those in TC group. In the intestinal type of gastric cancer patients, the OC group patients also had a higher rate of Grade III/IV neutropenia (30.2% vs 17.4%) and Grade II/III HFS (17.5% vs 0%) compared with TC group patients. Similarly, the OC group patients in the mixed type of gastric cancer had a higher rate of Grade III/IV neutropenia (21.8% vs 0%) and Grade II/III HFS (17.3% vs 0%) compared with TC group patients. On the whole, all the toxicity was tolerant after symptomatic treatments, and was generally brief, reversible, and manageable.

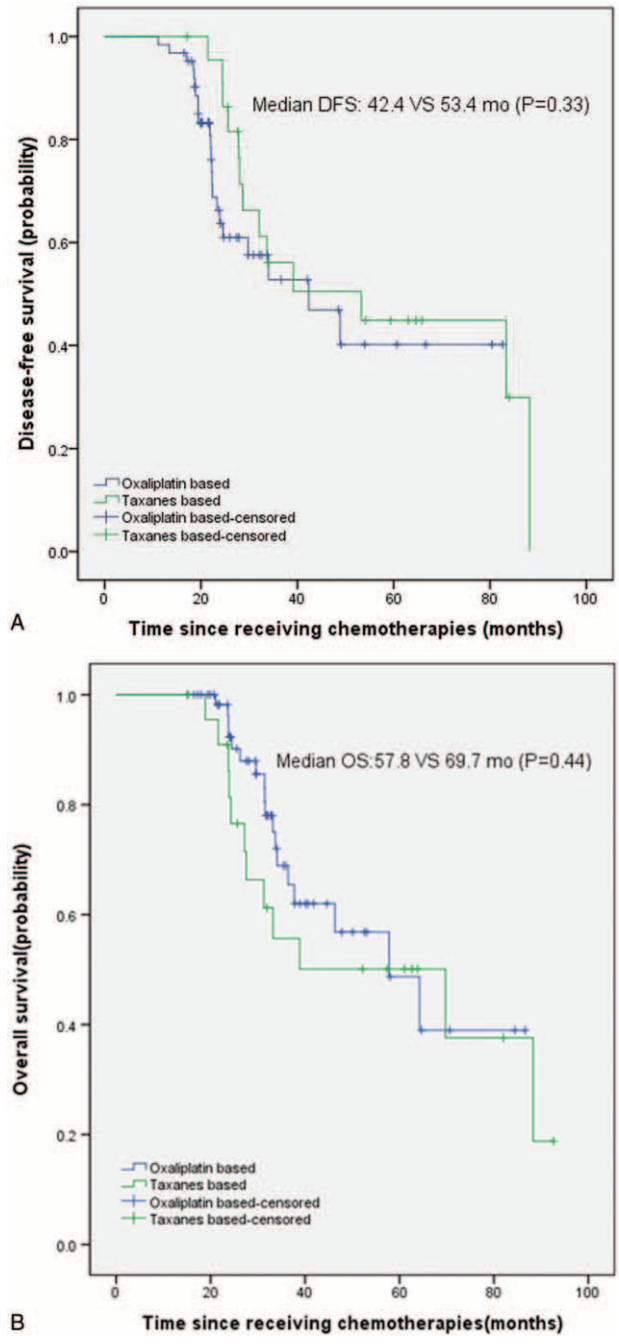

FIGURE 3. Progression-free survival (A) and overall survival (B) of intestinal type patients.

TABLE 4. Univariate and Multivariate Analyses for DFS and OS of Intestinal Type Gastric Cancer Patients

	DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
Parameters	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Gender	0.15	3.45 (1.27–9.41)	0.01	0.04	6.10 (1.38–26.99)	0.01
Age	0.32	1.34 (0.65–2.78)	0.43	0.22	1.76 (0.77–3.99)	0.17
Tumor location	0.92	1.02 (0.50–2.09)	0.96	0.85	0.71 (0.32–1.54)	0.38
Differentiation	0.15	0.50 (0.24–1.05)	0.06	0.02	0.32 (0.14–0.74)	0.008
pT-stage	0.005	1.77 (0.73–4.30)	0.20	0.03	1.52 (0.59–3.90)	0.38
pN-stage	0.01	2.35 (1.05–5.28)	0.03	0.06	1.87 (0.75–4.64)	0.17
TMN stage	0.01	2.28 (0.72–7.21)	0.16	0.008	2.07 (0.63–6.81)	0.23
Chemotherapy regimen	0.33	1.89 (0.87–4.09)	0.10	0.44	0.80 (0.37–1.76)	0.58

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, pN = pathological N-stage, pT = pathological T-stage.

DISCUSSION AND CONCLUSIONS

Although the Lauren classification system dates back to 1965, it is still widely accepted and employed by pathologists and physicians today.[20] Lauran classification had also been demonstrated to be a prognostic factor for gastric cancer.[22] Several studies have indicated that patients with intestinal type tumors had a better outcome than those with diffuse type tumors.[23–25] This was confirmed by our study in which the average median OS of diffuse type gastric cancer patients was 46.8 months compared with those of intestinal type patients of 64.2 months.

However, few studies had investigated the efficacy of adjuvant chemotherapy in the treatment of gastric cancer after D2 gastrectomy according different Lauran classification. In this study, a total of 299 gastric cancer patients after D2 gastrectomy were sorted by Lauren classification and subdivided into OC and TC groups for chemotherapy. Our study suggested that the diffuse type of gastric cancer patients was more sensitive to OC than TC. No significant difference in intestinal type and mixed type patients was observed. There were total of 237 diffuse type and intestinal type patients, accounting for 79.3% of the total 299 enrolled gastric cancer

TABLE 5. Characteristics of Mixed Type Gastric Cancer Patients

Characteristics	Total (%)	OC (%)	TC (%)	*P*
All patients	62 (100)	46 (100)	16 (100)	
Gender				
Female	9 (14.5)	6 (13.0)	3 (18.8)	
Male	53 (85.5)	40 (87.0)	13 (81.2)	0.58
Age				
≤60	26 (41.9)	21 (45.7)	5 (31.3)	
>60	36 (58.1)	25 (53.3)	11 (78.7)	0.32
Tumor location				
Other sites	19 (30.6)	17 (37.0)	2 (12.5)	
Antrum	43 (69.4)	29 (63.0)	14 (87.5)	0.06
Differentiation				
Poorly differentiated	58 (93.5)	44 (95.7)	14 (87.5)	
Well differentiated	4 (6.5)	2 (4.3)	2 (12.5)	0.27
pT-stage				
pT 1 + 2 + 3	35 (56.5)	29 (56.5)	6 (37.5)	0.08
pT 4	27 (43.5)	17 (43.5)	10 (62.5)	
pN-stage				
pN 1 + 2	45 (72.6)	34 (73.9)	11 (78.7)	
pN 3	17 (27.4)	12 (26.1)	5 (31.3)	0.69
TMN stage				
Stage IB + II	19 (30.6)	14 (30.4)	5 (31.3)	>0.99
Stage III + IV	43 (69.4)	32 (69.6)	11 (78.7)	

OC = Oxaliplatin-based chemotherapies, pN = pathological N-stage, pT = pathological T-stage, TC = Taxanes-based chemotherapies.

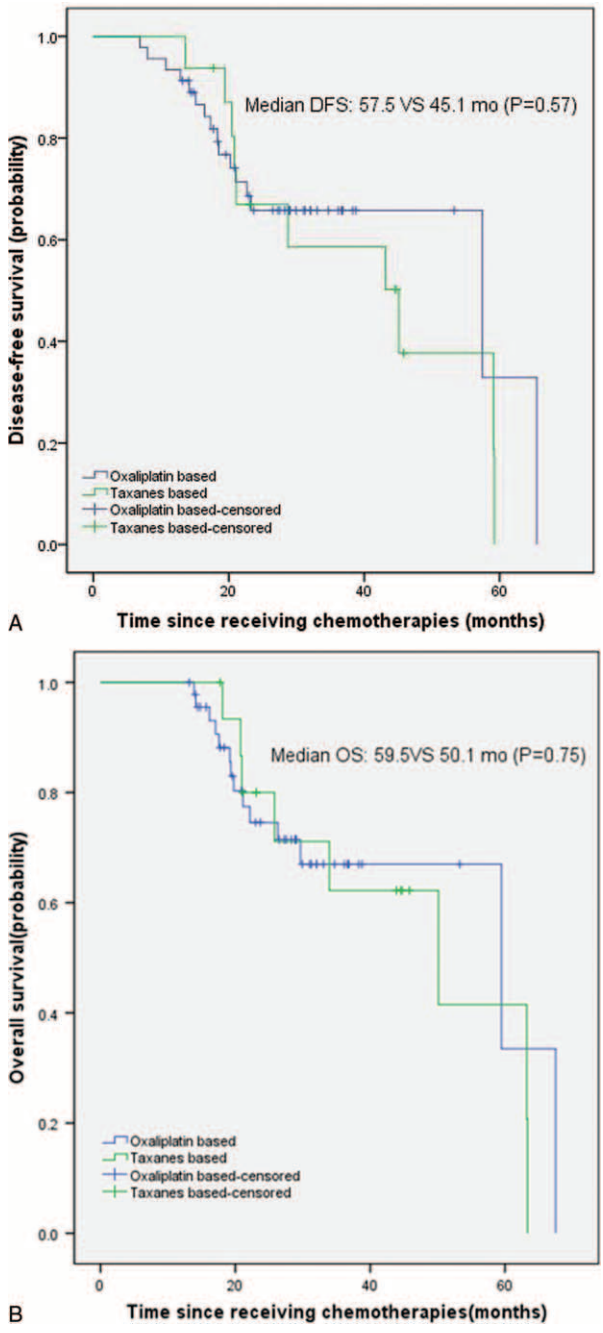

FIGURE 4. Progression-free survival (A) and overall survival (B) of mixed type patients.

patients. This was also consistent with previously reported statement that diffuse and intestinal types could account for approximately 85% of gastric carcinomas, and the remainder comprised mixed types and other less common histologies.[20]

Up to now, the mainstay of treatment for gastric cancer is surgery. D2 lymphadenectomy had been reported to improve outcomes of gastric cancer patients according to some Japanese and South Korean randomized trials.[26] In recent years, some studies demonstrated that gastric cancer after D2 gastrectomy obtain a benefit from adjuvant chemotherapy.[12,27,28] Although there is still a lack of consensus regarding the efficacy of different chemotherapies on gastric cancer, evidence suggests that Lauren classification may be a good predictor for gastric cancer patients after D2 resection.[29,30] The GC0301/TOP-002 study demonstrated that patients with unresectable or recurrent gastric adenocarcinoma, IRI-S (irinotecan plus S-1) was significantly more effective than S-1 monotherapy for patients with diffuse type histology (HR 0.632, 95% CI 0.454–0.880).[29] Ema et al[30] also reported that in Stage II/III gastric cancer underwent D1–D2 lymph node dissection and subsequent S-1 treatment, there was a difference on the 5-year relapse-free survival (RFS) based on Lauren classification, in which the RFS of diffuse type was 78.4% compared with that of 54.3% of intestinal type ($P = 0.049$), multivariate analysis revealed that Lauren classification was an independent predictors of prognosis ($P = 0.02$). Consistently, our results indicated that Lauren classification is an independent predictor for chemotherapy in the treatment of gastric cancer patients after D2 gastrectomy. As shown in our study, in diffuse type gastric cancer, the OC group patients had a longer median DFS (47.0 vs 28.6 months, $P = 0.04$) and OS (51.9 vs 34.5 months, $P = 0.048$) compared with those in TC group. This was also confirmed by the multivariate analysis on DFS and OS: chemotherapy regimen was an independent predictor for both DFS and OS for diffuse type gastric cancer patients as shown in Table 2.

For intestinal type gastric cancer patients, the ARTIST trail reported that subgroup analyses showed that gastric cancer patients with intestinal type may gain a potential benefit in 3-year DFS rate from the addition of radiotherapy to adjuvant chemotherapy (94% vs 83%; $P = 0.01$), although there were no significant differences between the adjuvant chemotherapy and the adjuvant chemoradiotherapy in terms of the DFS ($P = 0.09$) and OS ($P = 0.53$) for the all gastric cancer patients. Unfortunately, in our study, although the DFS and OS of intestinal type patients in TC group were higher than those in OC group (DFS: 53.3 vs 42.4 months; OS: 69.7 vs 57.8 months), there was no statistical significance observed. We speculated that the reasons may due to the higher proportion of patients with TNM stage (III + IV) and a relatively short follow-up time in our study. There was also no significant difference on chemotherapy efficacy between OC and TC groups for mixed type gastric cancer patients in our study.

The sensitive of diffuse type gastric cancer to OC shown in our result may be associated with discriminative biologic characteristics of different Lauren types. The intestinal type is characterized by the cohesive cells that form gland-like structures. For the diffuse type, tumor cells lack cell-to-cell interactions and infiltrate the stroma as single cells or small subgroups, leading to a population of noncohesive, scattered tumor cells,[20] which may make the diffuse type more insensitive to the OC compared with the TC. Many studies demonstrated that the difference between Lauren types in the molecular characteristics may be responsible for the survival variation.[31–34] Xie et al[35] reported that in MGC-803 cells, CD44, a tumor stem cell surface marker, antagonized Oxaliplatin-induced apoptosis, and Lauren classification was 1 of the risk factors for the positive CD44v6 expression. Hence, the difference of CD44v6 expression between Lauren types may provide a direction to explain why diffuse type is more sensitive to OCs compared with TCs.

It has been reported that the incidence of gastric cancer are falling, mainly due to the decrease in the intestinal type;

TABLE 6. Univariate and Multivariate Analyses for DFS and OS of Mixed Type Gastric Cancer Patients

	DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate	
Parameters	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Gender	0.72	1.13 (0.36–3.56)	0.84	0.88	1.23 (0.33–4.57)	0.75
Age	0.73	1.73 (0.68–4.35)	0.25	0.61	2.03 (0.71–6.83)	0.19
Tumor location	0.37	2.33 (0.79–6.89)	0.13	0.62	2.00 (0.64–6.25)	0.23
Differentiation	0.32	1.53 (0.36–6.60)	0.57	0.20	2.36 (0.48–11.56)	0.29
pT-stage	0.06	0.74 (0.27–1.98)	0.54	0.07	0.76 (0.25–2.33)	0.63
pN-stage	0.03	1.49 (0.58–3.45)	0.41	0.019	2.15 (0.71–6.58)	0.18
TMN stage	0.001	11.62 (2.00–68.41)	0.006	0.006	7.07 (1.12–44.55)	0.04
Chemotherapy regimen	0.57	1.55 (0.62–3.88)	0.35	0.75	1.22 (0.45–3.45)	0.70

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, pN = pathological N-stage, pT = pathological T-stage.

TABLE 7. Detailed Toxicity Results of Different Lauran Type Gastric Cancer Patients

Toxicity, N (%)	Nausea	Vomiting	Diarrhea	Stomatitis	Dizziness	HFS	Anemia	Neutropenia	Thrombocytopenia
Diffuse type									
OC (n = 117)									
Grade I	64 (54.7)	35 (29.9)	46 (39.3)	33 (28.2)	38 (32.5)	52 (44.4)	66 (56.4)	18 (15.4)	17 (14.5)
Grade II	35 (29.9)	11 (9.4)	10 (8.5)	7 (6.0)	3 (2.6)	18 (15.4)	35 (29.9)	42 (35.9)	3 (2.6)
Grade III	17 (14.5)	6 (5.1)	4 (3.4)	3 (2.6)	1 (0.9)	6 (5.1)	4 (3.4)	44 (37.6)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	1 (0.9)	5 (4.3)	0 (0.0)
TC (n = 34)									
Grade I	17 (50.0)	11 (32.4)	13 (38.2)	10 (29.4)	12 (35.3)	3 (8.8)	15 (44.1)	5 (14.7)	6 (17.6)
Grade II	8 (23.5)	4 (11.8)	3 (8.8)	3 (8.8)	2 (5.9)	0 (0.0)	9 (26.5)	12 (35.5)	2 (5.9)
Grade III	5 (14.7)	2 (5.9)	1 (2.9)	0 (0.0)	1 (2.9)	0 (0.0)	2 (5.9)	9 (26.5)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal type									
OC (n = 63)									
Grade I	30 (47.6)	17 (27.0)	26 (41.3)	17 (25.4)	22 (34.9)	25 (39.7)	35 (55.6)	7 (11.1)	8 (12.7)
Grade II	17 (27.0)	5 (7.9)	6 (9.5)	3 (4.8)	2 (3.2)	8 (12.7)	19 (30.2)	17 (30.0)	2 (3.2)
Grade III	8 (12.7)	3 (4.8)	2 (3.2)	1 (1.6)	0 (0.0)	3 (4.8)	2 (3.2)	18 (28.6)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (1.6)	0 (0.0)
TC (n = 23)									
Grade I	10 (43.5)	6 (26.1)	8 (34.8)	6 (26.0)	7 (30.4)	1 (4.3)	9 (39.1)	3 (13.0)	3 (13.0)
Grade II	4 (17.4)	2 (8.7)	2 (8.7)	2 (8.7)	2 (8.7)	0 (0.0)	4 (17.4)	6 (26.1)	1 (4.3)
Grade III	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.3)	4 (17.4)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	0 (0.0)
Mixed type									
OC (n = 46)									
Grade I	21 (45.7)	12 (26.1)	17 (40.0)	10 (21.7)	10 (21.7)	19 (41.3)	23 (50.0)	7 (15.2)	5 (10.9)
Grade II	12 (26.1)	4 (8.7)	3 (6.5)	2 (4.3)	1 (2.2)	6 (13.0)	10 (21.7)	10 (21.7)	2 (4.3)
Grade III	5 (10.9)	2 (4.3)	1 (2.2)	0 (0.0)	1 (2.2)	2 (4.3)	1 (2.2)	9 (19.6)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (2.2)	0 (0.0)
TC (n = 16)									
Grade I	5 (31.3)	6 (37.5)	7 (43.8)	3 (18.8)	7 (43.8)	0 (0.0)	5 (31.5)	3 (18.8)	5 (31.5)
Grade II	2 (12.5)	2 (12.5)	3 (18.8)	2 (12.5)	2 (12.5)	0 (0.0)	2 (12.5)	2 (12.5)	0 (0.0)
Grade III	2 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	0 (0.0)

HFS = hand-foot syndrome, OC = Oxaliplatin-based chemotherapies, TC = Taxanes-based chemotherapies.

however, the diffuse type had become increasingly prevalent.[36,37] And it has been mentioned that diffuse type has worse outcomes than other histological subtypes of gastric cancer and is more frequently in women and younger patients.[38] According to our study, the patients of diffuse type were more sensitive to OC, and the intestinal type patients may be benefit from TC. Therefore, it will be of benefit for gastric patients by introducing Lauren classification clinically and to help the choice of chemotherapy regimen for gastric patients after D2 gastrectomy.

One limitation of present study is that it is a retrospective methodology from a single-institution experience. The impact of various treatments related outcome could not be fully evaluated. The number of patients enrolled may be not sufficient enough and the follow-up duration of the study may be not long enough. External validation by using other large database for evaluating the prognostic effect of Lauren classification would be of value to further explore benefit of Lauren classification in the treatment of gastric cancer after D2 gastrectomy and to investigate the mechanism of different prognosis between diffuse type and intestinal type gastric carcinoma.

ACKNOWLEDGMENTS

The study was supported by a grant from the Wenzhou Municipal Science and Technology Bureau (H20100068).

REFERENCES

1. Moore MA, Eser S, Igisinov N, et al. Cancer epidemiology and control in North-Western and Central Asia—past, present and future. *Asian Pac J Cancer Prev.* 2010;11(Suppl 2):17–32.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
3. Zou XN, Sun XB, Chen WQ, et al. Analysis of incidence and mortality of stomach cancer in China from 2003 to 2007. *Tumor.* 2012;32:109–114.
4. O'Connor KG. Gastric cancer. *Semin Oncol Nurs.* 1999;15:26–35.
5. Wu HL, Tian Q, Peng CW, et al. Multivariate survival and outcome analysis of 154 patients with gastric cancer at a single Chinese institution. *Asian Pac J Cancer Prev.* 2011;12:3341–3345.
6. Fujitani K. Overview of adjuvant and neoadjuvant therapy for resectable gastric cancer in the East. *Dig Surg.* 2013;30:119–129.
7. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Group study 9501. *J Clin Oncol.* 2004;22:2767–2773.
8. Janunger KG, Hafstrom L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. *Eur J Surg.* 2002;168:597–608.
9. Panzini I, Gianni L, Fattori PP, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori.* 2002;88:21–27.
10. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355:11–20.
11. Group G, Paoletti X, Oba K, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *Jama.* 2010;303:1729–1737.
12. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol.* 2011;29:4387–4393.
13. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715–1721.
14. Ajani JA, Pazdur R, Dumas P, et al. Phase II study of prolonged infusion of Taxol in patients with metastatic colorectal carcinoma. *Invest New Drugs.* 1998;16:175–177.
15. Bang YJ, Kang WK, Kang YK, et al. Docetaxel 75 mg/m(2) is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. *Jpn J Clin Oncol.* 2002;32:248–254.
16. Keam B, Im SA, Han SW, et al. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer.* 2008;8:148.
17. Liu ZF, Guo QS, Zhang XQ, et al. Biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX-4 regimen) as first-line chemotherapy for elderly patients with advanced gastric cancer. *Am J Clin Oncol.* 2008;31:259–263.
18. Zhao JG, Qiu F, Xiong JP, et al. A phase II study of modified FOLFOX as first-line chemotherapy in elderly patients with advanced gastric cancer. *Anticancer Drugs.* 2009;20:281–286.
19. Fujitani K, Tamura S, Kimura Y, et al. Three-year outcomes of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy. *Gastric Cancer.* 2014;17:348–353.
20. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand.* 1965;64:31–49.
21. Zhou ZY, Xu L, Li HG, et al. Chemotherapy in conjunction with traditional Chinese medicine for survival of elderly patients with advanced non-small-cell lung cancer: protocol for a randomized double-blind controlled trial. *J Integr Med.* 2014;12:175–181.
22. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med.* 2013;11:58.
23. Tanner M, Hollmen M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol.* 2005;16:273–278.
24. Yamashita K, Sakuramoto S, Katada N, et al. Diffuse type advanced gastric cancer showing dismal prognosis is characterized by deeper invasion and emerging peritoneal cancer cell: the latest comparative study to intestinal advanced gastric cancer. *Hepato-Gastroenterology.* 2009;56:276–281.
25. Zheng H, Takahashi H, Murai Y, et al. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: an immunostaining study on the tissue microarray. *J Clin Pathol.* 2007;60:273–277.
26. Schmidt B, Yoon SS. D1 versus D2 lymphadenectomy for gastric cancer. *J Surg Oncol.* 2013;107:259–264.
27. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810–1820.
28. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet.* 2012;379:315–321.
29. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer.* 2011;14:72–80.

30. Ema A, Yamashita K, Sakuramoto S, et al. Lymph node ratio is a critical prognostic predictor in gastric cancer treated with S-1 chemotherapy. *Gastric Cancer.* 2014;17:67–75.

31. Kuang RG, Wu HX, Hao GX, et al. Expression and significance of IGF-2, PCNA, MMP-7, and alpha-actin in gastric carcinoma with Lauren classification. *Turk J Gastroenterol.* 2013;24:99–108.

32. Ma XQ, Wang LP, Luo QC, et al. Relationship between the expression level of miR-29c and biological behavior of gastric cancer. *Chinese J Oncol.* 2013;35:325–331.

33. Qiu M, Zhou Y, Zhang X, et al. Lauren classification combined with HER2 status is a better prognostic factor in Chinese gastric cancer patients. *BMC Cancer.* 2014;14:823.

34. Berlth F, Monig S, Pinther B, et al. Both GLUT-1 and GLUT-14 are independent prognostic factors in gastric adenocarcinoma. *Ann Surg Oncol.* 2015;22(Suppl 3):822–831.

35. Xie JW, Chen PC, Zheng CH, et al. Evaluation of the prognostic value and functional roles of CD44v6 in gastric cancer. *J Cancer Res Clin Oncol.* 2015;141:1809–1817.

36. Chen L, Shi Y, Yuan J, et al. Evaluation of docetaxel- and oxaliplatin-based adjuvant chemotherapy in postgastrectomy gastric cancer patients reveals obvious survival benefits in docetaxel-treated mixed signet ring cell carcinoma patients. *Med Oncol.* 2014;31:159.

37. Hass HG, Smith U, Jager C, et al. Signet ring cell carcinoma of the stomach is significantly associated with poor prognosis and diffuse gastric cancer (Lauren's): single-center experience of 160 cases. *Onkologie.* 2011;34:682–686.

38. Zheng H, Takahashi H, Murai Y, et al. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: an immunostaining study on the tissue microarray. *J Clin Pathol.* 2007;60:273–277.