



Clinical Impact of Delayed Initiation of Adjuvant Chemotherapy Among Patients With Stage II/III Gastric Cancer: Can We Do Better?

Qi-Yue Chen^{1,2,3,4}, Zhi-Yu Liu^{1,2,3,4}, Qing Zhong^{1,2,3,4}, Jian-Wei Xie^{1,2,3,4}, Jia-Bin Wang^{1,2,3,4}, Jian-Xian Lin^{1,2,3,4}, Jun Lu^{1,2,3,4}, Long-Long Cao^{1,2,3,4}, Mi Lin^{1,2,3,4}, Ru-Hong Tu^{1,2,3,4}, Ze-Ning Huang^{1,2,3,4}, Ju-Li Lin^{1,2,3,4}, Hua-Long Zheng^{1,2,3,4}, Ping Li^{1,2,3,4}, Chao-Hui Zheng^{1,2,3,4} and Chang-Ming Huang^{1,2,3,4*}

¹ Department of Gastric Surgery, Fujian Medical University Union Hospital, Fuzhou, China, ² Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China, ³ Key Laboratory of Ministry of Education of Gastrointestinal Cancer, Fujian Medical University, Fuzhou, China, ⁴ Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, China

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*Correspondence:

Chang-Ming Huang
hcmr2002@163.com

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Background: To investigate the prognostic effects and risk factors of the omission and delay of postoperative chemotherapy of stage II/III gastric cancer (GC).

Methods: The clinicopathological data of 1,520 patients undergoing radical gastrectomy for stage II/III GC were collected and retrospectively analyzed. We defined the chemotherapy delayed until more than 60 days after radical gastrectomy and the complete omission of chemotherapy as unacceptable chemotherapy initiation (UAC), whereas the chemotherapy conducted within 60 days of radical gastrectomy was defined as acceptable chemotherapy initiation (AC). The survival between the two groups was compared, and the trends and risk factors of UAC were analyzed.

Results: There were 539 (35.5%) patients with UAC. The overall survival (OS) and disease-free survival of the UAC group patients were significantly inferior to those in the AC group ($p < 0.001$). Cox multivariate analysis demonstrated that UAC is an independent predictor of OS ($p < 0.05$). The OS and disease-free survival of the patients in the UAC group were close to those of the patients without chemotherapy ($p > 0.05$). Logistic analysis showed that female, old age, a self-paid status, a very low social status, high American Society of Anesthesiologists scores, intra-abdominal surgery history, and serious postoperative complications were independent risk factors of UAC (all $p < 0.05$). The radar chart shows the risk factors of UAC changed with time.

Conclusions: UAC after radical gastrectomy is an independent risk factor for the prognosis of stage II/III GC patients. However, no significant decline of UAC has been achieved recently and should call for the attention of both government and clinicians.

Keywords: gastric carcinoma, prognosis, untimely, chemotherapy, risk factor

INTRODUCTION

Although the incidence of gastric cancer (GC) has declined in recent years, its mortality rate remains at the forefront of cancer-related deaths (1–3). Scholars have spent great effort to explore how to improve the survival rate of GC, particularly in advanced-stage patients, including the constant perfection of surgical methods and the continuous improvement of chemotherapy regimens (4–10); however, the effect is still not ideal. Therefore, it may not be enough to rely solely on clinicians to improve the overall survival (OS) rate of GC. The concerted efforts of the government, the family, and the patients should be used. In particular, for the majority of Chinese patients with locally advanced GC (stage II/III) (11), the regulation of D2 radical surgery may only be the beginning of treatment. Whether adjuvant chemotherapy can be performed in time may also determine the overall effect of treatment. We observed in clinical practice that some patients with delayed chemotherapy had a significantly poorer prognosis compared with those with timely chemotherapy. The delay or omission of chemotherapy may occur for various reasons in patients with GC, particularly in developing countries, such as China. It is critical for clinical workers and health departments to determine its precise effect on prognosis and how to detect high-risk patients as early as possible. However, to our knowledge, although several studies have reported the chemotherapy time impacting on the prognosis of patients with GC (12–15), the understanding of omission and delay of chemotherapy is still controversial. Closure of this knowledge gap is critical for researchers, surgeons, and administrators. Clearly, it is unfeasible and unethical to explore this issue through prospective trials. Therefore, this paper aims to investigate the effects of the omission and delay of chemotherapy in stage II/III GC and its risk factors in recent years from a large tertiary referral center in southern China; moreover, the goals are to assess the effect on prognosis and identify the high-risk factors of delayed chemotherapy and the trends in recent years to provide a reference for the intervention of relevant departments, including the government and clinicians.

MATERIALS AND METHODS

Study Design and Patients

In this study, the clinical and pathological data of 2,604 patients with GC at the Fujian Medical University Union Hospital (FMUUH) from January 2011 to April 2015 were retrospectively analyzed. The inclusion criteria were as follows: (1) Preoperative endoscopic biopsy-confirmed GC; (2) Receiving a D2 lymph node dissection surgery; and (3) Radical surgery. Furthermore, the case exclusion criteria were as follows: (1) GC was confirmed as stage I or IV by the postoperative pathology ($n = 1,025$ cases); (2) Histological identification of a tumor type other than

adenocarcinoma ($n = 13$ cases); (3) Remnant GC ($n = 23$ cases); and (4) Survival time is <3 months ($n = 23$ cases). Finally, 1,520 patients with stage II/III gastric adenocarcinoma treated with D2 radical resection were included. **Supplementary Figure 1** shows the screening process. This study was conducted with the approval of the institutional review boards at FMUUH. The time of chemotherapy was defined as the interval between the radical gastrectomy and the first initiation time of chemotherapy. According to the correlation between the OS rate and the chemotherapy time, the cutoff value of the chemotherapy time was selected (**Supplementary Figure 2**). The results showed that the OS of the patients treated with chemotherapy within <4 weeks, 4–6 weeks, and 6–8 weeks were significantly better than those who had no chemotherapy ($p < 0.05$), whereas the OS of the patients treated with chemotherapy after 8–10 weeks, 10–12 weeks, and more than 12 weeks were similar to those without chemotherapy ($p > 0.05$). To facilitate the analysis, we selected the cutoff point with the duration of chemotherapy of more than 60 days as the delay of chemotherapy.

Accordingly, we defined chemotherapy that was delayed until more than 60 days after radical gastrectomy and the complete omission of chemotherapy as unacceptable chemotherapy initiation (UAC group), whereas chemotherapy conducted within 60 days of radical gastrectomy was defined as acceptable chemotherapy initiation (the AC group). The chemotherapy regimen did not change for each patient unless there was a severe chemotherapy reaction. This retrospective study was approved and implemented by the Ethics Committee of Fujian Medical University Union Hospital.

Methods

Preoperative imaging studies were routinely performed after endoscopic and upper gastrointestinal examinations with contrast to confirm the tumor location and included chest radiography, computed tomography (CT) scanning, ultrasonography (US) of the abdomen and bone scanning, and positron emission tomography-computed tomography (PET-CT) as required to evaluate the clinical stage. We used CT scans and the seventh edition of the International Union Against Cancer (UICC) classification system to assess the clinical and pathologic stage (16). According to the 2014 version of the *Japanese Gastric Cancer Treatment Guidelines* (17), our center recommended 5-Fu-based chemotherapy for patients with postoperative pathological stage II/III. The patient's residential address, marital status, procreation status, type of medical insurance, occupation, smoking history, alcohol consumption, and other information were routinely recorded in the electronic database of the Fujian Medical University Union Hospital medical records. The financial condition of the patient was recorded by the health care system. We conducted a comprehensive assessment of the patient's social status based on the patient's occupation, residential address, education, and economic conditions, according to literature (18).

Follow-Up

The last follow-up time was April 2018. The follow-up rate of the 1,520 patients was 95.9%. Postoperative follow-ups

Abbreviations: UAC group, Unacceptable chemotherapy initiation; AC group, Acceptable chemotherapy initiation; GC, Gastric cancer; FMUUH, Fujian Medical University Union Hospital; CT, Computed tomography; US, Ultrasonography; PET-CT, Positron emission tomography-computed tomography; UICC, International Union Against Cancer; OS, Overall survival; DFS, Disease-free survival.

using outpatient, hospitalization, etc. were every 3 months for the first 2 years, every 6 months for 3–5 years, and every year for after 5 years. The overwhelming majority of the patients routinely received physical examinations, laboratory tests (including carbohydrate antigen 19-9, cancer antigen 72-4, and carcinoembryonic antigen levels), chest films, full belly color Doppler ultrasound or abdominal CT, and an annual gastroscopy. The OS time represents the time from the operation to the last follow-up or death. Disease-free survival (DFS) was defined as the time from the surgery to the time of recurrence or death from any other cause.

Statistical Analysis

All data were processed using SPSS 20.0 (SPSS Inc., Chicago, IL). Continuous variables were analyzed with Student's *t*-tests, and categorical variables were analyzed with χ^2 or Fisher's tests. The survival rate was calculated using the Kaplan–Meier method, and the survival rates were compared with the Log-rank test. The risk factors related to UAC were analyzed using a logistic model, with a Cox proportional risk model for multivariate prognostic analysis. Stepwise backward variable removal was applied to the multivariate model to identify the most accurate and parsimonious set of predictors. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics Between Unacceptable Chemotherapy Initiation and Acceptable Chemotherapy Initiation Groups

Of all patients, there were 539 patients with UAC, with an incidence of 35.5%. **Table 1** shows the clinicopathological data of the patients in the AC and UAC groups. There were significant differences in terms of age, sex, medical insurance type, income, social status, residential address, American Society of Anesthesiologists (ASA) score, intra-abdominal surgery history, comorbidities, Charlson score, surgery period, and postoperative complications between the two groups ($p < 0.05$); however, the body mass index (BMI), occupation, marital status, procreation status, smoking and drinking consumption, abdominal surgery history, tumor site, pathological tumor stage, pathological node stage, pathological tumor–node–metastasis (pTNM) staging, tumor size, number of harvested lymph nodes, lymphatic vessel infiltration, and pathological differentiation degree were not significantly different between the groups ($p > 0.05$). The median follow-up time for the AC and UAC groups were 43 (3–86) months and 37 (3–91) months, respectively.

Effect of Unacceptable Chemotherapy Initiation on Prognosis

Supplementary Figure 3 shows the OS of the 1,520 patients, with a median survival time of 41 months (range 3–91 months). **Figure 1** indicates that the OS and DFS of the UAC group patients are significantly inferior to those in the AC group ($p < 0.001$). In the UAC group, the OS and DFS of the patients

TABLE 1 | Sociodemographic and clinicopathologic variables of the AC and UAC groups.

Variable	AC group (<i>n</i> = 981)		UAC group (<i>n</i> = 539)		<i>P</i>
	No. of patients	%	No. of patients	%	
Sex					0.030
Female	234	23.9	156	28.9	
Male	747	76.1	383	71.1	
Age, year					<0.001
<65	669	68.2	234	43.4	
≥65	312	31.8	305	56.6	
BMI, kg/m²					0.470
<18.5	107	10.9	70	13	
18.5–24.9	732	74.6	395	73.3	
≥25.0	142	14.5	74	13.7	
Medical insurance type					<0.001
Self-paid	69	7.0	83	15.4	
Rural insurance	569	58.0	262	48.6	
Urban insurance	337	34.4	191	35.4	
Others	6	0.6	3	0.6	
Occupation					0.533
No	937	95.5	511	94.8	
Yes	44	4.5	28	5.2	
Income					0.004
Very low	176	17.9	136	25.2	
Low	602	61.4	296	54.9	
General	173	17.6	97	18.0	
High	30	3.1	10	1.9	
Social status					<0.001
Very low	5	.5	15	2.8	
Low	208	21.2	177	32.8	
General	686	69.9	297	55.1	
High	65	6.6	44	8.2	
Very high	17	1.7	6	1.1	
Residential address					0.011
Village	615	62.7	302	56.0	
City	366	37.3	237	44.0	
Marital status					0.542
No	11	1.1	8	1.5	
Yes	970	98.9	531	98.5	
Procreation status					0.799
No	13	1.3	8	1.5	
Yes	968	98.7	531	98.5	
Smoking and drinking consumption					0.211
No	582	59.3	344	63.8	
Smoking	229	23.3	114	21.2	
Drinking	31	3.2	15	2.8	
Both	131	13.4	56	10.4	
ASA score					<0.001
I	622	63.4	227	51.4	
II	328	33.4	228	42.3	
III–IV	31	3.2	34	6.3	

(Continued)

TABLE 1 | Continued

Variable	AC group (n = 981)		UAC group (n = 539)		P
	No. of patients	%	No. of patients	%	
Abdominal surgery history					<0.001
No	876	89.3	439	81.4	
Yes	105	10.7	100	18.6	
Intra-abdominal surgery history					0.500
No	912	93.0	496	92.0	
Yes	69	7.0	43	8.0	
Comorbidity					<0.001
No	730	74.4	345	64.0	
Yes	251	25.6	194	36.0	
Charlson score					<0.001
0	730	74.4	345	64.0	
1–2	236	24.1	187	34.7	
3–5	15	1.5	7	1.3	
Tumor site					0.684
Lower	352	35.9	194	36.0	
Middle	223	22.7	109	20.2	
Upper	272	27.7	157	29.1	
Overlapping lesion of stomach	134	13.7	79	14.7	
Surgery period					<0.001
2011	162	16.50	184	34.10	
2012	263	26.80	122	22.60	
2013	241	24.60	102	18.90	
2014	254	25.90	104	19.30	
2015	61	6.20	27	5.00	
Depth of invasion (pT)					0.296
Mucosa/Submucosa	24	2.4	9	1.7	
Proper muscle	82	8.4	33	6.1	
Subserosa	421	42.9	243	45.1	
Serosa	454	46.3	254	47.1	
Nodal status (pN)					0.284
N0	140	14.3	92	17.1	
N1	176	17.9	82	15.2	
N2	246	25.1	127	23.6	
N3	419	42.7	238	44.2	
pTNM stage					0.222
IIA	153	15.6	90	16.7	
IIB	159	16.2	80	14.8	
IIIA	171	17.4	72	13.4	
IIIB	234	23.9	144	26.7	
IIIC	264	26.9	153	28.4	
Tumor size, mm					0.105
<20	31	3.2	17	3.2	
20–50	546	55.7	270	50.1	
>50	404	41.2	252	46.8	
Examined LNs, no.					0.629
≤15	25	2.5	16	3.0	
>15	956	97.5	523	97.0	
Lymphatic vessel infiltration					0.326

(Continued)

TABLE 1 | Continued

Variable	AC group (n = 981)		UAC group (n = 539)		P
	No. of patients	%	No. of patients	%	
Negative	502	51.2	290	53.8	
Positive	479	48.8	249	46.2	
Postoperative complications					0.001
No	823	83.9	413	76.6	
Yes	158	16.1	126	23.4	
Clavien–Dindo grade					<0.001
None	823	83.9	413	76.6	
I–II	133	13.6	76	14.1	
III–IV	25	2.5	50	9.3	
Chemotherapy					
AC group	981	100	0	0.0	
UAC group	0	0	539	100.0	
Delay (>60 days)	0	0	62	11.5	
Omission	0	0	477	88.5	
Pathological differentiation degree					0.342
Differentiated	753	76.8	402	74.6	
Undifferentiated	228	23.2	137	25.4	
Follow-up, month					
Median	43	37			
Range	3–86	3–91			

AC, Acceptable chemotherapy; UAC, unacceptable delay or missing chemotherapy; pT, pathological tumor; pN, pathological node.

Bold values indicates $P < 0.05$, statistically significant.

with chemotherapy delayed until more than 60 days were close to those without chemotherapy ($p > 0.05$). Further analysis shows that the AC group had significantly better OS than the UAC group ($p < 0.05$) in both men/women, with or without complications, or stage II/III (Supplementary Figure 4).

The stratified analysis by stage II/III shows that the OS in the AC group in the IIA–IIIC patients was significantly better than that in the UAC group ($P < 0.05$). When the DFS was compared, the AC group was significantly superior to the UAC group in both males and females, with or without complications, or stage II/III patients ($P < 0.05$) (Supplementary Figure 5). A further stratified analysis by stage II/III demonstrates that the DFS in the AC Group exhibited a greater trend than that in the UAC group in the IIB, IIIA, and IIIC patients; however, the differences were not significant ($p > 0.05$). In contrast, in the AC group in the IIA and IIIB patients, the DFS was significantly better than that in the UAC group ($p < 0.05$). Supplementary Figure 6 shows that extended survival after recurrence in the AC group was superior to that in the UAC group ($P = 0.014$).

Analysis of Risk Factors for Patient Survival

Table 2 shows the results of the Cox univariate and multivariate analyses for OS. The univariate analysis indicates that age, BMI, medical insurance type, ASA score, comorbidities, tumor

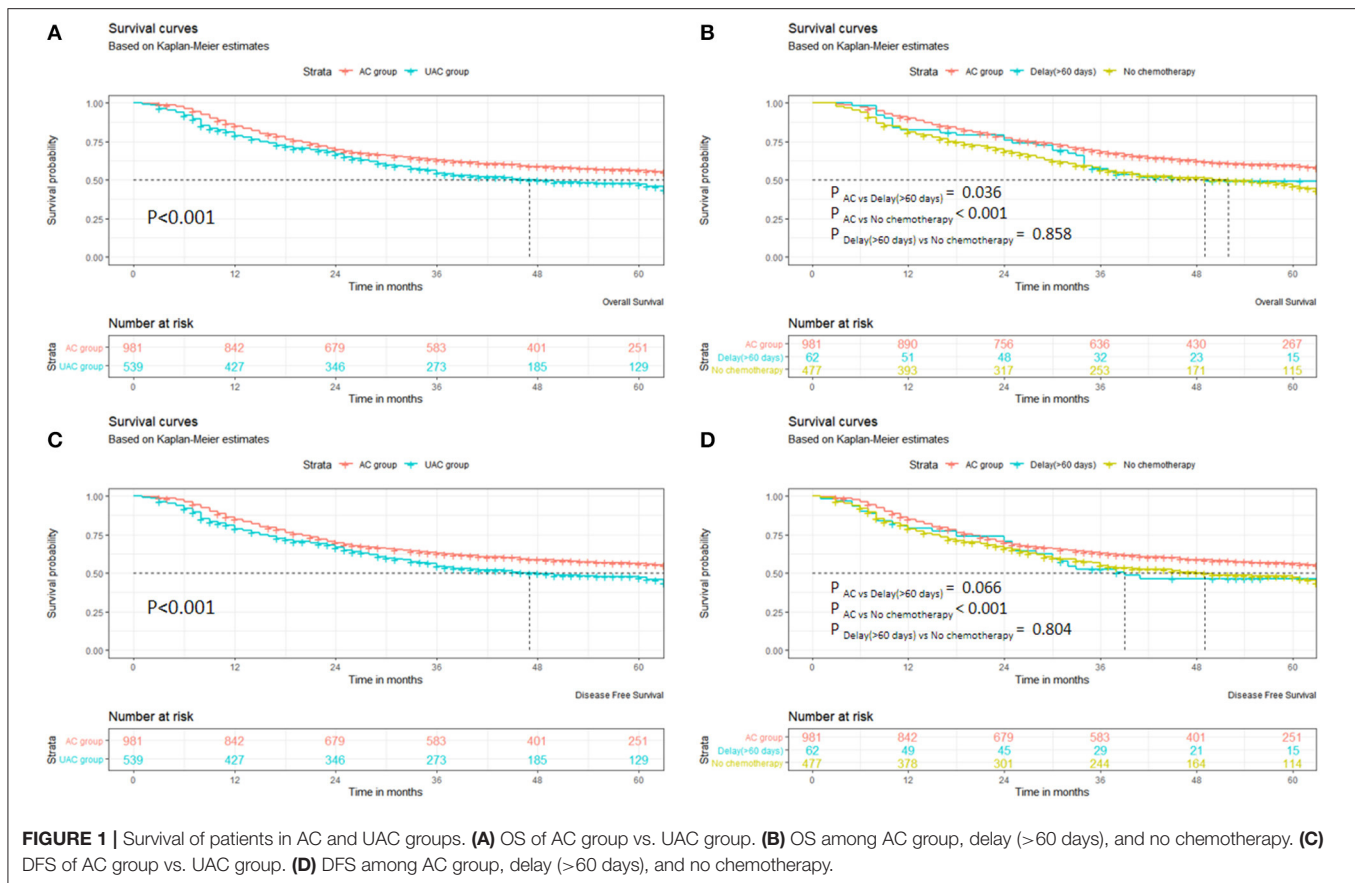


FIGURE 1 | Survival of patients in AC and UAC groups. **(A)** OS of AC group vs. UAC group. **(B)** OS among AC group, delay (>60 days), and no chemotherapy. **(C)** DFS of AC group vs. UAC group. **(D)** DFS among AC group, delay (>60 days), and no chemotherapy.

site, pTNM staging, tumor size, lymphatic vessel infiltration, pathological differentiation degree, number of examined lymph nodes, Clavien–Dindo grade, and UAC were associated with OS (all $p < 0.05$). The multivariate analysis indicates that age, BMI, ASA score, comorbidities, pTNM staging, number of examined lymph nodes, Clavien–Dindo grade, and UAC were independent predictors of OS ($P < 0.05$). **Supplementary Table 1** demonstrates that age, pTNM staging, tumor size, and number of harvested lymph nodes were independent predictors of DFS; however, UAC was not an independent risk factor ($p < 0.05$).

Analysis of Risk Factors of Unacceptable Chemotherapy Initiation

The analysis of the UAC status from 2011 to April 2015 showed that the rates in 2011, 2012, 2013, 2014, and 2015 were 53.2, 31.7, 29.7, 29.1, and 30.7%, respectively (**Figure 2**). The difference reached statistical significance ($P < 0.001$). Further stratified analysis showed a significant improvement in UAC in 2012 compared with that in 2011 ($p < 0.001$), whereas there was no significant improvement from 2012 to April 2015 ($p = 0.880$); moreover, it increased from 29.1% in 2014 to 30.7% in 2015. **Table 3** presents the results of the logistic univariate and multivariate analyses of risk factors associated with UAC. The univariate analysis shows that sex, age, type of medical insurance, income, social status, residential address, ASA score, history of intra-abdominal

surgery, Charlson score, and Clavien–Dindo grade were related to UAC (all $p < 0.05$). The reduced multivariate model analysis shows that female sex, old age, self-paid status, very low social status, high ASA score, intra-abdominal surgery history, and serious postoperative complications (Clavien–Dindo III–IV) were independent risk factors for UAC ($p < 0.05$).

Change of Risk Factors for Unacceptable Chemotherapy Initiation Over Time

The radar chart shows that the risk factors of UAC changed with time (**Supplementary Figure 7**). In general, the number of patients with self-funded and an extremely low social status significantly decreased from 2011 to April 2015 (all $p < 0.05$). The proportion of self-funded patients showed a downward trend year by year from 2011 to April 2015, whereas the proportion of extremely low social status patients gradually decreased (0–3.2%) from 2011 to 2014 and then increased again (4.5%) in 2015 (**Supplementary Table 2**). Between 2011 and April 2015, there was no significant change in the proportion of female patients, aged patients, patients undergoing intra-abdominal surgery, and high ASA patients (all $p > 0.05$). At the same time, the proportion of patients with severe postoperative complications was not significantly improved ($p = 0.549$).

TABLE 2 | Univariate and multivariate Cox regression models for overall survival.

Variable	Univariate model			Full multivariate model			Reduced multivariate model				
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P		
Patients' risk											
Sex											
Female	Ref										
Male	1.05	0.89	1.25								
Age, year											
<65	Ref			Ref				Ref			
≥65	1.27	1.09	1.48	0.002	1.29	1.09	1.53	0.003	1.29	1.09	1.52
BMI											
<18.5	Ref			Ref				Ref			
18.5–24.9	0.60	0.49	0.75	<0.001	0.74	0.59	0.91	0.006	0.74	0.59	0.92
≥25.0	0.50	0.37	0.66	<0.001	0.60	0.45	0.81	0.001	0.61	0.45	0.82
Medical insurance type											
Self-paid	Ref										
Rural insurance	0.71	0.56	0.91	0.006							
Urban insurance	0.73	0.57	0.94	0.015							
Others	0.95	0.35	2.60	0.923							
Occupation											
No	Ref										
Yes	1.03	0.74	1.43	0.872							
Income											
Very low	Ref										
Low	0.86	0.71	1.04	0.121							
General	0.96	0.76	1.22	0.745							
High	0.66	0.39	1.12	0.124							
Social status											
Very low	Ref										
Low	0.99	0.52	1.87	0.978							
General	0.88	0.47	1.65	0.692							
High	0.73	0.37	1.46	0.375							
Very high	0.91	0.40	2.11	0.832							
Residential address											
Village	Ref										
City	0.98	0.84	1.14	0.745							
Marital status											
No	Ref										
Yes	0.80	0.42	1.55	0.515							
Procreation status											
No	Ref										
Yes	0.68	0.38	1.24	0.209							
Smoking and drinking consumption											
No	Ref										
Smoking	0.88	0.72	1.06	0.167							
Drinking	1.26	0.83	1.90	0.273							
Both	0.95	0.75	1.21	0.683							
ASA score											
I	Ref				Ref				Ref		
II	1.10	0.94	1.29	0.252	1.24	0.98	1.58	0.072	1.25	0.98	1.59
III–IV	1.51	1.08	2.11	0.016	2.09	1.39	3.15	<0.001	2.09	1.38	3.14
Abdominal surgery history											
No	Ref										

(Continued)

TABLE 2 | Continued

	Variable	Univariate model				Full multivariate model			Reduced multivariate model				
		HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Tumor's risk	Yes	1.05	0.84	1.31	0.675								
	Intra-abdominal surgery history				0.615								
	No	Ref											
	Yes	1.07	0.81	1.41	0.615								
	Comorbidity				<0.001				0.043				0.040
	No	Ref				Ref				Ref			
	Yes	1.47	1.23	1.76	<0.001	1.32	1.01	1.72	0.043	0.76	0.58	0.99	0.040
	Tumor site				<0.001				0.111				0.098
	Lower	Ref				Ref				Ref			
	Middle	1.27	1.03	1.57	0.023	1.18	0.96	1.47	0.122	1.18	0.95	1.46	0.126
	Upper	1.12	0.92	1.36	0.280	1.06	0.86	1.30	0.589	1.06	0.86	1.29	0.591
	Overlapping lesion of stomach	1.91	1.53	2.38	<0.001	1.32	1.04	1.68	0.024	1.33	1.05	1.69	0.020
	pTNM stage				<0.001				<0.001				<0.001
	IIA	Ref				Ref				Ref			
	IIB	1.24	0.86	1.80	0.248	1.21	0.83	1.76	0.320	1.23	0.84	1.78	0.288
	IIIA	1.72	1.21	2.43	0.002	1.67	1.17	2.37	0.005	1.69	1.19	2.41	0.004
	IIIB	3.08	2.27	4.19	<0.001	2.81	2.04	3.86	<0.001	2.91	2.13	3.99	<0.001
	IIIC	5.41	4.02	7.28	<0.001	4.42	3.22	6.08	<0.001	4.64	3.39	6.34	<0.001
	Tumor size, mm				<0.001				0.013				0.012
<20	Ref				Ref				Ref				
20–50	1.37	0.78	2.38	0.272	1.00	0.57	1.77	0.997	1.01	0.57	1.78	0.975	
>50	2.60	1.50	4.53	0.001	1.29	0.73	2.28	0.385	1.30	0.73	2.29	0.370	
Lymphatic vessel infiltration				<0.001				0.231					
Negative	Ref				Ref								
Positive	1.32	1.14	1.54	<0.001	1.10	0.94	1.29	0.231					
Pathological differentiation degree				0.001				0.172					
Differentiated	Ref				Ref								
Undifferentiated	0.72	0.60	0.87	0.001	0.87	0.71	1.06	0.172					
Treatment risk Examined LNs, no.				<0.001				<0.001				<0.001	
>15	Ref				Ref				Ref				
≤15	2.15	1.47	3.14	<0.001	2.82	1.90	4.19	<0.001	2.72	1.84	4.03	<0.001	
Clavien–Dindo grade				<0.001				0.037				0.033	
None	Ref				Ref				Ref				
I–II	1.41	1.14	1.74	0.001	1.29	1.04	1.60	0.023	1.29	1.04	1.60	0.022	
III–IV	1.64	1.21	2.23	0.002	1.27	0.93	1.75	0.139	1.28	0.93	1.77	0.124	
Chemotherapy				<0.001				0.003				0.004	
AC group	Ref				Ref				Ref				
UAC group	1.48	1.27	1.73	<0.001	1.29	1.09	1.52	0.003	1.28	1.08	1.51	0.004	

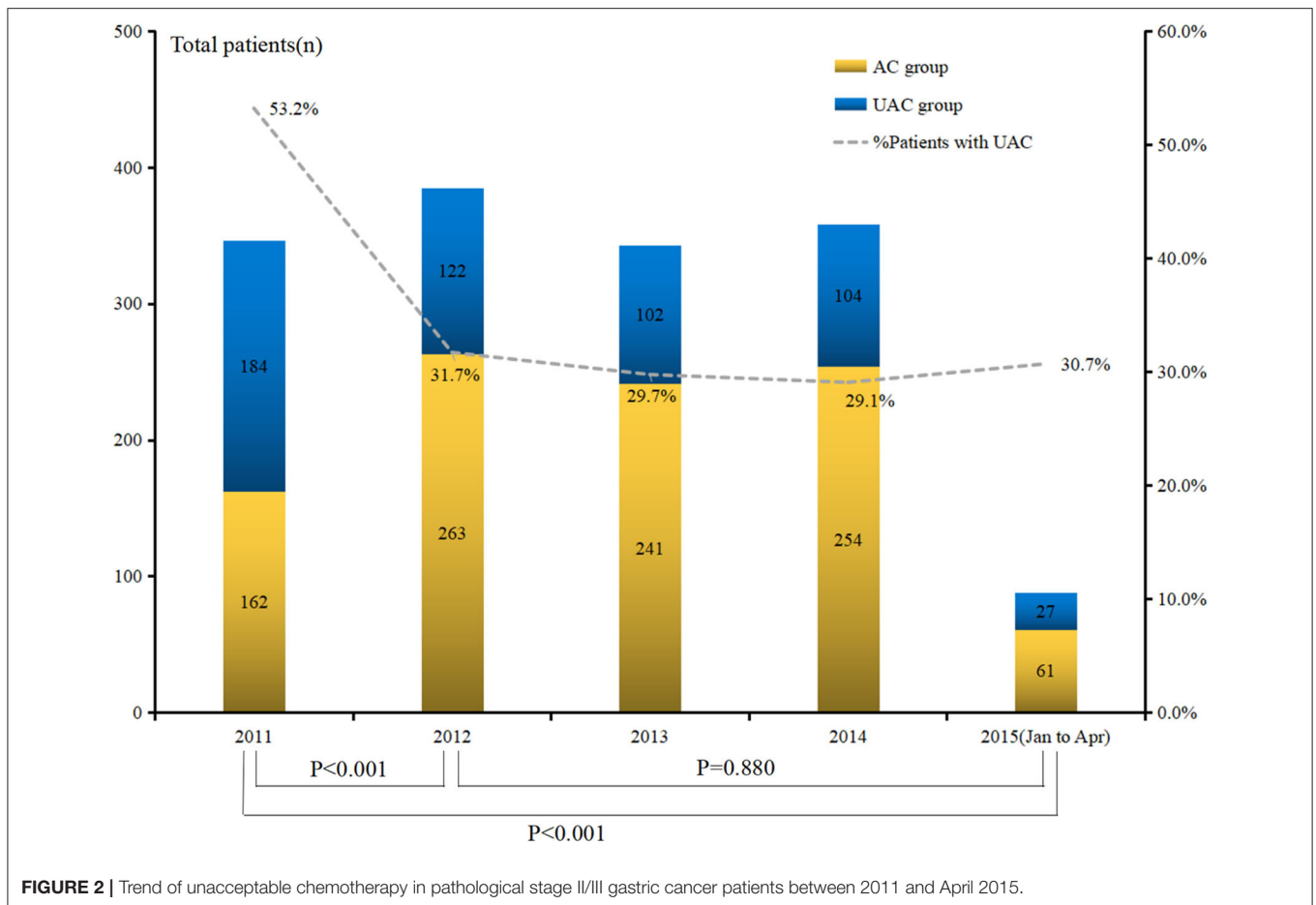
AC, Acceptable chemotherapy; UAC, unacceptable delay or missing chemotherapy; LN, lymph node; HR, hazard ratio.

Bold values indicates $P < 0.05$, statistically significant.

DISCUSSION

It has been confirmed in animal models that the angiogenesis of the micrometastatic foci will be significantly faster after resection of the primary cancer (19–21); thus, the treatment of advanced cancer cannot rely solely on surgical treatment (22–25). Therefore, although surgery is a key part of the comprehensive treatment for locally advanced GC, timely adjuvant chemotherapy plays an important role. Our results

show that the patients with a chemotherapy delay (delayed more than 60 days) or without chemotherapy have significantly worse overall survival and DFS than those with timely chemotherapy. The patients with delayed or omitted chemotherapy did not exhibit significant differences, and the chemotherapy delay patients' sample size was limited. Thus, we combined them in the subsequent analysis as UAC. Our data show that UAC is a risk factor for OS independent of tumor staging, age, and other factors for stage II/III GC patients. The reason may be



that a chemotherapy delay can affect the early inhibition of cytotoxic drugs on angiogenesis in micrometastasis, and it is easy to induce primary drug resistance (21, 26). Several reasons for this are possible. Firstly, UAC is not an independent risk factor for the DFS of all patients with stage II/III GC, and the reason may be that extended survival after recurrence in the AC group was superior to that in the UAC group. Previous studies also showed that extended survival after recurrence may influence the effect of treatment on prognosis and reduce the association between treatment effects on DFS and OS, where delay/omission of chemotherapy was a significant factor for OS but not DFS (27). Some patients may have a recurrence after surgery and mostly could be seen on physical examination or follow-up examination. However, due to the limited detection methods at present, some recurrence may be missed, especially in patients with concealed relapses. Therefore, some patients could have undiagnosed tumor recurrences, leading to loss of data. These factors may affect the results. These could be the reason why delay/omission of chemotherapy was a significant factor for OS but not for DFS.

As an independent risk factor for OS, clinicians should avoid the occurrence of UAC in patients. The rate of UAC in recent years was significantly reduced from 2011 to 2012; however, the rate did not significantly decrease from 2012 to 2015 and increased from 29.1% in 2014 to 30.7% in 2015.

Therefore, it is of importance to identify the high-risk factors of UAC and investigate their changes overtime to facilitate relevant departments to use appropriate measures to improve this situation. At the same time, we believe that the causes of UAC are not only related to clinical treatment factors, such as surgery, postoperative complications, and tumor factors, and individual factors, such as socioeconomic variables, may also play important roles. Therefore, we expanded the included variables, such as the medical insurance type, according to the characteristics of the regional socioeconomic factors, and divided the included factors into three categories, including individual, treatment, and tumor, for logistic analysis. The results showed that female, elderly, self-paid patients and patients with a low social status, high ASA score, preoperative abdominal operation history, and severe postoperative complications exhibited high-risk factors of UAC, whereas tumor factors, such as tumor size and staging, did not affect postoperative chemotherapy time. Further analysis indicated the risk factors that changed over time in the intervening factors, with the increase in time and the surgical experience accumulated, whereas serious postoperative complications did not significantly improve. Severe postoperative complications often require longer recovery times and may affect patients' confidence in themselves and their doctors' treatment (28), thus delaying their first time of receiving chemotherapy.

TABLE 3 | Univariate and multivariate logistic models for the risks of unacceptable chemotherapy.

Variable	Univariate model			Full Multivariate model			Reduced multivariate model		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Patients' risk									
Sex			0.030			0.011			0.015
Female	Ref			Ref			Ref		
Male	0.77	0.61 0.98	0.030	0.72	0.55 0.93	0.011	0.73	0.56 0.94	0.015
Age, year			<0.001			<0.001			<0.001
<65	Ref			Ref			Ref		
≥65	2.80	2.25 3.47	<0.001	2.47	1.92 3.19	<0.001	2.45	1.91 3.14	<0.001
BMI			0.470						
<18.5	Ref								
18.5–24.9	0.83	0.60 1.14	0.246						
≥25.0	0.80	0.53 1.20	0.279						
Medical insurance type			<0.001			<0.001			<0.001
Self-paid	Ref			Ref			Ref		
Rural insurance	0.38	0.27 0.54	<0.001	0.39	0.27 0.57	<0.001	0.39	0.26 0.57	<0.001
Urban insurance	0.47	0.33 0.68	<0.001	0.38	0.25 0.57	<0.001	0.36	0.24 0.55	<0.001
Others	0.42	0.10 1.72	0.226	0.18	0.04 0.93	0.040	0.19	0.04 0.92	0.040
Occupation			0.534						
No	Ref								
Yes	1.17	0.72 1.90	0.534						
Income			0.004			0.186			
Very low	Ref			Ref					
Low	0.64	0.49 0.83	0.001	1.40	0.94 2.08	0.094			
General	0.73	0.52 1.01	0.060	1.17	0.69 1.98	0.563			
High	0.43	0.20 0.91	0.028	0.63	0.19 2.09	0.447			
Social status			<0.001			0.001			0.001
Very low	Ref			Ref			Ref		
Low	0.28	0.10 0.80	0.017	0.25	0.08 0.73	0.012	0.26	0.09 0.78	0.016
General	0.14	0.05 0.40	<0.001	0.14	0.05 0.43	0.001	0.18	0.06 0.52	0.002
High	0.23	0.08 0.67	0.007	0.19	0.06 0.67	0.009	0.19	0.06 0.62	0.005
Very high	0.12	0.03 0.47	0.002	0.14	0.02 0.84	0.032	0.08	0.02 0.36	0.001
Residential address			0.011			0.063			0.072
Village	Ref			Ref			Ref		
City	1.32	1.07 1.63	0.011	1.34	0.98 1.82	0.063	1.31	0.98 1.76	0.072
Marital status			0.544						
No	Ref								
Yes	0.75	0.30 1.88	0.544						
Procreation status			0.799						
No	Ref								
Yes	0.89	0.37 2.16	0.799						
Smoking and drinking consumption			0.212						
No	Ref								
Smoking	0.84	0.65 1.09	0.198						
Drinking	0.82	0.44 1.54	0.534						
Both	0.72	0.52 1.02	0.062						
ASA score			<0.001			0.129			0.047
I	Ref			Ref			Ref		
II	1.56	1.25 1.95	<0.001	1.24	0.88 1.75	0.212	1.26	0.99 1.60	0.063
III–IV	2.46	1.48 4.09	<0.001	1.96	1.01 3.81	0.047	1.74	1.01 3.02	0.047
Abdominal surgery history			<0.001			0.002			0.003
No	Ref			Ref			Ref		

(Continued)

TABLE 3 | Continued

Variable	Univariate model				Full multivariate model				Reduced multivariate model			
	HR	95% CI		P	HR	95% CI		P	HR	95% CI		P
Yes	1.75	1.30	2.38	<0.001	1.65	1.18	2.29	0.002	1.65	1.19	2.30	0.003
Intra-abdominal surgery history				0.501								
No	Ref											
Yes	1.15	0.77	1.70	0.501								
Charlson score				<0.001				0.344				
0	Ref				Ref							
1–2	1.68	1.33	2.11	<0.001	0.95	0.65	1.40	0.798				
3–5	0.99	0.40	2.44	0.978	0.43	0.14	1.32	0.140				
Tumor's risk Tumor site				0.684								
Lower	Ref											
Middle	0.89	0.67	1.18	0.415								
Upper	1.05	0.81	1.36	0.731								
Overlapping lesion of stomach	1.07	0.77	1.49	0.688								
pTNM stage				0.224								
IIA	Ref											
IIB	0.86	0.59	1.24	0.413								
IIIA	0.72	0.49	1.05	0.084								
IIIB	1.05	0.75	1.46	0.791								
IIIC	0.99	0.71	1.37	0.929								
Tumor size, mm				0.105								
<20	Ref											
20–50	0.90	0.49	1.66	0.739								
>50	1.14	0.62	2.10	0.680								
Lymphatic vessel infiltration				0.326								
Negative	Ref											
Positive	0.90	0.73	1.11	0.326								
Pathological differentiation degree				0.342								
Differentiated	Ref											
Undifferentiated	1.13	0.88	1.44	0.342								
Treatment risk Examined LNs, no.				0.629								
>15	Ref											
≤15	1.17	0.62	2.21	0.629								
Clavien–Dindo grade				<0.001				<0.001				<0.001
None	Ref				Ref				Ref			
I–II	1.14	0.84	1.55	0.405	1.13	0.82	1.57	0.447	1.14	0.83	1.58	0.427
III–IV	3.99	2.43	6.53	<0.001	3.83	2.25	6.53	<0.001	3.73	2.20	6.33	<0.001

AC, Acceptable chemotherapy; UAC, unacceptable delay or missing chemotherapy; LN, lymph node; OR, odds ratio.

Bold values indicates $P < 0.05$, statistically significant.

Moreover, low-status groups typically suffer from substantial life pressures; thus, they often delay or give up chemotherapy due to personal or family factors after surgery. Therefore, although through the unremitting efforts of the government, the proportion of self-financed patients decreases year by year (which can improve the patient's willingness and timeliness of chemotherapy), the rate of UAC has not significantly improved in recent years.

We believe that to improve the OS of GC, the relevant departments or personnel should take corresponding measures in response to the various factors that cause UAC. For clinical workers, preoperative evaluation, intraoperative quality control,

and enhanced postoperative management should be performed to reduce postoperative complications, particularly severe postoperative complications. At the same time, postoperative care and education should receive attention in high-risk groups, such as individuals with a low social status, to inform them of the importance of timely postoperative chemotherapy. The government should continue to improve the medical insurance policy to continue to reduce the proportion of self-funded patients.

This paper incorporates multiple factors to explore high-risk groups to provide a reference for relevant departments and personnel to use corresponding measures. However, our

research has unavoidable shortcomings: First, as a retrospective study, it is difficult to exclude the effects of confounding factors on the results, that is, the patient's personal preferences may have an impact on the UAC. Second, there are significant differences in multiple factors between the UAC group and the AC group. This imbalance may have an impact on the subsequent prognosis analysis. Some patients, such as those with a very low social status, are limited in number at the time of stratification, which may affect the results. Third, the risk factors for UAC in different countries may vary due to different national conditions, such as health care policies and income conditions (29, 30). Nevertheless, the results of this retrospective study are important. We also look forward to international, multicenter, retrospective studies in the near future to explore the risk factors and their differences in each country, thus providing strategies for improving the overall prognosis of patients with GC worldwide.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee at the Fujian Medical University Union Hospital (the reference number is 2019KY063). Written informed consent for participation was not

required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Q-YC, Z-YL, QZ, and C-MH: conception and design. C-MH: provision of study materials or patients. Q-YC, Z-YL, QZ, C-MH, PL, H-LZ, J-XL, J-WX, J-BW, JL, L-LC, J-LL, and R-HT: collection and/or assembly of data. C-MH, Q-YC, Z-YL, QZ, and Z-NH: data analysis and interpretation. C-MH, PL, Q-YC, QZ, ML, and H-LZ: manuscript writing. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2020.01149/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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