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

Qiyue Chen

Fujian Medical University Union Hospital

Zhiyu Liu

Fujian Medical University Union Hospital

Qing Zhong

Fujian Medical University Union Hospital

Jianwei Xie

FMUHH

Jiabin Wang

FMUHH

Jianxian Lin

FMUHH

Jun Lu

FMUHH

Longlong Cao

FMUHH

Mi Lin

FMUHH

Ruhong Tu

FMUHH

Zening Huang

FMUHH

Juli Lin

FMUHH

Hualong Zheng

FMUHH

Ping Li

FMUHH

Chaohui Zheng

FMUHH

Chang-ming Huang (✉ hcmlr2002@163.com)

Research article

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

Posted Date: August 15th, 2019

DOI: <https://doi.org/10.21203/rs.2.12979/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Frontiers in Oncology on July 31st, 2020. See the published version at <https://doi.org/10.3389/fonc.2020.01149>.

Abstract

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 1520 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 group), while the chemotherapy conducted within 60 days of radical gastrectomy was defined as acceptable chemotherapy initiation (AC group). 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 OS and DFS 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 DFS of the patients in UAC group were close to those of the patients without chemotherapy ($p > 0.05$). Logistic analysis showed female, old age, a self-paid status, a very low social status, high ASA scores, intra-abdominal surgery history, and serious postoperative complications were independent risk factors of UAC ($p < 0.05$). 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.

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 rate of GC. The concerted efforts of the government, the family and the patients should be employed. 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, there are no accurate data for the omission and delay of chemotherapy in GC, and there is a lack of relevant research on its effect on the prognosis of GC patients. 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.

Methods And Materials

Study design and patients

In this study, the clinical and pathological data of 2604 patients with gastric cancer at the Fujian Medical University Union Hospital(FMUUH) from January 2011 to April 2015 were retrospectively analyzed, and the case exclusion criteria were as follows: (1) The postoperative pathology was confirmed as stage I or IV gastric cancer (n = 1025 cases); (2) Histological identification of a tumor type other than adenocarcinoma (n = 13 cases); (3) Remnant gastric cancer (n = 23 cases); and (4) Survival time is less than 3 months (n = 23 cases). Finally, 1520 patients with stage II/III gastric adenocarcinoma treated with D2 radical resection were included. Supplementary Fig. 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 overall survival (OS) rate and the chemotherapy time, the cutoff value of the chemotherapy time was selected (supplementary Fig. 2). The results showed that the OS of the patients treated with chemotherapy within less than 4 weeks, 4–6 weeks and 6–8 weeks were significantly better than those who had no chemotherapy ($p < 0.05$), while 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 over 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), while chemotherapy conducted within 60 days of radical gastrectomy was defined as acceptable chemotherapy initiation (the AC group). The chemotherapy regimen does not change for each patient unless there is 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 following 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 7th edition of the International Union Against Cancer (UICC) classification system to assess the clinical and pathologic stage(12). According to the 2014 version of the Japanese Gastric

Cancer treatment guidelines(13), 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(14).

Follow up

The last follow-up time was April 2018. The follow-up rate of the 1520 patients was 95.9%. Postoperative follow-up using outpatient, hospitalization, etc., 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 CA19–9, ca72–4, and CEA 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 less than 0.05 was considered statistically significant.

Results

Patient characteristics between UAC and AC groups

Of all patients, there were 539 patients with UAC, with an incidence of 35.5%. Table 1 shows the clinicopathologic data of the patients in the AC and UAC groups. There were significant differences in terms of age, gender, medical insurance type, income, social status, residential address, ASA score, intra-abdominal surgery history, comorbidities, Charlson score, surgery period, and postoperative complications between the two groups ($p < 0.05$); however, the BMI, occupation, marital status, procreation status, smoking and drinking consumption, abdominal surgery history, tumor site, pT stage, pN stage, 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 times for the AC and UAC groups were 43 (3–86) months and 37 (3–91) months, respectively. 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 (Fig. 1). The difference reached statistical significance ($P<0.001$). A further stratified analysis showed a significant improvement in UAC in 2012 compared to that in 2011 ($p<0.001$), while there was no significant improvement during 2012–2015 April ($p = 0.880$); moreover, it increased from 29.1 percent in 2014 to 30.7 percent in 2015.

The effect of UAC on prognosis

Supplementary Fig. 3 shows the OS of the 1520 patients, with a median survival time of 41 months (range 3–91 months). Fig. 2 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 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 Fig. 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 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 Fig. 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 ($p<0.05$).

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 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 UAC

Table 3 presents the results of the logistic univariate and multivariate analyses of risk factors associated with UAC. The univariate analysis shows that gender, 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 postoperative serious complications (Clavien-Dindo III-IV) were independent risk factors for UAC ($p < 0.05$).

The change of risk factors for UAC over time

The radar chart shows that the risk factors of UAC changed with time (Fig. 3). 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, while 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 (Supplement 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 ($p = 0.549$).

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(15–17); thus, the treatment of advanced cancer cannot rely solely on surgical treatment(18–21). Therefore, although surgery is a key part of the comprehensive treatment for local 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 and disease-free survival 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 stage 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(17, 22). UAC is not an independent risk factor for the survival of all patients with STAGE II/III GC, and the reasons require further discussion.

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 employ 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, while tumor factors, such as tumor size and staging, did not affect postoperative chemotherapy time. Further analysis indicated the risk factors change over time in the intervening factors with the increase in time, the surgical experience accumulated, while 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(23), thus delaying their first time of receiving chemotherapy. 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 gastric cancer, 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 is the first study of the effect of postoperative UAC on the prognosis of patients with gastric cancer. It incorporates multiple factors to explore high-risk groups to provide a reference for relevant departments and personnel to employ 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, i.e., the patient's personal preferences may have an impact on the UAC; Second, 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(24, 25). Nevertheless, the results of this retrospective study are important because it is difficult to conduct prospective studies due to ethical concerns. We also look forward to the international, multicenter, retrospective study 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 gastric cancer worldwide.

List Of Abbreviations

unacceptable chemotherapy initiation (UAC group);

acceptable chemotherapy initiation (AC group);

unacceptable chemotherapy initiation (UAC group);

acceptable chemotherapy initiation (AC group);

gastric cancer (GC);

Fujian Medical University Union Hospital(FMUUH);

computed tomography (CT);

ultrasonography (US);

positron emission tomography-computed tomography (PET-CT);

the International Union Against Cancer (UICC);

Disease-free survival (DFS);

Declarations

Ethics approval and consent to participate:

The research proposal was reviewed by the Research Ethics Committee at the Fujian Medical University Union Hospital (the reference number is NO.2019KY063), and all procedures were performed after obtaining written informed consent from the patients following an explanation of the surgical and oncological risks.

Consent for publication

All the authors agree to the publication of this article

Competing interests:

All authors declare no conflicts-of-interest related to this article.

Availability of data and material:

We declare that all the data of this article are availability.

Funding:

Scientific and technological innovation joint capital projects of Fujian Province (2016Y9031), Construction Project of Fujian Province Minimally Invasive Medical Center No. [2017]171, The second batch of special support funds for Fujian Province innovation and entrepreneurship talents (2016B013), General project of Miaopu scientific research fund of Fujian Medical University (2015MP021), Youth Project of Fujian Provincial Health and Family Planning Commission 2016-1-41, Nature Fund Health Joint Fund Project of Fujian Province (2015J01464)

Author contributions:

Conception/Design: Chen QY, Liu ZY, Zhong Q, and Huang CM; Provision of study materials or patients: Huang CM; Collection and/or assembly of data: Chen QY, Liu ZY, Zhong Q, Huang CM, Li P, Zheng CH, Lin JX, Xie JW, Wang JB, Lu J, Cao LL, Lin JL and Tu RH; Data analysis and interpretation: Huang CM, Chen QY, Liu ZY, Zhong Q and Huang ZN; Manuscript writing: Huang CM, Li P, Chen QY, Zhong Q, Lin M and Zheng HL;

All authors read and approved the final manuscript.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

References

1. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424.
2. *Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, et al.* Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health.* 2018;6(5):e555–e67.
3. *Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al.* Global surveillance of trends in cancer survival 2000–14 (CONCORD–3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 2018;391(10125):1023–75.
4. *Bang YJ, Xu RH, Chin K, Lee KW, Park SH, Rha SY, et al.* Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(12):1637–51.

5. *Hu Y, Huang C, Sun Y, Su X, Cao H, Hu J, et al.* Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol.* 2016;34(12):1350–7.
6. *Ishigami H, Fujiwara Y, Fukushima R, Nashimoto A, Yabusaki H, Imano M, et al.* Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S–1 Versus Cisplatin Plus S–1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial. *J Clin Oncol.* 2018;36(19):1922–9.
7. *Kinoshita T, Uyama I, Terashima M, Noshiro H, Nagai E, Obama K, et al.* Long-term Outcomes of Laparoscopic Versus Open Surgery for Clinical Stage II/III Gastric Cancer: A Multicenter Cohort Study in Japan (LOC-A Study). *Ann Surg.* 2019;269(5):887–94.
8. *Shitara K, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, et al.* Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE–061): a randomised, open-label, controlled, phase 3 trial. *Lancet.* 2018;392(10142):123–33.
9. *So JB, Rao J, Wong AS, Chan YH, Pang NQ, Tay AYL, et al.* Roux-en-Y or Billroth II Reconstruction After Radical Distal Gastrectomy for Gastric Cancer: A Multicenter Randomized Controlled Trial. *Ann Surg.* 2018;267(2):236–42.
10. *Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al.* Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2018;19(10):1372–84.
11. *Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al.* Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115–32.
12. *Edge SB, Compton CC.* The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17(6):1471–4.
13. *Japanese Gastric Cancer A.* Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer.* 2017;20(1):1–19.
14. *Yost K, Perkins C, Cohen R, Morris C, Wright W.* Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control.* 2001;12(8):703–11.
15. *Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E.* Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res.* 1989;49(8):1996–2001.
16. *Folkman J.* Endothelial cells and angiogenic growth factors in cancer growth and metastasis. Introduction. *Cancer Metastasis Rev.* 1990;9(3):171–4.

17. *Gunduz N*, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res.* 1979;39(10):3861–5.

18. *Gambardella V*, Cervantes A. Precision medicine in the adjuvant treatment of gastric cancer. *Lancet Oncol.* 2018;19(5):583–4.

19. *Ge S*, Xia X, Ding C, Zhen B, Zhou Q, Feng J, et al. A proteomic landscape of diffuse-type gastric cancer. *Nat Commun.* 2018;9(1):1012.

20. *Van Cutsem E*, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet.* 2016;388(10060):2654–64.

21. *Wang J*, Li C, Zhu X, Zhu J. Adjuvant therapy in resectable gastric cancer-the CRITICS trial. *Lancet Oncol.* 2018;19(7):e330.

22. *Goldie JH*, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep.* 1979;63(11–12):1727–33.

23. *Sprenger T*, Beissbarth T, Sauer R, Tschmelitsch J, Fietkau R, Liersch T, et al. Long-term prognostic impact of surgical complications in the German Rectal Cancer Trial CAO/ARO/AIO–94. *Br J Surg.* 2018;105(11):1510–8.

24. *Adler-Milstein J*, Sarma N, Woskie LR, Jha AK. A comparison of how four countries use health IT to support care for people with chronic conditions. *Health Aff (Millwood).* 2014;33(9):1559–66.

25. *Dare AJ*, Bleicher J, Lee KC, Elobu AE, Kamara TB, Liko O, et al. Generation of national political priority for surgery: a qualitative case study of three low-income and middle-income countries. *Lancet.* 2015;385 Suppl 2:S54.

Tables

Table 1. Sociodemographic and clinicopathologic variables of the AC and UAC groups

Variable	AC group(n=981)		UAC group(n=539)		P
	No. of Patients	%	No. of Patients	%	
Gender					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	
Vert 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	
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
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

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									
Gender			0.565						
Female	Ref								
Male	1.05	0.89 1.25	0.565						
Age,year			0.002			0.003			0.003
<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	0.003
BMI			<0.001			0.003			0.004
<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	0.007
≥25.0	0.50	0.37 0.66	<0.001	0.60	0.45 0.81	0.001	0.61	0.45 0.82	0.001
Medical insurance type			0.046						
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			0.872						
No	Ref								
Yes	1.03	0.74 1.43	0.872						
Income			0.218						
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			0.426						
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						
Vert high	0.91	0.40 2.11	0.832						
Residential address			0.745						
Village	Ref								
City	0.98	0.84 1.14	0.745						
Marital status			0.515						
No	Ref								
Yes	0.80	0.42 1.55	0.515						
Procreation status			0.209						
No	Ref								
Yes	0.68	0.38 1.24	0.209						
Smoking and drinking consumption			0.312						
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	0.043				0.002				0.002			
	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	0.068
	III-IV	1.51	1.08	2.11	0.016	2.09	1.39	3.15	<0.001	2.09	1.38	3.14	<0.001
	Abdominal surgery history	0.675											
	No	Ref											
	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's risk	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

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

Univariate		Multivariate	
OR	95% CI	OR	95% CI
Demographic			
Age			
≤ 60	1.0	1.0	1.0
> 60	1.2	1.1	1.3
Gender			
Male	1.0	1.0	1.0
Female	1.1	0.9	1.4
Clinical			
ECOG			
0-1	1.0	1.0	1.0
2-4	2.5	2.2	2.8
Performance			
Good	1.0	1.0	1.0
Poor	1.8	1.5	2.2
ECOG + Performance			
0-1 + Good	1.0	1.0	1.0
0-1 + Poor	1.5	1.3	1.7
2-4 + Good	2.0	1.8	2.3
2-4 + Poor	3.5	3.0	4.1
Laboratory			
WBC			
≥ 4.0	1.0	1.0	1.0
< 4.0	1.3	1.1	1.6
Hb			
≥ 12	1.0	1.0	1.0
< 12	1.4	1.2	1.7
Platelet			
≥ 150	1.0	1.0	1.0
< 150	1.2	1.0	1.5
Treatment			
Chemotherapy			
Yes	1.0	1.0	1.0
No	1.5	1.3	1.8
Radiotherapy			
Yes	1.0	1.0	1.0
No	1.2	1.0	1.5
Targeted therapy			
Yes	1.0	1.0	1.0
No	1.1	0.9	1.4

Variable	Univariate Model			Full Multivariate Model			Reduced Multivariate Model		
	OR	95%CI	P	OR	95%CI	P	OR	95%CI	P
Patients' risk									
Gender			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
Vert 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

Tumor's risk	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			
	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 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

Figures

Figure 1

Fig. 1 The trend of unacceptable chemotherapy in pathological stage II/III stage gastric cancer patients between 2011 and April 2015

Figure 2

Fig. 2 Survival of patients in AC and UAC groups. A: The OS of AC group vs UAC group. B: the OS among AC group, Delay (>60 days) and No chemotherapy. C: the DFS of AC group vs UAC group. D: the DFS among AC group, Delay (>60 days) and No chemotherapy.

Figure 3

Fig. 3 Analysis of the risk factors of unacceptable chemotherapy from 2011 to April 2015, † P value <0.05.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable.doc](#)