

ORIGINAL RESEARCH ARTICLE

Efficacy of a phlegm-resolving traditional Chinese medicine regimen in advanced gastric cancer: A retrospective observational study

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Abstract

Introduction: Traditional Chinese medicine has been shown to improve survival and immune function in patients with advanced gastric cancer (AGC).**Objectives:** This study aimed to evaluate the efficacy of a phlegm-resolving regimen (Ziyin Huatan recipe combined with Xiaoaiping injection) and syndrome differentiation-guided therapy combined with various antineoplastic Chinese patent medicine injections in AGC.**Methods:** Data from 150 patients with AGC were retrospectively analyzed: 75 in the study group and 75 in the control group. The clinical data were analyzed, including Karnofsky Performance Status (KPS), 1-, 2-, and 3-year survival rates, overall survival (OS), median OS, progression-free survival (PFS), and median PFS.**Results:** At 3 months, the mean KPS score significantly increased from 55.33 ± 6.44 to 73.07 ± 8.70 in the study group ($p = 0.001$ [<0.01]), and from 54.93 ± 6.23 to 72.40 ± 8.67 ($p = 0.001$ [<0.01]) in the control group. There was no significant difference in the changes of KPS score between the two groups. The median OS was 17.0 months in the study group (95% confidence interval [CI]: 13.16–20.84) versus 14.7 months in the control group (95% CI: 8.89–20.51). There was no significant difference in the OS between the two groups. The median PFS was 16.0 months in the study group (95% CI: 11.17–16.83) versus 12.0 months in the control group (95% CI: 7.48–16.52). The 1-year and 3-year PFS rates in the study group were higher than in the control group (61.33% versus 49.3% and 21.3% versus 14.7%, respectively).**Conclusion:** Our retrospective study suggests that phlegm-resolving regimens may confer survival benefits in patients with AGC; accordingly, such regimens can be considered for incorporation into standardized treatment strategies.**Keywords:** Advanced gastric cancer; Ziyin Huatan recipe; Xiaoaiping injection; Survival analysis[†]These authors contributed equally to this work.***Corresponding authors:**Dazhi Sun
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1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and the fifth leading cause of cancer-related mortality worldwide, with over one-third of new cases and deaths occurring in China.^{1,2} A large proportion of patients are diagnosed at an advanced stage of the disease, approximately 21.4% in China and 42.7% in the United States.³ The

treatment strategies for GC, including targeted therapy, immune checkpoint inhibition, antibody–drug conjugates, neoadjuvant conversion therapy, and minimally invasive radical gastrectomy, have evolved considerably over the last decade.^{4,6} However, the median survival of patients with advanced GC (AGC) is less than one year globally,⁷ and the 5-year overall survival (OS) of patients with AGC is approximately 13% in China.⁸ Therefore, there is still an unmet need for more effective treatments for AGC. Traditional Chinese medicine (TCM) has been widely used in China and other Asian countries for decades to treat AGC, relieve tumor-related symptoms, improve quality of life, and prolong survival.^{9–11} Multiple antineoplastic Chinese patent medicine injections (e.g., *Brucea javanica* oil emulsion injection, ShenQiFuZheng injection, Xiaoaiping) and TCM formulas have demonstrated beneficial effects in improving short- and long-term survival, myelosuppression, and immune function.¹² Nevertheless, TCM physicians usually prescribe variable Chinese herbal formulas for patients with AGC based on their academic background and expertise in clinical settings. The lack of standardized criteria for syndrome differentiation and intervention protocols limits the practicality and clinical applicability of TCM treatment for patients with AGC both domestically and internationally.

A standardized syndrome diagnosis plays a key role in developing a TCM treatment plan for a disease or its specific stage.¹³ In clinical practice, we have found that patients with AGC present complicated clinical manifestations concomitant with various concurrent syndromes. Deficiency of healthy *qi* intertwines with cancer toxin, phlegm turbidity, blood stasis, water-dampness, and *qi* stagnation, jointly contributing to the formation of pathological alterations. Stomach *yin* insufficiency is the root driver of disease deterioration; phlegm-toxin accumulation and metastatic spread are the superficial excess manifestations that persist throughout the entire disease course. Therefore, we propose that “*yin* deficiency combined with phlegm and toxin” may serve as a core syndrome differentiation pattern in AGC.¹⁴ The TCM treatment principle includes nourishing *yin*, resolving phlegm, dissipating nodules, clearing heat, removing toxin, and resolving dampness for this syndrome differentiation type. We developed a phlegm-resolving regimen consisting mainly of the Ziyin Huatan recipe (ZYHT) and the Xiaoaiping injection. Additional Chinese medicinal herbs are supplemented based on patients’ individual concomitant syndrome differentiation to enhance clinical efficacy. ZYHT is composed of *Lilii Bulbus* (Baihe), *Pinelliae Rhizoma* (Banxia), and *Hedyotis diffusa* (Baihua sheshecao). Xiaoaiping injection, a classic proprietary Chinese medicinal injection derived from the

radix and caulis of *Marsdenia tenacissima* (Tongguanteng) native to Yunnan and Guizhou, has gained extensive clinical application in oncotherapy. The main indications of Xiaoaiping include gastric, esophageal, lung, and liver cancers. It has the functions of clearing heat, resolving phlegm turbidity, dissipating stasis, and removing toxins associated with carcinoma.¹⁵ For patients diagnosed with the TCM pattern of “*yin* deficiency combined with phlegm and toxin,” ZYHT and Xiaoaiping injection share overlapping medicinal targets and jointly exert therapeutic interventions against this TCM syndrome. Both ZYHT and Xiaoaiping injections have improved objective response rate, survival, and quality of life among patients with AGC in previous studies.^{16,17} However, the actual efficacy of a phlegm-resolving regimen for AGC remains undetermined.

We conducted a retrospective exploratory observational study to preliminarily evaluate the efficacy of this phlegm-resolving regimen. In this retrospective clinical study, full medical records of all enrolled patients with AGC who underwent phlegm-resolving herbal regimens at Changzheng Hospital starting in 2015 were retrospectively collected and analyzed. Additionally, we enrolled AGC patients who received traditional syndrome differentiation-guided therapy combined with various antineoplastic Chinese patent medicine injections from 2005 to 2015. This study presents treatment outcomes for all included AGC patients, including survival and quality of life.

2. Materials and methods

2.1. Study population

This retrospective observational study included 150 AGC patients admitted to Changzheng Hospital between January 2005 and January 2022. Eligible patients were aged between 18 and 75 years; had histologically confirmed AGC;⁶ had a Karnofsky Performance Status (KPS) score > 50; and had survived for ≥ 3 months after admission. Patients were excluded if they had any of the following characteristics: serious complications (severe cardiac, hepatic, pulmonary, renal diseases or hematological disorders, or other severe conditions that affect survival); pregnancy or lactation; mental disorders; suspected alcohol or drug abuse; and inaccurate survival-time data or were lost to follow-up. The study group was comprised of 75 patients who received a phlegm-resolving regimen during hospitalization since 2015. The controls were randomly selected from 300 patients with AGC who were admitted to our hospital between January 2005 and May 2015 and matched to the study group by histologic subtype, surgical history, treatment modality, and other factors. Finally, 75 patients who had received the TCM physician’s choice

of traditional syndrome differentiation-guided therapy combined with various antineoplastic Chinese patent medicine injections were assigned to the control group. All patient data were anonymized in compliance with the Declaration of Helsinki to protect patient privacy.

2.2. Treatment

2.2.1. Phlegm-resolving regimen

The basic principles of TCM treatment were “nourishing *yin* and resolving phlegm” by ZYHT, “clearing heat and removing toxin,” and “resolving phlegm and softening masses” by Xiaoaiping injection. Chemotherapy and palliative surgery were tailored to the clinical characteristics of individual patients.

Formulation of ZYHT included: 30 g of *Lilii Bulbus* (Baihe), 15 g of *Pinelliae Rhizoma Preparata* (Banxia), and 30 g of *Hedyotis diffusa* (Baihuasheshecao). Herbs were modified and supplemented to the basic formula according to the differentiated concurrent TCM patterns of individual patients.

- (i) *Qi* deficiency of the spleen and stomach pattern: *Astragali Radix Preparata* (Huangqi) 15 g, *Atractylodis macrocephalae Rhizoma* stir-fried (Baizhu) 15 g, *Poria Cocos* (Fuling) 15 g;
- (ii) *Yang* deficiency of the spleen and stomach pattern: *Radix Aconiti Lateralis Preparata* (Fuzi) 6 g, *Rhizoma Zingiberis* (Ganjiang) 6 g;
- (iii) *Yin* deficiency of the spleen and stomach pattern: *Polygonati Odorati Rhizoma* (Yuzhu) 15 g, *Polygonati Rhizoma Preparata* (Huangjing) 15 g, *Glehniae Radix* (Shashen) 15 g;
- (iv) Blood deficiency: *Codonopsis Radix* (Dangshen) 15 g, *Angelicae Sinensis Radix* (Danggui) 15 g, *Spatholobi Caulis* (Jixueteng) 30 g;
- (v) *Qi* stagnation of the spleen and stomach pattern: *Aurantii Fructus* (Zhishi) 15 g, *Aucklandiae Radix* (Muxiang) 9 g, *Amomi Fructus* (Sharen) 6 g;
- (vi) Internal retention of pathogenic dampness: *Atractylodis Rhizoma* (Cangzhu) 15 g, *Magnoliae Officinalis Cortex* (Houpu) 15 g, *Agastaches Herba* (Huoxiang) 15 g;
- (vii) Stagnant blood obstructing the meridians pattern: *Aspongopus Chinensis* (Jiuxiangchong) 6 g, *Trogopterori Faeces* (Wulingzhi) 10 g, *Curcumae Rhizoma* (Ezhu) 15 g;
- (viii) Hyperactive pathogenic cancer toxin pattern: *Gekko Swinhonis* (Bihu) 6 g, *Vespae Nidus* (Fengfang) 9 g, *Bufois Cutis* (Chanpi) 6 g.

For patients presenting with the symptoms listed below, corresponding medicinal herbs were supplemented to the basic prescription.

- (i) Burping: *Haematitum* (Zheshi) 15 g;
- (ii) Acid regurgitation: *Impatiens Semen* (Jixingzi) 9 g;
- (iii) Epigastric upset: *Sepiae Endoconcha* (Haipiaoxiao) 30 g;
- (iv) Bleeding: *Notoginseng Radix et Rhizoma* (Sanqi) 6 g;
- (v) Loss of appetite: *Crataegi Fructus Carbonisatus* (Shanzha) 30 g;
- (vi) Ascites: *Phytolaccae Radix* (Shanglu) 15 g.

The fundamental ZYHT decoction with syndrome-modified supplementary herbs was prepared by the TCM Pharmacy at Changzheng Hospital according to TCM practitioners' prescriptions. Approximately 400 mL of decoction was prepared. After filtration, the filtrate was split into two equal aliquots of 200 mL each. Patients in the study group were instructed to take one aliquot warm in the morning and the other in the evening throughout the treatment course.

Xiaoaiping injection (20 mL/vial; Nanjing Sanhome Pharmaceutical Co., Ltd., China; approved by the National Medical Products Administration, Z20025868) was administered at a dose of 80 mL/d (4 vials, 20 mL/vial).

2.2.2. Physician's choice of various traditional Chinese medicine treatments

Patients in the control group received conventional Chinese medicinal herbs treatment based on TCM syndrome differentiation prescribed by attending TCM physicians. The regimens consisted of oral Chinese herbal decoctions combined with various anti-tumor Chinese patent medicine injections, selected by the TCM physician for the treatment of GC. Chemotherapy and palliative surgical interventions were individualized according to each patient's clinical profile.

2.3. Outcome measurements

Data were collected from the electronic inpatient medical records, and a standardized form was completed prior to the analysis. Performance status was assessed using the KPS scale at admission and 3 months after TCM treatment. The KPS is an 11-point assessment tool that ranges from 100 (normal, no complaints, no signs of disease) to 0 (death).¹⁸

Overall survival was defined as the time from the first treatment to death. Progression-free survival (PFS) was defined as the time from the date the patient started study treatment to the date the patient experienced disease progression or death. The clinical data of the two groups were compared, including KPS, 1-, 2-, and 3-year survival rates, OS, median OS, PFS, and median PFS.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 24.0 (IBM

SPSS Statistics; IBM Corporation, United States of America). Measurement data were expressed as mean $\pm$ standard deviation, and enumeration data were presented as rates. Data conforming to normal distribution were compared using the *t*-test, whereas non-normally distributed variables were analyzed with the rank-sum test. Categorical variables were compared across groups using the Chi-square test. Survival analysis was conducted using the Kaplan–Meier method, and multivariate survival analysis was performed using the Omnibus test and Cox regression analysis. A two-tailed test was used for all analyses, with the significance level set at $\alpha = 0.05$.

3. Results

3.1. Baseline characteristics

A total of 150 patients with AGC were included in this observational study. The study group was comprised of 75 patients who received a phlegm-resolving regimen. On the other hand, 75 patients were assigned to the control group and received a TCM physician's choice of traditional syndrome differentiation-guided therapy combined with various antineoplastic Chinese patent medicine injections. Most patients had a KPS functional status score of 50–60 points. The majority of baseline characteristics were well balanced between the two groups, with borderline imbalance observed in the proportion of patients receiving palliative surgery ($p = 0.060$; Table 1).

3.2. Karnofsky's performance status score

At 3 months, the mean KPS score significantly increased from 55.33 ± 6.44 to 73.07 ± 8.70 in the study group ($p = 0.001$ [<0.01]), and there was also a significant trend toward an increase in the mean KPS score in the control group (54.93 ± 6.23 versus 72.40 ± 8.67 ; $p = 0.001$ [<0.01]). However, there was no significant difference in KPS score changes between the two groups ($p > 0.05$; Table 2).

3.3. Survival analysis

The median OS was 17.0 months in the study group (95% confidence interval [CI]: 13.16–20.84) versus 14.7 months in the control group (95% CI: 8.89–20.51). The 1-, 2-, and 3-year survival rates were 64.0%, 32.0%, and 25.3% in the study group, and 54.7%, 32.0%, and 24.0% in the control group, respectively. There was no significant difference in the OS between the two groups ($\chi^2 = 0.243$; $p = 0.622$; Table 3; Figure 1).

The median PFS was 16.0 months in the study group (95% CI: 11.17–16.83) versus 12.0 months in the control group (95% CI: 7.48–16.52). The 1-, 2-, and 3-year PFS rates were 61.33%, 28.0%, and 21.3% in the study group, and 49.3%, 28.0%, and 14.7% in the control group,

respectively. The 1-year and 3-year PFS rates in the study group were higher than in the control group (61.33% versus 49.3% and 21.3% versus 14.7%, respectively). Although not statistically significant (log-rank test, $p > 0.05$), there was a tendency toward a PFS benefit for the study group (Table 4, Figure 2).

Table 1. Patient characteristics at baseline

Variables	Control group (<i>n</i> = 75)	Study group (<i>n</i> = 75)	<i>p</i>
Age	61.76 $\pm$ 11.12	64.36 $\pm$ 10.52	0.143
Gender			
Male	60	65	0.453
Female	15	10	
Smoking history			
Yes	20	22	0.716
No	55	53	
Drinking history			
Yes	11	14	0.511
No	64	61	
Family history			
Yes	10	10	1.000
No	65	65	
Gross type			
Elevated	25	34	0.146
Flat	42	38	
Depressed	8	3	
Tumor location			
Proximal	19	11	
Body	14	17	0.911
Distal	25	29	
Overlapping lesion	4	13	
Total stomach	13	5	
World Health Organization subtype			
Tubular adenocarcinoma	26	25	
Papillary adenocarcinoma	27	25	0.686
Mucinous adenocarcinoma	9	10	
Signet-ring cell	7	11	
Mixed adenocarcinoma	3	2	
Other	3	2	

(cont'd...)

Table 1. (Continued)

Variables	Control group (n = 75)	Study group (n = 75)	p
Histology			
Well and moderate	16	23	0.193
Poor	59	52	
Palliative surgery			
Yes	14	24	0.060*
No	61	51	
Chemotherapy			
Yes	57	51	0.275
No	18	24	

Note: *Palliative surgery yielded a borderline *p*-value of 0.060, indicating a trend toward imbalance.

Table 2. Karnofsky's performance status scores of the two groups

Duration	Study group n = 75	Control group n = 75	p
Baseline	55.33 ± 6.44	54.93 ± 6.23	0.598
After 3 months	73.07 ± 8.70*	72.40 ± 8.67*	0.534

Note: *Within-group pre- and post-comparisons: *p* < 0.001.

Table 3. Overall survival of the two groups

Survival outcome	Study group n = 75	Control group n = 75	χ ²	p
Median OS, months (95% CI)	17.0 (13.16–20.84)	14.7 (8.89–20.51)	0.243	0.622
Survival rate, n (%)				
1 year	48 (64.0)	41 (54.7)		
2 year	24 (32.0)	24 (32.0)		
3 year	19 (25.3)	18 (24.0)		

3.4. Multivariate survival analysis

Multivariate analysis showed no significant survival difference between the study group and the control group (hazard ratio [HR]: 1.000, 95% CI: 0.671–1.492; *p* = 0.998). Furthermore, smoking history (HR: 2.735, 95% CI: 1.626–4.598; *p* = 0.001 [*p* < 0.01]) and palliative surgery (HR: 0.571, 95% CI: 0.356–0.916; *p* = 0.020) were identified

as independent prognostic factors for survival in the multivariate analysis (Table 5). While the proportion of patients undergoing palliative surgery showed borderline statistical imbalance across study groups at baseline, this covariate was incorporated into the Cox proportional hazards regression model and emerged as an independent favorable prognostic marker.

Table 4. Progression-free survival of the two groups

Progression-free survival outcome	Study group n = 75	Control group n = 75	χ ²	p
Median PFS, months (95% CI)	16.0 (11.17–16.83)	12.0 (7.48–16.52)	1.37	0.242
Survival rate, n (%)				
1 year	46 (61.33)	37 (49.3)		
2 year	21 (28.0)	21 (28.0)		
3 year	16 (21.3)	11 (14.7)		

4. Discussion

Traditional Chinese medicine has demonstrated encouraging clinical efficacy in patients with AGC in China by mitigating tumor-related symptoms, improving quality of life, and prolonging survival.^{9–11} Phlegm-resolving formulas and proprietary Chinese medicinal preparations with comparable therapeutic efficacies play an important role in the management of AGC.¹⁴ This retrospective exploratory observational study collected clinical data of inpatients to preliminarily evaluate the efficacy of a phlegm-resolving regimen (study group) versus traditional syndrome differentiation-guided therapy combined with various antineoplastic Chinese patent medicine injections (control group) in patients with AGC. Our results demonstrated that both the phlegm-resolving regimen and other conventional therapies achieved clinical benefits in KPS, PFS, and OS for patients with AGC.

Improved performance status predicts favorable treatment outcomes, including prolonged survival in AGC.^{18,19} In a previous study, we compared the clinical efficacy of ZYHT combined with chemotherapy (S-1 and oxaliplatin [SOX]) and SOX only among AGC patients with KPS > 70.¹⁶ The mean KPS score was significantly improved in the ZYHT plus SOX group compared to that

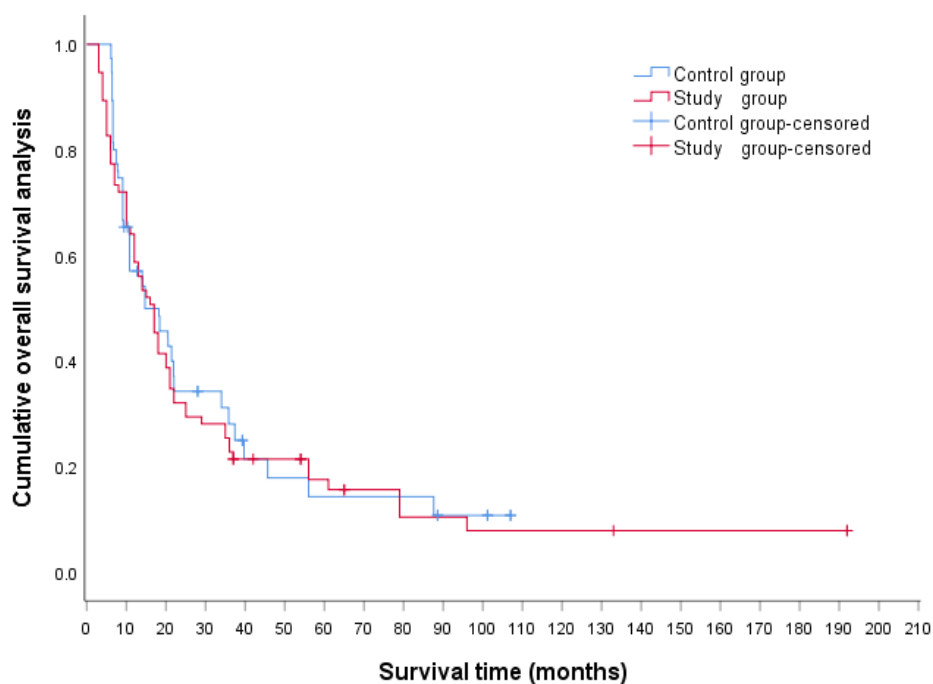


Figure 1. Overall survival

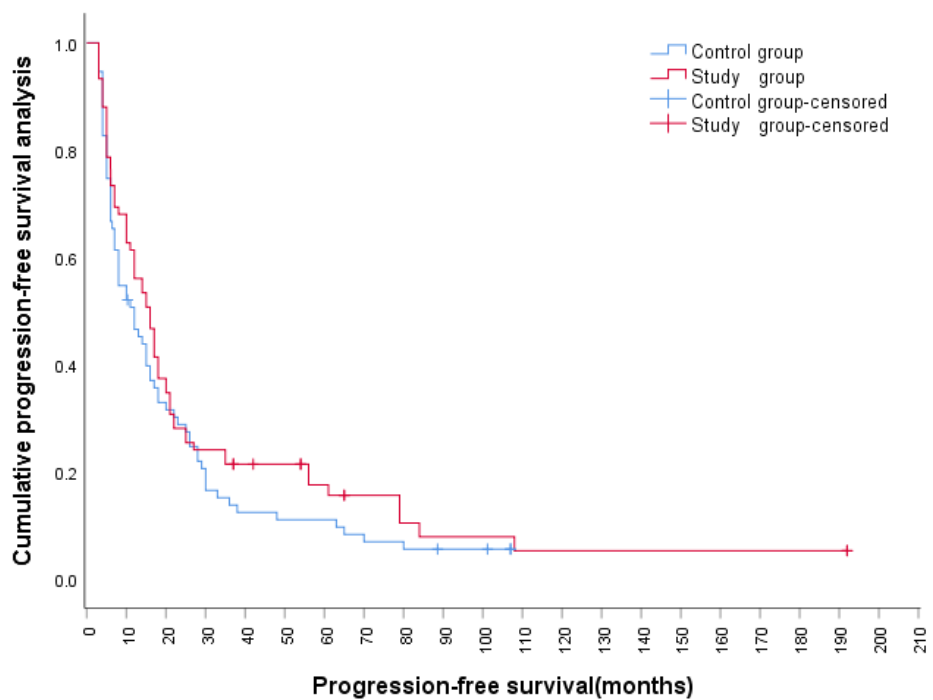


Figure 2. Progression-free survival

Table 5. Multivariate analysis of clinical variables for overall survival

Variables	Category	<i>p</i>	Hazard ratio	95.0% confidence interval	
Phlegm-resolving	Yes versus no	0.998	1.000	0.671	1.492
Smoking history	Yes versus no	0.001	2.735	1.626	4.598
Drinking history	Yes versus no	0.178	0.658	0.357	1.210
Family history	Yes versus no	0.844	0.948	0.558	1.612
Gross type	Flat versus elevated	0.645	0.913	0.620	1.344
	Depressed versus elevated	0.272	0.656	0.309	1.391
Tumor location	Body versus proximal	0.127	0.614	0.328	1.149
	Distal versus proximal	0.626	1.161	0.637	2.115
	Overlapping lesion versus proximal	0.280	0.685	0.344	1.362
	Total stomach versus proximal	0.302	0.637	0.271	1.499
World Health Organization subtype	Papillary adenocarcinoma versus tubular adenocarcinoma	0.048	0.584	0.343	0.996
	Mucinous adenocarcinoma versus tubular adenocarcinoma	0.924	1.030	0.560	1.895
	Signet-ring cell versus tubular adenocarcinoma	0.979	0.991	0.525	1.872
	Mixed adenocarcinoma versus tubular adenocarcinoma	0.579	0.736	0.250	2.169
	Other versus tubular adenocarcinoma	0.165	2.098	0.736	5.978
Histology	Undifferentiated versus differentiated	0.114	0.694	0.440	1.092
Palliative surgery	Yes versus no	0.020	0.571	0.356	0.916
Chemotherapy	Yes versus no	0.191	1.421	0.839	2.406

of SOX alone group, before and after treatment. The KPS score increased from 72.50 ± 4.94 to 79.50 ± 6.78 in the ZYHT plus SOX group, while it decreased from 71.00 ± 5.91 to 69.25 ± 14.03 in the SOX-only group. Our present study demonstrated that ZYHT + Xiaoaiping improved KPS in patients with even lower KPS scores. Almost all patients were scored at 50 or 60 on the KPS before receiving the TCM regimens in both groups. The mean KPS score significantly increased from 55.33 ± 6.44 to 73.07 ± 8.70 from baseline to month 3 in the study group ($p = 0.001$), and there was also a significant trend ($p = 0.001$ [<0.01]) toward an increase in mean KPS score in the control group (54.93 ± 6.23 versus 72.40 ± 8.67). However, there was no significant difference in KPS score between the two groups. Our results attest to the clinical value of TCM therapies in improving self-management capability among AGC patients. The phlegm-resolving regimen improves clinical practicability by using a single oral TCM decoction and a

single TCM herbal extract injection.

A large population-based cohort study, including data from 40,158 patients, described trends in stage distribution, treatment patterns, and survival among patients with GC in China between 1998 and 2022. At the national level, the 1- and 3-year OS rates of patients with AGC were 59.7% (95% CI: 57.8–61.6) and 22.7% (95% CI: 21.1–24.3), respectively.²⁰ Another similar study, which included data from 220,304 patients in China from 2017 to 2023, found that the median OS of AGC patients was 14.82 months (95% CI: 14.62–15.01), and the 1-, 2-, and 3-year OS rates were 57.52% (95% CI: 57.05–58.00), 33.58% (95% CI: 33.06–34.10), and 22.51% (95% CI: 22.00–23.05), respectively.⁸ The two studies represent the general outcomes of existing modern treatments such as surgery, chemotherapy, immunotherapy, and targeted therapy in China. In our study, the median PFS was 16.0 months and 12.0 months in the study and control groups,

respectively, whereas the median OS was 17.0 months and 14.7 months. The study group showed a trend toward longer median PFS and OS relative to the control group. In addition, the 1-, 2-, and 3-year survival rates were similar between the two groups: 64.0% versus 54.7%, 32.0% versus 32.0%, and 25.3% versus 24.0%, respectively. The 1-year and 3-year PFS rates in the study group were higher than in the control group (61.33% versus 49.3% and 21.3% versus 14.7%, respectively). There was no significant difference in PFS between the two groups (log-rank, $p > 0.05$). Multivariate analysis showed no significant survival difference between the study group and the control group (HR: 1.000, 95% CI: 0.671–1.492; $p = 0.998$). Our study cohorts exhibited similar trends in PFS and OS rates to national cohorts. Since participants in both groups received either a phlegm-resolving regimen or diversified TCM therapeutic schedules, TCM interventions are suggested to confer survival benefits to patients with AGC.

Meanwhile, the multivariate analysis showed that smoking history was associated with a higher mortality rate (HR: 2.735, 95% CI: 1.626–4.598; $p = 0.001$ [<0.01]). Our results are similar to an analysis by Zhang *et al.*,²¹ in which the mortality risk for GC patients who smoke is higher than for non-smokers. The multivariate analysis indicated that palliative surgery was an independent positive prognostic factor for OS (HR: 0.571, 95% CI: 0.356–0.916; $p = 0.020$). This finding aligns with a meta-analysis showing that OS was significantly prolonged (HR: 1.49, 95% CI: 1.12–1.99; $p = 0.006$) among AGC patients who underwent palliative surgery compared with those who did not receive surgery, regardless of the type of surgery performed and the length of hospitalization.²² For patients with AGC, palliative surgery can alleviate symptoms including obstruction, bleeding, pain, and nausea, and it may also contribute to prolonging their survival time and slowing down disease progression.²³

Previous experimental studies have demonstrated anticancer potential by removing pathological substances in the “tumor–phlegm microenvironment” using phlegm-resolving herbs in the treatment of AGC.^{24,25} “Yin deficiency combined with phlegm and toxin” may serve as a core syndrome differentiation type in patients with AGC.¹⁴ To relieve symptoms related to this syndrome type in AGC, we prescribed an herbal formula named ZYHT, which was composed of Lili Bulbus (nourishing yin), Pinelliae Rhizoma (resolving phlegm and dissipating nodules), and *Hedyotis diffusa* (clearing heat, removing toxin and resolving dampness) for patients with AGC. Additional TCM herbs were added to the principal formula to alleviate individual patients’ signs and symptoms to improve the prognosis. On this basis, a proprietary herbal preparation,

Xiaoaping injection (*Marsdenia tenacissima* extract), was incorporated into the phlegm-resolving regimen. In TCM, *Marsdenia tenacissima* has a bitter, slightly sweet taste with a cool medicinal property. It enters the lung, stomach, and bladder meridians and exerts effects such as clearing heat, resolving phlegm turbidity, softening masses, and removing toxins associated with carcinoma. Its chemical constituents mainly include steroidal saponins, alkaloids, flavonoids, polysaccharides, resins, and pigments; many of these compounds exhibit anti-tumor activity.¹⁵ Results from the present study may provide clinical evidence that the pattern of yin deficiency intermingled with phlegm-toxin is the predominant syndrome type among patients with AGC.

Several limitations of the present study should be noted. Firstly, there is a 10-year gap between the control cohort (2005–2015) and the study cohort (2015–2022). Except for TCM therapies, the non-TCM treatment regimens provided to AGC patients varied between the two study periods. This single-center retrospective cohort study is limited by hospital practice: standardized phlegm-resolving therapy was unavailable before 2015, with only routine treatment used from 2005 to 2015. Thus, we could not align the enrollment windows between the two groups, and this confounding factor cannot be fully excluded due to data constraints. Secondly, there existed a borderline baseline imbalance with regard to palliative surgical intervention across the two cohorts ($p = 0.060$). Adequately powered larger cohorts in follow-up studies are expected to reduce such marginal imbalance. Thirdly, this retrospective study has a key limitation: standardized prospective collection of adverse events (AEs) was not performed because medical records lacked unified AE-recording forms. Long follow-up gaps for most patients prevented the administration of supplementary structured AE surveys. Clinically, the regimen was Xiaoaping injection plus ZYHT herbal decoction prescription without potent or toxic herbs; liver and kidney function were regularly monitored during treatment. No serious AEs clearly linked to this combination were found in medical records. We recommend prospective trials that use standardized AE documentation to fully assess the regimen’s safety. Additionally, the use of single-center data restricts the generalizability of the findings to broader populations. Furthermore, other limitations include a relatively small sample size, which may compromise statistical power, and the inability to analyze certain key variables owing to the study design and limited data availability. These limitations warrant cautious interpretation of the current findings and underscore the need for further prospective studies to address research gaps and confirm the results.

5. Conclusion

This retrospective observational study demonstrated that a phlegm-resolving regimen is an effective TCM regimen in AGC patients. We suggest that this therapeutic regimen should be further tested in patients with AGC. The phlegm-resolving regimen could simplify routine clinical TCM diagnostic and therapeutic processes in the management of AGC. The implementation of a standardized TCM regimen may enable some patients to accept more aggressive treatment modalities, thereby further increasing life expectancy.

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Conflict of interest

The authors declare they have no competing interests that might influence the work reported in this paper.

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Ethics approval and consent to participate

This retrospective study was approved by the institutional review board at Changzheng Hospital (20211211). All patient data were anonymized in compliance with the Declaration of Helsinki to protect patient privacy.

Consent for publication

This is a retrospective study; therefore, consent for publication from the participants is not required.

Availability of data

The data used and analyzed in this study shall be provided by the corresponding author upon reasonable request.

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