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Original Article

Traditional Chinese medicine integrated chemotherapy can improve the prognosis of patients with stage III gastric cancer after radical surgery: a retrospective clinical analysis

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Abstract: Synchronous chemotherapy after radical surgery is the primary treatment for stage III gastric cancer. Traditional Chinese medicine (TCM) plays as a complementary and alternative medicine for the treatment of gastric cancer in China. In this study, 302 stage III gastric cancer cases were retrospectively analyzed to evaluate the effect of TCM combined with synchronous chemotherapy after radical surgery. Of the 302 patients, 170 were included in the integrated group and receiving combined therapy and 132 patients were included in the control group. Survival rates were calculated by Kaplan-Meier method. Karnofsky Performance Status (KPS) score was used to compare the rank sum test between the groups. Factors possibly affecting the survival were assessed by multivariate analysis in the Cox proportional hazard model. The median disease-free survival (DFS) was 29.5 months (95% confidence interval [95% CI], 21.04-37.96) in the integrated group vs 16.6 months (95% CI, 13.08-20.12) in the control group. The median overall survival (OS) was 39.7 months (95% CI, 33.94-45.46) in the integrated group and 25.9 months (95% CI, 22.38-29.42) in the control group. After 6 months of treatment, the KPS scores were significantly improved in the integrated group compared with the control group (81.47±17.70 vs 74.55±20.43). Cox regression analysis revealed that TCM treatment was a protective factor for patients to improve DFS and OS. Current study data demonstrated that TCM integrated chemotherapy may prolong DFS, OS, and improve the quality of life of patients with stage III gastric cancer after radical surgery.

Keywords: Gastric cancer, radical surgery, chemotherapy, traditional Chinese medicine, combination therapy

Introduction

Gastric cancer is the second leading cause of cancer-related deaths in the world, and approximately 700000 patient deaths occur each year [1, 2]. In China, there are approximately 405000 new cases diagnosed with gastric cancer each year, which accounts for 42.6% of the global incident rate [3]. Radical surgery offers the only chance of cure for patients with operable gastric cancer. The D2 radical surgery has been recognized as the standard surgery for locally advanced gastric cancer throughout the world [4]. Chemotherapy, radiotherapy and targeted therapy together have become the mainstay of treatment for locally advanced gastric cancer [5, 6]. This treatment demonstrated positive effects by improving the tumor resection rate and prognosis [7, 8]. However, most patients with gastric cancer in East Asia get diagnosed at the metastasis stage. Over the last 2 years, there are more than 70% of patients with recurrence and cancer-related deaths, but the overall effect showed no significant improvement and enhancement even after receiving synchronous chemotherapy and (or) radiotherapy after D2 radical surgery [9]. Therefore, it is of great significance to find an effective treatment strategy for improving the prognosis of patients with advanced gastric cancer.

Table 1. Patient characteristics in two groups

Characteristics	Integrated group (n=170)	Control group (n=132)	*P*-value
Age	60.58±10.89	56.64±11.52	0.005
Sex			0.819
Men	118 (69.41)	90 (68.18)	
Women	52 (30.59)	42 (31.82)	
Smoking history			0.492
Yes	38 (22.35)	34 (25.76)	
No	132 (77.65)	98 (74.24)	
Drinking history			0.147
Yes	34 (20.00)	18 (13.64)	
No	136 (80.00)	114 (86.36)	
Family history of cancer			0.654
Yes	6 (3.53)	6 (4.55)	
No	164 (96.47)	126 (95.45)	
Tumor type			0.121
Mass type	48 (28.24)	30 (22.73)	
Ulcer type	110 (64.71)	86 (65.15)	
Erosion type	12 (7.06)	16 (12.12)	
Tumor invasion range			0.913
Cardia-fundus	30 (17.65)	24 (18.18)	
Gastric body	70 (41.18)	52 (39.39)	
Gastric antrum	52 (30.59)	42 (31.82)	
Two parts	12 (7.06)	8 (6.06)	
Full of gastric	6 (3.53)	6 (4.55)	
Pathological type			0.749
Papillary adenocarcinoma	54 (31.76)	42 (31.82)	
Tubular adenocarcinoma	58 (34.12)	42 (31.82)	
Mucinous adenocarcinoma	10 (5.88)	12 (9.09)	
Signet ring cell carcinoma	16 (9.41)	24 (18.18)	
Mixed type carcinoma	26 (15.29)	10 (7.58)	
Others	6 (3.53)	2 (1.52)	
Degree of histological differentiation			0.500
High-medium differentiation	48 (28.24)	42 (31.82)	
Low or undifferentiated	122 (71.76)	90 (68.18)	
Lymph node metastasis			0.076
Yes	110 (64.71)	98 (74.24)	
No	60 (35.29)	34 (25.76)	
TNM stage			0.099
III A	50 (29.41)	34 (25.76)	
III B	62 (36.47)	38 (28.79)	
III C	58 (34.12)	60 (45.45)	
KPS score of prior treatment	74.12±6.21	73.71±5.44	0.361

KPS: Karnofsky Performance Status.

In recent years, traditional Chinese medicine (TCM) as a complementary and alternative medicine has played an important role in the comprehensive treatment of gastric cancer in China. Several new preparations of TCM, such as Lentinan (LNT) [10], Xiaoaiping injection [11] and KLT injection [12] etc, have proved superior efficacy over other therapies, lessened the damage caused by chemo- or radiotherapies and improved the quality of life of patients. The Department of TCM, Shanghai Changzheng Hospital, has long been engaged in the prevention and treatment of gastric cancer with integrated treatment of TCM and western medicine. A new preparation of Jinlongshe oral solution based on "Phlegm Syndrome" theory of gastric cancer has been put forward. Clinical studies showed that Jinlongshe oral solution could reduce fatigue, vomiting, pain and other symptoms, and improved the quality of life of patients with stage IV gastric cancer combined with chemotherapy [13]. So far, the survival benefit of gastric cancer patients with TCM, as well as the effect of TCM combined with synchronous chemotherapy still remains unclear. In this study, we conducted a preliminary retrospective analysis to evaluate the efficacy of TCM in patients with stage III gastric cancer after radical surgery with synchronous chemotherapy at Changzheng Hospital.

Material and methods

A retrospective case-control study was performed to report the result of synchronous chemotherapy in combination with or without TCM in patients with stage III gastric cancer after radical surgery. Between January 1, 2005 and May 30, 2015, 302 patients with stage III gastric cancer and those who accepted radical surgery at Changzheng Hos-

Table 2. Karnofsky performance status score in two groups ($\bar{x}$±S)

Group	Prior treatment	After 6 months of treatment
Control group	73.71±5.44	74.55±20.43
Integrated group	74.12±6.21	81.47±17.70
P-value	0.361	< 0.001

pital (Shanghai, China) were enrolled in this study. Diagnosis of gastric cancer was confirmed by the clinical diagnostic criteria issued by the Chinese Ministry of Health in 2011 [14] and TNM Staging Manual in 2010 [15]. The inclusion criteria were as follows: 1) patients with a definitive pathological diagnosis and who underwent initial therapy at our hospital, 2) patients who received synchronous chemotherapy (≥3 cycles) or synchronous chemotherapy (≥3 cycles) combined with TCM for one month after radical surgery, and had completed at least 6 months of treatment, 3) Karnofsky Performance Status (KPS) score of ≥60 points at the beginning of chemotherapy, 4) survival time of ≥6 months. The exclusion criteria were as follows: 1) non-epithelial cell origin or merged with other malignancies, 2) difficult to classify due to no standardized therapeutic medication, 3) patients combined with serious basic diseases, such as heart, brain, kidney and other diseases. There were 302 patients who met the above inclusion and exclusion criteria. Among the 302 patients, 170 patients who received combined therapy consisting of chemotherapy and a long-term maintenance treatment of TCM were grouped as integrated, while 130 patients who received chemotherapy alone were grouped as control. The 2 groups were comparable in sex, drinking, smoking, family history of cancer, tumor type, tumor invasion range, pathological type, histological grade, TNM stage and KPS score. Characteristics of 302 patients (208 men, 94 women; ratio, 2:1) are summarized in **Table 1**.

All 302 patients received radical surgery using a uniform technique. The patients in the control group received specific chemotherapy (≥3 cycles) after one month of radical surgery. The response and tolerance to chemotherapy were recorded and the physical functional status of the patients before and after chemotherapy was also evaluated.

The patients in the integrated group were initiated on standardized chemotherapy (≥3 cycles) and with a long-term maintenance treatment of TCM (≥3 months) after a month of radical surgery, including intravenous injection, oral decoction or Chinese patent medicine. TCM intravenous injection included were Kanglaite injection, Cinobufacini injection, Yadanziru injection, Elemene injection, and Xiaoaiping injection to eliminate dampness and reduce phlegm as a part of anti-tumor properties. These were administered once a day, and continuously for at least 7 days as a cycle. These include the oral decoction of Chinese herbal medicines, one dose each day, or the oral Chinese patent medicine (Xianrengu oral liquid, Jinlongshe oral liquid), three times a day, with a continuous intake time of ≥6 months, 30 minutes after meals.

Follow-up

All patients were followed up by telephone from the date of diagnosis to the date of death or till January 31, 2016. Death certificates for all cancer patients in Shanghai city are obtained from the Shanghai Municipal Center for Disease Control and Prevention of Cancer patient registration system. Two hundred and seventy eight patients were recurred or progressed with the disease, while 24 patients demonstrated DFS, censoring 8.61%. Sixty-six patients survived, and the remaining 236 patients died, censoring 21.85%. Of the 132 patients in the control group using chemotherapy, which may be combined with radiotherapy, molecular targeted therapy, 4 patients showed DFS, and the remaining 128 patients showed disease recurrence or progression, and of these 10 patients survived, and the remaining 122 patients died. Of the 170 patients in the integrated group using chemotherapy+TCM, 22 patients demonstrated DFS, and the remaining 148 patients showed disease recurrence or progression, and of these 56 patients survived, and the remaining 114 patients died. Statistical analysis showed that baseline pre-treatment in both the groups was comparable (P > 0.05). The mean follow-up period was 41.5±33.7 months.

Statistical analysis

Statistical analyses were carried out using SPSS18.0. The characteristics of the target groups were compared using t-test, chi-square test or nonparametric test. Survival analyses

Table 3. Disease-free survival time in two groups

Group	DFS rates (%)			Median DFS	95% CI	HR (95% CI)	χ^2	*P*-value
	1 year	3 years	5 years					
Control group	65	17	10	16.6	13.08-20.12	0.618 (0.474-0.805)	18.13	< 0.001
Integrated group	79	43	25	29.5	21.04-37.96			

DFS: Disease-free survival.

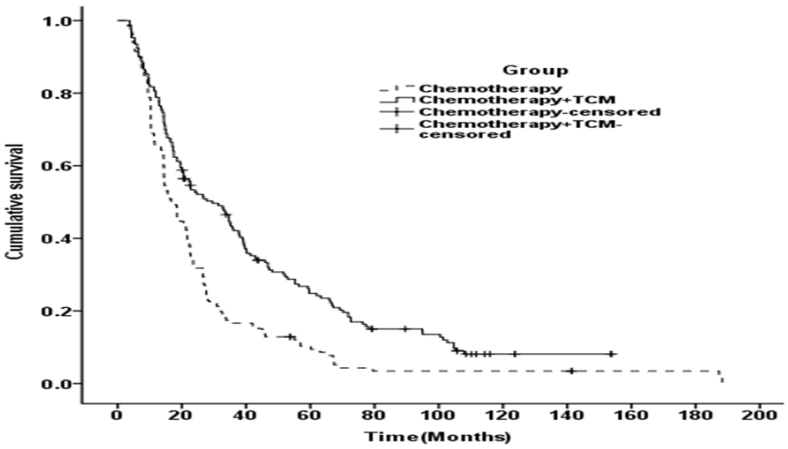

Figure 1. Overall disease-free survival was significantly longer in the integrated group (chemotherapy+TCM) compared with the control group (Chemotherapy alone), (median of 29.5 vs 16.6 months; relative risk [RR], 0.618, [P < 0.001]). TCM: Traditional Chinese Medicine; RR: relative risk.

for evaluating the overall survival (OS) and disease-free survival (DFS) rates were performed using Kaplan-Meier method and log-rank test. A Cox proportional hazards model was used to investigate the risk factors associated with gastric cancer death. The KPS scores were compared using either t-test or rank sum test. All test statistics were two tailed and *P* values < 0.05 were considered to indicate a statistically significant difference.

Results

Effect of TCM on quality of life of patients with survival

KPS scores were adopted to evaluate the quality of life of stage III gastric cancer patients after radical surgery before first chemotherapy and 6-months after radical surgery. The KPS score of patients before treatment in the integrated group was [(74.12±6.21) points], and in the control group was [(73.71±5.44) points]. The difference between the two groups showed no significant differences (P = 0.361). After 6 months, the KPS score of patients in the integrated group was significantly improved compared to the control group ([81.47±17.70] vs [74.55±20.43], P < 0.001, **Table 2**).

Effect of TCM on patients with disease-free survival

The overall median DFS time of 302 patients was 21.4 months (95% confidence interval [95% CI], 19.02-23.78 months). The median overall DFS was 29.5 months (95% CI, 21.04-37.96 months) in the integrated group, while it was 16.6 months (95% CI, 13.08-20.12 months) in the control group. The overall median DFS of the patients in the integrated group was significantly longer than that of the control group (29.5 vs 16.6 months; relative risk [RR], 0.618; 95% CI, 0.47-0.81, P < 0.001). The 1-year, 3-year, and 5-year DFS rates of the integrated group and the control group were 79% versus 65%, 43% and 17%, and 25% versus 10%, respectively. There was a significant difference in the survival rate between the 2 groups (log-rank test chi-square, 18.13; P < 0.001, **Table 3** and **Figure 1**).

Effect of TCM on patients with overall survival

The median overall survival time of the 302 patients was 30.2 months (95% CI, 26.74-33.66 months). The median overall survival was 39.7 months (95% CI, 33.94-45.46 months) in the integrated group, while 25.9 months (95% CI, 22.38-29.42 months) in the control group. The median overall survival of the patients in the integrated group was significantly longer than that of the control group (39.7 vs 25.9 months; RR, 0.545; 95% CI, 0.409-0.726, [P < 0.001]). The 1-year, 3-year, and 5-year survival rates of the integrated group versus the control group were 91% versus 89%, 56% versus 27%, and 39% versus 15%, respectively.

Table 4. Overall survival time in two groups

Group	Survival rates (%)			Median OS	95% CI	HR (95% CI)	χ^2	*P*-value
	1 year	3 years	5 years					
Control group	89	27	15	25.9	33.939-45.461	0.545 (0.409-0.726)	27.78	< 0.001
Integrated group	91	56	39	39.7	22.381-29.419			

OS: Overall survival; 95% CI: 95% Confidence interval; HR: Hazard ratio.

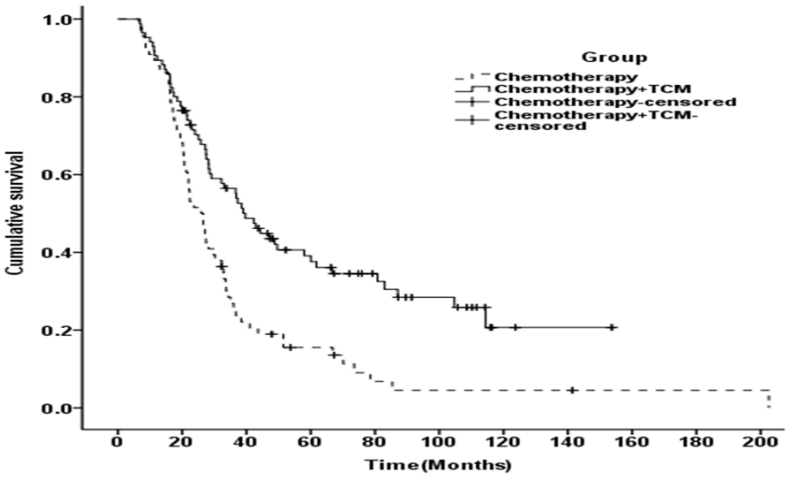

Figure 2. Overall survival was significantly longer in the integrated group (chemotherapy+TCM) compared with the control group (Chemotherapy alone), (median of 39.7 vs 25.9 months; relative risk [RR], 0.545, [P < 0.001]). TCM: Traditional Chinese Medicine; RR: relative risk.

Table 5. Single factor analysis

Factors	DFS		OS	
	χ^2	*P*-value	χ^2	*P*-value
Age	9.210	0.010	7.140	0.028
Tumor invasion range	16.520	0.002	16.679	0.002
Pathological type	19.952	0.001	17.753	0.003
Degree of histological differentiation	52.787	< 0.001	13.426	< 0.001
Lymph node metastasis	68.578	< 0.001	68.578	< 0.001
TNM stage	38.197	< 0.001	46.426	< 0.001
TCM treatment	18.125	< 0.001	27.779	< 0.001

DFS: Disease-free survival; OS: Overall survival; TCM: Traditional Chinese Medicine.

There was a significant difference in the survival rates between the 2 groups (log-rank test chi-square, 27.78; P < 0.001, **Table 4** and **Figure 2**).

Analysis of prognostic factors

Our study selected 12 potential confounders that may affect the prognosis of patients, including age, sex, smoking history, drinking history, family history of cancer, tumor type, tumor invasion range, pathological type, degree of histological differentiation, lymph node metastasis, TNM stage, and whether to accept TCM treatment. The results of single factor analysis showed that the following 7 parameters are as important as influential factors for DFS and OS in patients (P < 0.05, **Table 5**), which included tumor invasion range, pathological type, degree of histological differentiation, lymph node metastasis, TNM stage, and TCM treatment. The results of Cox regression analysis showed that the following 4 parameters are independent prognostic risk factors of DFS (**Table 6**) and OS (**Table 7**). Lymph node metastasis (P < 0.001), pathological type (P=0.017), degree of histological differentiation (P= 0.007), TCM treatment (P < 0.001) of DFS. Lymph node metastasis (P < 0.001), pathological type (P=0.024), degree of histological differentiation (P= 0.036), TCM treatment (P < 0.001) of OS. The RR of each variable ranged from 0.618 to 2.556. Among these factors, the regression coefficient of TCM treatment was negative, and the result of RR (0.618) was < 1, showing it as a protective factor for DFS and OS. The RR results of the other 3 factors was > 1, which belonged to the hazard factors.

Discussion

Gastric cancer is the second leading cause of death globally. Recent research showed that

Table 6. Cox regression analysis of independent prognostic risk factors associated with DFS

Factors	No. of patients	Regression coefficient	Standard error	Wald	Relative risk	95% CI
Lymph node metastasis						
No	94	-	-	-	1	-
Yes	208	0.939	0.149	39.833	2.556	1.910-3.421
Pathological type						
Papillary adenocarcinoma	96	-	-	13.744	1	-
Tubular adenocarcinoma	100	0.188	0.155	1.472	1.207	0.890-1.637
Mucinous adenocarcinoma	22	0.739	0.265	7.794	2.094	1.246-3.518
Signet ring cell carcinoma	40	0.324	0.212	2.330	1.382	0.912-2.094
Mixed type carcinoma	36	0.621	0.209	8.821	1.861	1.235-2.805
Others	8	0.461	0.377	1.491	1.585	0.757-3.319
Degree of histological differentiation						
High-medium differentiation	90	-	-	-	1	-
Low or undifferentiated	212	0.403	0.150	7.245	1.496	1.116-2.005
TCM treatment						
No	132	-	-	-	1	-
Yes	170	-0.481	0.135	12.691	0.618	0.474-0.805

DFS: Disease-free survival; 95% CI: 95% Confidence interval; TCM: Traditional Chinese Medicine.

Table 7. Cox regression analysis of independent prognostic risk factors associated with survival

Factors	No. of patients	Regression coefficient	Standard error	Wald	Relative risk	95% CI
Lymph node metastasis						
No	94	-	-	-	1	-
Yes	208	1.244	0.175	50.552	3.468	2.462-4.886
Pathological type						
Papillary adenocarcinoma	96	-	-	12.888	1	-
Tubular adenocarcinoma	100	0.328	0.169	3.757	1.388	0.996-1.934
Mucinous adenocarcinoma	22	0.774	0.285	7.385	2.168	1.241-3.788
Signet ring cell carcinoma	40	0.289	0.231	1.568	1.335	0.849-2.097
Mixed type carcinoma	36	0.662	0.233	8.036	1.938	1.226-3.062
Others	8	0.560	0.381	2.158	1.751	0.829-3.697
Degree of histological differentiation						
High-medium differentiation	90	-	-	-	1	-
Low or undifferentiated	212	0.343	0.163	4.408	1.409	1.023-1.940
TCM treatment						
No	132	-	-	-	1	-
Yes	170	-0.607	0.146	17.208	0.545	0.409-0.726

95% CI: 95% Confidence interval; TCM: Traditional Chinese Medicine.

the overall incidence of gastric cancer has been decreasing globally. However, the incidence and mortality rates of gastric cancer still remained stubbornly high in the East Asian countries, especially in China [16]. China has high incidence and mortality rates, new cases accounted for nearly 45%, and the proportion of gastric cancer-related deaths were as high as 40% in the world [16, 17]. Because of the low rates of early diagnosis and treatment of gastric cancer in China, the patients with advanced stage are in majority, and the overall prognosis still remained poor [18, 19].

At present, D2 lymphadenectomy on the basis of radical surgery (R0 resection) has become

the treatment consensus of gastric cancer with radical surgery in the East and West countries. Numerous clinical research and meta-analysis studies from China and other countries showed that the adjuvant radio-chemotherapy improved the OS rates in gastric cancer compared to the historical controls who were subjected only to surgical treatment [20-22]. Among them, Y Zhang's study reported an overall median survival time of 26.5 months, and 5-year overall survival rate of 28.6% in stage III gastric cancer patients with post radical surgery; while the overall median survival time was 29.9 months, the 5-year overall survival rate was 34.8% in the patients who received synchronous chemotherapy post radical surgery [22]. The results showed limited effect on gastric cancer patients with combined radiotherapy and chemotherapy, which might be due to the strong heterogeneity of gastric cancer. The 5-year overall survival rate was often less than 50% in stage III gastric cancer patients who underwent post radical surgery. In addition, chemotherapeutic drugs showed obvious adverse reactions. Many patients due to the intolerance to the side reactions were forced to discontinue the treatment, and have become the key factor for restricting the overall prognosis of patients.

In recent years, many experimental research studies regarding Chinese herbal monomers, Chinese herbal compounds and Chinese patent medicine reported that TCM has obvious effects of resisting gastric cancer. TCM, such as Elemene induced apoptosis and inhibited the proliferation of human gastric cancer cells [23], and produced anti-tumor angiogenic properties [24]. Similarly, lentinan (LNT) showed a significant inhibitory effect on the growth of gastric cancer cells, SGC-7901 [10]. KLT markedly enhanced the apoptosis of gastric cancer cells and inhibited their proliferation [25], which might in turn reversed the multiple drug resistance of tumor cells [26]. Jinlongshe oral solution also demonstrated significant inhibitory effects on the proliferation of human gastric cancer cells, MKN-45. This in turn promoted apoptosis [27], regulated the inflammatory microenvironment of gastric cancer by IL-8, and inhibited the adhesion and invasion of gastric cancer cells [28]. Clinical research showed that TCM combined with chemotherapy had certain advantages in increasing the efficiency of treatment, lessening the side effects, and improving the quality of life of gastric cancer patients [29-32]. The results of the current study demonstrated median DFS and median OS of 29.5 months and 39.7 months in the integrated group, which were significantly prolonged than that in control group (16.6 months and 25.9 months). The 1-year, 3-year, and 5-year DFS were 79%, 43% and 25%, respectively, while the 1-year, 3-year, and 5-year survival rates were 91%, 56% and 39%, respectively, in the integrated group. The DFS rates of integrated group were better than the control group (65%, 17%, 10%) and (89%, 27%, 15%), respectively. The KPS score in the integrated group [(81.47±17.70) points] was significantly improved compared to the control group [(74.55±20.43) points] after 6 months of therapy. The study suggested that the integrated TCM with chemotherapy was significantly better than chemotherapy alone in patients with stage III gastric cancer after radical surgery. To more objectively evaluate the effect of TCM, we selected 12 factors that may affect the disease prognosis in stage III gastric cancer patients. The results showed that TCM treatment was closely related with both DFS and OS in patients, and TCM is considered as a protective factor. The present study results are limited to local areas of Changzheng Hospital, which retrospectively analyzed the data. Subgroup analysis was not adequately performed because of the small sample size. Further prospective rigorous clinical trials must be performed to verify the exact effect and validity of TCM treatment combined with synchronous chemotherapy in stage III gastric cancer post radical surgery.

In conclusion, our retrospective analysis showed that TCM combined with synchronous chemotherapy may prolong DFS and OS, which in turn improves the quality of life of patients with stage III gastric cancer post radical surgery. More attention should be paid to evaluate the active role of TCM in combination therapy for gastric cancer.

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Disclosure of conflict of interest

None.

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