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ORIGINAL ARTICLE

Retrospective Cohort Study

Right- and left-sided colorectal cancers respond differently to traditional Chinese medicine

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Abstract

AIM

To explore the differences in the responses of left-sided colorectal cancer (LSCRC) and right-sided colon cancer (RSCC) to traditional Chinese medicine (TCM).

METHODS

Patients with postoperative stage I-III colorectal cancer (CRC) were enrolled and divided into the LSCRC with or without TCM and RSCC with or without TCM groups depending on the primary tumor side and TCM administration. Patients in the TCM group were given TCM for at least 6 mo. Our research adopted disease-free survival (DFS) as the primary endpoint. We applied a Cox proportional hazards regression model for the multivariate factor analysis using Stata 12.0 and SPSS 22.0 software for data analysis.

RESULTS
Of the 817 patients included in our study, 617 had LSCRC (TCM group, *n* = 404; Non-TCM group, *n* = 213), and 200 had RSCC (TCM group, *n* = 132; Non-TCM group, *n* = 68). The 6-year DFS for patients with LSCRC was 56.95% in the TCM group and 41.50% in the Non-TCM group (*P* = 0.000). For patients with RSCC, the 6-year DFS was 52.92% in the TCM group and 37.19% in the Non-TCM group (*P* = 0.003). Differences between LSCRC and RSCC were not statistically significant regardless of TCM ingestion.

CONCLUSION
Patients with either LSCRC or RSCC and who took TCM experienced longer DFS; furthermore, patients with RSCC benefited more from TCM in DFS.

Key words: Colorectal cancer; Left-sided; Right-sided; Traditional Chinese medicine; Disease-free survival

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Core tip: In this prospective, observational, multicenter, cohort study, we compared disease-free survival (DFS) of patients with postoperative stage I-III left- and right-sided colorectal cancers who were stratified by ingestion of TCM. The data analysis confirmed that TCM effectively prolonged DFS of patients with stage II-III on both sides, especially individuals with stage III right-sided colon cancer.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death in America[1,2]. Resection is the gold-standard treatment for CRC, but 35% of individuals will develop recurrence or metastasis within the first few years after resection[3]. Therefore, preventing postoperative recurrence and metastasis is critical in treating stage I-III CRC. In China, traditional Chinese medicine (TCM) is a common anticancer approach along with chemotherapy and radiotherapy[4,5]. Our preliminary study also proved that chemotherapy coupled with TCM could further reduce the risk of recurrence and metastasis as well as prolong the disease-free survival (DFS) of patients with CRC[6]. Recently, more studies have proposed that location of primary tumor was related to recurrence, metastasis and the therapeutic effect[7-9]. However, there was no evidence regarding whether TCM exerts variable effects on CRC based on the side where the lesion is located. Therefore, we undertook this study to determine whether TCM can prolong the DFS of individuals with either left-sided colorectal cancer (LSCRC) or right-sided colon cancer (RSCC).

MATERIALS AND METHODS

Study design

This was a retrospective, observational, multicenter, cohort study designed to elucidate whether primary tumor location is associated with a differential response to TCM. Eligible postoperative patients with stage I-III disease were screened at affiliated hospitals of Shanghai University of Traditional Chinese Medicine (Shanghai Municipal Hospital of Traditional Chinese Medicine, Shuguang Hospital and Yueyang Hospital) between April 2004 and November 2013. The study protocol was approved by these three individual ethics committees. A total 1020 patients were screened, among which 148 did not present a clear side of colon cancer, 4 presented other primary tumors, 24 were followed up for less than 6 mo, 5 presented an unclear TNM stage, and 22 were treated with non-systemic TCM medication. Notably, systematic TCM medication was defined as at least 6 mo of continuous TCM ingestion before relapse. Finally, 817 patients were included in our research (Figure 1) and divided into the following groups based on tumor location and TCM status: LSCRC with TCM, LSCRC without TCM, RSCC with TCM and RSCC without TCM. All the included patients were followed up by outpatient visits, returning visits or telephone follow-up every 6 mo; clinical data, including age, gender, colon cancer location, surgical pathology, histodifferentiation, TNM stage, lymph nodes examined in surgical specimen, chemotherapy, radiotherapy, comorbidities (including hypertension, diabetes, heart disease, and stroke), period of TCM, time to recurrence and metastasis or cancer-related death, were collected at each follow-up visit. The median follow-up for RSCC was 53.0 mo in the TCM group and 34.3 mo in the Non-TCM group; for LSCRC, the median follow-up was 54.3 mo in the TCM group and 38.5 mo in the Non-TCM group. Follow-up was completed for up to 6 years or until the patients either relapsed or died.

Statistical analysis

DFS, which is defined as the time from surgical resection to relapse, cancer-related death or the last follow-up (whichever occurred first), was evaluated using Kaplan-Meier curves and log-rank tests. Baseline characteristics were analyzed using Pearson's χ^2 test. Propensity score matching was created using logistic regression to model the probability that a patient exhibited a specific characteristic based on

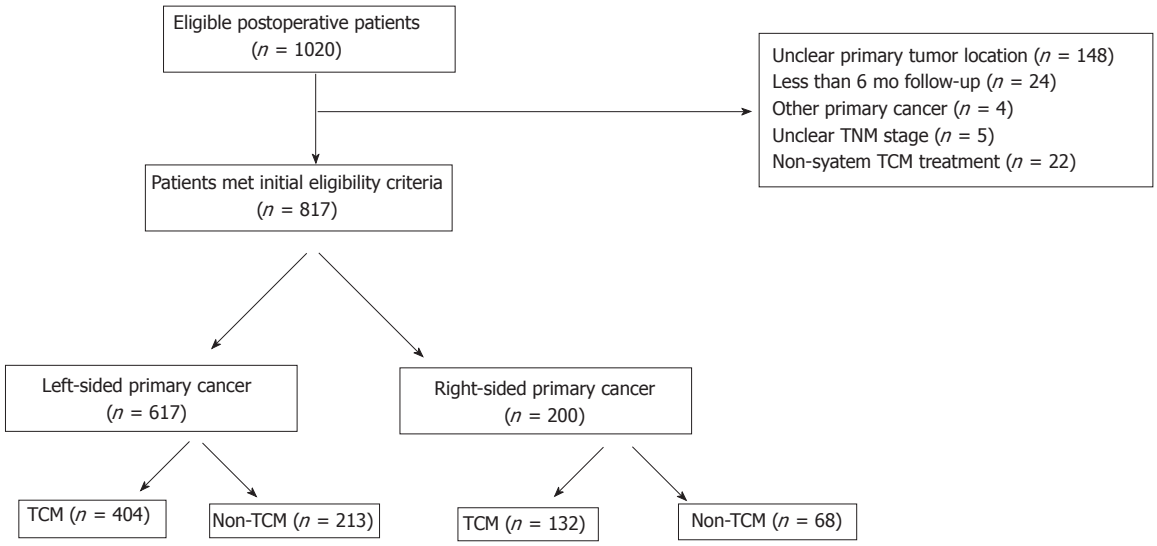
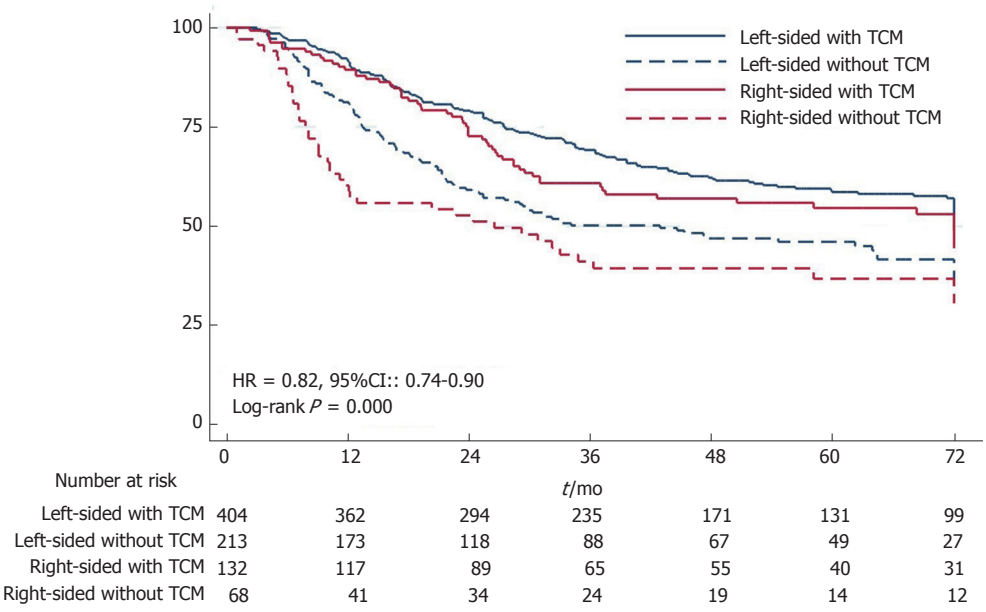


Figure 1 Flowchart of patient selection and grouping.

Table 1 Levels of sIL-2R, ALT, and HBV DNA in the sera of patients with chronic HBV infection (mean ± SD)

	Left-sided		Right-sided		*P* value
	TCM *n* = 404	Non-TCM *n* = 213	TCM *n* = 132	Non-TCM *n* = 68	
Gender					0.035[a]
Man	207	126	63	28	
Woman	197	87	69	40	
Age (yr)					0.027[a]
< 60	163	70	41	17	
≥ 60	241	143	91	51	
Histodifferentiatio, *n*					0.293
Poorly	47	19	18	8	
Moderately	252	123	80	34	
Well	9	7	6	2	
Unknown	96	64	28	24	
Lympho node metastasis					0.125
Yes	176	74	57	32	
No	228	139	75	36	
TNM stage					0.331
I	77	38	19	8	
II	148	95	54	28	
III	179	80	59	32	
Chemotherapy					0.000[a]
Yes	332	149	97	44	
No	72	64	35	24	
Radiotherapy					0.011[a]
Yes	44	19	5	1	
No	360	194	127	67	
Diabetes					0.995
Yes	61	33	21	10	
No	343	180	111	58	
Hypertension					0.872
Yes	131	76	44	22	
No	273	137	88	46	
Heart disease					0.367
Yes	38	30	15	7	
No	366	183	117	61	
Stroke					0.049[a]
Yes	22	13	1	2	
No	382	200	119	66	

[a]*P* < 0.05 statistical difference. LSCRC: Left-sided colorectal cancer; RSCC: Right-sided colon cancer.



Number at risk							
Left-sided with TCM	404	362	294	235	171	131	99
Left-sided without TCM	213	173	118	88	67	49	27
Right-sided with TCM	132	117	89	65	55	40	31
Right-sided without TCM	68	41	34	24	19	14	12

Figure 2 Kaplan-Meier disease-free survival curves for all patients.

gender, age, location, histodifferentiation, TNM stage, lymph node status, chemotherapy, radiotherapy and comorbidities; this matching was conducted to test the stability of our research. A 1:1 match with a random matching order and 0.1 caliper was performed between the TCM and Non-TCM groups in LSCRC and RSCC, respectively, and a 2:1 match was conducted between LSCRC and RSCC within the TCM and Non-TCM groups, respectively; additionally, replacements were not allowed. In addition, we applied multivariate regression analyses for multicollinearity diagnosis and Cox proportional hazards regression model for multivariate factor analysis. Hypothesis testing was conducted using a two-sided alpha set to a 5% level of significance. All analyses were performed using Stata 12.0 and SPSS 22.0 software. The statistical methods used in this study were reviewed by Weibing Wang from the Department of Epidemiology, School of Public Health, Fudan University.

Traditional Chinese medicine treatment

TCM prescriptions were determined by attending physicians on the basis of syndrome differentiation, and their composition, dose were modified every two weeks to tailor them to the distinctive symptom complex. The herbs were processed as a decoction for administration twice per day (200 mL per session). Notably, TCM treatment must have been continually managed for at least six months before relapse for inclusion in the TCM group and was ceased at the patient's request, by the physician or in an instance of relapse.

Definition of left-sided colorectal cancer and right-sided colon cancer

The primary tumor side was identified using post-operative pathology. LSCRC was defined as a primary tumor located between the splenic flexure and the rectosigmoid junction, whereas RSCC was defined as a primary site originating between the cecum and the proximal two-thirds of the transverse colon[10].

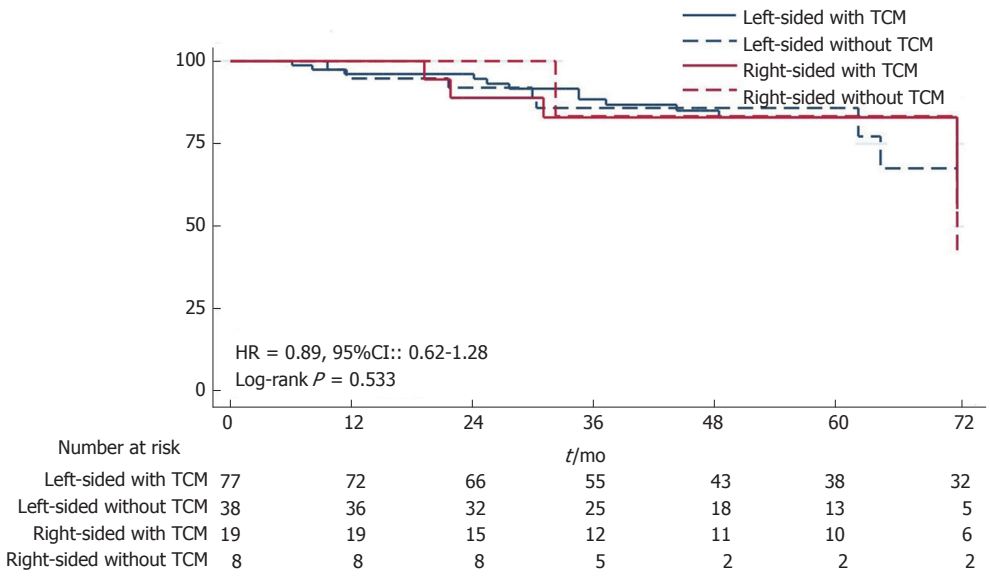
RESULTS

Patients

Among the 817 patients, 617 had LSCRC (TCM group, *n* = 404; Non-TCM group, *n* = 213), and 200 had RSCC (TCM group, *n* = 132; Non-TCM group, *n* = 68). Subjects with LSCRC were more likely to be male than those with RSCC. Patients were commonly older than 60 years old and were less likely to have a stroke. Most patients have received chemotherapy but very few have undergone radiotherapy. Other characteristics such as histodifferentiation, TNM stage, lymph node status, diabetes, hypertension, and heart disease were evenly distributed among the groups and showed no statistically significant differences. The baseline characteristics after propensity score matching were shown in Supplementary Tables 1 and 2.

Effects of traditional Chinese medicine on left-sided colorectal cancer and right-sided colon cancer patients

TCM conferred higher 1-6 year DFS rates on patients with LSCRC (91.98% at 1, 78.95% at 2, 69.15% at 3, 62.04% at 4, 58.45% at 5, and 56.95% at 6 years) than on LSCRC patients who did not receive TCM (81.22%, 59.05%, 50.05%, 46.92%, 46.12%, and 41.50%, respectively). The 1-6 year DFS rates of patients with RSCC in the TCM group were 89.35%, 72.82%, 60.68%, 56.77%, 54.43%, and 52.92%, respectively, whereas in the Non-TCM group, the DFS rates were 60.29%, 52.76%, 41.39%, 39.51%,



Number at risk							
Left-sided with TCM	77	72	66	55	43	38	32
Left-sided without TCM	38	36	32	25	18	13	5
Right-sided with TCM	19	19	15	12	11	10	6
Right-sided without TCM	8	8	8	5	2	2	2

Figure 3 Kaplan-Meier disease-free survival curves for patients with stage I disease.

37.19%, and 37.19%, respectively (Figure 2). DFS was significantly improved by TCM not only in patients with LSCRC (HR = 0.59, *P* = 0.000) but also in those with RSCC (HR = 0.56, *P* = 0.003) (Supplementary Figures 1 and 2). However, the LSCRC and RSCC TCM groups showed similar DFS rates (HR = 0.84, *P* = 0.239) as did the LSCRC and RSCC Non-TCM groups (HR = 0.76, *P* = 0.129) (Supplementary Figures 3 and 4). The above results were relatively unchanged after propensity score matching (Supplementary Figures 5, 6, 7 and 8).

Effect of traditional Chinese medicine on left-sided colorectal cancer and right-sided colon cancer patients in different disease stages

For patients with stage I disease, TCM did not exhibit an obvious advantage in extending DFS in patients with either LSCRC or RSCC (Figure 3; Supplementary Figures 9 and 10). TCM significantly prolonged DFS of patients with stage II LSCRC (HR = 0.60, 95%CI: 0.40-0.89, *P* = 0.011), whereas patients with stage II RSCC in the TCM group showed longer DFS than those in the Non-TCM group; however, this difference was not significant (HR = 0.56, 95%CI: 0.29-1.07, *P* = 0.077) (Figure 4; Supplementary Figures 11 and 12). For stage III disease, TCM was effective for patients with either LSCRC (HR = 0.44, 95%CI: 0.32-0.61, *P* = 0.000) or RSCC (HR = 0.47, 95%CI: 0.28-0.79, *P* = 0.004) (Figure 5; Supplementary Figures 13 and 14).

Cox analysis of baseline characteristics on disease-free survival in left-sided colorectal cancer and right-sided colon cancer

The multivariate regression analyses showed no multicollinearity among variables in this cox analysis (Supplementary Figures 15 and 16). TCM was an independent influencing factor for DFS of patients with either LSCRC (HR = 0.53, 95%CI: 0.41-0.67) or RSCC (HR = 0.47, 95%CI: 0.31-0.71); TNM stage was also an independent factor (HR = 2.39, 95%CI: 1.96-2.90 for LSCRC; HR = 2.63, 95%CI: 1.85-3.72 for RSCC). Histodifferentiation (HR = 1.16, 95%CI: 1.03-1.31) and hypertension (HR = 0.51, 95%CI: 0.31-0.81) were independent influencing factor for DFS of patients with LSCRC and RSCC, respectively (Table 2).

DISCUSSION

Recently, the sidedness of primary colon cancer was demonstrated to be a prognostic factor in survival. Because of their distinct biological characteristics, LSCRC and RSCC tend to be treated separately. To the best of our knowledge, this is the first study discussing the effects of TCM on LSCRC and RSCC separately. Our Cox analysis showed that TCM was an independent influencing factor on DFS for each side. Patients with LSCRC exhibited a relatively longer DFS than those with RSCC regardless of TCM administration, whereas patients with RSCC who took TCM gained a greater benefit regarding DFS-this partially narrowed the disparity in DFS between the different cancer sides.

Our study was somewhat similar to those of previous articles in that TCM coupled with chemotherapy was significantly effective in prolonging DFS of patients with CRC. Tao *et al*[11] L proved that compared to monochemotherapy, chemotherapy integrated with TCM obviously improved the prognosis of patients with stage II-III CRC by reducing recurrence and metastasis. Zhou *et al*[12] LY demonstrated that TCM effectively improved the quality of life, increased body weight and prolonged the survival of patients with CRC. Our preliminary study proposed that individuals with stage

Table 2 Cox analysis for disease-free survival in left- and right-sided colorectal cancer

	Left-sided colorectal cancer			Right-sided colon cancer		
	Univariate	Multivariate		Univariate	Multivariate	
	P value	*P* value	HR (95%CI:)	*P* value	*P* value	HR (95%CI:)
Gender	0.024[a]	0.079	0.81 (0.63-1.02)	0.339	0.023[a]	0.63 (0.42-0.94)
Age	0.955	0.792	1.04 (0.80-1.34)	0.712	0.612	1.12 (0.72-1.76)
Histodifferentiation	0.648	0.016[a]	1.16 (1.03-1.31)	0.685	0.407	1.09 (0.89-1.33)
TNM stage	0.000[a]	0.000[a]	2.39 (1.96-2.90)	0.000[a]	0.000[a]	2.63 (1.85-3.72)
TCM	0.000[a]	0.000[a]	0.53 (0.41-0.67)	0.003[a]	0.000[a]	0.47 (0.31-0.71)
Diabetes	0.948	0.716	0.94 (0.66-1.32)	0.240	0.200	0.67 (0.36-1.24)
Hypertention	0.650	0.120	1.24 (0.94-1.64)	0.019[a]	0.005[a]	0.51 (0.31-0.81)
Heart disease	0.710	0.988	1.00 (0.66-1. 50)	0.461	0.155	1.57 (0.84-2.93)
Stroke	0.171	0.091	0.60 (0.33-1.09)	0.681	0.449	1.34 (0.63-2.83)

[a]$P < 0.05$ statistical difference.

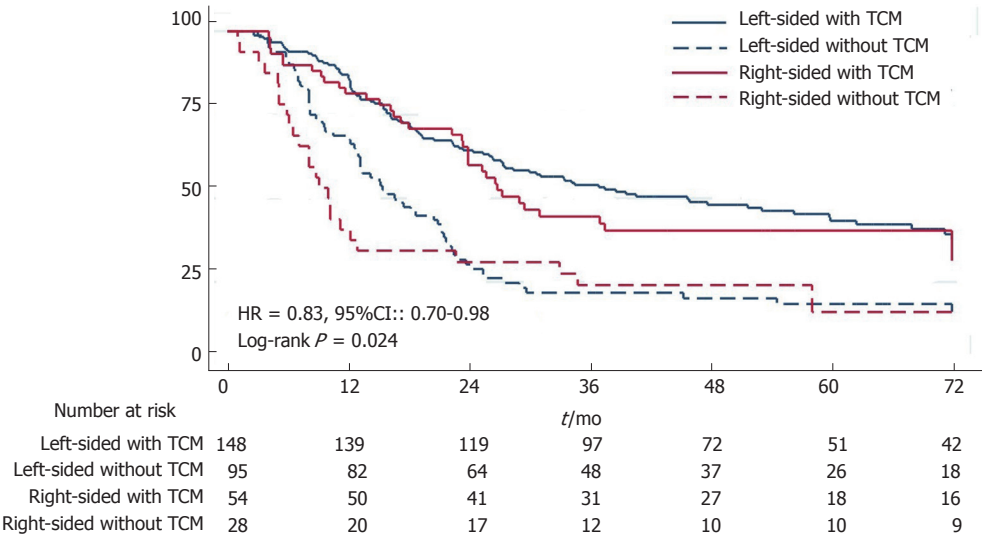


Figure 4 Kaplan-Meier disease-free survival curves for patients with stage II disease.

I CRC do not require TCM[6]. In this study, we found that patients with stage I CRC on either side did not benefit from TCM, whereas subjects with stage II-III LSCRC or RSCC who were administered TCM exhibited a distinct advantage in decreasing the risk of recurrence and metastasis; however, this advantage was not statistically significant in subjects with stage II RSCC. We thought that the primary reasons why TCM improved DFS of CRC on both sides lie in the advantages of TCM in attenuating toxicity, improving immunity and quality of life and enhancing medication sensitivity in patients with tumors, which can prevent metastasis and extend survival[13-17].

The different responses of LSCRC and RSCC to treatment have been previously reported. The GALGB/SWOG 80405 study, which investigated the effect of cetuximab and bevacizumab on cancer located on different sides, found that patients with LSCRC benefited more from cetuximab, whereas those with RSCC responded better to bevacizumab in terms of survival[18]. Moreover, Elsaleh *et al*[19] found that men with RSCC obtained increased benefits from adjuvant chemotherapy whereas men with LSCRC did not; one possible explanation may be partially due to the higher frequency of microsatellite instability (MSI) in RSCC which may be a prognostic factor for a more favorable response[19].

Whether due to differences in biological characteristics between the two sides or TCM producing a relatively better effect on RSCC, RSCC exhibited a greater benefit from TCM than LSCRC in our study; this finding is worth further study. Thus, differences between LSCRC and RSCC regarding embryological origin, blood supply, morphology, carbohydrate antigens and other factors should be considered[20]. In addition, RSCC was more commonly associated with RAS and BRAF mutations, a high CpG island methylator phenotype, mutagenic metabolites of cytochrome p450, MAPK signaling and MSI, whereas LSCRC was associated with APC, K-ras, DCC, p53 mutant EGFR signaling, Wnt signaling and HER1 and HER2 amplification which played a vital role in cancer generation and progression[21-24]. Interestingly, previous studies suggested that the prolonged survival of CRC patients by TCM was mediated by demethylating DNA, antagonizing gene mutations, targeting the MSI

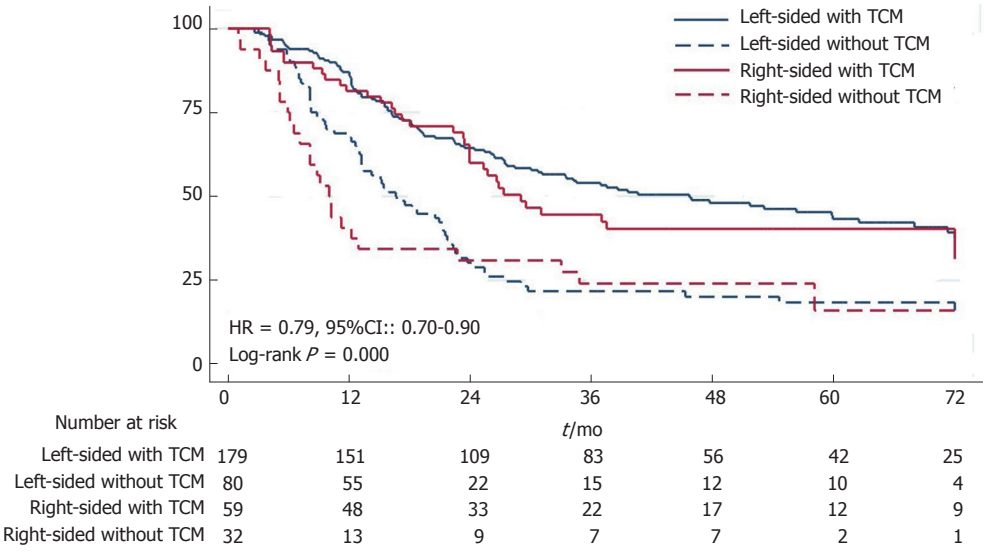


Figure 5 Kaplan-Meier disease-free survival curves for patients with stage III disease.

pathway and promoting apoptosis, which are more characteristics of RSCC[25-27].

There were some limitations in our study. Administration of TCM was tailored to each patient's symptoms, signs and constitution. Although these highly individualized TCM prescriptions were adapted to the patients' conditions to the greatest extent possible, the many different kinds and doses of herbs were difficult to be stratified in this paper[28]. In the future research, we are going to extract some core herbs used in treating CRC based on the primary tumor sides. In addition, TCM in our study was administered as a decoction, the quality of TCM herbs may differ based on the source region, season, and processing factories inevitably. We recommend granular or powder TCM formulations for future treatments. Another limitation lies in a lack of knowledge regarding the optimal period of TCM medication for patients with different TNM stages of CRC, which will be studied in our future research.

In conclusion, our study showed that TCM conferred longer DFS on patients with stage II-III CRC on both sides. Patients with LSCRC and RSCC responded differently to TCM; those with RSCC benefited more from TCM than those with LSCRC. Thus, TCM was recommended to postoperative patients with CRC of both sides, especially the right side. The mechanism of different responses of primary tumor location to TCM is worthy of further study.

ARTICLE HIGHLIGHTS

Research background

The background, present status and significance of the study have been described detailedly in the section "Introduction" of the text.

Research motivation

The background, present status and significance of the study have been described detailedly in the section "Introduction" of the text.

Research objectives

The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field were described in the last sentence of "Introduction", "Discussion".

Research methods

"Statistical analysis" has introduced the methods used in realizing the objectives of our manuscript in detail.

Research results

Research results have been detailedly described in the first and last paragraphs of "Discussion".

Research conclusions

The authors have addressed the above questions mainly in "Statistical analysis" and "Discussion". Recently, the sidedness of primary colon cancer was demonstrated to be a prognostic factor in survival. Because of their distinct biological characteristics, LSCRC and RSCC tend to be treated separately. However, there was no evidence regarding whether TCM exerts variable effects on CRC based on the side where the lesion is located. This is the first study discussing the effects of TCM on LSCRC and RSCC separately. Our results showed that patients with LSCRC exhibited a relatively longer DFS than those with RSCC regardless of TCM administration, whereas patients with RSCC who took TCM gained a greater benefit regarding DFS. Because of their distinct biological characteristics and the therapeutic effect, LSCRC and RSCC should be treated separately in future. The DFS was evaluated using Kaplan-Meier curves and log-rank tests. The authors adopted propensity score matching to model the probability that a patient exhibited a specific characteristic based on gender, age, location, histodifferentiation, TNM stage, lymph node status, chemotherapy, radiotherapy and comorbidities to test the stability of the research. In addition, the authors applied multivariate regression analyses for multicollinearity diagnosis and Cox proportional hazards regression model for multivariate factor analysis.

Research perspectives

Recent studies have proposed that location of primary tumor was related to recurrence, metastasis and the therapeutic effect. The author's results indicated that patients with LSCRC and RSCC responded differently to TCM; those with RSCC benefited more from TCM than those with LSCRC. Thus, TCM was recommended to postoperative patients with CRC of both sides, especially the right side. In the future research, CRC should be treated separately based on the primary tumor sides.

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