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Original Article

DC-CIK combined with chemotherapy on the efficacy, immune function, and life quality in colorectal cancer patients after radical resection

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Abstract: Objective: To investigate the efficacy of combined treatment of dendritic cell-cytokine-induced killer cells (DC-CIK) and chemotherapy on colorectal cancer (CRC) patients who have undergone radical resection, and its effect on immune function and quality of life. Methods: Data of 103 CRC patients after radical resection admitted to Xianyang First People's Hospital and Yanan University Affiliated Hospital from March 2018 to March 2020 were retrospectively analyzed. A total of 50 patients treated with XELOX chemotherapy were included in the control group (CG). The remaining 53 patients treated with XELOX chemotherapy combined with DC-CIK were included in the observation group (OG). The therapeutic efficacy, immune function indicators, serum tumor markers before and after the treatment, adverse reactions, 2-year survival rate, and quality of life 6 months after the treatment were observed and compared between the two groups. Results: The OG was identified to have a better therapeutic effect than the CG ($P<0.05$). After the treatment, the OG was assessed with significantly higher levels of IgG, IgA, and IgM than the CG. The CEA, CA724, and CA199 levels in the OG were significantly lower than those in the CG after the treatment ($P<0.05$). No significant difference was identified regarding the incidence of adverse reactions between the two groups ($P>0.05$). The quality of life six months after the treatment and the 2-year survival rate in the OG were significantly higher than those in the CG ($P<0.05$). The logistic regression analysis showed that pathological stage, differentiation, and treatment regimen were independent risk factors for poor prognosis ($P<0.05$). Conclusion: DC-CIK combined with chemotherapy can improve the clinical efficacy, immune function, and long-term survival rate of CRC patients who have undergone radical resection. This combined regimen shows safety and is worthy of promotion in clinical practice.

Keywords: DC-CIK, chemotherapy, colorectal cancer, immune function, prognosis

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in clinical practice. Its incidence ranks fourth and its mortality ranks second among malignant tumors worldwide [1]. In China, its incidence and mortality rank fifth among malignant tumors and keep ascending yearly [2]. According to guidelines for the diagnosis and treatment of CRC, the optimal treatment is radical resection. Patients generally have a good prognosis [3]. There are 50% of patients who develop postoperative metastasis after radical resection. Without effective and timely treatment, the 5-year survival rate of patients would be less than 10% [4]. Patients who have advanced CRC, benefit from postoperative adjuvant chemotherapy, often adopted in clinical comprehensive treatment.

Studies have shown that molecular targeted drugs combined with chemotherapy regimens can significantly enhance the clinical efficacy of advanced and metastatic CRC. The immune system function and life quality of patients are inhibited and reduced after long-term chemotherapy [5]. With the deepening of CRC immunity research, immunotherapy has been applied

in clinical practice in recent years. It enhances the anti-tumor ability by stimulating the activity of the immune system, accompanying with favorable features of high anti-tumor activity, small toxic side effects, and long-term stability of action [6, 7]. Immunotherapy with dendritic cell-cytokine-induced killer cells (DC-CIK) is an essential segment of cancer biological immunotherapy and a new anti-tumor model. Mature DCs can uptake, process, and present tumor antigens, significantly resisting the immune escape of tumor cells and initiating antigen-specific immune responses [8]. CIK is featured with ultra-wide tumoricidal spectrum and a very strong recognition ability for cancer cells. It improves the sensitivity of chemotherapy, directly and accurately kills cancer cells, and does not affect normal tissues and organs. Simple culture, rapid proliferation rate, high tumoricidal activity, and safety are its advantages [9]. DC-CIK has been shown to have good efficacy in tumors such as non-small cell lung cancer and gastric cancer [10, 11]. The therapeutic efficacy, abnormal distribution, and disproportion of cell subsets affect patients with cancer. The effect on patients' immune function is one of the indicators of concern to researchers [12]. There are few studies focusing on its effect with chemotherapy on CRC patients' immune function after radical resection.

We conducted this retrospective analysis to analyze the efficacy of the combined treatment of DC-CIK and chemotherapy on the immune function of CRC patients after radical resection, and to evaluate its therapeutic efficacy more comprehensively.

Materials and methods

Clinical data

Data of 103 patients with CRC after radical resection admitted to Xianyang First People's Hospital and Yanan University Affiliated Hospital from March 2018 to March 2020 were retrospectively analyzed. The mean difference in age of all patients was 64 years. A total of 50 patients treated with XELOX chemotherapy regimen were included in the control group (CG). The remaining 53 patients treated with XELOX chemotherapy combined with DC-CIK were included in the observation group (OG). Inclusion criteria: (1) Patients who were diagnosed with middle and advanced rectal cancer and colon cancer by preoperative colonoscopy; (2) Patients who were excluded from distant metastasis of liver and lung organs by transthoracic abdominal CT; (3) Patients who underwent laparoscopic radical resection of rectal cancer in Xianyang First People's Hospital and Yanan University Affiliated Hospital; (4) Patients who met the criteria for XELOX chemotherapy; (5) Patients who received DC-CIK; (6) Patients who underwent CEA, CA724, CA199, IgG, IgA, and IgM testing; (7) Patients who had complete data. Exclusion criteria: (1) Patients with anemia, leukopenia, thrombocytopenia, or hypoproteinemia; (2) Patients with uncontrolled diabetes; (3) Patients with previous immune system disease, connective tissue disease, or hematologic disease; (4) Patients who did not meet the treatment criteria of XELOX regimen; (5) Patients combined with other malignancies.

All patients agreed to participate in the study and signed written informed consent forms individually. This experiment conformed to the Helsinki Declaration and gained approval from the ethics committee of Xianyang First People's Hospital.

Treatment methods

Preparation of DC-CIK cells: On the morning of chemotherapy, 50 ml of peripheral blood was drawn. It was added to a Ficoll-Hypaque lymphocyte separation solution. Mononuclear cells were obtained after centrifugation and placed in GT-T551 medium for static culture (37°C, 5% CO_2, 1-2 h). DC and CIK cells were cultured, respectively. ① DC cell culture: Suspended cells were removed, and adherent cells were added with 5% autologous plasma and 1% solution I in D100 dendritic cell medium at a density of 1×10^6 cells/mL and cultivated in 5% CO_2 at 37°C. On day 3, half of the culture medium was changed. Tumor antigen was added to load DC cells on day 5, and 1% solution II was added to promote DC cell maturation on day 6. Cells were recovered on day 7. ② CIK cell culture: Suspension cells were added to L500 medium containing 5% autologous plasma and 1% CIK cytokine I solution at a density of 2×10^6 cells/mL, which was incubated in 5% CO_2 at 37°C prior to a supplement of 1% solution II 24 hours later. On the second day, medium containing

1000 IU/ml IL-2 and 5% autologous plasma was supplemented in equal volumes. Medium was supplemented every 2 days and co-cultured with DC cells on day 7. Mature DC-CIK cells were harvested by co-culturing the two at a 10:1 ratio for 7 d. DC-CIK cell reinfusion: Samples were collected 2 days before cell reinfusion to detect bacteria, fungi, endotoxin, mycoplasma, and cell surface markers. The number of cells reinfused each time was $\geq 5\times10^9$, with cell viability >85%. After filtration with 70 μm cell mesh, the cells were resuspended in normal saline (100 ml). The infusion rate was controlled at 60-70 drops/min.

Treatment regimens: (1) Patients in the CG were treated with XELOX chemotherapy, with oxaliplatin (130 mg/m^2, Jiangsu Hengrui Medicine Co., Ltd.) on d 1 plus capecitabine (850-1250 mg/m^2, Jiangsu Hengrui Medicine Co., Ltd.) twice a day in the first 14 days, and 21 days were taken as a cycle. (2) On the basis of the CG, 100 ml peripheral blood was taken from patients in the OG 1 day before the chemotherapy cycle for DC-CIK induction and expansion culture, which was reinfused twice on days 8 and 10, with 14 days as a cycle, and 4 cycles per treatment.

Outcome measures

(1) Therapeutic efficacy was evaluated and compared between the two groups according to the evaluation criteria for solid tumors established by WHO [13]. Based on the physical examination and imaging data of the patients after the treatment, the efficacy was categorized into the following four types, complete remission (CR): complete tumor disappearance; partial remission (PR): tumor size reduction ≥50%; stable disease (SD): tumor size enlargement <25% or reduction <50%, which was maintained for more than 4 weeks; progressive disease (PD): tumor size enlargement >25%. The overall response rate (ORR) = CR rate + PR rate. (2) Serum tumor markers carbohydrate antigen 125 (CA724), carcinoembryonic antigen (CEA), and CA199 were detected by electrochemiluminescence automatic analyzer (Cobase 601, Shanghai Roche Pharmaceutical Co., Ltd.) before the treatment and after 4 weeks of the treatment in both groups. (3) The expressions of immune parameters before and after the treatment were compared between the two groups. (4) Toxicity was recorded and compared between the two groups during treatment, including leukopenia, bone marrow suppression, gastrointestinal reactions, abnormal liver, and kidney function. (5) The 2-year survival rate was assessed and compared between the two groups. (6) Patients were divided into groups according to their survival status. Independent risk factors leading to poor prognosis were analyzed. (7) The QLQ-C30 quality of life scale [14] was used to assess the quality of life 6 months after the treatment. It included five aspects: physical function, role function, social function, cognitive function, and emotional function. The higher scores indicated a better quality of life.

Statistical methods

SPSS 18.0 (IBM) software was utilized for data analysis, and GraphPad Prism 8 was used for figure plotting. The enumeration data were analyzed with the Chi-square test. The łinter-group comparison and intra-comparison of the measured data before and after the treatment were conducted by the independent sample t test and the paired t test, respectively. The survival analysis was performed by the log-rank analysis. The Kaplan-Meier was used to delineate survival curves. The multivariate logistic regression analysis was used to identify independent risk factors for poor patient outcome. Statistical difference was considered when $P<0.05$ (one-sided test).

Results

General data comparison

No significant difference in sex, age, and smoking history was identified between the two groups ($P>0.05$, **Table 1**), showing comparability.

Comparison of treatment efficacy

In the OG, there were 0 patient with CR, 32 with PR, 18 with SD, and 3 with PD. In the CG, there were 0 patient with CR, 20 with PR, 14 with SD, and 16 with PD. The OG held a much higher ORR than the CG (94.34% vs. 68.00%, **Table 2**).

Comparison of immune parameters before and after the treatment between the two groups

Before the treatment, no significant difference was identified in IgG, IgA, and IgM between the two groups ($P>0.05$). After the treatment, the

Table 1. General information table [n (%)]

Variable	Observation Group n=53	Control Group n=50	t/χ^2	P
Sex			0.003	0.951
Male	30 (56.60)	28 (56.00)		
Female	23 (43.40)	22 (44.00)		
Age (years)			0.007	0.933
≤64	25 (47.17)	24 (48.00)		
>64	28 (52.83)	26 (52.00)		
BMI (kg/m^2)			0.005	0.942
≤23	29 (54.72)	27 (54.00)		
>23	24 (45.28)	23 (46.00)		
Smoking history			0.001	0.978
Yes	20 (37.74)	19 (38.00)		
None	33 (62.26)	31 (62.00)		
Clinical phase			0.001	0.997
Stage III	35 (66.04)	33 (66.00)		
Stage IV	18 (33.96)	17 (34.00)		
Degree of differentiation			0.195	0.907
Low	23 (43.40)	20 (40.00)		
Mid	19 (35.85)	20 (40.00)		
High	11 (20.75)	10 (20.00)		
Pathological type			0.001	0.999
Elevated type	20 (37.73)	19 (38.00)		
Infiltrative type	18 (33.96)	17 (34.00)		
Ulcerated type	15 (28.30)	14 (28.00)		

BMI: body mass index.

Table 2. Comparison of efficacy between the two groups [n (%)]

Efficacy	Observation Group n=53	Control Group n=50	χ^2	P
Complete response	0	0	-	-
Partial response	32 (60.27)	20 (40.00)	4.274	0.039
Stable Disease	18 (33.96)	14 (28.00)	-	-
Disease progression	3 (5.66)	16 (32.00)	-	-
Overall response rate	50 (94.34)	34 (68.00)	11.87	0.001

above three indicators in the CG were all down-regulated and were observed to be significantly lower than those in the OG. The OG held up-regulated levels of IgG, IgA, and IgM after the treatment (P<0.05, **Figure 1**).

Comparison of tumor markers before and after the treatment between the two groups

Before the treatment, no significant difference was identified regarding serum CEA, CA724, and CA199 levels between the two groups (P>0.05). After the treatment, the above serum levels were significantly decreased in both groups (P<0.05). The levels in the OG were all identified significantly lower than those in the CG (P<0.05, **Figure 2**).

Comparison of toxicities during the treatment

The incidence of adverse reactions was assessed to be 9.43% in the OG and 28.00% in the CG. This suggested that the OG had much lower adverse reactions than the CG did (P<0.05, **Table 3**).

Comparison of 2-year survival rate

Without loss to follow-up, a total of 18 patients died 2 years after the operation in the OG, with a 2-year survival rate of 66.04%. There were 29 patients who died in the CG, with a 2-year survival rate of 42.00%. A significantly higher 2-year survival rate was seen in the OG than in the CG (P<0.05, **Figure 3**).

Analysis of risk factors affecting the prognosis of the patients

Patients were divided into a survival group (n=56) and a death group (n=47) according to individual prognosis. The univariate analysis showed that the pathological stage, differentiation, and treatment regimen were factors affecting their prognosis (**Table 4**). The logistics regression analysis showed that the pathological stage, differentiation, and treatment regimen were all independent risk factors affecting poor prognosis (**Tables 5**, **6**, P<0.05).

Comparison of life quality 6 months after the treatment

Compared with the CG, the OG had a better quality of life, including physical, role, emotional, cognitive, and social dimensions (P<0.05, **Table 7**).

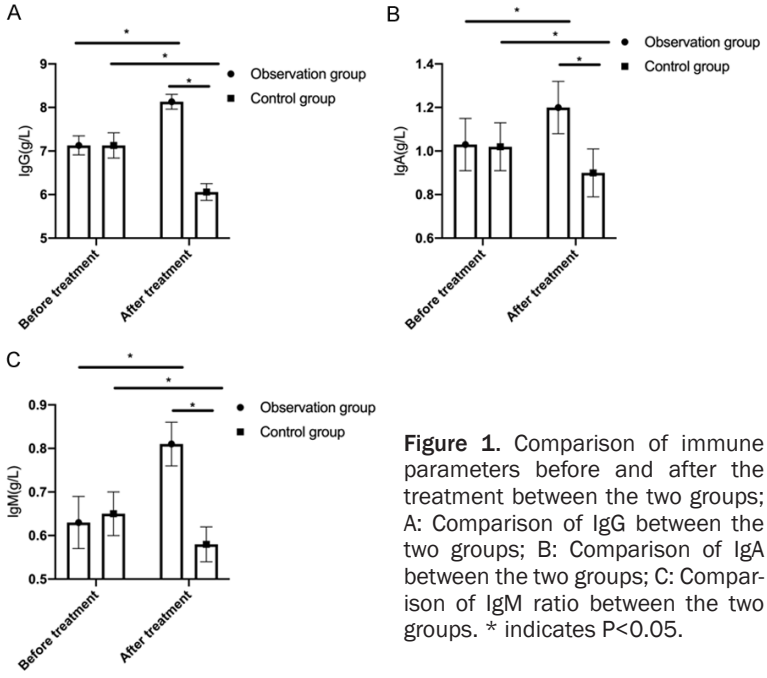

Figure 1. Comparison of immune parameters before and after the treatment between the two groups; A: Comparison of IgG between the two groups; B: Comparison of IgA between the two groups; C: Comparison of IgM ratio between the two groups. * indicates P<0.05.

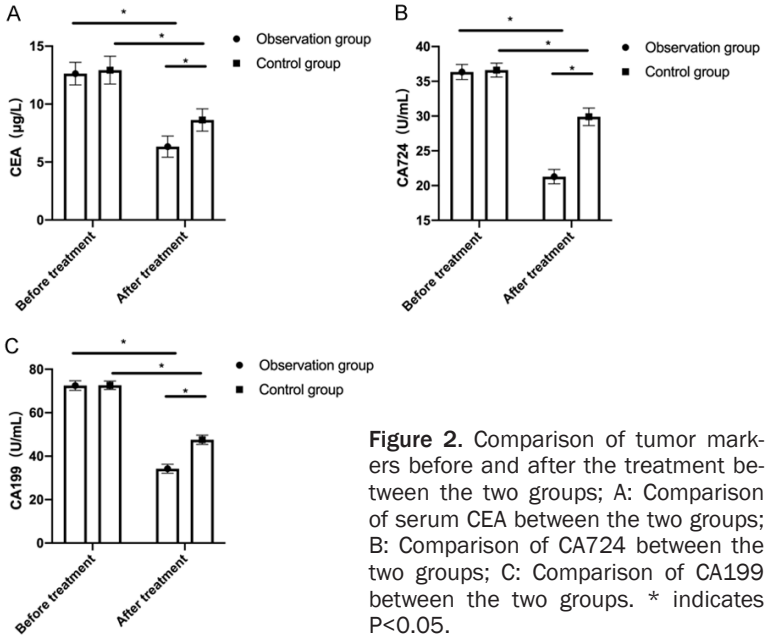

Figure 2. Comparison of tumor markers before and after the treatment between the two groups; A: Comparison of serum CEA between the two groups; B: Comparison of CA724 between the two groups; C: Comparison of CA199 between the two groups. * indicates P<0.05.

Discussion

CRC, one of the most common malignant tumors worldwide, is reported to have a yearly increasing incidence and mortality in China by epidemiological surveys [15]. Surgery as the first treatment choice of CRC, brings an unsatisfactory 5-year recurrence and metastasis rate of more than 50%. A comprehensive treatment regimen of postoperative adjuvant chemotherapy is often continued for CRC patients after radical resection in clinical practice [16]. Chemotherapy has toxic side effects and causes an inhibition of immune system function in patients. Tumor metastasis or recurrence poses serious threats to patients' life [17]. Significantly improving the survival and quality of life in CRC patients after radical resection has always been the focus of clinical discussion.

DC-CIK is a therapeutic method in which monocytes are isolated from autologous blood and induced to expand into DC/CIK cells in vitro, and reinfused into patients to exert anti-tumor effects. DC cells can activate naive CD4+T cells and CD8+T cells after binding to antigens to maintain the balance and stability of the immune function in the human body. It affects the proliferation of B cells to activate the humoral immune response function [18, 19]. DC cells can activate the immune response by capturing the surface antigens of tumor cells and secreting cytokines. It has been found that DC combined with CIK cell therapy have synergistic anti-tumor effects with chemotherapy. The combined culture of CIK and DC cells can produce new cell populations, with much higher cell proliferation activity than that of CIK cells alone [20]. The combination of DC and CIK cells is more potent and effective when it comes to malignant tumors treatment than chemotherapy alone. The efficacy of DC-CIK combined with chemotherapy was evaluated and investigated to provide a feasible clinical treatment option for CRC patients after radical resection.

Table 3. Comparison of incidence of adverse reactions [n (%)]

Adverse reactions	Observation Group n=53	Control Group n=50	χ^2	P
Abnormal liver and kidney function	2 (3.77)	3 (6.00)	0.276	0.599
Leukopenia	1 (1.89)	4 (8.00)	2.082	0.149
Gastrointestinal Reactions	1 (1.89)	3 (6.00)	1.166	0.280
Myelosuppression	1 (1.89)	4 (8.00)	2.082	0.149
Incidence of adverse reactions	5 (9.43)	14 (28.00)	5.895	0.015

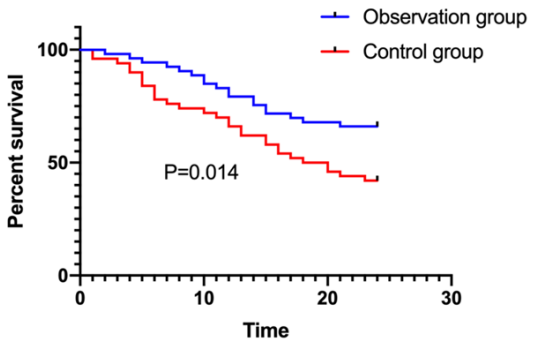

Figure 3. Comparison of 2-year survival rate between the two groups.

In this study, the treatment efficacy of the OG was found to be significantly higher than that of the CG. This indicated that combined treatment of DC-CIK and chemotherapy significantly improved the treatment response rate. CEA, CA724, and CA199 are the most common laboratory tumor indicators and have been widely applied in the early diagnosis and prognostic evaluation of CRC [21]. To evaluate the efficacy of the combined treatment in CRC patients after radical resection, we compared the tumor markers between the two groups before and after the treatment. We found significantly improved serum tumor markers in the OG after the treatment than in CG. This demonstrated that the combined treatment of DC-CIK and chemotherapy was of better effect for CRC patients after radical resection. Previous studies have shown that tumor occurrence, development, and metastasis are closely relevant to the body's immune status. The T lymphocyte-mediated cellular immune response is the principal host anti-tumor response [22]. Among the immunoglobulins presented in body fluids, IgG is an antibacterial and antiviral antibody that plays a major role in the anti-infection response. IgA can form a local immune system that protects the body together with surrounding cells. IgM is a highly effective antibody that can activate the body's early defense [23, 24]. We compared immune function-related parameters between the two groups before and after the treatment. It was suggested that the combined treatment directly killed cancer cells and increased the expressions of humoral immune markers. This indicated that this regimen could restore patients' ability of removing tumor cells and improve their immune function. It has been shown [25] that DC and CIK cells have stronger anti-tumor activity than CIK cells alone after co-culture. It accelerated T cell proliferation and played a stronger role in killing tumors. This significantly improved the immune function of patients and significantly inhibited the growth of tumors. This explains our findings. We compared the adverse reactions during the treatment, the 2-year survival rate, and the quality of life between the two groups. The results showed that the adverse reactions in the OG were significantly lower than those in the CG. This suggested that DC-CIK cell immunotherapy can significantly lessen the toxic and side effects caused by chemotherapy and alleviate the pain, improving patients' quality of life. This was confirmed by our observation results. The OG was observed to have a significantly higher 2-year survival rate than the CG. The multivariate regression analysis showed that the choice of treatment regimen was an independent risk factor affecting the prognosis of patients. This indicated that the combined therapy of DC-CIK and chemotherapy is beneficial to up-regulating the long-term survival rate of patients.

In summary, combined treatment of DC-CIK and chemotherapy has a better efficacy, leads to less side effects, and can significantly improve the prognosis and quality of life in CRC patients after radical resection. This regimen can be promoted in clinical practice. This study had some shortcomings. Due to the small sample size included, it is necessary to carry out more multi-center, large-sample, and large-

Table 4. Univariate analysis

Variable	Survival Group (n=56)	Death Group (n=47)	X^2	P
Sex			0.034	0.853
Male (n=58)	32 (57.14)	26 (55.32)		
Female (n=45)	24 (42.86)	21 (44.68)		
Age			0.020	0.887
≤64 years (n=49)	27 (48.21)	22 (46.81)		
>64 years (n=54)	29 (51.79)	25 (53.19)		
BMI			0.031	0.859
≤23 kg/m2 (n=56)	30 (53.57)	26 (55.32)		
>23 kg/m2 (n=47)	26 (46.43)	21 (44.68)		
Smoking history			1.950	0.163
Yes (n=39)	25 (43.86)	14 (30.43)		
No (n=64)	32 (56.14)	32 (69.57)		
Clinical phase			29.61	<0.001
Stage III (n=68)	50 (89.29)	18 (38.30)		
Stage IV (n=35)	6 (10.71)	29 (61.70)		
Degree of differentiation			11.30	<0.001
Low (n=43)	15 (26.79)	28 (59.57)		
Mid and High (n=60)	41 (73.21)	19 (40.43)		
Treatment Regimen			9.570	0.002
Monotherapy (n=53)	21 (37.50)	32 (68.09)		
DC-CIK combined therapy (n=50)	35 (62.50)	15 (31.91)		

BMI: body mass index.

Table 5. Value Assignment

Factor	Assignment
Pathologic stage	Stage IV =1, Stage III =0
Degree of differentiation	Medium and low differentiation =1, high differentiation =0
Treatment Regimen	Chemotherapy alone =1, DC-CIK combined with chemotherapy =0

Table 6. Multivariate analysis

Factor	B	S.E	Wals	P	Exp (B)	95% C.I.	
						Lower Limit	Upper Limit
Pathologic stage	2.574	0.721	12.624	0.001	13.143	3.173	53.824
Degree of differentiation	1.623	0.665	5.645	0.021	4.965	1.326	18.467
Treatment Regimen	3.253	0.813	14.577	0.001	27.925	5.047	154.346

Table 7. Comparison of quality of life

Variable	Observation Group n=53	Control Group n=50	t	P
Physical function	72.98±2.24	63.74±1.66	21.10	<0.001
Role Function	71.46±1.81	61.22±1.87	23.99	<0.001
Emotional function	73.1±1.74	63.38±1.97	22.01	<0.001
Cognitive function	71.51±2.16	61.62±2.08	20.30	<0.001
Social functioning	65.29±2.08	56.82±2.22	16.91	<0.001

scale studies. There are few relevant studies on the combined therapy of DC-CIK and chemotherapy on CRC. Our findings remain to be confirmed by future studies.

Disclosure of conflict of interest

None.

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