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Research Progress on the Pathogenesis of Colorectal Cancer and Integrated Traditional Chinese and Western Medicine Treatment

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Abstract: *Colorectal cancer, as a common cancer, is still poorly understood in terms of the molecular mechanisms of its pathogenesis. Despite the fact that research on the pathogenesis of colorectal cancer is gradually deepening and providing enhanced screening strategies, the prevalence of the disease is still on the rise due to the fact that early symptoms of the disease are not obvious and are difficult to diagnose, causing many patients to miss the best opportunity for surgical treatment. Most studies have shown that the early onset of colorectal cancer is mainly due to the role of the body's environment, diet, genetics and other factors present in the patient. Therefore, this article reviews the pathogenesis and main treatment methods of colorectal cancer in Chinese and Western medicine, aiming to provide a reference basis for the clinical prevention and treatment of this type of disease and the elucidation of the related pathologic mechanisms.*

Keywords: *Colorectal cancer; Pathogenesis; Western medicine treatment; Chinese medicine treatment*

1. Introduction

Colorectal cancer, which the third most common type of cancer [1], is a heterogeneous disease with multiple pathogenic mechanisms involving somatic mutations, gene fusions, genetic instability and epigenetic alterations [2]. Approximately 70% of sporadic colorectal cancers develop from adenomatous polyps, whereas 25-30% arise through sessile serrated lesions [3]. In China, colorectal cancer ranks 3rd in malignant tumors and 5th in mortality [4], and in recent years, its age of onset tends to be younger. The pathogenesis of colorectal cancer is very complex and diverse, and is caused by a variety of risk factors, including environmental and dietary factors, personal habits, familial and hereditary [5]. And advanced age, high-fat diet, obesity, smoking, familial polyposis, and chronic inflammatory bowel disease are considered to be high risk factors [6]. The current colorectal cancer treatment mainly includes surgical treatment, radiotherapy, molecular targeted therapy, immunotherapy and integrated therapy, especially the immunotherapy of tumor has become a big hot spot. Immunotherapy applied to colorectal cancer includes single-agent anti-PD-1 monoclonal antibody or double-antibody immunotherapy combined with anti-CTLA-4 monoclonal antibody, which can make the overall survival of advanced colorectal cancer extend from 4 months to 6 months [7]. However, it still faces dilemmas such as prominent adverse effects and limited median survival time. In order to better elucidate the pathogenesis of colorectal cancer as well as good therapeutic means, this article focuses on the pathways involved in the progression of colorectal cancer, the main therapeutic approaches in clinical practice, and the research progress of Chinese medicine in the treatment of colorectal cancer.

2. Pathogenesis of colorectal cancer

2.1. Wnt/β-catenin pathway

The Wnt signaling pathway is a classical pathway that was discovered early and has been continuously studied and evolved, and is involved in several developmental events in the body's embryonic development and homeostatic homeostasis within the tissues, including cell proliferation, stem cell self-functional renewal, and cell differentiation [8]. The classical Wnt pathway leads to the accumulation of β-catenin, which binds to T-cell factors and lymphoid enhancement binding factors in

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the nucleus. In addition to this, β-catenin is also associated with the coactivator p300 and Creb-binding proteins [9]. Components of the Wnt pathway that regulate mutations in colorectal adenomatous polyposis coli are found in >80% of colorectal carcinomas, appearing early in the progression of the disease, and are thought to initiate malignant transformation of the colorectal epithelium [10]. In addition, Wnt signaling has been associated with CRC invasion and metastasis, chemotherapy resistance, and plays a key role in promoting epithelial-mesenchymal transition by inducing the corresponding epithelial-mesenchymal transition as well as the expression of its associated transcription factors [11].

2.2. VEGF Pathway

VEGF directly affects a variety of cancer cells mainly through autocrine signaling mechanisms. It has been shown that in colorectal cancer, vascular endothelial growth factor levels and its activity are enhanced and associated with poor prognosis [12]. VEGF expression was measured in the colonic mucosa and compared to normal expression in healthy intestinal mucosa, which was significantly upregulated in benign adenomas and increased with further progression, with tumor cells within the tumor having the highest VEGF expression [13]. In colon cancer, activation of the ERK pathway in the presence of serum starvation plays an essential role in the upregulation of vascular endothelial growth factor [13].

2.3. Farnesol X receptor signaling

Elevated levels of intestinal bile acids are risk factors for colorectal cancer [14]. Abnormally high levels of intestinal bile acids trigger simultaneous deleterious effects in the colonic mucosa, such as oxidative DNA damage, inflammation, and hyperproliferation, which greatly contribute to colorectal cancer progression in the post-initiation phase. The farnesol X receptor exhibits critical anticancer functions in vitro and in vivo against several types of cancer [15] and plays a role in intestinal tumorigenesis in addition to regulating metabolic disorders [13]. The farnesol X receptor is a major regulator of the dynamic homeostasis of intestinal bile acids, controlling synthesis, exocytosis, endocytosis, and detoxification throughout the intestinal-hepatic axis, effectively slowing the progression of colorectal cancer [13]. It has been shown that loss of systemic farnesol X receptors enhances the progression of spontaneous colorectal cancer and that obesity-induced intestinal bile acid water imbalance promotes intestinal stem cell proliferation by inhibiting intestinal farnesol X receptors in Apcmin/+ mice [16].

2.4. Nuclear factor-κB signaling pathway

Over-activation of nuclear factor-κB signaling pathway is closely related to cell proliferation, apoptosis, angiogenesis, inflammation, metastasis and drug resistance in colorectal cancer [17]. Receptors that can be stimulated on the cell surface through external stimuli (microorganisms, oncogenic factors, radiotherapy, etc.) include Toll-like receptors, T/B cell receptors, and tumor necrosis factor receptors, which interact with their specific ligands, leading to the upregulation of the IκB kinase complex.The activation of nuclear factor-κB is caused by the ubiquitin-proteasome pathway that degrades phosphorylated IκB, which is involved in the immune response , cell survival, cell death and inflammation all play key roles [18].

2.5. Chinese medicine's understanding of the etiology and pathogenesis of colorectal cancer

Colorectal cancer belongs to the category of "cancer" in traditional Chinese medicine, and corresponds to the diseases of "accumulation", "intestinal Qin", "dirty poison" and "lock-anal hemorrhoid" in the literature of past dynasties. It corresponds to the diseases of "accumulation", "intestinal qin", "dirty poison", "lock-anal hemorrhoid" and so on in the literature of the past dynasties. It is induced by the deficiency of positive qi, the invasion of six kinds of evils and poisons, dietary imbalance and internal injuries of emotions and feelings, which leads to the downward injection of dampness-heat and stagnant poison into intestinal tract and the malfunction of the conduction of the large intestine, thus resulting in the present disease, which is located in intestines, and has a close relationship with the spleen, stomach, liver and kidney. According to Chinese medicine, the spleen is the source of the latter part of the body, the source of qi and blood biochemistry, the transportation of water and grains, and the resistance to evil, if the spleen qi is strong, it is not easy to be attacked by external evils. Jin Gui Yao Lve emphasizes that "if the spleen is strong, the seasons will be free from evil", and the spleen can control the differentiation and maturation of immune cells, while a deficient

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spleen will form an immunosuppressive microenvironment [19]. Abnormalities in the tumor microenvironment affect cell metabolism and have a screening effect on tumor cells, which in turn increases the degree of tumor malignancy and promotes tumor metastasis. Spleen deficiency can lead to chronic, low-grade inflammation inducing the release of factors such as HIF-1α and promoting the generation of the Warburg effect [20]. In addition, spleen deficiency is related to the regulation of immunity by intestinal flora, and an increase in the beneficial bacterium Bifidobacterium bifidum is associated with a high level of positive qi, which is able to activate the immune response and induce the anti-tumor effect of killer T cells [21].

3. Treatment of colorectal cancer in modern medicine

3.1. Surgical treatment

Surgical treatment is a comprehensive selection of local treatment methods with the most accurate effect according to the location and staging of the tumor, which is divided into radical rectal cancer resection with abdominal union, transabdominal rectal cancer resection, transsphincteric resection, minimally invasive laparoscopic rectal cancer resection, etc. The scope of resection is very large, and it is suitable for locally advanced colorectal cancer. Abdominal meeting combined rectal cancer radical resection has a large resection range and good radical effect, which is suitable for locally advanced rectal cancer. However, it can be used in the early stage of rectal cancer to obtain better survival rate. Because of the large resection area, there will be different degrees of damage to the surrounding normal tissues and organs, and postoperative pain is more obvious and recovery time is long due to permanent intestinal stoma and perineal trauma, and postoperative complications are easy to occur [22]. While transabdominal rectal cancer resection has the advantages of smaller incision, less intraoperative blood loss and shorter hospitalization time than radical rectal cancer resection with abdominal association, there is no significant difference between recurrence rate and survival rate and radical rectal cancer resection with abdominal association. However, with the arrival of minimally invasive treatment, laparoscopic rectal cancer resection can make the scope of the surgical field clearer, thus reducing intraoperative damage to the pelvic nerves and protecting the patient's voiding function [23], and is suitable for neoadjuvant and adjuvant treatment of non-metastatic disease in stage II and III. Advantages include narrowing the surgical incision and reducing postoperative pain. Compared with open surgery, laparoscopic resection has the advantages of low complication rate, short hospitalization time, and rapid recovery of bowel function [23]. In addition, traditional open surgeries include rectal cancer resection, local excision, and colorectal anastomosis. Rectal cancer resection, also known as "proximal stoma and distal closure surgery", expands the scope of diagnosis and treatment of rectal cancer surgery and raises the survival rate of patients due to the small surgical incision and fast postoperative recovery.The surgery is suitable for those who have poor general condition such as high age, obesity, etc., those who can not bear radical surgery, those who have acute obstruction before surgery, those who are uncomfortable with transabdominal rectal cancer resection, those who have heart disease, cerebral infarction and other concomitant diseases, or those with metastatic rectal cancer。 It is an effective surgical method for elderly and weak rectal cancer patients. While local excision surgery has smaller incision, less stimulation to patient's organs, more treatable effect, quicker postoperative recovery, lower local recurrence rate, and preserves the normal shape of anus, patients have higher quality of life. It is suitable for patients with early rectal cancer with small tumor size, confined to mucosa or submucosa, high differentiation of tumor, advanced age with other diseases and low tolerance to radical surgery. Colorectal anastomosis is a transanal anastomosis of the colon and anal canal, the anastomosis is performed above the anorectal ring or the dentate line, and the procedure preserves the overall structure of the anorectal ring and preserves the function of the anus. It is suitable for patients whose tumor is more than 5cm from the anus and the distal cut end of the tumor reaches 2-3cm. Early postoperative defecation dysfunction occurs, recurrence rate is low, but anastomotic leakage is common. The modified procedure can effectively reduce the incidence of anastomotic leakage, and compared with the Miles procedure, the hospitalization time is shorter. It is compared with the Miles procedure, the hospitalization time is shorter, the complications and hospitalization cost are lower, and the postoperative recovery is better and faster.

3.2. Chemotherapy and radiotherapy

Colorectal cancer is still at risk of recurrence after surgery, and radiotherapy used before surgery is called neoadjuvant therapy, and used after surgery is called adjuvant radiotherapy. Currently, the

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commonly used chemotherapeutic agents in clinical practice are fluorouracil, oxaliplatin, capecitabine, irinotecan, etc [24]. Fluorouracil is the most commonly used drug for adjuvant chemotherapy of rectal cancer and is often administered intravenously. Chemotherapy can reduce the size of the lesion and can control the surrounding and distant lymphatic metastases, but radiotherapy has only a transient effect on tumor shrinkage. Usually in conjunction with surgery, chemotherapy can be used to lower the stage prior to tumor resection, with the benefit of significant disease-free and overall survival from adjuvant therapy. In a phase III trial, surgery in conjunction with capecitabine or 5-FU in patients with stage II or III rectal cancer showed that capecitabine had a higher 5-year overall survival and 3-year disease-free survival than 5-FU [23]. Patients had similar overall survival rates comparing preoperative and postoperative radiotherapy, 59.6% and 59.9%, respectively, and local recurrence rates of 7.1% and 10.1%, respectively [23]. Treatment criteria: fluorouracil chemotherapy followed by total mesenchymal excision after 6-10 weeks, or a short course of preoperative radiotherapy (5 consecutive d) and immediate surgery within 2-5 days, short-term radiotherapy possesses the advantages of shorter duration, low toxicity, high compliance, and low cost compared with long-term chemotherapy [25]. Preoperative radiotherapy has three advantages over postoperative radiotherapy: (1) It can reduce the tumor volume to help surgical resection and increase the probability of sphincter-preserving surgery. (2) Reduces complications and avoids the occurrence of intra-pelvic, small bowel radiation damage due to postoperative adhesions. (3) Increase the possibility of anastomosis between the resected tissue and healthy intestine.

3.3. Immunotherapy

Immunotherapy has rapidly become available for many types of solid cancers. It has been found that tumor immune evasion is involved in tumorigenesis, progression, metastasis and recurrence, demonstrating better efficacy and tolerance in clinical trials [26]. Immunotherapy for colorectal cancer proceeds from specific active, non-specific active and passive immunity [27]. The most common immune checkpoints are cytotoxic T-lymphocyte-associated antigen 4, programmed death receptor 1, and its ligand PD-L1, which influence the production of cytokines such as interleukin 2, tumor necrosis factor, and interferon γ by modulating early and late T-cell proliferation [28].

4. Treatment of Colorectal Cancer in Chinese Medicine

4.1. Research on treatments

Currently, the treatments for colorectal cancer still focus on strengthening the spleen and resolving dampness, clearing heat and detoxification, resolving phlegm and dispersing knots, cooling blood and eliminating blood stasis, etc. For example, based on Sijunzi Tang, Sun Bo et al [29] observed that the method of strengthening the spleen and benefiting the qi in combination with chemotherapy for the treatment of intermediate- and advanced-stage colorectal cancer had the definite effects of stabilizing the tumor, improving the quality of patients' survival and improving the immune function. In the treatment of colorectal cancer, Zhou Zhongying took anti-cancer and detoxification as the method of disease identification, supplemented by moving qi and relieving depression, eliminating phlegm and dispersing knots, activating blood circulation and removing blood stasis, and searching and eliminating collaterals, with particular emphasis on the application of the method of clearing heat and resolving turbidity. In middle and late stage colorectal cancer, there is often a mixture of deficiency and solidity, so the core characteristics of spleen deficiency, stasis and toxicity should be captured to strengthen the spleen and remove dampness, activate blood circulation and detoxify toxins, and it is appropriate to use qi tonifying and spleen strengthening medicines, firstly ginseng and astragalus because ginseng is good at replenishing the qi of the five viscera, and it keeps the qi and doesn't go away. Astragalus is good at replenishing the qi of the five organs and keeping the qi without going. The two medicines match, a go a guard, static and dynamic, complement each other. In addition, fried atractylodes, Angelica sinensis, Poria, Job's tears, yam and other corrective products can be added with the evidence. Treatment, special emphasis should be placed on regulating the smooth viscera gas, restore its through the descending, pointed out that the large intestine is one of the six viscera, the Division of conduction of the duties, with a "transmission of chemicals and not hidden, to pass for the use of the descending and" physiological characteristics of the treatment should be "through the supplementation of the concurrently should not be stagnant.

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4.2. Research on the evidence and its biological basis

4.2.1. Recognition of symptoms

At present, there is no uniform conclusion on the identification and classification of colorectal cancer.There is no uniform conclusion on the identification and staging of colorectal cancer, and many medical practitioners have based on their clinical experience or literature research to identify and stage colorectal cancer.Many medical practitioners recognize and classify colorectal cancer according to their own clinical experience or literature research, among which the deficiency of qi and blood is the most common.Among them, the deficiency of qi and blood is the most common, followed by stasis and toxin accumulation syndrome, spleen and kidney deficiency syndrome.

4.2.2. The relationship between deficiency and colorectal cancer

According to Chinese medicine, the spleen is the source of qi and blood, and it transports water and grains and fights against evil.Jin Gui Yao Lve emphasizes that "if the spleen is vigorous, it is not subject to evil in all seasons", and that the spleen can control the differentiation and maturation of immune cells. The spleen can control the differentiation and maturation of immune cells, and a weak spleen will form an immunosuppressive microenvironment.Tumor Abnormalities in the tumor microenvironment affect cell metabolism and have a screening effect on tumor cells, thus improving the quality of tumor cells.Screening effect on tumor cells, thereby increasing the degree of tumor malignancy and promoting tumor transfer metabolism of tumor cells, thereby increasing the degree of tumor malignancy and promoting tumor migration. The tumor microenvironment can affect the cell metabolism, which has a screening effect on tumor cells, thus increasing the degree of tumor malignancy and promoting tumor transformation. If the spleen is deficient, the zongqi is insufficient, and it cannot pass through the heart vein to carry out respiration, so the body is in a state of chronic hypoxia. This will directly cause the protein B region on the erythrocyte membrane of human body at the cellular molecular level. The Protein B region on the human erythrocyte membrane at the cellular molecular level, which is not able to carry out exchange of anions, resulting in a lack of oxygen and an insufficient supply of oxygen and insufficient supply of oxygen. Spleen deficiency can also lead to chronic, low-grade inflammation inducing the release of factors such as HIF-1α, which promotes the Warburg effect. In addition, spleen deficiency is associated with intestinal flora to regulate immunity, and an increase in the beneficial bacterium Bifidobacterium bifidum is positively can activate the immune response and induce killer T cells to exert anti-tumor effects. Spleen-enhancing traditional Chinese medicine can regulate the tumor microenvironment, which is of great significance to the treatment of colorectal cancer.

4.2.3. Relationship between blood stasis and colorectal cancer

Cancer patients with malignant disease are mostly in the state of survival with tumors. Cancer tumors are always caused by qi stagnation and blood stasis, phlegm obstruction and toxicity aggregation, which can lead to localized impassability of qi, blood and meridians, which is similar to the pathological changes caused by inflammatory reactions acting locally in the human body. Blood stasis is a kind of pathological product formed when the blood leaving the meridian cannot be eliminated in time or dissipated quickly and stagnates in the body, or when the blood in the body is stagnated and accumulated in the meridian or other internal organs due to poor operation, and it is also called "bad blood". It is also known as "bad blood". It is related to the occurrence and development of diseases. The clinical biochemical indexes of leukocytes, C-reactive protein, interleukin (IL-1, IL-6, IL-8, etc.), tumor necrosis factor α (TNF-α), etc. have significant differences in blood stasis, and combined with metabolomics, it is found that blood stasis involves energy metabolism, oxidative stress, inflammation, etc., which suggests that inflammation and oxidative stress play a more important role in blood stasis.

4.3. Clinical Application of Traditional Chinese Medicine

4.3.1. Inducing apoptosis and inhibiting proliferation of cancer cells

Li et al [30] experimentally found that the isolated psoralenetin from psoralen could inhibit the AKT/GSK-3β/β-catenin pathway in colorectal cancer cells, inhibit the proliferation of tumor cells and induce their apoptosis.Park et al [31] found that the anticancer activity of cinnamon might inhibit tumor cell proliferation through proteasomal degradation and transcriptional inhibition by down-regulation of cyclinD1, and possibly act by inducing tumor cell apoptosis through reactive oxygen species-dependent NF-κB and ATF3 activation. In addition, tretinoin effectively regulates the active expression of HSF1,

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further activates the expression of AMPKα and YAP by enhancing the transcription of LKB1, and inhibits colorectal cancer cell proliferation in vitro and in vivo by increasing the degradation of β-catenin via the ubiquitin-proteasome pathway [32]. The results of Zhong Yu et al [33] further demonstrated that isobutyryl comedones significantly induced apoptosis in a variety of human colon cancer cells, and the inhibition of proliferation showed a certain correlation with the time and concentration of the drug action, and also inhibited the PI3K/Akt/m-TOR signaling pathway, which led to the alteration of the cell growth cycle.

4.3.2. Regulation of tumor microenvironment

The immune system eliminates transformed intestinal cells by first destroying them, sculpting them and selecting for variants that are no longer recognized and are insensitive to immune effectors, ultimately inducing them to assume a state of immunosuppression within the tumor's microenvironment, capable of promoting immune escape and tumor growth. Buhrmann C et al [34] showed that multiple molecular targets of resveratrol/Sirt1 signaling could inhibit the proliferation and invasion of colorectal cancer tumor cells in pro-inflammatory multicellular TME. TCM anti-cancer methods can effectively regulate the microenvironment of colorectal cancer in multiple ways, such as Tenglong tonic Chinese broth can not only effectively increase the number of human colorectal cancer immune cells CD4+, CD8+ T-cells, but also have an inhibitory effect on macrophages, and play a therapeutic role in colorectal cancer through these pathways [35]. The main effect of Garcinia cambogia tonic soup is that it can effectively improve the autoimmunity of patients with advanced malignant colorectal cancer, and its action is related to the increase in the number of cell subsets in the body and the immune response generated by the differentiation of Th1 cells, which involves CD3+, CD4+, CD8+ T cells [36].

4.3.3. Inhibition of tumor angiogenesis

Angiogenesis is a key event in maintaining tumor cell survival and invasiveness, and the expression of vascular endothelial growth factor A, an indispensable pro-angiogenic factor secreted by tumor cells, is frequently upregulated in colorectal cancer. Tanshinone IIA not only greatly reduced the expression of HIF-1αand inhibited the secretion of vascular endothelial growth factor and basic fibroblast growth factor in human umbilical vein endothelial cells, but also effectively reduced the proliferation, angiogenesis and metastasis of human umbilical vein endothelial cells. Oleanolic acid, a natural pentacyclic triterpenic acid compound present in various herbs, mediates an OA-dependent inhibition of tumor angiogenesis by blocking the phosphorylation of vascular endothelial growth factor receptor-2, which leads to the inhibition of the MEK/ERK/JNK pathway [37]. In a study by Li et al. it has been found that Xiaguanqiu possesses therapeutic efficacy for the treatment of human colon carcinoma in HT-29 nude mice with transplantation of tumor angiogenic generation, and its mechanism of action mainly mediates the pathway of STAT3 signaling, and it is also able to directly downregulate the expression of VEGF-A and VEGF-R-2, among others [38].

4.3.4. Combination of Chinese and Western medicines

The combination of traditional Chinese medicine has been applied in clinics, which can be combined with radiotherapy to enhance the efficacy and improve the quality of life, as well as combined with surgery to enhance immunity and resist metastatic recurrence. Six-flavored dihuang pill can regulate the balance of neuroendocrine immune network, strengthen antibody-forming cells and enhance antibody secretion by restoring the function of "hypothalamus-pituitary-gonadal axis", protect the organism, and alleviate the toxic side effects of chemotherapy [23]. Ginseng-mai injection is a kind of traditional Chinese medicine injection widely used in Chinese cancer combination therapy, which can not only effectively remodel the homeostasis of angiogenesis-promoting factors and anti-angiogenesis factors in the body, but also promote the normalization of blood vessels in tumors, thus enhancing drug delivery and anti-tumor effects [39]. Ginsenoside Rg is a traditional Chinese medicine ingredient with antiangiogenic effects, and the results of the study showed that it not only inhibits the growth and migration of colorectal cancer cells in vitro and in vivo, but also enhances the toxicity of 5-fluorouracil and oxaliplatin on cells in vivo [40]. In the observation of postoperative colon cancer patients, it was found that, in addition to conventional chemotherapy after surgery, when taking Tianma granules again for treatment, the quality of survival of the patients was improved, the side effects on the gastrointestinal tract after conventional chemotherapy were reduced, and the recurrence and metastasis of patients with colon cancer could be effectively reduced, and the immunity of the body was strengthened [23].

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5. Summary

As a common solid tumor of the gastrointestinal tract, colorectal cancer ranks at the forefront of the world's disease spectrum in terms of morbidity and mortality, and thus more and more studies on its pathogenesis as well as treatment have been conducted in clinical practice. Due to the limitations of early colorectal cancer, such as the lack of obvious clinical symptoms, complex pathogenesis, and the damage of radiotherapy to the human organism, the emergence of traditional Chinese medicine (TCM) has brought new opportunities for the treatment of colorectal cancer. Chinese medicine has many advantages such as multi-targeting, symptomatic integrated therapy, combining with various chemotherapeutic drugs that have been applied in clinical practice, effectively reducing serious side effects of drugs, and dramatically improving the therapeutic effect of drugs, etc. However, it is still necessary to strengthen the communication and deliberation among various disciplines, and to be cautious about the patients' demands in order to guarantee the safety and efficacy of its treatment.

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