

Research Progress of Chinese and Western Medicine in the Treatment of CRC

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Abstract: Colorectal cancer (CRC), with its high incidence and high mortality, has been a popular topic of research in China in recent years. At present, the treatment of CRC mainly includes surgery, radiotherapy and chemotherapy, molecular targeted therapy, and immunotherapy. Traditional Chinese medicine has unique advantages in reducing toxicity and increasing efficiency, improving patients' quality of life, and prolonging survival time. In this paper, the research progress of Chinese and western medicine treatment of CRC was reviewed in recent years, in order to provide positive reference for clinical treatment.

Keywords: Colorectal cancer; integrated Chinese and Western medicine; treatment progress; review; CRC

1. Introduction

Colorectal cancer (CRC), also known as colorectal cancer, is a malignant tumor of the digestive tract with a high incidence and mortality. With the rapid development of economic level, people's living conditions have been improved day by day, but the changes in diet structure, living habits and living environment have made the incidence and mortality of cancer rise year by year, and its mortality rate has become the first of all kinds of diseases. Data show that in the past 10 years, the number of patients with CRC has increased by more than 1 million per year worldwide, ranking third in the incidence of malignant tumors, as shown in Figure 1 and Figure 2. And the incidence is high in Western developed countries, greatly affecting the quality of life of patients, and has become a very urgent social problem worldwide. A large number of studies [1] have shown that the incidence of CRC in China has exceeded the global average growth rate, with a rapid growth rate of about 4.2% per year, and the number of new cases has exceeded 170,000 per year. The incidence and mortality rate of CRC in China account for the 5th and 6th place respectively among all tumors. The incidence and mortality of CRC account for the second and fourth place respectively in all tumors, and it increases with age, and has become one of the important factors that seriously threaten human life and health.

At present, the treatment of CRC mainly includes surgery, chemoradiotherapy, immunotherapy, molecular targeted therapy and so on. For early detection of CRC patients, surgical treatment effect is the most ideal, and even some can achieve the level of cure, the 5-year survival rate can be as high as 90%. However, because many early CRC patients do not show relevant discomfort, the incidence is high, but the early diagnosis rate is very low, and it is not diagnosed until the middle and late stages or even after the occurrence of hematogenous metastasis. According to the study, the 5-year survival rate of such patients is much lower than that of patients with early detection, about 7 percent. In addition, some patients who underwent surgery and chemotherapy in the early stage, due to the influence of toxic side effects, trauma and other factors, the quality of life after surgery is not ideal, and even some patients give up continuing treatment. Therefore, the diagnosis and treatment status of CRC is not optimistic, and alleviating patients' pain and improving patients' quality of life must be put on the agenda.

In recent years, researchers have carried out a lot of research and expansion in the treatment of malignant tumors, and found that western medicine combined with Chinese medicine can play a positive role in reducing toxicity and increasing efficiency, improving the quality of life of patients, extending survival time and other aspects. Therefore, the treatment of CRC by integrated Chinese and western medicine has been highly valued by experts and patients at home and abroad.

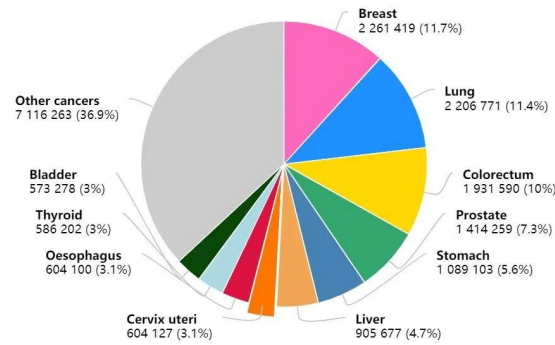


Figure 1: Top 10 cancer types with new cancer cases in 2020

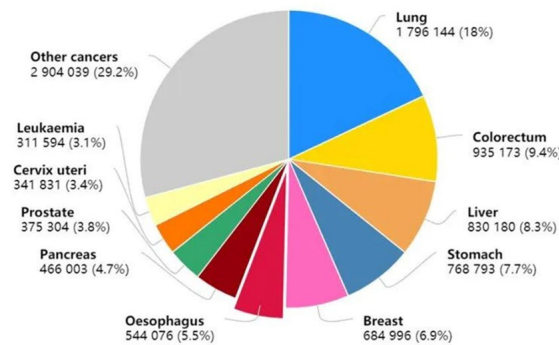


Figure 2: Top 10 types of cancer deaths in 2020, Data sources: The international Agency for Cancer Research (IARC) of the WHO

2. Western medical treatment of CRC

2.1. Surgical Treatment

Surgical treatment is still the most effective treatment for CRC patients, the only possible cure for patients, and the most important treatment for patients with early diagnosis of CRC. In recent years, with the improvement of medical technology, surgical methods for CRC have been compared with Traditionalopensurgery (OS) alone, and include Laparoscopic assistedsurgery (LAS), robotic surgery and so on. The operation of endoscopy is becoming more and more proficient, and the clinical application of laparoscopic surgery is more and more extensive. Studies have shown that compared with OS, LAS has many advantages, such as clear visual field, less intraoperative blood loss, less surgical trauma, less patient pain, shorter postoperative gastrointestinal function recovery time, fewer postoperative complications, beautiful appearance and shorter hospital stay [2-3]. However, studies have pointed out that in some complex CRC operations, laparoscopic surgery is more troublesome and time-consuming than traditional surgical dissection due to less exposure and no direct contact [4]. In general, colon cancer and rectal cancer with higher position are more suitable for laparoscopic surgery, while robot surgery for middle and low rectal cancer can be selected, and the more minimally invasive conditions are more conducive to the preservation of pelvic autonomic nerve, and the quality of life of patients is higher [5]. The specific surgical method should be decided according to the comprehensive consideration of tumor site, stage, invasion range, medical history and other factors. As far as possible for the patient to strive for radical treatment, the diseased intestinal segment, mesangium, lymphatic drainage area of the entire resection, and the corresponding intestinal segment innervated blood vessels were ligation. However, for patients who cannot achieve radical resection, palliative resection can be used to improve the quality of life of patients and extend the survival period of patients to varying degrees.

2.2. Radiotherapy and Chemotherapy

Chemoradiotherapy in the treatment of CRC can be divided into neoadjuvant chemoradiotherapy

and adjuvant chemoradiotherapy according to the application time. The application before surgery is called neoadjuvant chemoradiotherapy, and the application after surgery is called adjuvant chemoradiotherapy. According to the needs of the disease and the treatment site, there are also palliative chemotherapy and local chemoradiotherapy [6]. Because the early symptoms of CRC patients are not obvious, some patients miss the opportunity for surgery after the diagnosis of CRC. Appropriate preoperative chemoradiotherapy can reduce the stage and shrink the tumor volume, thereby increasing the surgical resection rate and improving the long-term postoperative efficacy. Adjuvant chemoradiation after resection of CRC can also help to inhibit the recurrence and metastasis of the tumor, prolong the disease progression-free period (PFS) and overall survival (OS) of the patient. 2023CSCO guidelines also point out that patients with stage I and stage II general risk CRC may not use chemotherapy and continue to observe, and patients with stage II high risk stage III are the main objects of chemotherapy.

Commonly used chemotherapy drugs in clinical practice mainly include fluorouracil, oxaliplatin, capecitabine, irinotecan, and Ticeo [7]. A large number of studies have confirmed that the efficacy and survival of 5-FU combined with oxaliplatin or irinotecan in the treatment of mCRC patients are superior to 5-FU/LV monotherapy. At present, there are three commonly used combination chemotherapy regimens: (1) XELOX regimen: mainly composed of capecitabine and oxaliplatin; FOLFOX scheme: mainly composed of 5-FU, LV, oxaliplatin; (3) FOLFIRI scheme: mainly composed of irinotecan, 5-FU and LV. Among them, FOLFOX and FOLFIRI have similar efficacy, and NCCN recommends the first and second line treatment for each other. Studies have also shown that the 5-year overall survival rate and 3-year disease-free survival (75.7% and 75.2%) of patients with stage II or III CRC treated with surgery combined with capecitabine are higher than those treated with 5-FU (66.6% and 66.6%) [8]. At the same time, XELOX regimen has lower adverse reactions than FOLFOX regimen and is better tolerated by patients. Therefore, XELOX regimen is recommended first and may become a routine first-line treatment for mCRC. For advanced rectal cancer that cannot be cured, palliative chemotherapy can control tumor progression and prolong patient survival time.

Due to the particularity of the lesion site of CRC and the technical requirements of radiotherapy, radiotherapy for CRC was not used much before, but now it is often combined with chemotherapy in preoperative neoadjuvant therapy and postoperative adjuvant therapy, which can effectively reduce the size of the tumor, reduce the invasion of the tumor and reduce the clinical stage. It can not only help reduce the difficulty of surgery, but also "give a new life" to some patients who have lost the opportunity of surgical treatment, improve the disease outcome, and improve the survival time and quality of life of patients [9]. The 2022 CSCO guidelines also indicate that local radiotherapy can improve the response rate of treatment and increase the probability of transformational resection in some patients with T4b. For patients with low rectal cancer, neoadjuvant radiotherapy can effectively increase the chance of anal preservation surgery.

2.3. Targeted therapy

With the advancement of science and technology and the further development of related studies, patients with advanced CRC can achieve better results by using different targeted drugs for different targets.

At present, the targeted drugs for the treatment of CRC mainly include the following classes [10]: (1) Vascular endothelial growth factor receptor inhibitors (VEGFR): including monoclonal antibodies and small molecule tyrosinekinaseinhibitors (TKI). Among them, the main monoclonal antibodies were bevacizumab, aliocept, ramumab, etc. Small molecule TKI is mainly composed of regorfenib and fuquitinib. (2) Epidermal growth factor receptor inhibitors (EGFR): Cetuximab and panizumab are mainly used, among which Cetuximab is recommended as the first-line targeted drug for combination chemotherapy by several guidelines such as EMSO and NCCN of the European Society of Medical Oncology due to its high safety and obvious efficacy, especially for patients with primary focus in the left half of the colorectal. (3) Multi-kinase inhibitors: such as regorafenib, which is recommended by NCCN guidelines as a third-line treatment for CRC. (4) In recent years, we have done a lot of work. At present, we have found some new targets for CRC targeted therapy, and some corresponding targeted drugs have been developed, including the well-known HER-2 and BRAF targets. The main targeted drugs include trastuzumab, pertuzumab and lapatinib, novel antibody conjugate drugs (ADC) DS-8201, Vemorafenib and Conafenib, in which the combination of trastuzumab with pertuzumab or lapatinib can make up for the deficiency of anti-HER-2 treatment alone. DS-8201 continued to control the development of mCRC after trastuzumab resistance, while vermorafenib and Conefenib effectively inhibited BRAFV600E mutations. Also includes some new targets such as neurotrophic original

myosin receptor kinase gene (neurotrophinreceptorkinase NTRK) and KRASG12C etc., the main targeted drugs for NTRK targets are for, lalo grace for; New targeted drugs for KRASG12C and other targets are under intense development. In addition, research and development of more efficient targeted drugs for the treatment of CRC are still continuing at home and abroad, and it is believed that targeted therapy will perform better in the comprehensive treatment of CRC.

2.4. Immunotherapy

Immunotherapy mainly uses immunomodulatory drugs to regulate the biological activity of immune cells and change the immune microenvironment around tumors, so that the human body has a relatively strong ability to resist tumors, inhibit the development and reproduction of tumor cells, and ultimately achieve the therapeutic effect. Some studies have found that the use of immunotherapy for slow-cycle tumor cells can significantly reduce tumor volume and prolong patient survival. It has been proven that immunotherapy combined with chemotherapy can play a role in enhancing efficacy and reducing toxicity, and greatly improve the quality of life of CRC patients.

At present, there are mainly immunotherapy methods such as immune checkpoint inhibitors, tumor vaccines, adoptive therapy and various compound preparations. Clinically commonly used immune checkpoint inhibitors, including programmed death receptor-1 (PD-1) inhibitors, programmed death ligand-1 (PD-L1) inhibitors, and cytotoxic T lymphocyte-associated protein 4(CTLA4) inhibitors, have enabled more advanced patients in various tumor species to achieve longer survival [11].

For CRC patients, We are mainly divided into microsatellite instability (MSI) population and mismatch repair (MMR) gene-like population according to the situation of genome mutation, and MSI is divided into microsatellite stable (microsatellite) population according to the degree stability (MSS), microsatellite instability-low (MSI-L) and microsatellite instability-high (MSI-H); MMR is classified into mismatch repair-deficient (dMMR) and proficient mismatch repair (pMMR). Among them, MSI-H/dMMR patients benefit from immune checkpoint inhibitor treatment. As early as 2017, the US FDA has successively approved Pembrolizumab and nivolumab, two PD-1 inhibitors, for second-line treatment of MSI-H/dMMR CRC patients [12-13]. KEYNOTE-177 uses PD-1 inhibitor Pembrolizumab as first-line therapy versus first-line chemotherapy. Various excellent data show that immunotherapy has challenged the first-line chemotherapy status of MSI-H type mCRC, and is even better than chemotherapy. In June 2020, the FDA approved pembrolizumab as the first-line treatment for MSI-H/dMMR CRC patients [14]. In MSI-H/dMMR CRC patients, a study compared the efficacy of the combined treatment of nabolumab plus ipimumab with that of nabolumab monotherapy, and the results showed that the ORR, DCR, PFS and OS of the combined treatment were higher than the performance data of nabolumab monotherapy. It has been shown that the effect of dual-drug immunotherapy is better than that of single-drug immunotherapy [15]. However, in MSS/pMMR CRC patients, the effect of immunotherapy is not satisfactory, but with the in-depth study of the tumor characteristics of CRC and the primary resistance mechanism of immune checkpoint inhibitors, immune checkpoint inhibitors combined with other treatments have also achieved certain therapeutic effects in these patients. The main manifestations are the dual drug combination of immune checkpoint inhibitors, the combination of immune checkpoint inhibitors with targeted drugs, chemotherapy drugs and radiotherapy.

As a new type of anti-tumor immunotherapy, tumor vaccine therapy combined with other treatments has achieved satisfactory efficacy in the treatment of CRC in a number of studies [16-17]. It activates the immune system of patients through vaccines, making itself produce strong specific tumor antibodies, so as to play a continuous role in inhibiting the growth and development of tumors. At present, the vaccines widely used in clinic include autologous tumor cell vaccine, nucleic acid vaccine, polypeptide vaccine, DC vaccine, bacterial or viral vector vaccine and so on.

Adoptive cell therapy (ACT) is another kind of immunotherapy that is relatively hot in research. The principle is mainly to return the patient's own or allogeneic active immune cells to the patient after culture and expansion in vitro, in order to enhance its ability to kill tumors, so as to achieve the purpose of treating the disease. Among them, CAR-T cell therapy is a relatively mature treatment method at present and has achieved considerable results. A number of studies have shown that the application of CAR T cell therapy in a variety of complex and refractory mCRC patients is well tolerated, treatment-related grade 3 or more adverse reactions are less, and the efficacy is also considerable.

In addition to the above immunotherapy, various combination immunotherapies such as CTLA-4 monoclonal antibody combined with PD-L1 monoclonal antibody therapy are also rapidly developing

and are expected to further bring better benefits to CRC patients.

3. Traditional Chinese Medicine treatment for CRC

3.1. Syndrome differentiation and treatment

At present, although there is no specific standard for the dialectical classification of CRC in traditional Chinese medicine, CRC can be divided into the following five syndrome types according to the etiology and pathogenesis ^[18]: (1) damp-heat accumulation type: The treatment is to clear heat and remove dampness, detoxify and eliminate abscess, and the prescription is to add or reduce Qingchangyin; (2) Internal obstruction type of stasis poison: to remove blood stasis and promote blood circulation, detoxification and detumescence, the prescription is reduced with septuagint Zhuyu decoction; (3) Spleen-kidney Yang deficiency type: to warm kidney tonifying spleen, helping Yang to stop diarrhea, the prescription with Fuzi Lizhong pills and Sishen pills to add or reduce; (4) Qi-blood two deficiency type: to treat Qi-blood double supplement, with eight Zhen decoction to add or reduce; (5) Liver and kidney Yin deficiency type: to treat nourishing Yin and clearing heat, soft and hard dispersive, with Zhibai Dihuang pill. Although different doctors have their own characteristics in the use of prescription, their common focus is on the weakness of temper, dampness blocking phlegm, qi and blood disharmony.

3.2. Acupuncture Treatment

Acupuncture and moxibustion therapy has the effect of luck in blood circulation, thinning channels and collaterals. For the acupuncture treatment of CRC patients, acupuncture at Erjian and Yangxi points can first play a role in regulating dampness and cold, and moxibustion treatment can play a role in regulating deficiency and deficiency. In CRC patients treated with acupuncture, complications such as abdominal pain, constipation, diarrhea and fatigue can be significantly reduced. At present, it is believed that human immune function is closely related to tumor prognosis and outcome. Clinical practice has shown ^[19] that acupuncture and moxibustion can stimulate part of immune active cells in the body, improve human immune function, and realize its inhibitory effect on tumor. Zhao Changlin et al. ^[20] selected 60 patients with CRC liver metastasis and treated them with acupuncture (Zusanli, Taichong, Taixi, etc.) and moxibustion (Guanyuan, Shenque, Qihai, etc.) respectively, and found that the number of CD3, CD8, CD4 and NK cells in both groups increased. The clinical application of acupuncture treatment is simple and convenient, the economic burden is small, the adverse reactions are rare and the curative effect is good, and it is worthy of targeted promotion and use.

3.3. TCM external treatment

At present, Chinese medicine external treatment has been widely used in the treatment of clinical CRC. Its operation is relatively easy, and it can quickly relieve symptoms and improve quality of life. Studies have proved that the application of traditional Chinese medicine paste to acupoints such as Shenque, combined with the use of remote acupoints, the drug will stimulate the acupoints to affect the gastrointestinal function, and can effectively help other therapies to treat tumors. Qu Yuanyuan ^[21] selected 30 patients with CRC complicated with intestinal obstruction and applied traditional Chinese medicine to Shenque, Zusanli and other points for treatment. A total of 18 patients were cured, 10 cases improved, although there were 2 cases with less obvious effect, but the total effective rate was as high as 93.3%. Therefore, traditional Chinese medicine external treatment of CRC is also a more efficient and convenient treatment in clinical practice.

3.4. Traditional Chinese Medicine Preparations

The treatment of traditional Chinese medicine preparations can effectively control the further development of CRC patients' disease, relieve their symptoms, and also be of great help in extending the survival period of patients. For example, Borning capsule is a traditional Chinese medicine preparation used for softening and dispersing, replenishing Qi and blood, and fuzhenggu, which is mainly developed by Astragalus, perillus seed, solanum and other drugs. Pei et al. ^[22] set (1) control group: CRC patients were treated with FOLFOX4 chemotherapy alone; (2) Observation group: Based on the control group, the combined use of Borning capsule in the treatment of CRC patients was studied, and it was found that the effective rate of the latter was significantly higher than that of the

former, and the patients in the observation group were better tolerated and had lower adverse reactions.

4. Integrated treatment of traditional Chinese and Western medicine

With its advantages of small toxic and side effects and mild effects, traditional Chinese medicine has been applied more and more widely in the treatment of cancer. In the treatment of CRC, integrated Chinese and western medicine can not only give full play to the advantages of chemotherapy drugs to kill cancer cells quickly, but also quickly treat local lesions, and pay attention to improving patients' quality of life, restoring healthy qi to improve patients' immune function and effectively prevent tumor recurrence and metastasis. Greatly prolong survival. In recent years, experts have conducted a large number of studies on various aspects of the treatment of CRC with integrated Chinese and western medicine. For example, Tan Guanggen et al. [23] found that Shenqi Fuzheng injection combined with chemotherapy can effectively improve the therapeutic effect of CRC by comparing the therapeutic effect of CRC patients treated with different methods, peripheral blood T cell subsets and NK cell levels, etc. And the patients' immune function and quality of life were greatly improved. Zhang Lina et al. [24] conducted comparative experiments between the control group (CRC patients were treated with chemotherapy alone) and the observation group (combined with compound matrine injection on the basis of the control group). It was found that the effective rate and quality of life improvement rate of the observation group were 83.3% and 75.0% ($P < 0.05$), respectively, which were improved compared with the control group and the adverse reactions were significantly improved. Yu Peng [25] studied Shenlingbaizhu Decoction plus minus chemotherapy in the postoperative treatment of CRC and found that its clinical efficacy was good and the effective rate increased significantly.

The above research results show that the treatment of CRC with integrated Chinese and western medicine has highlighted great advantages in improving the effect of simple chemotherapy, reducing the occurrence of adverse reactions, and improving the quality of life of patients. Not only that, it also has a good prospect in reducing the recurrence and metastasis of tumors, extending the survival period and other aspects.

5. Outlook

Although different Western medicine treatment methods are still preferred in the treatment of CRC according to different conditions, in recent years, it has been confirmed in a number of studies and clinical practice that integrated Chinese and western medicine has shown good therapeutic effects in preventing postoperative complications, reducing adverse reactions of radiotherapy and chemotherapy, improving quality of life, extending survival and other aspects. Chinese medicine has gradually achieved an irreplaceable position in the treatment of CRC. However, the future development of TCM treatment of CRC is also full of challenges and shortcomings, such as there is no unified standard in syndrome differentiation and treatment, and there are huge differences in prescription drugs, which is not conducive to large-scale promotion, evaluation of efficacy and academic exchanges. However, with more comprehensive research and grasp on the etiology, pathogenesis and treatment of CRC, and more learning and communication, we believe that in the future, the status of traditional Chinese medicine will be increasingly prominent in the comprehensive treatment of CRC, and the integration of traditional Chinese and Western medicine will also shine in the world.

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