ISSN 2618-1584 Vol. 6, Issue 9: 49-54, DOI: 10.25236/FMSR.2024.060908

Research Progress on Improving the Toxic Side Effects of Tumor Radiotherapy with Traditional Chinese Medicine

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Abstract: *With the increasing incidence rate and mortality of malignant tumors, the means of treatment for malignant tumors are also growing, but radiotherapy is still one of the important means of treatment for tumor patients. However, the toxic side effects of radiotherapy make it difficult for patients to tolerate the subsequent pain and psychological pressure, leading to the termination or interruption of treatment, thereby reducing the efficacy of radiotherapy and causing tumor progression. Modern research has shown that the combination of traditional Chinese medicine and radiotherapy can improve adverse reactions caused by radiotherapy, enhance the body's immunity and clinical efficacy, improve patients' quality of life, and prolong survival. This article reviews the research progress on the toxic side effects of traditional Chinese medicine on radiotherapy for malignant tumors in recent years, providing a basis and suggestions for subsequent clinical research.*

Keywords: *Traditional Chinese Medicine; Tumors; Radiotherapy; Toxic Side Effects*

1. Introduction

Tumors are new organisms formed by abnormal proliferation of local tissue cells due to changes in the genetic material of the body caused by long-term effects of various tumor treatment factors. Although cancer is one of the common and frequent diseases in China (Figure 1 and Figure 2), many cancer diseases lack typical prodromal manifestations in the early stages of onset and progression, making it difficult to diagnose in the early stages. Therefore, once diagnosed, the disease usually progresses to the terminal stage, resulting in poor prognosis [1,2]. Radiotherapy is one of the important methods for tumor treatment, but it is accompanied by adverse reactions such as bone marrow suppression, gastrointestinal reactions, and skin damage, which seriously affect the subsequent treatment of tumors.

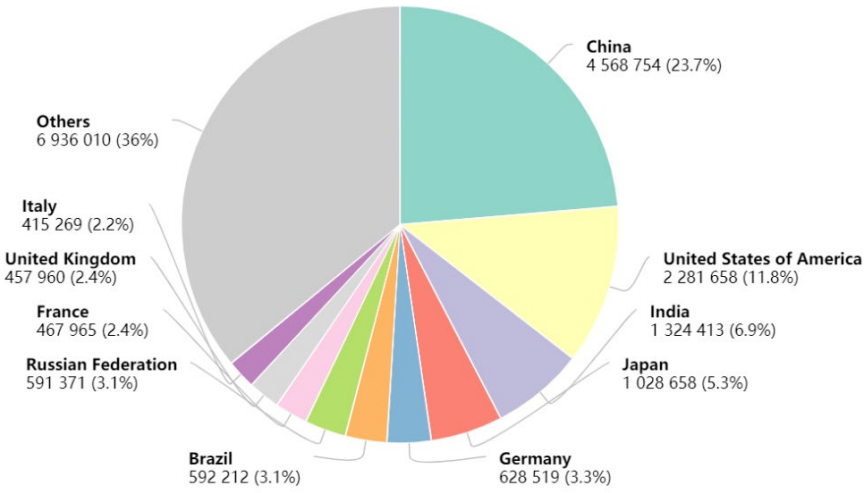

Figure 1: The Number of new cancer cases in various countries in 2020

ISSN 2618-1584 Vol. 6, Issue 9: 49-54, DOI: 10.25236/FMSR.2024.060908

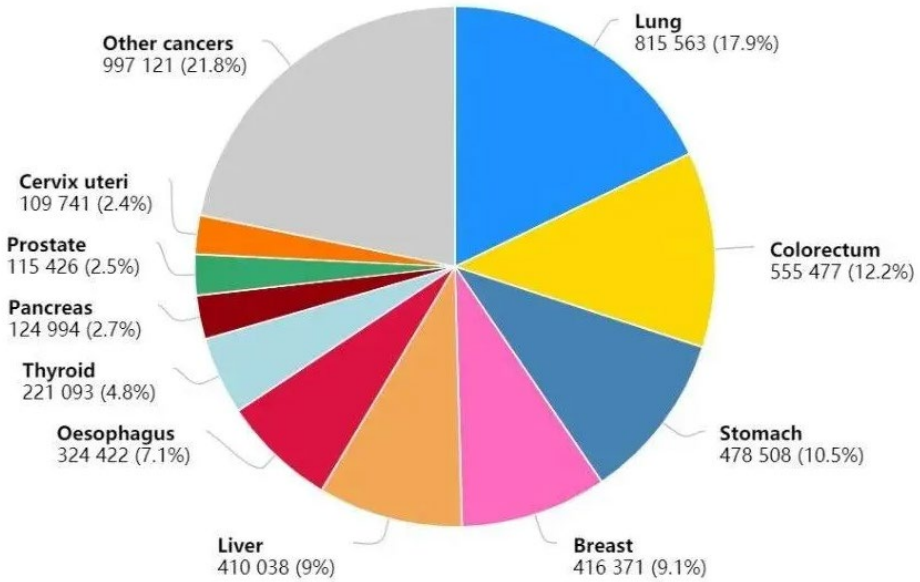

Figure 2: The top ten cancer types with the highest number of new cancer cases in China in 2020

Traditional Chinese medicine is a future exploration field for the prevention and treatment of malignant tumors, and it has its unique advantages and characteristics in preventing and treating tumors. Modern research has confirmed that radiation therapy combined with traditional Chinese medicine treatment, based on syndrome differentiation and treatment, can effectively alleviate radiation toxicity. This article provides a review of the research progress on the toxic side effects of traditional Chinese medicine on radiotherapy for malignant tumors in recent years, providing a basis and suggestions for subsequent clinical research.

2. Definition and toxic side effects of radiotherapy

Radiotherapy (Figure 3) is one of the main treatment methods for cancer patients. Tumor radiotherapy is a local treatment method that uses radiation to kill tumor cells or reduce their proliferation and growth activity. About 70% of cancer patients require radiation therapy during cancer treatment, and about 40% of cancer can be cured with radiation therapy. Radiotherapy is often used as a direct or adjuvant treatment for tumors. The high energy during radiotherapy can indirectly or directly kill tumor cells, while reducing their activity and controlling their growth rate. In addition, radiotherapy also has a good analgesic effect, which can effectively alleviate the pain of patients. However, radiotherapy lacks obvious specificity. While killing tumor cells, it inevitably leads to damage to normal cells and tissues. Different organs and tissue sites may also experience corresponding radiation reactions when irradiated. Subsequently, a series of chemotherapy toxic side effects are manifested, such as bone marrow suppression, gastrointestinal reactions, fever, skin damage, etc. The occurrence of these adverse reactions can cause radiotherapy patients to be unable to tolerate their pain and systemic reactions, and abandon or interrupt treatment, reducing the efficacy of radiotherapy and leading to tumor progression.

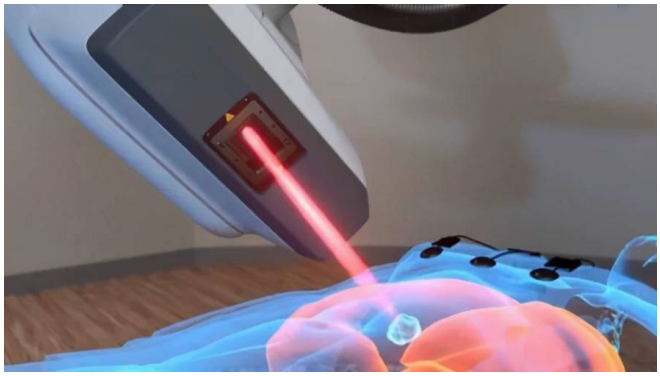

Figure 3: Radiotherapy

ISSN 2618-1584 Vol. 6, Issue 9: 49-54, DOI: 10.25236/FMSR.2024.060908

3. Progress of Traditional Chinese Medicine in Improving the Toxic and Side Effects of Radiotherapy

3.1. Bone marrow suppression

During tumor radiotherapy, due to the lack of specificity of radiation, while killing tumor cells, it can also cause serious damage to bone marrow hematopoietic cells, leading to bone marrow suppression. Bone marrow suppression refers to a decrease in the activity of blood cell precursors in the bone marrow, resulting in a reduction in the number of blood cells, particularly white blood cells. In severe cases, complications such as infection, bleeding, fatigue, and fever may even occur, forcing the interruption of radiotherapy [3].

Western medicine mainly uses symptomatic treatments such as blood transfusion, hematopoietic stem cell transplantation, white blood boosting drugs, and colony-stimulating factors to treat bone marrow suppression caused by radiotherapy drugs, thereby stimulating the generation of bone marrow cells, increasing the total number of peripheral blood cells, and helping to restore blood count. Although patients' conditions are comprehensively evaluated in clinical practice to adjust medication plans or take measures to reverse adverse drug reactions, the high cost and serious side effects such as fever, nausea, vomiting, and capillary leakage syndrome make the treatment ineffective.

The basic pathogenesis of tumors is an imbalance of yin and yang, with excess of positive and negative factors. From the perspective of traditional Chinese medicine, radiation belongs to the category of "external toxicity". External toxicity invades and contains blood, leading to unfavorable qi and blood in the three burners, ultimately affecting the transformation of qi, blood, and body fluids in the body, resulting in qi and blood deficiency. Modern traditional Chinese medicine theory holds that bone marrow suppression belongs to the category of "deficiency and fatigue" in traditional Chinese medicine. The main pathogenesis is "deficiency", which is closely related to the five organs, mainly spleen and kidney deficiency [4,5]. The kidney is the foundation of innate nature, the spleen is the foundation of acquired nature, and the source of qi and blood biochemistry. If the spleen and kidney are deficient, the source of qi and blood biochemistry is lacking, and the deficiency of both qi and blood is insufficient to nourish the organs. The deficiency of righteous qi leads to the deficiency of pathogenic qi in the body. Therefore, the basic treatment principle of traditional Chinese medicine in reducing bone marrow suppression caused by radiotherapy is to nourish qi and blood, and warm and nourish the spleen and kidneys [6,7]. In the prevention and treatment of bone marrow suppression caused by radiotherapy, drugs such as ginseng, astragalus, Codonopsis pilosula, Astragalus membranaceus, Cinnamomum cassia, deer antler, etc., which have the effects of nourishing qi and spleen, warming yang and tonifying kidney, are commonly used in clinical practice. Through research, it has been confirmed that the various active ingredients in these drugs play an extremely important role in anti-tumor, anti radiation, enhancing the body's immunity, and promoting the proliferation of hematopoietic stem cells. For example, Astragalus polysaccharides can promote the proliferation of bone marrow hematopoietic stem cells, inhibit bone marrow cell apoptosis, and enhance the body's immunity [8]. Ginsenosides can protect hematopoietic stem cells by promoting the expression of transcription factor NF-E2-related factor 2 (Nrf2) [9]. Qi Lin et al. [10] found that flavonoids from Astragalus membranaceus can increase the activity of superoxide dismutase and glutathione peroxidase, thereby reducing the damage of radiation to hematopoietic cells. In addition, when preventing and treating bone marrow suppression caused by radiotherapy, traditional Chinese medicine formulas are more effective than single herbs in treating radiotherapy side effects. Shi Yaping et al. [11] found that the formula granules of Shi-Quan-Da-Bu-Tang can promote the expression of EPO mRNA in kidney and bone marrow nucleated cells at the transcriptional level, and promote the recovery of damaged bone marrow erythroid hematopoietic function in bone marrow suppressed mice. Jiang Tao et al. [12] applied Left and Right Return Pills to treat bone marrow suppression mouse models after radiotherapy, which effectively improved their hematopoietic function. Chen Jiaojiao et al. [13] found in clinical studies that the application of modified Sijunzi Tang in the treatment of bone marrow suppression resulted in a significant increase in neutrophils, platelets, and white blood cells in the observation group.

3.2. Gastrointestinal reactions

Gastrointestinal reactions are the most common toxic side effects caused by radiotherapy. The gastrointestinal adverse reactions caused by radiotherapy include nausea and vomiting, loss of appetite and appetite, changes in bowel habits, etc. These gastrointestinal reactions can cause serious consequences such as water and electrolyte imbalance, arrhythmia, etc., which affect the continuation of chemotherapy.

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Western medicine treatment for gastrointestinal reactions caused by radiotherapy usually uses drugs such as serotonin (5-HT) receptor antagonists, antihistamines, NK1 receptor antagonists, dopamine receptor blockers, and dietary adjustments to alleviate symptoms. For example, for nausea and vomiting, serotonin (5-HT) receptor antagonists such as ondansetron are often used to alleviate symptoms. For diarrhea, symptomatic supportive treatment measures such as loperamide and other antidiarrheal drugs, as well as hydration and electrolyte supplementation, are commonly used. Although these measures can alleviate gastrointestinal reactions to a certain extent, they may cause adverse reactions such as headaches, constipation, elevated transaminase levels, and cardiac toxicity.

Traditional Chinese medicine believes that the gastrointestinal response to radiotherapy is the invasion of "external toxins" into the body, leading to the accumulation of "deficiency", "toxicity", and "stasis", resulting in dysfunction of the spleen and stomach, abnormal rise and fall of qi, weak qi and blood circulation, and unfavorable secretion of clear and turbid intestines, resulting in symptoms such as decreased appetite, nausea and vomiting, diarrhea, and abdominal pain. The gastrointestinal reactions caused by radiation therapy belong to the categories of "abdominal pain", "diarrhea", "constipation" and other traditional Chinese medicine. Therefore, the treatment of gastrointestinal adverse reactions caused by radiation therapy can be based on the "spleen and stomach" theory, combined with emotional regulation, adjusting yin and yang, and balancing the duration. The spleen is the source of qi and blood biochemistry, nourishing the qi of the spleen and stomach, regulating the rise and fall of qi, transforming the body's qi, blood, and body fluids, harmonizing yin, yang, qi, and blood, and allowing the vitality to be filled. When the righteous qi is sufficient, evil cannot be dried up. Traditional Chinese medicine often uses single herb treatments such as ginseng, Atractylodes macrocephala, Medicated Leaven Massa, and licorice, which have the functions of strengthening the spleen, nourishing qi, and protecting the spleen and stomach. Medicated Leaven Massa is the most commonly used type of traditional Chinese medicine, and its digestive and gastric effects are often applied to symptoms such as spleen and stomach accumulation and decreased appetite. Studies have found that Medicated Leaven Massa has good antibacterial effects on many common intestinal pathogenic bacteria [14]. Clinical observations by Song Yuanyuan and others [15] have found that the treatment method of strengthening the spleen and qi, nourishing yin and reducing reflux can effectively improve gastrointestinal adverse reactions caused by tumor treatment. The application of Banxia Xiexin Tang and Sijunzi Tang, with modifications, can restore the function of regulating the spleen and stomach qi, increasing clarity and reducing turbidity, thereby improving symptoms such as diarrhea and abdominal pain. Scutellaria baicalensis, ginseng, and licorice have the effect of nourishing qi and strengthening the spleen, which can enhance the body's immunity and promote the recovery of patients. Zong Xiaoming et al.'s [16] application of Yinxuan Xiexin Tang can significantly alleviate the diarrhea symptoms caused by the treatment of tumors. Lu Xiyan and Zhao Ningxia [17] found that the combination of Wumei Wan and Sijunzi Tang in the treatment of radiation enteritis had a significantly higher effective rate in the experimental group than in the control group treated with mesalazine enteric coated tablets. Hou Guilan and others [18] applied the concept of "treating diseases before they occur" in traditional Chinese medicine, preventing diseases before they occur. Before radiotherapy, they used traditional Chinese medicine to regulate the spleen and stomach, improve the body's immunity, and effectively reduce adverse digestive reactions such as nausea and vomiting during radiotherapy, thereby improving patients' tolerance to radiation and the efficacy of radiotherapy. In addition, traditional Chinese medicine external treatment methods have significant therapeutic effects on gastrointestinal reactions caused by radiotherapy. Jiang Lin et al. [19] found that the use of Qingre Liangxue Jiedu Decoction enema can alleviate radiation-induced enteritis caused by cervical cancer radiotherapy.

3.3. Skin Damage

Skin damage is caused by radiation therapy, which damages skin cells. The skin is most sensitive to radiation damage, and 95% of cancer patients will experience severe radiation-induced skin damage after receiving radiation therapy. Skin damage is related to the formation of cytokines and chemokines, as well as an imbalance of pro-inflammatory and fibrotic cytokines. It usually appears in the areas irradiated by radiotherapy, such as the head and neck, chest and back, abdomen, and pelvic cavity. The symptoms of skin injury include itching, redness, peeling, erosion, ulcers, etc. In severe cases, it can cause a series of effects, leading to complications such as lymphedema, skin shrinkage, persistent pigmentation, and joint atrophy, which seriously affect the patient's quality of life and treatment progress.

Western medicine mainly uses corticosteroid cream, ketoconazole, statins, nerve growth factors, hyperbaric oxygen and other symptomatic treatments in treatment. These drugs have antioxidant, anti-inflammatory, and reparative effects, which can promote wound healing of radiation-induced skin lesions,

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reduce inflammatory exudation, prevent atrophy and fibrosis of the skin lesion site, but they are also accompanied by compliance and rebound phenomena, making them difficult to widely use.

From the perspective of traditional Chinese medicine theory, radiation belongs to the category of "heat toxicity". Heat toxicity invades, dampness and heat accumulate, and damages the skin. The basic pathogenesis of skin damage is the accumulation of fire toxins on the skin, stagnation of meridians and qi, resulting in local redness, swelling, burning sensation, and pain in the skin. In treatment, it is recommended to use drugs that clear heat and cool blood, promote blood circulation and eliminate stasis. Treatment should be based on the stage of disease occurrence. In the early stage, when evil qi is abundant, clearing heat and detoxifying should be the main approach. In the middle stage, when evil and positive qi are in conflict, cooling blood and eliminating stasis should be the main approach. In the later stage, when positive qi is deficient, it should be supplemented with nourishing qi and yin. According to the theory and treatment principles of traditional Chinese medicine on skin damage, when preventing and treating skin damage caused by radiotherapy, single herbs such as honeysuckle, forsythia suspensa, and purple grass are often used for treatment, which have the functions of clearing heat, detoxifying, cooling blood, and promoting blood circulation. Traditional Chinese medicine ointment also has a good effect on treating skin damage caused by radiotherapy. Traditional Chinese medicine ointment is often made from herbs that have the functions of clearing heat and detoxifying, promoting blood circulation and removing blood stasis, and removing dampness and pus, which helps to restore skin damage. Tian Shiyu et al. [20] found that lithospermum erythrorhizon ointment can significantly shorten the healing time of skin lesions caused by radiotherapy and reduce patients' pain. The homemade Yuchuang Zicao oil from Anhui University of Traditional Chinese Medicine Affiliated Hospital [21] can inhibit serum inflammatory factors, thereby improving radiation-induced skin damage caused by radiotherapy. The combination of Liu Shen Wan and radiotherapy for esophageal cancer can reduce the expression of TNF - α, IL-6, and NF - κ B, thereby reducing radiation damage to normal skin cells [22]. Qi Runzhi's [23] research found that the addition of compound ginseng and bellflower decoction can not only reduce its side effects compared to the use of antibiotics alone in the treatment of radiation-induced skin lesions, but also effectively improve endothelial cell damage, reduce exudation and inflammatory cell infiltration.

4. Discussion and outlook

Radiotherapy is an important means to treat tumor patients. However, the adverse reactions of radiotherapy increase the pain or interruption of treatment for patients, and even cause serious complications, making it difficult to continue treatment and affecting the efficacy. The combination of traditional Chinese medicine and radiotherapy takes a holistic approach, incorporating the concept of "preventing disease before it occurs" throughout the treatment process. Through syndrome differentiation and treatment, it has a significant effect on enhancing the efficacy and reducing toxicity of radiotherapy. However, due to the complex composition of traditional Chinese medicine decoctions, different radiation doses for radiotherapy, lack of large samples and representative research data, a clear treatment system for the prevention and treatment of toxic side effects of radiotherapy in traditional Chinese medicine has not yet been formed. Therefore, it is necessary to strengthen the continuous exploration of traditional Chinese medicine, attach importance to and enhance the research on effective ingredients of traditional Chinese medicine, in order to fully play its important role and superiority.

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