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Research Progress on Multifactor Therapy for Lung Metastasis of Colorectal Cancer

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Abstract: *In recent years, the number of incidence and deaths of digestive tract tumors in the world has been increasing year by year, and colorectal cancer accounts for the largest proportion of digestive tract tumors, and its important cause of death is metastasis and recurrence after surgery. According to statistics, 20% of colorectal cancer patients have already developed distant metastasis at the time of first diagnosis. 50%-60% of colorectal cancer patients develop metastasis during the whole course of the disease, of which 10%-20% show lung metastasis. At present, the medical profession has proposed various treatment modes, such as drugs, surgery and intervention, for lung metastasis of different stages and degrees of colorectal cancer, which have effectively improved the prognosis of patients with lung metastasis of colorectal cancer. Therefore, this paper reviews the progress of colorectal cancer lung metastasis treatment.*

Keywords: *Colorectal cancer; lung metastasis; surgical treatment; research progress*

1. Introduction

Colorectal cancer is the third most common malignant tumor and the second leading factor in cancer deaths worldwide [1], and in China, deaths due to colorectal cancer rank fifth among malignant tumors [2]. In addition, 30% to 40% According to statistics, 20% of colorectal cancer patients have already developed distant metastasis at the time of first diagnosis [3]. And 50% to 60% of colorectal cancer patients develop distant metastasis throughout the course of the disease. Liver and lung are the common metastatic sites for distant metastasis of colorectal cancer, and the data of foreign studies show [4] that the second most common site of distant metastasis is lung, second only to liver, and its metastasis rate is 10% to 20% [5]. The median survival time of patients with colorectal cancer combined with lung metastasis was reported to be 17.7 months, which is shorter than the median survival time of patients with colorectal cancer only [6]. Data from Peking University Cancer Hospital in China showed that lung metastases accounted for 32.9% of all colorectal cancer patients, of which the proportion of patients with primary lung metastases could reach 24.5% [7]. The Expert Consensus on Multidisciplinary Treatment of Colorectal Cancer Combined with Lung Metastases (2019 Edition) [8] states that colorectal cancer lung metastases are classified into simultaneous and heterochronous metastases according to the interval between the primary tumor and lung metastases, initial and non-initial metastases according to the sequence of lung metastases and other distant metastases, and isolated and non-isolated lung metastases according to whether or not they are accompanied by extrapulmonary metastases. Only 21.1% ~ 32.5% of patients with isolated lung metastases are reported to receive radical surgical treatment, and the rest of patients with isolated lung metastases have no chance to receive radical treatment [9]. For non-isolated lung metastases, there is still a great deal of uncertainty about the treatment and management options [10]. Therefore, the 2019 colorectal cancer treatment guidelines of the Japanese Society for Colorectal Cancer (JSCCR) state that patients with colorectal cancer combined with lung metastases should undergo multidisciplinary discussions for individualized treatment plans, regardless of the availability of radical resection [11]. In this article, we review the literature on colorectal cancer lung metastases in conjunction.

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2. Anatomical basis and pathologic staging of colorectal cancer

2.1. Fundamentals of Anatomy

Since most of the mesenteric venous blood flow returns to the portal vein system, the preferred site of distant metastasis of colorectal cancer is firstly the liver, followed by lungs, bones and so on. The rectal venous plexus consists of superior rectal vein and inferior rectal vein, and the superior rectal vein flows back to portal vein through inferior mesenteric vein. The inferior rectal vein flows back to the inferior vena cava through the internal iliac vein. Therefore, distal rectal tumors can initially metastasize to the lungs, and the incidence of lung metastasis of middle and lower rectal cancer is significantly higher than that of upper rectal cancer.

2.2. Mechanism of occurrence

Tumor metastasis is not only dependent on the cancer cells themselves, but the tumor microenvironment also plays an important role in it, and tumors will constantly interact with the tumor microenvironment stroma in the process of development. Tumor-associated fibroblasts, as the main cells in the stroma, interact with tumor cells through multiple pathways to promote or inhibit the proliferation and invasion of tumor cells. It is currently believed that tumor-associated fibroblasts are mainly derived from tissue-resident fibroblasts, which are transformed into tumor-associated fibroblasts under constant stimulation of tumor cells, while other sources include transformation of bone marrow-derived mesenchymal stromal cells, and transformation of adipocytes. Tumor-associated fibroblasts are classified into various subtypes through different classification methods, but in colorectal cancer, tumor-associated fibroblasts are mainly classified into tumor-associated fibroblasts-A and tumor-associated fibroblasts-B, which are subtypes with different gene expression. Tumor-associated fibroblasts are a major component of the extracellular matrix and a major player in the remodeling of the extracellular matrix to maintain matrix stability. Tumor-associated fibroblasts promote immune escape, and in colorectal cancer are able to recruit monocytes and promote their adhesion to tumor cells, thereby inhibiting natural killer cells and creating an immunosuppressive environment. In addition, tumour-associated fibroblasts promote macrophage polarisation into immunosuppressive and tumour-promoting phenotypes. Colorectal cancer tumor cells and tumor microenvironment together promote liver metastasis and lung metastasis of colorectal cancer.

2.3. Staging of lung metastases

High resolution chest CT has been proved to be able to detect small lung metastases, and as it becomes one of the important examinations for preoperative evaluation and postoperative follow-up, more and more patients with colorectal cancer lung metastases have been detected, and now the lung has become the first largest metastatic organ besides the liver. Colorectal cancer lung metastasis can be divided into "simultaneous lung metastasis" and "heterochronous lung metastasis" according to the order of appearance of colorectal primary foci and lung metastasis, and "simultaneous lung metastasis" and "heterochronous lung metastasis" according to the order of appearance of lung metastasis and metastases from other parts of the body. According to the order of the appearance of lung metastases and metastases from other parts of the body, lung metastases can be classified into "primary lung metastases" and "non-primary lung metastases"; according to whether they are accompanied by extrapulmonary metastases or not, lung metastases can be classified into "simple lung metastases" and "non-simultaneous lung metastases". According to whether it is accompanied by extrapulmonary metastases, lung metastases can be categorized into "simple lung metastases" and "non-simple lung metastases".

3. Methods of treatment

Over the past two decades, as new chemotherapeutic agents have been developed, such as irinotecan, oxaliplatin, and monoclonal antibodies against epidermal growth factor receptor and vascular endothelial growth factor, these new agents have prolonged progression-free survival and overall survival in mCRC. In addition, advances in surgery and anesthesia have made surgery an aggressive treatment for patients with colorectal cancer, with 5-year survival rates as high as 50%. However, the clinical efficacy of surgery in the treatment of lung metastases is still controversial. Meanwhile, with the emergence of emerging treatment modalities for metastases such as radiotherapy

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and interventional therapy, it have a 3-year local control rate of about 60%-80%. It achieves similar results to surgery, has less damage, faster postoperative recovery and higher patient acceptance rate. It can provide multi-mode minimally invasive and convenient treatment for postoperative colorectal cancer metastasis patients. However, the overall efficacy of these options is not supported by a large amount of effective evidence-based medicine, which are only the best treatment modes based on multidisciplinary discussions in various centres in most cases.

3.1. Chemotherapy

Early clinical manifestations of colorectal cancer patients are not specific, so when patients are diagnosed, they are already in middle or late stage, and some of them have metastasis and local treatment cannot achieve the expected effect, so chemotherapy has been taken as the standard treatment means for colorectal cancer patients. However, the limitations of chemotherapy are inevitable, such as systemic toxicity, because chemotherapy is to kill cancer cells through chemotherapeutic drugs, but chemotherapeutic drugs are unable to recognize the difference between cancer cells and human body's normal, and damage the human body at the same time of killing cancer cells, which results in the chance of producing adverse reactions compared with other treatments, and the emergence of serious adverse reactions is also the reason that some patients are unable to receive regular treatment.

3.1.1. Chemotherapy for resectable lung metastases

Current chemotherapy for resectable colorectal cancer lung metastases includes preoperative chemotherapy and postoperative adjuvant chemotherapy. The research group from Milan Lorenzo Spaggiari and Giulia Veronesi et al [12] reported that 65 out of 199 patients with colorectal cancer lung metastases were resected with chemotherapy, and the 5-year survival rate in the group receiving adjuvant chemotherapy after metastasectomy was 45%, compared with 25% in the neoadjuvant group, and the 5-year survival rate for both received was 29%.NCCN guidelines state that adjuvant chemotherapy may be considered for patients after resection of lung metastases from colorectal cancer. In a study by Park et al [13], 176 patients received adjuvant chemotherapy after resection of lung metastases, the adjuvant chemotherapy group showed a trend towards longer disease-free survival than the surgery alone group, and both had similar results in terms of overall survival, with no significant benefit in the adjuvant chemotherapy group.

3.1.2. Chemotherapy for unresectable lung metastases

For the treatment of unresectable colorectal cancer lung metastases, transformation therapy can be applied to make unresectable lung metastases transformed into resectable. However, the success rate of conversion therapy is low, and if there is no chance of conversion therapy, it is usually handled in accordance with advanced colorectal cancer, and fluorouracil drugs, oxaliplatin, irinotecan, bevacizumab, cetuximab, ramorubicin, regorafenib and other molecularly-targeted drugs and immunotherapeutic drugs are usually used to formulate the treatment plan.

3.2. Targeted therapy

Targeted therapy is to kill specific cancer cells through targeted drugs, which will not damage normal cells of human body, so as to achieve the purpose of treatment. Targeted therapy not only regulates and controls tumor growth and reduces its drug resistance, but also reduces metastatic spread as well as neovascularization. Targeted drugs are more widely used in the clinic and have improved the median overall survival of patients with colorectal cancer lung metastasis by more than 30 months.Shen et al [14] found that Erbin-positive B-cell isoforms play a key role in colorectal cancer lung metastasis through single-cell RNA sequencing and functional studies, confirming that Erbin is a potential therapeutic target for colorectal cancer lung metastasis.Wang et al [15] study found that serum exosomes miR-146a-5p and miR-155-5p could be used as potential biomarkers and therapeutic targets for inhibiting colorectal cancer metastasis. And immunotherapy for tumor kills tumor tissues by activating the human immune system and relying on autoimmune function.Lin et al [16] found that targeting CD73 increased the therapeutic response to chemotherapy and inhibited lung metastasis, affirming the therapeutic targeting potential of tumor CD73 immunotherapy, which can benefit colorectal cancer patients.

3.3. Immunotherapy

Immunotherapy of tumor is to activate the body's immune system and kill cancer cells through

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autoimmune function. Unlike other treatments, immunotherapy targets not cancer cells but the body's own immune system. Cancer cell variants become resistant to immune effector cells by decreasing their immunogenicity and/or secreting and recruiting immunosuppressive factors in the tumor microenvironment. If the autoimmune system is unable to eliminate its clonal variants, the tumor will evolve mechanisms to evade immune attack, leading to tumor progression, whereas immunotherapy is designed to enhance the natural immunity and anti-tumor function of T cells, as well as targeting the immunosuppressed tumor-associated macrophages to enhance the patient's immune response. of tumor-associated macrophages, enhancing the anti-tumor effect of the patient's own immune system and curbing tumor progression. When immunotherapy is combined with other therapies to address low mutational load by increasing tumor immunogenicity, thereby overcoming the immunosuppressive microenvironment. It is proven to be both correct and effective.

4. Local treatment of colorectal cancer lung metastasis

4.1. Surgery

According to the NCCN guidelines, the criteria for resectability of colorectal cancer lung metastases are: (1) Complete resection must take into account the extent of the tumor and anatomical site, and adequate lung function must be maintained after lung resection. (2) The primary focus must be amenable to radical resection. (3) The presence of an extrapulmonary resectable lesion does not preclude resection of pulmonary metastases. (4) Multiple resections may be considered in certain patients as tolerated and residual lung function allows [17]. Statistically, 9.4%-12.2% of patients with colorectal cancer lung metastases are suitable for local radical treatments, and these local radical treatments include R0 surgery, stereotactic radiotherapy and radiofrequency ablation therapy [18]. Studies have shown that patients with colorectal cancer lung metastases treated with radical surgery have a 5-year survival rate of 35%-70% [19]. In general, sublobar resection, such as wedge resection of the lung or segmental resection, is preferred to lobectomy for resectable colorectal cancer lung metastases, and lobectomy is not recommended.A study by Vogelsang et al [20] noted that the risk of death in patients with colorectal cancer lung metastases who underwent sublobar resection was 40% of that in patients who underwent lobectomy. Another study showed that the presence of multiple lung metastases, the presence of pulmonary lymph node metastases, preoperative CEA >5 ng/mL, large tumor diameter, disease-free survival <24 months, age >70 years, late stage of primary colorectal cancer, primary tumor located in the rectum, and undergoing R1 or R2 resection all lead to poor postoperative prognosis in patients with colorectal cancer lung metastases [20]. It has been reported that patients with colorectal cancer lung metastases have a recurrence rate of up to 68% after undergoing a first pneumonectomy, and approximately 50% of patients exhibit secondary lung metastases from the tumor, and only a small percentage of these patients are able to undergo a repeat pneumonectomy [20]. A study by Menna et al [21] noted that for colorectal cancer patients who developed multiple lung metastases from their tumors and underwent either a second or a third pneumonectomy, their overall survival was not significantly different from that of patients who underwent only a single pneumonectomy. Patients with metastatic colorectal cancer should be offered adjuvant chemotherapy. In contrast, a study by Younes et al [22] stated that in patients with recurrence after resection of initial colorectal cancer lung metastases, a second performance of pulmonary metastasectomy should be considered as the optimal therapeutic strategy for the second recurrence, but it should be carefully considered before performing a third metastasectomy, as their findings showed that the rate of tumor recurrence after the third resection was significantly higher compared to the previous one.

4.2. SBRT treatment

SBRT is a high-precision, high-dose, less frequent non-invasive and non-invasive radiation therapy, the principle of which is to apply stereotactic technology and special ray devices to focus multiple beams of high-energy rays on a target area in the body, so as to achieve the purpose of directional killing of tumor cells in the target area [23]. With the development of radiotherapy and imaging technology, the application of SBRT in the treatment of colorectal cancer lung metastases has become more and more widespread [24]. A review of the literature revealed that in the past 10 years, some researchers included patients with colorectal cancer lung metastases who underwent SBRT and calculated the local control rate and overall survival rate, which showed that their 3-year local control rate was 65%-70.6% and their 3-year survival rate was 56%-64% [25]. However, lung metastases of colorectal origin have poorer local control rates after SBRT compared to lung metastases of other

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origins. In addition, how to select appropriate patients with colorectal cancer lung metastases for SBRT is also worthy of clinicians' focused consideration, because SBRT may also cause damage to the surrounding normal tissues when ablating the tumor, but the fact that SBRT on lung tissues usually causes less damage to lung function is also an advantage of SBRT compared with other localized radical therapies [26]. The Expert Consensus on Multidisciplinary Treatment of Colorectal Cancer Combined with Lung Metastases (2019 Edition) [8] states that for solitary lung metastases, if located in the peripheral lung bands, RFA treatment is considered first. If located in the middle band, both SBRT and RFA can be considered. If it is located in the medial band or close to blood vessels or bronchi, SBRT is considered first.In addition, not being limited by age is one of the advantages of SBRT, and several studies have been conducted to confirm the efficacy and safety of SBRT in patients aged ≥75 years [27]. It has been shown that for patients with metastatic colorectal cancer who had previously undergone SBRT with recurrence of tumor lung metastasis, the incidence of grade 3-5 adverse events was significantly higher in patients who underwent SBRT again.

4.3. RFA therapy

RFA therapy refers to a therapeutic means in which the radiofrequency current generated by the radiofrequency therapeutic instrument flows through the human tissues and kills the tumor cells and tissues by generating a local thermal effect in the body due to the rapid change of the electromagnetic field.The study of Ahmed et al [20] found that the tissue environment around the target foci significantly affects the results of RFA therapy, and that there exists an organ-specificity of the lungs that facilitates the RFA therapy as compared to the other organs, because the the same intensity of energy produces a larger ablation volume in lung tissue. For patients with colorectal cancer lung metastases, RFA therapy is indicated for a number of unilateral lung metastatic lesions ≤3 or bilateral lung metastatic lesions ≤5. Other studies have shown that patients with colorectal cancer lung metastases have a greater hope of improving their short- to intermediate-term survival after RFA treatment [20]. In a retrospective study by Zhong et al [28], the 1-year, 3-year, and 5-year overall survival and progression-free survival of patients with colorectal cancer lung metastases treated with RFA were evaluated, and the results showed that 1-year, 3-year, and 5-year overall survival and progression-free survival. The results showed that the 1-year, 3-year and 5-year overall survival rates of patients with colorectal cancer lung metastases treated with RFA were 96.7%, 74.7% and 44.1%, respectively, and the 1-year, 3-year and 5-year progression-free survival rates were 66.7%, 31.2% and 25.9%, respectively. RFA treatment appears to be more traumatic to the patient's lungs compared to SBRT, which leads to a higher complication rate after RFA. Its most common postoperative complication is pneumothorax, the incidence of which usually ranges from 20% to 50%, and other complications include pleural effusion, bleeding, and hemoptysis [29].

4.4. Radiotherapy

Intensity-modulated conformal radiotherapy (IMR) is scanned and localized by a CT simulator, transmitted to a specific treatment planning system, and individualized design of treatment plan through three-dimensional GPS planning software, which ultimately achieves to effectively increase the optimal dose of tumor treatment, and to minimize the damage to the normal tissues around the tumor, and to adequately and effectively protect the surrounding normal tissues, so as to minimize the damage to the human body.Stage II-IV Colorectal Cancer One of the main local treatments for stage II-IV colorectal cancer includes radiation therapy [30], in which IMR can increase the most effective radiation dose to the lesion tissue and reduce the radiation dose to the surrounding normal tissues, so as to reduce the incidence of adverse reactions after radiotherapy [31]. Ying Qiaoling et al. [32] showed that in the aspect of adverse effects of conformal intensity-modulated radiation therapy for oligometastatic colorectal cancer, acute hematologic toxicity accounted for the majority of cases, and most of them were grade 1-2, and there was only one case of grade 3 adverse effect, which was a low neutrophil in the course of radiotherapy, and grade 4 or more severe hematologic toxicity did not occur, and there was no occurrence of chronic toxicity. Therefore, three-dimensional conformal intensity-modulated radiotherapy for oligometastatic colorectal cancer is recognized as one of the local therapeutic modalities with high safety and efficacy. In order to avoid the occurrence of adverse reactions to treatment, measures such as early intervention are usually used to reduce the incidence of adverse reactions and maximize the benefits to patients.IMRT can cause adverse reactions such as peripheral neurotoxicity, hematotoxicity, liver and kidney function damage, etc. In addition to psychoeducation and emotional comfort, Aidi injection can be used as an adjuvant treatment to control the occurrence of adverse reactions, thus increasing immune function and improving patients' life quality [33].

ISSN 2618-1584 Vol. 5, Issue 11: 63-70, DOI: 10.25236/FMSR.2023.051110

4.5. Detection of lung metastasis molecular typing

Detection of molecular typing of colorectal cancer lung metastasis is helpful for the development of individualized treatment plan and prognosis, Kim et al [2] showed that among colorectal cancer patients, those with high expression of KRAS gene mutation were prone to lung metastasis, and El-Deiry et al [34] showed that compared with the primary foci, the expression of Her2 protein was higher in lung metastases. Therefore, clinicians need to fully consider and carefully select drugs when treating patients with lung metastases with targeted drugs.

4.6. Relative prognostic influences in patients with colorectal cancer lung metastases

One study analyzed the results suggesting that the number of pulmonary metastases is an independent risk factor affecting postoperative survival, and the prognosis of single pulmonary metastases is significantly better than that of multiple pulmonary metastases [35]. Surgical treatment of pulmonary metastasis in colorectal cancer patients:Current practiceand results The study was analyzed based on a series of 25 studies of colorectal cancer lung metastases from 2000 to 2018, which included a total of 2925 patients, and proposed that a total of four risk factors were associated with poor survival (1) Short disease-free interval between primary tumor resection and development of lung metastases. (2) Multiple lung metastases. (3) Positive hilar and/or mediastinal lymph nodes. (4) Elevated carcinoembryonic antigen prior to lung surgery. Meanwhile, Salah et al. published a pooled analysis of individual patient data from 8 previously published studies in 2013, in which 927 patients had a 5-year overall survival rate of 54%. A multifactorial analysis identified 3 poor prognostic factors CEA levels persistently elevated for more than 5 months, 2 or more lung metastases, and DFS for more than 36 months. They proposed a simple clinical model and stratified the risk of 5-year survival based on the number of risk factors to derive the adverse influences affecting 5-year survival in patients with colorectal cancer lung metastases [36].

5. Summary

The variability of tumor extent and the heterogeneity of tumors in patients with colorectal cancer lung metastases make the treatment of these patients quite challenging. With the progress of comprehensive treatment, it is becoming more and more common that patients with limited lung metastases from colorectal cancer can be treated with the aim of cure. Adequate surgical treatment at the appropriate time can improve survival and prevent tumor-related complications. For patients who are unable or unwilling to undergo surgical resection, localized treatments, such as SBRT and RFA treatments, which have the advantages of low trauma, low operating difficulty, high reproducibility, etc. It is favorable for wide clinical application. In addition, the direction of future exploration should also cover individualized intervention, including how to screen patients who are more likely to develop lung metastasis through genetic testing, as well as the optimization of individualized treatment for patients with colorectal cancer lung metastasis.

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