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Research progress on the establishment of brain metastasis risk models for non-small cell lung cancer

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Abstract: *Non-small cell lung cancer brain metastases are one of its most serious complications, with patients suffering severe irreversible neurological damage due to its low rate of early diagnosis. Numerous risk factors are the main cause of brain metastases in non-small cell lung cancer. The establishment of multiple risk models is an important method for the prediction and prevention of NSCLC brain metastasis. This paper intends to discuss the research progress of NSCLC brain metastasis risk model, and provide ideas for the prevention and treatment of NSCLC brain metastasis in clinical practice.*

Keywords: *NSCLC brain metastasis; risk factors; model establishment; research progress*

1. Introduction

Lung cancer is one of the malignant tumors with the highest incidence and mortality in China, due to its low early diagnosis rate, the 5-year survival rate is less than 10%. Non-small cell lung cancer (NSCLC) accounts for about 80% of lung cancers [1], and the incidence of NSCLC brain metastases is generally greater in men than in women, and in men, especially smokers and drinkers, is significantly higher than that in women. Symptoms are mainly dizziness, headache, nausea, and limb disorders. Men without extracranial metastases are more likely to develop brain metastases [2]. The risk of early NSCLC brain metastasis is not high, but the risk of locally advanced NSCLC brain metastasis is 30%~50% [3]. After the occurrence of locally advanced NSCLC brain metastases, if not treated, the average survival of patients is only 1 month, the use of whole-brain radiotherapy can extend the median survival to 4 months [4-5], and the use of immunotherapy can increase the cure rate of advanced lung cancer from 3% to about 30% [6]. Xia Jing et al. [7] retrospectively analyzed the clinical data of 40 patients with T790M-positive non-small cell lung cancer brain metastasis, of which 24 received osimertinib targeted therapy and 16 did not receive osimertinib targeted therapy. The results showed that the progression-free survival of 24 patients with T790M-positive non-small cell lung cancer who received osimertinib targeted therapy was 9~11 months, the median progression-free survival was 10 months, and the progression-free survival of 16 patients who did not receive osimertinib targeted therapy was 2~5 months, and the median progression-free survival was 4 months.

Therefore, it is of great significance to screen for risk factors for brain metastasis and carry out reasonable interventions, such as prophylactic whole brain irradiation [8-9], which can reduce the incidence of brain metastasis and play a significant role in improving the prognosis of patients with locally advanced NSCLC. The study of the related high-risk factors of NSCLC brain metastasis, and the mathematical model of high-risk factors of brain metastasis were established through multiple regression analysis, which gradually became a research hotspot for the prevention and treatment of NSCLC brain metastasis. Through the comprehensive analysis of multiple high-risk factors of brain metastasis, the quantitative processing of data can more comprehensively and accurately predict high-risk patients with brain metastasis, so as to provide a basis for preventive treatment and provide clues for further treatment options.

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2. Physiopathology of brain metastases

2.1. Physiopathology of brain metastases

Metastatic tumors of the brain account for about 20% of all clinical brain tumors, and the most likely malignant tumor to develop brain metastases is lung cancer. The forms of metastasis include (1) metastatic nodules, which are more common at the junction of cortex and white matter and deep in the brain; (2) Leptomeningeal carcinomata: tumor cells along the subarachnoid space diffuse infiltration, local nodules or plaques of different sizes, due to cerebrospinal fluid circulation obstruction, can produce intracranial hypertension and hydrocephalus; (3) Encephalitic metastasis: diffuse periangioma cell infiltration can form localized tumor nodules or extensive invasion, and accompanied by leptomeningeal carcinoma. The tissue morphology of metastases is similar to that of primary tumors, often accompanied by bleeding, necrosis, cystic degeneration, and liquefaction. If necrosis is present, foam cells may be seen. Most of the metastasis routes of intracranial metastases are primary tumors in distant sites metastasizing to intracranial tumors through bloodstream, and the other route is direct invasion of tumors in adjacent sites, such as nasopharyngeal carcinoma and intraorbital tumors.

2.2. Blood-brain barrier (BBB)

The blood-brain barrier (BBB) is located in the central nervous system microvessels and consists of a single layer of continuous, non-porous endothelial cells that separate the brain from the circulating blood. The functional BBB is composed of central nervous system endothelial cells, pericytes, astrocytes, microglia and neurons, etc., which protect the brain from bloodborne toxins, supply brain material metabolism and regulate central nervous system homeostasis. Endothelial cells are tightly linked by continuous tight junction proteins and express efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) to limit drug infiltration.

2.3. Blood-tumor barrier (BTB)

Cancer cells metastasize to the cerebral vasculature of the brain to colonize, induce angiogenesis and reshape the microenvironment, promote tumor metastasis and growth, produce vascular abnormalities, there is a heterogeneous and partially intact blood-brain barrier, and the newly formed neurovascular tumor unit is called the blood-tumor barrier (BTB). Although BTB has a higher permeability than BBB, increased efflux transporters such as P-gp and BCRP still limit effective drug absorption. With the exception of surgery and radiation therapy, very limited systemic treatment options are one of the main contributors to poor prognosis for patients with brain tumors. Brain tumors can only be cured if the tumor cells hidden behind the blood-brain barrier are adequately treated. At present, the research on BBB and BTB is mainly in rodent models, due to the blood-brain barrier (BBB) and blood-tumor barrier (BTB), brain tumor patients can rarely benefit from drug treatment, special structure makes it difficult for drugs to penetrate into the brain, can not achieve effective therapeutic concentrations, but also brings great obstacles to preclinical research. Clinically, the BBB/BTB structure is destroyed by transcranial focused ultrasound, radiotherapy, etc., or the effective osmotic absorption rate of drugs is improved by hyperosmotic agents and special drug carriers, but the efficacy needs to be further improved.

2.4. Role of nano-delivery systems in brain therapy

Nanodelivery systems are increasingly being developed, using strategies of nanodelivery systems to enhance the penetration and accumulation of the blood-brain barrier in the brain parenchyma. Transport of nanomaterials on the blood-brain barrier has been successfully improved through receptor-mediated endocytosis and shutter peptide-mediated blood-brain barrier crossing. In addition, changing the characteristic properties such as particle size, composition, hydrophobicity, charge and dissociation of nanomaterials provides a broad space for researchers to modify the system, thereby developing a more promising BBB crossover strategy based on nanomaterials. The application of existing non-permeable phytochemicals to nanodelivery systems in the central nervous system will promote new applications of nanodelivery in brain diseases.

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3. Diagnosis of NSCLC brain metastases

3.1. Tumor markers and NSCLC brain metastases

NSCLC brain metastases often present dizziness, headache, nausea, limb movement disorders and other symptoms, which may or may not be accompanied by neurological symptoms. Although there are several new molecular markers for diagnosing NSCLC brain metastases, the true specificity and sensitivity markers are not clear. CEA is a structurally complex soluble serum glycoprotein and was one of the earliest tumor markers used in the diagnosis of NSCLC. CA19-9 is a glycolipid expressed on the cell membrane, belongs to oligosaccharide mucin, which is mainly distributed in serum in the form of salivary mucin, and is expressed in the normal fetal intestine, liver, gallbladder and pancreas and adult pancreas and bile duct epithelium, is a tumor marker for clinical diagnosis of pancreatic cancer and rectal cancer, recent studies have shown that CA19-9 has broad-spectrum antigen characteristics, and is also elevated in lung cancer, ovarian cancer and other malignant tumors. CA125 as tumor carbohydrate antigen in normal human serum content is low, serum CA125 half-life is short, the appearance of tumors will be released into the blood to cause its content to continue to rise, serum CA125 is the first molecular marker found in ovarian tumors, and then it was found that it was expressed in a variety of tumor cells, data show that ≥50% of lung cancer patients have elevated serum CA125 levels. CYFRA21-1 belongs to the cytokeratin family, mainly present in a variety of multilayer tumor epithelial cells, usually in the form of an oligomer in the malignant tumor epithelial cell protein intermediate filament, only after the cell cancer, apoptosis and lysis of the abnormal expression and release into the blood, serum CYFRA21-1 is the cytokeratin 19 fragment released when normal cells become cancerous, adenocarcinoma and squamous cell carcinoma have the expression of CYFRA21-1, especially in patients with squamous cell carcinoma serum increase is the most obvious, With a positive rate of 60% ~ 74%, CYFRA21-1 levels often rise earlier than clinical symptoms and imaging, making CYFRA21-1 one of the most diagnostic serum markers for NSCLC. SCC-Ag is a cancer-related antigen released during the abnormal division of cancer cells, its essence is a glycoprotein, can increase the DNA replication rate of cancer cells, isolated from cervical squamous cells, one of the components of the antigen TA4, widely expressed in malignant epithelial cells, related studies have shown that it is related to the invasion, metastasis and prognosis of squamous cell carcinoma, can be used as a molecular marker of squamous cell carcinoma, has high specificity for the diagnosis of lung squamous cell carcinoma, but the sensitivity is not high. NSE is a key enzyme in the glycolysis process, catalyzing the cleavage of 2-phosphoglycerate to produce aqueous and enol phosphopyruvate, which synthesizes and releases more NSE, consisting of 3 different subunits A, B and R, which are widely present in nerve cells, neuroendocrine cells, and tumor cells caused by these cells. NSE is one of the common lung cancer markers and can be the tumor marker of choice for SCLC.CEA, CA19-9, CA125, CYFRA21-1, SCC-Ag, and NSE have advantages in the diagnosis of NSCLC brain metastasis, but there are still shortcomings in sensitivity and specificity, and a single tumor marker has certain limitations in diagnosis, which needs to be combined with a variety of molecular markers [10-15].

3.2. Imaging with NSCLC brain metastases

Magnetic resonance imaging (MRI) is used as the gold standard for the presence of intracranial metastases [16], and is important for early diagnosis of NSCLC brain metastases, which can often detect metastases larger than 5 mm. Minor lesions smaller than 5 mm are difficult to detect, so evaluation of history and neurologic examination are important in intracranial metastases in patients with NSCLC. Clinically, it is found that NSCLC brain metastasis is usually the patient's obvious neurological symptoms, at this time, the patient's condition has progressed, although in most cases radiotherapy can be effectively controlled, but irreversible damage to the nervous system is often a fatal blow to break the patient's psychological defense. Therefore, the principles of early detection, early diagnosis and early treatment seem to have become an unattainable means. The early detection of NSCLC brain metastases has become a top problem to be solved.

3.3. Single brain metastases

3.3.1. Features of single brain metastases

Single brain metastases have hidden onset, easy to misdiagnose and miss diagnosis, single brain metastases are more likely to occur in middle-aged and elderly patients, with 50~70 years old as the

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peak of incidence, lung cancer is the most common in the primary tumor, and the metastasis site is more common in the supratentorial area, most of the single brain metastases occur in the gray-white matter junction area of the cerebral hemisphere, on the one hand, this distribution feature is more likely to enter the terminal branches of the middle cerebral artery because of hematogenous metastases; Anatomically, the blood supply of the cerebral cortex is 3~4 times that of the subcortical white matter, and its blood supply artery suddenly thins at the gray-white matter interface, making the metastatic tumor thrombus easy to obstruct here. The clinical manifestations are non-specific, which is related to tumor mass effect, dizziness, headache, nausea, vomiting and other intracranial hypertension symptoms and slurred speech, ataxia, papilledema, etc., and even hemiplegia.

3.3.2. Features of single brain metastases CT

Single brain metastases occur in the cerebral hemisphere cortex and subcortical area, most of which are low or equal density on plain scanning, and a few are high-density, and their CT value depends on the composition of the tumor, the degree of necrosis, cystic change, and the presence or absence of bleeding, calcification, and blood supply. The enhanced scan lesions were enhanced to varying degrees, mostly irregular ring strengthening, nodular strengthening, and cystic strengthening. Parenchymal tumors showed uniform and obvious strengthening, and ring strengthening was seen in cystic and necrotic metastases; Peritumor edema is more obvious and disproportionate to the size of the tumor, and the so-called "small tumor, large edema" is an important feature of single metastasis. Typical single-point brain metastases can be diagnosed on imaging CT and history, but some patients with atypical CT findings are prone to misdiagnosis, especially those without a clear history of primary tumor.

4. Numerous risk factors are the main cause of NSCLC brain metastasis

4.1. Risk factors and NSCLC brain metastases

People gradually realized that a variety of risk factors are the main causes of NSCLC brain metastasis, and have fallen into the exploration of NSCLC brain metastasis risk factors in an attempt to escape the predetermined trajectory of NSCLC brain metastasis. Risk factors mainly include: (1) General condition of the patient: including gender, age, ethnicity, occupation, smoking (index greater than 400); (2) Clinicopathological status: tumor site, tumor size, pathological classification, TNM stage, treatment methods (radiotherapy, chemotherapy, gene targeted therapy, cell immunotherapy, traditional Chinese medicine differentiation therapy). (3) Laboratory tests: blood routine, urine routine, coagulation six, liver and kidney function, blood sugar, blood lipids, electrolytes, cellular immunity, tumor markers. (4) Radiomics status; (5) Genomics type, etc. Studies [17] have concluded through multivariate logistic regression analysis that race, medical security status and uninsured status, relatively high T stage, N stage, low differentiation grade, and bone metastasis, liver metastasis and lung metastasis are positively correlated with the occurrence of brain metastases, while high age and non-adenocarcinoma histology are negatively correlated with the incidence of brain metastases.

4.2. Molecular biology and NSCLC brain metastasis

A review of the available literature showed that EGFR mutations [18], non-squamous cell carcinoma type, elevated serum CEA levels, and lymph node metastases (especially mediastinal lymph node metastases) were independent risk factors for brain metastases. <60 years of age) and elevated serum NSE levels should also be considered, and several literature [19-21] support that patients with EGFR mutations are more likely to develop brain metastases on initial diagnosis or progression. Liu Yang et al. [22] reported that hypoxia can promote the production of hsp70 in A549 cells, and then upregulate miR-155 expression, miR-155 can inhibit the expression of occludin in brain endothelial cell tight-junction protein, resulting in increased blood-brain barrier (BBB) permeability and promoting brain metastasis. Wei et al. [23] showed that miR-550a-3-5p inhibits the growth and migration of HBMEC by directly targeting YAP1, thereby controlling brain metastasis in lung cancer. In addition, miR-330-3p [24] has been reported to promote the process of epithelial-mesenchymal transition (EMT) in NSCLC through the miR-330-3pGRIA3-TGF-β1 pathway, and miR-217 has been reported to inhibit the occurrence of NSCLC brain metastasis through the miR-217-SIRT1-P53-KAI1 pathway [25]. Dai et al. [26] retrospectively analyzed 139 patients with NSCLC with brain transfer, and also reported that the upregulation of CADM2 expression in cancer tissues was closely related to disease progression and poor prognosis in patients with brain metastases.

Integrin can promote the adhesion of tumor cells, which affects the angiogenesis of tumor cells, leading to the invasion and migration of tumor cells. Endothelial cells typically express a variety of

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adhesion molecules, including intercellular adhesion molecules, vascular cell adhesion molecules, and platelet-endothelial adhesion molecules, which play important roles in immune and inflammatory responses. Upregulation of the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 can increase the adhesion of tumor cells to the brain capillary endothelium, resulting in brain metastasis. The expression of leukocyte adhesion molecules in NSCLC brain metastasis was significantly upregulated, and the incidence of cell adhesion capacity and brain metastasis was significantly reduced after gene knockout of leukocyte adhesion molecules. Secondly, calcin is also involved in tumor progression and metastasis, and the loss of calcin expression can induce epithelial-mesenchymal transformation of cancer cells, thereby increasing cell motility and metastasis.

Angiogenesis is an important factor influencing tumor metastasis, and vascular endothelial growth factor can affect both angiogenesis and vascular permeability. The proliferation rate and vascular maturity of vascular endothelial growth factor in NSCLC brain metastases were significantly higher than those in patients without brain metastases, indicating that vascular endothelial growth factor may be related to the occurrence of brain metastases. Chemokines play important roles in cell migration, invasion, and tumor angiogenesis, and the CXCR4/CXCL12 signaling axis (a member of the chemokine CXC subfamily) may be involved in the development of NSCLC brain metastases. In addition, proteolytic enzymes are involved in processes such as blood-brain barrier penetration, endothelial cell formation, and migration of tumor cells. Matrix metalloproteinases play an important role in the process of tumor cells crossing the blood-brain barrier.

5. The establishment of a brain metastasis risk model for non-small cell lung cancer is an important prevention and treatment method

Research progress on cancer risk prediction models The International Union for Cancer Control pointed out that one-third of cancers are generally preventable, one-third of cancers can be cured if diagnosed early, and one-third of cancers can greatly reduce pain and prolong life. However, 90% of early-stage cancer patients have no obvious symptoms, and 80% of cancer patients have advanced when they are diagnosed, and the best treatment time has long been missed. In recent years, the continuous development of surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy technology has made it possible for NSCLC patients to receive more treatment options. Surgical treatment can improve the prognosis of patients with NSCLC brain metastasis, when the number of tumors is small (1~3), tTumors are larger than 3 cm in diameter, the tumor location is in the superficial non-functional area, and the patient is in good condition, surgical treatment can be performed. However, surgery may not be the best option for patients with oligometastases in the lungs. Whole-brain radiotherapy is the standard treatment for patients with NSCLC, which is suitable for patients with multiple intracranial metastases and small metastases (≥ 3 metastases, tumor diameter <3 cm), and good physical status, and can also be used as adjuvant therapy after stereotactic radiosurgery or surgery for brain metastases. Whole-brain radiotherapy can improve the median survival of patients for about 4~6 months. Stereotactic radiosurgery is to achieve better local tumor control through high-dose irradiation, and the damage to normal tissues is relatively small, and has gradually become one of the main treatment methods for NSCLC brain metastasis. Stereotactic radiosurgery is mainly suitable for intracranial single disease, tumor diameter of 4 ~ 5cm, ≤ 4metastases, rescue therapy after whole brain radiotherapy and adjuvant treatment after single brain metastasis. Early identification of high-risk patients with NSCLC who may have brain metastases, and prophylactic brain irradiation can reduce the risks associated with surgical treatment. Therefore, the prevention and control and monitoring of risk factors for brain metastasis are of great significance to the prognosis of patients.

In recent years, models that can predict the occurrence of cancer have gradually entered people's field of vision, and there is great room for the implementation of the treatment principles of early detection, early diagnosis and early treatment. The prediction model of cancer risk is to evaluate the risk of specific diseases by selecting relevant risk predictors and further combining them into a multivariate model, traditionally often used Logistic regression analysis, Cox regression analysis and Joint model three multivariate statistical modeling methods, these three methods are more used in the exploration of common disease risk factors; By comparing the area size under the ROC curve, the prediction accuracy and efficiency of the model were evaluated and analyzed [27-29]. Logistic regression is commonly used clinically for short-term prediction of a disease, while Cox regression is most commonly used for long-term prediction of disease [30-31].

The rise of a variety of predictive models is undoubtedly a great tool for predicting early onset, and provides excellent conditions for solving the problem of early diagnosis of brain metastasis of non-small cell lung cancer. Sun Yiyuan et al. [32], using Cox regression model analysis to study the risk factors for brain metastasis in patients, and established a Nomo model of the probability of intracranial

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metastasis 3 years and 5 years after the diagnosis of non-small cell lung cancer, which was used to predict the probability of brain metastasis in NSCLC. With the rapid development of proteomics and related technologies, especially SELDI-TOF-MS technology has brought vitality to the detection of tumor markers, and decision tree software for protein data analysis has become an important technology for the establishment of predictive models. The decision tree establishes a stable decision tree through continuous dichotomous load-ratio peaks. This technology provides great convenience for the establishment of protein profiling diagnostic models for brain metastases of non-small cell lung cancer [33]. Genome wide association studies (GWAS) are an important strategy for molecular epidemiological research, and a large number of susceptibility genes and genetic loci associated with tumor risk have been discovered so far. Tongguo incorporates genetic information on the basis of traditional tumor risk prediction models, and uses a combination of stepwise weighted GRS (sGRS) and linear mixed models (LMMs) to build models, which can improve the accuracy of lung cancer risk prediction models to a certain extent [34]. This provides a new idea for the construction of a clinical model of brain metastasis of non-small cell lung cancer, which is worthy of further research and exploration.

6. Discussion

Non-small cell lung cancer brain metastasis is one of its most serious complications, because of its low early diagnosis rate so that patients suffer from severe irreversible neurological symptoms, often leading to loss of confidence in life, the study of NSCLC brain metastasis risk factors makes people gradually see the main causes of disease from the fog, so as to effectively avoid the probability of disease, and the establishment of risk model further makes non-small cell lung cancer brain metastasis can be more accurate prediction and prevention, which can slow down the course of non-small cell lung cancer patients, So as to prolong the survival of patients and improve the quality of life of patients.

This article summarizes the research progress of the establishment of non-small cell lung cancer brain metastasis model, through the screening of multiple influencing factors, the correlation analysis of influencing factors, and finally the establishment of nomograms, quantified the calculation of risk factors, which can effectively slow down and avoid the probability of non-small cell lung cancer brain metastasis, slow down the course of the disease can improve the survival and quality of life of patients. Non-small cell lung cancer brain metastasis is related to a variety of factors, and the mechanism of non-small cell lung cancer brain metastasis has not been elucidated, most studies only find risk factors for lung cancer brain metastasis, from risk factors combined with biological characteristics to study the mechanism of lung cancer brain metastasis is a research blind spot, therefore, further analysis should be used to explore the mechanism of lung cancer brain metastasis risk factors combined with biological characteristics.

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