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ADVANCES IN THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare primary tumor originating from pleural mesothelial cells with insidious onset, high invasiveness and malignancy. Early symptoms are not obvious, lack of specific symptoms, and the diagnosis is difficult, and it depends on the pathological tissue for immunohistochemistry to confirm the diagnosis. Only a small number of patients can receive radical surgery, and the current treatment method is chemotherapy. This article reviews the diagnosis, treatment and progress of MPM diagnosis and treatment status.

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Introduction.

Mesothelioma is an occult tumor that develops on the mesothelial surface of the pleural cavity, peritoneal cavity, testicular sheath, or pericardium. 80% of cases originate from the pleura. The main cause of malignant mesothelioma is inhaled asbestos exposure, with approximately 70% of pleural mesothelioma cases having proven asbestos exposure. In 1767, Lieutaud J. first described primary tumors of the pleura. Then, back in the 20th century, in 1937, Klemperer D. and Rabin C. first described pleural mesothelioma in detail. In 1942, experiments by Stout A. and Murray M. led to the elucidation of mesothelioma. However, for a long time, isolated cases of mesothelioma have been described in the literature. In 1960 alone, Wagner J. described 33 cases of pleural mesothelioma in asbestos miners. In 1965, Selikoff I. showed that exposure to a representative material with asbestos is a major risk factor for the development of pleural mesothelioma. In the 1972 literature, only 175 cases of pleural mesothelioma were described. In the ensuing years, key researchers gained access to multiple avenues for the treatment of pleural mesothelioma, due to the small number of patients, biological tumors, and lack of randomized trial diagnosis.

In the United States, the annual incidence of mesothelioma is estimated to be approximately 3300 cases per year [1]. The incidence of mesothelioma in the United States peaked around 2000 and is currently declining, thanks to the control of asbestos exposure [2].

Clinical manifestations.

The onset of MPM is insidious, and the most common first symptoms are chest pain, cough, and shortness of breath. There are also those who complain of fever, sweating or joint pain. About half of the patients had massive pleural effusion with severe shortness of breath. People without a large amount of pleural effusion often have severe chest pain and weight loss is common. Systemic symptoms, such as weight loss and fatigue (cancer), often indicate a poor prognosis.

Imaging diagnosis.

Most patients with MPM lack specific imaging features. Ordinary X-ray chest X-ray found pleural effusion, while the lungs were wrapped by tumor tissue, etc. In advanced cases, cardiac shadow enlargement, soft tissue shadow and rib destruction caused by pericardial effusion may occur. For patients suspected of malignant pleural mesothelioma, CT examination is most useful. Cytological examination of pleural fluid is also helpful in diagnosis. In routine laboratory tests, some patients may have thrombocytosis and elevated serum carcinoembryonic antigen (CEA). For those who cannot be diagnosed clearly by routine examination, thoracoscopy can be used for pleural biopsy. Generally, most patients can be diagnosed as a result. PET-CT has great advantages in the identification of benign and malignant pleural tumors and the detection of intrathoracic and extra-thoracic lymph nodes and distant metastases, and has a more accurate judgment on tumor staging and post-treatment review. Magnetic resonance imaging (MRI) has high value in identifying local infiltrates of the intrathoracic fascia and diaphragm, and evaluating the invasion to surrounding tissues and organs.

Others.

At present, there are no specific serum markers for early screening and diagnosis of MPM, efficacy and prognosis evaluation. Commonly used tumor markers such as carcinoembryonic antigen (CEA), NSE, CYFRA21-1, CA153, etc. have low specificity and sensitivity. Soluble mesothelin-related peptide (SMRP) has been studied more at present. SMRP has low specificity and high false positive rate. It has certain value in detecting the recurrence of epithelial MPM after surgery. Fibrin 3 has high sensitivity and specificity and deserves further clinical research. Pleural effusion cytology can be performed in patients with symptoms of pleural effusion, but its sensitivity is poor. The diagnosis of MPM depends on histopathological examination, and the acquisition methods include B-mode ultrasonography or CT-guided percutaneous biopsy, thoracoscopy and thoracotomy. The diagnostic yield of needle biopsy is low, and tumor cells are easy to spread and metastasize through the needle tract. The trauma of thoracotomy is large, and many patients cannot tolerate it. Thoracoscopy can comprehensively examine the pleura, obtain sufficient tissue, have a high detection rate, and be less traumatic than thoracotomy. At the same time, pleural effusion and diseased pleura can be further treated, and tumor resection or pleurodesis can be performed. The diagnosis of MPM requires immunohistochemical examination, and no single antibody has high specificity and sensitivity for the diagnosis of MPM. According to the positive expression rate, specificity and sensitivity of each antibody, the following antibody combination packages can be used as the first choice for the diagnosis of MPM: cytokeratin 5/6 (CK5/6), mesothelial cell (MC) antibody, calretinin (CR), epidermal growth factor receptor (EGFR), vimentin. Thyroid transcription factor 1 (TTF-1) and CEA are hardly expressed in MPM and can be used as the first-choice antibodies for negative control in the diagnosis of MPM. The deletion of p16 gene is a recent research hotspot, which has high specificity and sensitivity. Studies have shown that the homozygous deletion of the p16/CDKN2A gene located at 9p21 is as high as 80% in MPM, which can be used to diagnose MPM and indicates a poor prognosis [3].

Therapeutic technology development for MPM.

The average life expectancy of untreated MPM patients is 6-8 months. To date, almost all antitumor treatments have been used to treat mesothelioma, including traditional surgery, chemotherapy, and radiation therapy, as well as less common approaches: immunotherapy, gene therapy, photodynamic therapy. However, despite the existence of this Despite the diversity, even compared with other malignancies, the treatment effect of patients with MPM remains low. Not coincidentally, in the treatment of MPM patients, the traditional 5-year survival rate is not used, but a "median survival" parameter of an average of 13-15 months. Surgical treatments are palliative (pleurodesis, shunts), cytoreductive (pleurectomy/cortical removal PLE), and relatively radical (extrapleural pneumonectomy (EP)) approaches. Talc pleurodesis is the main type of palliative surgery for MPM. The most appropriate pleurodesis is achieved by spraying talc during diagnostic thoracoscopy [4]. At the same time, the effectiveness of this treatment (without recurrence of pleural effusion and corresponding symptoms) is 80–100% [5]. However, with complete damage to the visceral pleura and formation of a fixed lung collapse, talc pleurodesis effectiveness has dropped sharply. In this case, the patient is given a thoracoabdominal shunt (method effectiveness is 95%), and a "palliative care pleurectomy" can also be performed. Pleurectomy/Decortex (PLE) is an induction and relatively low-invasive intervention. The purpose of PLE is to remove the maximum amount of

tumor tissue, which allows for further effective use of adjuvant therapy, as well as reduction of major pain symptoms. The scope of standard PLE includes resection of all parietal pleura and partial/complete resection of visible central pleura. Some authors also recommend resection of a single subpleural tumor foci of the lung, resection of the pericardium and septum. The effect of thoracoscopic pleurectomy (VTS) was discussed in a study by Halstead J. et al. Demonstrated that in advanced disease VTS-PLE not only Symptoms of the disease were reduced, and median survival (14 months) was significantly increased.

Extrapleural pneumonectomy (EPP) is one of the most radical surgical treatments for PMP. Including resection of the entire parietal pleura, resection of the pulmonary pleura, resection of half of the diaphragm, and pericardectomy (viscous pulmonary vessels in the pericardium). The high morbidity of surgery requires careful patient selection. Criteria for operability were functional status (PS 0–1), assumed p/o FEV1 > 1, PaO2 > 65 mm Hg, PCO2 < 45 mm Hg, ejection fraction > 40%, mean pulmonary pressure arterial < 30 mmHg. However, even with careful selection of operable resectable patients, according to Sugarba-ker D. et al., 328 EPPs were analyzed with a mortality rate of 4% (reaching 9-11% in some centers) and a complication rate of 60%. % . Meanwhile, most of the time atrial fibrillation (44.2%), vocal cord paresis (6.7%), deep vein thrombosis (6.4%), technical complications (6.1%). Effectiveness of EPP and PLE, based on various prospective and retrospective studies, when evaluating the data presented, it should be noted that comparing the effectiveness of EPP and PLE is not entirely correct for the following reasons:

None of the studies listed were randomized, controlled, disease stage, histological type, adjunctive treatment - identified as dominant predictors in parametric multivariate analysis, which have been studied by Rusch V. et al. The diversity of adjuvants and different combination treatments also make comparing data difficult. We agree with the majority of researchers who believe EPP as an early "resectable" stage of the disease that should be intervened in patients. However, some authors (Rusch V., Pass N.) argue that EPP is slightly higher than PLE, implying that PLE is a rather aggressive intervention in the initial stages of the disease, with EPP full of ubiquitous "marginal" resectable tumors.

The algorithm for selecting surgical treatment was compiled according to Swift S. et al. In our opinion, this is the most logical [6]. This work also provides the following content recommendations:

- Talc pleurodesis and bypass surgery are available for most patients undergoing radical surgery. Patients with cytoreductive interventions can improve quality of life.
- Treatment of correctly staged patients. Hopefully - but in combination with other types of treatments using surgical approaches, the most favored proposes a three-component treatment (surgery + chemotherapy + radiation).

Radiation therapy (RT) is an independent treatment for MPM, the following options are currently in use:

1. Adjuvant radiotherapy after the surgical phase. EPP lung failure allows the use of high doses, which in turn leads to a significant reduction in local recurrence after EPP. Intensity-modulated radiation therapy (IMRT), providing more reliable local CON-control: According to Ahmad A. et al., who studied IMRT, none of 28 patients experienced local recurrence after EPP [7].

2. Intraoperative high-dose radiotherapy, brachytherapy. These methods are not well understood, but the first results indicate frequent complications.

3. Symptomatic radiotherapy (average dose of about 30g)

IMRT has good local control and can protect normal tissues such as liver and heart, but IMRT has also been reported to be complicated by severe pneumonia. Intensity-modulated proton therapy (IMPT) has been shown to be a method to achieve higher therapeutic doses while limiting exposure to organs at risk (OAR).

Immunity therapy.

Immunotherapy has become a research hotspot in tumor treatment in recent years, among which significant progress has been made in immune checkpoint therapy. T cells are the core executors of anti-tumor immunity, and their activation requires not only the stimulation of the first signal provided by antigen-presenting cells (APC), but also the stimulation of the second signal provided by costimulatory molecules, which can provide inhibitory immunity. These immunosuppressive signals are immune checkpoints. Tumor cells often exploit the properties of

immune checkpoints to evade attack by immune cells. The well-studied immune checkpoints are cytotoxic T lymphocyte-associated antigen (CTLA-4), programmed death receptor 1 (PD-1) and programmed death receptor ligand 1 (PD-L1). Immune checkpoint inhibitors are a new class of anti-tumor agents, which can improve the anti-tumor effect by blocking the interaction of inhibitory receptors expressed on T cells and related ligands, and regulating the body's normal immune cell activity. Currently, several drugs have been approved by the FDA for the treatment of advanced non-small cell lung cancer, melanoma and other malignant tumors [3].

Targeted therapy.

The development of molecular targeted therapy has provided a new direction for the individualized treatment of MPM. The VEGF inhibitor bevacizumab has been used in the chemotherapy regimens of cisplatin and pemetrexed with good results [3].

Prognostic analysis of MPM.

MPM is highly aggressive, with a high degree of malignancy and a very poor prognosis. The median survival time with supportive care alone is 4 to 12 months, and the median survival time after comprehensive treatment can reach 20 to 29 months. Age, performance status score, stage, histological subtype, high platelet count, low hemoglobin level, and chemotherapy were considered independent prognostic factors. New serum markers associated with poor prognosis, such as median estrone and osteopontin, are currently under investigation. High levels of soluble mesothelin-related peptide suggest poor prognosis, homozygous deletion of p16/CDKN2A gene indicates poor prognosis, and positive PD-L1 expression indicates poor prognosis [3].

Conclusions.

The diagnosis of MPM relies on histopathological examination, combined with immunohistochemistry. The main treatment methods include surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy are also current research hotspots, and some progress has been made. At present, there are few studies on MPM, and this hospital (Hanyang Hospital Affiliated to Wuhan University of Science and Technology) has encountered very few cases. Therefore, the progress of the treatment of malignant pleural mesothelioma is reviewed, in order to have more treatment methods to relieve such patients.

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