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Review Article

Ependymoma diagnosis and treatment progress

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Abstract: Ependymoma originated from the ventricular surface of ependymal epithelium cells are neuroepithelial tumors, 90% in the brain, and most of them are located in the posterior fossa, especially in the bottom wall of the fourth ventricle, 10% in spinal cord. Slightly more men than women, the annual incidence rate of about 2/100 million. Because the disease is relatively rare, almost no randomized controlled clinical study, coupled with lesions involving intracranial and spinal cord, and general guidance and principle of treatment often fails to distinguish between, just general statements, failed to form a diagnosis and treatment principles of a system. This paper summarized the clinical features, diagnosis, classification, treatment methods are reviewed, a guide to clinical.

Keywords: Ependymoma, chemotherapy, radiotherapy

Introduction

Ependymoma originates in ependymal epithelium cells on the surface of ventricle, which belongs to neuroepithelial tumors. With an annual incidence of about 2/1 millionth [1], men are slightly more prone to this disease than women. Ependymoma accounts for 4% adult central nervous system tumors, and 10% central nervous system tumors in children [2]. The occurrence of ependymoma in adults usually peaks between the ages of 35 to 45, with one-third occurring in the cranium and two-thirds in spinal cord [3], while in pediatric cases, ependymoma occurs usually under the age of 10, and more often in children younger than 3 years old [4], with 90% occurrence in the cranium, mostly located in the posterior fossa, especially in the floor of the fourth ventricle, and 10% occurrence in spinal cord [5, 6]. According to foreign statistics, more than 70% intracranial ependymoma is located in the subtentorium, with about half of supratentorial ependymoma situated in the lateral ventricle, and the rest usually arising from brain parenchyma. Eependymoma in the third ventricle is very rare [7].

Classification and characteristics

According to WHO histological classification in 2007, ependymoma can be divided into four types: (1) subependymal (WHO I grade); (2) myxopapillary ependymoma (WHO I grade); (3) ependymoma (WHO II grade), including cellular leiomyoma, clear cell type, papilla cell type and tanycyte; (4) anaplastic ependymoma (WHO III grade), belonging to a malignant tumor [8].

Pathology shows that ependymoma mostly occurs in a ventricle or a place surrounding a ventricle. The tumor tissue mostly demonstrates expansive growth within clear boundaries, while a few demonstrate infiltrating growth, invading the surrounding brain tissue [7, 9].

Based on biology genetics research, ependymoma can be classified into three types: firstly, posterior fossa ependymoma group A, a disease which often occurs in young patients, and men tend to be more susceptible to this disease than women. Its prognosis is poor, usually being classified into WHO III grade, with a chromosome aberration that often manifests CpG island methylation. Secondly, posterior fossa ependymoma group B, which shows extensive genomic instability, with a chromosome aberration developing through the entire chromosome or chromosome arm. Genetic manifestation of the spinal cord ependymoma is similar to posterior fossa group B. Thirdly, supratentorial ependymoma [10], which mostly exists as C11orf95 - RELA fusion gene, which arises from "chromosome fragmentation" [11].

Clinical manifestation

Clinical manifestations of ependymoma vary widely according to the location. Supratentorial ependymoma has a slow growth, featuring relatively late intracranial pressure elevation, and course of the disease can last several years. Subtentorial ependymoma originates in the fourth ventricle, which leads to the obstruction of cerebrospinal fluid flow, causing an early occurrence of elevated intracranial pressure with initial symptoms including a headache, accompanied by dizziness, nausea and vomiting, diplopia and epilepsy, etc. When the tumor grows and oppresses cerebellar vermis and hemisphere, the symptoms can become as severe as unstable walking, balance disorder and ataxia [12]. When the tumor oppresses the brain stem or cranial nerve, it will cause cranial nerve symptoms such as hearing impairment, difficulty in swallowing and hoarseness, etc. The clinical manifestations of spinal cord ependymoma include a lack of specificity, including limb sensory disturbance, pain, limb weakness, urinary bladder dysfunction, etc.

Ependymoma may spread through cerebrospinal fluid, which is also one of the main factors for its poor prognosis [13]. Different literature reports on the proportion of spread vary greatly, ranging from 3% to 12% [14]. Most ependymoma relapses occur in the original location without the spread to the other parts.

Imaging diagnosis

CT manifestation of intracranial ependymoma mostly shows equal density or mixed density shadows inside or surrounding the ventricle, demonstrating medium intensity after enhancement. A few tumors are calcified, showing single or multiple spots, which occur more often on the subtentorium, while rarely on the supratentorial ventricle. Most tumors are accompanied by cystic changes [15].

Intracranial ependymoma MR demonstrates a clear tumor boundary, with T1 weighted imaging showing uneven low signals or equal signals, and T2 weighted imaging demonstrating high signals. Tumor parenchyma is often significantly enhanced, while cystic change and calcification parts are not. Identification of supratentorial ependymoma and astrocytoma: if a solid tumor component appears in the shape of a streak or has punctate calcification, it is more likely to be ependymoma, and calcification of an astrocytes tumor is rare. There is light or no edema around ependymoma, and astrocyte tumors edema is relatively obvious. Ependymoma frequently occurs in young people while astrocyte tumors are more common in the middle-aged and elderly.

Spinal ependymoma CT shows that the spine becomes thicker and thicker from the outside of a tumor to the center, but MR is still the main diagnosis method. Typical manifestation of spinal cord ependymoma is as follows: T1 weighted signal is lower than nearby normal spinal cord signal, T2-weighted imaging signal is relatively higher and the contour is clear after enhancement [16]. The upper and lower pole of a tumor are often accompanied by a cyst or cavity, caused by spinal cord interstitial edema and the oppression of surrounding tissue when the tumor expands outwardly due to cerebrospinal fluid pressure elevation [17].

Surgical treatment of ependymoma

Surgical treatment is preferred in both intracranial ependymoma and spinal cord ependymoma. With the increasing development of surgical techniques, and continual application of micro neurosurgery, neuronavigation, intraoperative ultrasound and magnetic resonance (NMR), neuro-physiological monitoring, surgical treatment has developed from the method of removing tumor mass effects in order to obtain pathological diagnosis to radical treatment which can remove the tumor as completely as possible with lower complications (below 13%) [18], better protecting the nervous function. According to reports, nervous function of 79% spinal ependymoma patients undergoing surgery treatment can be maintained and improved [19]. Despite the lack of extensive sample data, many reports show that patients who have had ependymoma completely removed experience better survival rates and higher life quality [20-24].

Supratentorial ependymoma

Supratentorial ependymoma may occur in the ventricular system or brain parenchyma, where the tumor volume is usually relatively large. A surgical approach depends upon the location of tumor, application of neural navigation, and

intraoperative ultrasound, while intraoperative MRI technology may facilitate a clear identification of tumor location in order to remove the tumor to the greatest extent. Drainage tubes can be used for ventricle ependymoma patients who are also accompanied by serious hydrocephalus according to circumstances such as external intraventricular drainage, ventricle peritoneal shunts or fistulation. A clear boundary between parenchymal ependymoma and normal brain tissue provides the basis for total removal, and tumors located in a deep functional area or malignant ependymoma can only be partially removed [25, 26].

Subtentorial ependymoma

Subtentorial ependymoma usually arises from the floor of the fourth ventricle and may invade the aqueduct of sylvius upwards, leading to adhesion with the medulla obex downwards, and invading the posterior cranial nerves or posterior inferior cerebella artery. Consequently, surgery is difficult and easily leads to disability or great nervous dysfunction, while neural electrophysiological monitoring technology greatly facilitates the removal of the tumor. According to circumstances, a second operation can be carried out if a residual tumor is found through MRI. According to reports, second surgery can remove the tumor without causing complications [27].

Intramedullary ependymoma

This disease mostly originates from the neck - upper thoracic segment, followed by lower thoracic segments - and waist, as myxopapillary ependymoma are mainly located in cauda equina. There is a clear boundary between the tumor and normal spinal cord tissue, so theoretically operation through the posterior median approach can be adopted in order to totally cut out the tumor. Due to the characteristics of ultrasonic echo on the ependymoma, an echo may be produced in the junction of tumor tissues and normal spinal cord tissues [28], so intraoperative ultrasound can accurately define the operation scope of spinal ependymoma. Physiological monitoring technology can avoid irreversible spine injury [29]. Most scholars believe that the complete resection of a tumor can achieve ideal results compared with piecemeal resection [30], for piecemeal resection may lead to interface loss, increased hemorrhage, and increase the risk of spreading when the tumor breaks, so this approach can only be used when the tumor size is too big. There is controversy about the choice of operation time, with some scholars holding that once the intramedullary ependymoma is diagnosed, the operation should be carried out as soon as possible, as the earlier the surgery, the smaller the damage on the spinal cord function [31]. However, other scholars believe that tumor size is small at the initial stage and it's located in a deep place, so the operation may have the risk of injuring the spinal cord, and so surgery should be conducted only when the tumor grows to a medium-large size and is close to the rear surface of spinal cord [32].

Radiotherapy of ependymoma

According to the traditional treatment method, ependymoma patients should be treated with radiotherapy after surgery in order to improve their prognosis. But recent studies have proved that low-grade ependymoma patients who are treated with whole surgical resection don't need radiotherapy if there is no CSF spread [33]. Ependymoma and anaplastic ependymoma patients who receive whole surgical resection can experience an improved rate of survival [34-36], as short-term survival rate and 10-year survival rates are 70% and 50% respectively [37, 38]. As to intramedullary ependymoma patients, some scholars argue that radiotherapy can improve a patient's survival rate, and reduce the risk of recurrence whether the patients is applied with total surgical resection or not [39]. However, most scholars think that radiotherapy after surgery shows no effect on intramedullary ependymoma patients [40-42].

According to the past treatment, supratentorial ependymoma is treated by local radiation on tumor bed or in combination with whole brain irradiation. Subtentorial ependymoma (including intramedullary ependymoma) adopts the approach of whole brain and whole spinal cord irradiation and intensifies the local focal area approach. The main theoretical basis is: ependymoma cells may easily fall off and spread into the cerebrospinal fluid which causes implantation metastasis. But recently more and more research brings different conclusions: the main cause of treatment failure was local recurrence. The incidence of cerebrospi-

nal spread is low; protective irradiation cannot prevent spinal metastasis [43, 44]. Teo [26] found that local recurrence in the original place is a major cause of implantation metastasis, as usually metastasis spreads to distant places, followed by a local recurrence in original location. Sgouros [45] conducted a survey on 38 intramedullary ependymoma patients, discovering that the 10-year survival rate of patients with and without postoperative radiotherapy is 48% and 96% respectively, and believed radiotherapy after surgery is meaningless to prevent the occurrence of a tumor. Paulino [46] conducted a follow-up survey on 49 ependymoma patients from 1965 to 1997 with 9.6 years of average follow-up, finding that both the overall survival period and local control rate of patient who had local radiotherapy and preventive radiotherapy experienced no significant difference. Merchant [47] performed follow-up research on 153 child patients from 1997 to 2007, among which 122 patients suffered lesions located in the subtentorial ventricle. The patients who had preventive radiotherapy and patients without preventive radiotherapy saw same survival period without disease.

Current radiation treatments-*National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines* since 2006 has recommended that ependymoma can be treated with regular local radiotherapy. Whole brain and spinal radiation therapy can only be carried out on positive spinal MRI or CFS patients, with the local dosage for adult being 54-59.4 GY, and a fractional dosage 1.8 2 GY. Whole brain and spinal cord dosage is 36 GY, and fractional dosage 1.8 GY. Later spinal cord local dosage can be added up to 45 GY, and brain dosage to 54-59.4 GY. For child patients, some scholars think that the dosage should be reduced to 80% of that of adults [38].

Stereotactic radio-surgery treatment has also gradually been applied to the treatment of ependymoma, and shows good control of tumors in the tumor bed area, although there is still a lack of long-term observation data. Kano [48], in a retrospective study, conducted stereotactic radio-surgery treatment of 39 ependymoma patients who were treated with conventional fractionated radiotherapy after radiotherapy. The average dosage is 15 GY, with the 3-year and 5-year survival rate being recorded as 60.1% and 32.1% respectively. LOSS [49] carried out stereotactic radio-surgery treatment on 8 ependymoma patients who had recurrence after conventional fractionated radiotherapy treatment, and observed them 30.2 months on average, noting that 6 patients (75%) were still alive. Mansur [50], in another retrospective study gave stereotactic radio-surgery treatment to 9 ependymoma patients who received conventional fractionated radiotherapy treatment after radiotherapy (average dosage of 54 GY) with 14-20 GY dosage range. The 3-year overall survival rate was 71.7% and 3-year progression-free survival rate was 55.6%. He believes that the application of stereotactic radio-surgery treatment in the initial treatment of ependymoma is worthy of studying.

The main side effects of ependymoma radiotherapy include cognitive impairment, eyesight and hearing impairment, child growth and development retardation and endocrine system disorder, etc. However, as the development of radiotherapy technology continues, along with the application of intensity modulated radiation therapy and stereotactic radiation surgery techniques, the adverse effect can be reduced to great extent. Korshunov [51] observed 88 ependymoma child patients who were treated with three-dimensional conformal radiotherapy with a dosage of 54~59.4 GY in 38 average follow-up months. It was discovered that no cognitive dysfunction was found.

Chemotherapy of ependymoma

Ependymoma is not sensitive to chemotherapy, and as it lacks a large sample data, there is no generally accepted standard plan.

Grill gave chemotherapy to 73 ependymoma children patients under five years old first, then conducted delayed radiotherapy after 2-4 years, alternately combining the use of carboplatin and methyl hydrazine benzyl, Cisplatin and VP - 16 as well as Vincristine and cyclophosphamide, resulting in 2-year and 4-year survival rates of 79% and 59% respectively [52]. According to a randomized control study by Children's Oncology Group, 10-year progression-free survival rate and overall survival rates for children treated with multidrug therapy of vincristine, CCUN and prednisone were 36% and 39% respectively, but it didn't improve their

prognosis, so there was no significance [53]. Sunanda Pejavar carried out retrospective analysis on 39 ependymoma children aged 8 who all received surgery, among which 26 patients underwent radiotherapy, and 14 received adjuvant chemotherapy of cyclophosphamide, vincristine and etoposide. The 15-year progression-free survival rate was 30% and the 15-year overall survival rate was 67%.

Whether chemotherapy can improve the prognosis remains controversial in the adult ependymoma treatment. NCCN guidelines in 2014 also only recommended that appropriate chemotherapy can be conducted on patients who have recurred ependymoma after radiotherapy or palliative care ependymoma. Clinical trials have proved that chemotherapeutic drugs used alone or in combination have a limited effect [54, 55]. Platinum drugs are considered to be one of the basic drugs required to cure ependymoma [56], and phase II clinical study shows the efficiency of cisplatin to cure ependymoma is around 30% [57]. In a retrospective study, eight ependymoma patients were given carboplatin treatment after surgery, with 3 of them experiencing more than 7 years of progression-free survival period [58]. However, an Italian randomized controlled study which divided 28 ependymoma post-operative patients into 2 groups - a chemotherapy group with treatment of cisplatin and a chemotherapy group without treatment of cisplatin - showed the median survival time of the two groups was 31 months and 40.7 months respectively, and the cisplatin group failed to prolong survival time [59]. In the phase II clinical study of irinotecan and TPT, the reaction rates were 20% [60] and 0-40% [61]. In a research of ependymoma adult patients who had an occurrence after temozolomide treatment, the standard 5/28 plan could only result in 2-8 months survival time [62]. Green reported that 8 ependymoma adult patients who had occurrence after bevacizumab treatment gained 9.4 months of median survival time.

Ependymoma prognostic factor analysis

The more tumor resection, the longer the survival time. Many studies [63-65] emphasize the fact that tumor resection degree is a clear prognostic factor. Foreign scholars analyze many variables which may affect surgical prognostics [66]: the location of the tumor or histological types will not affect the outcome of the disease, the resection degree is related to prognosis, namely the outcomes of total resection and non-total resection are very different. The main factors related with improving progression-free survival include small tumor volume [49].

Prospect

Steve Mack found that 70% supratentorial ependymoma patients carry the RELA genetic mutation, which plays an important role in the regulation of inflammation cell signaling system. That is the NF-KB signaling channel, and the mutation leads RELA to fuse with the C11orf95 gene. In a mouse model, the expression of the C11orf95 gene in neural stem cells caused the formation of a brain tumor. All of the findings provide a potential new therapeutic targets [67].

Disclosure of conflict of interest

None.

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