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Комплексний огляд високозлоякісної астроцитоми III ступеня: анапластична астроцитома – поширеність, патологія, лікування та рецидив

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Анапластична астроцитома (АА), класифікована Всесвітньою організацією охорони здоров'я як астроцитома високого ступеня злоякісності III, являє собою значну групу злоякісних пухлин головного мозку. Цей огляд літератури має на меті надати повний огляд АА, охоплюючи її поширеність, типи, патологічні особливості, методи лікування та моделі рецидивів. АА переважно вражає дорослих віком від 30 до 50 років, дещо частіше чоловіків. Пухлина характеризується підвищеною клітинною та ядерною атипією та жвавою мітотичною активністю, що відрізняє її від астроцитом нижчого ступеня. Патологічно АА демонструє гетерогенність у молекулярних змінах, включаючи мутації в генах IDH1 та IDH2, втрату гетерозиготності на хромосомі 10 та зміни в алелі p53, що сприяє її агресивній поведінці та резистентності до звичайних методів лікування. Стандартне лікування передбачає максимальну хірургічну резекцію з подальшою променевою терапією та ад'ювантною хіміотерапією темозоломідом, яка, як було показано, покращує виживаність без

прогресування пухлини. Незважаючи на агресивне лікування, доволі поширені рецидиви, які часто прогресують до мультиформної гліобластоми або астроцитоми IV ступеня, які мають поганий прогноз. Останні досягнення в галузі молекулярного профілювання та цільової терапії дають надію на покращення лікування та прогнозів. Поточні дослідження мікрооточення пухлини та імунотерапевтичних підходів є перспективними для майбутніх терапевтичних стратегій. Цей огляд підкреслює необхідність продовження дослідження інноваційних методів лікування та персоналізованої медицини для підвищення виживання та якості життя пацієнтів з анапластичною астроцитомою.

Ключові слова: астроцитома, анапластична астроцитома, гліома, гліома високого ступеня злоякісності.

Comprehensive review of high-grade astrocytoma grade III: Anaplastic astrocytoma – prevalence, pathology, treatment, and recurrence

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Anaplastic astrocytoma (AA), classified as a Grade III high-grade astrocytoma by the World Health Organization, represents a significant subset of malignant brain tumors. This literature review aims to provide a comprehensive overview of AA, covering its prevalence, types, pathological features, treatment modalities, and recurrence patterns. AA primarily affects adults between the ages of 30 and 50, with a slightly higher incidence in males. The tumor is characterized by increased cellularity, significant nuclear atypia, and brisk mitotic activity, distinguishing it from lower-grade astrocytomas. Pathologically, AA displays heterogeneity in molecular alterations, including mutations in the IDH1 and IDH2 genes, loss of heterozygosity on chromosome 10, and alterations in the p53 pathway, contributing to its aggressive behavior and resistance to conventional therapies. Standard treatment involves maximal surgical resection followed by radiotherapy and adjuvant chemotherapy with temozolomide, which has been shown to improve progression-free survival. Despite aggressive treatment, recurrence is common, often progressing to glioblastoma multiforme, a Grade IV astrocytoma, which portends a poor prognosis. Recent advancements in molecular profiling and targeted therapies offer hope for improved management and outcomes. Ongoing research into the tumor microenvironment and immunotherapeutic approaches holds promise for future therapeutic strategies. This review underscores the need for continued exploration of innovative treatments and personalized medicine to enhance survival and quality of life for patients with anaplastic astrocytoma.

Keywords: Astrocytoma, Anaplastic astrocytoma, Glioma, High-grade glioma.

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Introduction

Anaplastic astrocytoma (AA) is a sporadic and aggressive brain tumor. Astrocytes, which are star-shaped cells in the brain, can transform into tumors known as astrocytes or astrocytomas [1]. Anaplastic astrocytomas account for more than 30% of all astrocytomas. Astrocytes and related cells create a protective sheath around other nerve cells in the brain and spinal cord. The group of these cells is called glial cells, and the tissue they create is called glial tissue. Grade III Anaplastic Astrocytomas are what the World Health Organization (WHO) calls high-grade astrocytomas. A primary brain tumor known as anaplastic astrocytoma (AA) typically begins to grow at a median age of 41. It is astrocytic and spreads throughout the brain. Among the two kinds of high-grade (malignant) astrocytomas, anaplastic astrocytomas predominate compared to low-grade astrocytomas [1, 2].

Methods

Data sources and search strategy:

A comprehensive electronic search was performed on PubMed/Medline. The search was conducted using the following query: (Astrocytoma OR grade III astrocytoma OR Anaplastic Astrocytoma). In addition, we conducted a thorough manual screening of referenced publications from prior meta-analyses, systematic reviews, cohort studies (both retrospective and prospective), and other review articles to find any relevant research.

Study selection:

All studies were included if they satisfied the following eligibility criteria, which may be represented as PICOS: 1) P (Population): Individuals diagnosed with Anaplastic Astrocytoma, a Grade III astrocytoma. 2) I (Intervention): Occurrence and nature of the disease; 3) C (Control): Surgical and adjuvant therapeutic intervention; 4) O (Outcome): Overall survival and recurrence. 5) S (Studies): Evaluate and analyze review and cohort studies published in English.

Data extraction and quality assessment of studies:

Two reviewers conducted separate searches on electronic databases. The searched studies were transferred to the EndNote Reference Library software version 20.0.1 (Clarivate Analytics), and any duplicate studies were reviewed and eliminated.

Incidence/epidemiology/distribution of AA

The correlation between chronological age and anaplastic astrocytoma (AA) occurrence and relative survival was examined in the research by Smoll and Hamilton (2014) [3]. The Surveillance, Epidemiology, and End Results database was used to identify 3,202 individuals with AA. These data were examined across different age groups to find the standardized mortality ratio, relative survival rate, and incidence rates. Delay-entry modeling was employed to represent temporal patterns. The overall age-adjusted incidence rate of AA was 3.5 per million person-years. After adjusting for age, the rate ratio was 1.28, with a total of 4.0 per 100,000 person-years for males and 3.1 per 100,000 person-years for females. As people age, they are more likely to have AA ($P < .001$). Kids had a rate of 0.9 per 1,000,000 person-years. Adults had a rate of 4.7 per 100,000, while older people had a rate of 8.4 [3].

Using Join point analysis to examine trends, Fang et al. (2018) provided rates (95% confidence intervals) for the age-adjusted incidence and incidence-based mortality of WHO grade III gliomas from 2000 to 2013 [4]. Despite a 0.16% rise in overall incidence rates between 2000 and 2013, there was no statistical significance. The 95% confidence interval was 0.55–0.87%. On the other hand, incidence rates increased significantly among those aged 18 to 39, with an APC of 0.99% (95% CI: 0.34% 1.63%). The 40–59-year-old age group and the 60+-year-old age group both saw non-significant decreases between 2000 and 2013 (APC = 0.30%; 95% CI: 1.21% 0.62% and APC = 0.11%, respectively; 95% CI: 1.57% 1.38%) [4].

Symptoms and Characteristics of AA

Anaplastic astrocytoma symptoms can range from mild to severe, and they are size and location-dependent. Blood pressure rises in the brain, which manifests most of the symptoms. Though it often progresses at a snail's pace, anaplastic astrocytoma can grow rapidly in rare cases. The exact symptoms that a brain tumor produces are correlated with its precise location. The cerebrum, the big spherical brain that fills most of the skull, is the most typical site for anaplastic astrocytomas to grow. However, they can occur elsewhere in the central nervous system [1]. Each hemisphere of the

brain is responsible for a different function. In the brain, anaplastic astrocytomas can develop in the occipital, parietal, frontal, and temporal lobes. Memory loss, changes in personality and temperament, and hemiplegia (paralysis on the opposite side of the body) can all be symptoms of a tumor in the frontal lobe. Seizures, difficulties with memory and coordination, and trouble speaking are all symptoms of a tumor in the temporal lobe. Neurologic complaints, either localized or widespread, are common in AA patients (Grimm and Chamberian, 2016) [5]. A variety of localized symptoms, such as weakness, sensory loss, visual impairment, linguistic dysfunction, gait disturbance, and tumor location-specific symptoms, might manifest. Generalized symptoms can manifest in various ways, including changes in personality, seizures, and headaches.

Headaches and nausea are common early signs of a tumor, which can be caused by the tumor's growth or a buildup of cerebrospinal fluid around the brain and spinal cord. The widespread distribution of glial cells in the central nervous system allows these tumors to develop in several locations, each of which can produce a unique set of symptoms. Depending on the tumor's location, gliomas can cause various symptoms, including problems with language function, double or distorted vision, convulsions, paralysis or numbness in the limbs, memory loss, and gradual changes in temperament or conduct. Additionally, seizures and specific neurological deficits are diagnostic of high-grade astrocytomas [1, 2, 5].

Histopathology and Molecular features of AA

It is believed that AA develops from a lower-grade tumor precursor since the histology of the disease is usually diverse, including parts of the low- and high-grade tumor. WHO classifies AA as a grade III anaplastic glioma with aberrant nuclei, greater cell density, glial markers, and no neuronal markers [1, 5]. On the other hand, glioblastoma is characterized by the absence of microvascularization and necrosis (Louis et al., 2007) [6]. Though it can vary greatly within tumors and overlap with low-grade astrocytoma and glioblastoma (GBM), the MIB-1 labeling index in anaplastic astrocytoma (AA) usually falls within the 5–10% range [7, 8]. Theeler et al. (2012) dis-

covered that pathologists frequently struggle to accurately forecast clinical prognosis [9].

Radiological features of Anaplastic Astrocytoma

Grade III tumors are diagnosed using imaging examinations and tumor biopsies. Unlike anaplastic astrocytomas, glioblastoma multiforme (GBM) tumors show signs of cell death, known as necrosis, in biopsy samples. These days, no imaging technique can compare to magnetic resonance imaging (MRI). Computed tomography (CT) scans are also used. To help neurosurgeons visualize the tumor in contrast to the normal brain, they inject an agent that generates image contrast intravenously in both cases [5].

In some cases, an MRI with frameless stereotactic guidance might be useful for neurosurgeons. To do this study using a high-resolution contrast MRI, the patient may be asked to have certain markers—called fiducials—placed on their scalp. A computer generates a 3D brain model by analyzing MRI scans. This has the potential for use in the operating room to lessen the risk of brain damage during surgery while simultaneously increasing tumor clearance and decreasing surgical exposure [10].

Diagnosing anaplastic astrocytoma with magnetic resonance imaging (MRI) necessitates a thorough clinical assessment, complete patient medical background, and several imaging techniques, including computed tomography (CT) scanning and magnetic resonance imaging. In addition to guiding potential surgical procedures, these imaging modalities can help determine the tumor's size, location, and extent [2].

Surgical Treatment of Anaplastic Astrocytoma

The management of high-grade astrocytomas necessitates a thorough approach. Despite its importance, surgery is rarely a cure-all. Due to the microscopic level at which malignant tumors penetrate healthy brain tissue, complete microscopic excision is extremely unusual, and recurrence is almost assured. It is the goal of the neurosurgeon doing the surgery to remove the astrocytoma in its entirety [5]. Unfortunately, complete tumor excision is not always achievable because of the astrocytoma's proximity to fragile brain tissue. For some, surgery is their only choice. Some

patients may need further treatments to completely eradicate cancer cells and reduce the chances of recurrence [1, 5].

To achieve the maximum possible excision of gliomas, their clinic has reportedly been using "information-guided surgery" with intraoperative MRI and updated navigation since 2000. An improved navigation system and intraoperative MRI were utilized to ensure maximal resection of all lesions, whether they were T2-weighted high-signal intensity or contrast-enhanced T1-weighted [5]. It was standard practice to use intraoperative monitoring methods like somatosensory evoked potentials and motor evoked potentials. Intraoperatively, in particular, awake speech/language mapping and direct cortical motor stimulation were used for patients with eloquent area injuries. Chemo and RT were administered after surgical procedures in every instance.

In a 2006 study, Kramm et al. looked at the effect of tumor excision on survival rates in children and adolescents with cancerous gliomas [11]. While in a 2020 study, the researcher found that the amount of tumor removed was the best predictor of both overall survival (OS) and event-free survival (EFS) in both single and Cox regression models. Gross total resection (GTR) had an OS rate of around 48% and an EFS rate of around 14% after four years, while non-total resection had an OS rate of around 13% and an EFS rate of around 2% [12].

Radiotherapy (RT)

Radiation therapy administered after surgery is standard practice for the treatment of anaplastic astrocytomas to eradicate any remaining cancerous cells. Radiation treatment is a viable option to surgery in cases when the precise location and/or advancement of the malignancy render surgery unfeasible. Most cells that proliferate quickly are cancerous; radiation therapy targets these cells specifically [5]. Some unwanted side effects may occur if healthy cells (such as bone marrow and hair follicles) are killed. Radiation therapy aims to eliminate cancer cells while minimizing harm to healthy cells by accurately assessing and delivering doses to the affected tissue. Radiation treatment hinders or halts the proliferation of cancer cells by accessing their DNA with high-energy beams [2]. Postoperative radiation treatment was administered to all

patients in the Scocianti et al. (2012) research [13]. Conventional fractionation was used by 90.5% of patients, whereas 3D-CRT was used by 86.1% of patients. In 80 cases (27.1%), the CRT treatment plan relied on registered CT and MRI. Patients treated with hypo-fractionation (3 Gy for every fraction) had a median dosage of 39 Gy (range, 30-45 Gy), compared to patients treated with conventional fractionation (1.8-2 Gy for each fraction) whose median dosage was 60 Gy (range, 54-66 Gy). The time it took from surgery to the beginning of radiation therapy was an average of 47 days (14-91 days) [13].

Chemotherapy (CT)

Chemotherapy with targeted anticancer medications is another viable treatment option for anaplastic astrocytoma. Currently, there is just one authorized chemotherapeutic therapy available for anaplastic astrocytoma. As of yet, no agents have obtained the required authorizations for use in pediatric patients. Regarding anaplastic astrocytoma, most chemotherapy medicines have shown relatively limited efficacy. Scocianti et al. (2012) found that 166 out of 198 patients (83.8% of those who had postoperative chemotherapy) received concurrent and sequential TMZ according to the standard schedule, while 67.1% of the total sample received TMZ as part of their postoperative chemotherapy [13]. Only a tiny fraction of the population got sequential TMZ (n=14, 10) or only contemporaneous (n=14, 22). The patient did not get any more chemotherapy drugs. Both the RT-only group and the RT + TMZ group had similarly balanced pretreatment characteristics, except for a significant imbalance in postoperative KPS, 3D-CRT, conventional fractionation, and a total dose of 60 Gy [12]. Anaplastic astrocytoma treatment by chemotherapy was the subject of retrospective research by Kim et al. (2012) [14].

They looked at the survival rates of three different groups using different treatment procedures at one facility. The research included 86 people, 39 of whom were men and 47 of whom were women, who had just been diagnosed with AA after surgery. In the RT Group, 31 patients (36.0%) were exposed just to radiation; in the ACNU-CDDP Group, 30 patients (34.9%) were administered nimustine-cisplatin chemotherapy before RT; in the PCV Group, 25 patients (29.1%) were administered pro-

carbazine, lomustine, and vincristine chemotherapy following irradiation [14].

Radiotherapy and Chemotherapy Combine Therapy

Additional treatment options for anaplastic astrocytoma include chemotherapy with specific anticancer drugs. There is currently just one approved chemotherapeutic treatment for anaplastic astrocytoma. Yet, no agents have received the necessary approvals for pediatric patients. When it comes to anaplastic astrocytoma, the majority of chemotherapeutic medications have demonstrated only moderate effectiveness. Scocciati et al. (2012) found that 166 out of 198 patients (83.8% of those who had postoperative chemotherapy) received concurrent and sequential TMZ according to the standard schedule, while 67.1% of the total sample received TMZ as part of their postoperative chemotherapy [13]. Only a tiny fraction of the population got sequential TMZ ($n=14$, 10) or only contemporaneous ($n=14$, 22). The patient did not get any more chemotherapy drugs. Both the RT-only group and the RT + TMZ group had similarly balanced pretreatment characteristics, except for a significant imbalance in postoperative KPS, 3D-CRT, conventional fractionation, and a total dose of 60 Gy. Anaplastic astrocytoma treatment by chemotherapy was the subject of retrospective research by Kim et al. (2012) [14]. They looked at the survival rates of three different groups using different treatment procedures at one facility [13, 14].

Complication and Recurrence

Holm et al. (2017) researched anaplastic gliomas to identify recurrence patterns following maximum surgical resection and postoperative radiation [15]. Of the patients, 31 (42.4%) had illness progression or recurrence. This occurred at different time intervals, ranging from 3 to 143 months following their initial diagnosis, with a median time of 19 months. Out of 31 instances of failure, 27, which accounts for 87.1% of the total, occurred during a span of 60 months following the therapy [15]. The extent of Resection (EOR) affected patterns of recurrence. According to Fisher's exact test, the amount of resection and recurrence patterns were found to be significantly different ($p < 0.05$). There were no in-field CTV/marginal failures among the Sub-total Resection (STR) and Partial Resection (PR) – Biopsy (Bx)

groups, and the vast majority of recurrences (14/18, 77.8%) were in-field GTV failures. Six recurrences, or 46.2% of the total, occurred in the Gross Total Resection (GTR) group due to CTV/marginal failures. There are three types of radiation treatment adverse effects: acute, early-delayed, and late. Headache, nausea, drowsiness, fever, and perhaps worsening of neurological symptoms may arise within two weeks after starting radiation therapy (RT). One of the early-delayed effects, which typically manifests between two weeks and three to four months after radiation treatment ends, is the "somnolence syndrome," a combination of hypersomnia, lethargy, and irritability [16]. The most prevalent long-term consequences of brain irradiation include radionecrosis, cognitive impairment, and leukoencephalopathy. An investigation of cognitive problems in survivors of low-grade glioma who did not experience progression was unable to confirm a previously postulated association between radiation and cognitive impairments. The research of Grimm and Thomas (2013) uncovered hypothalamic-originating radiation-induced endocrine disruption that occurs gradually [5].

Overall Survival

The age-standardized rates for RS after 5 and 10 years were 23.6% and 15.1%, respectively, according to research by Smoll and Hamilton (2014) [3]. It was nevertheless clear that the elderly did much worse at the beginning and end of the study compared to the younger participants, even after accounting for overall mortality rates. At age 10, the RS rate was 36% among the youth and just 3.5% among the elderly. There is no statistically significant difference between the total and relative survival rates, as shown in Figure 3. The median survival duration in the study conducted by Scocciati et al. (2012) was 20.6 months, and 210 out of 295 individuals passed away during the research [13]. In the first year, actuarial survival was 70.2%; in the fourth year, it dropped to 28.6%. The study conducted by Holm et al. (2017) reported a median follow-up duration of 55 months (ranging from 8 to 180 months) for all patients [15]. The median follow-up duration among the survivors was 84 months (30 to 180 months). The overall survival rates were 56.6% after five years and 60.4% after ten years, while the progression-free survival rates were 60.4% and 60.4%, respectively [15].

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