International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 01 Janaury 2023

Page No: 16-21

DOI: https://doi.org/10.47191/ijmscrs/v3-i1-04, Impact Factor: 5.365

Astrocytoma, Diagnosis and Treatment. Literature Review

Alejandro Arias Mendoza[1], Giovanna Aldonza Rios López[2], Gladys Montserrat Ballesteros Solís[3], Gabriela Cruz Islas[4], José Antonio Soto Sánchez[5], Laura Yoana Cervantes Ramírez[6]

[1]Hospital General de Zona 1-A Dr Rodolfo Antonio de Mucha Macías. Hospital de Especialidades Dr. Bernardo Sepulveda Gutiérrez. Centro Médico Nacional Siglo XXI.

[2,3]Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud. Guadalajara, Jalisco, México.

[4,5]Facultad de Medicina de la Universidad Nacional Autónoma de México, Ciudad Universitaria. Ciudad de México, México.

[6] Universidad de Guadalajara, Centro Universitario del Sur. Ciudad Guzman Jalisco, México.

ABSTRACT

Most primary CNS tumors are astrocytic tumors. Glial tumors are classified according to histological criteria. The WHO classification for primary malignant gliomas in adults includes grades II through IV. Terms for tumors that classify in grade II are astrocytomas (A), oligodendrogliomas (ODG), or mixed gliomas (GM). Grade III tumors are named similarly, and preceded by the word anaplastic, for example, anaplastic astrocytoma (AA), anaplastic oligodendroglioma (ODGA), or mixed anaplastic glioma (GAM). The most malignant form, the grade IV tumor, is designated glioblastoma or GBM. GBMs are diagnosed more frequently than lower grade astrocytomas. The recent GBM classifications reflect the genetic aspects involved in the tumor and have prognostic value.

The most important prognostic factor in malignant gliomas is the histopathological diagnosis of the tumor. The survival of patients with AA is much higher than that of patients with glioblastoma. Other important factors that are associated with the survival of patients with malignant gliomas are the age of the patients, Karnofsky scale, surgery, radiotherapy, and chemotherapy. There is evidence suggesting an association between younger patients and longer survival in adults with supratentorial AA and glioblastoma.

ARTICLE DETAILS

Published On:
07 Janaury 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Central nervous system (CNS) tumors represent 2% of all neoplasias.1 They seem to be becoming more frequent, not so much due to a true increase in their incidence, but rather due to the increase in the life expectancy of the general population and by technological advances that allow a more timely diagnosis. These tumors constitute a heterogeneous group of neoplasms that range from well-differentiated and relatively benign lesions, such as meningiomas, to highly invasive and poorly differentiated lesions, such as glioblastoma multiforme (GBM). [1]

Increasing knowledge of the cytodifferentiation of the system nervous system and recent advances in genomics and proteomics have allowed us a better understanding of the biology of these tumors, which has the potential to improve the prognosis of patients, as it allows us to design increasingly specific and effective treatments. Currently, the overall incidence rate of primary CNS tumors is 10.82 per 100,000 person-years. The epidemiology of these tumors is complex, and several meta-analyses evaluating their basic demographic and clinical characteristics find considerable heterogeneity in the data. [2,3]

Cancer constitutes a serious health problem for humanity, with high incidence and mortality rates. Currently, cancer is the third leading cause of death, and it is estimated that in 2007 there were more than 12 million new cases and 7.6 million people who died worldwide. By the year 2030 it is estimated that there will be 26 million new cases and 17 million deaths annually. This increase will be largely related to the aging of the population, and said increase will be higher in undeveloped countries. [4]

In 2002, 27,446 new patients with some malignant tumor were diagnosed in Cuba, for a rate of 186 per 100 000 inhabitants. In 2008, for malignant tumors, a crude and adjusted mortality rate per 100,000 inhabitants of 189 and 118, respectively, was reported. In the same year, the number of deaths from cancer located in the brain was 257 men and

238 women, for a total of 495.Malignant gliomas are the most common tumor of the Central Nervous System (CNS). [5]

Mortality from these tumors increases as the age at which they are diagnosed increases. In developed countries, only 14% of patients diagnosed with CNS tumors have a survival of more than 10 years and only 1% of them are preventable. [6]

Some varieties of tumors are particularly frequent in certain age groups; for example, pilocytic astrocytoma is more common in children while GBM is more common in adults. Meningiomas are the most common primary brain tumors, accounting for 36.4% of all cases, followed by gliomas, which make up 27%. Gliomas are more common in adults, with an incidence of 14.07 per 100,000 person-years versus 0.18 cases per 100,000 person-years in children. On the other hand, medulloblastoma occurs more in children, with an incidence of 0.49 cases per 100,000 person-years, compared to 0.05 cases per 100,000 person-years in adults. [7,8] On the other hand, we know that the group The most important of brain tumors are metastases, since they constitute 50% of all intracranial neoplasias. Unlike primary brain tumors, metastases have a 9-17% incidence of neurological complications based on various studies, although it is thought to be higher. The malignant neoplasms that most frequently present with brain metastases are lung cancer, breast cancer, and melanoma. [9]

Brain metastases are sometimes the first indication of the existence of these tumors.5 Classification The most complete and up-to date classification system for CNS tumors is that of the World Health Organization (WHO), which was revised and modified in 2016. This classification system divides CNS tumors according not only to histological type, but also uses molecular markers for cytodifferentiation. Recently, researchers from the Cancer Genome Atlas (TCGA): The Cancer Genome Atlas) established the existence of four subtypes of glioblastoma. The classification proposed by the TCGA is based on basic demographic characteristics (such as age) and on genomic and cytodifferentiation aspects, but also includes therapeutic (response to treatment) and prognostic (duration of survival) aspects. This new proposal aims to group patients based on the different glioblastoma subtypes and constitutes an important step towards the development of personalized treatments, which are targeted at the specific genetic alterations of each tumor. [10,11]

Many glioblastomas multiforme (GBM) are thought to arise from the progression of low-grade astrocytomas (World Health Organization (WHO) classification, grade II) and anaplastic astrocytomas (WHO, grade III). The molecular mechanisms involved in the malignant phenotype and progression are beginning to be understood and seem to be, in part, associated with the inactivation of tumor suppressor genes (including, for example, p53 and p16) and the overexpression of oncogenes (ras, epidermal growth factor receptor (EGFR) and Akt). Astrocytic tumors are characterized by EGFR overexpression. High concentrations of this receptor have also been found in meningiomas. [12]

EGFR expression seems to increase with the degree of malignancy. One group of GBM expresses a truncated receptor variant, which possesses constitutive, ligand-independent activity. In contrast, the receptor is not expressed in normal brain tissue. [13]

The median survival in patients with GBM is less than a year, even when using the most aggressive regimens of cytoreductive surgery, radiation, and chemotherapy. Neoplastic cells are prone to migrate from the primary tumor mass. So far, no treatment has been discovered that can prevent residual neoplastic cells that remain viable after surgery and radiation therapy from proliferating and causing tumor recurrence. [14]

RISK FACTORS

Environmental and Occupational Factors

Factors Exposure to ionizing radiation, in the form of X-rays or gamma rays, is the only factor that the International Agency for Research on Cancer (IARC) on Cancer) established as a cause of CNS tumors.8 Studies conducted in people exposed to atomic radiation show an increased number of glioma cases compared to people who were not exposed. Likewise, there is an increase in tumors in patients exposed to radiation from the use of computed tomography, where more than two CT scans imply a risk for an exposure of 60 milligrays per study. [15]

The use of radiation therapy as a treatment for a primary CNS tumor increases the risk of a secondary CNS tumor by 55%, compared to those patients who do not receive radiotherapy. It is still debated whether the use of cell phones constitutes a risk factor for the development of brain tumors, this due to the fact that The brain is the organ that receives the greatest amounts of radiofrequency with the use of this equipment. [16]

Epidemiological studies carried out to date do not find a statistically significant association. However, some authorities believe that longer-term follow-up is required to establish whether the use of cell phones plays an important role in the genesis of CNS tumors. [17]

Although no significant association has been found between development of gliomas or glioblastomas and exposure to low intensity magnetic fields, it appears that exposure to very low frequency magnetic fields (<3 mG) is linked to glioblastomas in men, but not in women. It is postulated that there is a greater risk of developing gliomas in women who use agricultural, textile, and electrical products, as well as in those who work in department stores or are engaged in retail sales. On the other hand, it has been seen that forestry workers and fishermen have a decreased risk for gliomas. Occupational exposure to combustion products results in an 8 to 20% increased risk of primary CNS tumor presentation, and diesel products are associated with increased risk for gliomas. Dust and sulfur dioxide, according to the INTEROCC study of occupational exposure risk factors, show no significant association with the development of primary CNS tumors. [18]

Hormonal and Reproductive Factors

The risk of meningioma is 19% higher in women who are receiving postmenopausal hormone replacement therapy (HRT) compared to those who have not. The risk of glioma is 29% lower in regular users of contraceptives compared to those who have never used them. Age, menarche, menopause, or age at first childbirth have not been associated with tumor development. [19]

Genetic Predisposition Syndromes

These low-prevalence syndromes constitute only a small proportion of all cases of primary central nervous system tumors. The best known are neurofibromatosis types 1 and 2, tuberous sclerosis complex, Cowden's disease, von-Hippel Lindau disease, Turcot syndrome, Li-Fraumeni syndrome, Gorlin syndrome, and neurofibromatosis syndromes. of predisposition associated with rhabdoid tumors. Most of these syndromes have autosomal-dominant inheritance, except in the case of Turcot syndrome type 1, which has an autosomal-recessive pattern of inheritance. Its clinical and genetic characteristics are summarized in Table III. Having a history of a parent with a primary CNS tumor increases the risk of developing a CNS tumor in the child by 70%, compared to the general population. Also, having a sibling with a CNS tumor is associated with twice the risk. [20]

Pathophysiology Gliomas play an important role in primary brain tumors. The new advances in the pathogenesis and genetic associations have allowed to establish some theories that lead to the mechanisms of production of the disease in gliomas. Recent studies show that cancer cells originate from tumor stem cells, which are undifferentiated neural cells. Different mutations have been described that lead to histological dedifferentiation, which culminates in the establishment of cancerous neural cell clones. Knowing the mutations and the different alterations can allow us to discover the new treatment targets and establish the prognosis of the patients. [21]

Clinical Manifestations

The symptoms caused by a primary central nervous system tumor are divided into two groups: focal symptoms and generalized symptoms. The focal symptoms are related to the location of the tumor and its extension and the generalized symptoms are those that are related to the growth and compression generated secondarily, which gives rise to headache, nausea, papilledema and seizures, among others. The most frequent symptoms in the presentation of a rapidly growing tumor are headache, nausea or vomiting, as well as seizures. [22]

The headache is most severe at night or early in the morning and worsens with Valsalva maneuvers. It is generally constant, with a tendency to be progressive and to partially improve with the use of analgesics, and depending on the location, it is associated with focal symptoms, as well as nausea and vomiting. The intensity of the headache is greater when it is associated with obstructive hydrocephalus or meningeal irritation. The type of headache reported by patients in 77% is tension-type, 9% migrainous type, and 14% other types. [22]

Certain characteristics of nausea and vomiting suggest the presence of CNS tumors, such as the fact that are triggered by abrupt changes in position and that are associated with focal neurological signs and headache. Seizures associated with a tumor process in the CNS are generally associated with gliomas or metastases, of which the former are more frequent. These crises can be the initial symptom or develop later and their presentation depends on the location of the lesion. Frontal lobe lesions usually cause focal tonic or clonic seizures; those of the occipital lobe give rise to visual disturbances, and those of the temporal lobe generate sensory (gustatory, auditory, olfactory, etc.) or autonomic seizures. [22]

When seizures are the initial symptom, they are generally smaller lesions than those who have headache. Patients with primary CNS tumors may have associated Todd's palsy. The cognitive alterations that can occur in the context of CNS tumors are memory alterations, as well as personality changes. Patients generally complain of fatigue, tiredness, loss of interest in pleasurable activities, and lack of energy, so the presence of one of these tumors can be confused with a depressive syndrome. Imaging studies The diagnostic approach requires suspicion clinic necessarily combined with neuroimaging evaluation. These studies are also fundamental because they provide information for preoperative planning, as well as the probable etiology, although finally the definitive diagnosis is given by the histopathological study. Computerized axial tomography Also known as CT, by its acronym, is useful as a study of initial approach, in which a lesion, its location and morphology are generally identified. However, it has lower sensitivity and specificity than magnetic resonance imaging to assess tumor characteristics. It is useful when the tumor infiltrates bone, when the patient has contraindications for magnetic resonance, or when obtaining an image is urgent. [23]

Nuclear magnetic resonance Nuclear magnetic resonance is made up of six different types, which we present below:

• Magnetic resonance (MR) with gadolinium: it is the study of choice for the diagnosis of a CNS tumor, as well as the characteristics that can guide the etiology. For example, high-grade gliomas are typically hypointense on T1 and enhance heterogeneously with gadolinium. Low-grade gliomas present as an infiltrating hemispheric lesion that produces little mass effect. On the other hand, astrocytomas have increased signal intensity on T2 and FLAIR, although they are not always contrast enhanced. In addition, MRI has the advantage over computed tomography (CT) in that it better visualizes the meninges, the subarachnoid space, the posterior fossa, and the vascular distribution of the neoplasm. [23]

• Magnetic resonance spectroscopy (MRI): has been This has become a very useful tool in the evaluation of CNS tumors, since it allows to improve the differentiation of infiltrating tumors from other lesions through the analysis of the

chemical composition of the area of interest selected by the radiologist. The chemical signals measured by spectroscopy are N-acetylaspartate (NAA), choline, lactate, and 2-hydroxyglutaramate. NAA is responsible for signaling neurons and is decreased in gliomas. On the other hand, choline, which is a component of cell membranes, is increased in CNS tumors; lactate is elevated when there is necrosis, and 2-hydroxyglutaramate is elevated when there are mutations in the IDH1 and IDH2 genes. MRI is not a substitute for histopathological diagnosis: its objective should be limited to differentiating between a neoplasm and another non-neoplastic process. [23]

• Diffusion, weighted imaging (DWI): used to determine the cell density of the lesion. When there is an increase in the size or number of cells, diffusion is restricted and an image with increased uptake signal is observed. This sequence is useful in the detection of a recurrent tumor due to increased vascular permeability, especially if the patient was previously treated with Bevacizumab. [23]

• Tractography (or diffusion-weighted imaging): uses the same concept as diffusion imaging. , with the exception that it allows distinguishing the spatial relationship between the tumor boundary and the white matter through the visualization of the fibres. It is very useful for preoperative planning to avoid compromising functional tissue and nerve tracts. [23]

• Perfusion magnetic resonance imaging (pMRI): Used to visualize blood flow in CNS tumors. Computed axial tomography perfusion can also be used. It allows detection by pulsating water molecules as they pass through the carotid and vertebral arteries. It is useful in newly diagnosed or recurrent tumors, since increased perfusion is observed due to the presence of hypervascularity. [23]

• Functional magnetic resonance imaging (fMRI): this variant of the resonances makes it possible to measure the difference in blood flow in specific regions of the brain when these are activated. It is useful for preoperative planning when the tumor is adjacent to eloquent areas of the brain, allowing differentiation between tumor tissue and functional tissue. In addition, it has higher resolution for the detection of edema at tumor boundaries. [24]

TREATMENT

The three lines of specific treatment for primary CNS tumors are surgery, radiotherapy and chemotherapy. Management depends on the location, histopathology, and characteristics of the tumor. [25]

MEDICAL TREATMENT

Generally, primary CNS tumors are accompanied by vasogenic edema and their treatment is the use of long-acting glucocorticoids such as dexamethasone. The dose and duration of treatment will depend on the size and location of the lesion and the individual response. In most cases, high doses are used, which can be accompanied by adverse effects, such as hyperglycemia, cognitive alterations, myopathy, and susceptibility to infections. [26]

Anticonvulsants such as diphenylhydantoin and carbamazepine are commonly used and can be decreased. the initial dose, depending on the degree of stability that the patient shows. The use of levetiracetam and lacosamide for the prevention and treatment of seizures in CNS tumors has recently been very effective. [27]

SURGERY

Surgery not only aims to reduce tumor mass, but, more importantly, its function is to obtain tissue to establish a more precise diagnosis that allows defining a treatment plan. Surgical treatment is the treatment of choice for those primary CNS tumors in which complete resection is sought. In some cases, surgery is sufficient as a curative therapy, especially in those benign tumors without infiltration into other tissues. Surgical treatment is only contraindicated when the tumor is inaccessible or in an eloquent area, such as language, vision, or motor cortex. [28]

Radiation therapy Radiation therapy is the standard treatment as adjuvant management for high-grade gliomas. Three types have been described: conventional radiotherapy, stereotactic radiosurgery and brachytherapy. Conventional radiotherapy generally consists of a range of daily treatments that goes from 25 to 35 for a period of 5 to 7 weeks; conforms to histopathology and tumor location. On the other hand, stereotactic radiosurgery consists of a single day session and can be extended to two or three more days. It is generally used as a palliative measure in recurrent tumors. Finally, brachytherapy consists of placing a radioactive implant directly inside the tumor. [29]

CHEMOTHERAPY

Currently, the standard treatment drug for CNS tumors is temozolamide, which is a drug that acts directly on DNA methylation, breaking the double strand and generating cell apoptosis. The combination of temozolamide with radiotherapy increases the five-year survival in patients diagnosed with high-grade gliomas from 10% of individual radiotherapy to 27%. Bevacizumab, imatinib and irinotecan are currently under study, which have shown promising results due to their anti-growth factor effect. [30]

CONCLUSIONS

The future of primary tumors of the central nervous system is based on early diagnosis, as well as timely incidence on known risk factors and those new ones that have been evidenced, mainly those that involve lifestyle. Knowledge of this is vital to facilitate the health professional establishing a diagnosis and referring a patient to offer better survival, as well as better treatment. There are several factors that will continue to be studied, such as cell phone use and occupational exposures. There are still factors that are not known and it is expected that the continuous knowledge about

the biological characteristics of the tumors will improve their prognosis.

REFERENCES

I. Central Brain Tumor Registry of the United States (CBTRUS). CBTRUS Fact sheet 2016. CBTRUS; 2016. Available at http://www.cbtrus.org/factsheet/factsheet.html
II. De Robles P, Fiest KM, Frolkis AD, Pringsheim T, Atta C, St Germaine-Smith C, et al. The worldwide incidence and prevalence of primary brain tumors: a systematic review and meta-analysis. Neuro Oncol. 2015 Jun;17(6):776-83.
III. Ostrom QT, Gittleman H, de Blank PM, Finlay JL, Gurney JG, McKean-Cowdin R, et al. American Brain Tumor Association Adolescent and Young Adult Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 20082012. Neuro Oncol. 2016 Jan;18 Suppl 1:i1-i50.
IV. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol. 2015 Oct;17 Suppl 4:iv1-iv62.
V. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012 Feb;14(1):48-54.
VI. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun;131(6):803-20.
VII. Verhaak RG1, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al; Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010 Jan 19;17(1): 98-110.
VIII. Cogliano VJ, Baan R, Straif K, Grosse Y, LaubySecretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011 Dec 21;103(24):1827-39.
IX. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 Aug 4;380(9840):499-505.
X. Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol. 2011; 12(4):353-60.
XI. The INTERPHONE Study Group. Brain tumor risk in relation to mobile telephone use: results of the INTERPHONE international case–control study. Int J Epidemiol. 2010; 39(3):675-94.
XII. Hardell L, Carlberg M, Söderqvist F, Mild KH. Case control study of the association between malignant brain tumors diagnosed between 2007 and 2009 and mobile and cordless phone use. Int Jour Onc. 2013; 43: 1833-45.
XIII. Benson VS, Pirie K, Schüz J, Reeves GK, Beral V, Green J, et al. Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int Jour Epidemiol. 2013; 1-11.
XIV. Lacourt A, Cardis E, Pintos J, Richardson L, Kincl L, Benke G, et al. INTEROCC case-control study: lack of association between glioma tumors and occupational exposure to selected combustion products, dusts and other chemical agents. BMC Public Health. 2013; 13:340.
XV. Ricard D, Idbaih A, Ducray F, Lahutte M, HoangXuan K, Delattre JY., et al. Primary brain tumors in adults. Lancet. 2012; 379:1984-96.
XVI. McCarthy BJ, Rankin KM, Aldape K, Bondy ML, Brännström T, Broholm H, et al. Risk factors for oligodendroglial tumors: a pooled international study. Neuro Oncol. 2011; 13(2):242-50.
XVII. Wang PF, Ji WJ, Zhang XH, Li SW, Yan CX. Inverse association between eczema and meningioma: a meta-analysis. Cancer Cause Control. 2011;22(10):1355-63.
XVIII. Triplett TA, Curti BD, Bonafede PR, Miller WL, Walker EB, Weinberg AD. Defining a functionally distinct subset of human memory CD4 T cells that are CD25pos and FOXP3neg. Eur J Immunol. 2012; 42:1893-905.
XIX. Xie L, Mo M, Jia HX, Liang F, Yuan J, Zhu J. Association between dietary nitrate and nitrite intake and site-specific cancer risk: evidence from observational studies. Oncotarget. 2016 Aug 30;7(35):56915-32.
XX. Mandelzweig L, Novikov I, Sadetzki S. Smoking and risk of glioma: a meta-analysis. Cancer Cause Control. 2009; 20(10):1927-38.
XXI. Kitahara CM, Wang SS, Melin BS, Wang Z, Braganza M, Inskip PD, et al. Association between adult height, genetic susceptibility and risk of glioma. Int J Epidemiol. 2012;41(4):1075-85.
XXII. Shao C, Bai LP, Qi ZY, Hui GZ, Wang Z. Overweight, obesity and meningioma risk: a meta-analysis. PLoS One. 2014;9(2):e90167.
XXIII. Harder T, Plagemann A, Harder A. Birth Weight and Subsequent Risk of Childhood Primary Brain Tumors: A Meta-Analysis. Am J Epidemiol. 2008;168(4):366-73.
XXIV. Tong JJ, Tao H, Hui OT, Jian C. Diabetes mellitus and risk of brain tumors: A meta-analysis. Exp Ther Med. 2012;4(5):877-82.

XXV. Edlinger M, Strohmaier S, Jonsson H, Bjørge T, Manjer J, Borena WT, et al. Blood pressure and other metabolic syndrome factors and risk of brain tumor in the large population-based Me-Can cohort study. J Hypertens. 2012; 30(2):290-6.

XXVI. Ong EL, Goldacre R, Goldacre M. Differential risks of cancer types in people with Parkinson's disease: a national record-linkage study. Eur J Cancer. 2014; 50(14):2456-62.

XXVII. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009;52(5):611-22.

XXVIII. Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. PLoS One. 2013;8(12):e83261.

XXIX. Qi ZY, Shao C, Zhang X, Hui GZ, Wang Z. Exogenous and endogenous hormones in relation to glioma in women: a meta-analysis of 11 case-control studies. PLoS One. 2013;8(7):e68695.

XXX. Johansson G, Andersson A, Melin B. Recent developments in genetic predisposition syndromes. Act Oncol. 2015; 1-11.