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# Treatment of Astrocytoma

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**ABSTRACT**

Astrocytoma is a primary grade III (malignant) brain tumor. Astrocytoma grows quickly & often spreads into nearby areas of the brain. It can infiltrate into adjacent areas of brain tissue as small fingers of cells or even individual cells. This makes it nearly impossible in most patients to achieve surgical removal of each cancer cell. The majority of the tumors are focal low grade astrocytomas that are amenable to surgical cure & long term survival. Chemotherapy is now used on patients as initial therapy when their functional status is congruent with further treatment. Here we discuss the other agents like radiation therapy, matrix metalloproteinase (MMPs) inhibitors, gene therapy & anti-angiogenic agents are also discussed.

**Keywords**: Astrocytoma, Radiation therapy, Matrix metalloproteinase inhibitors (MMPs), Anti-angiogenic agents.

## INTRODUCTION

Astrocytomas are a type of neoplasm of the brain. They originate in a particular kind of glial-cells, star-shaped brain cells in the cerebrum called astrocytes. This type of tumor does not usually spread outside the brain and spinal cord and it does not usually affect other organs. Astrocytomas are the most common glioma and can occur in most parts of the brain and occasionally in the spinal cord. Within the astrocytomas, there are two broad classes recognized in literature, those with:

Narrow zones of infiltration (mostly invasive tumors; e.g., pilocytic astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma), that often are clearly outlined on diagnostic images

Diffuse zones of infiltration (e.g., low-grade astrocytoma, anaplastic astrocytoma, glioblastoma), that share various features, including the ability to arise at any location in the CNS, but with a preference for the cerebral hemispheres; they occur usually in adults; and an intrinsic tendency to progress to more advanced grades.[1]

Astrocytoma can occur throughout the CNS, including the following places:

1. Cerebellum (the back part of the brain responsible for co-ordination & balancing).
2. Cerebrum (the top part of the brain controls motor activities & talking).
3. Di-encephalon or central part of the brain (control vision, hormone production & leg movement).
4. Brainstem (controls eye & facial movements, arm & leg movements & breathing).
5. Spinal cord (controls sensation & arm & leg motor function).

Astrocytoma are of two main types- high grade & low grade. High grade tumors grow rapidly & can easily spread through the brain. Low grade astrocytoma are usually localized & grow slowly over a long period of time. High grade tumors are much more aggressive & require very intensive therapy. The majority of astrocytoma tumors in children are low grade where as the majority in adults are high grade. These tumors can occurs anywhere in the brain & spinal cord. Common sites in children are cerebellum (the area just above the back of the neck), cerebral hemispheres (the top part of the brain) & the thalamus or hypothalamus (located in the center of the brain).

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*Some of the more common low grade astrocytoma are:*
1.    Juvenile pilocytic  astrocytoma (JPA).
2.    Fibrillary astrocytoma.
3.    Pleomorphic  xantroastrocytoma (PXA).
4.    Desembryoplastic    neuroepithelial    tumor (DNET).

*The two most common high grade astrocytoma are:*
1. Anaplastic -astrocytoma  (AA).
2. Glioblastoma multiforme (GBM).

Astrocytoma are the most common of the primary brain tumors. The pathologist, using a microscope, grades this tumors on a scale of I to IV based on how quickly the cells are reproducing, as well as their potential to invade nearby tissue. Grade IV astrocytoma also called glioblastoma multiforme, are the most aggressive of the astrocytomas. Glioblastoma cells reproduce rapidly. Grade III astrocytoma also known as anaplastic astrocytomas, reproduce at an intermediate rate.  Grade I & II astrocytoma are the slowest growing tumors & are also called low grade astrocytomas.
An astrocytoma is one of several different types of brain tumour that may affect children. Brain tumours are caused by cells growing and multiplying in an uncontrolled way to form an abnormal lump. This happens because the DNA, which programmes how cells behave, changes. The cells that form an astrocytoma are star-shaped and called 'astrocytes'. Astrocytes are one of a group of cells known as 'glial' cells, whose function is to support and feed other brain cells. So, an astrocytoma is sometimes called a 'glioma'. Astrocytomas often contain a fluid-filled cyst rather than being solid tissue.
An astrocytoma can develop in any area of the brain and sometimes in the spinal cord. For instance, when the tumour grows in the cerebellum (Childhood brain and spinal tumours), it is called a 'cerebellar astrocytoma' or 'posterior fossa astrocytoma'. Astrocytomas are sometimes further classified, so they may be called 'juvenile cerebellar astrocytoma', 'piloycytic astrocytoma' or 'low grade astrocytoma'. They may also be graded, with grade 1 or 2 being benign and grade 3 or 4 being malignant.
Sign & Symptoms

**Low-grade astrocytomas** (LGAs):
•    Generally present with a long history of signs and symptoms
•    Often non-specific and non-localizing initially
*School age children may present with:*
•    Personality changes

•    Declining academic performance
•    Fatigue
•    Intermittent headaches related to increased intracranial pressure (ICP)
     **High grade astrocytomas** generally have a much shorter history of these problems prior to presentation.

**Raised Intracranial Pressure**
*Three symptoms and signs (RED flags) for increased ICP may also develop:*

1. Headaches:
•    Severe, progressive
•    Awaken the child at night
•    Associated with or relieved by morning vomiting
•    Worse first thing in the morning and when the patient coughs.
2.  Abducens (cranial nerve VI) palsy "False localizing" sign:
•    Due to effect of increased ICP on the course of CNVI
•    This nerve has a long intracranial course up the clivus and is easily affected by pressure.

**Papilledema:**
This is optic disc (optic nerve head) swelling secondary to raised intracranial pressure Results from long-standing increased ICP. Appearance on retinal examination:
•    Optic disc is swollen and elevated
•    There is venous engorgement (hyperemia) of the disc
•    Indistinct, blurred disc margin
•    Venous congestion develops with hemorrhages around the disc.
•    Spontaneous venous pulsations are lost

There is classically no visual loss secondary to papilledema.

**Cushing's Triad:**
*The combination of these three physical signs means that the raised intracranial pressure is very severe and there is impending brainstem herniation:*
**1. Abnormal respirations**
Change in respiratory pattern with irregular respirations

**2. Hypertension**
Progressively increasing systolic blood pressure
An increase in the difference between systolic and
diastolic pressure over time          **53**

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**3. Bradycardia**
**Infant Presentation:**
*Infants with astrocytoma often present with non-specific problems such as:*
- Irritability
- Feeding difficulties
- Failure to thrive
- Gross motor delay or regression
- Increasing head circumference, bulging fontanelles and prominent scalp veins
- Parinaud's syndrome.

**Parinaud's syndrome:**
*Physical findings are related to increased ICP in the dorsal midbrain:*
- Paralysis of up gaze
- This vertical palsy is supranuclear, so a doll's head maneuver may elevate the eyes, but eventually all upward gaze mechanisms fail
- Pseudo-Argyll Robertson pupils
- Pupils respond poorly to light but will constrict with accommodation
- Nystagmus
- Attempts at upward gaze often produce this phenomenon
- Upper eyelid retraction (Collier's sign)

Parinaud's may be associated with cranial nerve IV palsy, resulting in "down and out" deviation of the affected eye and often accompanied by a compensatory **head tilt** to the contralateral side.
*As the tumor progresses, symptoms may relate directly to areas of brain involvement:*
- Posterior fossa lesions are associated with:
- Ataxia
- Clumsiness
- Intention tremor
- Hemispheric tumors involving the motor cortex may cause:
- Focal motor deficits
- Seizures
- Astrocytomas of the visual pathway often cause:
- Visual deficits

**Pathophysiology**
Astrocytoma causes regional effects of astrocytomas by compression, invasion, and destruction of brain parenchyma, arterial and venous hypoxia, competition for nutrients, release of metabolic end products (e.g., free radicals, altered electrolytes, neurotransmitters), and release and recruitment of cellular mediators (e.g., cytokines) that disrupt normal parenchymal function. Secondary clinical sequelae may be caused by elevated intracranial pressure (ICP) attributable to direct mass effect, increased blood volume, or increased cerebrospinal fluid (CSF) volume.

Neurological signs & symptoms attributable to astrocytomas result from perturbation of CNS function. Focal neurological deflects (e.g. weakness, paralysis, sensory deflects, cranial nerve palsies) & seizures of various characteristics may permit localization of lesions.

Infiltration low grade astrocytomas grow slowly compared to their malignant counter parts. Doubling time for low grade astrocytomas is estimated at 4 times that of anaplastic astrocytomas. Several years often intervene between the initial symptoms & the establishment of a diagnosis of low grade astrocytoma. One recent series estimated the interval to be approximately 3.5yrs. The clinical course is marked by a gradual deterioration in half of cases, a stepwise decline in one third of cases & a sudden deterioration in 15% cases. Seizures often generalized are the initial presenting symptom in about half of patients with low grade astrocytoma for patients with anaplastic astrocytomas[2], the growth rate & interval between onset of symptoms & diagnosis is intermediate between low grade astrocytomas & glioblastomas. Although highly variable, a mean interval of approximately 1.5-2 years between onset of symptoms & diagnosis is frequently reported. Compared to low grade lesions, seizures are less common among patients with anaplastic astrocytomas. Initial presenting symptoms most commonly are headache, depressed mental status & focal neurological deficits.

CAUSE:- The cause of an astrocytoma tumor is not known.

**Diagnosis**
A physical exam by a neurologists assist in evaluating the symptoms. The physical examination includes testing for hearing, vision, reflex & balances. The result of the physical exam determine the next step for diagnosis. If required for diagnosis, a CT Scan or MRI allows the neurologist to view the soft tissue in the head. These tools assist with locating the tumor. A biopsy is generally required once a tumor is found through imaging. The biopsy removes a portion of the tumor to evaluate the type of cancer present & assist the physician in choosing the best treatment type. In rare cases where these examination are inconclusive, the fluid of the brain & spinal cord is evaluated.

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**Treatment**
Surgery is often the treatment of choice. Total resection is often possible; however, the location could prohibited access to the neoplasm & lead to incomplete or no resection at all. Removal of the tumor will generally allow functional survival for many years. The 5yrs survival has been reported to be over 90% with well resected tumors. In particular for pilocytic astrocytomas (that are commonly indolent bodies that may permit normal neurological function). Surgeons may decide to monitor the neoplasm evolution & postpone surgical intervention for some time. However, left unatteneded these tumors may eventually undergo neoplastic transformation. Ultrasonic aspiration as a minimal invasive technique for solid neoplasm. Because of the age of people diagnosed with pilocytic astrocytoma, the treating medical team will often try to avoid radiotherapy & chemotherapy in order avoid damage to the developing brain. There is evidence in literature to suggest that the careful use of chemotherapy and/or radiation therapy may be useful as a complementary treatment in case of incompletely resection of the neoplasm.

Successful treatment depends on –
…….The grade of Patients  brain tumor.
…….How much of the tumor surgeon can remove.
…….Where is the brain the tumor is.
……Patients age-treatment for children may differ & they usually have a better outlook.

**Surgery**
Tumors may be surgically removed by the open-skull procedure called craniotomy. When a patient presents with symptoms that are either life-threatening or significantly affect the quality of life, a craniotomy is usually the first treatment offered. Even partial surgical removal may alleviate symptoms and facilitate treatment of the rest of the tumor. A tumor may not be surgically removed if it is in an inaccessible location or too near to critical structures, meaning that the removal of the tumor might further cause great damage to other areas of the brain. Also, surgery may not be performed if the patient is not healthy enough to tolerate the surgery.
Surgical biopsies of brain tumors are no longer considered absolutely necessary because of the development of new imaging techniques. With the current scanning ability with contrast dyes, CT and MRI scans, a brain tumor may be diagnosed as malignant or benign without opening the skull for a biopsy. There has always been controversy over whether the act of obtaining a biopsy may allow the spreads of cancerous cells to other brain areas.
When surgery is required, a high-powered microscope may be used during the operation. This is called microsurgery. The surgeon uses the microscope to magnify the surgical field. Newer technologies, including intraoperative neuronavigation, allow the surgeon to visualize the extent of tumor resection on a computer screen during the operation. This enables the surgeon to be more aggressive with tumor removal while avoiding damage to surrounding critical structures. Intraoperative CT and MRI scan capabilities are also available in some centers.

**Ultrasonic Aspiration and Polymer Wafers**:
Instead of using a scalpel to remove a brain tumor, ultrasonic aspiration may be used. Ultrasonic waves fragment the tumor, and the fragments are removed by suction. After a tumor has been surgically removed by any method, BCNU polymer wafer implants may be inserted at the tumor site. These wafers are biodegradable and release chemotherapeutic agents over time

**Stereotactic Radiosurgery:**
Stereotactic radiosurgery is a one-session non-invasive treatment directed by a neurosurgeon. The most common type of neurosurgical radiosurgery is performed with the Gamma KnifeÒ instrument. During treatment many beams of cobalt60 radiation enter the brain at different sites, precisely targeted to a focal point within the brain corresponding to the tumor location to act like a scalpel. Individually, these beams are too weak to damage tissue, so normal tissue is not damaged. However, where the radiation beams converge within the tumor - tumor cells are damaged and will lose the ability to reproduce and perform other cellular activity.
There is a limit to the size of a tumor that can be treated with this method, which is generally around 4 cm. Radiosurgery provides a precisely targeted high radiation dosage to the tumor area with very little overlap to healthy tissue. Therefore, multi-session radiotherapy may be required for malignant brain tumors that have 'tentacles' which have invaded the brain.
Stereotactic radiosurgery is used on benign, malignant and metastatic (seeded from body cancers) brain tumors. Radiosurgery may be the primary treatment if the patient is not highly symptomatic and does not require open-skull surgery. It is frequently used in combination with conventional fractionated radiation (radiotherapy) as well                    **.55**

Radiosurgery may be a secondary treatment after conventional surgery that reduced the original tumor or surgery that was performed conservatively so that the healthy brain was not injured. In these cases radiosurgery acts as a 'boost' to assist in killing any malignant cells that may be left in the tumor bed.

**Radiotherapy**:
Radiotherapy may be used to treat a brain tumor. This treatment is usually directed by a radiation oncologist using one of many types of linear accelerators machines. Radiotherapy is not a one-session treatment like radiosurgery but occurs over time. The dosage of radiation is not as high as with radiosurgery, and the targeting is not as precise as with radiosurgery. Normal cells may be damaged by this treatment, as the targeting of radiotherapy machines is not as precise as the cobalt machines, such as Gamma Knife. Intensity modulated radiation therapy (IMRT) is one form of radiotherapy that patients may hear about.

With radiotherapy, the treatment is given over time, to allow the normal cells time to heal from the radiation. Radiotherapy may be used to kill remaining tumor cells after a surgical resection, or for tumors that are very responsive to this treatment. It may also be used for larger tumors that are unacceptable for radiosurgery. In some cases radiotherapy is used after a patient has had open-skull surgery and radiosurgery. Radiotherapy may be especially effective for the spreading areas of the tumors that are invading healthy tissue.

With conventional daily-fractionated radiation therapy, the common short term side effect (which occurs in days to weeks) are fatigue, loss of appetite & nausea. Skin rashes & hair loss often also occur over substantial regions of scalp. Delayed side effects (occurring within months to year) can include varying degrees of memory loss & imparement of reasoning or thinking. More rarely, patients can experience impairement of pituitary function or radiation necrosis (a collection of dead tumor cell & scar tissue). Radiation necrosis can produce symptoms that are often very similar to the initial tumor presentation & includes severe headache, motor weakness, visual problems or seizures.

**Chemotherapy:**
Chemotherapy treatment uses medicine to weaken & destroy cancer cells in the body, including cells at the original cancer site & any cancer cells that may have spread to another part of the body. Chemotherapy, often shortened to just "Chemo", is a systemic therapy, which means it affects the whole body by going through the blood stream. There are quite a few chemotherapy medicine. In many cases a combination of two or more medicine will be used as chemotherapy treatment for breast cancer.

## STANDARD CYTOTOXIC THERAPY

**Agent Classes**
**NITROSOUREAS**
Nitrosoureas are the most frequently used and the most studied agents in the treatment of malignant astrocytomas. They produce their cytotoxic effect by methylation of DNA mainly at the O6 position of guanine, a mechanism of action shared by all the alkylating agents. The interest in these agents comes from their important liposolubility, which enables them to effectively cross the blood-brain barrier to interact with the tumor cells. Nitrosoureas toxicity consists mostly in myelosupression, gastro-intestinal effects, cumulative nephrotoxicity and pulmonary fibrosis.

**PCV**
Combination regimens were designed to increase the efficacy of the nitrosoureas. The most notable of these is the PCV regimen, consisting of procarbazine, CCNU and vincristine, which was designed by Levin *et al.* [3] Moreover, the anaplastic glioma group comprised patients with a heterogeneous mixture of tumor histology, including astrocytomas, oligodendrogliomas and oligo-astrocytomas. It is now well accepted that tumors displaying an oligodendroglial component are relatively chemosensitive compared to pure fibrillary astrocytomas, and that these different histologies should be analyzed separately in clinical trials.[4] A recently published by the Medical Research Council Brain Tumour Working Party reported no difference in overall survival for patients with high grade astrocytomas who either received radiotherapy alone (9.5 months) or radiotherapy followed by PCV therapy (10 months), after diagnosis.[5]

**Platinum salts**
Platinum salts are broad-spectrum alkylating agents composed of a central platinum atom attached to two ammonia groups and one or more leaving groups, which confer its properties to the molecule.[6],[7],[8] The most widely used agents in this category are cisplatin and carboplatin. Platinum derivatives have mainly been tested in a rescue setting for malignant astrocytomas, when progression occurs after standard treatment.[9],[10],[11] Most investigators have administered carboplatin, but trials of cisplatin have generated similar results.[12] Few investigators have

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studied platinum salts in an adjuvant setting. One such study was published in 1996 by Lunardi et al. [13] These investigators compared carboplatin to BCNU following resection and irradiation of malignant gliomas. Newer platinum derivatives with activity against tumors traditionally resistant to this class of agents are becoming available. Oxaliplatin is one such agent. Trials of oxaliplatin against colorectal tumors have generated enthusiastic results, and many phase II trials are presently underway to assess the effect of this compound against malignant astrocytomas.

## Temozolomide
Temozolomide (TMZ), an imidazotetrazine derivative, is one of the newer alkylating agents. One of its major advantages over other agents is its complete bioavailability after oral intake.[14],[15],[16] Moreover, it has a good blood-brain barrier penetration when compared to other agents (25% CSF:serum ratio). Main toxicity consists in thrombo-cytopenia, but nausea, fatigue, constipation and headache can also be encountered. Originally approved for use in patients with recurrent anaplastic astrocytomas, it has also recently been approved by the Food and Drug Administration for the treatment of newly diagnosed glioblastoma multiforme, administered concurrently with radiation therapy. The standard TMZ regimen consists of a daily dose of 200 mg/m2 for 5 consecutive days, repeated every 28 days.[14],[15],[16],[17],[18] For the treatment of GBM, the treatment protocol consists in a daily dose of 75 mg/m2 during the six weeks of radiation therapy, followed by the 5-day regimen over the following months. [19]

## Etoposide and topo-isomerase II inhibitors
Etoposide, an epipodophyllotoxin derivative, is the prototype and most commonly used topo-isomerase II inhibitor. Topo-isomerases are enzymes involved in creating temporary breaks in DNA strands to allow unfolding and uncoiling during the process of replication. In the presence of etoposide, the enzyme cannot detach itself from the DNA strand, which leads to replication of defective DNA and eventually, apoptosis[20],[21],[22]. Typically, it has been combined with platinum salts because of its demonstrated synergistic effect with these agents.[22] It is now well accepted that a prolonged schedule of administration for etoposide gives better response rates than standard schedule.[21],[22],[23] Investigators have tried many regimens of oral etoposide in recurrent glioma patients.[24],[25],[26]

## Topo-isomerase I inhibitors
Drugs that can inhibit topo-isomerase I have been developed based on an extract from the tree Camptotheca acuminata. Mechanism of action and toxicity are similar to topo-isomerase II inhibitors. Irinotecan and topotecan are the two drugs in this class that are currently available for clinical use. Both were tested in the setting of recurrent glioma patients. A recent study reported the use of topotecan concomitantly to radiation therapy in newly diagnosed GBM patients. [27]

## Taxanes derivatives
Paclitaxel and docetaxel are cytotoxic agents that cause microtubule polymerisation, thereby blocking the cell cycle transition from G2 to the M phase.[28], [29], [30] These drugs are usually administered i.v., and main toxicity consists in myelosuppression, mucositis, myopathy and peripheral neuropathy. [28], [29], [30] Dosage needs adjusting when patients also use anti-epileptic drugs, because these can lower serum taxane concentration by hepatic induction. [31]

## Anthracyclines
Anthracyclines, first isolated from fermentation products of Streptomyces peucetus, were originally developed to be used as antibacterial agents. [32], [33] These molecules exert their cytotoxic effect through different mechanisms. [32], [33] Intercalation between DNA bases and inhibition of topo-isomerase II are the main action of these drugs. However, they also produce inhibition of helicase, an enzyme which splits double-stranded DNA into single strands. Finally, these agents are anthraquinones, which confers them the capability of generating free radicals. This last property is responsible for the main toxicity of the anthracyclines, cumulative non reversible cardiotoxicity, which leads to chronic heart failure after prolonged courses of treatment. [32]Other important side effects include myelo-supression and mucositis. These agents are usually administered intravenously, and poorly penetrate the blood-brain barrier. [32]

## Delivery of cell cycle genes to block astrocytoma growth
Current therapies for astrocytoma are ineffective. Therefore, novel therapies that target specific difference between normal & malignant cells are urgently needed. Abnormalities of cell-cycle related genes are a common feature of cancer in general & astrocytic tumors in particular. The role of these

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proteins is to help to regulate cell proliferation, differentiation & apotosis. Restoring wild-type activity of critical regulators of the cell cycle to astrocytic tumors generally results in modification of the growth properties & often the viability, of the cancer cells. Transfer of p53 induces growth arrest & more importantly apotosis. Restoration of the Rb pathway results in either reversible growth arrest or senescence. Expression of E2F-1 induces transient increases of proliferation followed by massive apotosis. Over expression of MMAC/PTEN arrest cell cycle progression in $G_1$ & promotes anoikis. Current knowledge of the function of these cell cycle controllers can be used to design small peptide & drugs to induce cell cycle related anticancer effect. Inactivation of the p53 & Rb pathways in cancer cells is also being used to engineer mutant viruses that are able to replicate exclusively in cancer cells. [34]

**The role of Matrix Metalloproteinase inhibitors in progression of astrocytic tumors**
Since the discovery of MMPs in 1962 by gross & La pierre, these enzyme has attracted great interest among researchers for their involvement in various physiological & pathological events. However, only in the 1980's, MMPs were discovered to be involved in the development & progression of tumors, a function that is widely studied to this day. [35] The invasive properties of CNS tumors are of great clinical importance because they contribute to the aggressive behavior of these tumors. For reasons still not well classified yet, most primary neuro epithelial tumors do not evolve into metastatic disease. However, these tumors invade surrounding tissues, infiltrate their cells into normal tissue & (more rarely) spread along the neuro-axis into the CSF. The mechanism of astrocytic tumor invasion is a complex process in which tumor cells separate from the parenteral tumor & rejoin the ECM. This process is associated with an increase in cell motility & with the ability of tumor cells to hydrolyze proteins, carbohydrates & proteoglycans in the ECM. These cells perform this task through the excessive production of protease that modify the ECM, thus creating access to the surrounding tissues& promoting migration to other parts of the brain. [36] MMPs are among the protease that can degrade the ECM in the brain tissue. Classically MMPs are consider to be responsible for promoting tumor growth, while TIMPs are through to block the invasive ability of tumors. [37]High grade astrocytomas & meduloblastomas are neuro epithelial tumors of different cellular origins & are highly invasive.

A study by Jaalinoja et al. (2000) [38] demonstrated that the high expression of MMP-2 is a characteristic of highly malignant tumors & is associated with poor patient survival, similar data were also observed by kunishio [39] who used immune histochemistry analysis to show that MMP-2 & MMP-9 are not associated with increased aggressiveness in astrocytic tumors. Some observations suggest that over expression of MMP-9 increases the invasiveness of astrocytic tumors, making it a potential target for combating these neoplasms. Other authors, such as vince et al. (2001) [40] have found higher levels of expression of this galatinase in medulloblastomas than in glioblastoma. MMPs is more commonly found in areas of intensive proliferative activity, while MMP-9 is associated with sites of angiogenesis, a typical feature of the invasive of these tumors. Accordingly, MMPs play a critical role in the process of angiogenesis. MMPs both promote & inhibit angiogenesis. [41]
Arroyo et al. (2007) & Basile et al. (2007) demonstrated that MT-1-MMP plays a crucial role in angiogenesis & that this protein is usually hyper expressed at sites of non angiogenesis. [42], [43] High grade pilocytic astrocytoma have a significant level of vascularization. The over expression of MTI-MMP & its relationship with the aggressive behavior of tumors have also been described in soft tissue cancer[44] & more recently by in prostate tumors. [45]

**Angiogenesis Inhibitors**
Neoangiogenesis is characteristically an active process in malignant neoplasms and, as such, endothelial cells constitute an important part of the neoplastic bulk in high grade astrocytomas. This fact renders the endothelial cellular compartment an attractive target for antineoplastic treatment. Endothelial cells are a much more homogenous cellular population than malignant astrocytes, and are less subject to drug resistance. [46] Moreover, these cells are easily reached by drugs in the systemic circulation. There are many known endogenous pro-angiogenic factors, some of which are specific for this purpose, such as vascular endothelium growth factor (VEGF) & angiopoietin. Non-specific factors include primarily mediating cellular adhesion and migration. Over expression of many of these factors has been demonstrated in many subsets of malignant astrocytomas. [46], [47], [48], [49], [50] Endogenous inhibitors of angiogenesis have been characterized, and include platelet factor 4, thrombospondin, angiostatin and endostatin [46] Of those, angiostatin and endostatin have generated the most interest for

use in anticancer strategies. Angiostatin is a 38 kDa protein generated by the cleavage of a terminal fragment of plasminogen by elastase, and endostatin is a 22 kDa fragment derived from collagen XVIII. Recombinant forms of these molecules have been synthesized and have shown promising results in preclinical trials, with apoptosis induction and inhibition of proliferation in vitro [51] and regression of intracranial and subcutaneous gliomas in a mouse model. [52] Moreover, the combination of both molecules seems to be synergistic [53] as is their

combination with ionizing radiation. [54] Clinical studies are presently underway.

**CONCLUSION**
An awareness of existence astrocytoma is essential to facilitate an accurate diagnosis & to minimize possibility of mistaking it for a more aggressive fibrillary or anaplastic astrocytoma. Newer modalities help in diagonising this indolent tumor which is amenable to surgical cure.

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