



A Simplified Overview of the Current Non-Surgical Treatment of Brain Tumor Patients with Special Emphasis on Its Complications. A Much Needed Contemporary Review Especially for Neurosurgeons

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Abstract

Brain tumors are complex entities with facts as numerous as stars in our sky, uncountable. They exist and thus every treating physician and surgeon happens to come across it. We try to put major contemporary practices and facts in a single bucket from learned skills of neurology and oncology tradition and things we received as feedback from our patients in clinical settings. Purpose of this work is to refresh your knowledge and preparedness for seeing patients with brain cancer. Brain tumors are molecularly heterogeneous and their features depend upon size, site, and genetic make-up of tumor; aggressive growth, and adjacent structures. Complications and their management are very challenging. This article will comfortably sail you through various aspects of management of brain cancers.

Keywords: Brain tumor, Glioblastoma, Non surgical therapy, Complications

Running Title: current non-surgical treatment of brain tumor and its complications

Introduction

Brain Tumors are diverse special neoplasm's, distinct from other tumors of human body, due to their cellular origin, complexity, blood-brain barrier, confinement within sphere of skull and potential to encroach and damage important structures of brain. The presentation of brain tumor may be silent, subtle or bizarre. It is of prime importance for Neurologist, Neuro Surgeons and Oncologist to be prepared to tackle these effects in patients. This is a concise plain review for above health care providers who are involved in management of CNS (Central Nervous System) Neoplasm's. From

last two centuries, surgical removal of brain tumor was primary intervention, and so it is today. Surgery alone does not always suffice tumors of brain with malignant nature, because its neo plastic activities continue beyond excision. The very special character of brain neoplasm is recurrence and this led to development of other modalities of treatment: radiotherapy, chemotherapy, targeted therapy etc. There are special issues with each therapy. Here we delineate the adverse effects and long-term complications of non-surgical therapies. To understand this, we should follow classification of brain tumors.

Quick Response Code:



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Broadly brain tumors are grouped as *Primary* and *Metastatic*. American Association of Neurological Surgeons

WHO classification of Brain Neoplasm

It is much widely accepted based upon the character of tumor and different treatment options for individual group (Table 2 & Table 3).

Further Primary tumor is of glial and non-glial cells. Metastatic tumors are spread from other organs (Table 1).

Table 1: Difference between primary and secondary GBM (Glioblastoma Multiforme).

Primary GBM	Secondary GBM
>90% GBM are primary	Others are secondary
De novo GBM formation	Progression from LGG (Low Grade Glioma) to HGG (High Grade Glioma)
Younger patient (<40 years)	Older patients (>55 years)
Minimal duration from symptoms to diagnosis (3 months)	Indolent clinical course as tumor progress from low grade to high grade
EGFR amplification or over expression (>40%)	TP53 mutation (60%) in Secondary GBM
PTEN Deletion (15- 40%)	IDH1 and IDH2 mutation common in Grade II/III glioma
LOH of Chromosome 10q (80%)	1p19q codeletion seen in Oligodendroglioma progressing to GBM
>90% GBM are primary	Others are secondary
Life span 6-9 months	Life span 1-1.5 years

EGFR: Epidermal Growth Factor Receptor; PTEN: Phosphatase and Tens in homolog; IDH: Isocitrate dehydrogenase; LOH: Loss of heterozygosity

Table 2: Characteristics of various World Health Organization (WHO) grading of glioma.

WHO Grade	Survival in years	MRI characteristics	Histological hallmark
Grade I (Pilocytic Astrocytoma)	8-10	No mass effect, no enhancement	Cytological atypia present
Grade II (Diffuse Astrocytoma)	7-8	mass effect present, no enhancement	nuclear atypia present
Grade III (Anaplastic Astrocytoma)	2-3	Complex contrast enhancement	Anaplasia and mitotic activity
Grade IV (Glioblastoma)	1	Ring enhancement with necrotic center	Neovascularization and necrosis

MRI, Magnetic Resonance Imaging

Table 3: Clinical presentation of patient with CNS neoplasm.

<ul style="list-style-type: none"> ■ Headache ■ Decreased consciousness ■ Dysarthria/ speech problem ■ Hemiparesis/ hemiplegia 	<ul style="list-style-type: none"> ■ Vomiting ■ Seizure ■ Visual problems ■ Gait disturbances etc.
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The success of new drug and treatment methods are evaluated and explained in terms of overall survival (OS) and progression free survival (PFS) in relation to comparisons of time in months or weeks. But these measures do not include the quality of life and comorbidity a patient sustains between PFS and OS.¹ The initial clinical presentation (symptoms and signs) of brain tumor patient is important. More important is the sign, symptoms and adverse effects presented during initiation of any treatment, revising a chemotherapy plan, changing treatment modality and stopping the treatment. The treating Neuro surgeons, Neurologists and Oncologist should

be vigilant and be ready to deal with any unprecedented event. It means the doctor has to keep in mind chronologically all “disease and treatment” events of a brain tumor patient.

Methyl Guanine Methyl Transferase (MGMT), Isocitrate dehydrogenase-1 (IDH 1) mutation and 1p19q co-deletion tumor has good prognosis.² Patient’s age more than 40 years, poor performance score, tumor size ≥ 6 cm, prominent neurological deficit, tumor crossing midline of brain are to be remembered as poor prognostic factors (Figure 1).

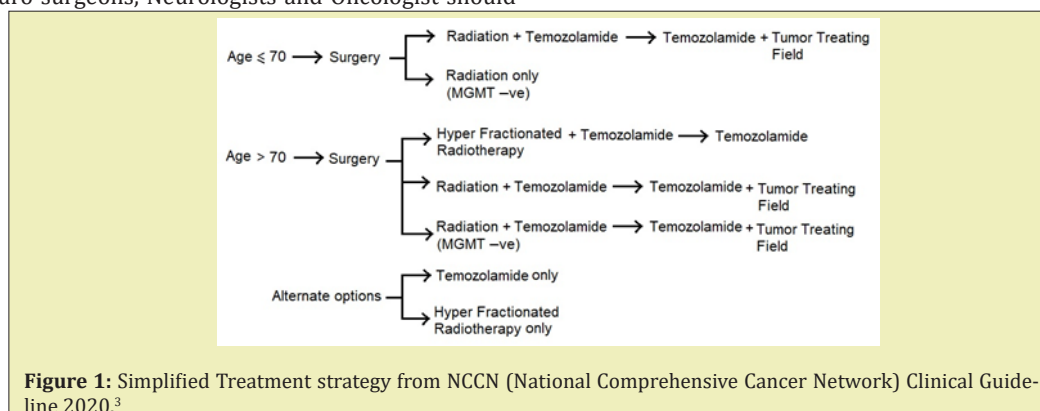


Figure 1: Simplified Treatment strategy from NCCN (National Comprehensive Cancer Network) Clinical Guideline 2020.³

Radiotherapy

Radiotherapy is important because it helps in controlling growth of tumor and improves survival duration. It has adverse effect of brain tissue necrosis. Generally, 56 to 60Gy is given. ('Gy' means 'Gray', a unit of quantification of radiation energy absorbed by 1 gram of body's tissue or mass. One Gray equals to 100 rads that is equivalent to 1Joule energy per kilogram. It has replaced the older measurement unit "rad").^{4,5} Radiation is applied in fractionated doses.⁶ Radiation induced brain damage is grouped as

Acute: within days to weeks

Early delayed: within weeks to months

Late delayed: within months to years.⁷

Acute and early delayed radiation injury: Acute and early delayed injury happens due to damage to endothelium and blood brain barrier. It results in edema. It is reversible and cures spontaneously.⁸

Patient presents with headache vomiting seizures and altered level of consciousness in acute phase. It will be difficult to distinguish between baseline vasogenic edema due to original tumor and radiation induced brain edema in early injury. In the early delayed injury, brain edema near the irradiated border may be accompanied by temporary demyelization. It appears as new area of enhancement, near the margin of tumor. Patient may present with focal neurological deficit.⁹ Late delayed radiation injury is caused by permanent damage to vascular and glial cells. Gliosis occurs resulting progressive white matter necrosis. Loss of brain matter is seen. Radiation induced micro angiopathy and vasculopathy can lead to carotid artery stenosis. Carotid artery stenosis is rare complication but it can occur in highly vascular tumor like Glioblastoma. Ischemic stroke is a common presentation in Carotid stenosis but an unsuspecting highly vascular glioblastoma may be underlying cause. Thus, we need to be careful while making diagnosis based on radiology scans (Figure 2).¹⁰

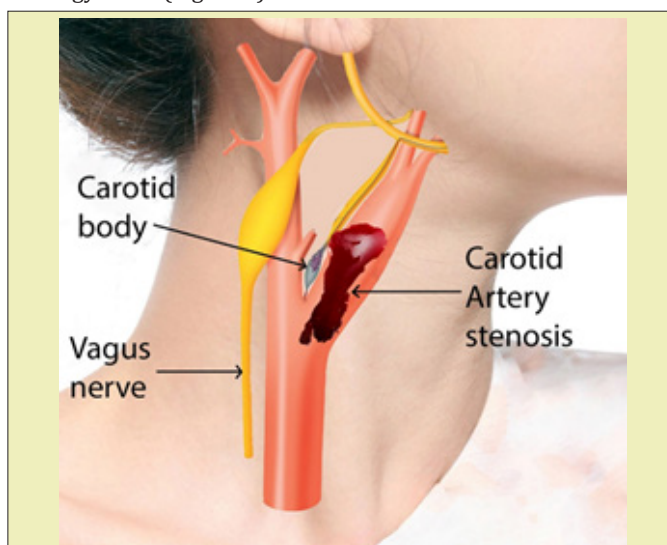


Figure 2: Carotid Artery Stenosis following whole brain radiation therapy.

Radiation induced leukoencephalopathy occurs due to injury to white matter of brain without direct necrosis. Mostly patient who receive whole brain irradiation show progressive leukoencephalopathy within 6 months.¹¹ Patient presents with deterioration of higher mental function after months though he may be asymptomatic initially (Figure 3). Sometimes treatment with anti VEGF (Vascular Endothelial Growth Factor) like Bevacizumab can lead to progressive multifocal leukoencephalopathy (PML). The image is confluent, symmetric and progressive in per ventricular white matter. It is difficult to identify this white matter changes.¹² Laser Interstitial Thermal Therapy (LITT) is a thermo-coagulative therapy in which an optical fiber is used to cause necrosis and death of tumor cells. It is a novel treatment for recurrent Glioblastoma. It has adverse effect such as seizure in less than 2% of patients and transient hemiparesis 1%. No mortality seen due to this treatment. It is one option for recurrent Glioblastoma and also primary disease. Chemotherapy is given after LITT treatment.¹³

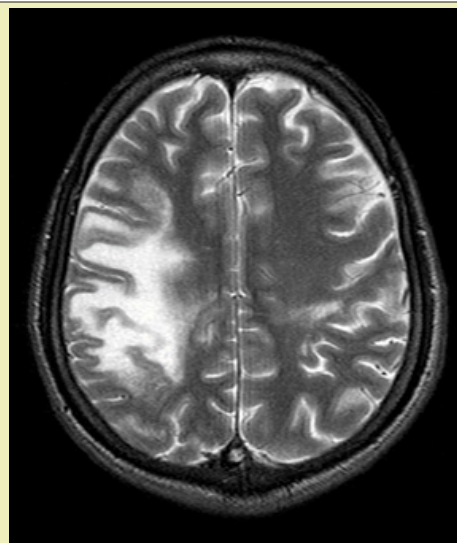


Figure 3: Progressive Multifocal Leukoencephalopathy following brain irradiation.

Chemotherapy

Temozolomide, an alkylating agent, is the standard chemotherapy currently used in treatment of Glioblastoma. The standard dose, dose dense and metronomic dose of Temozolomide, studied across by different researchers has mixed results. Dose dense Temozolomide has no significantly good prognosis than the standard dose. Few researches have shown metronomic regimen has better control of disease. Despite that, more than half of patients treated with Temozolomide have recurrence within 2 years. Common side effects of these drugs are alopecia, leucopenia, headache, vomiting etc.^{14,15} Side effects are waned off after discontinuation of treatment.

Chemotherapy has important role in brain tumors. A recent study conducted in Taiwan, concluded that the overall survival of patients, treated Bevacizumab (a monoclonal antibody) with chemotherapy Vincristine and low dose Carboplatin has significant overall survival as compared to those not treated with chemotherapy (p value=0.006). Vincristine is a anti angiogenic drug which is

effective in glioblastoma.¹⁶ It is also given in combination with Lomustine.

Bevacizumab is a VEGF inhibitor, an antineoplastic monoclonal antibody which neutralizes the VEGF expression in cancer cells. It is helpful because glioblastoma is tumor with rich angiogenesis, blood vessels and neovascularization. Bevacizumab targets blood supply of glioblastoma. Common serious side effects of bevacizumab are bleeding poor wound healing. Some of our patients has presented with oral ulcers, pain and mucositis in oral cavity. In our experience, these adverse effects are treated/ well controlled with local analgesic, ointment and chlorhexidine mouth gargle. Diarrhea, abdominal bloating and loss of appetite were seen. These adverse reactions disappeared within few days to a week as soon as the therapy was postponed.¹⁷

Immunotherapy

Nivolumab is an immune check point under investigation. It is tried in combination with radiotherapy and Temozolomide in Glioblastoma. Currently immunotherapy is not showing any promise for excellent results.¹⁸ Majority of glioblastoma has significant PDL 1 (Programmed Death Ligand-1) expression, which can be exploited for immunotherapy. Various clinical researches has indicated some benefit of these therapies, yet vast dimension needs be explored.¹⁹

Intracerebro ventricular chemotherapy

Intrathecal Cytarabine or Methotrexate and Prednisolone is administered for treatment of CNS Lymphoma via Ommaya reservoir. Usually complications like headache, vomiting, fever (due to local infection), meningeal signs, ventriculitis, meningitis, CSF (cerebrospinal fluid) leakage, and somnolence may occur. We should be fluent in management of this dangerous complication. Steroids, antibiotics and septic precautions should be considered with best supportive care. Methotrexate can cause seizure and acute ventriculitis when administered through intrathecal route.²⁰

Targeted therapy

Mammalian target of rapamycin (mTOR) inhibitor like Everolimus is approved for giant cell astrocytoma. Dose of Everolimus is decreased to alternate day if adverse drug reaction is seen. If symptoms increase then the drug can be held for a week. Commonly available medicine is used to treat adverse effects.²¹ Before introduction of targeted therapy, surgery was performed to majority of giant cell astrocytoma. Currently, we have option of targeted therapies for recurrent tumors. Stomatitis, infections, diarrhea, constipation anemia etc. are main adverse reaction of this drug.

Kinase inhibitor

Sorafenib is a multiple kinase inhibitor [Raf (Rapidly Accelerated Fibro sarcoma)/MEK (mitogen-activated protein kinase)/ERK (extracellular signal regulated kinase) and VEGF]. It is given twice a day; it has adverse events of skin and gastrointestinal toxicity. Sorafenib is an option of treatment, proven in clinical trials, when brain tumor is recurrent and patient cannot undergo repeated surgery or had already received brain irradiation. Common toxicities

of this drug can be minimized. Patient can have benefit with corticosteroid. It has a beneficial effect on sorafenib toxicities.²²

Hand foot syndrome

Hand foot syndrome a complication occurring in patients receiving chemotherapy and targeted therapy. An example of Sorafenib caused appearance of "Hand and Foot rash" within a week of beginning therapy (Figure 4). Characteristic tender, blanching hypopigmented rash also known as Bergdorf's syndrome or Palmar-plantar Erythro-dysesthesia syndrome. The novel treatment of brain tumor has tolerable and manageable adverse effects. Toxicities can be managed with supportive treatment and general medicine.²³



Figure 4: Hand Foot Syndrome in a recurrent meningioma patient.

Targeted Therapy

Cyclin D 4/6 kinase inhibitors

Abemaciclib or Palbociclib are suitable for treatment of metastatic brain tumors such as metastasis from breast cancer. May be used to treat primary brain tumor such as Glioblastoma to some extent. These inhibit CDK4 and CDK6 (cyclin dependent kinase). Addition of Abemaciclib to Temozolomide was beneficial in rat experiments. Abemaciclib can cross blood brain barrier effectively and inhibits Rb (Retinoblastoma) protein in early G1 phase restricting cancer growth. Abemaciclib at lower doses has better CNS levels compared to Palbociclib.²⁴ In our center, few patients receiving Palbociclib for metastatic brain cancer have reported of prolonged mild grade diarrhea, oral stomatitis loss of taste of food, for 3 to 4 weeks. Diarrhea was controlled using loperamide and oral mucositis was treated with oral analgesics, folic acid tablets and supplement vitamins. Few patients were advised to postpone treatment for a week. Their conditions improved quickly.

In radiological studies, Pseudo-progression mimics like a progression of disease. It looks like new enhancement and increase in size of treated brain tumor. Initially it looks like progression of tumor but decreases in size weeks later. This occurs after treatment with chemo radiation or Temozolomide.²⁵ In Pseudo-response phenomena it looks rapid decrease in enhancement within a recently treated brain tumor. But, T2 imaging shows flair hyper intensity. Thus, we should cautiously interpret post treatment imaging results.²⁶

Why it is important to follow up and test for therapy toxicity?

The rationale behind 3 weeks treatment and 1 week treatment free interval, and similar other chemo-planning, is for recovery from toxicity sustained by organs during days of active treatment.

It is time given for healing of normal structures. Because there is no standard protocol of chemotherapy for recurrent brain tumors at current time, different centers are undertaking clinical trials for search of more effective treatments (Table 4).²⁷

Table 4: Proposed simplified patient investigation record for neuro oncology patients.

Tests	Time	Evaluation	Time
Complete blood count with Differential count Platelet count	Base line before beginning treatment Then weekly for 1 month	Medical history	First time presentation
Liver function tests		Clinical Examination including skin, oral cavity, hand foot and ano-genital	Examined at each visit
Xray of Chest	Once Every 2 months	Neurological Examination	Examined at each visit
USG Abdomen	Once in Every 2 months	Performance score	Estimated at each visit
ECG	Monthly	Grading of clinical and hematological adverse effects/ results should be done National Cancer Institute Common Terminology Criteria for Adverse Events (CTACE)	Note down clinical in "Remarks" section of medical record assigned to specific date in chronological order.
Pregnancy test	As per sexual history of patient		
Computerized Tomography (CT) scan/ Magnetic Resonance Imaging (MRI) Brain/ Magnetic Resonance Spectroscopy (MRS)	(i) Before initiation of treatment. (ii) For evaluation in between cycles of treatment. (iii) After completion of treatment		

Prognostic Implications

Isocitrate dehydrogenase 1 (IDH1) positivity is hopeful report, one should explain to patient, the good survival outcome related to it. Researchers in this path have found that IDH 1 mutant tumors have survival up to 3 times more than that of Wild IDH mutants. Younger age, TP53 mutation and IDH1 positive result is positive prognostic factors for GBM patients.²⁸ Similarly, MGMT promoter methylation independent of IDH1 mutation has proven a powerful prognostic and predictive factor in glioblastomas patients.²⁹ Patients treated with Temozolomide with MGMT promoter has significant difference in survival, (increased overall survival) compared to those who received Temozolomide and radiation therapy but have no MGMT methylation.³⁰ Lower grade gliomas those which harbor

1p19q chromosome co-deletion and IDH 1 mutation have good prognosis compared to other types of gliomas. The co-deletion of 1p19q chromosome is more efficient in predicting good outcome than histological grading of brain tumor. IDH mutant tumors with no co-deletion of 1p19q chromosome have shorter overall survival.³¹ EGF Receptor expression is responsible for increased tumorigenicity via invasion and angiogenesis. It evades apoptosis. It confers bad prognosis in brain tumor. In one hand if EGFR promotes brain tumor, so do we have chances of treating CNS tumor by targeting EGFR points with targeted therapy? It is shown in recent research that EGFR mutation disappears after therapy and reappears after stopping therapy for brain tumor. Thus, taking advantage of EGFR mutation in context of brain tumors for treatment is controversial and debatable. More research is awaited in this arena (Table 5).³²

Table 5: Molecular markers commonly tested for glioma patients.

Specific molecular markers	Prognostic implications	Specific comments
IDH1 and IDH2 mutation	Protective factor	Longer survival (2 years)
IDH wild type	Risk factor	Life expectancy similar to GBM (1 year)
1p19q deletion	Protective factor	Longer PFS and OS, better response to chemotherapy
MGMT Methylation	Protective factor	Better response to Temozolomide
TP53 mutation	Risk factor	Progression to higher grade of glioma, seen in majority of secondary Glioblastoma
EGFR vIII amplification	Risk factor	Poor prognosis, but better response to Receptor Tyrosine Kinase inhibitors
PTEN mutation	Risk factor	Poor prognosis in pediatric Glioblastoma

Take away message for neurosurgeons and neurologists involved with neuro-oncology patients from Oncologist point of view

1. Malignant Glioma patients are heterogeneous genetically, even though they have similar histopathology.
2. Immunohistochemistry, epigenetic changes and molecular markers will soon take center stage in providing a tailor made, personalized treatment for patients with malignant glioma.
3. Request to Neuro- pathologist- Desired Molecular markers for
 - a) LGG- IDH mutation, 1p19q co-deletion.
 - b) HGG- MGMT methylation, EGFR vIII amplification/over expression, PTEN deletion, LOH of Chromosome 10

Special imaging tools in glioma diagnosis

- a) MR Spectroscopy
- b) MR Perfusion
- c) PET Scan
- d) SPECT(Single Photon Emission Computed Tomography) scan
- e) PET (Positron Emission Tomography) and SPECT scan merged with CT or MRI brain
- f) In general, above tests can give information regarding:
- g) Low grade glioma Vs High Grade Glioma
- h) Radiation induced necrosis Vs recurrence of tumor
- i) Localization of stereotactic biopsy site in case of intra-tumoral heterogeneity

Consequences of Long-Term Brain Cancer Survivors

Most patients present with chronic fatigue syndrome, stroke, leukoencephalopathy, deteriorating mental function. Hypopituitarism, hypogonadism and Adrenocorticotrophic hormone (ACTH) deficiency is also seen. Cerebral radiation necrosis, Strokelikemi-graine attacks after radiation therapy (SMART), Radiation induced optic neuropathy are long term outcomes. Impaired hearing-auditory nerve damage, Chemotherapy Induced Peripheral Neuropathies (CIPN), Secondary neoplasms are seen.³³ All of these patients should be given treatment, best support care, pain management. The long-term survival and complications depend on many factors. Genetic factors IDH mutations and MGMT promoter methylation are very important for long term survival.³⁴

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Conflicts of Interests

The authors declare no conflict of interest.

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