Modern Trends in Non-surgical Treatment of Brain Tumors

Essay Submitted For Partial Fulfillment of the Master Degree in

Neuropsychiatry

By

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Introduction

- **Brain tumors** are **the second** most common cause of death from neurological disease, after stroke.
- **Glioma** is the most common **primary** brain tumor.
- **Brain Metastasis** is the most common **intracranial tumor**, with estimated annual incidence of more than **100,000** cases.

- **In adults,** malignant astrocytoma and meningioma are the most common tumors.
- **In children,** low grade astrocytoma and medulloblastoma predominate.
- **Neurosurgery** showed limited success as a management of brain tumors.
- **Collected data** on symptoms before and after surgical resection report that **32%** had an improvement in their symptoms, **58–76%** were not different, and **9–26%** had a worsening in their symptoms.

Molecular Pathogenesis of Brain Tumors

- Genetic Alterations.
- Defects in Growth Factor Signaling.
- Pathogenesis of Brain Tumors Spread.
- Cell-Of-Origin of Brain Tumors.

Targeting Critical Points in Brain Tumors Pathogenesis

- Targeting Growth Factors and their Receptors.
- Targeting Downstream Intracellular Effector Molecules.
- Targeting Cancer Stem Cells.
- Targeting Tumor Spread.

Non-Surgical Treatments of Brain Tumors

- Immunotherapy.
- Anti-angiogenic Therapy.
- Stereotactic Radiosurgery.
- Chemotherapy.
- Endocrinal Therapy.
- Gene & Viral Based Therapies.

Immunotherapy

- **Passive immunotherapy:** giving **antibodies** or **toxins** to the patients without specifically inducing antitumor immune response.
- **Active immunotherapy*:*** immunization of the patients to induce specific antitumor immune response.
- **Adoptive immunotherapy:** expansion of sensitized immune cells outside the patients then introducing of these cells to the patients (not used nowadays).

Passive immunotherapy

- **Monoclonal Antibodies :**

  (1) Against epidermal growth factor receptor mutant variant III.

  (2) Against vascular endothelial growth factor such as Bevacizumab.

  (3) For delivery of Radionucleotides.

- **Immunotoxins:**

  Plant and bacterial toxins that are conjugated to either antibodies or peptide ligands. They are designed to selectively deliver these toxins to the tumors.

Active Immunotherapy

- **Peptide-Based Vaccines:** using

  (1) Epidermal growth factor receptors mutant variant III-specific peptide OR

  (2) Wilms' tumor peptide.

- **Dendritic Cell-Based Vaccines:** vaccination with patient dendritic cells that have been treated with various tumor components. It was helpful in overcoming chemotherapy resistance.

- **Viral Vaccination Strategies.**

- **Heat-Shock Protein Vaccine.**

Current Vaccines

- **CDX-110:** peptide-based vaccine that showed median survival exceeded 18 months.
- **DCVax:** autologous dendritic cell vaccine that showed evidence of antitumor response but no clinical response or survival benefit were found.
- **Oncophage:** heat-shock protein vaccine that showed evidence of a tumor-specific immune response correlating with favorable clinical response to therapy.
- **Poly-ICLC:** stimulates the immune system broadly. **66%** of patients showed objective response and the median survival for glioblastoma patients was 19 months.

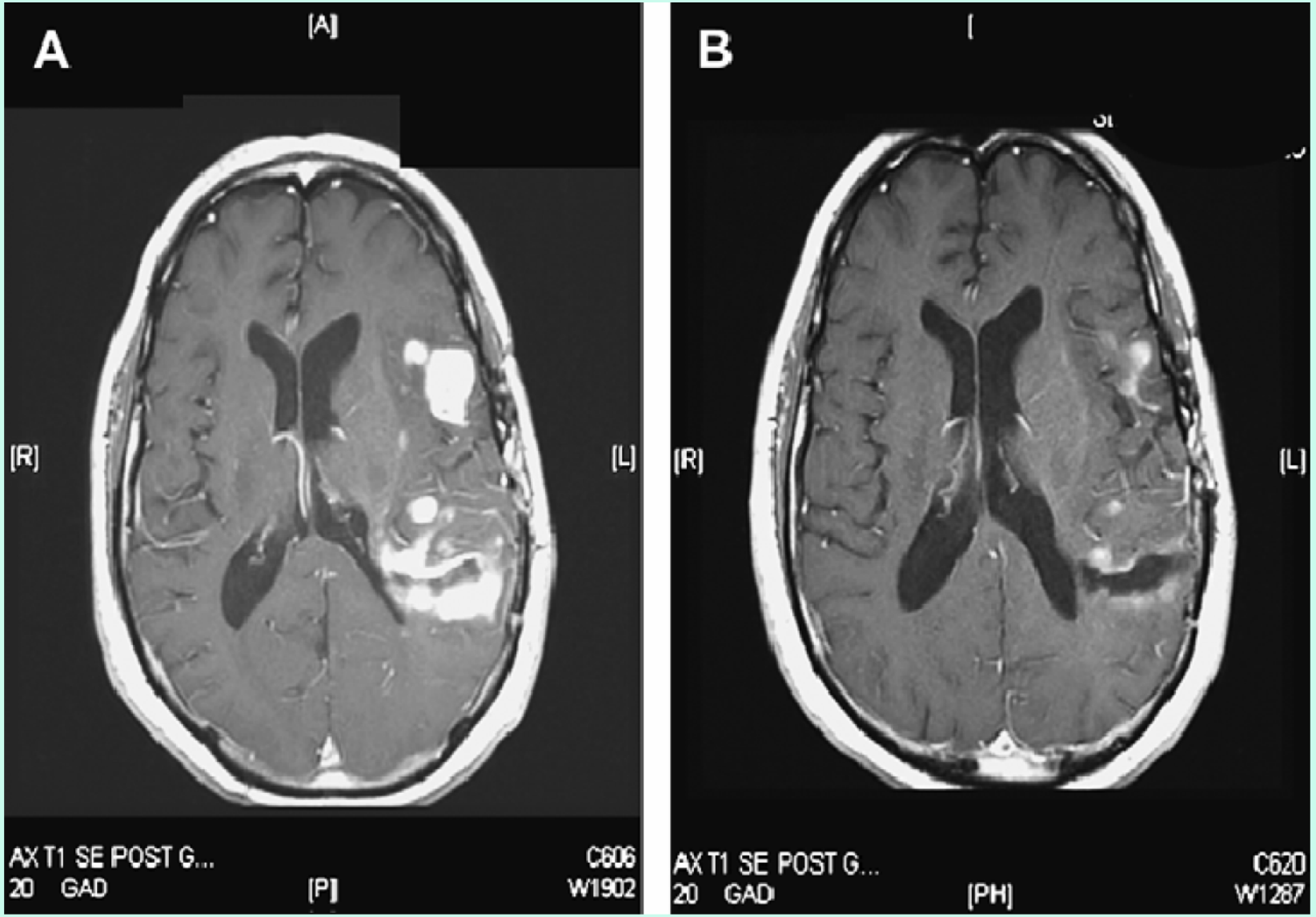
Anti-angiogenic Therapy

- **Vascular Endothelial Growth Factor Pathway Inhibitors:**
  - **(1) Ligand Inhibitors**
  - **(2) Receptor Inhibitors**
- **Non-Vascular Endothelial Growth Factor Pathway Inhibitors.**
- **Endothelial Cell Migration Inhibitors.**
- **Metronomic Chemotherapy.**

Vascular Endothelial Growth Factor Pathway Inhibitors

(1) Ligand Inhibitors: as **Bevacizumab & Aflibercept.**
High radiographic response & 6-month progression-free survival were observed with the combination of bevacizumab and conventional chemotherapy.

(2) Receptor Inhibitors: as **Cediranib & Vatalanib.**
They showed good radiographic response & powerful anti-edema effect.



Recurrent glioblastoma (A) treated with **bevacizumab** and **chemotherapy** (irinotecan) : showing marked reduction in enhancement after 4 weeks of therapy (B).

Non-Vascular Endothelial Growth Factor Pathway Inhibitors

- **Epidermal Growth Factor Receptor Inhibitors:** Gefitinib & Erlotinib.
- **Platelet Derived Growth Factor Receptor Inhibitors:** Imatinib & Dasatanib.
- **Fibroblast Growth Factor Inhibitors:** Thalidomide & Lenalidomide.
- **Protein Kinase C Inhibitors:** Enzastaurin.
- **COX-2 Inhibitor:** Celecoxib.

- **Endothelial Cell Migration Inhibitors:**

  Cilengitide showed 6-month progression-free survival in 65% of patients with good tumor penetration after intravenous administration.

- **Metronomic Chemotherapy:**

  It is a conventional chemotherapy administered at low doses. It targets mainly tumor vasculature and delays tumor growth.

Stereotactic Radiosurgery

- **Definition:** It refers to precisely localizing a target with application of ionizing radiation energy, aiming at accurate & complete destruction of this target, without significant concomitant or late radiation damage to adjacent tissues. The total dose of radiation is typically delivered in one fraction.

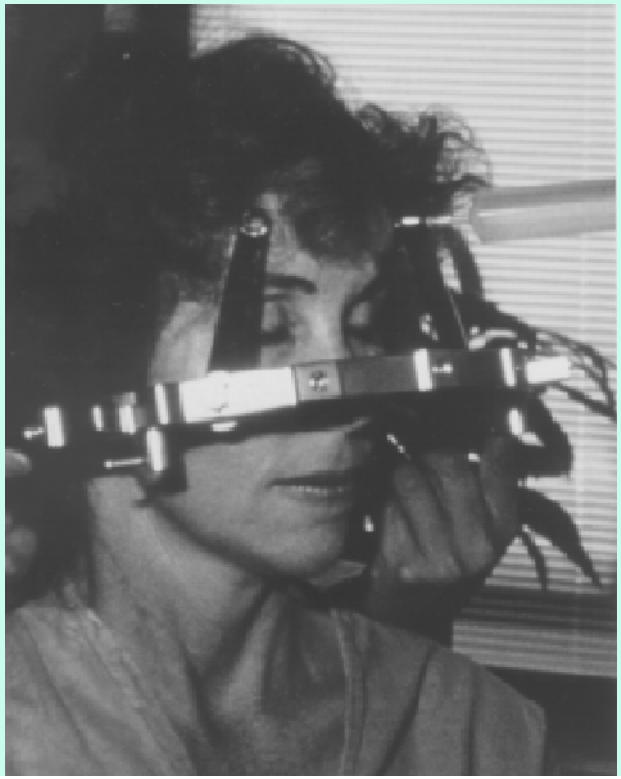
- **Performed by:**

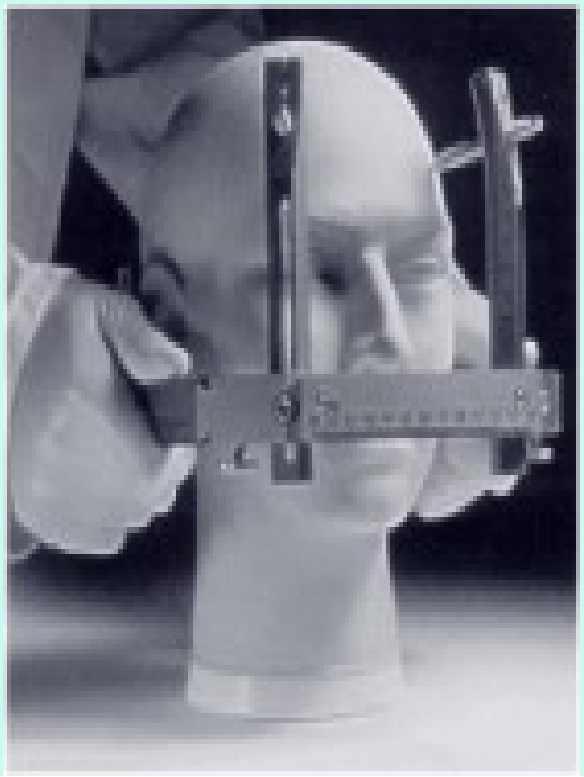
  (1) Gamma Knife.

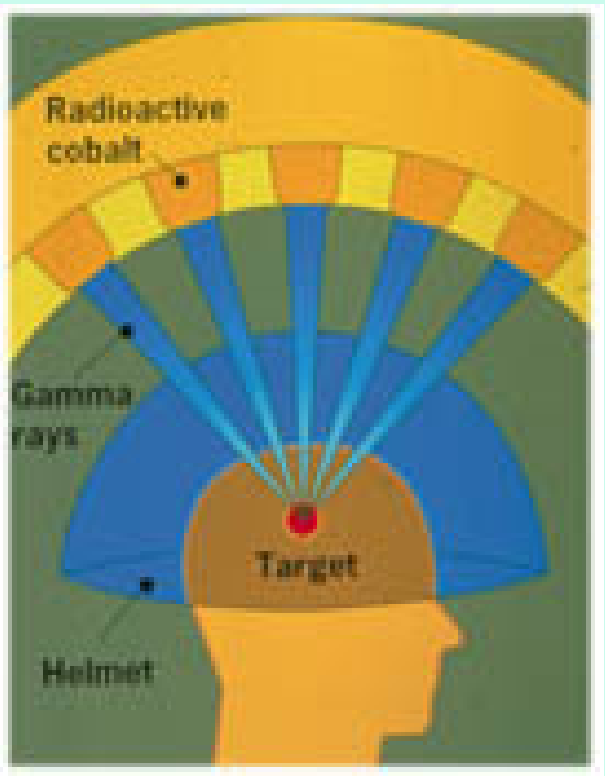
  (2) Linear accelerator system.

Gamma Knife

- **A head frame** is attached to the patient's skull and the patient is positioned within the helmet.
- **Inside the helmet,** multiple fixed cobalt sources are arranged to intersect at a given point.







In Gamma Knife

(1) There is a need to attach a frame to the skull.

(2) Limitation of use to lesions above foramen magnum.

(3) Inability to fractionate the dose.

Linear Accelerator Systems

(1) Linear Accelerator Scalpel®

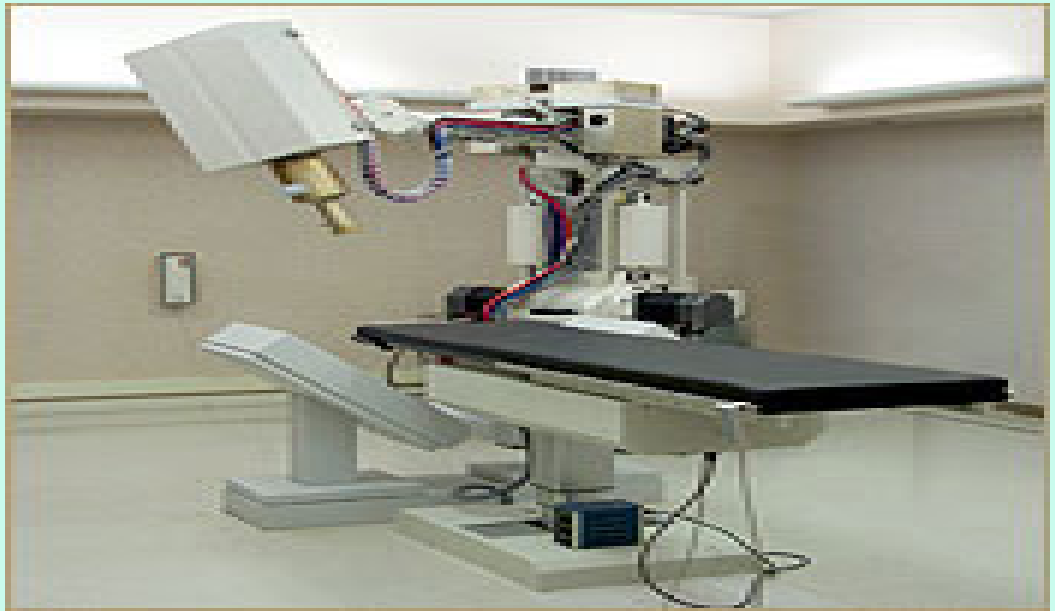
(2) Peacock System®

(3) Novalis®

(4) XKnife®

(5) CyberKnife®


Linac - from Varian product literature

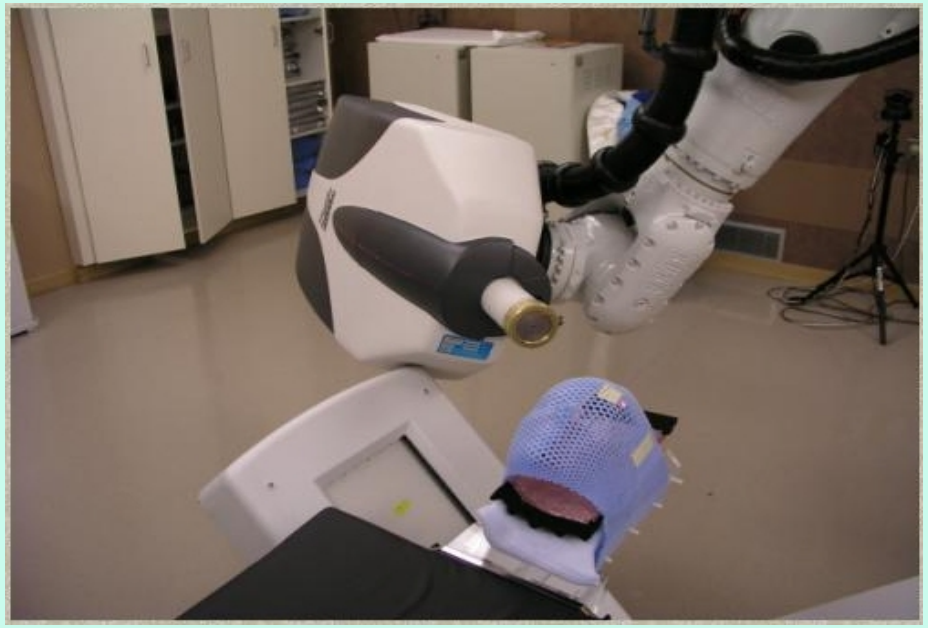


In Linear Accelerator system (CyberKnife)

(1) There is a need to put a mask on the skull.

(2) Used for lesions any where in the body.

(3) The dose can be fractionated.



Radiosurgery for Brain Metastasis

- Gamma Knife or CyperKnife is now being used in brain metastasis as:

  (A) A primary management OR

  (B) Booster treatment with whole brain radiation therapy.

- Although the size limitation on treatable lesions that preferred to be **< 4** cm, tumor control rates of **90%** can be expected if **1-4** lesions are irradiated with a peripheral dose of **20 Gy** or more. In such cases, true recurrence is rare.

Radiosurgery for Brain meningiomas

- Multiple studies demonstrated the efficacy and safety of stereotactic radiosurgery in treatment of meningiomas, with tumor control rates ranging from **60** to **100%** depending on the proportion of **atypical** or **malignant** meningiomas.
- Radiosurgery is considered as an effective management choice for patients with small to medium-sized, symptomatic, newly diagnosed or recurrent meningiomas.

- **Radiosurgery for pituitary adenomas:**

  Radiosurgery provides control of tumor growth in nearly all cases & hormonal normalization in the majority of secretory tumors.

- **Radiosurgery for brain gliomas:**

  It represents an alternative or supplementary modality to surgery in small-volume low-grade gliomas.

Chemotherapy

- Chemotherapy has played primarily an **adjuvant role** in treatment of brain tumors due to **efficacy limitations** related to drug-delivery issues & inherent tumor chemoresistance.

- Recent developments in chemotherapy of brain tumors include the combination of **cytotoxic**, **cytostatic** and **targeted therapies**.

Cytotoxic Chemotherapy

- **Nitrosureas:** were the mainstay of adjuvant therapy. They were used either **alone** as carmustine (BCNU) & lomustine (CCNU) or **in combination** with other agents as in PCV (procarbazine, CCNU & vincristine).

- **Nitrosurea-based chemotherapy:** after its addition to radiotherapy, it showed a modest but significant prolongation of survival. There was an absolute increase in 1-year survival of **6%** and in 2-year survival of **5%**.

- **Temozolomide:** is an oral alkylating agent that can cross the intact blood-brain barrier with excellent toxicity profile.

- **Temozolomide:** was **FDA** approved for treatment of recurrent anaplastic **astrocytoma** only, whereas the European authorities approved the drug for both anaplastic **astrocytoma** and **glioblastoma**.

- **Temozolomide's** approved schedule or standard regimen was a dose of **150– 200** mg/m2/day for **5** days of every **28**-day cycle.

- **Molecularly Targeted Therapy:**

  Trials of targeted drugs as monotherapy for gliomas were disappointing, with some potential benefit when used in combination with nitrosurea or temozolomide.

- **Combination of Cytotoxic Agents:**

  The best tolerated combination represented by carmustine (on day 1) followed by temozolomide (days 1–5). This combination showed promising activity. To avoid overlapping toxicities, the combination occurs between the locally administered carmustine (Gliadel Wafers) and temozolomide.

- **Concomitant chemo-radiotherapy** followed by single-agent adjuvant treatment with temozolomide was associated with a significant improvement in median survival and also it was well tolerated in all patients.

- **Concomitant chemo-radiotherapy** is the current standard of care for glioma patients, as well as the early introduction of chemotherapy appears to be the key to improve outcome.

Endocrinal Therapy

- Pituitary tumors represent about **15%** of the primary intracranial tumors and hormone-secreting tumors account for about **30%** of all pituitary tumors.
- The medical approach to pituitary adenomas has been greatly improved since the availability of **Dopamine agonists** such as: Bromocriptine, Cabergoline & Quinagolide, and availability of **Somatostatin analogues** such as: Lanreotide & Octreotide.

- **In Prolactinomas:**

  Bromocriptine is successful in **80–90%** of patients with microprolactinomas & in about **70%** of patients with macroprolactinomas.

  Cabergoline has a very rapid tumor shrinking effect. It is superior over bromocriptine and can be given to patients previously resistant to bromocriptine .

- **In Growth Hormone secreting adenomas:**
  Somatostatin analogues appear to be more effective. They showed tumor reduction in **45%** of patients.

- **In Thyroid Stimulating Hormone secreting adenomas:**
  Somatostatin analogues are only used in treatment.

Corticosteroids

- **Corticosteroids** are an established treatment for symptomatic relief of **brain edema.**
- **Dexamethasone** is used most commonly as it has little mineralocorticoid activity and lower risk for infection & cognitive impairment.
- **Corticosteroids** produce symptomatic improvement within **24** to **72** hours.

- **Generalized symptoms**, such as headache and lethargy, tend to respond better than focal ones.
- Improvement on **CT** and **MRI** often lags behind clinical improvement.
- **The usual starting dose** is a **10** mg load, followed by **16** mg /day in patients with significant edema. Lower doses may be effective, especially for less severe edema.
- **Side effects** of corticosteroids are dose-dependent, while the degree of **neurological improvement** is independent of the dose.

Gene & Viral Based Therapies

Five gene therapy approaches are currently being explored:

(1) Suicide gene therapy.

(2) Tumor suppressor gene therapy.

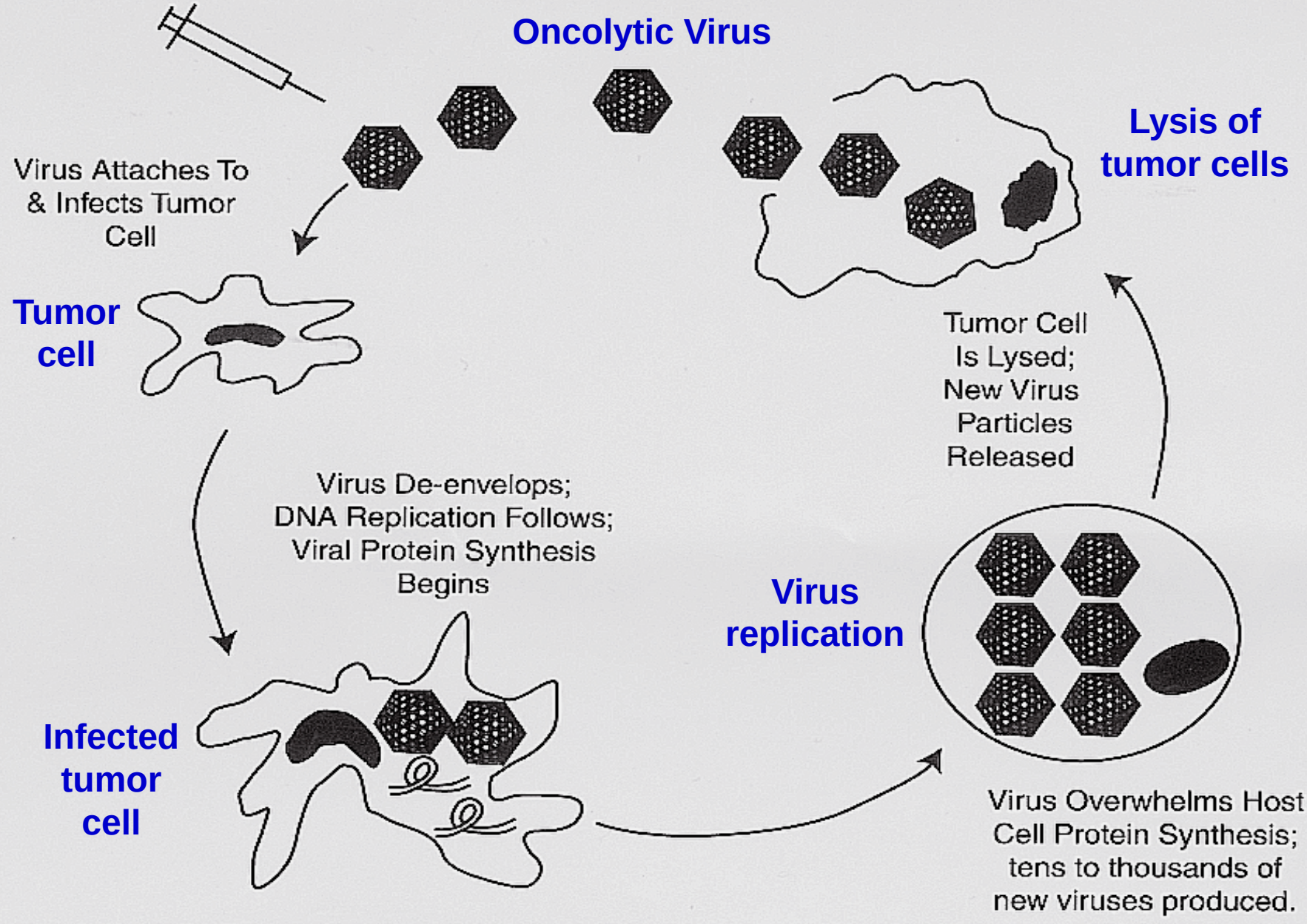
(3) Immunogene therapy.

(4) Anti-angiogenic gene therapy.

(5) Oncolytic virotherapy.

- **Suicide gene therapy** is the most commonly used technique. Preclinical studies showed marked tumor elimination. Tumor cells treated with this approach displayed enhanced sensitivity to radiation.
- **Tumor suppressor gene therapy** includes transfer of tumor suppressor genes as *p53* and cell-cycle modulators.
- **Immunogene therapy** aims at genetic immune modulation to enhance immune response against the tumor by expressing cytokines and lymphokines.
- **Anti-angiogenic gene therapy** aiming at reduction of expression of the pro-angiogenic factors.
- **Oncolytic Virotherapy** utilizes viruses that are engineered to selectively replicate in cancer cells killing them without affecting healthy cells.

Oncolytic Virotherapy



Finally

- There is no **magic bullet** for malignant brain tumors and clinical improvements will likely be due to the synergistic effects of a multi-targeted attack.
- Although preclinical data are promising, clinical trials have been delayed and all treatment modalities are still searching for a significant **survival benefit.**

Thank You