"RECENT ADVANCES IN THE TREATMENT OF PEDIATRIC BRAIN TUMOR"

A PROJECT SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

UNDER THE GUIDANCE OF

Guide: DR. Jigar N. Shah

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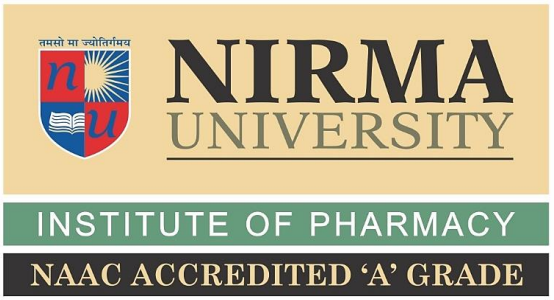

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MAY 2020

CERTIFICATE

This is to certify that ***"RECENT ADVANCES IN THE TREATMENT OF PEDIATRIC BRAIN TUMOR"*** *is the bonafide work carried out by* ***KACHHADIYA RAVIKUMAR*** *(16BPH082), B. Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019-2020. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work entitled ***"RECENT ADVANCES IN THE TREATMENT OF PEDIATRIC BRAIN TUMOR"*** *Submitted by* ***KACHHADIYA RAVIKUMAR*** *(16BPH082), B.Pharm. Semester VIII is a bonafide review work carried out by me at the Institute of Pharmacy, Nirma University under the guidance of "Jigar N. Shah" and "Snehal S. Patel". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review work carried out by me is not reported anywhere as per best of my Knowledge.*

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DECLARATION

*I, **KACHHADIYA RAVIKUMAR** (16BPH082), student of VIII[th] Semester of B. Pharm at Institute of Pharmacy, Nirma University, hereby declare that my project entitled **"RECENT ADVANCES IN THE TREATMENT OF PEDIATRIC BRAIN TUMOR"** is a result of culmination of my sincere efforts. I declare that the submitted project is done solely by me and to the best of my knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. I also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

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➢ ***ABSTRACT***

According to the observation, the study of disease transmission, and final products program the most common cause of cancer-related death in children are pediatric brain tumors. In the last few decades it have been seen that survival rate of these pediatric brain tumor's patient is increased 35% in 5 years and these is because of advances in treatment like surgical techniques, neuroimaging techniques which includes MRA, MSA , DSA and pet scan radiation therapy and by using this neuroimaging techniques and guided stereotactic surgery, advances in surgical resection leads to decrease the rate of morbidity. Advances in molecular targeted therapy and radiation therapy like fractionated stereotactic radiotherapy (SRT) and MRT also shows improvement in the decrease the rate of morbidity. Immunotherapy, convection enhanced delivery, and gene therapy like strategies and approaches are currently in clinical trials and which will help in future advances.[1][2][3][4]

➢ ***AIM***

- To collect overall data and information by studying different publication and articles, and to give review of "Recent advances in treatment of pediatric brain tumor"

➢ ***OBJECTIVE***

- Readers should be able to understand after reading this article based on following points:
- Basics of general anatomy of brain and pathophysiology of pediatric brain tumor.
- Justification regarding how of brain tumors classified according to their histology, location and degree of malignancy (who classification)
- Readers can recognize signs which represent the pediatric brain tumor.
- All over basic knowledge and understanding regarding paediatric brain tumor.
- Recent advancement in the treatment of pediatric brain tumor.

[1. INTRODUCTION]

1. INTRODUCTION

Pediatric brain tumors are masses of abnormal cells that generally occurs in the children which is the result of uncontrolled cell growth. As per the surveillance, epidemiology, and end results program the most normal reason for malignant growth-related passing in kids are pediatric brain tumors. Cancer is the 9th most common reason for the deaths in the children between 5 to 14 years of age in India. About 148000 cancers cases occurred in year of 2008 that is estimated in children aged 0–14 years in less-developed regions. The ratio of childhood cancers relative to all cancers reported by Indian cancer registries is varied from 0.5% to 3.4% in girls and 0.8% to 5.8% in boys in the united states primary malignant and non-malignant brain tumor's incidence rate found to be 5.67 per 100,000 person-years. [5][6][7][8]

On a different type of factors, in which location of the tumor, age of child, and growth rate of the tumor, signs and symptoms depend. Between ages 4 and 10 infratentorial Tumors are more common and Supratentorial tumors are most common in children and infants Up to 3 years of age and after age 10 again it is more common. The cause of pediatric brain tumors is unknown. The most common tumor types by age are shown in Figure.12 and 13. which is given by Central Brain Tumor Registry of the United States (CBTRUS) [9][10]

Survival rate of patient with pediatric brain tumor has improved notably in the last three decades because of recent advances in the treatment of pediatric brain tumors like neuroimaging, neurosurgical advances which include MRS, PET scan, fluorescence guided surgery, electrical corticography, magnetic resonance angiography (MRA), Digital subtraction angiography (DSA).

In radiation therapy stereotactic radiosurgery, intensity modulated radiation therapy (IMRT), 3-dimensional conformal radiation therapy (3D-CRT), and proton beam therapy, radio sensitizing agents. intensity modulated and 3-d conformal radiation therapy is more effective and safer which is resulted of advances in knowledge of molecular brain tumor and biology.

Recent advances like novel drug delivery system which include convection enhanced delivery, evaluation and use of biomarker for the optimal treatment of the patients. Very well-known recent drug therapies like treatment by immunotherapy, targeting immunoregulation, inhibition mechanism of blocking tumor cell (by blocking engaging process of PD-L1 with receptor on T cell (PD-1) it can be possible to keep the T-cell on and that can kill the tumor cell.), inhibition of various molecular pathway which play important role in tumor genesis, anti-angiogenic therapy, and gene therapy.[11][12]

Recent advances in therapeutic viruses like oncolytic viruses which can only reproduce within tumor which is present in brain and leaving normal cell which leads to tumor cell die.

Benefit of these development of new approach are to reducing toxicity of therapy as well as increasing the survival rate of the patient so that quality of life of patient will improve.

In this review some of the usual child brain tumors are reviewed in terms of overall classification, epidemiology and treatment and current advances in the treatment.

[2. ANATOMY OF BRAIN]

2. ANATOMY OF BRAIN

- Pediatric brain tumor are masses of abnormal cells that generally occurs in the children which is the result of the uncontrolled cell growth within the brain for general information basic anatomy of brain is given here.

- **There are 3 parts of the brain**
  a) Cerebral cortex (super tentorial) (above the tentorium)
  b) Tentorium
  c) Cerebellum (infratentorial) (below the tentorium) [13][14]

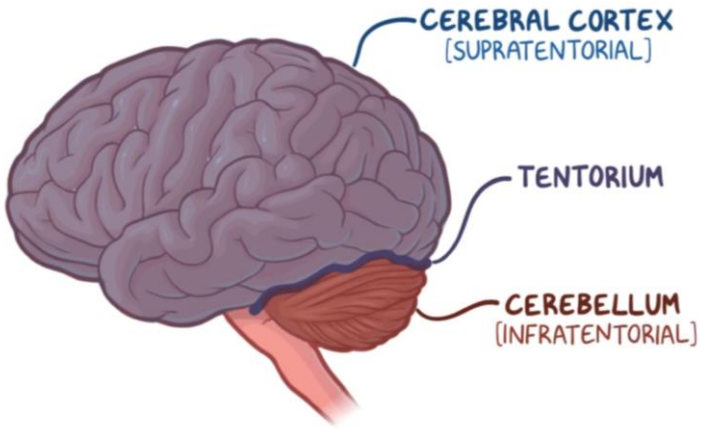


Fig. 1 Anatomy of Brain
Adopted from, JN Geed, JL Rapoport - Neuron, 2010

- **Ventricles**
  Brain has 4 inter connected cavity filled with cerebrospinal fluid which is known as ventricles which provides protection and buoyancy and metabolic fuel to the brain

- **Two "c" shaped lateral ventricles and 3rd ventricle**
  Two ventricles lie deep in each cerebral hemisphere. The 3rd ventricles which is narrow, funnel shaped cavity at the centre of the brain in which the 2 lateral ventricles drain their cerebrospinal fluid.

- **Cerebral Aqueduct**
  Via this cerebral aqueduct the 3rd ventricles make a little more cerebrospinal fluid and then sends it to the 4th ventricle.[1]

- **Fourth ventricle**

  A tent shaped cavity located between the brainstem and cerebellum which is known as 4th ventricle.

- **Subarachnoid Space**

  The cerebrospinal fluid enters the subarachnoid space after the 4th ventricle which is the space between the arachnoid and pia matter, 2 of the inner lining of the meninges. Which cover and protect both the spine and brain so this makes it possible for cerebrospinal fluid to also flow through the central canal of the spine. [13][14]

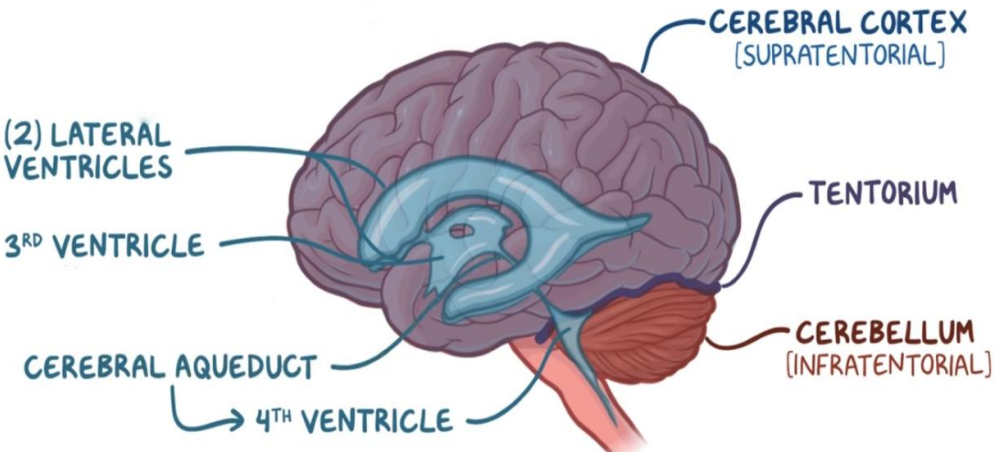


Fig. 2 Ventricles in the brain

Adopted from, JN Geed, JL Rapoport - Neuron, 2010

- **Cells within the brain**
  - There are many different types of cells which have specialized function E.g.,

- **Neuron**

  It communicates neurologic information through neurotransmitter which regulate electrical impulses.[1]

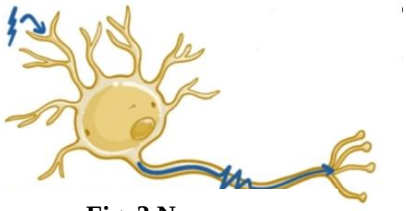


Fig. 3 Neuron

Adopted from, JN Geed, JL Rapoport - Neuron, 2010

- **Cells that secrete hormones**

  In the supratentorial pineal gland some cells are found which is located just behind the just 3rd ventricle or the infratentorial pituitary gland located near the front of the 3rd ventricle, which secrete hormones into circulation and regulate the functions of other cells throughout the body. [13][14]

Fig. 4 Cell that secrete hormone
Adopted from Eileen Daly, Veena Kumari *Brain*, Volume 125

- **Neuroglial Cells**
  - For help and support neuronal functions and brain homeostasis neuroglial cells are available in the brain. For e.g. Astrocytes.
  - **Astrocytes**
    - They have cellular processes in their cell body, so these processes give them star shaped appearance.
    - They are found throughout the brain and spinal cord and they have 3 main roles which are
      - It maintains blood brain barrier,
      - It provides nourishment to neurons
      - It recycles neurotransmitters. [1]

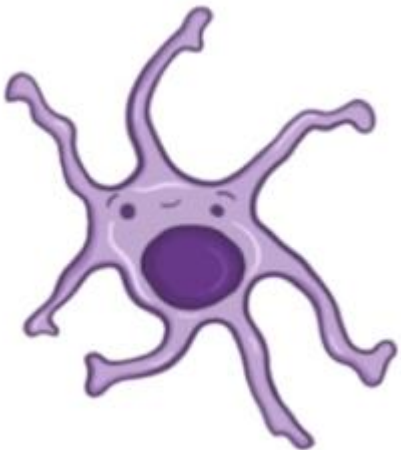


Fig. 5 Astrocytes
Adopted from Eileen Daly, Veena Kumari *Brain*, Volume 125

- **Ependymal cells**
  - They are also neuroglial cells
  - They are cuboidal to columnar, so square to rectangular shaped ependymal cells that line the ventricles and central canal.
  - Regulate the circulation of cerebrospinal fluid is the main role of ependymal cells. [13][14]

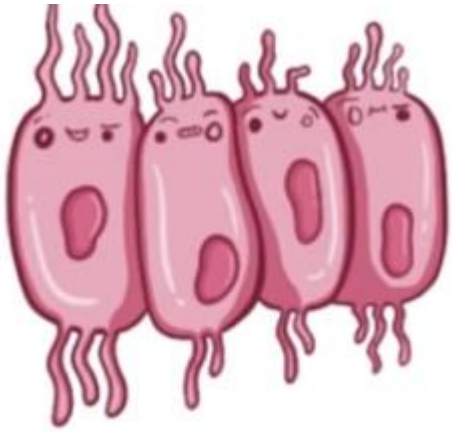


Fig. 6 Ependymal Cells

Adopted from Eileen Daly, Veena Kumari *Brain*, Volume 125

- **Embryonic stem cells**
  - Especially during injury Some brain cells have a limited ability to be replaced and they do it by having undifferentiated stem cells called embryonic stem cells,
  - Main role is to brain activate and mature into a specialized cell.[13][14]

Fig. 7 Embryonic Stem Cells

Adopted from JN Geed, JL Rapoport - Neuron, 2010

[3. PATHOPHYSIOLOGY]

3. ***PATHOPHYSIOLOGY***

- If there is a DNA mutation in any of described above cell types than tumor develops and that mutation leads to uncontrolled cell division.
    - **Mutation of proto oncogenes (accelerator)**
      Typically, this result in to the promotion of cell division
    - **Mutation of tumor suppressor genes (brake)**
      Typically, this results in to the loss of inhibition of cell division

- If an inability to brake this or too much acceleration is there than it can lead to more and more rapidly cell division and that will result into a mutated cell are start piling on each other and it becomes tumor lump or mass. In this result few of these tumor are benign and malignant tumor.
    - Benign (stay well contained or localized)
    - Malignant tumor (cancers)
        - Malignant tumors are also known as cancer tumor which break through the basement membrane and occupy nearby tissue.

- **Metastasis**
    - Malignant tumor cells can go into near around blood or lymph vessels and by circulation it can go from the essential primary site to the establish secondary site of tumor and grow anywhere in the body which is known as metastasis. [15]

- **Hydrocephalus**
    - Tumor prevents the normal circulation of the fluid in the brain to outside the brain and because of this fluid builds up in the normal fluid space in the brain which can cause pressure which is known as hydrocephalus or water in the brain. [13][14]

- How tumor is occurs due to long term chemical and radiation exposure in the child brain is given in the chart.
- Step by step process is given below. [13][14][15]

Due to chemical and radiation exposure.

⇩

Due to this, irritation and damage is happened in the cell structure

⇩

Changes in cell's morphology

⇩

If the radiation exposure continues, change in cell structure become irreversible and which cause genetic mutation.

⇩

Inactivation of tumor suppressor gene and activation of oncogenes

⇩

Uncontrolled cell division

⇩

Hyperplasia of brain cell

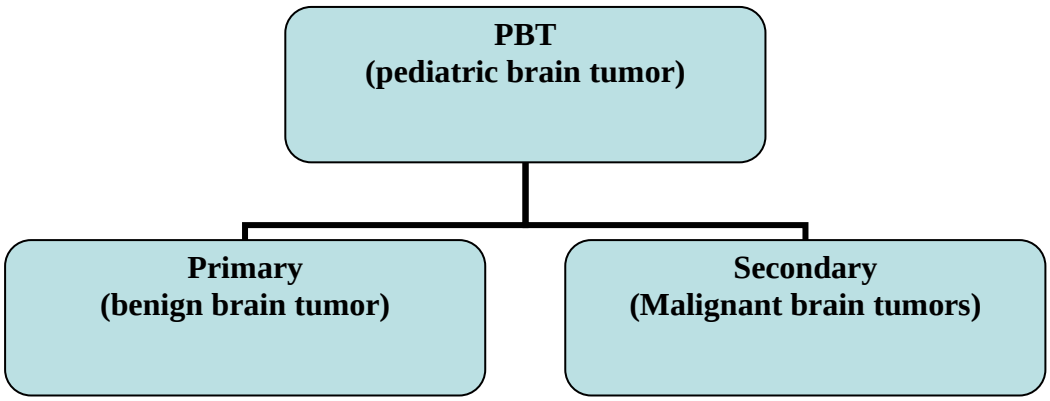
⇩

brain tumor

[4. CLASSIFICATION AND EPIDEMIOLOGY]

4. CLASSIFICATION

The types of brain tumor are listed below and this is the normal classification given in here. [16][17][13]



1) tumors are slow growing. 120 different types of primary brain tumors are observed till date Primary brain tumor has tendency to stay in brain. **E.g. Gliomas**	**1)** it is rapidly-growing, invasive and life-threatening and some-times called as brain cancer and has tendency to spread within the spine along with brain and hardly spread to other parts of the body. **E.g. medulloblastoma**
2) under microscope these cells have mostly normal appearance like distinct border and rarely spread.	**2)** because of their ability to spread "roots" into near around normal tissue and overlapping with normal tissue they have lack of distinct border.
3) small in size	**3)** large in size
4) Necrosis is not observed.	**4)** Necrosis is observed
5) Do not metastasis	**5)** Metastasis
6)capsulated and well differentiable	**6)** Unencapsulated and very less differentiable

1. INFRATENTORIAL TUMORS

A. Medulloblastoma

It is originating from embryonic stem cells. It is the most common pediatric brain tumor because 20% of total brain tumor in the children are medulloblastoma. Male is predominant. It is form in or around the cerebellum. It can metastasize through cerebrospinal fluid and can spread to the spine base this process is called as "drop metastasis" and so that it is putted in grade iv. In this type, tumor prevents the normal circulation of the fluid in the brain to outside the brain and because of this fluid builds up in the normal fluid space in the brain which can cause pressure which is known as hydrocephalus or water in the brain. In recent research it is found that medulloblastoma may be one or more sub types and which will influence probably outcome of the treatment goal. [18][19]

B. Ependymoma

It is infratentorial tumors. Ependymal cells are found in spinal cord and brain so that ependymoma can form in the spinal cord and brain. In children it is found in 4^{th} ventricle. WHO classified ependymoma in to Grade I to III. Tumor cells formed ring like structure which is known as perivascular peudorosette for example cilia around the centralized blood vessels. hydrocephalus or water in the brain is observed invasion of vomiting centre near the tumor so that prominent vomiting is observed.[20][21] [22]

C. Astrocytoma

According to the location, treatment and outcome it covers wide range of tumors and can be classified in Grade I to IV.

a. Juvenile Pilocytic Astrocytoma (grade I)

It is infratentorial tumors. astrocytoma can occur at back of the brain or mostly found in Cerebellum and near the brain stem and generally benign and slow growing so that it is putted in to Grade I. it contains cysts, granular like material and fibres which is clumped in to cytoplasm of the cell and known as "Rosenthal fiber". These fibers are made up of glial fibrillary acidic protein which is structural protein. [23]

b. Diffuse Astrocytoma (grade II)

Astrocytoma can occur anywhere in the body.

c. Malignant astrocytoma

Malignant astrocytoma occurs in the front part of the brain

d. Diffused pontine astrocytoma (brainstem Gliomas)

It is occurring in the critical part of the brain and about 70% of brainstem tumors. In this type characteristics image shows diffuse infiltration of the pons and biopsy may be helpful for characterization. This tumor invades the brainstem so that Surgery cannot be done. Chemotherapy is not effective. Radiation therapy shows improvement but it is temporary, so tumor comes again.[24]

e. Focal brainstem astrocytoma

It occurs in midbrain, medulla or cervicomedullary and about 30% of brainstem tumor.[25]

2. SUPRATENTORIAL TUMORS

A. Craniopharyngiomas

Near the pituitary gland tumors forms which is known as Craniopharyngioma. This is the most common supratentorial tumor. Posterior pituitary is formed because of during development some cells migrate down. Anterior pituitary gland is formed because of during development some cells (oropharynx: cells from back of the throat) migrate up and form "Rathke's pouch" which is later form anterior pituitary. Unmatured Rathke's pouch forms tumors which is known as "Craniopharyngiomas". It is slow growing and benign so that WHO putted in Grade I.

B. Pinealoma

It is the rare supratentorial tumors. It is form in the part of pineal gland and it is originated from the endocrine cells of the pineal gland. WHO classified this tumor in to I to IV Grade. "Tumor resembling germline" and "Homer-wright rosettes" is the significant of this tumor.[26]

- Generally primary brain tumor is seen in the children which is given below according to different types.

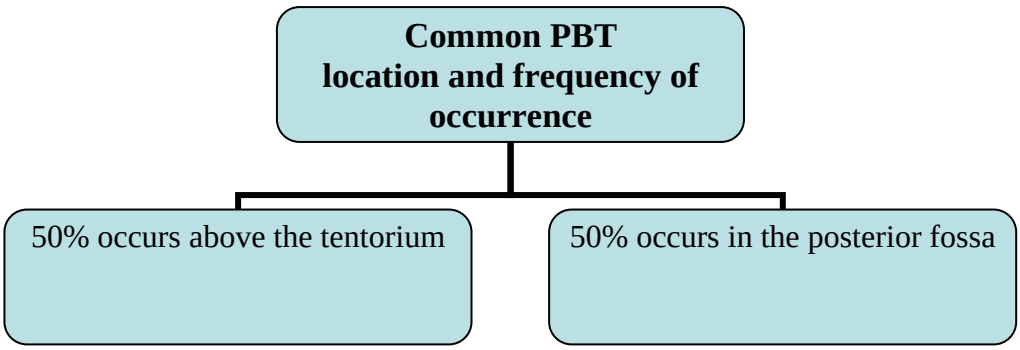
Table 1. General Classification of PBT [17][14][27][26]

1). Gliomas (Most common primary brain tumor)	
Gliomas astrocytic tumors	**Mixed glioma**
Low-grade astrocytoma.	
Glioblastoma multiforme.	
Anaplastic astrocytoma.	
Oligodendroglioma	**Ganglioglioma**
Anaplastic.	Benign.
Benign.	Anaplastic c.
Ependymoma	**Choroid plexus tumor**
Anaplastic.	Papilloma.
Benign.	Carcinoma.

2). Primitive neuroectodermal tumors
1. Supratentorial primitive.
2. Neuroectodermal tumors.
3. Medulloblastoma.
Pine blastoma.

3). Congenital
Craniopharyngioma.
Teratoma.

4). Pineal tumors
Choriocarcinoma.
Endodermal sinus tumor.
Pineocytoma/pine blastoma.
Germinoma.
Embryonal cell carcinoma.



- Pediatric brain tumors have better prognosis than adult because….
- The two common highly malignant tumor of adults like glioblastomas and metastases that children rarely develop.
- As well as children also rarely develop 3 common benign tumors of adult like meningiomas, pituitary tumors and acoustic neuromas.
- Staging of the tumors is very important in the treatment of many pediatric brain tumors. [17][14][27]

WHO (World Health Organization) classification

WHO considers that three separate classification of tumors are needed according to.

A) Histologic type

1. Metastatic Tumors
2. Tumors of Neuroepithelial Tissue
3. Lymphomas and Hematopoietic Neoplasm
4. Tumors of the Sellar Regions
5. Tumors of Cranial and Spinal Nerves
6. Tumors of the Meninges
7. Tumors of Uncertain Histogenesis
    - Hemangioblastoma from primitive vascular structures
8. Germ Cell Tumor
    - Ex: Germinoma – common in pineal gland area
9. Cysts and Tumor-like lesions
    - Usually in the third ventricle
10. Local Extension from Regional Tumours

B) Degree of malignancy (Grade)

Table 2. WHO classification of PBT as per Degree of malignancy

1. Grade I (juvenile pilocytic astrocytoma)
Least malignant.
Practically typical appearance under a microscope.
Usually connected with long-term endurance.
Slow-growing cells, mostly found in Cerebellum and near the brain stem.

2. Grade II (low grade astrocytoma) (fibrillary astrocytoma)
comparatively slow-growing cells.
It gives little abnormal appearance under a microscope.
It Can occupy adjacent normal tissue.
It Can reoccur as a higher-grade tumor.

3. Grade III (anaplastic astrocytoma) (oligodendroglioma)
Abnormal cells which reproduce actively.
It gives abnormal appearance under a microscope.
Invade nearby typical cerebrum tissue.
It has tendency to recur, generally as a higher grade.

4. Grade IV (glioblastoma multiforme)
Abnormal cells which expand quickly.
It gives Very abnormal (comparatively) appearance under a microscope.
To maintain quick growth, it can produce new blood vessels.
There is necrosis in the center.

This is the classification based on the degree of malignancy or grade in which cell growth, appearance under microscope(microscopy), degree of risk for developing in nearby tissue and area of grade is examined and class is given accordingly and putted in to the class I to IV [14][27][16]

- PBT location and frequency of occurrence. Which is given in below table 3.

Table 3 PBT location and frequency of occurrence [28][14]

Hemispheric	Midline	Posterior fossa
Gliomas 37%	**Chiasmal gliomas** 4%	**Brain stem gliomas** 15%
(Astrocytoma) **High grade** 11% **Low grade** 23% **Others** 3%	**Craniopharyngiomas** 8% **Pineal region tumors** 2%	**Medulloblastomas** 15% **Ependymomas** 4% **Cerebellar astrocytoma** 15%

➢ ***EPIDEMIOLOGY***

- Worldwide around 13% of the yearly deaths occurs due to cancer and the low- and middle-income countries are more affected in this death, around 70% of these deaths are in the low- and middle-income countries[7]
- There are lots of different organizations work on the tracking the incidence of gliomas. It can be done by the collection of the data through government surveillance for example collection of data from state-wide or country-wide cancer registries.[10][29][30]
- 1/285 children in the U.S. will be diagnosed with the disease before the age of 20. In all the pediatric cancer pediatric brain tumors is the most second common cancer, and it is approximately 20% of the all of the childhood cancer. Advances in the treatment of cancer increases the survival rate but still it is the second most cause of death. [30] [31]
- About 3/100,000 children yearly affected by childhood brain tumors and that is very huge incidence. Brain tumors has shown an increase number from 3.45 per 100,000 years in 1994 to about 4.92 per 100,000 person-years.[13][32]
- CNS tumors account for 11.4% to 20.1% of pediatric tumors as per data collected from India.[7]
- There are different types of cancers occurs most commonly in the age between 0 to 14 and 15-19 (ascending order according to percentage is given here in table 4) [33][31]

Table 4. Types of Cancers in Different Age

Types of cancer (AGE 0-14)	**%**
CNS and Brain	**21%**
Acute Lymphocytic Leukaemia	14%
Neuroblastoma	7%
Non-Hodgkin Lymphoma	6%

Types of cancer (AGE 15-19)	**%**
Hodgkin Lymphoma	15%
Thyroid Carcinoma	11%
Brain and CNS	**10%**
Testicular Germ Cell Tumors	8%

- Chart of Table 4 is given here as a figure 8 and 9

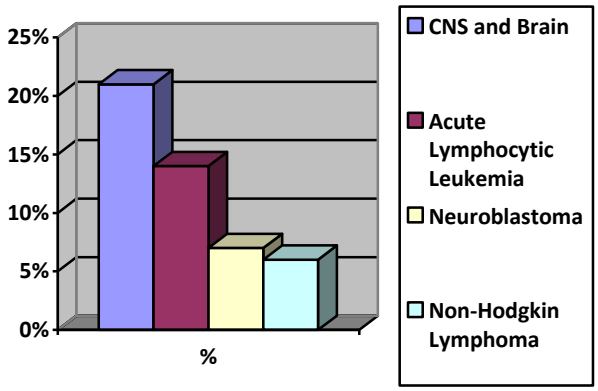


Figure 8 Types of Cancers in Age 0-14 Years

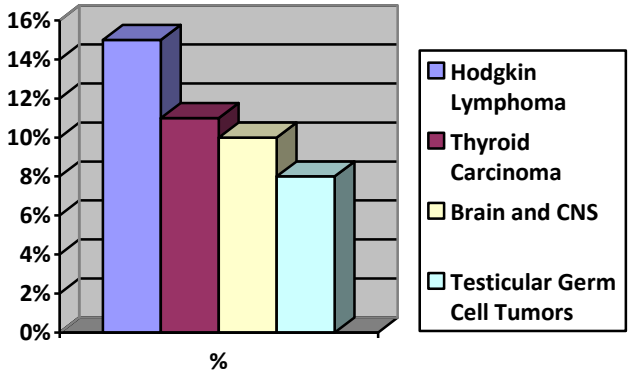


Figure 9 Types of Cancers in Age 15-19 Years

➢ **PBT incidence Fact sheet 2014 (AGE 0-14) (N=16044) by CBTRUS**

- Table 5 Shows Data About Childhood Primary Brain Tumors and Other CNS Tumors as per Histology.
- Collection of data is done by Central Brain Tumor Registry of the United States (CBTRUS) in 2014.
- In the children of between ages 0 and 14 years.
- Total 16,044 incident of tumors is counted and incidence rate of pediatric brain tumor (non-malignant and malignant) and other than that, is CNS tumor is calculated so it was found that total 5.47cases/100000 for total count. [31]
- It is also founded that male is more prone to develop tumor than female so that incidence rate is high in male as compare to the female. Which is given here as per CBTRUS fact data sheet 2016 **[**Male (5.69 per 100,000) and females (5.24 per 100,000).**]**[28]

Table 5 CBTRUS fact data sheet 2014[28]

Pineal region tumor	0.40%
Lymphomas and haematopoietic neoplasm	0.90%
High grade gliomas	11.11%
Pilocytic astrocytoma	17.60%
Ependymal tumor	5.50%
Low grade glioma	14.30%
other glioma	4.40%
Embryonal tumor	15%
Unclassified tumor	4.90%
Cranial and spinal nerves tumors	4.70%
Neuronal and mixed neuronal glial tumors	4.40%
Craniopharyngioma	4.00%
Pituitary tumor	3.90%
Meninges tumor	2.90%
Choroid plexus tumor	2.90%

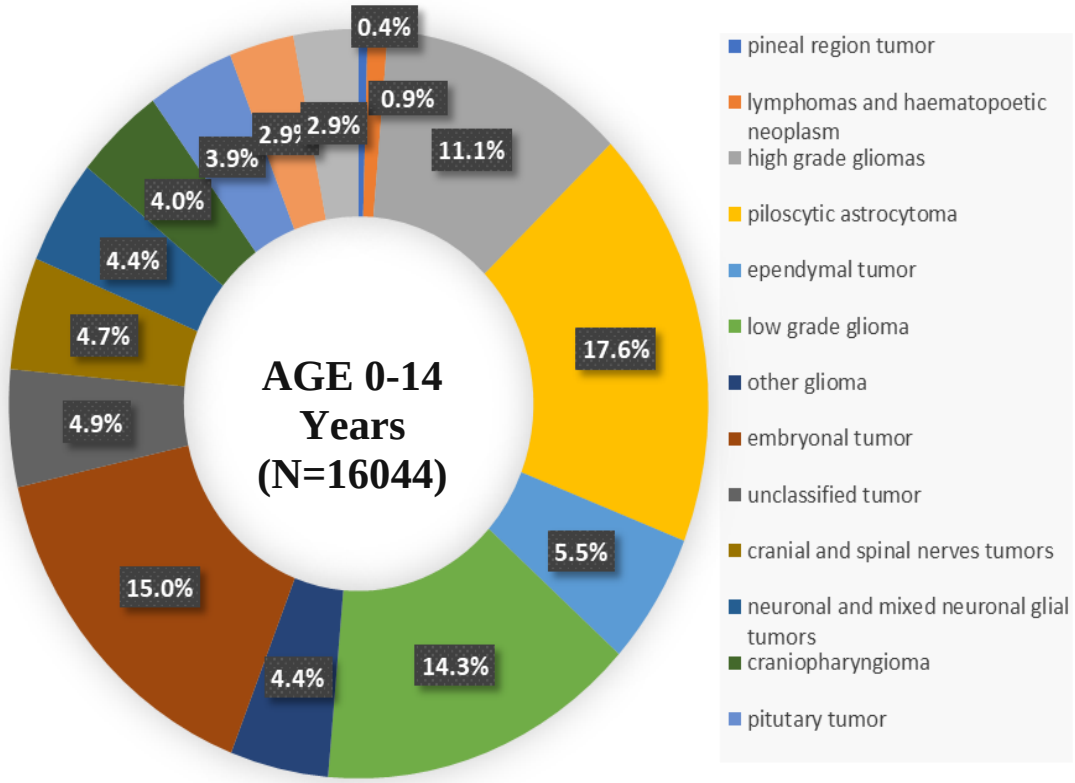


Fig. 12 PBT incidence Fact sheet 2014 (AGE 0-14) (N=16044) by CBTRUS

- **PBT incidence Fact sheet 2014 (AGE 15-19) (N=6747) by CBTRUS[28]**

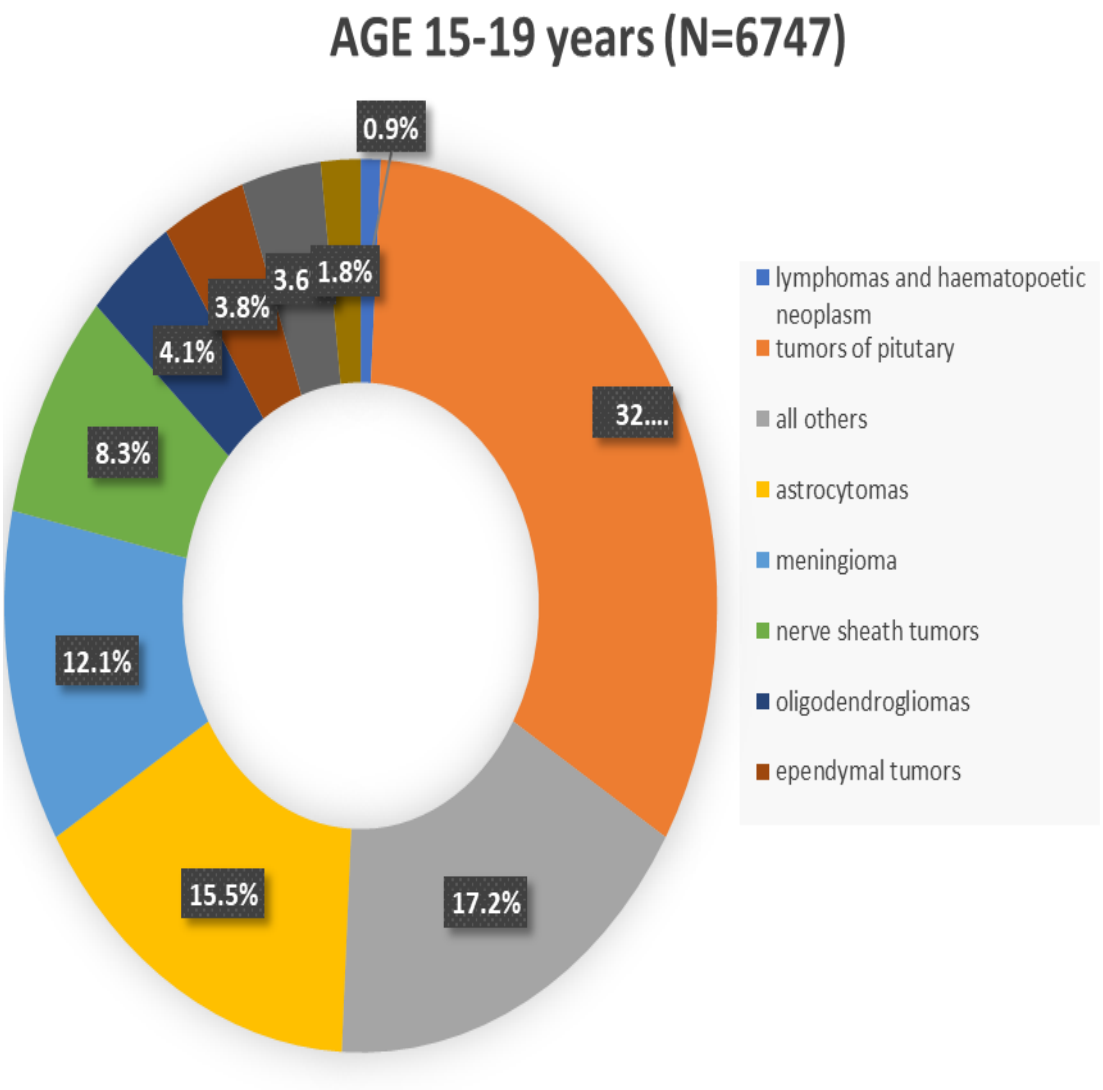


Fig. 13 PBT incidence Fact sheet 2014 (AGE 15-19) (N=6747) by CBTRUS

- With the data from the CBTRUS for adolescents between ages 15 and 19 years, Distribution of pediatric primary brain tumors and other CNS tumors according to histology is given here. [28]

[5. SIGN AND SYMPTOMS]

5. SIGN AND SYMPTOMS

- **Headache associated with neurological deficit**

Most common symptoms are headache and not all headache is a sign of brain tumor. It is worrisome if it is also associated with neurological symptoms like weakness of one side of the body, brain or spinal cord is not working properly. Sleepiness, personality change, clumsiness of hands, double vision, slow heart rate, high blood pressure.

- **Headache not associated with neurological deficit**

Headache is worrisome if the child awakens at night or in the morning with headache or it is associated with vomiting and headache improves after the child throws up and the child feels better. Vomiting often occurs in the morning but not later in the day. And vomiting may lead to weight loss.

There are also some Other worrisome characteristics of headache in which when child lying down, coughing, laughing, straining headache becomes even more worsened. Distinct change in the pattern or severity of pre-exciting headache, or progressive worsening over time

- **Brain tumor and Epileptic seizures**

Epileptic seizures may be symptom of a brain tumor, especially when a child has not had a seizure before and when the seizure is not associated with fever.[34]

- **Infant**

Brain tumors can occur in the children of any age so sometimes very young children who are less than 3 years of age and children are hard to identified, after a period of normal growth of head, there is a rapid growth of head is observed.

Pressure inside the head is transmitted to the back of the eye and can be seen and this condition is known as papilledema.[35]

Table 6. Symptoms based on brain tumor location.[36][37]

FRONTAL LOBE
Confusion,
Paralysis on one side of the body,
Mood swings,
Difficulty thinking,
Weakness observed,
Mood disturbances.

PARRIETAL LOBE
Seizures,
Loss of sense of touch,
Problem with hand writing,
Mathematical difficulty,
Motor skill deficits,
Paralysis,

TEMPORAL LOBE
Inability to understand multi step commands (memory),
Perceptual/partial disturbances,
Seizures.

OCCIPITAL LOBE
Seizures,
Hallucination,
Loss of vision.

CREBELLUM
Ataxia,
Loss of coordination,
Headache,
Vomiting,
Dizziness.

HYPOTHALAMUS
Deficits in perception of temperature,
Emotional changes,
Pituitary (problem with growth/nutrition).

[6. TREATMENT AND RECENT ADVANCES]

6. *TREATMENT AND RECENT ADVANCES*

- In the selection of optimal therapy perfect diagnosis is very important for the selection of optimal therapy in the patient of childhood brain tumor.
- In the treatment and outcomes of patients with pediatric brain tumors diagnostic/prognostic modalities play an important role.
- Diagnostic/prognostic modalities is required to separate the patient who required aggressive therapy and intensive therapy.[8][38]

Table 7 :Different therapeutic treatment and their recent advances [2]

THERAPEUTIC TREATMENT	RECENT ADVANCES
1.Surgery	Surgery guided by CT or MRI, MRA/DSA Endoscopic ventriculostomy electrical corticography
2.Radiotherapy	"3D-CRT With the help of Fractionated Radiotherapy, Intensity modulated radiotherapy, radiosensitizers"
3.Chemotherapy	"with help of PBSC Myeloablative chemotherapy, with regional therapy"
4.Targeted therapy	''with gene therapy and Immunotherapy''

❖ SURGERY AND RECENT ADVANCEMENT.

The initial and continuous most important treatment for the maximum patient of pediatric brain tumors is surgery. surgical resection plays an important role in the survival of the most of the brain tumors. Surgery is helpful in the cerebellar astrocytomas of low grade if the complete resection of the tumor is done by the surgery. Tumors other than low grade astrocytomas, e.g. medulloblastoma and ependymoma's tumors resection is done as much as

possible and it directly corelates with the rate of survival. Radical resection is perfect, however is conceivable in just half of CNS tumors situated in superficial areas territories and about 8% of profound or midline tumors so that for other tumors additional therapies like chemotherapy and/or radiation therapy is required too. Because of the resection obviously it has benefit but chances of risk also increase. While performing surgery sometimes injury occurs in critical neuroanatomic structures and that is very dangerous. Some recent advances allow surgery of tumor in critical region with better margin of safety. [8][2][39]

Surgery guided by **CT or MRI techniques** gives appropriate significant improvement in surgery outcome of tumor which is located in critical part. Magnetic resonance imaging (MRI) and computerized tomography (CT) are first choice for diagnosis because it provides better resolution and there is no use of any radiation in this technique so that it is the major advantage. MRI which also allows determination of tumor in the exact brain region and gives its relationship to critical structure so that risk of neurological morbidity is decreased.

Magnetic resonance spectroscopy (MRS)

It gives idea about measurement of sensory and motor responses of brain cells during surgery so that the goal is that the degree of resection is constrained if the critical loss of function is encountered and it is evaluated by the various metabolic peaks.

Before the resection of the tumor is undertaken on the surface of the brain two electrodes is placed for mapping of the crucial region and this technique is known as **electrical corticography**.

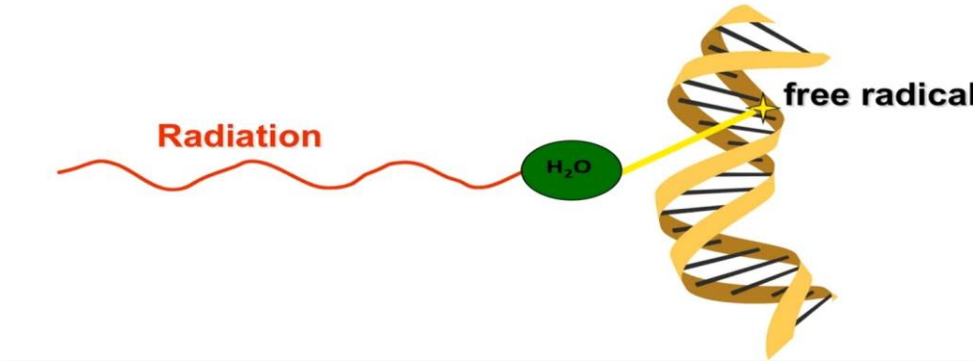
Before many years conventional angiography technique is used but in present it is rarely used because **magnetic resonance angiography (MRA)** takes place because with the help of it, it is easy to recognize vascular deformities from tumors. For differentiation of vascular deformities from bleed in tumors **DSA** can be used.[3]

❖ RADIATION THERAPY

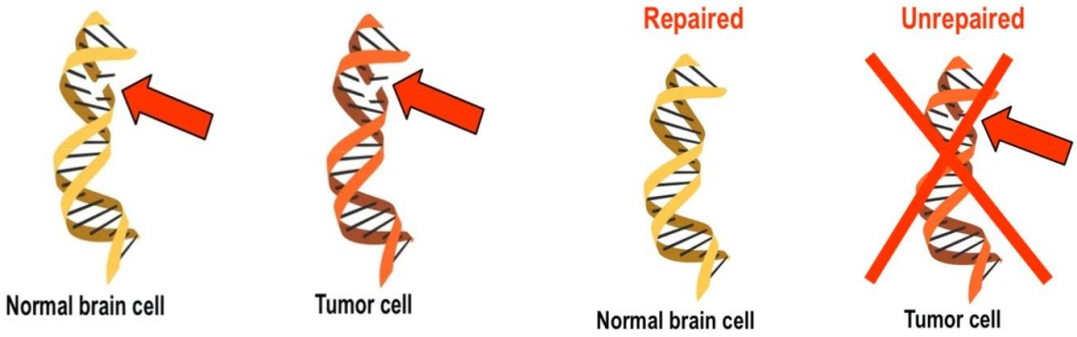
In the treatment of gliomas and pituitary tumors in adult radiation therapy was used in early 1900 and in many malignant child brain tumor it is very effective option available which gives contribution to duration of survival and increase chances of cure. It is used to treat large no of pediatric brain tumor like oligodendroglioma, astrocytoma, ependymoma, craniopharyngioma, germ cell tumor, CNS leukaemia, meningioma, AVM and PNET. effects of radiations are limited to area and that is specific target sometimes it also affects the site other than target which is known as secondary effects. It is not a really good option with few exception and blade of treatment in other words it's does not actually destroy a tissue like surgery does but we can use this therapy in areas where surgery cannot be used where there might be large amount of normal tissue with just few scattered tumor cell inside and don't want to take that whole normal area out because that would have lots of bad side effects but with radiotherapy it can be possible to treat the small amount of tumor in targeted way. There are many types of radiation but only few can be used for the treatment which is called as an electromagnetic radiation and generally x-rays and gamma rays are used for the treatment. Radiation is measured in the unit of gray. Distribution of radiation inside the body is different so that based on the intensity of radiation it gives effect on different parts. several strategies are needed for radiotherapy for pediatric treatment because along with tumor cell it also affects the normal tissue and in children effects on normal tissue are magnified compared to adults because the DNA damage that the radiation causes is mostly going to affect the growing tissue.

Strategies to protect normal tissue[40][1][3]

1. **Fractionated Stereotactic Radiotherapy** (SRT)
    - Radiation is given on daily bases often five times a week and for many weeks because from the stand points of how radiation affects cells. Fewer the number of doses of radiation is given, more the radiation is going to affect the tumor and the normal tissue the same.
    - Low Radiation damages the DNA of both the tissue but normal tissue repairs its self-better than tumor tissue.so that this process is repeated and at some stage tumor tissue cannot tolerate this damage and dies. [41]



Radiation delivers energy to DNA



Radiation damages both Normal and Tumor cells

Tumor cells are unable to repair damage like normal brain cells

Fig. 14 Fractionated Stereotactic Radiotherapy

Adopted from Johnnie K.Bass IJ Volume 72, Issue 3, 1 November 2008

2. **Magnetic resonance imaging (MRI) and computerized tomography**
    - These techniques are used for radiation planning and delivery.
    - Radiation is delivered to normal tissue sometimes it is imagined before by design because tumors can often have fingers that extend beyond what the actual tumor its self-look like what it can be seen by this recent advancement in the imagining technique.[42]

3. **Three-dimensional conformal radiation therapy (CRT)**
    - **MLC (Multi leaf collimator)** gives shape of tumor to the radiation beam which gives more accurate and focused beam which meets the

profile of tumor so that only tumor will affect by radiation and risk of other damages can be minimized.

- By using this type of approach and combining the number of these beams that are shaped and make them come in all from different angles each one delivering just a portion of the amount of radiation for e.g. 3D conformal radiation therapy
- 3D conformal radiation therapy is a very useful technique for focus a radiation on tumors which are fairly regular in size and shape, not too many curves in indentations.
- In this lower dose purple area but they all converge on an area and create high dose zone of radiation and its required that focused to be on the tumor which is known as 3D conformal radiation therapy.[43]

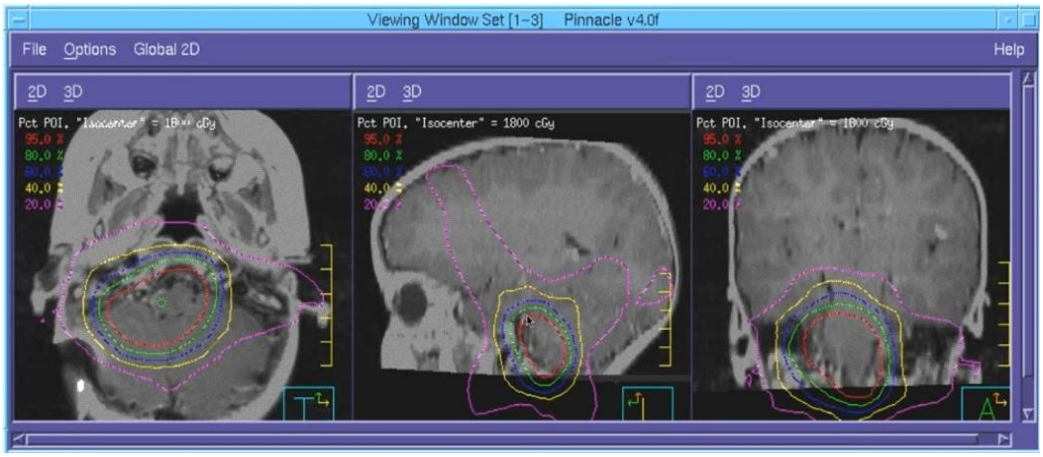


Fig. 15 3D conformal radiation therapy

Adopted from Kathy L Baglan IJ Volume 55, Issue 2, 1 February 2003

4. **Intensity modulated radiotherapy (IMRT)**

- This is a very valuable technique used in the treatment of children with brain tumors and that is high intensity modulated radiotherapy which is also generally known as **IMRT.** It can create more complex shape of these radiation zones so tumor that is sitting at the bottom of the brain it can be possible to create shape of radiation around that tumor which is right next to spinal cord which is actually very sensitive to radiation and requires protection.

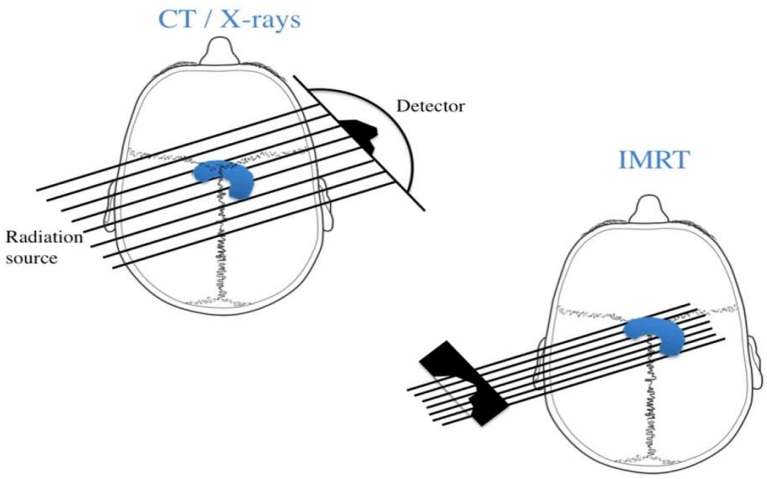


Figure 16 CT/X-Rays and IMRT
Adopted from H.M Kooy, IJ , Volume 58, Issue 3, March 2004

IMRT help by carving that area out and short shrink wrapping the radiation around that irregularly shaped tumor. It is like CT/Xray scan and reverse which is shown in the figure.

- In IMRT tumor is first detected by the CT/X-Ray by passing rays so certain amount of radiation is absorbed differently depending upon weather it goes through and those amounts of radiation are registered on a detector which combined and pictures or anatomy is made from different angles. Now this same anatomy used on the entry side of IMRT with covering other part than anatomy with the material which can absorb all the radiation.[44][45]

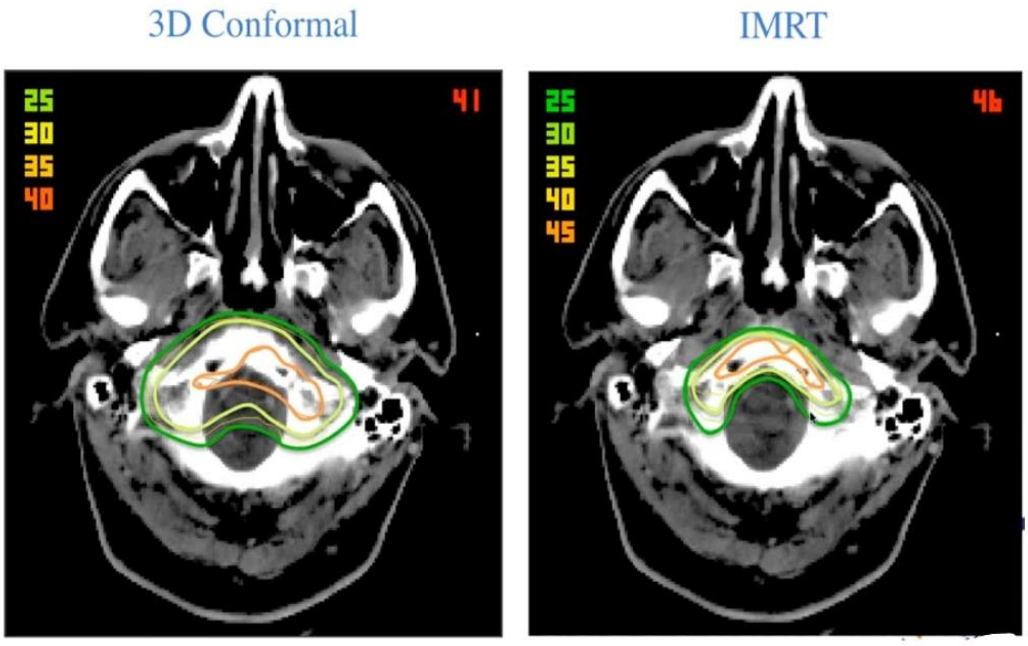


Fig. 17 3D Conformal and IMRT

Adopted From Kathy L Baglan IJ Volume 55, Issue 2, 1 February 2003

5. Radiosurgery

- Radiosurgery is an exception to rule which is about radiation is not being a blade of treatment. In a radio surgery there is use of a singles dose so that everything is bombard on the cell wanted to kill so there is no prisoners approach.
- so, this uses only one single treatment for very high doses, tightly focused on the area of the tumor. There are variety of different equipment that do radiosurgery. E.g. gamma knife, linear accelerator, cyberknife. This equipment mounted on the robotic arms.[46][12]

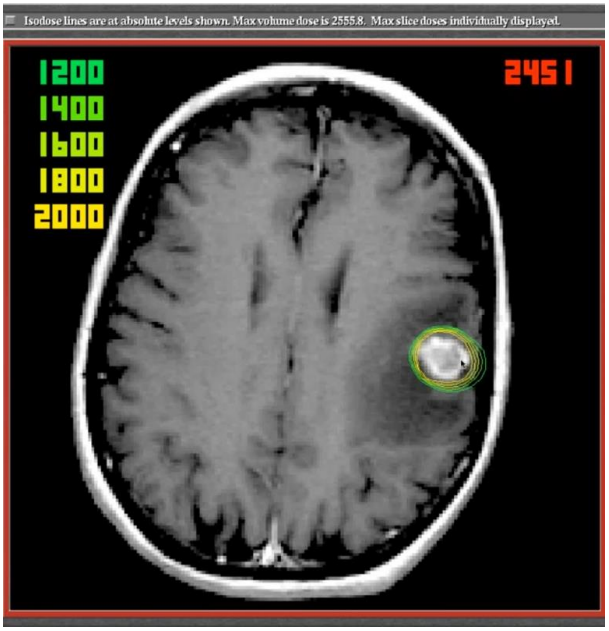


Fig. 18 Radiosurgery

Adopted from Peter Mc L Black, IJ, Volume 50 Issue 4, 15 July 2001

❖ CHEMOTHERAPY

- Cancer at the back of the brain in child which is medulloblastoma is most common tumor. Advances in the chemotherapy is needed because classic chemotherapy kills rapidly dividing cells it does not discriminate between the normal or tumor cell which is rapidly dividing and so it is not targeted. But it kills cancer cells because its grow uncontrollably. there are collateral damages of the chemotherapy, common toxicities of the chemotherapy that is observed are due to the normal cell which are rapidly divided like cancer cell. **E.g.** blood cells divide rapidly, line of gut or stomach

cell divide rapidly and hair cells divide rapidly. So that all these are affected by chemotherapy. So, it is not optimal.

- commonly used Drugs in chemotherapy are carboplatin, vincristine, cyclophosphamide, cisplatin, BCNU, and temozolomide. In clinical trials (8 in 1 regimen), There is disappointment result is observed when cisplatin is used in pediatric high grade glioma. So that advancement requires like targeted based drug therapy, immunotherapy.[2]

- Latest drug Temozolomide which is presently used in pediatric brain tumors, but it has only moderate and short-lived response. So that Temozolomide is now used with various biologic agents to improve and increase its therapeutic efficacy.[47][48]

❖ **Drug Resistance**

- Recent advances in chemotherapeutic is for decrease the drug resistance. In study it is observed that temozolomide and BCNU like drug is not much effective because arginine guanyl transferase (AGT) is enzyme which repairs the DNA protein and this enzyme is responsible for the resistance of the drug. So that chemotherapy with combination or multiple chemotherapy is currently used. O6 benzyl guanine with chemotherapeutic agent is currently used because it inactivates the arginine guanyl transferase and increases activity of the drugs.[2]

❖ **Blood Brain Barrier**

- Chemotherapeutic efficacy is directly related to blood brain barrier. Between the brain and circulating blood there is continuous barrier which is made up of monolayer of specialized capillary endothelial cell. Because of this blood brain barrier some chemotherapeutic and other agent cannot penetrate and that leads to inappropriate therapeutic activity.

- For widening of the neuronal vessels and enhance the penetration of drugs into the brain various types of approaches are used. e.g. RMP-7 or Lobradimil or Cereport, aB2 (bradykinin 2 receptor),
- To enhance therapeutic efficacy of carboplatin, effective strategy like Cereport-induced transient permeation of Blood brain barrier is used.
- to improve the pharmacotherapy and increase BBB penetration of the latter effective strategy like 'Cereport-induced' transient permeation of Blood brain barrier is used with radiation and carboplatin.
- In clinical phase I study it is proved that use of Lobradimil with carboplatin is safe, so that it is ready for a phase II study .[49]

❖ **Differentiating agents**

- derivative of retinoic acid like fenretidine is known as differentiating agent which enhances the maturation of the tumors. Use of this differentiating agent is well known in neuroblastomas because this agent does the help in the differentiation of malignant cells of human glioblastoma and medulloblastoma. [2]

❖ TARGETED MOLECULAR THERAPY

Microscope have ability to look at a section of tissue so till now by that result it is decided that how to treat brain tumor. Some set of experiment is done by group in Montreal in Ajab Otto's lab. She took a whole bunch of adult glioblastoma multiforme (a highly malignant tumor) and did the molecular profile and also did molecular profile of pediatric glioblastoma multiforme. She found that all of these tumor look same under the microscope but all are not same in fact all tumors have different abnormalities. So that it is concluded that adult and pediatric tumor are not same even all the pediatric tumor are not same so that same treatment can not be given to adult and pediatric as well as in all the pediatric tumor. So, this concept of looking at differences not from microscopic view but from a molecular point of view develops the molecular pathway based targeted

molecular therapy. Continuous research is still going on to better understanding biology of these tumors. [28][8]

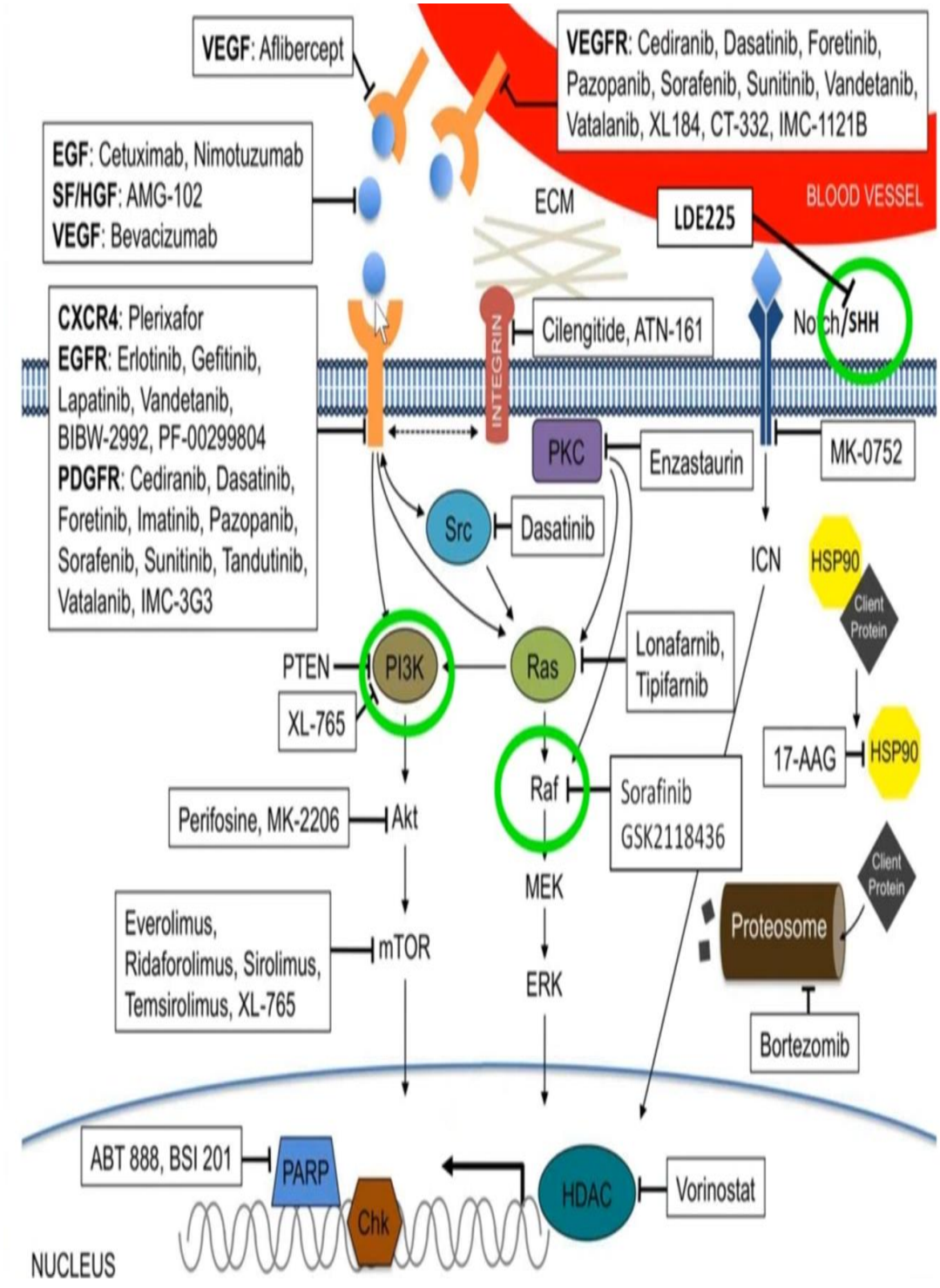


Fig. 19 Biological pathway and drugs molecule

Adopted from Tyler E Miller, Nature Neuroscience, volume 19,2016

Malignancy cell express different surface antigen for example growth factor receptors GFR which can bind with ligand inside the cell membrane and induces different signalling molecular pathway for example pathway like PI3K pathway, Ras-Raf pathway. In targeted molecular therapy signalling pathway and surface antigen of tumor is targeted. Because of mutation this signal produces on their own so that if it is possible to find out which signal is abnormal then after it is possible to inhibit by targeted therapy. [1][2]

Biological pathway and Some of the drugs molecule which is invented by pharmaceutical company which work on different target are given here.

Angiogenic molecules

"Epidermal-GFR (EGFR) and platelet-derived GFR (PDGFR)" is targeted with molecules such as ST-1571 and ZD1839 in clinical trial studies.

EGFR is a surface antigen which induces RAS oncogene pathway which is started by enzyme farnesyl transferase. SCH66336 molecule inhibit this enzyme observed in phase I clinical trials. "Rapamycin and its ester analogue CCI-779" is a molecule which inhibit PI3-Akt signalling pathway.[50][2]

Table 8 Some molecules and Target

Molecules	Targets
Marimastat (BB-251)	Matrix metalloproteinase 1, 2, 7 and 9
ST 1571	PDGFR
ZD 1839	EGFR
SU5416	VEGFR 2, PDGFR
CCI 779	Mammalian target of rapamycin (mTor)
SCH 44342	Farnesyl transferase
Cilengitide Thalidomide	Integrin alphavbeta 3 and alphavbeta 5

In paediatric brain tumor few different Molecules presently used for molecular Targeted Therapy which are given here in the table 9.

In phase I and II clinical trial study of molecule IL13-PE38QQR, in patient with recurrent pediatric malignant gliomas, it is found that it is not distributed uniformly and nonspecific neuronal toxicity is also observed so that for delivering this types of agent Convection-enhanced delivery is novel delivery system and come close to optimal method which is shown in Fig. 34.

So that by targeted therapy it can be possible to assess tumors at their molecular level not just histological level. This therapy opens up the whole new area of therapeutic intervention. Due to specificity, less toxicity and more activity it is more useful. [2]

❖ IMMUNOTHERAPY

Idea of cancer immunotherapy was recognized in the field of science and it is remarkable and development is still going on.

Study of cancer immunotherapy started in early 1863 by experiment of William Coley who is the father of cancer immunotherapy. He injected bacterial product in to patient tumor and noticed that tumor would shrink away and also noticed that not only tumor would improve but patient have distal metastasis diseases those tumor would also improve. So, it is the first evidence that immune system can be effective or harnessed against cancer. [51]

In 2010 first FDA approved drugs Sipuleucel-T for prostate cancer and ipilimumab for melanoma.

Cancer immune editing

Immune system does develop a response against cancer and this is known as elimination phase where cancer may be starting and immune system recognizes it as foreign and develops a response against it and when it kills the cancer cell, new cancer cell which sprout up that have resistance mechanism against patient's own immune system so that equilibrium phase comes where these cells evading the immune system thus immune system can kill only the

cells which are very sensitive against immune system but cannot kills the cells which have develop resistance mechanism against immune system.[52][8][2]

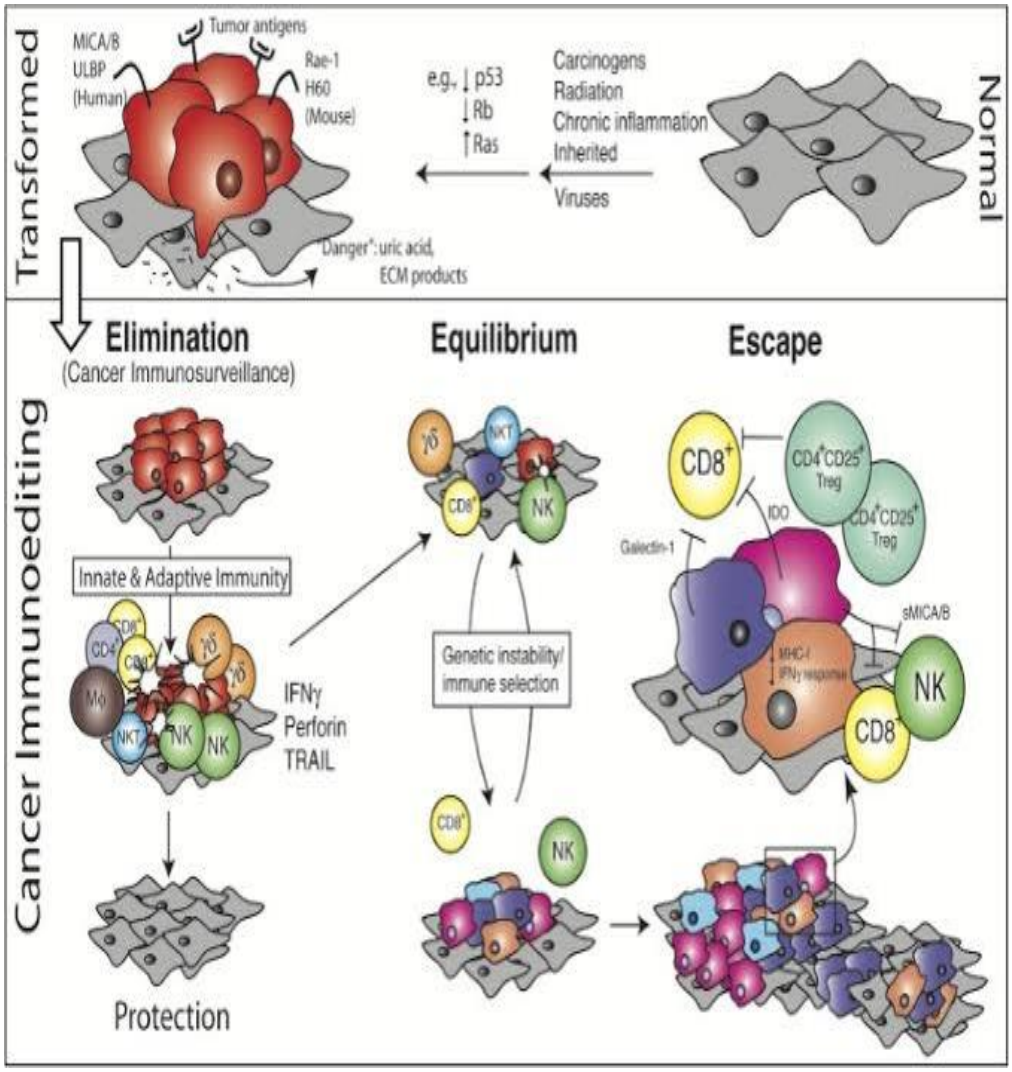


Fig. 19 Cancer immune editing

"Adopted from Kershaw M rt al. Nature Reviews cancer Volume: 13, Pages: 525-541 2013"

Immune system has 2 different arms like innate and adaptive immune arm. Innate arm is the first line of defence in this arm cells like macrophages, dendritic cell, natural killer cells that finds the invader and presenting that invader to the adaptive immune system and adaptive immune system can make specific response against infection. In this response T cells and B cells involves. B cells makes antibodies and T cells makes macular cell that are very good at finding out the cancer cells. [51][1]

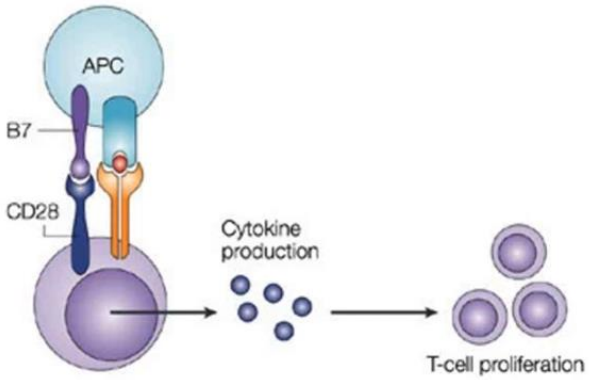


Fig. 20 Anti-Cancer immunity requires activated T cells

"Adopted from Kershaw M rt al. Nature Reviews cancer Volume: 13, Pages: 525-541 2013"

T cells are activated by APC which stands for antigen presenting cell, APC present the parts of the tumor or the virus to the t cell so that t cell becomes active against those pieces of tumor and that requires two signals 1. Epitope: MHC presented tumor 2. Co-stimulatory signal. These two signals together can make the T cell off or inactive and this is the way of regulating the T cells so that there is no problem of autoimmune diseases. Now this activated t cell divides and makes cytokines and proliferate and find the tumor and get rid of it. So that T cell are very important in the cancer immunotherapy because **activated T cell can cross BBB.** Traditionally in chemotherapy more and more drug is given to get some penetration across the BBB, some drugs like Cisplatin and Piazzolla can penetrate but not very effectively.[53]

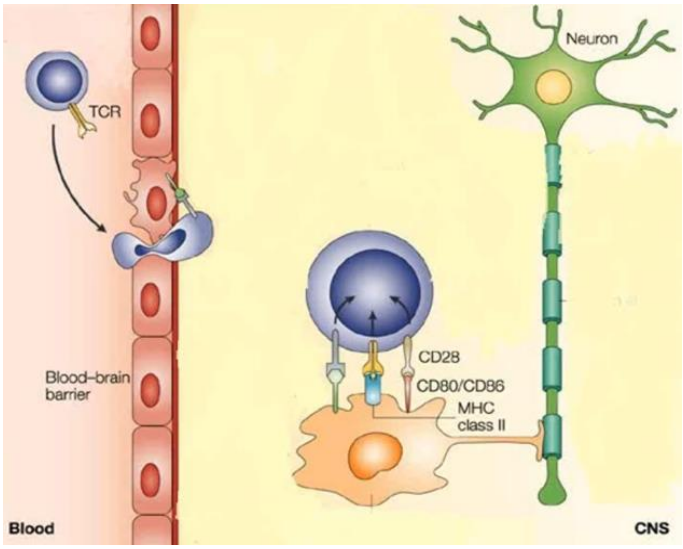


Fig. 21 T cells can cross BBB

Adopted from Sugamura et al. Nature Reviews Immunology 4, 420-431 (June 2004)

Unfortunately, when cancer is advanced like medulloblastoma, glioblastoma. These tumor cell transformed the landscape of the immune system to regulatory for example glioma cell present the MHC to the T cell so that can be identified as foreign by the immune system. These cancer cells secrete the cytokines signals than can decrease the activation or killing capacity of these t cells (CD4 and CD8) which are very important for T cell responses. So that it is major problem than cancer cell manipulates the immune system.

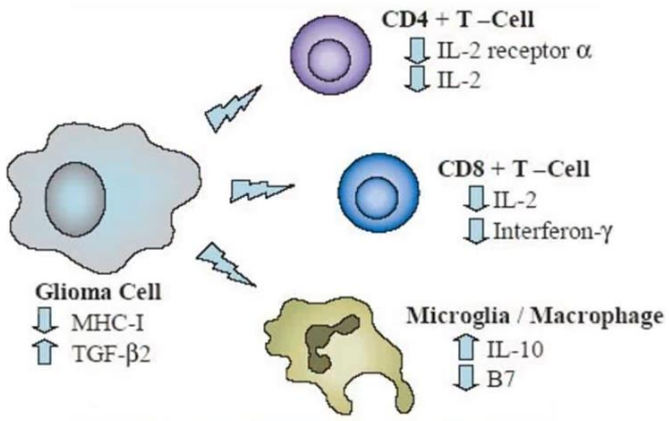


Fig. 22 Suppression of the immune system by cancer cell

Adopted from H. Lee Moffitt CCRI, Inc. Cancer Control 2004

To overcome this problem chemotherapy can be used because chemotherapy can work on these regulatory cells which manipulates the immune system's landscape. Chemotherapy does damage to these cells so that new immune cell can pick the MHC and develop immune response against it so that chemotherapy can be used with combination of immunotherapy to potentiate the immune response that is desired in patient.[54]

1. ADOPTIVE CELLULAR THERAPY (ACT)

Two immunotherapeutic approaches: advances of different tumor vaccines and monoclonal antibodies for tumor-specific receptors that can be bind to tumor toxins.

It is making T cells either genetically engineering them outside the patient's body. It is come from the work done by Dr Steve Rosenberg at the national cancer institute. He performs the experiment in the patient with

melanoma by taking out the tumor as much as access and from that t cell is taken out. These t cells are grown up with cytokines signals which allows T cell active and these T cells is given to the patient and the very positive results came.

A. CAR T-cell (Genetically engineered T cell)

The term CAR is for chimeric antigen receptor which is genetically modified T cell which is super active. Which bypass the way through which T cell normally get activated by 2 signals because it is developed in a laboratory by modifying patient's own t cell by fusing this CAR on to active domains of T cells so that it produces chimeric antigen receptor on the surface of the T cell which is known as CAR T-cell and again these modified cells are given to the patient by IV. Now these CAR T-cells have ability to naturally recognize cancer cell so that it kills the cancer cells. [55][56]

Phase I study of intracranial injection of T-Cell expressing HER2-specific CAR which is genetically modified T cells in patient (age > 18 y/o) with glioblastoma at Baylor/Texas Children's Hospital by Dr. Nabil Ahmed. [57]

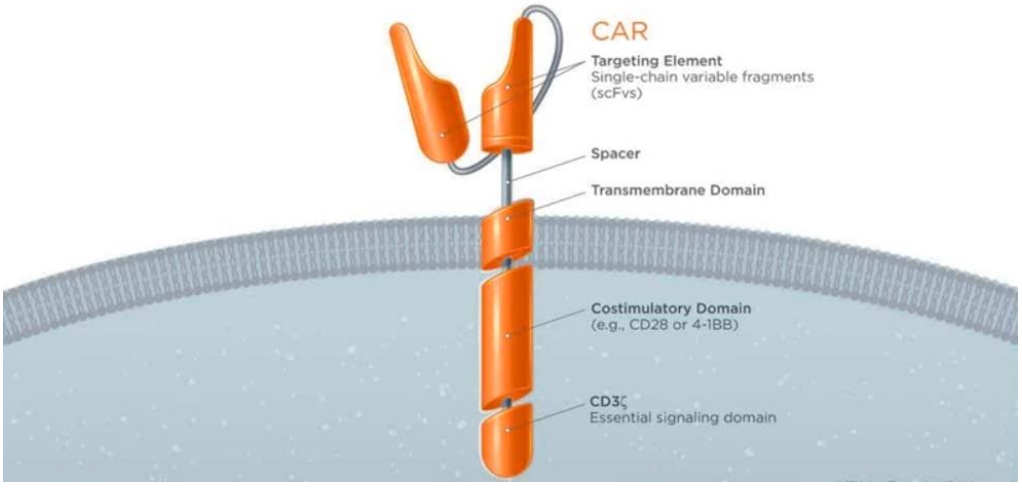


Fig. 23 Genetically Engineered T Cells against Cancer

Adopted from Christof M. Kramm, gene therapy, Vol 5, 2001

B. T-cell (Activated by APC and DC)

In another way tumor cell is collected by using biopsy and RNA is extracted and RNA is messenger nucleic acid and which is made from DNA which have actual information of tumor. That information is extracted from the RNA from the tumor cells and this RNA are putted inside the dendritic cells which are master cells of the immune system. actually, APC activate the T cell, so that by using extracted RNA, we can educate dendritic cell and culture them outside the body with patient's T-cell. So that now theses T-cells are activated not by genetically but by naturally outside the body. Now these T-cell with dendritic cell vaccine is given to the patient.[58]

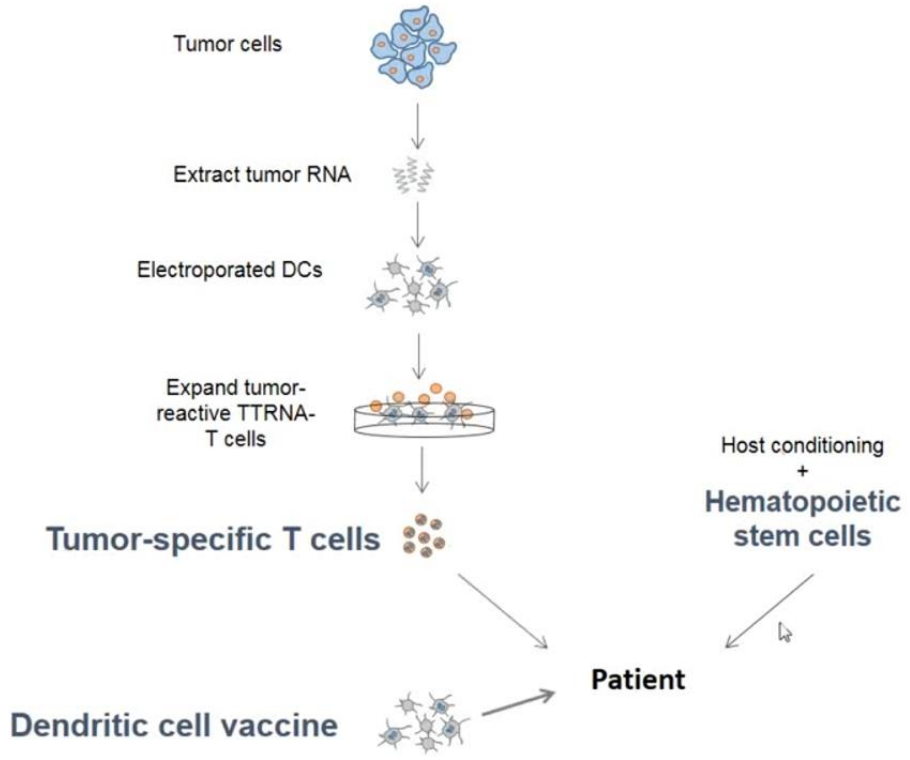


Fig. 24 Expanding T cells from scant amounts of tumor tissue

Adopted from Clin Dev Immunol. 2010, Hanka Janich et al

Phase II study of RNA loaded dendritic cell with T-cells in the patient of recurrent medulloblastoma and primitive Neuroectodermal Tumor at University of Florida.[59]

2. CANCER VACCINES

One of the issues with adoptive cell therapy is that it requires lot of engineering outside the patient's body and that is very costly, very complex and requires long time to produce so that patients not get product on time when it required. So that real time therapy for patient is required.

A. Passive cancer vaccine

In several different types of cancer monoclonal antibodies are used because that can recognize the antigen on the surface of different types of tumor cells. Here some example of passive vaccine is given.

Rituximab anti-CD20 Ab (Non-Hodgkin's Lymphoma)
Alemtuzumab anti-CD52 Ab (T-cell Lymphoma,)
Gemtuzumab anti-CD33 Ab (AML)
Brentuximab anti-CD 30 Ab (Hodgkin's Lymphoma)

Table 9 Passive Cancer Vaccine

it can be given like a drug but they pass the immunity that means these monoclonal antibodies may not lead to long term immunologic memory. it important when the cancer returns to kick starts the endogenous or natural immune system and to kill those cancer cells. So that these is a major problem with passive cancer vaccine.

B. Active cancer vaccine

Major problem of the passive vaccine is, it not lead to long term immunologic memory and that problem can be solved by active vaccine. From the pieces of the tumor peptide, protein and RNA coding of tumor protein is loaded in to the APC such as DC. These DC activates CTLs or CD8 T-cells and CD4 T-cells which kill the tumor and kick start the endogenous cycle.[60]

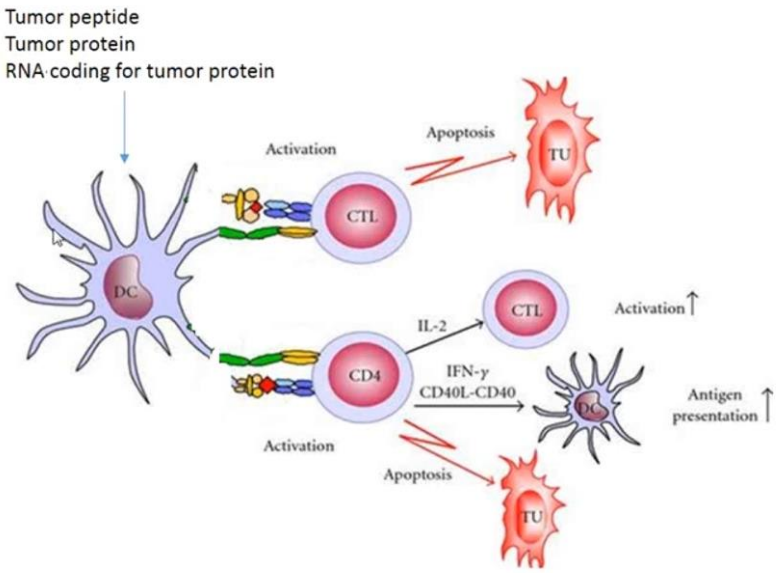


Fig. 25 Active cancer vaccine

Adopted from Clin Dev Immunol. 2010, Hanka Jahnich et al.

C. Peptide vaccine

It is studied in the context off malignant brain tumors for children. These peptides are artificially synthesized outside the patient's body with very specifically from the protein that are expressed on the tumor itself. These is given in the context of an adjuvant which is inflammatory material which allows the immune system to get really active. so that combination of artificially synthesized peptide and adjuvant is injected as a vaccine.[52][61]

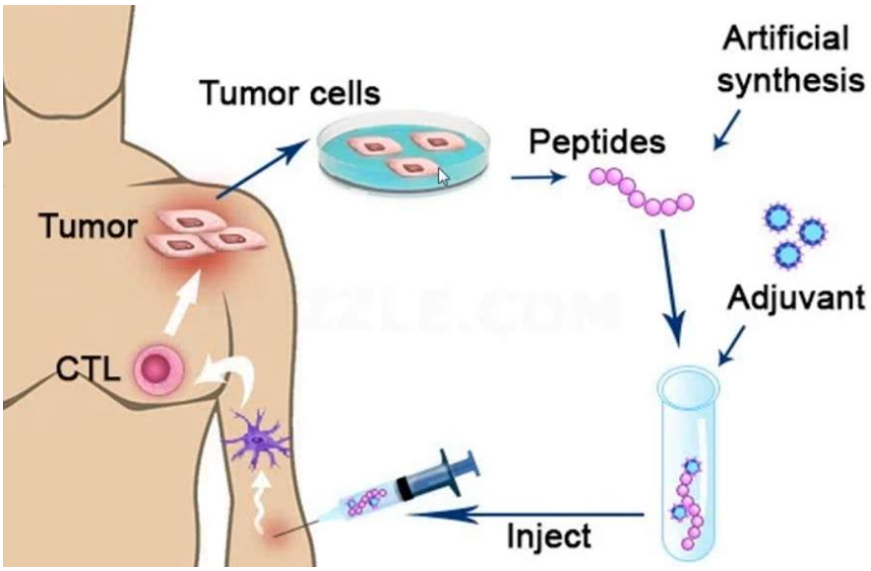


Fig. 26 Peptide Cancer Vaccine

Adopted from Reardon ASCO:2005

D. Nucleic acid vaccine

It is another strategy; RNA can be advantageous for vaccine because they don't need adjuvant. RNA its self can act as an inflammatory adjuvant. Tumor DNA to be integrated in a person's genome. RNA is only expressed in the cytoplasm of cell so it requires only cytoplasm entry. It is very patient specific and easy to produce and store. It can be easily amplified from as few as 500 tumor cells. [62]

E. dendritic cell vaccine

nucleic acid vaccine can be loaded in a dendritic cell which are obtained from the patient. It can be given in the context of chemotherapy with or without adjuvant.

One small pilot study by Duane Mitchell in adult patient with glioblastoma shows that DCV shows very promising survival benefits. in this study patient who received DCV had promising more improved progression free and overall survival benefit compared to patient who received unpulsed DCV. DCV still required lot of complicated cell therapy processing like obtaining cell from the patients, grow them outside the patient's body.[63][64][65][66]

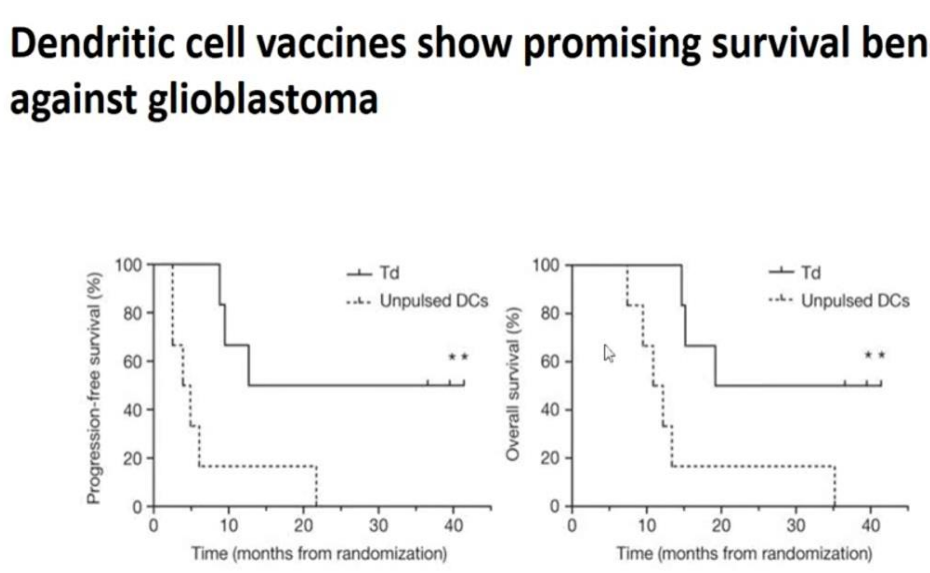


Fig. 27 Dendritic Cell Vaccine show promising survival benefits against glioblastoma
Adopted from Mitchell et al. Nature, 2015

F. Translatable RNA-nanoparticle Vaccine.

To overcome the problem of DCV another strategy like Translatable RNA-nanoparticle Vaccine is required. In this type of vaccine, extraction of information of tumor is required and after that instead of putting in to dendritic cell, combined it with nanoparticle. Now these nanoparticles are given as vaccine, it localized naturally to patient's APCs and DCs in the body and then these DCs activates the T-cell response. These shows very promising result in patient's with medulloblastoma but it is very costly and complex. Nanoparticle approach could be available for everyone.[67][68][69]

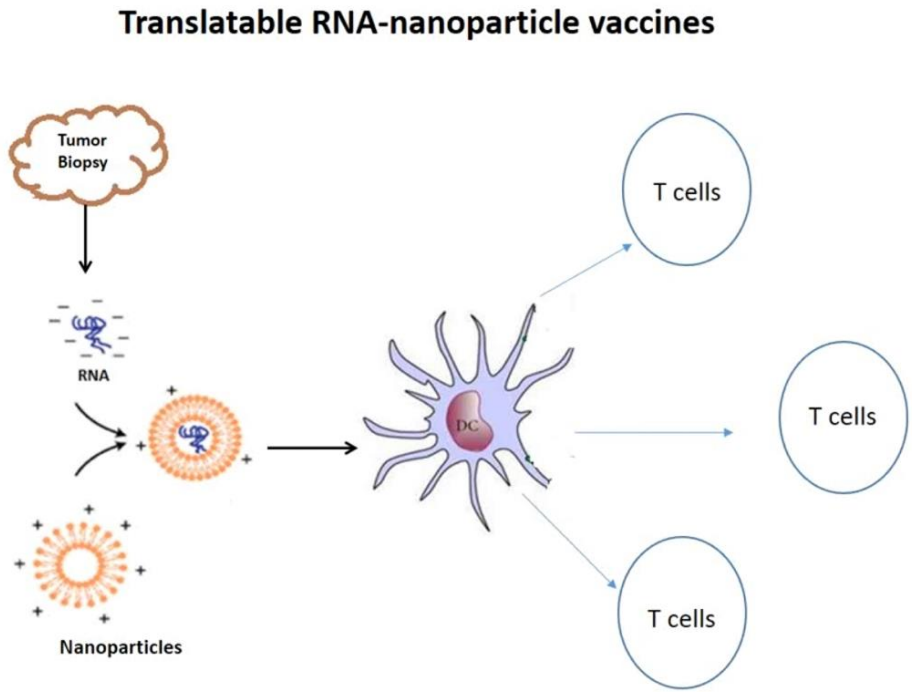


Fig. 28 Translatable RNA-nanoparticle vaccines

Adopted from Hanka jahnisch et al, Reviews in Molecular Medicine, Cambridge University Press, 2033

3. ONCOLYTIC VIRAL THERAPY

Viruses usually infect any cells but theses oncolytic viruses have been attenuated in such a way that allow them to replicate in only tumor cells. Tumor cell doesn't have lot of natural defence mechanism like healthy cells. Thus, these very weak viruses can actually replicate in just the tumor cells and very quickly from one tumor cell to another tumor cell for the next tumor cell and process goes continuously and kill those tumor cells.

This is immunotherapy because as the virus replicate inside just the tumor cell, immune system then recognizes the inflammation that's happening as a result of this and then immune system comes in and end the killing process of the tumor cells than virus does in the first place. These viruses actually lead to very strong immune response that kick starts endogenous cycle.[70][71]

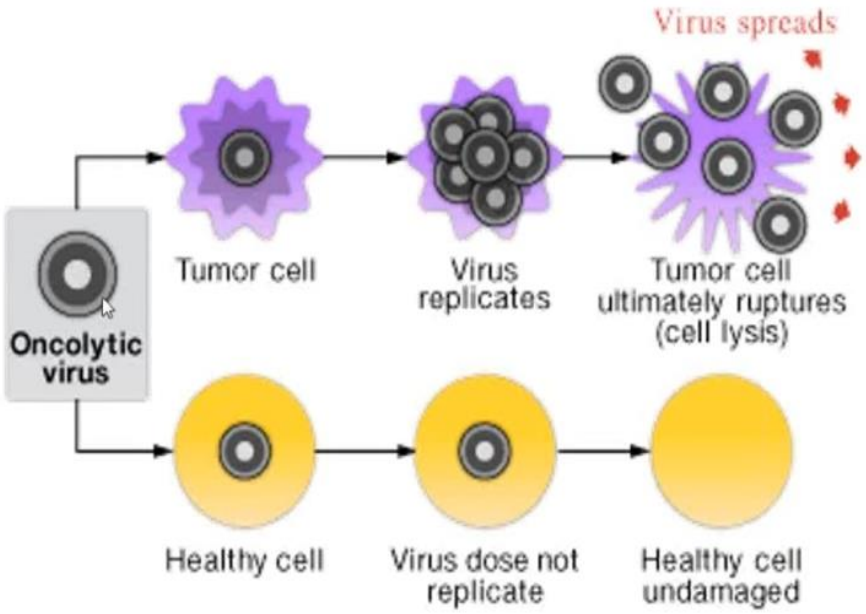


Fig. 29 Oncolytic Viral Therapy

Adopted from Clin Dev Immunol. 2010, Hanka Jahnich et al.

Open clinical trials for patients with pediatric brain tumor using these cancer vaccine, study of Dr Ian Pollak at the university of Pittsburgh in patients with recurrent ependymomas and low grade gliomas, high grade gliomas, brainstem gliomas where peptides are used and which are signals on those tumors that can combined in a vaccine (HLA-A2-Restricted Glioma antigen peptide vaccine) which generate T cell response against these tumors.

In a viral study of phase I clinical trial of Herps simplex virus (HSV G207 alone or with a Single radiation dose) at the university of Alabama in patient with superior super tentorial brain tumor that are recurrent.

There is also phase I b clinical trials of oncolytic poliovirus/Rhinovirus by Dr. Matthias grow at Duke university in children with recurrent malignant glioma.[72][73]

4. TARGETING IMMUNOREGULATION

This is based on targeting the check points By targeting the check points t cell of the patient can be unlocked against tumor. Tumors express checkpoint molecule such as PD-L 1 (programmed death ligand 1), even if there are activated T cell that can kill the tumors but It will not because tumor expresses death marker that turn off the activated T cell by engaging process so that by blocking this engaging process of PD-L1 with receptor on T cell (PD-1) it can be possible to keep the T-cell on and that can kill the tumor cell. E.g. **Ipilimumab, MK-3475 (Pembrolizumab; Anti PD-1)** [74][75]

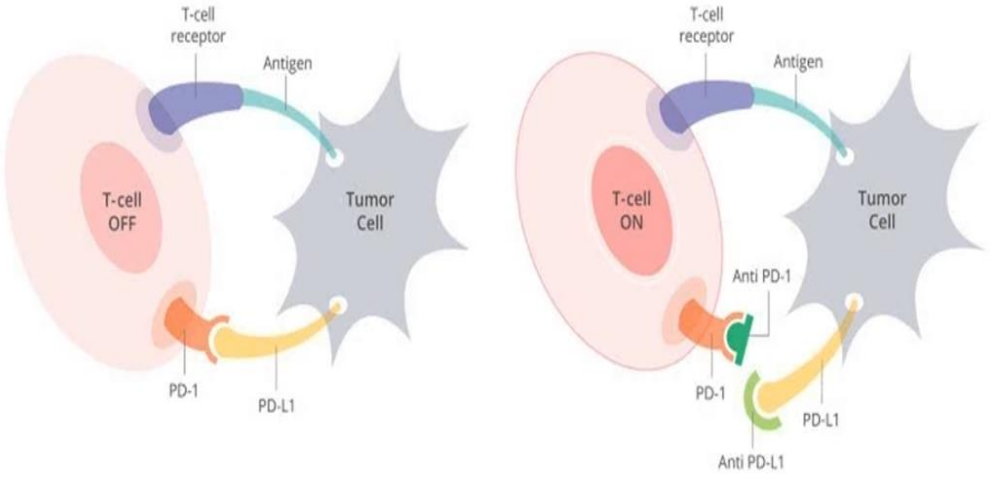


Fig. 30 Immune Check point Inhibitors
Adopted from Clin Dev Immunol. 2010, Hanka Jahnich et al.

In patient with melanoma who received ipilimumab which blocks checkpoints an improved survival outcome in patient with melanoma has been observed. But this response is only seen in the tumors that have a lot of mutation, it is not seen the tumor with very few mutations. In pediatric cancer, it doesn't have many mutations but melanoma have lots of mutation. [76] [77]

Pilot study of Nivolumab that blocks the PD L1 in pediatric patient with lots of mutation in cancer cell at Hospital for sick Children, Toronto.

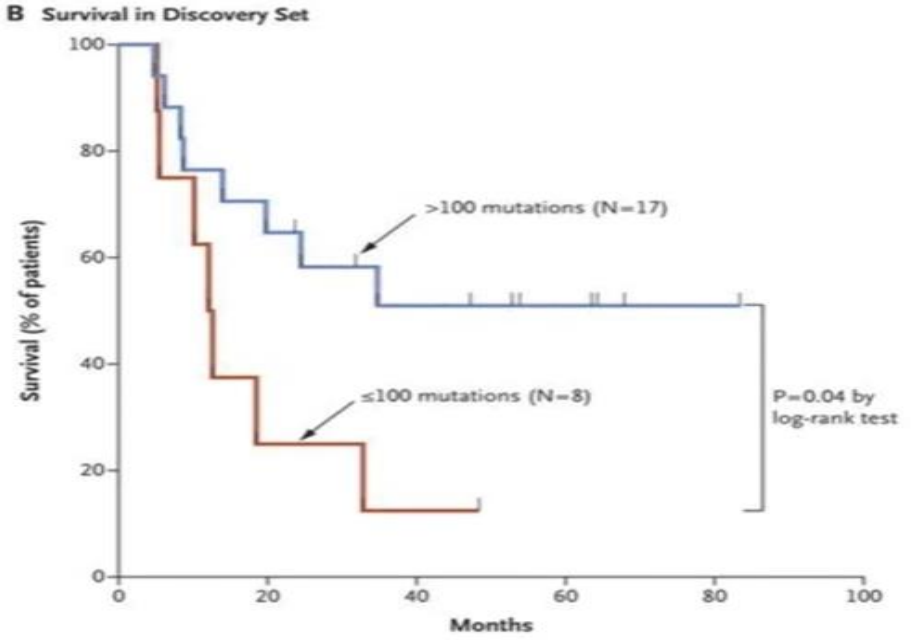


Fig. 31 "Mutation Landscape of tumors according to clinical benefit from Ipilimumab treatment."

Adopted from Snyder A et al. N Engl J Med 2014; 371:2189-2199

Medulloblastoma has very few mutations but it has lots of epigenetic modification which indicates that it's not a gene or mutation so much in these tumors that's driving them but how those genes are expressed and reprogrammed in these tumor and specifically in lots of pediatric tumor like medulloblastoma, there are developmental genes that should not stay off and That are being turned on again. Medulloblastoma can be divided into 4 distinct entities so it may be possible to target these developmental antigens because developmental epigenetically regulated antigen should not be expressed on normal cells. so, it just kills the tumors and not act on the normal tissue.[77]

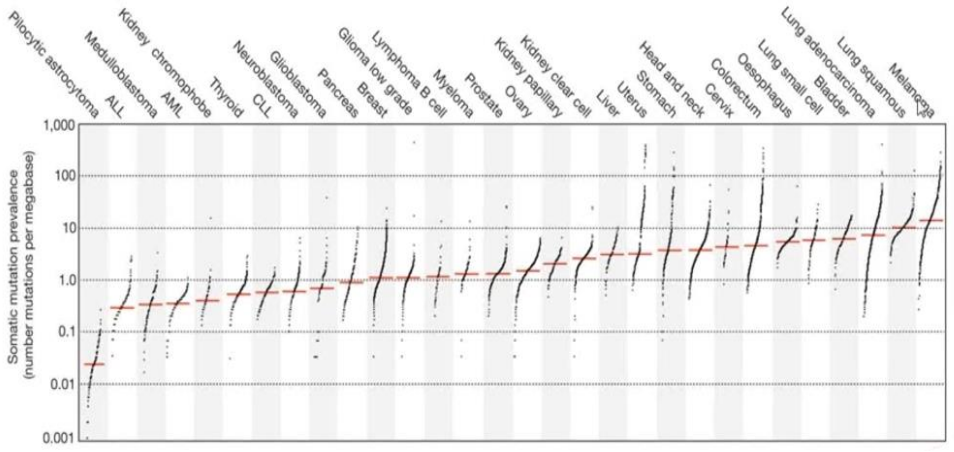


Fig. 32 Prevalence of mutation across human cancer types.

Adopted from Ludmil B. et al. Nature 2013, 500;415-421

5. INDOLEAMINE 2,3 DIOXYGENASE (IDO)

this enzyme actually starves nutrients of T cells which t cells uses to fight the cancer cell. If this enzyme is blocked inside the tumor it is possible to keep the source of nutrient for these t cells intake and allow these t cell to fight with cancer even better.[78][79]

Phase I study of Indoximod and Temozolomide in children with progressive primary brain tumors at Children's healthcare of Atlanta, Augusta University by Dr. Mod.[80]

➢ NOVEL THERAPIES

Many types of novel chemotherapy are currently under clinical trials. For novel therapies novel drug administration is required which includes convection therapy, intrathecal chemotherapy, implantation (wafer, beads), photodynamic therapy.[81]

convection enhanced delivery

New area in novel therapies is convection enhanced delivery. E.g. delivery of IL 13-PE38QQR (pseudomonas Exotoxin linked to IL 13) it is a concept of bypassing the BBB by putting the catheter right in to the brain so that it is a major advantage of this system.[82][83][84]

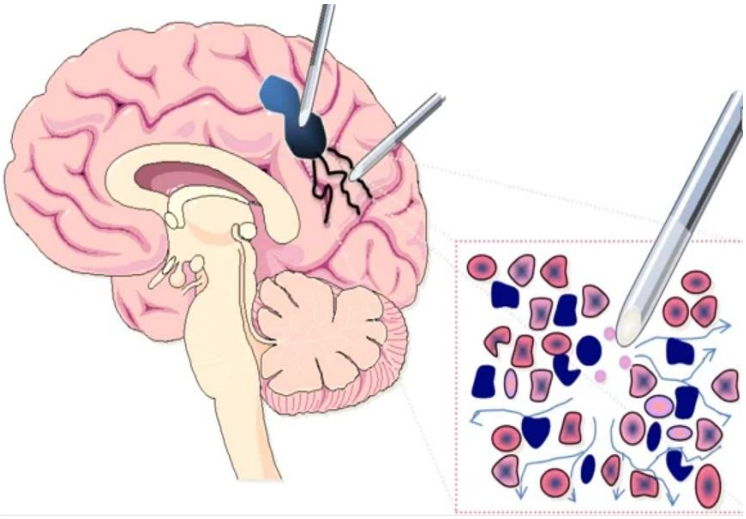


Fig. 34 convection enhanced delivery
Adopted from Reardon ASCO:2005

[7. CONCLUSION]

7. CONCLUSION

Over the last some decades survival rate of some malignant tumor is very poor and there is also some therapeutic challenge and to deal with these various difficult tumors, advances in treatment is required to prevent morbidity related to treatment. Recent advances in the treatment like preoperative and intraoperative imaging can help in the removal of brain tumors of more complexes region and improve patient's quality of life. There is intense research is still going on in novel design, molecular targeted therapy, different convectional treatment. These all ongoing research for advances in treatment of childhood brain tumors maybe it will give significance improvement and efficacy enhancement in the patient of pediatric brain tumor in future.

[8. REFERENECE]

8. REFERENCE

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