

Neuro-Oncology Disease Management Group (DMG) Website

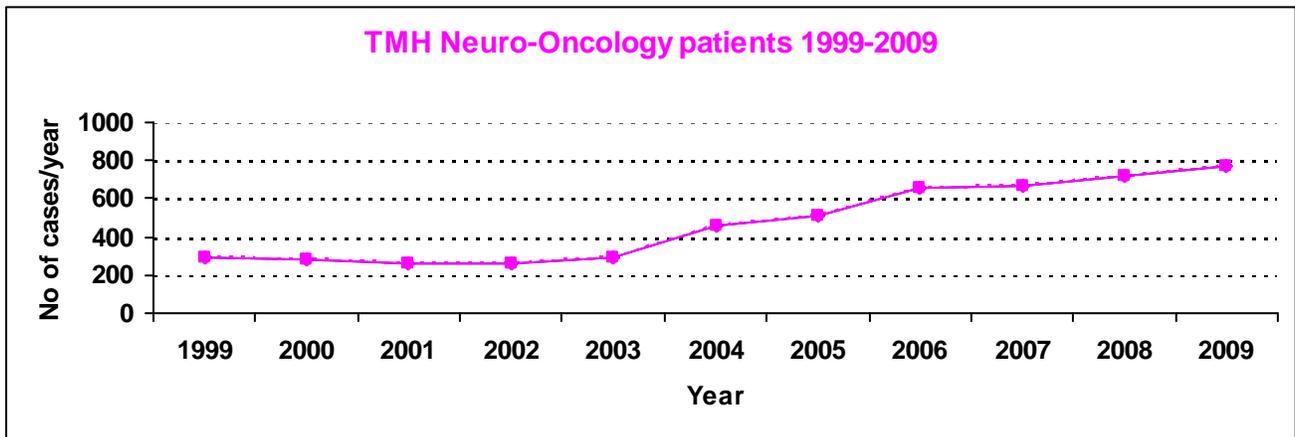
(A) INTRODUCTION

Central Nervous System (CNS) tumours, though uncommon are not a rare entity in clinical practice. These tumours are quite diverse in neurosurgical and neuro-oncological practice ranging from benign to malignant tumour and affecting all age groups right from the very young to the very old. Management of these tumours poses several challenges from therapeutic modalities to ancillary care including rehabilitation and support services. Several newer surgical innovations, chemotherapeutic agents and radiation therapy delivery techniques are being studied with emerging evidences, which mandates a critical appraisal of current evidences in the management of such tumour. One of the primary aims of this conference and book would be to sift the evidence critically, particularly to address its applicability in the Indian scenario and evolve management guidelines as per the best available evidence appropriate.

There is no organized brain tumour registry in India; hence, robust epidemiologic data is not available for the country. All currently quoted data is based on hospital-based cancer registries under the National Cancer Registry Program. The situation is compounded by the fact that major academic neurosurgical centers are not affiliated to comprehensive cancer centers and as such are not obliged to report their data to the national cancer registry.

The crude incidence of primary brain tumour in India is 3.4 per 100,000 populations for males and 1.2 per 100,000 populations for females. It represents < 1% of new cancer cases detected every year in the country. However, there has been a steady increase in the incidence of primary brain tumours over the last decade or so primarily due to higher detection rates due to more widespread availability of diagnostic imaging.

Tata Memorial Hospital has witnessed an increasing trend of primary brain tumours over the years and currently registers over 800 patients annually, which are being enrolled on a prospective Neuro-oncology database.

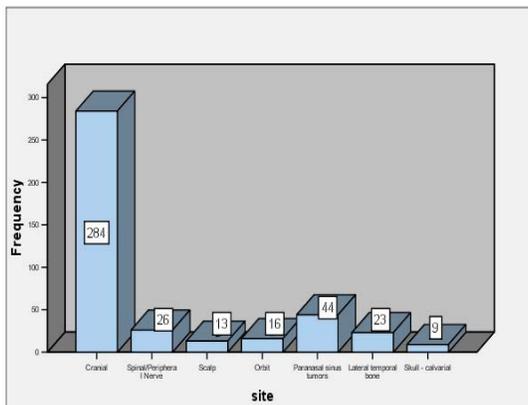


Total No of New Registrations in Yr 2010: 935

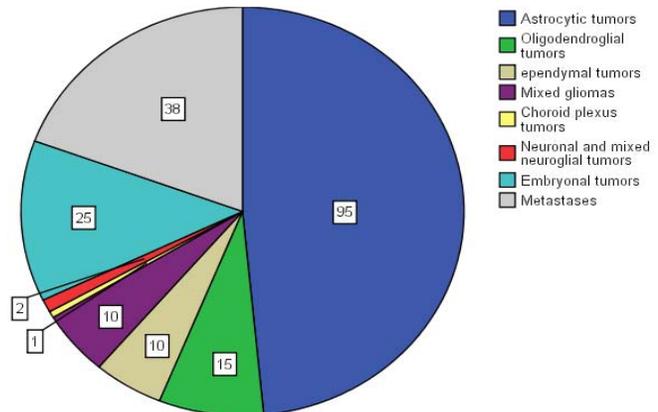
Neurosurgery in TMC: Census of 2007-2009

- Total 415 cases operated
- Spectrum of cases (see bar chart)
- Included 196 intra-axial tumors
- Spectrum of histology of intra-axial tumors (see pie diagram)

Spectrum of Cases (2007-2009)



Histological spectrum of Intra-axial tumors (2007-2009)



BRAIN TUMOUR: Brain tumours can be *benign* or *malignant*

- A. **Benign** brain tumours **do not** contain cancer cells: Usually, benign tumours can be removed, and they seldom grow back.
- The border or edge of a benign brain tumour can be clearly seen. Cells from benign tumours do not invade tissues around them or spread to other parts of the body. However, benign tumours can press on sensitive areas of the brain and cause serious health problems.
 - Unlike benign tumours in most other parts of the body, benign brain tumours are sometimes life threatening.
 - Very rarely, a benign brain tumour may become malignant.
- B. **Malignant** brain tumours **contain cancer cells:**
- Malignant brain tumour is generally more serious and often is life threatening.
 - They are likely to grow rapidly and crowd or invade the surrounding healthy brain tissue.
 - Very rarely, cancer cells may break away from a malignant brain tumour and spread to other parts of the brain, to the spinal cord, or even to other parts of the body. The spread of cancer is called *metastasis*.

Primary brain tumour: Tumours that begin in brain tissue are known as *primary tumour* of the brain. The most common primary brain tumours are *gliomas*. They begin in glial cells. There are many types of gliomas:

- **Astrocytoma** - The tumour arises from star-shaped glial cells called *astrocytes*. In adults, astrocytomas most often arise in the cerebrum. In children, they occur in the brain stem, the cerebrum, and the cerebellum. A grade III astrocytoma is sometimes called an *anaplastic* astrocytoma. A grade IV astrocytoma is usually called a *glioblastoma multiforme*.

- **Brain stem glioma** - The tumour occurs in the lowest part of the brain. Brain stem gliomas most often are diagnosed in young children and middle-aged adults.
- **Ependymoma** - The tumour arises from cells that line the ventricles or the central canal of the spinal cord. They are most commonly found in children and young adults.
- **Oligodendroglioma** - This rare tumour arises from cells that make the fatty substance that covers and protects nerves. These tumours usually occur in the cerebrum. They grow slowly and usually do not spread into surrounding brain tissue. They are most common in middle-aged adults.

Some types of brain tumours do not begin in glial cells. The most common of these are:

- **Medulloblastoma** - This tumour usually arises in the cerebellum. It is the most common brain tumour in children. It is sometimes called a *primitive neuroectodermal tumour*.
- **Meningioma** - This tumour arises in the meninges. It usually grows slowly.
- **Schwannoma** - A tumour that arises from a *Schwann cell*. These cells line the nerve that controls balance and hearing. This nerve is in the inner ear. The tumour is also called an acoustic *neuroma*.
- **Craniopharyngioma** - The tumour grows at the base of the brain, near the *pituitary gland*. This type of tumour most often occurs in children.
- **Germ cell tumour** of the brain - The tumour arises from a *germ cell*. Most germ cell tumours that arise in the brain occur in people younger than 30. The most common type of germ cell tumour of the brain is a *germinoma*.
- **Pineal region tumour** - This rare brain tumour arises in or near the *pineal gland*. The pineal gland is located between the cerebrum and the cerebellum.

Secondary brain tumours:

When cancer spreads from its original place to another part of the body, the new tumour has the same kind of abnormal cells and the same name as the primary tumour. Cancer that spreads to the brain from another part of the body is different from a primary brain tumour. When cancer cells spread to the brain from another organ (such as the lung or breast) doctors may call the tumour in the brain a *secondary tumour* or *metastasis* tumour. Secondary tumours in the brain are *far more common* than primary brain tumours.

DIAGNOSIS OF A BRAIN TUMOUR: POSSIBLE SYMPTOMS

- A new seizure in an adult
- Gradual loss of movement or sensation in an arm or leg
- Unsteadiness or imbalance, especially if it is associated with headache
- Loss of vision in one or both eyes, especially if the vision loss is more peripheral
- Double vision, especially if it is associated with headache
- Hearing loss with or without dizziness
- Speech difficulty of gradual onset
- Nausea or vomiting that is most severe in the morning, confusion and disorientation, and memory loss.
- The following symptoms are usually not caused by a brain tumour, but may sometimes be as a headache, abnormal change in behavior, infertility or amenorrhea.

Based on the above mentioned symptomatology which is always backed up with a sound history taking, the next eminent step is the diagnostic imaging techniques that have evolved immensely over the past years and have become a valuable adjunct to the sphere of Neuro-oncology.

DIAGNOSTIC IMAGING: Contemporary imaging modalities

Imaging	Remarks	Pros	Cons
CT scan	First line imaging modality	Good anatomic visualization Cheaper & Faster More widely available Can be used with metal objects	Limited reconstruction ability Exposure to ionizing radiation Poor resolution Contrast reaction
MRI	Gold standard imaging modality	Unparalleled resolution True multiplanar imaging No exposure to ionizing radiation	Susceptible to motion artifacts Cannot be used with metal objects Claustrophobic, noisy, long times Expensive
MR Spectroscopy	Assesses tumour metabolites	Useful for discriminating radiation necrosis from tumour	Limited utility near bone, vessels or air spaces Wide variability in interpretation
MR Perfusion	Assesses blood flow & volume	Generally correlates with grade Useful to distinguish radiation necrosis from tumour progression	Limited utility near bone, vessels

(B) WORK FLOW

- I. Appointment for New cases
- II. Decision Making Process

APPOINTMENT FOR NEW CASES: Tata Memorial Hospital is arguably one of the largest referral centre for patient with primary brain or spinal tumours in the country. Most patients are referred following surgery by neurosurgeons room teaching Hospitals like KEM, JJ, SION, and other hospitals from Mumbai and many other parts of the country, as well as few patients from Indian subcontinent, Middle east, Africa etc.

For appointments or enquiries please meet the Medical Secretaries in Room No. 115 (main building) or 102 (GJ Block), phone (022) 2417 7000extn. 4161,4545, 7153, 4538. The site map and information about how to reach is given in the hospital website <http://www.tmc.gov.in> .The referring doctor should send all pre and post op CT/MRI scans, clinical findings, detailed operative notes, pathology report and 2 unstained slides for review. For difficult or interesting cases where Immunohistochemistry (IHC) studies are necessary (pineal tumours, PNET, lymphoma, non-specific diagnosis etc.) please send paraffin blocks or 4-6 unstained slides.

General Patients Clinic:

Tuesday: 9.15 am - 1.30 pm Room No 102, 1st floor, G.J BLOCK, TMH. - Dr. Tejpal Gupta.

Thursday: 9.15 am - 1.30 pm Room No 102 G.J BLOCK, TMH - Dr Rakesh Jalali.

Tuesday & Thursday: 9.15 am - 1.30 pm Room No 1, GJ BLOCK, TMH -Dr. Aliasgar Moiyadi

Private Patients Clinic:

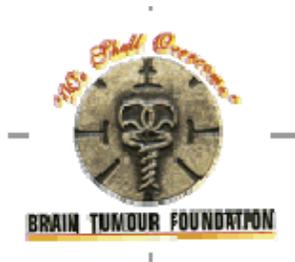
Monday to Friday (except Thursday): Dr. Rakesh Jalali and Dr. Tejpal Gupta -10am - 1pm Room No 125, Ground Fl, Main Bldg, TMH

Monday to Friday (except Tuesday & Thursday): Dr. Aliasgar Moiyadi -10am - 1pm Room No 48, Ground Fl, Main Bldg, TMH

Trial Patients Clinic: Wednesday: 2.00 pm - 5.30 pm Room No 707, 7th Floor, Annexe building, TMH.

DECISION MAKING PROCESS: All new cases are evaluated by the respective consultants and a treatment plan is formalized. Patients requiring multidisciplinary postoperative management, those with a diagnostic or therapeutic problem, interesting cases and patients eligible for trial are discussed in the weekly **Joint NeuroOncology meeting (JNOM)**. JNOM is held every Thursday at 2 pm at 'Dr. Sirsat Room', Dept of Pathology, 8th floor, Annexe Bldg. Very soon we shall be updating the BTF website with the discussions held and the decision taking of the challenging and interesting cases discussed in the meet on a weekly basis.

Brain Tumour Foundation (www.braintumourindia.com) —



With the central theme of “WE SHALL OVERCOME” the Brain Tumour Foundation is a charity, concerned with improving the care and treatment available to people with brain tumour and their families. We work in partnership with other organizations to develop and support services for people with brain tumour. We hope to help all patients in and around Bombay and expand our services to involve the whole country. The Foundation offers funds for treatment and care of brain tumour patients in financial need. It also funds research, nursing, and medical education programmes.

(C) MANAGEMENT OF BRAIN TUMOURS

- 1) **SURGERY:** Surgery is generally the initial and sometimes only treatment required. The aim is to remove as much of the tumour as is safely possible. Before the operation the neurosurgeon carefully studies the CT/MRI scans. The route and type of operation is then decided after discussing the risks and benefits of this operation with the patient. Hair is completely shaved before the operation. The operation is performed after giving anesthesia to the patient. While it is desirable to remove the tumour completely, this is not always possible if the tumour is very deep-seated or is in a very critical area. Therefore a tumour may be either completely or partially removed or only a biopsy may be taken. High-powered operating microscopes make it easier to see and remove tumours while sparing the normal brain. The operation may take many hours. The patient usually wakes up as soon as the effect of the anaesthesia wears off, but is kept in the ICU for some time to allow close observation and care.



The department performs routine microneurosurgical procedures at TMH. In addition regular ORs are conducted at ACTREC where patients enrolled on clinical trials are provided surgical care. The surgical department has state-of-the-art equipment including operating microscope (Zeiss OPMI Pentero), pneumatic drills, stereotactic frames, intraoperative ultrasound and Neuro-endoscope.

The department performs all major neurosurgical procedures for tumors including craniotomy (supra-and infratentorial), CSF diversion, stereotactic biopsy, transsphenoidal surgery, spinal laminectomy and laminoplasty for intradural and intramedullary tumors. Additionally, in collaboration with the Head-Neck services, we offer complex craniofacial and skull base surgeries including conventional anterior / anterolateral craniofacial resections, temporal bone surgery and transtemporal procedures, endoscopic as well as endoscopic-assisted craniofacial resections.

Image guided surgery: intraoperative ultrasound is routinely utilized during tumor surgery to facilitate accurate localization and maximal safe resection. The department is in the process of acquiring advanced ultrasound based navigation as well as intraoperative optical imaging for tumors. **Stereotactic surgery:** the department is equipped with a Leksell stereotactic frame each at TMH and ACTREC and provides stereotactic biopsies, as well as stereotactically guided therapeutic procedures. **Minimally invasive neurosurgery:** the neurosurgical service is equipped with neuro-endoscope for endoscopic surgery as well as endoscopic assisted microneurosurgical procedures. In addition, in conjunction with the head-neck surgical services, we provide fully-endoscopic and endoscopically-assisted craniofacial resections. **Pediatric neuro-oncology:** the department provides surgical care for pediatric brain and spinal tumors and performs surgeries for all types of pediatric brain and spinal tumors. Along with the pediatric oncology group, comprehensive care for all such patients is provided. **Skull base surgery and craniofacial resections:** A joint multidisciplinary Skull Base Clinic is conducted every week (4 pm, every Thursday, Room 37, Main building, TMH). Along with our head-neck and reconstructive colleagues complex craniofacial resections (conventional as well as endoscopic assisted) are performed routinely.

In addition, the department maintains a prospective database of all patients to document the clinicoepidemiological, radiological, and pathological features of these tumors

Education and training: The service provides training for specialist registrars in neurosurgical oncology as well as craniofacial and skull base surgery. This involves regular bedside teaching, didactic lectures, as well as interactive joint clinic decision making sessions, besides supervision during operative procedures. Additionally, training of nursing and paramedical staff is also provided.

- 2) **RADIOTHERAPY:** Radiotherapy is an integral component of the multimodality management of primary brain tumours with potential impact upon local control, symptom improvement, and progression free survival for low-grade and benign neoplasm and also overall survival for malignant brain tumours. Following maximal safe resection, adjuvant radiotherapy is indicated for all high-grade primary brain tumours in the postoperative setting. For completely excised benign tumours, such as pituitary adenomas and benign meningiomas, currently there is no role of upfront adjuvant radiotherapy. For low grade gliomas too, with no residual tumour on neuroimaging, surveillance alone is a reasonable option. However radiotherapy is recommended in such tumours either if a macroscopic residual tumour is evident on postoperative imaging or if tumour progression is documented on serial imaging. For tumours in the eloquent cortex where only a partial excision or biopsy if possible, radical radiotherapy is needed to improve outcome.

Conventional radiotherapy: includes planning on the Varian simulator (Ximavision) with treatment delivery on 4 Telecobalt machines and 3 Linear accelerators.

Three-dimensional (3D) conformal radiotherapy (3DCRT): with the help of 3-D planning systems and Eclipse. Treatment is delivered on Trilogy, Varian 2100 CD and Varian 6 Ex linear accelerators with standard leaf multileaf collimators. Quality assurance (QA) includes verification with digitally reconstructed radiographs (DRR) and electronic portal imaging. Stereotactic Radiosurgery (SRS) and Radiotherapy (SCRT) using the BrainLab microMultileaf Collimator system(M3). **Intensity modulated radiotherapy (IMRT):** using Helios software of Cadplan and Eclipse with treatment delivered with dynamic MLC (DMLC) technique. **Stereotactic conformal radiotherapy (SCRT) and Stereotactic radiosurgery (SRS):** using Brain lab software and microleaf collimators (micro MLC). **TOMOTHERAPY:** state of the art tomotherapy technique is also available at our centre and we are the only setup to possess this facility in the entire country which guarantees extremely precise treatment delivery with high accuracy.



Stereotactic Radiosurgery with Micro Multi Leaf Collimator [BrainLab]



3) **CHEMOTHERAPY: Principles of chemotherapy and biological therapy**

The role of chemotherapy and biological therapy in the multidisciplinary management of primary brain tumours continues to evolve rapidly. The goal of chemotherapy is to kill tumour cells directly by making them unable to replicate or to enhance normal process of cell death - apoptosis. Chemotherapy drugs may be cytotoxic or cytostatic. Some chemotherapy drugs act during specific parts of the cell cycle (cell-cycle specific drugs). Other drugs are effective at any time during the cell cycle and are referred to as non cell-cycle specific drugs. Combining non cross-resistant drugs to improve efficacy and reduce toxicity is the basis of contemporary multi-agent chemotherapy regimens.

- TEMOZOLOMIDE
- PCV (Procarbazine, CCNU, Vincristine)
- BEVACIZUMAB is a VEGF inhibitor used in recurrent high grade gliomas (most commonly in glioblastomas)

4) **PAEDIATRIC BRAIN TUMOURS**

Medulloblastoma: Medulloblastoma is the most common brain tumour in children accounting for approximately 7-8% of all intracranial tumours and 30% of pediatric brain tumours. It was originally described by Bailey and Cushing in 1925, and is now thought to arise from neural stem cell precursors in the granular cell layer of the cerebellum. It has a high propensity of spreading throughout the neuraxis via the cerebrospinal fluid (CSF). Extraneuraxial systemic metastases though well recognized are uncommon. The cornerstone of treatment is surgery in the form of maximal safe resection followed by adjuvant radiotherapy (craniospinal irradiation followed by tumour bed boost). Adjuvant chemotherapy is indicated in high-risk disease with standard dose CSI or in average risk disease whenever CSI is reduced. Apart from providing histologic confirmation, surgery also has the added benefit of restoring the natural CSF pathways in the brain

Adjuvant *chemotherapy* has become an integral part of treatment for medulloblastoma (MB). Several chemotherapeutic agents (especially alkylators and platinum) have been shown to be effective against medulloblastoma, and various chemotherapeutic strategies have been studied.

Primary CNS germ cell tumours: Germinomas: Germinomas are highly chemotherapy-sensitive tumours. Regimens that use cisplatin, carboplatin, or cyclophosphamide, along with vinblastine or vincristine, bleomycin, and etoposide, are capable of producing complete and partial response rates in as high as 90% in newly diagnosed patients. The current focus centers on the optimal balance of chemotherapy and radiation therapy.

Nongerminomatous germ cell tumours (NGGCT): The secreting intracranial NGGCT show an inferior prognosis compared to germinoma. In NGGCT, with standard chemotherapeutic regimens along with radiation, response rates exceeding 80% and survival rates of 48% to 80% have been seen. Relapse rates appear to be higher in the patients treated with involved field RT only. Therefore, craniospinal irradiation for all patients is advisable. At TMH, these patients receive 4 cycles of cisplatin based chemotherapy (PEI, appendix) are applied, followed by a delayed tumour resection and craniospinal irradiation (30-35 Gy plus 20-24 Gy tumour boost).

5. ANTIEPILEPTICS AND STEROIDS

Antiepileptic prophylaxis: Management of seizures in patients with brain tumours is a very contentious issue. The incidence of seizures in patients with brain tumours varies from 20-75% depending on the age, location and type of tumour. The highest incidence is in young patients with low grade tumours of the temporal lobe. Moreover, a large proportion of patients who do not present with seizures initially ultimately develop seizures during the course of disease.

Management of patients who present with seizures: Following perioperative prophylaxis, these patients are continued on AEDs for at least 2 years. They are assumed to have an established epileptogenic focus secondary to tumour and need to be treated with antiepileptic drugs (AEDs) as any other patient with symptomatic epilepsy. The AEDs can be discontinued if they have been continuously seizure free for 2 years.

Choice of AEDs: Commonly used AEDs include phenytoin, phenobarbitone, carbamazepine, and valproic acid. The first three have a narrow therapeutic window. Moreover, they are enzyme inducers and may produce drug interactions with concurrent chemotherapy leading to subtherapeutic levels. They also may cause extensive (rare) skin reaction with RT. Phenytoin remains the most commonly prescribed AED. Serum levels should be monitored and potential drug interactions borne in mind. Newer drugs like oxycarbamazepine, topiramate (as first choice) and levetiracetam (as add on) are promising and need further evaluation in trials.

(D) CLINICAL GUIDELINES

High grade glioma: High-grade gliomas (WHO grades III & IV) arise from malignant transformation of glial precursor cells and include anaplastic astrocytomas (AA), glioblastoma multiforme (GBM), anaplastic oligodendroglioma (AODG) and anaplastic ependymoma (AE). **(Fig 1)**

Low Grade Glioma: Low-grade gliomas (LGG) are a heterogeneous group of intrinsic CNS neoplasms that share certain similarities in clinical presentation, radiologic appearance, prognosis, and treatment. **(Fig 2) (Fig 3)**

Oligodendroglioma: Oligodendrogliomas (ODG) are primary glial brain tumours that arise from oligodendrocytes and are divided into grade II and anaplastic grade III tumours (WHO). Typically, they have an indolent course, and patients may survive for many years after symptom onset.

Ependymoma: Ependymomas are glial tumours that arise from ependymal cells within the CNS. The WHO classification scheme for these tumours includes 4 divisions based on histologic appearance: grade I (myxopapillary ependymoma and subependymoma); grade II (cellular, papillary, and clear cell variants); grade III (anaplastic ependymoma); and grade IV (ependymoblastoma) **(Fig 4)**

Brainstem Glioma: Brainstem gliomas are tumours that occur in the region of the brain referred to as the brain stem, which is the area between the aqueduct of Sylvius and the fourth ventricle. **(Fig 5)**

Craniopharyngioma: Craniopharyngioma is a histologically benign, extra-axial, slow-growing tumour that predominately involves the sella and suprasellar space. The primary treatment of choice is complete surgical excision. Local recurrence is common after surgical excision alone, with reported recurrence rates of 25-40% without adjuvant radiation. In recent times conservative surgery (maximal safe resection) followed by adjuvant radiation therapy is preferred to aggressive radical excision to improve outcome. A 5-year survival rate of 70-80% is achieved with contemporary microsurgery and adjuvant radiation therapy. The 10-year overall survival is 60-75%.

Meningiomas: Meningiomas are a group of tumours thought to arise from arachnoidal cap cells, which reside in the arachnoid layer covering the surface of the brain. They account for approximately 20% of all primary intracranial neoplasms. The cornerstone of management is complete neurosurgical resection. For completely excised benign and low grade meningiomas, there is no role of any adjuvant radiation therapy. For atypical meningiomas or those invading the brain extensively, adjuvant radiation therapy may be used to improve local control and progression free survival. The estimated 5-year survival for low grade meningiomas varies from 70-90%. Malignant and atypical meningiomas have a far more aggressive clinical course with a 5-year survival of 40-60%.

Fig 1: High Grade Glioma (AA/AOA/AODG/GBM)

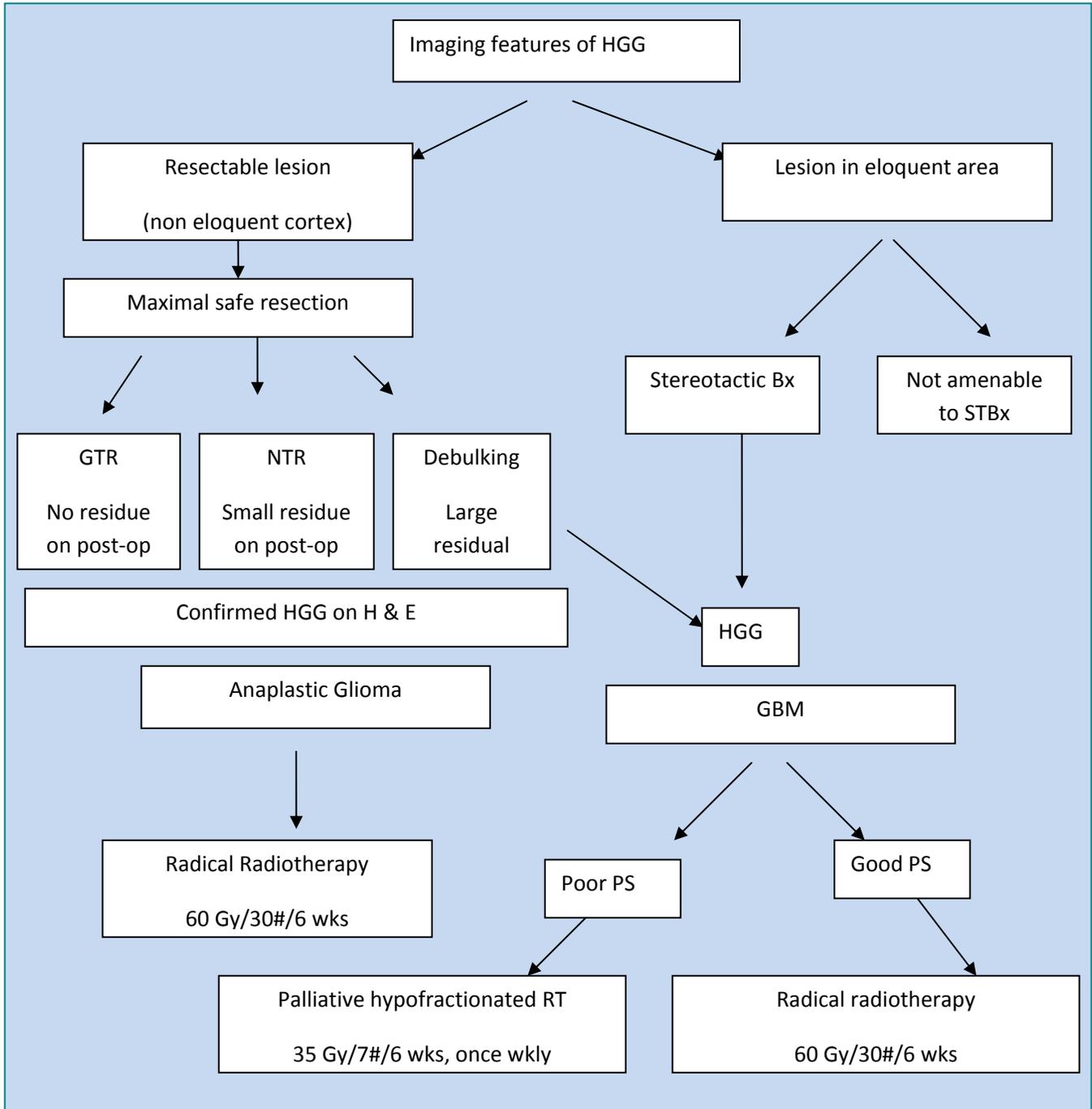


Fig 2: Infiltrating Low Grade Glioma including ODG

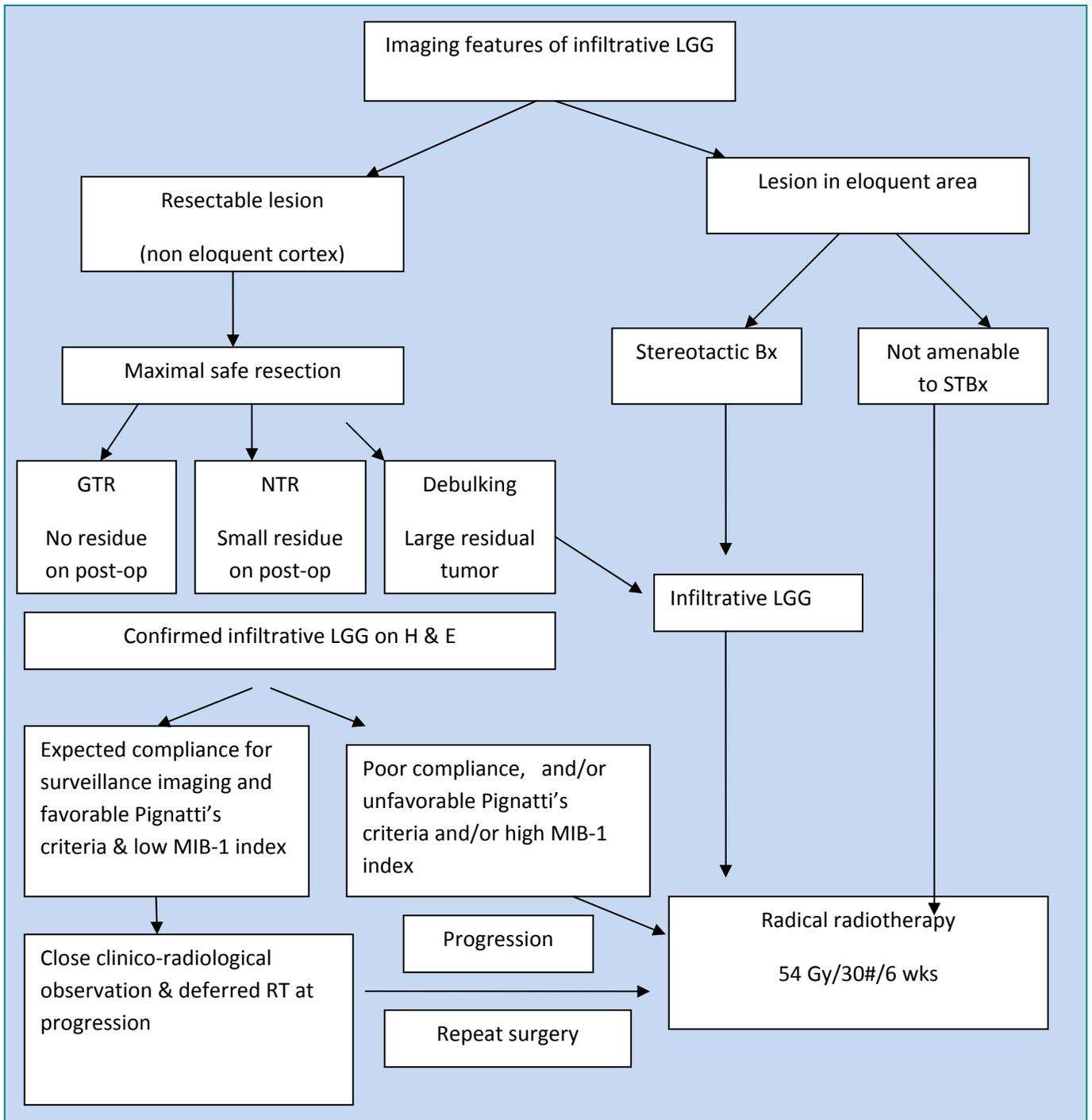
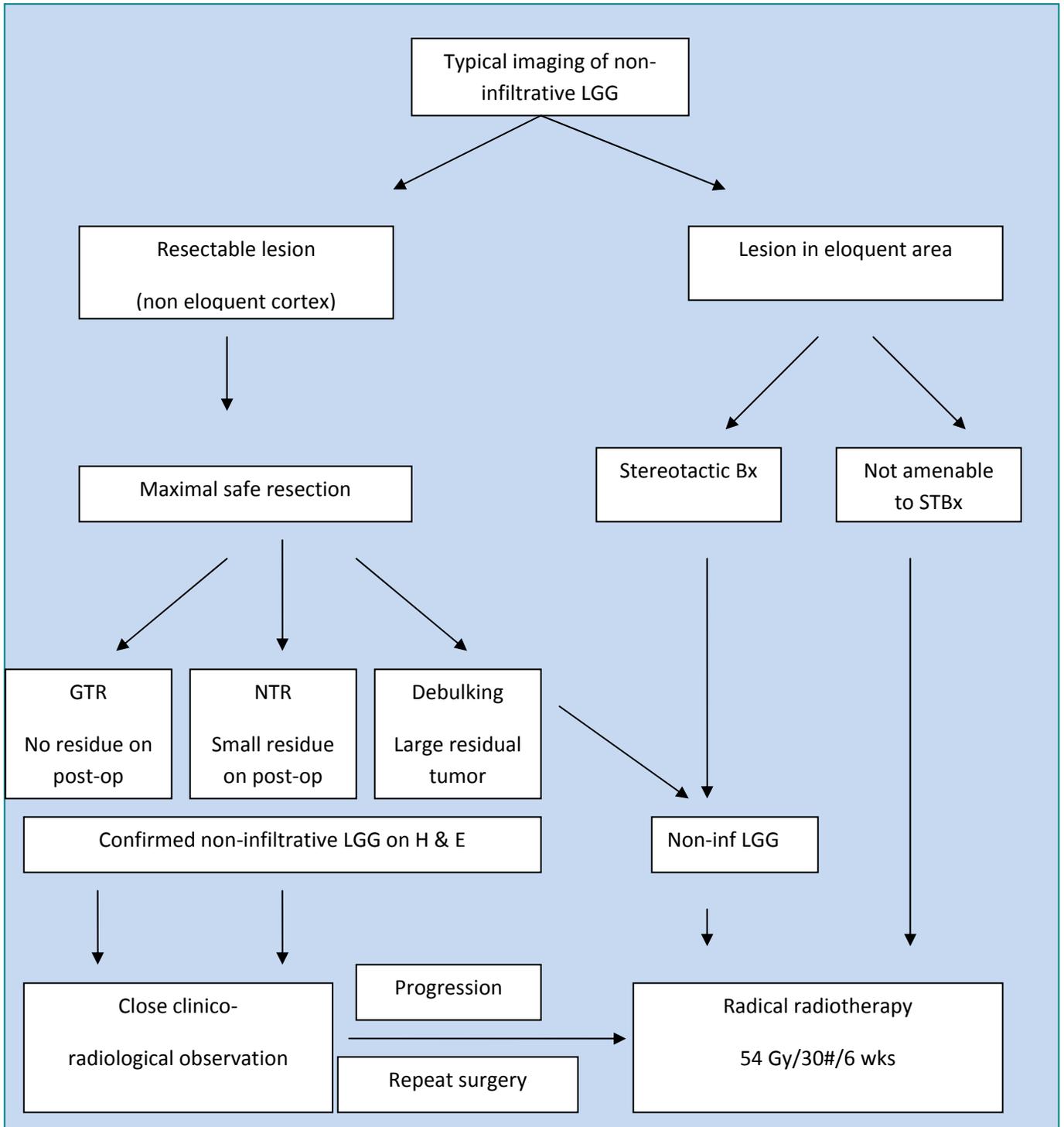


Fig 3: Non-infiltrative Low Grade Glial/Glioneuronal Tumours

(Juvenile Pilocytic Astrocytoma / Dysembryogenic Neuro Ectodermal Tumours / Ganglioglioma / Subependymal Giant cell Astrocytoma/ Neurocytoma)



(Fig 4): Ependymomas

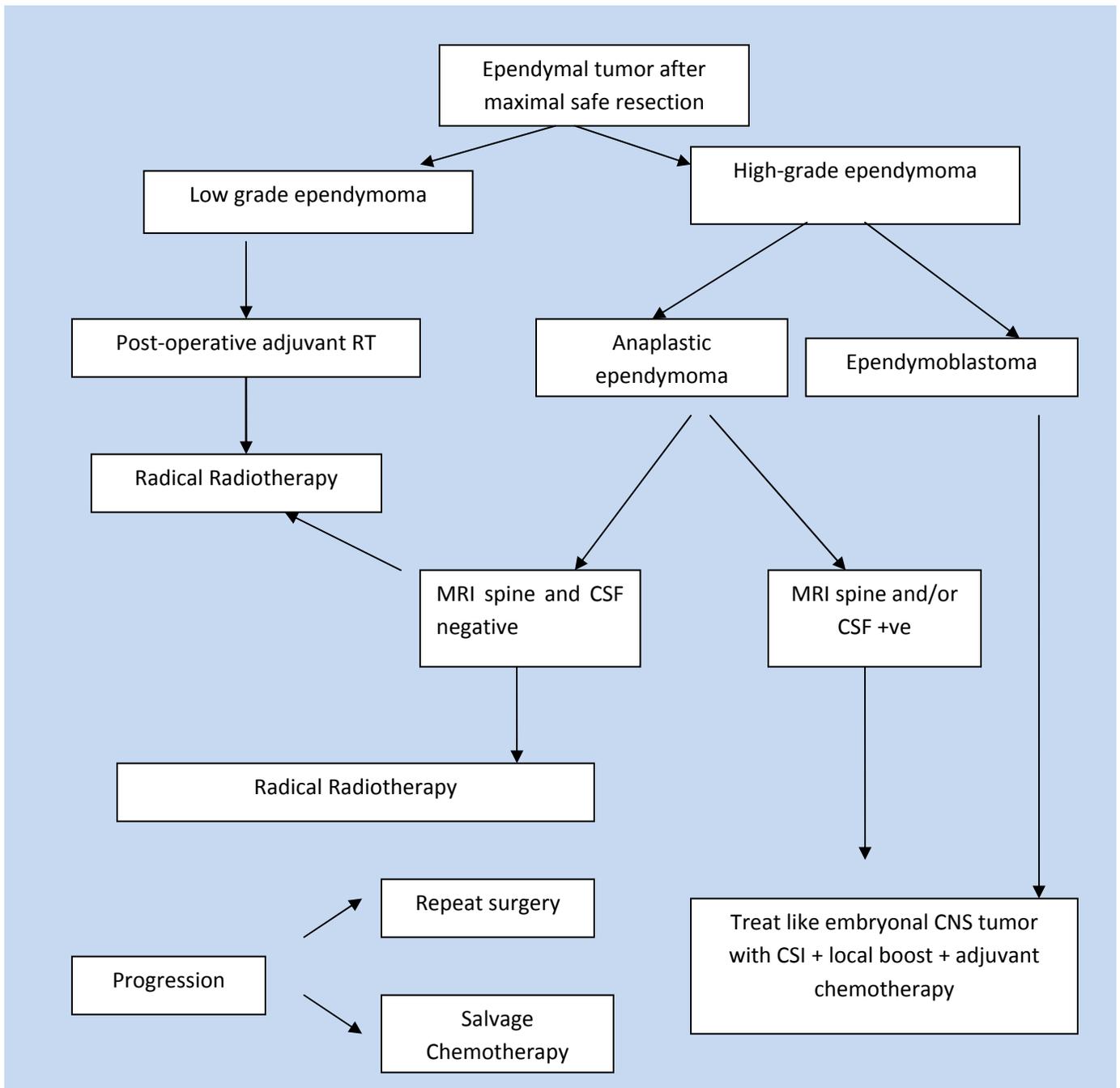


Fig 5: (DIPG / focal exophytic / cervicomedullary / tectal plate gliomas)

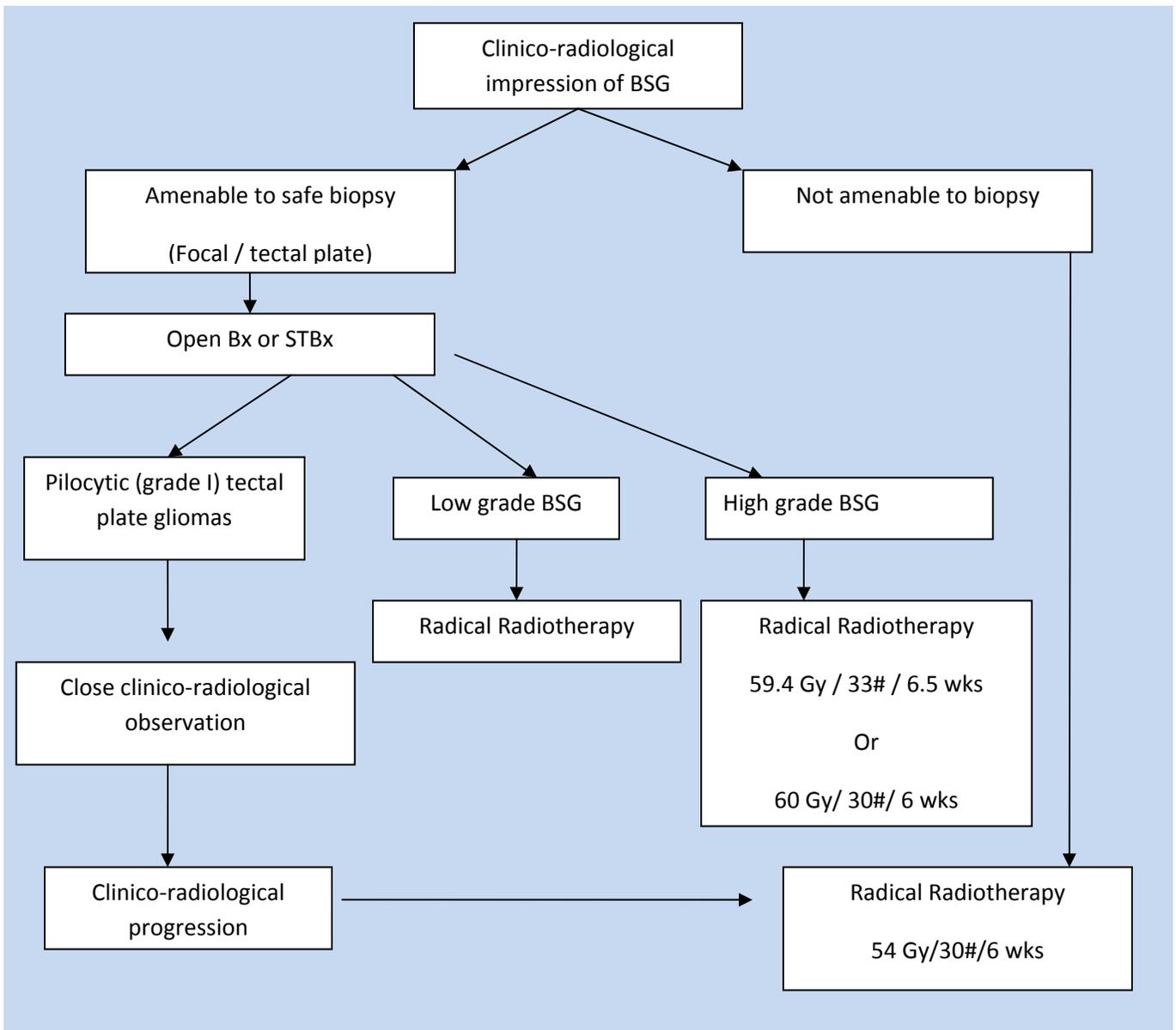
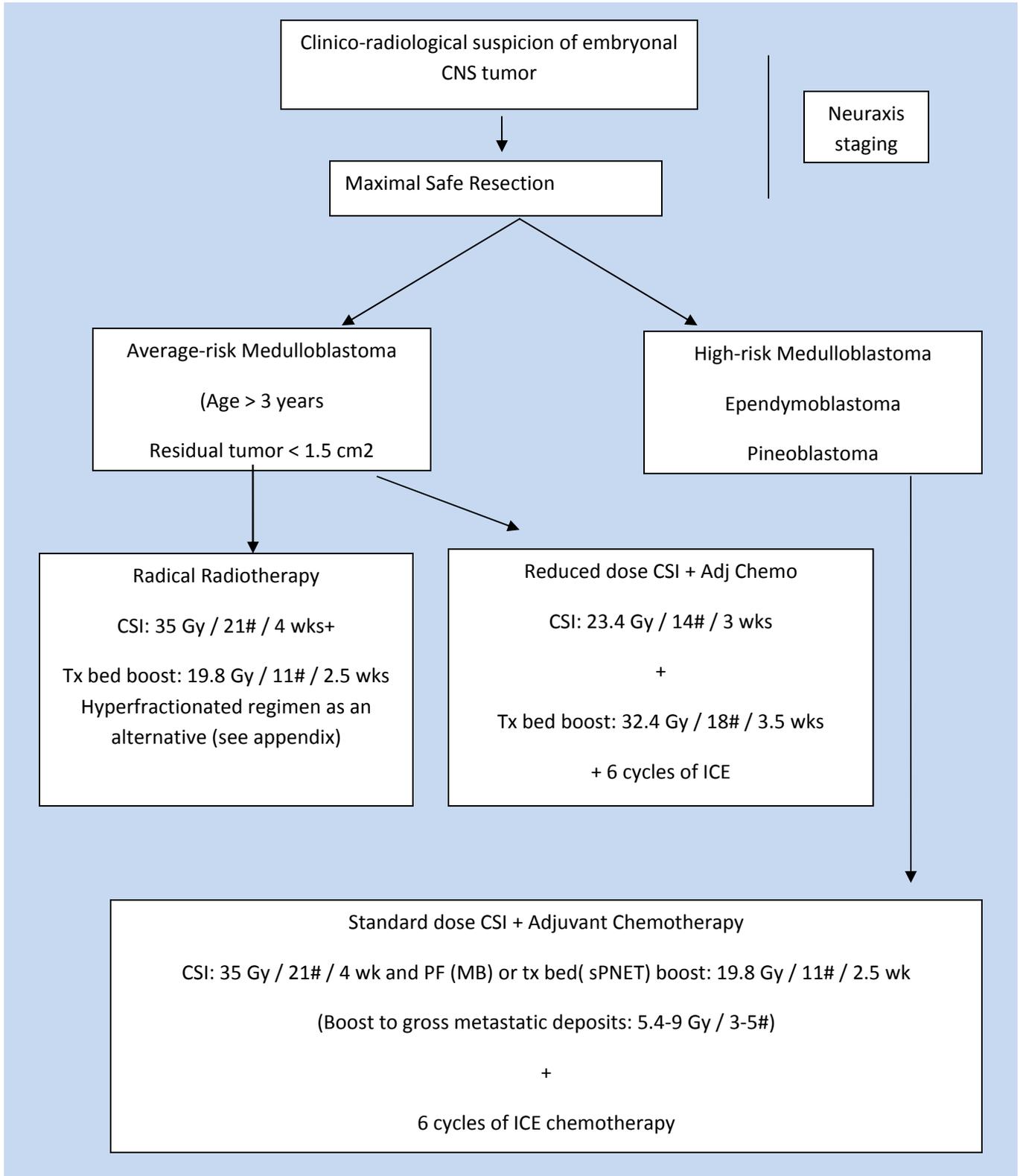


Fig 6: Primitive / Embryonal CNS tumours

(Medulloblastoma / sPNET / ATRT / Ependymoblastoma / Pineoblastoma)



Performance scales

KPS (Karnofsky Performance Score)

- 100% = Normal; no complaint; no evidence of disease
- 90% = Able to carry on normal activity; minor signs of disease
- 80% = Normal activity with effort, some signs or symptoms of disease
- 70% = Cares for self, unable to carry out normal activity or to do active work
- 60% = Requires occasional assistance, but is able to care for most of own needs
- 50% = Requires considerable assistance and frequent medical care
- 40% = Disabled, requires special care and assistance
- 30% = Severely disabled, hospitalization is indicated although death not imminent
- 20% = Hospitalization necessary, very sick, active supportive treatment necessary
- 10% = Moribund, fatal processes progressing rapidly

Neurological Performance Scale (MRC)

- 0 = No neurologic deficit
- 1 = Some neurologic deficit but function adequate for useful work
- 2 = Neurologic deficit causing moderate functional impairment, e.g. ability to move limbs only with difficulty, moderate dysphasia, moderate paresis, some visual disturbance (e.g. field defect)
- 3 = Neurologic deficit causing major functional impairment, e.g. inability to use limb/s, gross speech or visual disturbances
- 4 = No useful function - inability to make conscious responses

ECOG / WHO PS Scale

- 0 = Able to carry out all normal activity without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out light work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
- 3 = Capable only of limited self-care; confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair

(E) OUTCOME DATA

30-day Perioperative outcomes for intra-axial tumors (2007-2009)

Major morbidity:

Overall :	17%
Neurological worsening:	11%
Surgical site infection:	07%
Perioperative Mortality:	3.5%

SURVIVAL— GBM

We report 5-year survival data in patients with newly diagnosed glioblastoma treated with radiotherapy along with concurrent and adjuvant temozolomide (TMZ). Patients with newly diagnosed histopathologically proven glioblastoma underwent surgery followed by external radiotherapy to a total dose of 60 Gy in 30 fractions over 6 weeks. Concurrent oral TMZ (75 mg/m²) was given daily with RT followed by adjuvant TMZ for 5 days every 28 days for six cycles (150 mg/m² for the first cycle and 200 mg/m² for rest of the cycles). Patients were monitored clinicoradiologically as per standard practice. All six adjuvant cycles were completed in 68%. The 2-, 3-, 4-, and 5-year survival was 34%, 24%, 11%, and 11%, respectively (95% CI 14.03–21.96). The median overall and progression-free survival was 18 (2–92 months) and 16 months (2–72 months), respectively. On multivariate analysis, completion of all six cycles of adjuvant TMZ was associated with significantly better survival ($p = 0.000$). Neurological performance score (NPS) of 2–3 ($p = 0.06$) and Recursive Partitioning Analysis class V ($p = 0.093$) showed a trend towards poorer outcome. Treatment was generally well tolerated with only 2.5% of patients developing grade 3 anaemia, leucopenia, and neutropenia. Grade 3 or 4 thrombocytopenia was seen in 5% patients. We therefore concluded that concurrent radiotherapy and TMZ followed by adjuvant TMZ results in encouraging survival even at a long follow-up. (*Journal of Clinical Oncology*, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition)).

The purpose of this study was to report our experience with concomitant and adjuvant temozolomide (TMZ) with radiotherapy in patients with newly diagnosed glioblastoma multiforme (GBM). Forty-two newly diagnosed histopathologically proven patients with GBM underwent maximal safe resection followed by external radiotherapy to a total dose of 60 Gy in 30 fractions over 6 weeks along with concomitant oral TMZ (75 mg/m²) daily followed by adjuvant TMZ for 5 days every 28 days for six cycles (150 mg/m² for the first cycle and 200 mg/m² for rest of the cycles). All patients received concomitant radiation and TMZ with 74% of the patients completing six cycles of adjuvant TMZ. At a median follow-up of 12.5 months, the 1- and 2-year survival was 67 and 29%, respectively. The median

overall and progression-free survival was 16.4 and 14.9 months respectively. Concomitant radiotherapy and TMZ followed by adjuvant TMZ prolongs survival in patients with glioblastoma multiforme and is well tolerated in our patient population (*British Journal of Neurosurgery*, December 2007; 21(6): 583 – 587).

CHILDREN LOW GRADE TUMOURS

We reported local control and follow up outcome data of high precision conformal radiotherapy in childhood brain tumours. Between December 1999 and December 2002, 26 children (17 boys and 9 girls, median age 11.5 years) with incompletely excised or recurrent benign and low-grade brain tumours [13 craniopharyngiomas, 11 low-grade gliomas (LGG) and 2 others] were treated with three-dimensional (3D) conformal radiotherapy (CRT) (12 patients) and stereotactic conformal radiotherapy (SCRT) (14 patients). Treatment was delivered with 3–9 conformal fixed fields to a median dose of 54 Gy/30 fractions. The actuarial 2 and 3 year disease free and overall survival was 96 and 100%, respectively (median follow up: 25 months, range 12–47 months) High-precision conformal techniques delivering irradiation to a computer generated target volume employing 7–10 mm 3D margins beyond the visible tumour and/or resected tumour bed appear to be safe in children with incompletely resected or recurrent benign and low-grade brain tumours, based on these data (*Radiotherapy and Oncology* 74 (2005) 37–44).

QUALITY OF LIFE (QOL) — We have conducted studies to assess the QOL in patients seen in routine clinical practice under the BTF and the work has been published in indexed journal.

The aim of this study was to evaluate and assess the impact of various factors on quality of life (QOL) in adult patients with primary brain tumours seen consecutively in routine neurooncology practice. Two hundred and fiftyseven adult patients, after undergoing surgical intervention and histologically proven primary brain neoplasms were registered in the NeuroOncology Clinic at our centre during 1 full calendar year. And found that Patients with a HGG and from high economic strata had more preserved global QOL function than patients in middle/low economic strata. It may well be that patients with HGG have usually functional impairments. Patients from high economic strata with comparatively better supportive care and rehabilitation may have helped them to preserve global QOL score to some extent. However, in benign and low grade tumours where functional impairments are not so severe had no significant difference in different economic strata. (*J Neurooncol* (2009) 95:413–419 DOI 10.1007/s11060-009-9939-8)

ACTIVITIES OF DAILY LIVING (ADL)—

Barthel's Index has been used to assess the functional status with degenerative neuronal disorders in elderly patients with cerebrovascular accidents, brain injury, motor neuron disease, and hemiplegia. In patients with CNS tumours, BI has been used as well to evaluate the efficacy of supportive care or any intervention (radiotherapy or surgery), primarily in elderly patients with high-grade glioma. we, at TMH conducted a study for the Prospective assessment of activities of daily living using Modified Barthel's Index in children and young adults with low-grade gliomas treated with stereotactic conformal radiotherapy and concluded that Young patients with low-grade gliomas after surgical intervention had a lower than normal BI before starting radiotherapy, suggesting a decrease in ADL possibly due to tumour- and surgery-related factors. At 2-year and 3-year follow-up after SCRT, there was no further decrease in mean BI. A significant improvement in BI was seen in visually handicapped patients, patients with poor performance status, and younger

patients. Patients who developed tumour recurrence at follow-up had a significantly lower BI at baseline than patients with controlled disease (P < 0.001). (*J Neurooncol DOI 10.1007/s11060-008-9666-6*)

These encouraging outcome data that is arguably one of the best around the world is an indication of the hard work, dedication and the policies of our BTF which is proving to be a boon for the patients of all classes and socio economic strata in their fight against brain tumours.

Patients with brain tumors have varied degree of functional and psychological impairments because of factors relating to the tumor or to the treatment they receive. The functional independence measurement and functional activity measurement system (FIM–FAM) is an activity of daily living (ADL) scoring system that may be able to determine impairments in different domains objectively. The mean total FIM–FAM score of the entire patient population was 167.5 (range 30–208). Scores in self care, sphincter control, mobility items, locomotion, communication items, psychological, and cognitive item domains were 39.49, 10.95, 22.70, 16.44, 28.93, 18.96, and 30.1, respectively. Univariate analysis showed total FIM–FAM scores not significantly different with age (<35 years vs. ≥35 years; P = 0.994), sex (male versus female; P = 0.133), and grade of the tumor (high-grade versus lowgrade; P = 0.142) but were significantly higher in patients with a Karnofsky performance score (KPS) of ≥70 as compared with <70 (P = 0.001), neurological performance scale (NPS) of 0 or 1 vs. 2 or 3; P = 0.001), disease type (benign versus malignant; P = 0.001), and site of disease (cerebral versus cerebellar; P = 0.024). Multivariate analysis confirmed these findings for KPS (P = 0.001) and NPS (P = 0.012) only. Age was a significant factor for poorer cognitive function (P = 0.005), psychological (P = 0.045), and self care function (P = 0.001). A trend for correlation between tumor sites with the corresponding function as assessed on the FIM–FAM score was observed. FIM–FAM system is relatively simple, easy to perform in routine clinical practice and may be used as a tool for assessment of rehabilitation program. There is strong correlation with age, type of tumor, and site of disease with different functional and cognitive domain impairment. (*J Neurooncol DOI 10.1007/s11060-009-9810-y*)

The ***BTF*** works with the prime objective to minimize the physical, emotional and financial suffering associated with the diagnosis, treatment and rehabilitation of patients with brain and spine tumours, and their families.

- Facilitate the treatment, accommodation, transportation, rehabilitation and special education of such patients. Support the cost of investigation, treatment and rehabilitation for really needy patients with potentially curable tumour. Support research into the causes, treatment and rehabilitation of brain tumour patients. Provide information and support to patients and care-givers of patients with brain tumours. Provide all types of counselling services, including psychological and grief counselling for the patient and the family before and after treatment.
- Public education via print and electronic media
- The ***BTF*** involves agencies such as Hospitals, doctors, occupational therapists, physiotherapists, speech therapists, psychologists and nurses (*presently from the Tata Memorial Hospital (TMH) and King Edward Memorial Hospital (KEM), Mumbai. Later, we plan to involve other centers in Mumbai and elsewhere*) Medical Social Workers (at the Tata Memorial Hospital and from other agencies) Cancer Patients Aid Association and V-Care Indian Cancer Society Ambulance services National Association for Blind Spastics Society of India and

other organizations which can help us with their expertise and network. Schools: (Special Education Schools as well as normal schools that admit children with various degrees of neuropsychological problems).

- Patient's Support groups: A group of brain tumour survivors and their families in different parts of the country.

(F) MAIN CLINICAL TRIALS**A. Investigator-initiated trials: Clinical**

IRB No	Title of Project	Investigators	Date of approval	Status	Budget	Funding agency
270	Optimizing the physical and biological parameters in craniospinal irradiation (CSI) for average risk medulloblastoma: a feasibility study	<u>Gupta T</u> , Jalali R, Sarin R, Muzumdar D, Sanghavi D, Merchant N	July 2006	Ongoing; 19 pts accrued; 1 remaining	Rs 3.4 Lakhs	CRC- ACTREC
200	A prospective study of concurrent carboplatin and radiotherapy followed by adjuvant chemotherapy in patients with newly diagnosed high-risk central nervous system embryonal tumours	<u>Kurkure PA</u> , Arora B, Bhagwat R, Gupta T, Sarin R, Jalali R, Muzumdar D, Kumar C, Kane S	June 2004	Ongoing; Over 50 patientts accrued	Rs 4.5 lakhs	CRC- ACTREC
197	Intensity modulated radiotherapy (IMRT) for craniospinal irradiation (CSI) in pediatric brain tumours- a dosimetric and feasibility study	<u>Jalali R</u> , Sharma D, Sarin R, Gupta T, P Reena, Shrivastava SK, Dinshaw KA	July 2004	Ongoing; 19 pts accrued, 1 remaining	Rs 3.0 lakhs	CRC- ACTREC
556	Feasibility of a low cost image based approach for safe and optimal resection of brain tumours.-A pilot study	<u>Moiyadi A</u> , Thakur MH, R Sarin, R Jalali, T Gupta, A Munshi	March 2008	Await of equipmeting procurement	Rs 60 Lakhs	DAE
653	Safety and efficacy of oral valproate in recurrent /progressive brain tumours	<u>Gupta T</u> , V Gota, S Gupta, R Jalali, A Munshi, R Sarin, A Moiyadi, H Menon, P Kurkure, S Medhi, N Merchant	Conditional approval granted in July 2009	Yet to receive final HEC clearance	Rs 5 Lakhs	To be sought
408	Head-Shaving in Neurosurgery – Implications on Surgical Site Infection and Cosmesis - A Feasibility Study	<u>Moiyadi A</u> .	2008	Ongoing; initial accrual over; permission for extended accrual obtained	Rs 1 lakh	Intramural grant
53	Efficacy of stereotactic conformal radiotherapy (SCRT) compared to conventional radiotherapy in minimising late sequelae in children and young adults with brain tumour: a randomised clinical trial (SCRT trial).	<u>Sarin R, Jalali R</u> , Merchant N, Goswami S, Shah N, Dinshaw KA	2001	Ongoing	Rs 14 lakh approx	Terry Fox

B. Investigator-initiated trials: Basic/Translational

329	Genome wide expression profiling to determine the molecular basis of sensitivity to temozolomide in patients with glioblastoma multiforme	<u>N Shirsat, R Jalali,</u> R Sarin, T Gupta, A Moiyadi	Mar 2008 Grant as ICMR Centre of Excellence Genomics Proteomics	Ongoing	Rs 20.32 lakhs	ICMR
495	Proteomic analyses of medulloblastoma to identify sensitive biomarkers to detect, diagnose, and monitor disease: a biological correlative link-up study to currently ongoing clinical trials in medulloblastoma	<u>P Venkatraman,</u> T Gupta, P Kurkure, A Moiyadi, B Arora, R Jalali, R Sarin	July 2008 Grant as part of ICMR Centre of Excellence Genomics Proteomics	Ongoing	NK	ICMR
385	Identification of molecular sub-classes of medulloblastomas by genome wide expression analysis coupled with array-CGH	<u>N Shirsat,</u> R Sarin, R Jalali, T Gupta, A Moiyadi		Ongoing	NK	

C. Industry-sponsored trials:

694	Cilengitide for subjects with newly diagnosed glioblastoma multiforme and methylated MGMT gene promoter - a multicenter, open-label, controlled Phase III study, testing cilengitide in combination with standard treatment (temozolomide with concomitant radiation therapy, followed by temozolomide maintenance therapy) versus standard treatment alone (CENTRIC)	<u>T Gupta, R Jalali,</u> R Sarin, A Munshi, A Moiyadi, H Menon, S Epari, N Merchant, S Juvekar	January 2010	Site initiated; Patients being pre-screened	Rs 43.5 Lakhs approx	Merck- Serono
687	Efficacy and safety of AP 12009 in adult patients with recurrent or refractory anaplastic astrocytoma (WHO grade III) as compared to standard treatment with temozolomide or BCNU: a randomized, actively controlled, open-label clinical phase III study (SAPPHIRE)	<u>A Moiyadi,</u> T Gupta, R Jalali, A Munshi, R Sarin	October 2009	Site initiated; patients being pre-screened	Rs 20 Lakhs approx	Antisense Pharma