Cancer Education Day

Brief Overview: Oligodendroglioma / Astrocytoma

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Declarations

No Conflicts of Interest
No AI was used or injured in the generation of these slides

(aka: ‘old school presentation’)

Is there a ‘Working Definition?

A Relative Term

Relative Compared to What?

What to Choose for Topics?

Challenges:

1. Understanding the nature and pathobiology of cancer is based on:

- Basic Medical Research
- Funding
- Interest in the Scientific Community
- Impact of the disease in the population (Incidence and Prevalence)

Challenges:

2. Developing an Evidence Base

- Less common - smaller numbers to study
- The Power of Clinical Studies
- Levels of Clinical Evidence
- Funding of Research

Primary CNS Tumors

Low Grade Astrocytomas (gliomas)

Oligodendrogliomas (Low and High Grade)

Objectives

- Overview
- Clinical Presentations
- Work-up
- Treatment
- Outcomes and Follow-up

Terminology

Diffuse astrocytic and oligodendroglial tumors:
Diffuse astrocytoma, IDH mutant
Gemistocytic astrocytoma, IDH mutant
Diffuse astrocytoma, IDH wild type
Diffuse astrocytoma, NOS
Anaplastic astrocytoma, IDH mutant
Anaplastic astrocytoma, IDH wild type
Anaplastic astrocytoma, NOS
Glioblastoma, IDH wild type
Giant cell glioblastoma
Gliosarcoma
Epithelioid glioblastoma
Glioblastoma IDH mutant
Glioblastoma, NOS
Diffuse midline glioma H3 K27M mutant
Oligodendroglioma, IDH mutant and 1p / 19q codeleted
Oligodendroglioma, NOS
Anaplastic oligodendroglioma, IDH mutant and 1p / 19q codeleted
Anaplastic oligodendroglioma, NOS
Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS

Other astrocytic tumors:

Pilocytic astrocytoma
Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma

Ependymal tumors:
Subependymoma
Myxopapillary ependymoma
Ependymoma
Papillary ependymoma
Clear cell ependymoma
Tanycytic ependymoma
Ependymoma, RELA fusion positive
Anaplastic ependymoma

Other gliomas:

Chordoid glioma of the third ventricle
Angiocentric glioma, astroblastoma

Choroid plexus tumors:
Choroid plexus papilloma
Atypical choroid plexus papilloma
Choroid plexus carcinoma

Neuronal and mixed neuronal glial tumors:
Dysembryoplastic neuroepithelial tumor
Gangliocytoma ganglioglioma
Anaplastic ganglioglioma
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Desmoplastic infantile astrocytoma and ganglioglioma
Papillary glioneuronal tumor
Rosette forming glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Paraganglioma

Lymphomas:

Diffuse large B cell lymphoma (DLBCL) of the CNS
Immunodeficiency associated
AIDS related DLBCL
EBV positive DLBCL
Lymphomatoid granulomatosis
Intravascular large B cell lymphoma
Low grade B cell lymphomas of the CNS
T cell and NK / T cell lymphomas of the CNS
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK negative
MALT lymphoma of the dura

Risk Factors

- Previous radiation therapy
- Certain genetic conditions
- Family history of brain tumours
- Weakened immune system

GENETIC SYNDROMES

..NF-1: von Recklinghausen, chromosome 17q11.2, 1/3500 live births, *NF1* encodes neurofibromin, autosomal dominant, 50% germline, 50% de novo, peripheral nerve sheath neurofibromas, café au lait spots, optic and intracranial gliomas, and bone abnormalities.

..NF-2: chromosome 22, 1/50,000 live births, *NF2* encodes merlin, autosomal dominant, bilateral acoustic neuromas, gliomas, ependymomas, and meningiomas.

..von Hippel-Lindau: chromosome 3, autosomal dominant, renal clear cell carcinoma, pheochromocytoma, hemangioblastoma, pancreatic tumors, and renal cysts.

Certain genetic conditions

- Neurofibromatosis affects the nerves, muscles, bones and skin. Both neurofibromatosis type 1 (von Recklinghausen disease, or NF1) and neurofibromatosis type 2 (acoustic neuroma, or NF2) increase the risk for brain and spinal cord cancer. But these cancers occur more often in people with NF1. Some research shows that brain and spinal tumours caused by NF2 tend to be slow growing and non-cancerous.
- Von Hippel-Lindau (VHL) syndrome – chromosome 3 – autosomal dominant- is a rare condition where people develop tumours and cysts in many different parts of the body. Tumours may be non-cancerous or cancerous.
- Li-Fraumeni syndrome- germline P53 mutation- is a rare condition that increases the risk of developing different types of cancer, including brain tumours.

Immune Deficiency Conditions

- The immune system is a complex group of cells and organs that defend your body against infection, disease and foreign substances. When the immune system isn't working well, you are at greater risk for primary central nervous system lymphoma (PCNSL). People at high risk include those who:

- take drugs to suppress their immune system after an organ transplant
- receive treatments that suppress their immune system, such as chemotherapy, to treat other cancers
- have HIV or AIDS

EPIDEMIOLOGY

3,300 Canadians will be diagnosed with brain and spinal cord cancer.
2,600 Canadians will die from brain and spinal cord cancer.
1,850 men will be diagnosed with brain and spinal cord cancer and 1,500 will die from it.
1,400 women will be diagnosed with brain and spinal cord cancer and 1,100 will die from it.

(CCS Statistics 2024)

..Malignant tumors comprise ~40% of all primary brain/ CNS tumors.

..Adult primary CNS tumors: 30–35% meningioma, 20% GBM, 10% pituitary, 10% nerve sheath, 5% low-grade glioma, <5% anaplastic astrocytoma, <5% primary CNS lymphoma.

..Of adult gliomas, ~80% are high-grade and ~20% are low-grade.

..Children: 20% of all pediatric tumors (second to ALL). Twenty percent pilocytic astrocytoma, 15–20% malignant

Overview

- Symptoms presentation
- Clinical Evaluation
- Investigations/Imaging
- Referral for Neurology, Neuro Sx, Oncology opinions

Symptom Presentation

- seizures
- nausea and vomiting
- changes in personality, thinking, memory and behaviour
- difficulty speaking or understanding words
- abnormal movements
- trouble walking
- weakness on 1 side of the body
- difficulty with fine motor skills
- trouble swallowing and eating
- vision problems including blurred vision, double vision and loss of vision
- hearing problems
- problems with balance
- drowsiness
- fatigue
- numbness in part of the body
- confusion
- coma

Computed Tomography

- CT with and without contrast
- CT Angiography

MRI

- MRA (magnetic resonance angiography) shows the structure of blood vessels in the brain and is useful in planning surgery.
- MRS (magnetic resonance spectroscopy) shows some features of brain tumours that are not clearly seen by MRI. It may help determine the possible tumour type and may be used after treatment to see if an abnormal area is a tumour or scar tissue.
- Perfusion MRI (magnetic resonance perfusion) shows the amount of blood going through different parts of the brain and can give an idea of how fast a tumour is growing. It can help determine the best place to take a biopsy and may be used after treatment to see if an abnormal area is a tumour or scar tissue.

MRI IMAGING

..Common MRI sequences: T1 pre- and postgadolinium, T2, fluid attenuation inversion recovery (FLAIR), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion, dynamic contrast enhanced (DCE), Spectroscopy.

..Enhancement with gadolinium is indicative blood–brain barrier (BBB) disruption.

..Acute blood is bright on T1 pregadolinium.

..Postop MRI with DWI should be completed within 48 h.

Devascularized normal tissue at the resection cavity border can exhibit reduced diffusion and can enhance on subsequent scans. Must take caution to distinguish this enhancement from tumor recurrence or treatment effect.

Management Overview

- Imaging guides initial management decisions in combination with patient factors, working diagnosis/differential of lesion type
- Surgical management: 1) confirmation of Dx 2) resection indications
- Non-surgical Primary vs Adjuvant vs Sequential treatment
  - radiotherapy (standard photon beam- external beam)
  - FSRT/HSRT (fractionated stereotactic xrt)
  - Radiosurgery (single fraction – Gammaknife vs Cyberknife)

Chemotherapy- temozolomide
- lomustine
- PCV

Low Grade Gliomas

- 10% of primary intracranial tumors, 20% of gliomas.
- Age of onset: 30–40 for Grade II gliomas and 10–20 for pilocytic astrocytomas.

Presentation:

- seizures (60–70%, better prognosis) > headache > paresis.

Low Grade Gliomas

Favorable prognostic factors:

- age < 40 years, good KPS,
- GTR, low proliferative indices,
- oligodendroglioma (IDH1 mutant, 1p/19q codeleted),
- absence of neurologic symptoms, size <6 cm.
- LGGs - often non-enhancing

..Pathology: See WHO 2016 revised

Adult Low Grade Glioma: Management

Maximal safe resection (GTR or STR)

Low-Risk (eg. IDH mut, 1p/19q co-deleted, GTR): Observation vs. chemoRT vs. chemo

High-Risk (eg. IDHwt, STR, Age ≥ 45): ChemoRT vs. chemo

Refractory Seizures: chemoRT

Low Grade Gliomas (LGG)

- Treatment of adult low grade gliomas is controversial
- Standards of care – continue to evolve with new molecular classifications and targeted therapies
- Based upon RTOG 9802, addition of chemotherapy to radiation should be strongly considered for every subgroup.
- PCV was used in 9802; however, TMZ is an acceptable alternative based upon NOA-04 and RTOG 9813.
- Results from ongoing trials will further clarify management.

LGG- Management

- For patients who wish to delay radiation, chemotherapy alone may be a reasonable alternative for asymptomatic grade 2 gliomas.
- Timing of chemotherapy and radiation is the subject of an ongoing trial.

LGG - Management

STUDIES

TIMING OF RT

..*EORTC 22845 "Non-Believers"* (Karim IJROBP 2002, van den Bent Lancet 2005): Phase III. 311 patients (WHO 1–2, 51% A, 14% O, 13% OA) treated with surgery (42% GTR, 19% STR, 35% Bx) randomized to observation vs. postop RT (54 Gy). RT improved median progression-free survival (5.3 vs. 3.4 yrs), 5-year PFS (55 vs. 35%), but not OS (68 vs. 66%). 65% of patients in the observation arm received salvage RT. No difference in rate of malignant transformation (66–72%). Seizures were better controlled at 1-year in the radiation arm.

LGG - Management

RTOG 9802 Low-Risk Arm (Shaw JNS 2008): Phase II. 111 patients with supra-tentorial LGG age < 40, GTR (determined by neurosurgeon) who were observed after surgery.

5-year OS and PFS were 93% and 48%. Poor prognostic factors:

- Initial size > 4 cm
- A vs OA histology
- > 1 cm residual post –resection on MR review

LGG - Management

.*EORTC 22033* (Baumert Lancet Oncol 2016, Reijneveld Lancet Oncol 2016): Phase III. 477 patients with previously-untreated high-risk low-grade glioma (age > 40, radiographic progression, tumor size >5 cm, tumor crossing midline, or neurologic symptoms) randomized to RT alone 50.4 Gy or TMZ up to 12 cycles. Median FU 4 yrs. Median PFS overall: RT 51 mo, TMZ 40 mo. IDH1/2 mutation and 1p19q codeletion status are prognostic factors. Median PFS IDH mutated and codeleted: RT 62 mo, TMZ 55 mo. Median PFS IDH mutated & noncodeleted: RT 55 mo, TMZ 36 mo. Median PFS IDH wild type: RT 19 mo, TMZ 24 mo. No difference in 3 yr. HRQOL or cognitive dysfunction by MMSE. Criticism: RT alone arm has similar PFS to the RT alone arm of RTOG 9802, but is clearly inferior to the RTOG 9802 chemoRT arm.

DOSE

..*EORTC 22844 "Believers"* (Karim IJROBP 1996): Phase III. 343 patients (WHO 1–2, astro., oligo. and mixed) treated with surgery (25% GTR, 30% STR, 40% biopsy) randomized to postop RT 45 Gy vs. 59.4 Gy (shrinking fields). No difference in OS (59%) or PFS (49%). 5-year OS was better with oligo histology (75 vs. 55), and age < 40 (80 vs. 60%). Age < 40, oligo histology, small tumor size, GTR, and good neurologic status are prognostic factors.

INTERGROUP (Shaw JCO 2002): Phase III. 203 patients (WHO I–II, astro, oligo, mixed) treated with surgery (14% GTR, 35% STR, 51% Bx) randomized to postop RT 50.4 Gy vs. 64.8 Gy. No difference in 5-year OS (72% low dose vs. 64% high dose). Best survival in patients age < 40, tumor <5 cm, oligo histology and GTR. Increased Grade 3–5 toxicities (2.5 vs. 5%) with higher dose. Pattern of failure: 92% in field, 3% within 2 cm of RT field.

CHEMORT

..*RTOG 9802 High-Risk Arm* (Buckner NEJM 2016): Phase III. 251 patients with high-risk (age ≥ 40 or STR/biopsy) LGG randomized to postop RT alone vs. RT → PCV × 6 cycles. RT 54 Gy to FLAIR +2 cm margin. PFS and OS curves diverged with long-term follow-up. OS (7.8 vs. 13.3 yrs) and PFS (4.0 vs. 10.4 yrs) favored the RT-PCV arm. 10-year PFS and OS were 21% vs. 51%, and 40% vs. 60%, respectively. On post hoc analysis, PFS was improved for oligodendrogliomas, oligoastrocytomas ($P < 0.05$), and a trend was observed in astrocytomas ($p = 0.06$), and IDH R132H mutants with chemoRT. OS was improved for oligodendrogliomas, oligoastrocytomas, and R132H mutants ($p \leq 0.05$), but the finding was not significant for astrocytomas.

RTOG 0424 (Fisher IJROBP 2015): Phase II. 129 patients with high-risk LGG (≥3 risk factors: age ≥ 40, astrocytoma, bihemispheric, tumor ≥6 cm, neurologic function status >1) treated with TMZ, concurrent and adjuvant TMZ.

3-year OS was 73.1%, which was higher than the prespecified historical control ($p < 0.001$). Stratification by molecular subtype not yet reported.

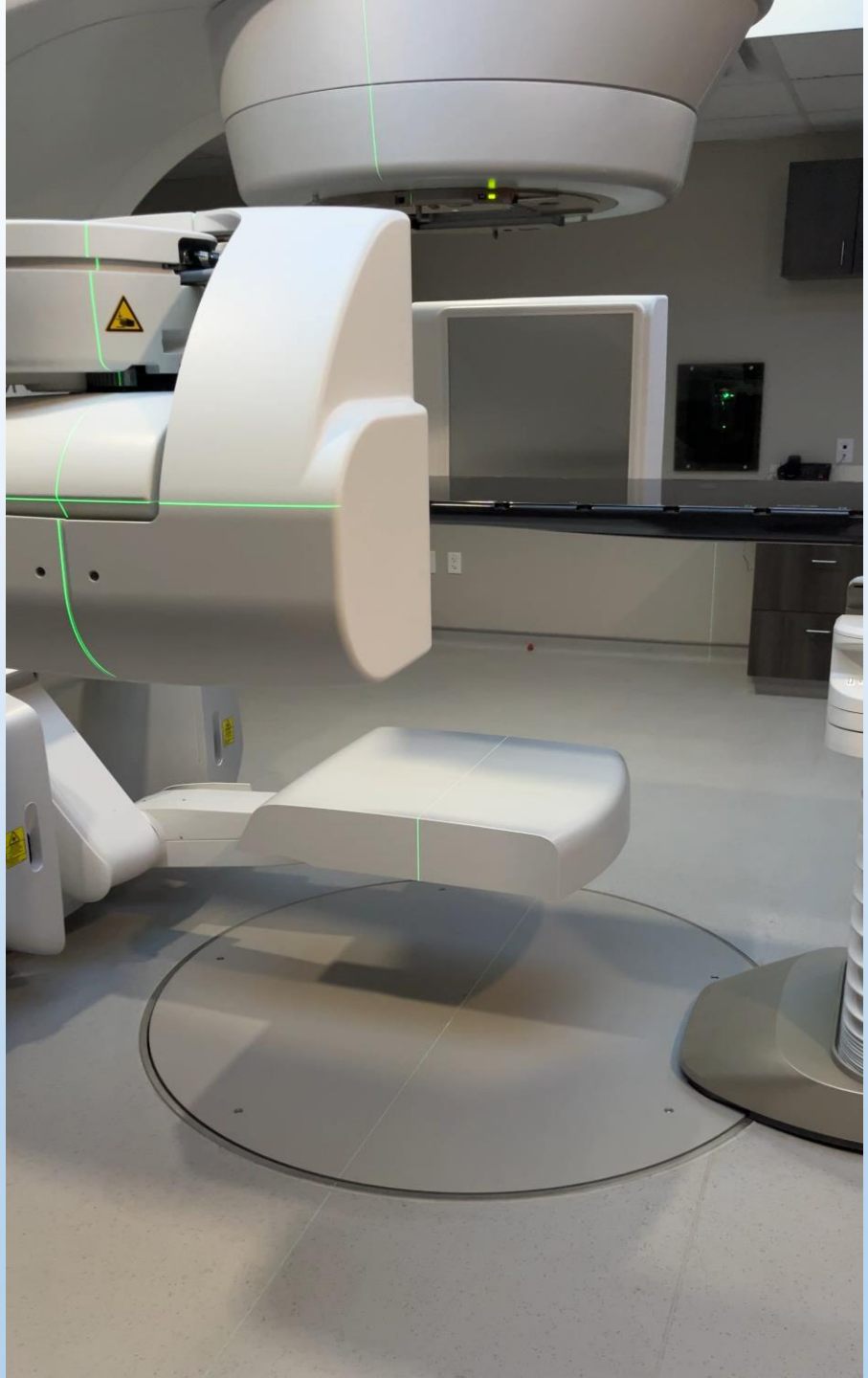
MOLECULAR SUBTYPE

..*TCGA* (NEJM 2015): Exome, DNA copy number, DNA methylation, mRNA expression, microRNA expression, targeted protein expression profiling for 293 lower-grade gliomas. Three groups identified based upon IDH, 1p/19q, and TP53 status. IDHmut 1p/19q codeleted tumors have the most favorable prognosis, followed by IDHmut 1p/19q intact, which are associated with TP53 mutations and ATRX loss. IDHwt low-grade gliomas behave similarly to primary GBM.

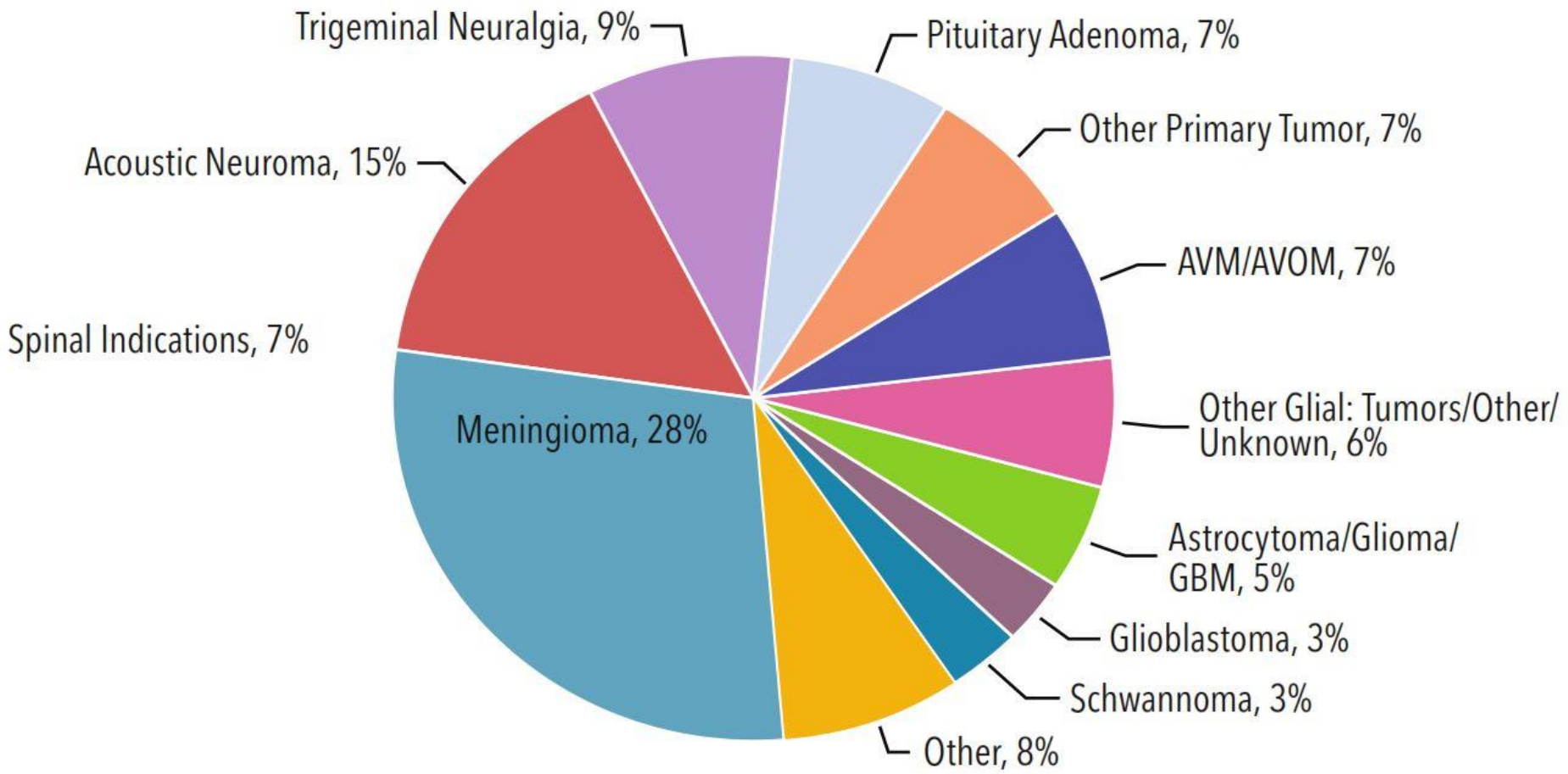
Mayo-UCSF (Eckel-Passow NEJM 2015): Genomic analysis of 1087 gliomas was performed from 3 different data sets (Mayo Clinic, UCSF, TCGA). Tumors were classified based upon IDH, 1p/19q codeletion, and TERT promotor mutations. 5 subtypes were identified. Subtype correlated with prognosis in grade II/III gliomas; patients with glioblastomas had poor prognosis regardless of subtype.

DOSE

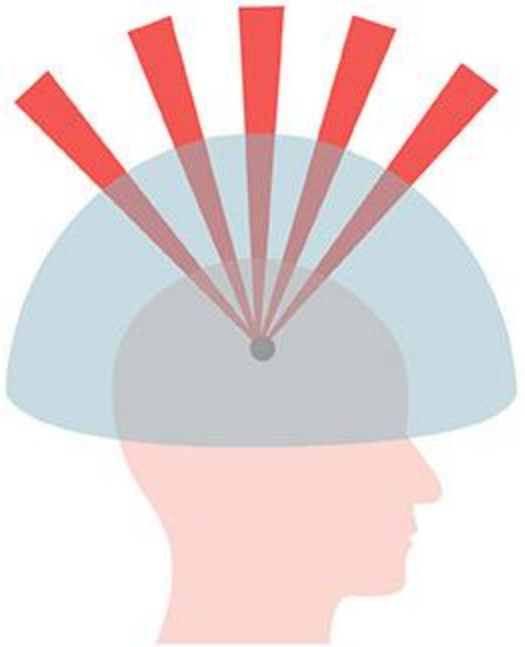
- EBRT: 1.8 Gy/fx to 50.4–54 Gy.
- GTV = T1 enhancement and mass-like FLAIR.
- CTV = GTV + 1–2 cm margin.
- PTV = CTV + 0.3–0.5 cm.



Global Usage of CyberKnife for Intracranial Indications



Gamma Knife



200 angles of treatment
Limited to 1 treatment session

vs

CyberKnife

1400 angles of treatment
1 or 2-5 treatment sessions

RADIATION COMPLICATIONS

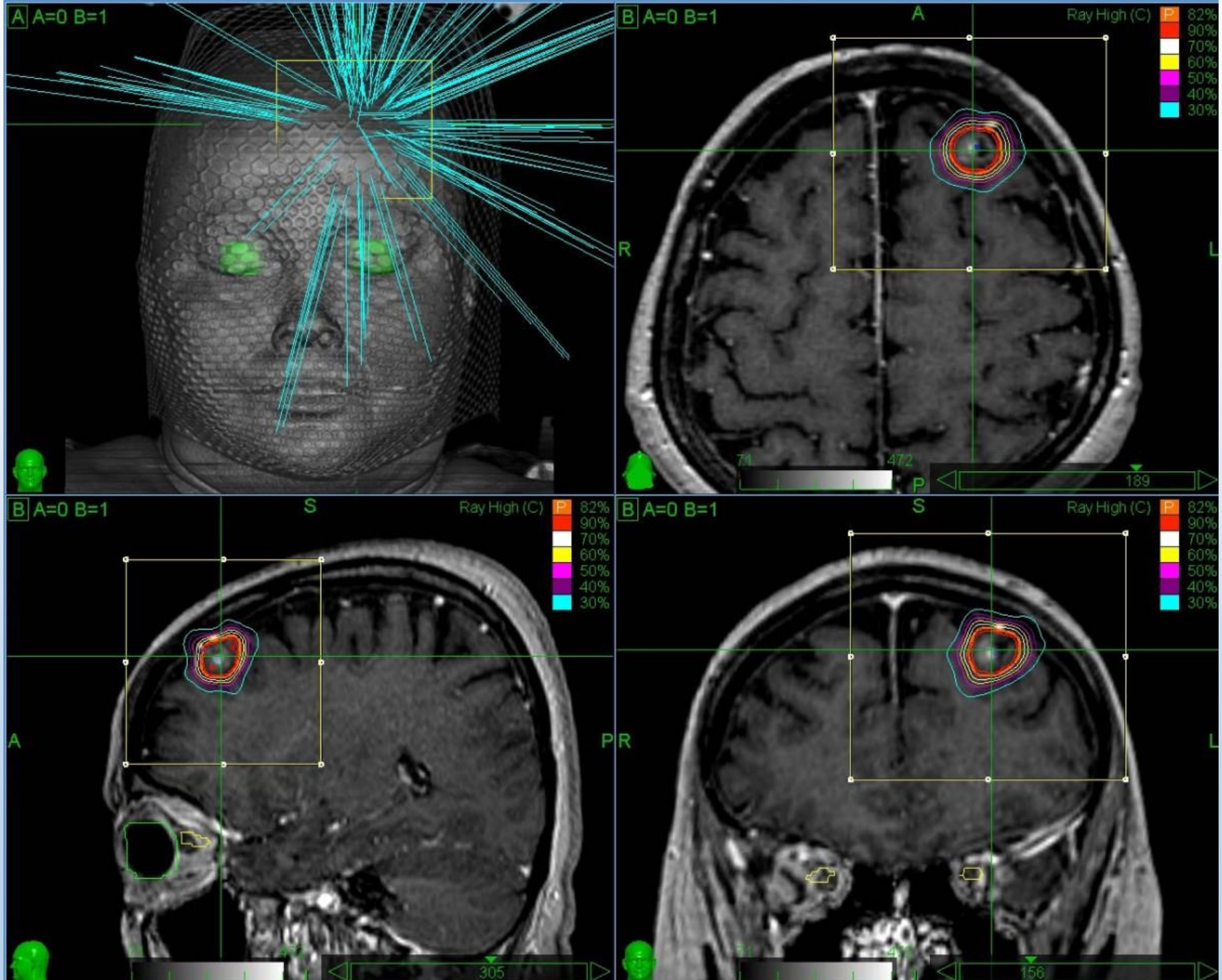
***Acute*:** alopecia, radiation dermatitis, fatigue, transient worsening of symptoms due to edema, nausea, and vomiting (particularly with brainstem [area postrema] and posterior fossa [PF] radiation), and otitis externa. Mucositis, esophagitis, and myelosuppression are associated with craniospinal irradiation and subside within 4–6 weeks after radiation (dose-related).

Subacute (6 weeks to 6 months after RT): somnolence syndrome, fatigue, neurologic deterioration, perhaps caused by changes in capillary permeability and transient demyelination.

RADIATION COMPLICATIONS

. . ***Late*** (6 months to many years after RT):

- radiation necrosis
- diffuse leukoencephalopathy (especially with chemo, but **not** necessarily correlated with clinical symptoms)
- hearing loss, retinopathy, cataract, visual changes, endocrine abnormalities (if hypothalamic pituitary axis is irradiated)
- cerebrovascular accidents,
- cavernous mal-formations
- decreased new learning ability, short-term memory and problem solving skills.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Prognosis and survival for brain and spinal cord tumours

- Tumour grade
- Tumour type
- Age
- Location and size of the tumour
- Surgical removal
- Tumour spread
- Performance status and neurological function
- Chromosomal abnormalities