## TTE UNIVERSITY OF SOUTH FLORIDA.

## COMMON BRAIN TUMORS

## Yarema Bezchlibnyk MD, PhD <br> Assistant Professor of Neurosurgery

Morsani School of Medicine, University of South Florida

## OVERVIEW

- To review the epidemiology, diagnosis, management, and prognosis of common brain tumors, including:
- Metastatic tumors
- Meningiomas
- Glial tumors
- High-grade astrocytomas/GBM
- Anaplastic gliomas (AA, AO, AOA)
- Low-grade gliomas (LGG)


## EPIDEMIOLOGY OF BRAIN TUMORS

- Overall incidence of brain tumors
- ~21/100 000
- Metastases are the most common brain tumor seen clinically in adults
- $\sim 50 \%$ of brain fumors
- Meningiomas = $\sim 18 \%$
- Gliomas = ~12\%
- $\mathrm{GBM}=\sim 7 \%$
- Anaplastic and low-grade gliomas $=\sim 5 \%$
- Pituitary adenomas = ~7\%
- Schwanommas = ~5\%
- Other = ~8\%


# METASTATIC BRAIN TUMORS 



## EPIDEMIOLOGY OF METASTATIC BRAIN TUMORS

- 98,000-170,000 new cases diagnosed each year in U.S.
- Peak age 50-70
- $25 \%$ of patients with systemic cancer have CNS metastasis on autopsy
- 50-80\% are multiple


## TUMOR TYPE AND INCIDENCE/RISK OF BRAIN METS

TABLE 1.1. Influence of primary tumor type on the number of clinically detected brain metastases, disease progression, and survival time ${ }^{\text {a }}$

| Primary tumor <br> type | Total <br> $(\%)$ | Single <br> metastasis <br> $(\%)$ | Multiple <br> metastases <br> $(\%)$ | Diagnosis to <br> metastases <br> $(\mathbf{m o})$ | Metastasis <br> to death <br> $(\mathbf{m o})$ |
| :--- | :---: | :---: | :---: | :---: | :---: |
| Lung | 40 | 48 | 52 | $3-6$ | 4 |
| Breast | 17 | 49 | 51 | 40 | 4 |
| Melanoma | 11 | 49 | 51 | 31 | 5 |
| Renal cell | 6 | 56 | 44 | 28 | 6 |
| Gastrointestinal | 6 | 67 | 33 | 14 | 3 |
| Uterine/vulvar | 5 | 53 | 47 | 23 | 3 |
| Unknown | 5 | 70 | 30 | $<1$ | 7 |
| Ovarian | 2 | 57 | 43 | 23 | 8 |
| Bladder | 2 | 64 | 36 | 15 | 3 |
| Prostate | 2 | 82 | 18 | 22 | 3 |
| Testicular | 2 | 55 | 45 | 15 | 4 |
| Miscellaneous | 4 | 65 | 47 | 16 | 3 |
| Total | 100 | 53 | 47 | 12 | 4 |

${ }^{a}$ From, Nusbaum ES, Djalilian HR, Cho KH, Hall WA: Brain metastases: Histology, multiplicity, surgery, and survival. Cancer 78:1781-1788, 1996 (26).

TABLE 1.2. Risk of brain metastases: Autopsy incidence by primary cancer ${ }^{a}$

Histology
$\%$ of patients

| Testicular | 46 |
| :--- | ---: |
| Melanoma | 40 |
| Lung | 21 |
| Renal cell | 21 |
| Osteosarcoma | 10 |
| Breast | 9 |
| Head and neck | 6 |
| Cervix | 5 |
| Neuroblastoma | 5 |
| Ovarian | 5 |
| Gastric | 0 |
| Prostate | 0 |

Prostate
${ }^{\text {a }}$ Adapted from Greenberg M: Cerebral metastases, in Greenberg M (ed): Handbook of Neurosurgery. New York, Thieme, 2001, pp 463-469 (16).

## LOCATION OF BRAIN METASTASES



Most commonly found at the grey-white matter junction and superficial distal arterial fields

The distribution reflects the blood flow to different regions
80\% in cerebrum
15\% cerebellum
5\% brainstem

## CLINICAL PRESENTATION

- $80 \%=$ Metachronous (>2 month after diagnosis of cancer)
- $20 \%=$ Precocious ( $1^{\text {st }}$ sign of cancer) or Synchronous (identified at or around the time of the cancer diagnosis)
- Neurological symptoms may develop gradually or acutely
- Headache, alteration in cognitive function
- Other symptoms depending on location:
- Focal weakness, ataxia, gait disturbance, cranial nerve findings, hydrocephalus, headache
- $20 \%$ develop seizures
- $15 \%$ present with brain bleed


## IMAGING

SL: 5.0 thk $/-3.5 \mathrm{sp}$
FOV: (75\%)
SP: - 43.1
S-65915
PP:HFS
APPLIED

AM: $512 \times 192$
RC:CP Head
RM(se1)
Tl:0
TR:600
TE:12
$\begin{array}{ll}{[P]} & \text { L:502 } \\ & \text { W:985 }\end{array}$

## MANAGEMENT: OVERVIEW

- Look for primary cancer
- Stage the disease
- Precocious
- Biopsy or resection for tissue diagnosis
- Synchronous or metachronous
- Resection vs. SRS
- Radiation
- Biopsy $\rightarrow$ SRS
- Resection $\rightarrow$ SRS or WBRT
- Palliative WBRT


## MANAGEMENT: SURGERY?

- Clear evidence for benefit of surgical resection in solitary accessible lesions in patients with good performance status.


## Tumor Factors

- Less than 3 brain mets
- Surgically accessible (although condsider laser therapy)
- No leptomeningeal dissemination
- Favorable tumor histology
- Breast cancer (vs. RCC, melanoma)
- No progression of systemic tumor in last 3 months
- Radiosensitivity
- Most radiosensitive
- leukemia, Iymphoma, multiple myeloma, SCLC, germ-cell tumors
- Intermediate radiosensitivity
- breast, non-small-cell lung Ca (the two most common mets)
- Least radiosensitive
- melanoma, RCC, sarcoma, colon Ca


## Patient Factors

- Life expectancy >3 months
- Karnofsky score >70 (i.e. independent)
- No contraindications for surgery
- Life-threatening mass effect from fumor

| RPA class | KPS | Age | Systemic disease |
| :--- | :--- | :--- | :--- |
| I | $\geq 70$ | 65 or less | Not controlled |
| II | $\geq 70$ | $\geq 65$ | Controlled |
| III | $<70$ | Any | Either |

RPA II patients require careful consideration of likely duration of survival and operative risk.
RPA III patients have poorest prognosis and usually not chosen for surgery

## MANAGEMENT: STEREOTACTIC RADIOSURGERY

- RS delivers a high dose of radiation in a single fraction to a target volume, destroying all the cells within a target boundary
- Dose depends on tumor size, location, and previous radiation treatments
- Maximum tolerable doses 24 Gy, 18 Gy, 15 Gy, for tumors less than $20 \mathrm{~mm}, 21$ to 30 mm , and 31 to 40 mm , respectively
- Control decreases with increasing tumor size


## MANAGEMENT: STEREOTACTIC RADIOSURGERY

- Advantages:
- Surgery + WBRT vs. SRS alone
- No difference in median survival - 9.5 months (Sx + WBRT) vs. 10.3 months (SRS)
- Muacevic et al., 2007
- Can treat small, deep lesions (<5mm is best for SRS, not surgery)
- Fewer immediate post-op risks
- Shorter hospital stay
- SRS + vigilant F/U may be better vs. SRS + WBRT
- better median survival (15.2 months SRS alone vs. 5.7 months SRS + WBRT)
- better KPS (80 vs. 70)
- BUT less local and distant control,
- Disadvantages:
- No histological diagnosis
- Limited to $\leq 3$ lesions $\leq 3 \mathrm{~cm}$
- Delayed resolution of symptoms
- Transient increased edema possibly requiring higher dose steroids or surgery


## MANAGEMENT: WBRT

- 30 Gy in 10 fractions over 2 weeks

| Tumor type | Complete <br> response <br> $(\%)$ | Partial <br> response <br> $(\%)$ |
| :--- | :---: | :---: |
| Small cell lung carcinoma | 37 | 44 |
| Breast cancer | 35 | 30 |
| Squamous cell carcinoma | 25 | 31 |
| Adenocarcinoma (nonbreast) | 14 | 36 |
| Renal cell carcinoma | 0 | 46 |
| Melanoma 24 35 <br> All metastases <br> a Adapted from, Nieder C, Berberich W, Schnabel K: Tumor-related prog- <br> nostic factors for remission of brain metastases after radiotherapy. Int J <br> Radiat Oncol Biol Phys 39:25-30, 1997 (55).   |  |  |

- Complications:
- Acute: Nausea, vomiting, alopecia, hearing loss, skin reactions
- Late: Necrosis, personality and memory changes, cognifive deficits
- Provides symptomatic relief in a majority of patients
- $70-90 \%$ of patients with serious neurologic dysfunction
- 33\% of patients with moderate dysfunction
- Helps eliminate micrometastases
- The rate of new metastasis and/or local failure are better in SR + WBRT (28\%) than SR alone (69\%)
- Sneed, 1999
- RS boost after WBRT is better than WBRT alone for surgically unresectable single brain metastases


## MANAGEMENT: PALLIATIVE WBRT

- Treatment of choice when:
- Metastases are too large, numerous, or disseminated for surgery
- Systemic disease is progressive/significant
- Patient is a poor surgical candidate
- i.e. median survival $=4-6$ months



## PROGNOSIS

| Strategy | Median OS <br> (months) |
| :--- | :---: |
| No treatment | 1 |
| Medications alone | 2 |
| WBRT | $4-6$ |
| Surgery | $7-9$ |
| Surgery + WBRT/SRS | $10-14$ |
| SRS | $6-14$ |

- 2 -year survival $=20 \%$
- Median independent functioning is about 1-2 months less than survival
- All patients dead by 21 months


## MENINGIOMAS



## OVERVIEW



- A slow-growing, usually benign ( $\sim 90 \%$ ), extra-axial tumor that arises from the arachnoid layer of the meninges
- Meningiomas associated with greater risk of recurrence/aggressive growth include:
- Atypical meningiomas (57\%)
- Anaplastic meningiomas (1-3\%)


## EPIDEMIOLOGY



Fig. 1 Age and gender-specific incidence rates (per 100,000 population) for meningioma in the United States (2002-2006) (from reference 4). The left $Y$-axis scale refers to the bar graphs. The ratio of female to male incidence is indicated by a diamond at each age group, and the axis for the ratio is along the right hand side of the figure. The peak ratio of 3.15 , female:male, is among the $35-44$ year age group

- Most common primary intracranial tumor ( $\sim 35 \%$ )
- $2-3 \%$ of population has at least 1 asymptomatic meningioma
- Multiple meningiomas occur in ~8\% of sporadic cases
- Increased use of imaging $\rightarrow$ increased incidental discoveries
- Incidence peaks at 45 years of age
- <2\% occur in childhood
- Higher likelihood of malignancy in childhood meningiomas


## RISK FACTORS: HORMONES

- Female:male = 1.8:1
- For spinal lesions 9:1
- Suggestion of association between hormones and meningiomas:
- Preference doesn't occur at extremes of life
- Highest ratio of 3.15:1 during peak reproductive years
- Meningiomas change in size during luteal phase/pregnancy
- In a series from Finland on 500 meningiomas
- $88 \%$ progesterone receptor +
- $40 \%$ estrogen receptor +
- $39 \%$ androgen receptor +

- Association between breast CA and meningiomas
- Epidemiologic measures of endogenous and exogenous hormones are not consistently associated with meningioma incidence
- Atypical and anaplastic meningiomas more common in men


## ETIOLOGY: GENETICS

Table 13.03 Diagnostic criteria for NF2.

## Definite NF2

1. Bilateral vestibular schwannomas; or
2. First-degree family relative with NF2 and either a) Unilateral vestibular schwannoma at $<30$ years; or
b) Any two of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity.

## Probable NF2

1. Unilateral vestibular schwannoma at $<30$ years and at least one of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity; or
2. Multiple meningiomas and either
a) Unilateral vestibular schwannoma at $<30$ years; or
b) One of the following: schwannoma, glioma, posterior lens opacity.

- Neurofibromatosis 2 (NF2) - primary genetic risk factor
- multiple
- earlier in life
- all subtypes $\rightarrow$ NO increase in frequency of atypical/anaplastic subtypes
- Loss of material from chromosome 22a (location of NF2 gene/gene suspected fo initiate meningioma growth)



## ETIOLOGY: RADIATION

- Ionizing radiation - primary environmental risk factor
- Studies include atomic bomb survivors, Tinea Capitis Cohort
- 8 Gy radiation of scalp to treat tinea capitis $\rightarrow$ life time risk of $2.3 \%$ for meningioma after latency of 35 yr
- Dental radiography?
- Cell phones?


Studies obtained in a 56-year-old woman who had undergone radiotherapy for tinea capitis at age 6 years.

## PRESENTATION

- Average time to diagnosis in cases with known doses of ionizing radiation $\geq 20-30 \mathrm{yr}$
- Seizure = 50\%
- Asymptomatic = $10 \%$

- Focal deficit is location dependent
- Olfactory groove - anosmia, papilledema, vision loss
- Suprasellar - asymmetric visual field loss
- Parasagittal - leg weakness
- Clivus - facial numbness/tingling, hearing loss
- CP angle - hearing loss, vertigo, tinnitus
- Foramen magnum - clockwise loss of lunction
- Ipsi arm $\rightarrow$ ipsileg $\rightarrow$ contra leg $\rightarrow$ contra arm
- Pain from CN irritation / compression
- Raised ICP
- Spontaneous bleed (rare)



## PATHOLOGY

Meningiomas with low risk of recurrence and aggressive growth:

Meningothelial meningioma
Fibrous (fibroblastic) meningioma
Transitional (mixed) meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma

WHO grade I WHO grade I WHO grade I WHO grade I WHO grade I WHO grade I WHO grade I WHO grade I WHO grade I

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour:

Chordoid meningioma
Clear cell meningioma (intracranial)
Atypical meningioma
Papillary meningioma
Rhabdoid meningioma
Anaplastic (malignant) meningioma

WHO grade II
WHO grade II
WHO grade II
WHO grade III
WHO grade III WHO grade III

Meningiomas of any subtype or grade with high proliferation index and/or brain invasion

- In addition to histological subtype...
- WHO GRADE I
- Bland cytology
- WHO GRADE II
- Any 1 of the following 3
- $\geq 4$ mitoses $/ 10 \mathrm{HPF}$ ( $1 \mathrm{HPF}=0.16 \mathrm{~mm} 2$ )
- Brain invasion or :
- Atypical cytology $=3$ or more of :
- Increased cellularity
- Small cells w/ high N/C ratio
- Prominent nucleoli
- Patternless sheet-like growth
- Foci of necrosis (no prior embolization)
- Also important:
- High MIB1 index;
- Cytological atypia w/macronuclei
- No progesterone receptors
- WHO GRADE III
- $\geq 20$ mitoses / 10 HPF
- Anaplastic/ malignant cytology
- Obviously malignant cytology


## MOLECULAR BIOLOGY

- Partial or complete deletion of chromosome 22q
- Oncogene overactivation
- Telomerase reactivation
- Progesterone receptor upregulation
- Arachnoidal cells
$\downarrow \quad$ [NF2 mutation, 22q loss]
- WHO I: meningioma
$\downarrow \quad[l o s s: 1 p, 6 q, 10 q, 14 q, 18 q$; gain: 1q, 9q, 12q, 15q, 17q, 20q]
- WHO II: atypical meningioma
$\downarrow \quad[l o s s: 6 q, 9 p, 10,14 q$; rare mutations: p53, PTEN]
- WHO III: anaplastic meningioma


## PATHOLOGY AND RISK OF RECURRENCE

Meningiomas with low risk of recurrence and aggressive growth:

Meningothelial meningioma
Fibrous (fibroblastic) meningioma
Transitional (mixed) meningioma
Psammomatous meningioma
Angiomatous meningioma
Microcystic meningioma
Secretory meningioma
Lymphoplasmacyte-rich meningioma
Metaplastic meningioma

WHO grade I
WHO grade I
WHO grade I
WHO grade I
WHO grade I
WHO grade I
WHO grade I
WHO grade I
WHO grade I

Meningiomas with greater likelihood of recurrence and/or aggressive behaviour:
Chordoid meningioma
Clear cell meningioma (intracranial)
Atypical meningioma
Papillary meningioma
Rhabdoid meningioma
Anaplastic (malignant) meningioma

## WHO grade II

WHO grade II
WHO grade II
WHO grade III
WHO grade III
WHO grade III
Meningiomas of any subtype or grade with high proliferation index and/or brain invasion

- WHO I: ~90\% of all meningiomas
- Low recurrence (7-25\%)
- Relatively nonaggressive growth
- WHO II: $5-7 \%$ of all cases
- Recurrence = 29-52\%
- WHO III: 1-3\% of all cases; incidence as low as 0.17/100 000 per year
- Recurrence $=50-94 \%$


## MANAGEMENT: <br> ASYMPTOMATIC MENINGIOMAS

- Incidental meningiomas with no brain edema or those presenting with seizures that are easily controlled medically $\rightarrow$ can be managed expectantly w/ serial imaging
- Slower growth rate in asymptomatic meningiomas with calcifications on CT
- Of 63 cases followed for $>1 \mathrm{yr}, 68 \%$ showed no increase in size on average F/U 36.6 months
- Kuratsu et al., 2000
- Management:
- Obtain F/U imaging study 3-4 months after first study to R/O rapid progression
- Repeat imaging annually $\times 2-3 \mathrm{yr}$
- Intervention when ...
- Symptoms develop that cannot be controlled medically
- Significant continued growth on serial imaging


## MANAGEMENT: SYMPTOMATIC MENINGIOMAS

- The decision to operate is based on
- Age
- More morbidity once >70 y.o.
- Accessibility of tumor
- Estimation of clinical benefit achievable by surgery
- Primary goal = complete removal of meningioma (incl. dural attachment/infiltrated bone)


## RISK OF RECURRENCE AFTER SURGERY

| Grade | Description | 10 yr Recurrence |
| :---: | :--- | :---: |
| I | macroscopically complete removal, excision <br> of dural attachment/removal of involved bone | $10 \%$ |
| II | macroscopically complete removal, <br> coagulation of dural attachment | $20 \%$ |
| III | macroscopically complete removal, without <br> resection or coag of dural attachment | $30 \%$ |
| IV | partial removal | $40 \%$ |
| V | decompression/biopsy | $\mathrm{n} / \mathrm{a}$ |

## MANAGEMENT: STEREOTACTIC RADIOSURGERY

- Preferred treatment modality for management of wellcircumscribed/small/benign/intracranial meningiomas smaller than 3 cm/inaccessible to surgery
- In large series of 972 patients, SRS either as 1 st-line or at recurrence provided following rates of tumor growth control/regression:
- WHO grade I: $97 \%$
- WHO grade II: 50\%
- WHO grade III: $17 \%$
- Complications of SRS:
- 13\%
overall
- 8\% CN deficit
- $3 \%$ symptomatic parenchymal changes
- 1\% ICA stenosis
- Most common complication was trigeminal/eye movement abnormalities in cavernous sinus meningiomas


## MANAGEMENT: RADIATION THERAPY

- Generally ineffective as primary modality of treatment
- Indications for focal XRT:
- Recurrence (after considering re-op)
- Atypical meningioma (even after GTR)
- Anaplastic meningioma (even after GTR)
- Downsides to XRT
- Side effects
- Case report of development of malignant astrocytoma after XRT used to treat meningioma


## MANAGEMENT: CHEMOTHERAPY

- Not very effective
- Some modest efficacy shown for:
- Anti-progesterone (mifepristone = RU-486) - reduction in size of $30 \%$ of growing, recurrent meningiomas
- Hydroxyurea - has shown some shrinkage
- Avastin for higher grade tumors to decrease edema
- Generally reserved for tumours that progress/recur after surgery and XRT


## PROGNOSIS

- 5 yr survival for patients with meningiomas = 91.3\%
- $40 \%$ for anaplastic or atypical meningioma
- Progression-free survival of benign meningiomas with total excision:
- $5 \mathrm{yr}=93 \%$
- $10 \mathrm{yr}=80 \%$
- $15 \mathrm{yr}=75 \%$
- Goldsmith \& McDermott, 2006
- Most important factor in prevention of recurrence = extent of surgical removal of tumor
- Other factors:
- High histological grading
- Papillary/hemangiopericytic morphology
- Large tumor size
- High mitotic index


## POST-OPERATIVE FOLLOW UP

- Imaging
- 3-6 months after resection
$\rightarrow 6$ month intervals $\times 2 \mathrm{yr}$
$\rightarrow$ Yearly
$\rightarrow$ Every other year
- If atypical or malignant meningioma
- 3 month intervals x 1 yr
- Then same routine as for malignant brain tumors


## GLIAL TUMORS

Low Grade Gliomas


Anaplastic Astrocytomas


High Grade Gliomas

## GLIAL TUMORS: OVERVIEW

## Astrocytic tumours

Pilocytic astrocytoma Pilomyxoid astrocytoma
Subependymal giant cell astrocytoma
Pleomorphic xanthoastrocytoma
Diffuse astrocytoma
Fibrillary astrocytoma
Gemistocytic astrocytoma
Protoplasmic astrocytoma
Anaplastic astrocytoma
Glioblastoma
Giant cell glioblastoma
Gliosarcoma
Gliomatosis cerebri
Oligodendroglial tumours
Oligodendroglioma
Anaplastic oligodendroglioma
Oligoastrocytic tumours
Oligoastrocytoma
Anaplastic oligoastrocytoma


| WHO <br> Grade | Age |
| :--- | :--- |
| I | $0-20$ |
| II | $30-40$ |
| III | $40-50$ |
| IV | $45-65$ |

## LOW GRADE GLIOMAS

| WHO I | WHO II |
| :---: | :---: |
| subependymal giant cell <br> pilocytic | diffuse astro/oligo/oligoastro |
|  | pilomyxoid |
|  | pleomorphic xanthoastrocytoma |

Low grade diffuse infiltrating tumors that have a tendency towards anaplastic transformation

|  | Low Grade Gliomas |
| :--- | :---: |
| comprise most <br> low grade <br> gliomas in <br> adults | astrocytoma (fibrillary or protoplastmic) |
| less frequent |  |
| histologies | oligodendroglioma |

## EPIDEMIOLOGY: PILOCYTIC ASTROCYTOMA

- Slow growing, little tendency to progress to higher grade
- Most common glioma in children
- $10 \%$ of cerebral and $85 \%$ of cerebellar astrocytoma
- Present in first two decades of life
- Rare presentation after 50 years old
- No sex predilection
- Arise throughout neuroaxis, but preferred sites include optic nerve, optic chiasm/hypothalamus, thalamus and basal ganglia, cerebral hemispheres, cerebellum, brainstem (may appear intraventricular)
- Presentation depends on location


## EPIDEMIOLOGY: LOW GRADE ASTROCYTOMA

- 5-7 per 100,000
- $25 \%$ of childhood brain tumors
- Slight male preponderance
- Biphasic age distribution
- First peak between 6 and 12 years old
- Second peak between third and fourth decades
- African Americans have higher risk of death (40\%) than non-Hispanic whites


## EPIDEMIOLOGY: LOW GRADE OLIGOASTROCYTOMA

- Incidence of 0.1 per 100,000
- Numbers vary due to histological diagnosis varying significantly amount pathologists
- Majority arise in adults with peak incidence in third and fourth decades


## EPIDEMIOLOGY: LOW GRADE OLIGODENDROGLIOMA

- Incidence of 0.3 per 100,000
- $4.2 \%$ of all primary brain tumors
- Majority arise in adults with peak incidence in fourth and fifth decades


## EPIDEMIOLOGY: HIGH GRADE GLIOMA

- Most common primary malignant brain fumor in adults
- Peak incidence between $45-65$ years of age
- 35-45 - secondary GBM; 59-62 - primary GBM
- $3-5 / 100,000$ cases per year
- Male to female ratio 1.5:1
- Arise in the sub-cortical white matter; local invasion is via white matter as well
- Multi-focal/multicentric GBM:
- $\geq 2$ foci of enhancing tissue separated by $>1 \mathrm{~cm}$
- ~ $2 \%$ at autopsy
- Gliomatosis cerebri:
- Involvement of $\geq 3$ lobes with neoplastic astrocytes


## ETIOLOGY

- Genetic:
- Syndromic (Li Fraumeni, Turcot-1, NF-1, multiple enchondromatosis)
- Familial
- Sporadic (likely most GBMs)
- Radiation:
- Children with RTX for ALL (22x risk), tinea capitis, CNS tumors (craniopharyngioma, pit adenoma, germinoma)


# ETIOLOGY: PRIMARY VS. SECONDARY HIGH GRADE GLIOMA 

- Most glioblastomas manifest rapidly de novo, without recognizable precursor lesions (primary glioblastoma)
- Secondary glioblastomas develop slowly from diffuse astrocytoma WHO grade Il or anaplastic astrocytoma (WHO grade III)


|  | Primary | Secondary |
| :--- | :--- | :--- |
| Mean Age | 55 yrs | 40 yrs |
| Proportion | $90 \%$ | $10 \%$ |
| Clinical <br> course | Rapid | Progression <br> of LGG |
| Genetics | EGFR <br> PTEN | P53 <br> IDH-1/2 |

## PRESENTATION: LOW GRADE GLIOMAS

- 50-80\% present with seizure or are neurologically intact
- Headaches
- Acute changes may occur with hemorrhage, cystic expansion, or CSF obstruction
- Neurological manifestations depend on location
- Occur throughout the CNS
- Supratentorial - 2/3
- Frontaf lobes $1 / 3$, temporal lobes $1 / 3$, relative sparing of occipital lobes
- Seizures, increased intracranial pressure/mass effect, impaired cognitive function
- Infratentorial - 1/3
- Brainstem (50\% of brain stem "gliomas" are low-grade astrocytoma); pons and medưla in children/adolescents
- Hydrocephalus, cranial nerve deficits, weakness/sensory changes


## PRESENTATION: HIGH GRADE GLIOMA

- Clinical history is typically <3 months

| Presenting complaint | Incidence |
| :--- | :--- |
| Focal neurological deficit | $38 \%$ |
| Seizures | $32 \%$ |
| Headache | $30 \%$ |

Salcman M. Brain tumors. New York: Churchill Livingstone; 1995.
Glioblastoma and malignant astrocytoma; pp. 449-477.

## IMAGING: PILOCYTIC ASTROCYTOMA



## IMAGING

## Astrocytoma



- Typically no calcifications

Oligodendroglioma


- Calcifications commonly present

NOTE: Imaging alone is not sufficient to predict tumour grade, as ~20\% of LGGs enhance with contrast, while $20-30 \%$ of HGGs ao not - it does not reveal anything about underlying vascularity

## IMAGING: HIGH GRADE GLIOMA



## PATHOLOGY: WHO GRADING

- Performed on the area of tumor with the highest degree of anaplasia

- GRADE 1
- Clear interface between tumor and surrounding brain tissue
- GRADE 2
- Absence of clear tumor interface
- Low mitotic activity (<3/10 hpf)
- Nuclear atypia:
- Hyperchromatasia and/or obvious variation in size and shape of nucleus
- Cellular pleomorphism:
- Variation in size and shape of cell
- Cellular proliferation
- GRADE 3
- Increased mitotic activity (>3/10 hpf)
- MIB1/Ki67 10\%
- NO necrosis, vascular proliferation
- GRADE 4 = at least one of:
- MIB1/Ki67 >10\%
- Endothelial proliferation:
- Vascular lumina are surrounded by "piled up" endothelial cells
- Pseudopallisading necrosis

| Marker | Association |
| :--- | :--- |
| p53 | tumor suppressor gene altered in most low-grade astrocytomas transforming to high grade |
| MDM2 | negative regulator of p53; alterations occur early in low-grade gliomagenesis |
| p14ARF | cell-cycle regulator inhibiting MDM2; alterations occur early in low-grade gliomagenesis |
| PDGF | platelet-derived growth factor; typically associated w/ oligodendrogliomas |
| 1p/19q codeletion | genetic signature of oligodendroglioma; combined loss in $50 \%-80 \%$ of all cases |
| MGMT | DNA repair protein; methylated MGMT predicts favorable LGG response to temozolomide |
| PTEN | tumor suppressor gene altered in LGGs at risk for transformation |
| PGDS | arachidonic acid metabolite; associated w/ LGG malignant progression \& poor survival |
| tenascin-C | extracellular matrix glycoprotein; potential marker of LGG invasiveness |
| IDH1 | Krebs cycle enzyme gene; mutations associated w/ LGG astrocytoma histology |
| IDH2 | Krebs cycle enzyme gene; mutation associated $w /$ LGG oligodendroglioma histology |

## MOLECULAR PATHOLOGY: ASTROCYTOMA

- IDH-1 (70-80\%)
- LGGs with IDH mutations have a shortened time to recurrence
- HOWEVER, even in recurrence the IDH-1 mutation confers a better prognosis
- median OS = 151 vs. 60 months for all grade II gliomas
- P53 (>60\%)
- the genetic hallmark of low grade diffuse astrocytomas
- the frequency of p53 mutations does not increase significantly with tumour progression to secondary GBM
- MGMT
- As with HGG, MGMT promotor methylation predicts shorter progression-free survival after surgery alone
- BUT with TMZ therapy = similar overall survival to diffuse astrocytomas without MGMT methylation
- EGFR/PTEN/Akt/mTOR
- more prevalent in primary GBM

|  |
| :--- |
| Promoter methylation |
| $p 14^{\text {AFF }}$ |
| p16KAa |
| RB1 |
| MGMT |
| TIMP-3 |

> Primary glioblastoma

> Secondary glioblastoma


Marker platelet-derived growth factor; typically associated w/ oligodendrogliomas genetic signature of oligodendroglioma; combined loss in $50 \%-80 \%$ of all cases DNA repair protein; methylated MGMT predicts favorable LGG response to temozolomide tumor suppressor gene altered in LGGs at risk for transformation arachidonic acid metabolite; associated w/ LGG malignant progression \& poor survival extracellular matrix glycoprotein; potential marker of LGG invasiveness Krebs cycle enzyme gene; mutations associated w/ LGG astrocytoma histology Krebs cycle enzyme gene; mutation associated w/ LGG oligodendroglioma histology

## MOLECULAR PATHOLOGY: OLGODENDROGLIOMA

- $1 p / 19 q$ codeletion (50-70\%)
- Identified via FISH: centromeres are red, should be same number of green telomeres / nuclei - if not, LOH
- 19q $\rightarrow$ most frequent, 50-80\%
- $1 \mathrm{p} \rightarrow$ 2nd most frequent, 40-90\%
- more common in frontal, parietal, occipital lobe lesions vs. infrequent in diencephalic and insular and temporal lobe lesions
- associated with improved outcomes with chemo and RT+chemo
- ALL 1p/19q tumours should get chemotherapy
- PDGF/R overexpression without amplification
- P53 mutation is uncommon (10-15\%)
- Mutually exclusive with 1p/19q codeletion
- MGMT - no prognostic role in oligodendrogliomas



## MANAGEMENT: PILOCYTIC ASTROCYTOMA

- Slow growing tumors, so...
- Observation vs. biopsy if tissue diagnosis required
- Surgery only for symptoms/rapid change in size/imaging
- Maximal safe surgical resection
- Invasion of brainstem or cranial nerves limit resection
- In tumors with a nodule with a true cyst excision of the nodule suffices
- Where the cyst wall is thick and enhances (false cyst) the wall must also be removed
- No radiation recommended due to slow growth incompletely resected tumors should be followed with serial imaging



## MANAGEMENT : LOW GRADE GLIOMA

- Observation
- ...is an option in very carefully selected patients who choose not to have surgery initially

Patient

- <40 yo
- epilepsy only - responsive to AEDs
- neuro intact
- no papilledema

Imaging

- small lesion (<6 cm in max. diameter)
- doesn'† cross midline
- no enhancement
- NO mass effect
- Surgery alone
- In low risk patients (<3 RTOG RF) with GTR
- Surgery + XRT + Chemo
- In low risk patients with subtotal resection and high risk patients regardless of extent of resection


## MANAGEMENT : SURGERY

- Surgical resection:
- Indications:
- Diagnosis - exclude masses mimicking glioma (e.g., brain abscess)
- Neurological deficit (focal or $\uparrow$ ICP)
- Cytoreduction prior to adjuvant therapy
- Stratified for degree of resection, survival of patients with complete resections was longer in RPA classes IV and V; 17.7 vs . 12.9 months, and 13.7 vs. 10.4 months for complete vs. partial)
- Decrease steroid requirement.
- Stereotactic biopsy:
- For lesions that are deep, diffuse, eloquent area, multiple, or for patients that are too old or unwell
- Diagnostic rate >90\%
- $60 \%$ risk of hemorrhage ( $90 \%$ are silent, so $6 \%$ risk of clinically significant bleed)


## MANAGEMENT : LOW GRADE GLIOMA

- XRT + chemo is the new standard of care for high risk (age >40 and/or STR) LGG


Figure 1: Biomarker-based approach to anaplastic glioma
ellow boxes indicate new standard practice. Blue boxes indicate practice needs
to be confirmed. $\mathrm{RT}=$ radiotherapy. $\mathrm{PC}=$ = procarbacine, lomustin, and vincristine.
RT/TMZ $\rightarrow$ TMZ=radiotherapy plus temozolomide followed by temozolomide.
"ClinicalTrials.gov, number NCTOO626990. †Alternative options.

- RTOG 0424: First Phase II data to suggest TMZ+RT superior treatment in High RIsk-LGG
- Compared patients with high risk LGG ( $\geqslant 3$ RTOG risk factors) treated with TMZ + XRT to XRT alone.
- 3-year OS rate: $73.1 \%$ ( $65.3 \%-80.8 \%$ ) vs. $54 \%$ (P<.01)
- EORTC RND Phase III: Suggests similar outcome of TMZ alone vs. RT alone
- RTOG 9802: the addition of PCV to RT increased median PFS from 4.0 to 10.4 years, and median OS from 7.8 to 13.3 years
- This is new data on OS which was not available when the guidelines went out


## MANAGEMENT : ADJUVANT THERAPY

- Stupp protocol:
- 60Gy total, given fractionated 5x/week for 6 weeks
- Delivered to gross tumour volume plus a $2-3 \mathrm{~cm}$ margin
- Given with concomitant temozolomide
- 75 mg / square meter of body-surface area / day, 7 days/week from the first to the last day of radiotherapy
- Then, after radiation finished, give 6 cycles of adjuvant temozolomide ( 150 to 200 mg per square meter for 5 days during each 28 -day cycle - basically for 1 working week/month for $\sim 6$ months).


|  | RT (n=286) | RT+TMZ ( $\mathrm{n}=287$ ) |
| :--- | :--- | :--- |
| Progression- <br> free survival | 5 months | 7.2 months |
| Median survival <br> 2 year survival | 12.1 | 14.6 |

## MANAGEMENT: RECURRENCE OF HIGH GRADE GLIOMA

- <10\% of gliomas recur away from original site
- Distant recurrence is associated with IDH-1/2 wt status
- IDH-1/2 mutant tumours tend to recur locally
- Consider re-operation if:
- Long initial remission
- Major localized recurrence in surgically accessible area
- $\uparrow$ ICP or focal deficit
- Reoperation can add 4-9 mths extra survival, but depends on:
- Grade (AA rather than GBM)
- Performance (KPS > 70)
- Frontal lobe location
- Long interval to recurrence (>1 year)
- GTR
- Consider Gliadel wafers OR novoTTF therapy as alternatives to chemo


## PROGNOSIS: LOW GRADE GLIOMA

- May remain low-grade for many years, or may dedifferentiate into malignant tumors (in $\sim 70 \%$, most commonly older patients)
- Mean time interval = 4-5 yrs
- Many patients die within 10 yrs, although some die at <2 yrs and $\sim 25 \%$ of patients survive >20 yrs
- Median survival of WHO Grade 2 = 6-8 years ( $\sim 5$ yrs for astrocytoma, 9 yrs for oligdendroglioma)

BAD Prognostic facłors $=\geq 3$ of

- Patient:
- Age $\geq 40$
- Pre-operative neurological deficit
- Imaging
- tumour size $\geq 6 \mathrm{~cm}$ max. diameter
- tumour crossing midline
- Pathology
- Astrocytoma


## GOOD Prognostic factors

- Patient:
- Good pre-operative cognition (MMSE
- Imaging
- tumour size < 6 cm max. diameter
- Pathology
- Oligodendroglial (1p/19q; MGMT; IDH1/2)
- Surgery (RTOG)
- Gross Total Resection (vs. subtotal vs. Bx)


## PROGNOSIS: HIGH GRADE GLIOMA

| Stage | Characteristics | Median OS | 1 year and 5 yr OS |  |
| :---: | :---: | :---: | :---: | :---: |
| III | $<50 \mathrm{y}$ and KPS $\geq 90$ | 17.1 | 70\% | 14\% |
| IV | $<50$ y and KPS <90; <br> $\geq 50 y$, KPS $\geq 70$, resection, working | 11.2 | 46\% | 4\% |
| V | $\geq 50 \mathrm{y}$, KPS $\geq 70$, resection, not working $\geq 50 \mathrm{y}$, KPS $\geq 70$, biopsy only $\geq 50$ y, KPS $<70$ | 7.5 | 28\% | 0\% |

- IDH 1 or 2 mutation:
- Longer OS and PFS regardless of grade
- MGMT promoter methylation:
- Repair protein that removes promutagenic alkyl groups from DNA, thereby protecting cells against alkylating agents (i.e. Temozolomide)
- Methylation = loss of MGMT expression = deficient repair
- Works best patients with wt IDH-1/2)


B Gliomas Classified According to Molecular Subtype


| Genetics | Classification | Median <br> OS (yrs) |
| :--- | :--- | :---: |
| IDH+/p53-/lp19q+ | Oligodendroglioma | 8 |
| IDH+/p53-/1p19q- | Astrocytoma | 6.3 |
| IDH+/p53+/lp19q- | Astrocytoma/ <br> Secondary GBM | 2.1 |
| IDH-/p53-/lp19q- | Astrocytoma | 1.7 |
| IHD-/p53+/lp19q- | Primary GBM | 1.1 |

