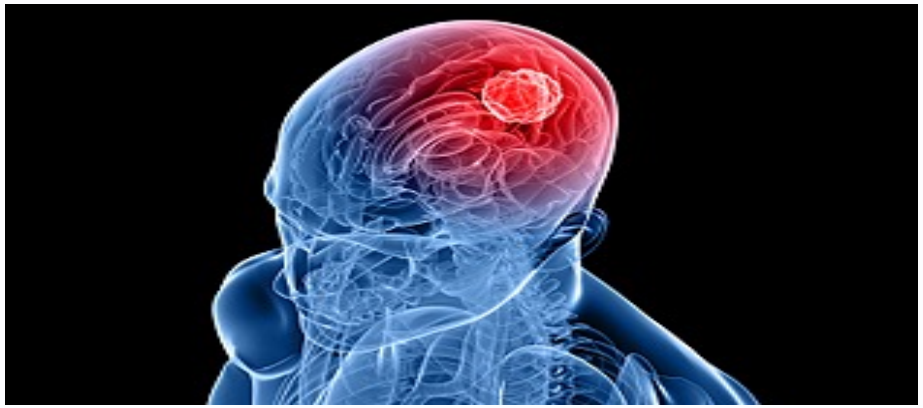
Primary Brain Tumors



- Elizabeth B. Claus, MD, PhD
- Professor, Departments of Biostatistics and Neurosurgery, Yale University
- Attending Neurosurgeon, Department of Neurosurgery, Brigham and Women's Hospital

Acknowledgement/Disclosures

Incidence and Survival data for this presentation are provided by the Central Brain Tumor Registry of the United States (CBTRUS) 2015-2019 and are available at http://www.cbtrus.org.

I am on the Board of Directors for CBTRUS but receive no financial compensation.

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CBTRUS Data Sources

- Incidence data are for 2015-2019, are population-based and collected from 52 central cancer registries (CCR)
- Data are also obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI)
- Sources of geographic population-based cancer survival data are for 2001-2018 from 42 central cancer registries (CCR) of the National Program of Cancer Registries (NPCR)

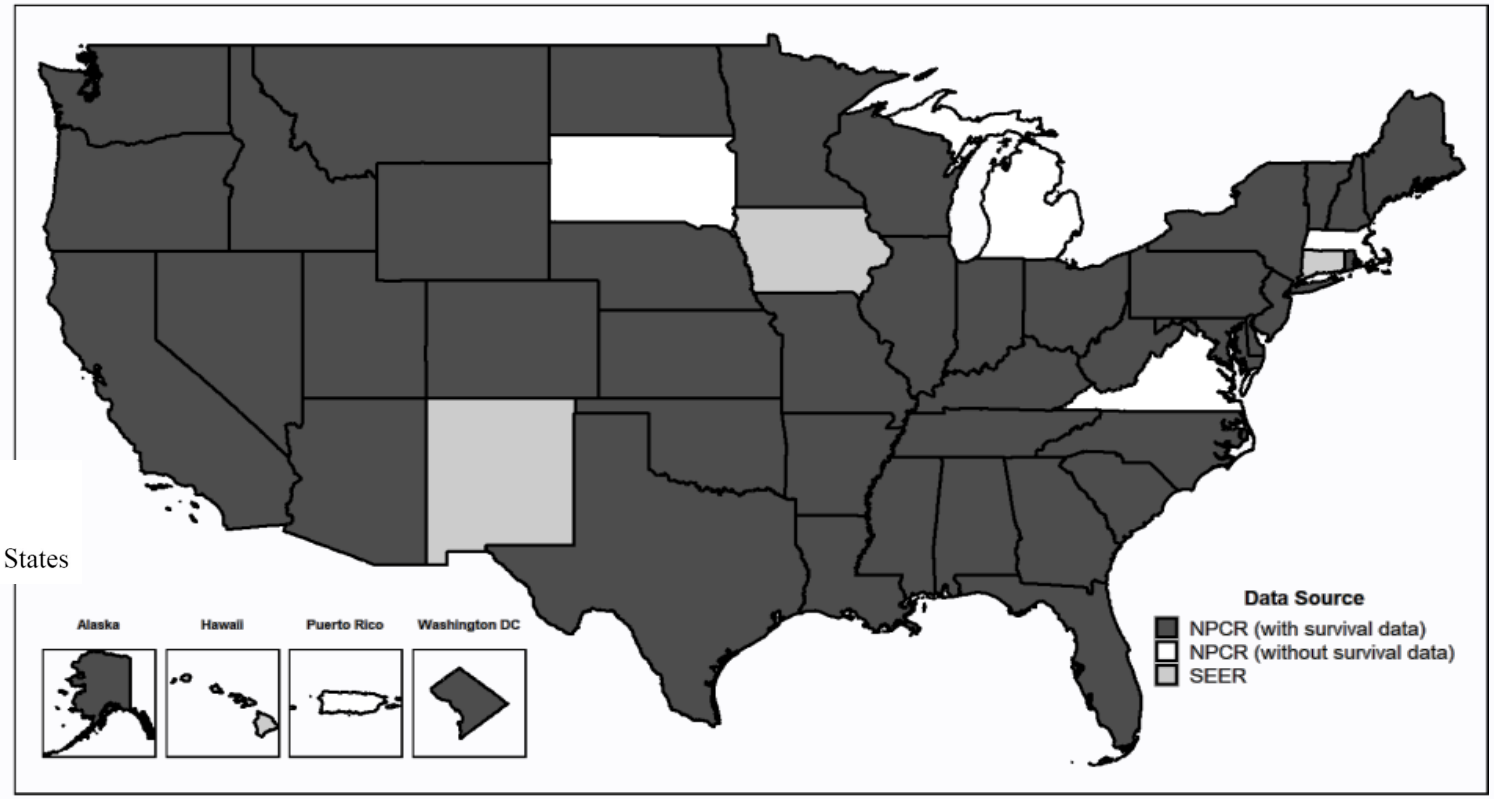
Figures and Graphs are prepared by CBTRUS
Co-Scientific Principal Investigator Quinn T. Ostrom, PhD, MPH and her team

CBTRUS
Central Brain Tumor Registry of the United States

Figure 1. Availability by Central Cancer Registry for SEER and NPCR Incidence (2015-2019) and Survival Data (2001-2018)

CBTRUS

Central Brain Tumor Registry of the United States

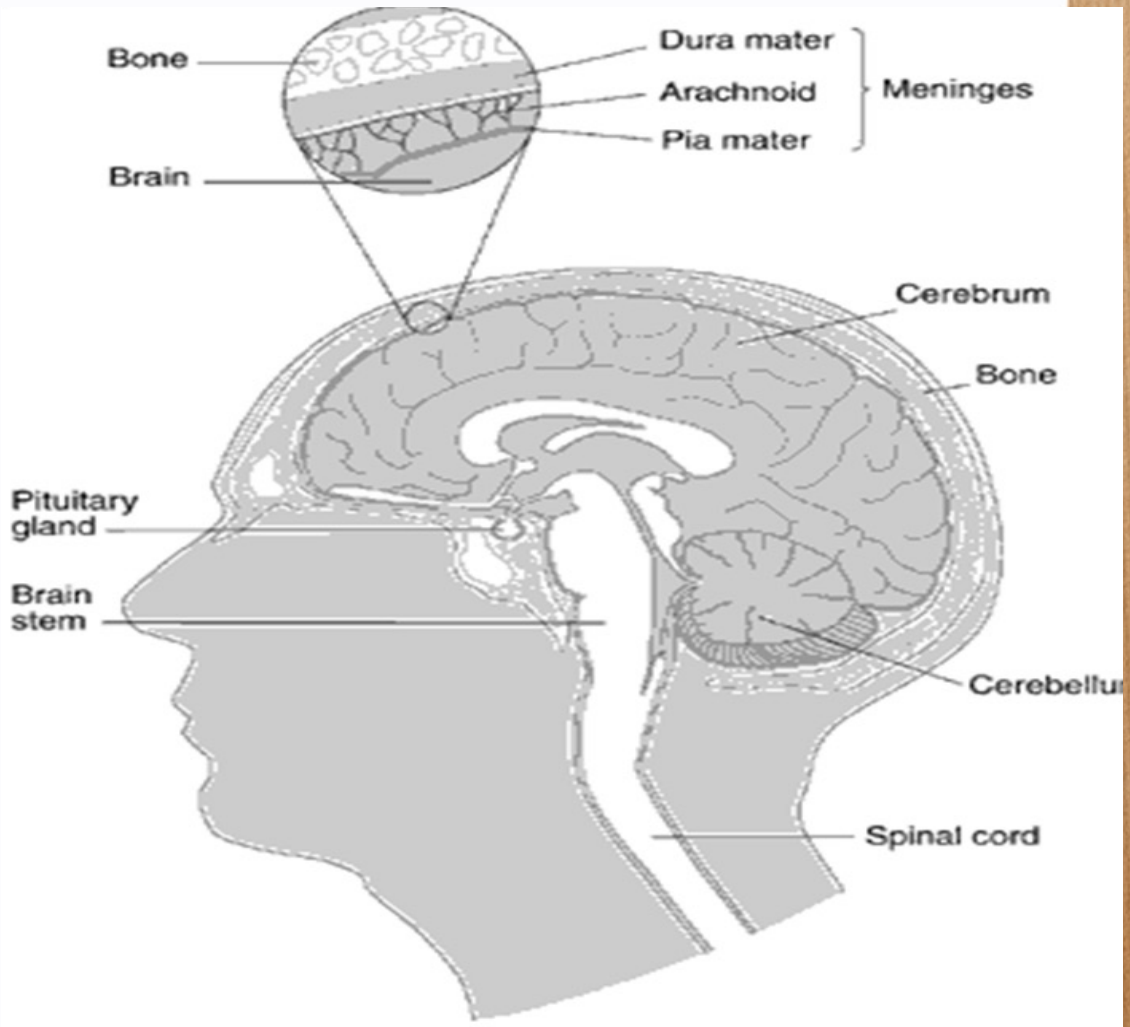


Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results Program.

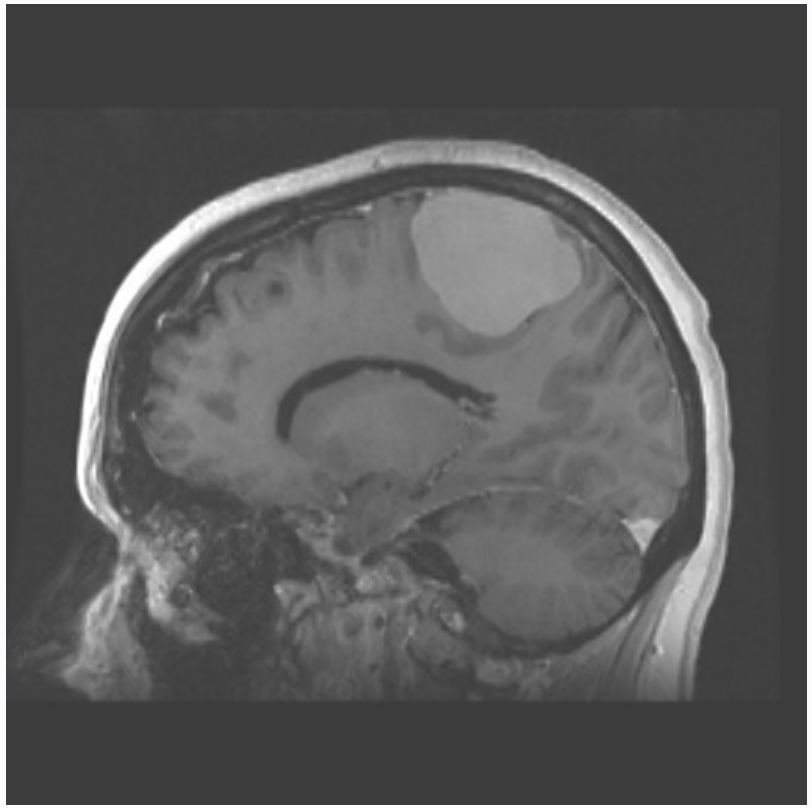
Brain Tumors

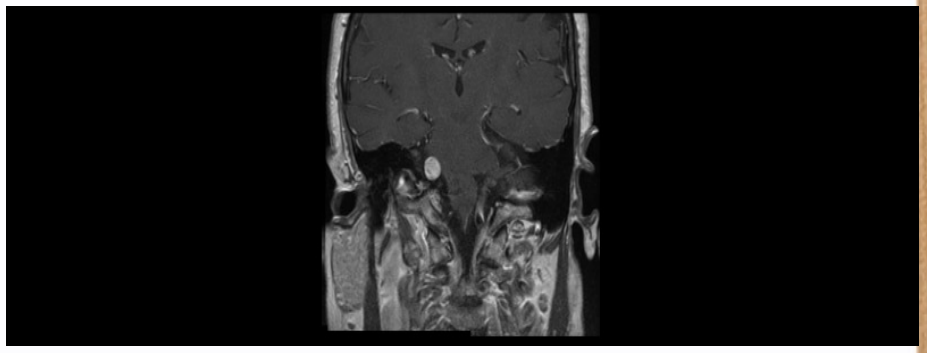
- ***Primary***

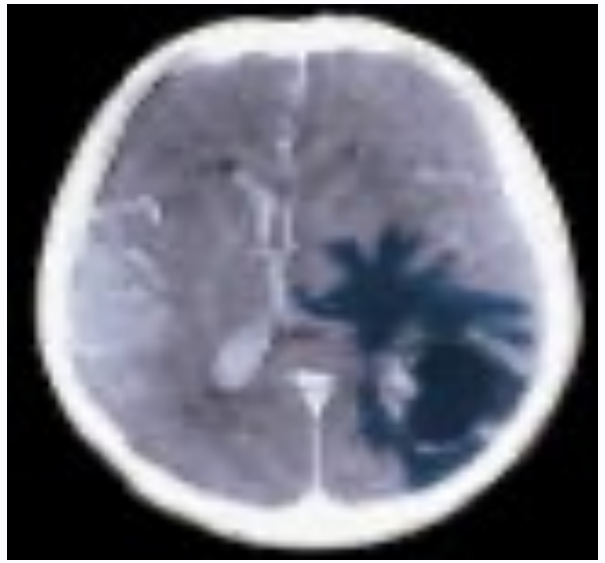
Primary brain tumors originate from the tissues of the brain or the brain's immediate surroundings. Primary tumors are categorized as glial (composed of glial cells) or non-glial (developed on or in the structures of the brain, including nerves, blood vessels and glands) and further defined as malignant or non-malignant.



Primary Brain Tumors





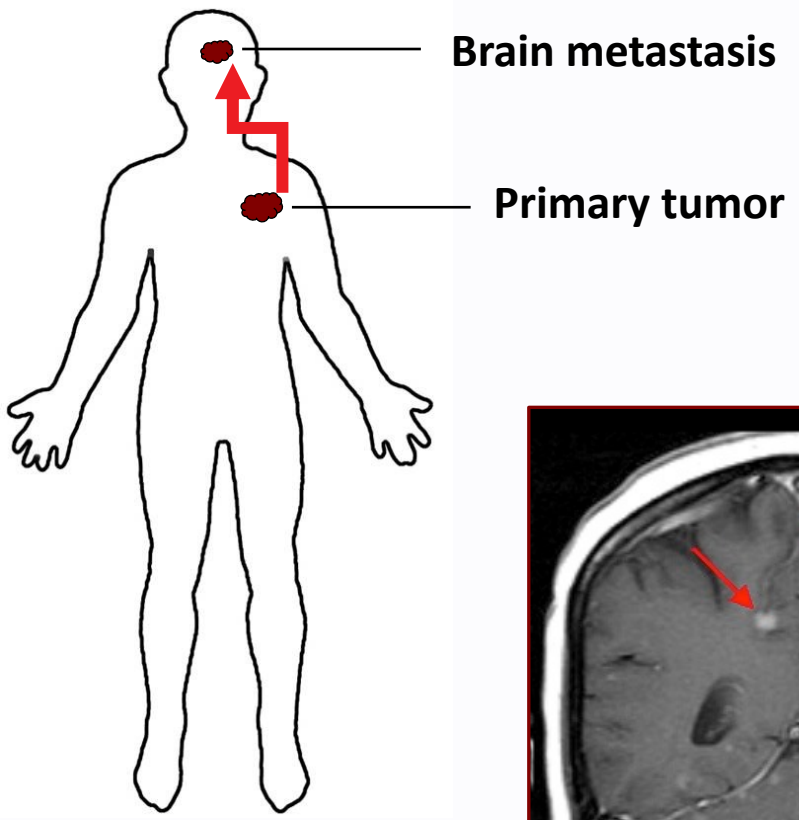


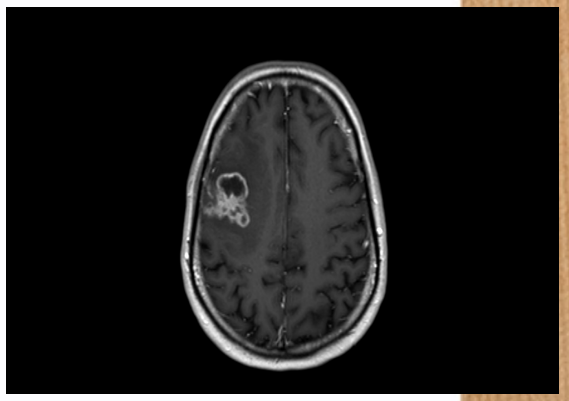
Brain Tumors

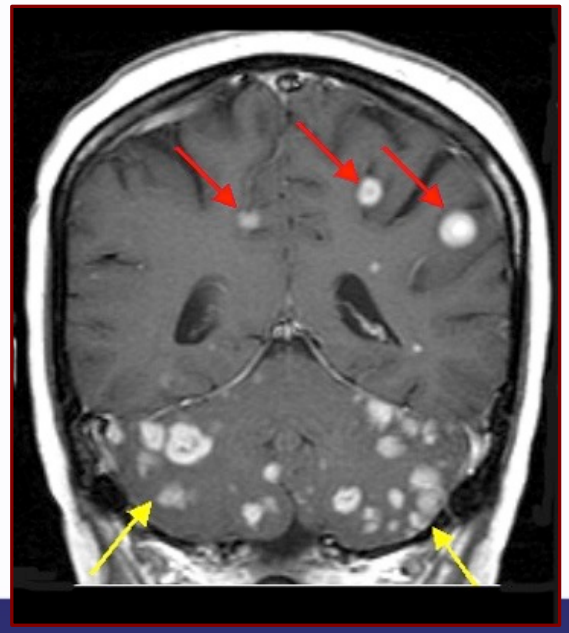
- ***Secondary (Metastatic)***

Metastatic brain tumors arise elsewhere in the body (lung, breast, skin, kidneys, etc) and move to the brain-they are defined are malignant. The majority of brain tumors are metastatic and are reported in at least 25-30% or persons with cancer, or an estimated 200,000 people a year within the United States.

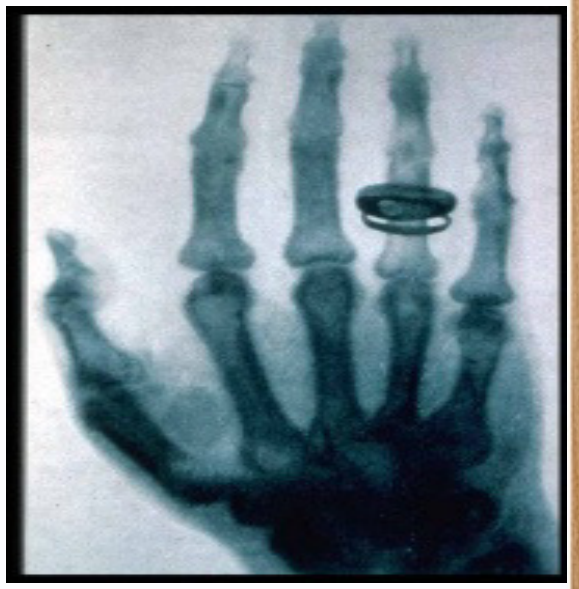
FOCUS of this presentation is Primary Brain Tumors in a Adult Population







Primary Brain Tumor Risk Factors



- Genetics (NF2), Family History
- Ionizing Radiation
- Immune Factors
- Hormones (meningioma)
- Occupation/Environmental Exposure?

Overall Incidence

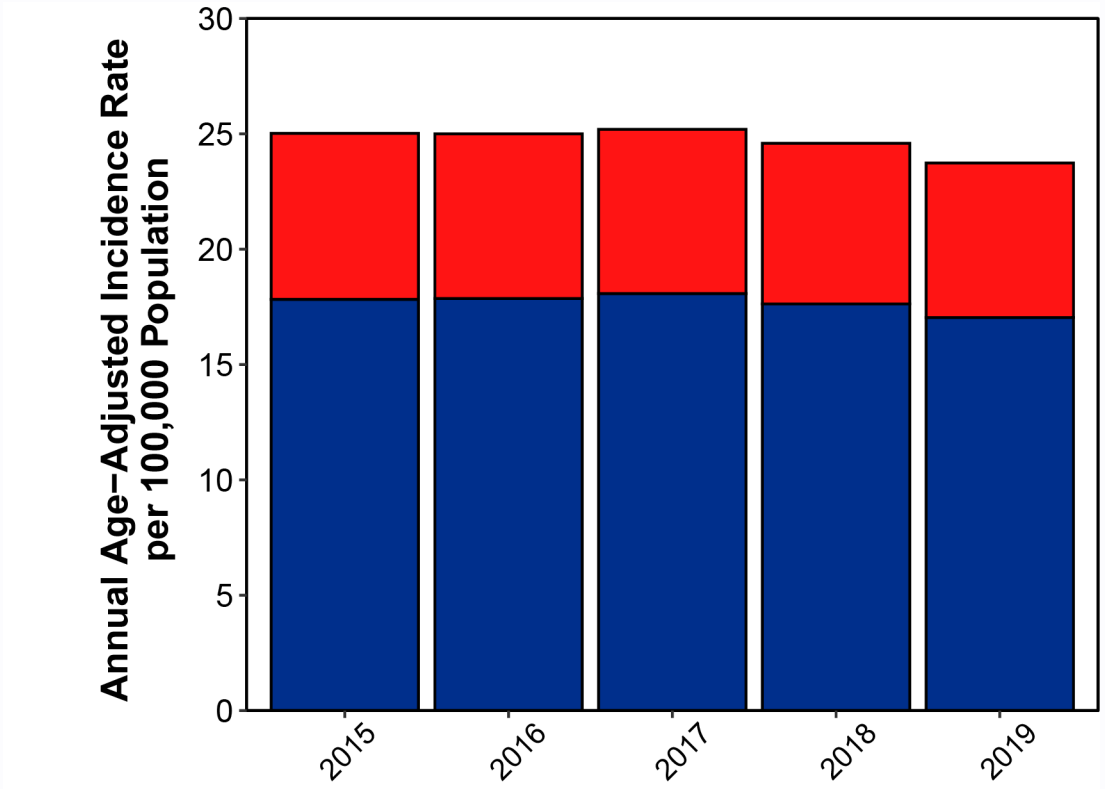
- The average annual age-adjusted incidence rate (AAAIR) of all malignant and non-malignant brain and other Central Nervous System (CNS) tumors was 24.71 per 100,000 population (malignant AAAIR=7.02 and non-malignant AAAIR=17.69).

- This overall rate was higher in females compared to males (27.62 versus 21.60 per 100,000) and non-Hispanic persons compared to Hispanic persons (25.09 versus 22.95 per 100,000).

- The most commonly occurring **malignant** brain and other CNS tumor was glioblastoma (14.2% of all tumors and 50.1% of **malignant tumors**), and the most common **non-malignant** tumor was meningioma (39.7% of all tumors and 55.4% of **non-malignant** tumors). Glioblastoma was more common in males, and meningioma was more common in females.

The majority of primary brain tumors are non-malignant

- An estimated 91,650 new cases of **malignant** and **non-malignant** brain and other CNS tumors are expected to be diagnosed in the US population in 2022 (26,130 **malignant** and 65,520 **non-malignant**).



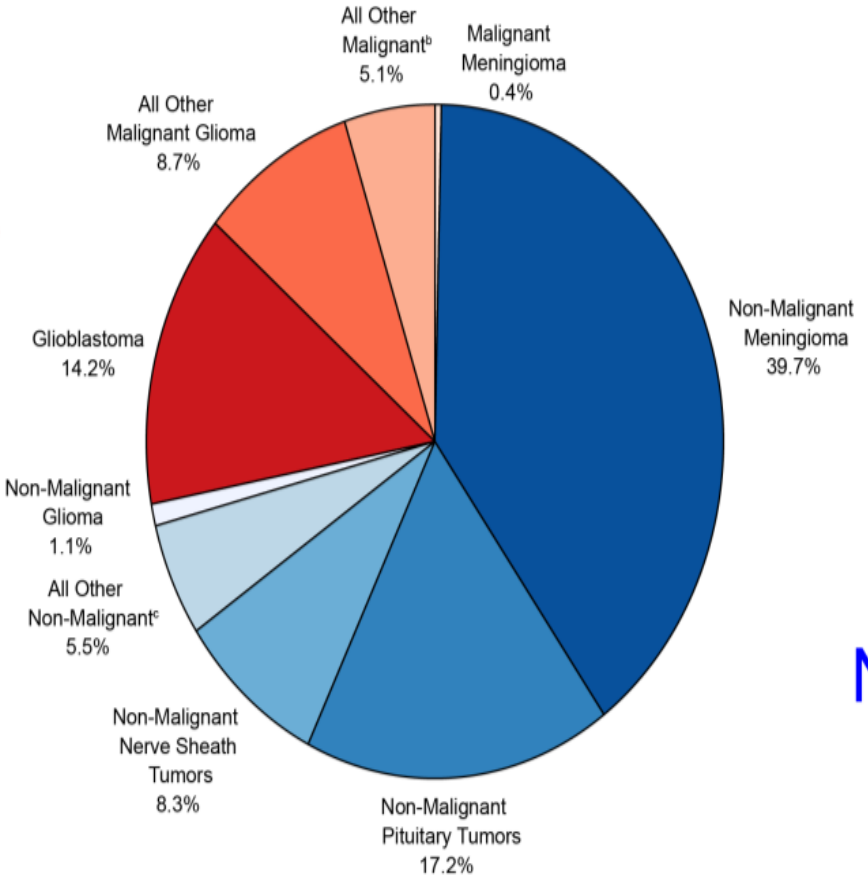
	2015	2016	2017	2018	2019
Malignant	7.19	7.14	7.12	6.96	6.70
Non−Malignant	17.83	17.86	18.08	17.63	17.04

Figure 1. Distribution[a] of All Primary Brain and Other Central Nervous System Tumors by Behavior (Five-Year Total=445,792; Annual Average Cases=87,427), CBTRUS Statistical Report: US Cancer Statistics - NPCR and SEER, 2015-2019

Malignant

N = 126,345

28.3%



CBTRUS

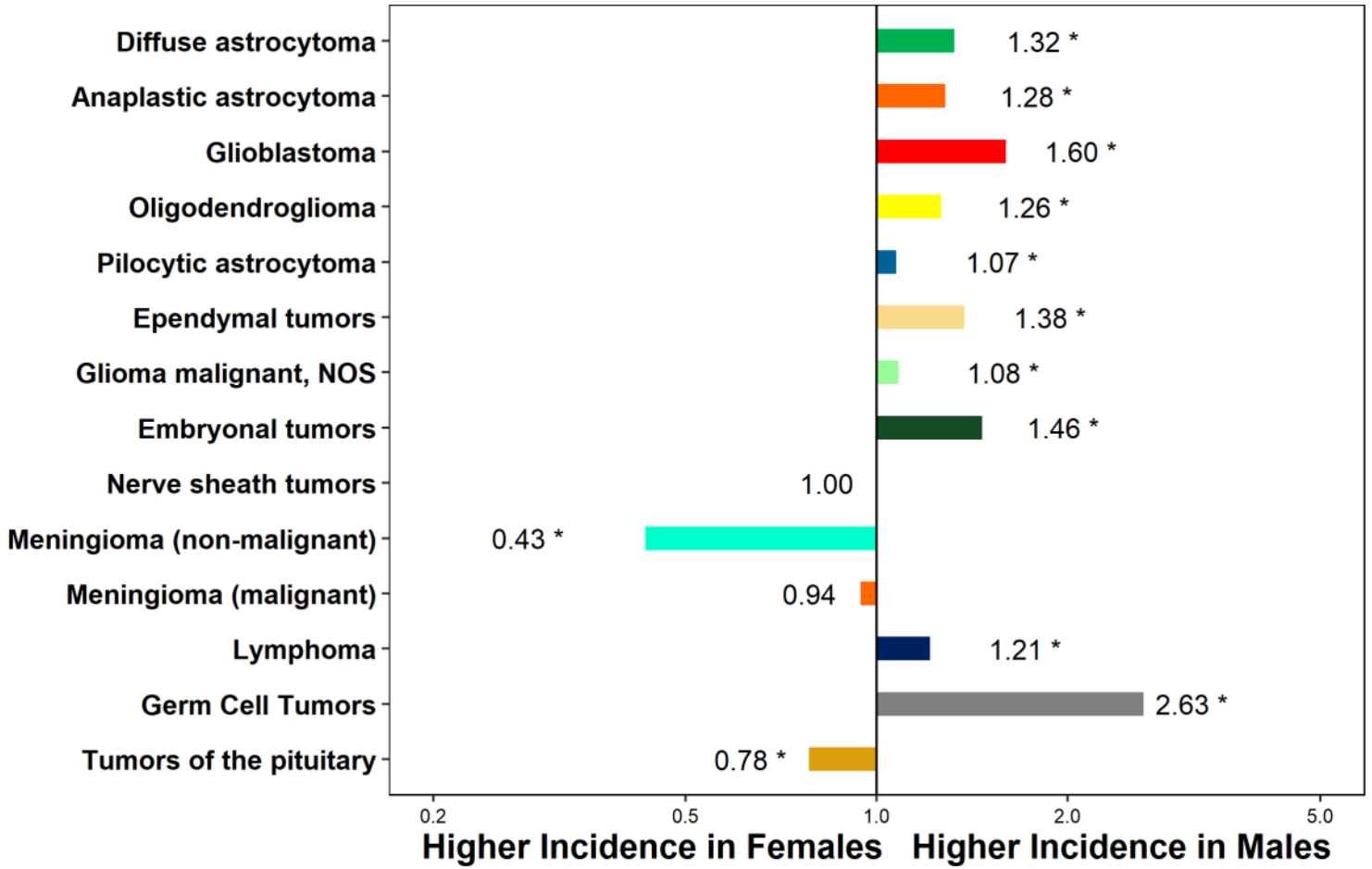
Central Brain Tumor Registry of the United States

Non-Malignant

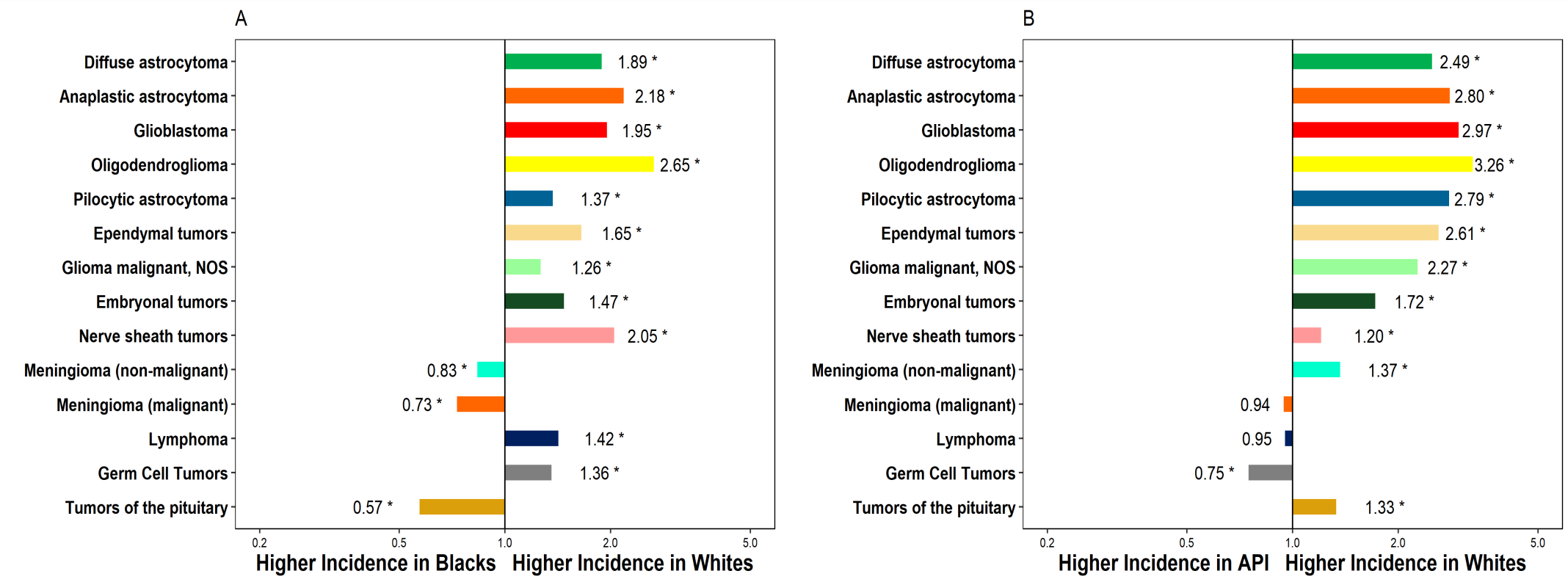
N = 319,447

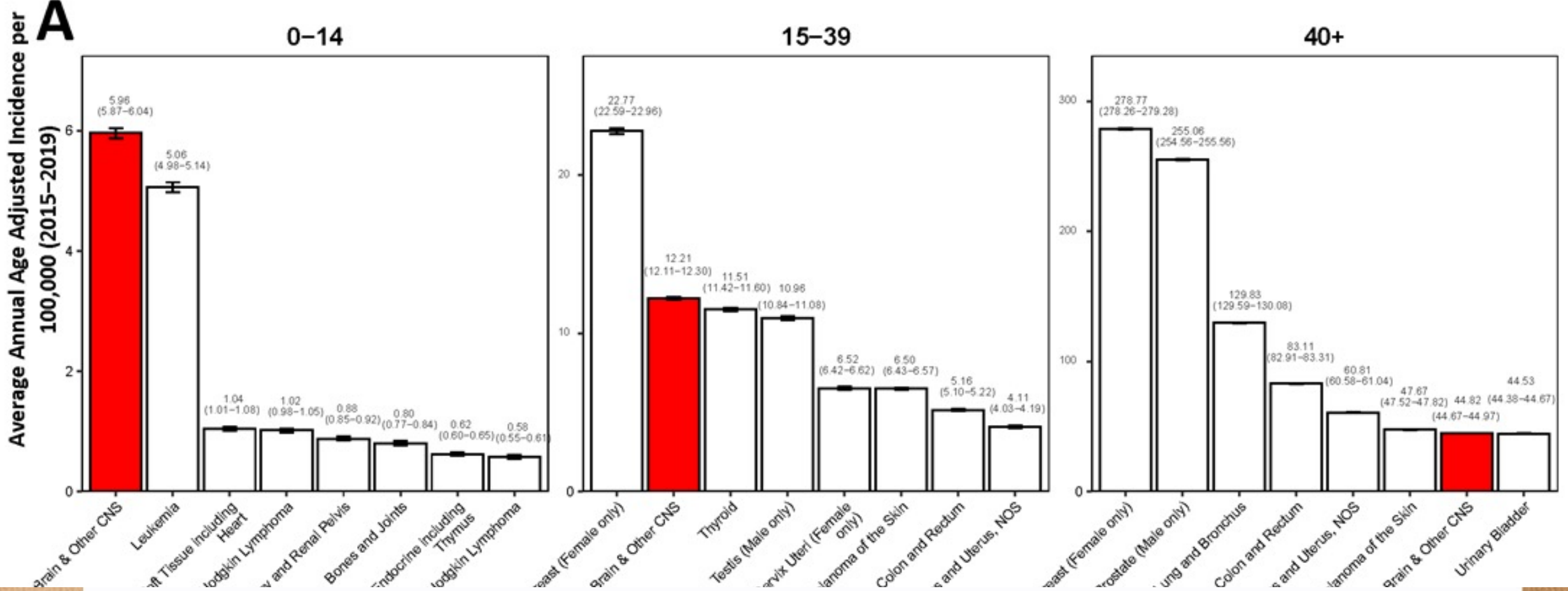
71.7%

Figure 1. Incidence Rate Ratios[a] by Sex (Males:Females) for Selected Primary Brain and Other Central Nervous System Tumor Histopathologies, CBTRUS Statistical Report: US Cancer Statistics - NPCR and SEER, 2015-2019



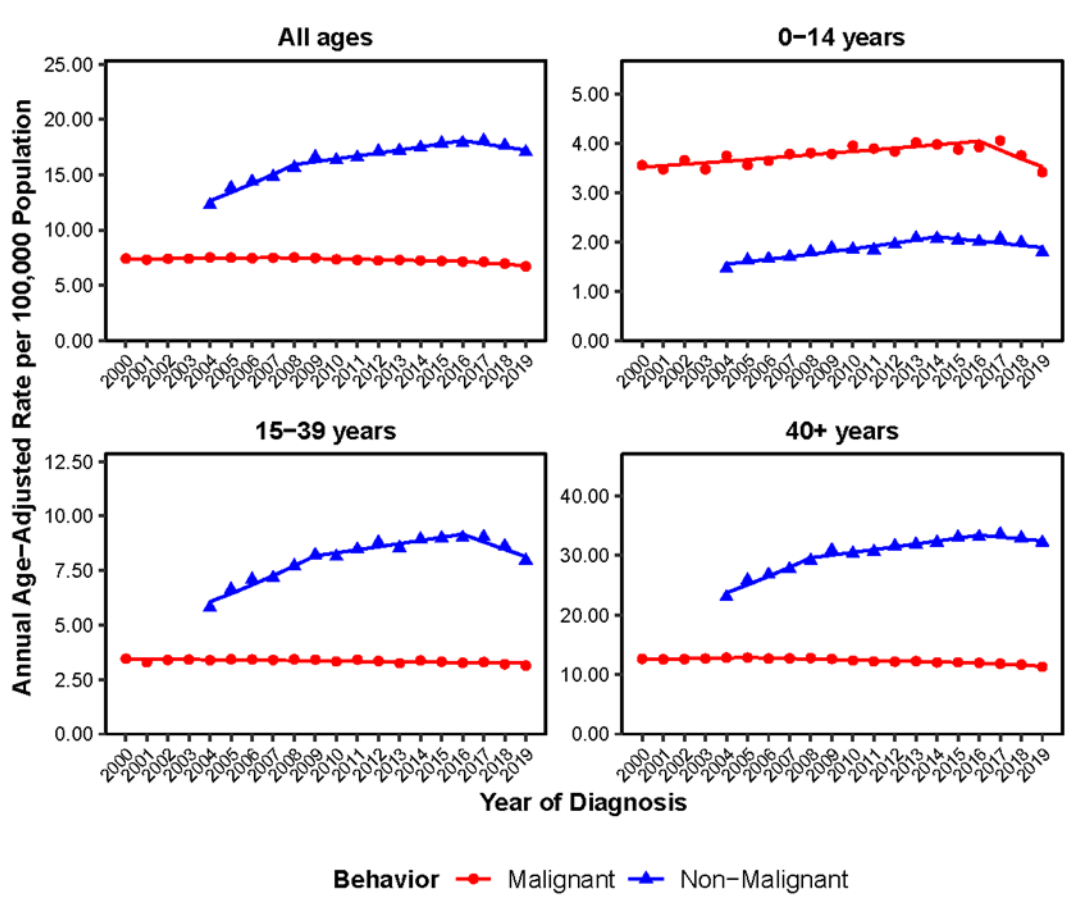
Incidence by Race





Average Annual Age-Adjusted Incidence Rates with 95% Confidence Intervals of All Primary Brain/Central Nervous System Tumors in Comparison To Top Eight Highest Incidence Cancers by age.
Figures courtesy of CBTRUS.

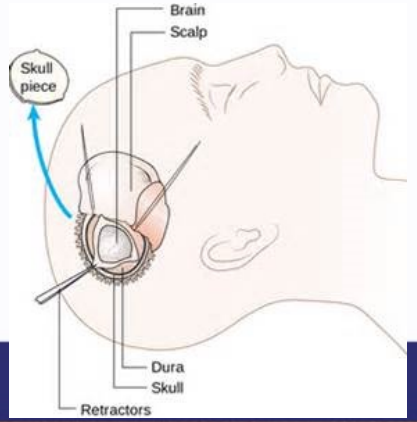
Annual Age-Adjusted Incidence Rates of All Primary Brain and Other Central Nervous System Tumors, and Incidence Trends by Behavior and Age Group at Diagnosis, CBTRUS Statistical Report: US Cancer Statistics - NPCR and SEER, 2000-2019 (varying)



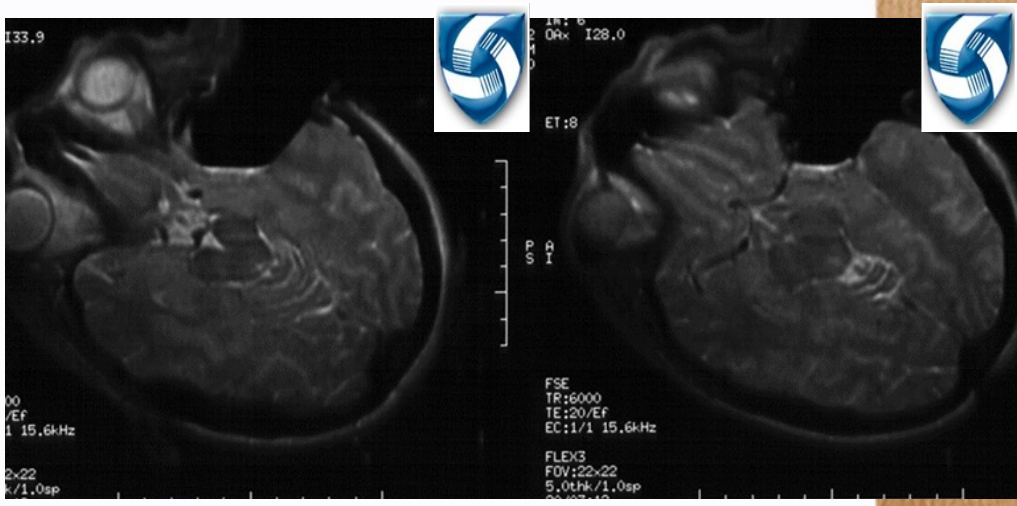
Treatment of Primary Brain Tumors

NEUROSURGERY

- The great majority of malignant brain tumor patients receive surgery as possible, some non-malignant patients receive surgery while others are managed conservatively
- A craniotomy is the surgical removal of part of the bone from the skull to expose the brain for surgery. The surgeon uses specialized tools to remove tumor. At end of the surgery the surgeon replaces the bone flap.
- Generally done under general anesthesia but in some instances, light sedation may be used
- A number of tools may be used including functional and intra-operative MRI, microscope, endoscope, ultrasound, laser, and intra-operative computer guidance.



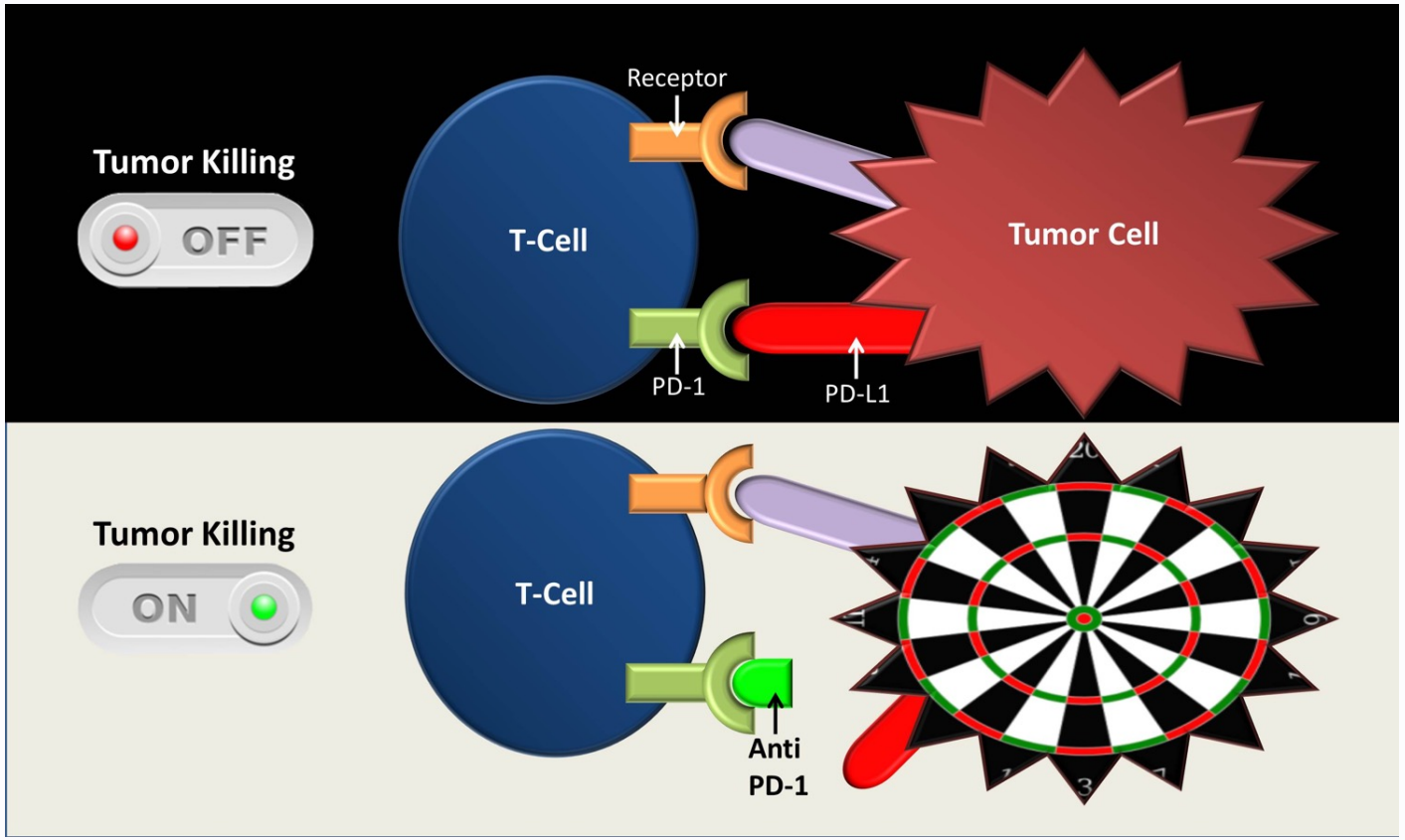
Goals of surgery



- Diagnosis-including histology, grade and tumor marker
  Therapeutic benefit – Cytoreduction
  - Extend survival
  - Preservation of neurologic function

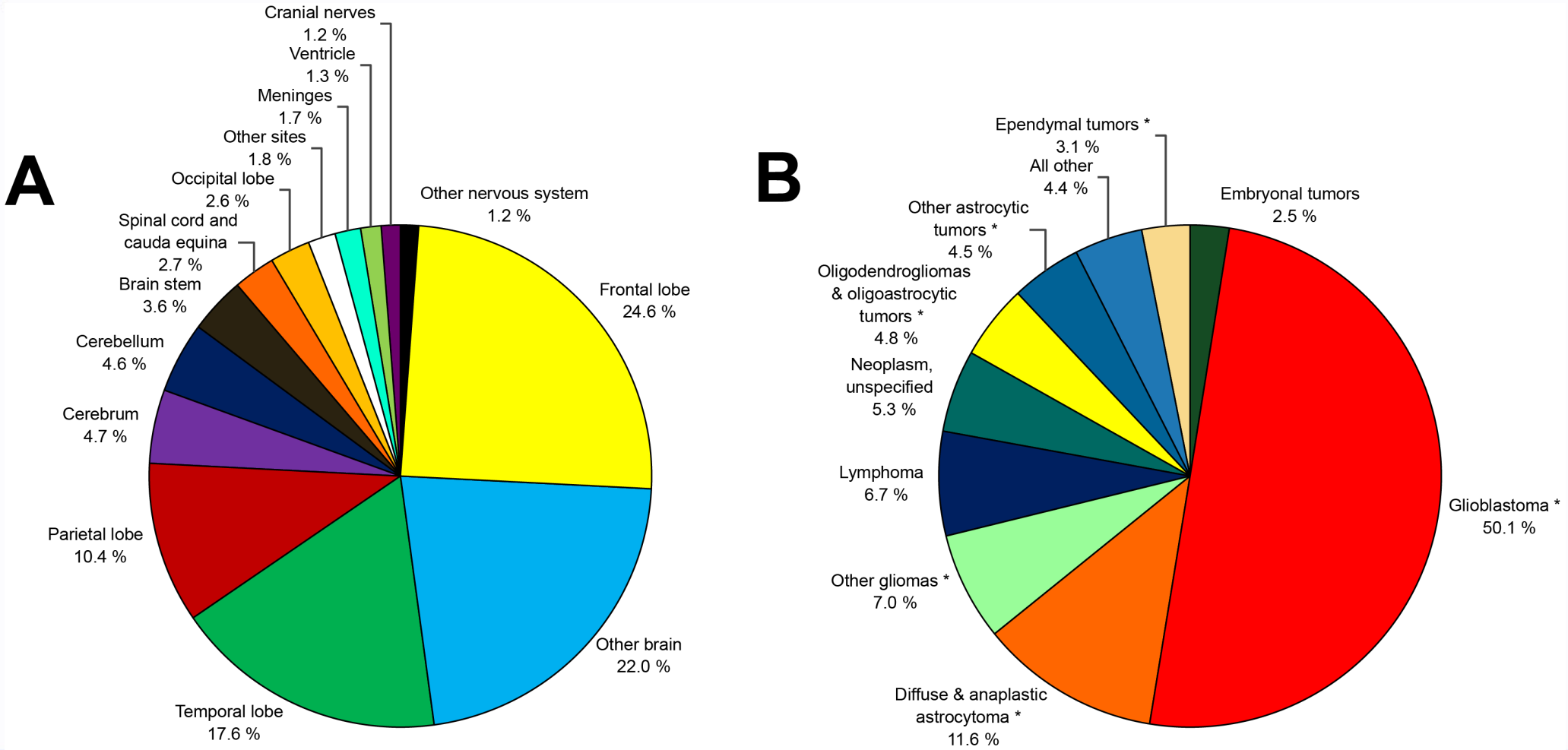
- "Take out the optimal amount!"
  - Evidence-based practice derived from retrospective studies of associated clinical benefit.
  - For diffuse gliomas, balance tumor removal with normal function preservation
  - Can use intraoperative MRI guidance
  - Help, don't hurt

Chemotherapy, Radiation Therapy, immunotherapy



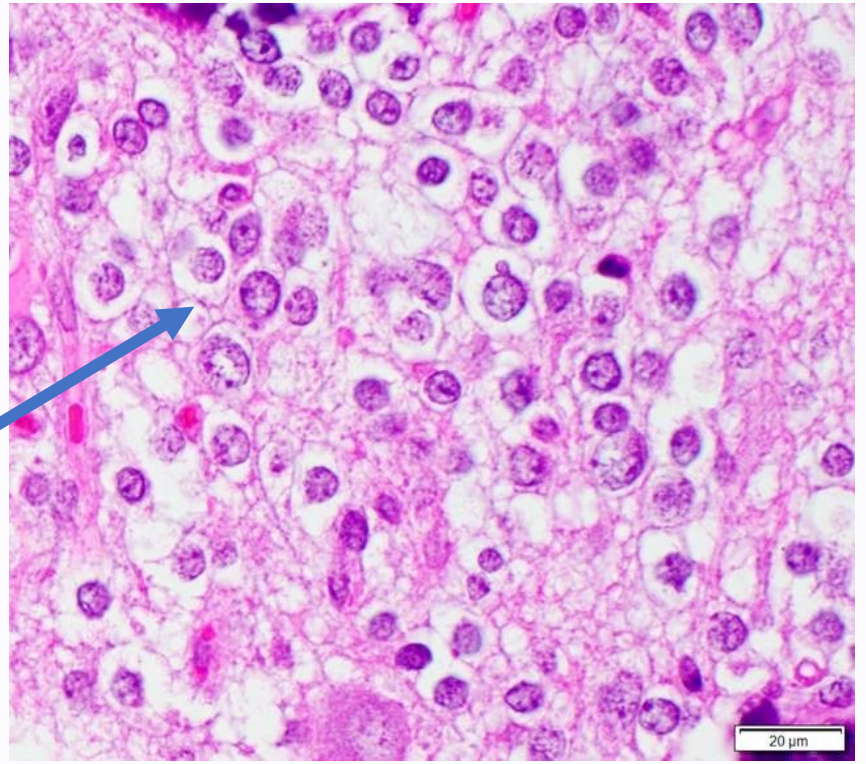
Malignant Brain Tumors

Figure 9. Distribution[a] of Malignant Primary Brain and Other Central Nervous System Tumors (Five-Year Total=126,345; Annual Average Cases=25,269), by A) Site and B) Histopathology, CBTRUS Statistical Report: US Cancer Statistics – NPCR and SEER, 2015-2019



Glioma-Old Classification

- Traditionally, gliomas have been classified as grade **I to IV** based on histology and clinical criteria.
- Grade I tumors primarily in children, an entity separate from grade II-IV (seen primarily in adults).
- Grade II/III tumors (Lower Grade Gliomas or LGG) have been defined by histology (what does the tumor look like under the microscope) as astrocytoma, oligoastrocytoma (aka mixed glioma), or oligodendroglioma.
- Grade IV tumors are high grade glioma (HGG) (aka glioblastoma (GBM))-primary if arising de novo and secondary if transformed from LGG.



Oligodendroglioma-Classic “Fried Egg” appearance after fixation

Glioma-New Classification

Neuro-Oncology

23(8), 1231–1251, 2021 | doi:10.1093/neuonc/noab106 | Advance Access date 29 June 2021

The 2021 WHO Classification of Tumors of the Central Nervous System: a summary

David N. Louis, Arie Perry, Pieter Wesseling, Daniel J. Brat, Ian A. Cree, Dominique Figarella-Branger, Cynthia Hawkins, H. K. Ng, Stefan M. Pfister, Guido Reifenberger, Riccardo Soffietti, Andreas von Deimling, and David W. Ellison

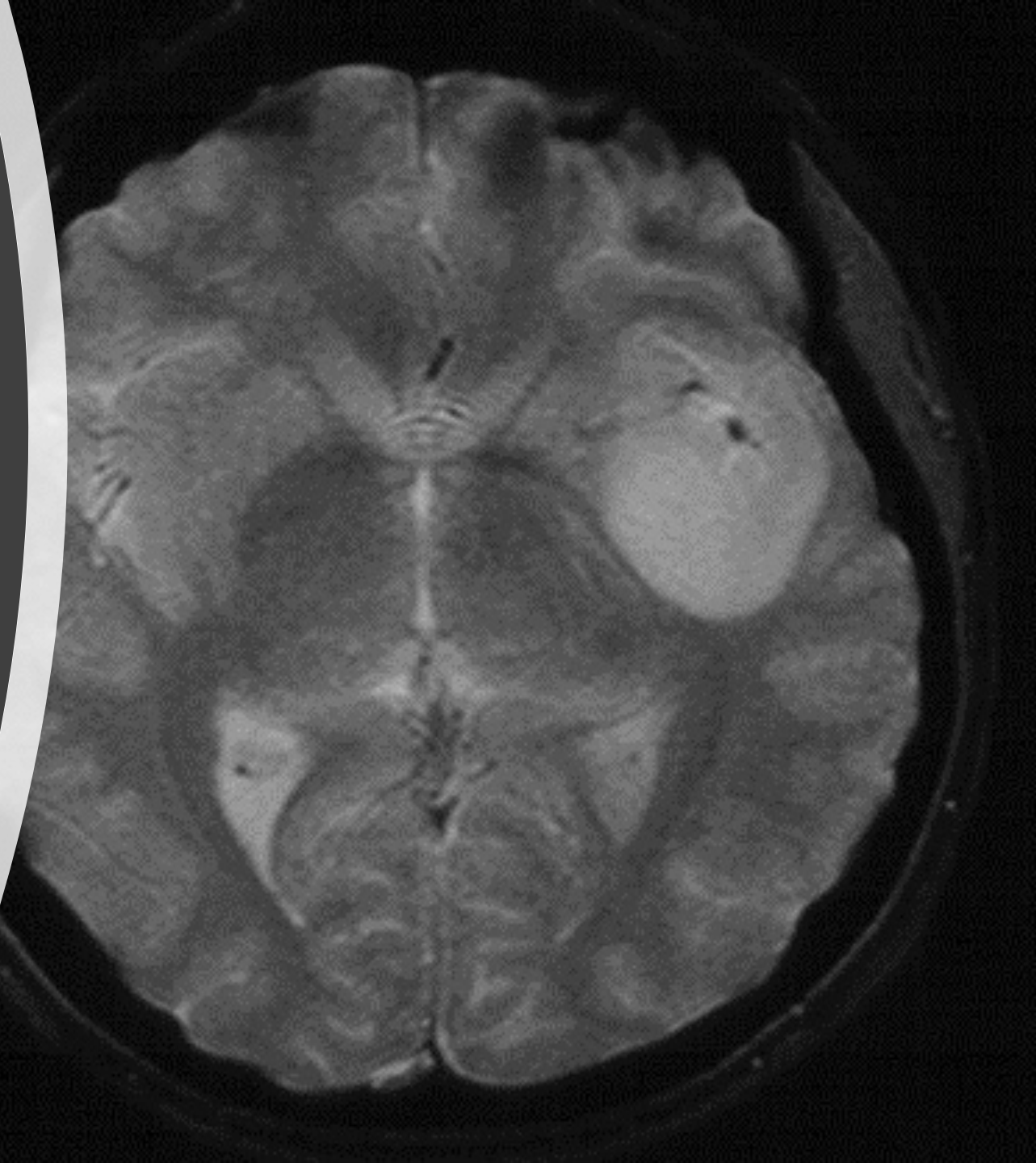
https://pubmed.ncbi.nlm.nih.gov/34185076/

Glioma-WHO 2021 Changes

	Then	Now
Taxonomy	Histology and Tissue-Based Analyses (immunohistochemistry, etc)	Molecular ***Biomarkers, Genes*** (IDH1/2 mutation, 1p/19q co-deletion, etc)
Grading	• Arabic Numerals (I-IV) • Grading **across** tumor types	• Roman Numerals (1-4) • Grading **within** tumor type

Glioma, Glioneuronal and Neuronal Tumors

- Adult type Diffuse Gliomas
- Pediatric-type Diffuse Low Grade Gliomas
- Pediatric-type High Diffuse High Grade Gliomas
- Circumscribed astrocytic gliomas
- Glioneuronal and Neuronal Tumors
- Ependymomas



Note

In the past tumors graded based on expected natural history (i.e. survival rates)-generally without consideration of use of therapy –thus extremely important to consider diagnosis using updated criteria

6). For instance, WNT-activated medulloblastoma is an embryonal tumor that has an aggressive behavior if left untreated but that is responsive to current therapeutic regimens such that nearly all patients have long-term survival. Designating this tumor as CNS WHO grade 4, and therefore equivalent to many untreatable pediatric brain tumors with a dismal outcome, potentially risks giving a false sense of prognosis when therapeutic options are discussed in the clinic. Conversely, designating this tumor as CNS WHO grade 1 on the basis of its good outcome, and therefore equivalent to neoplasms with a similar prognosis on the basis of surgery alone, certainly gives a false sense that the tumor is biologically benign.

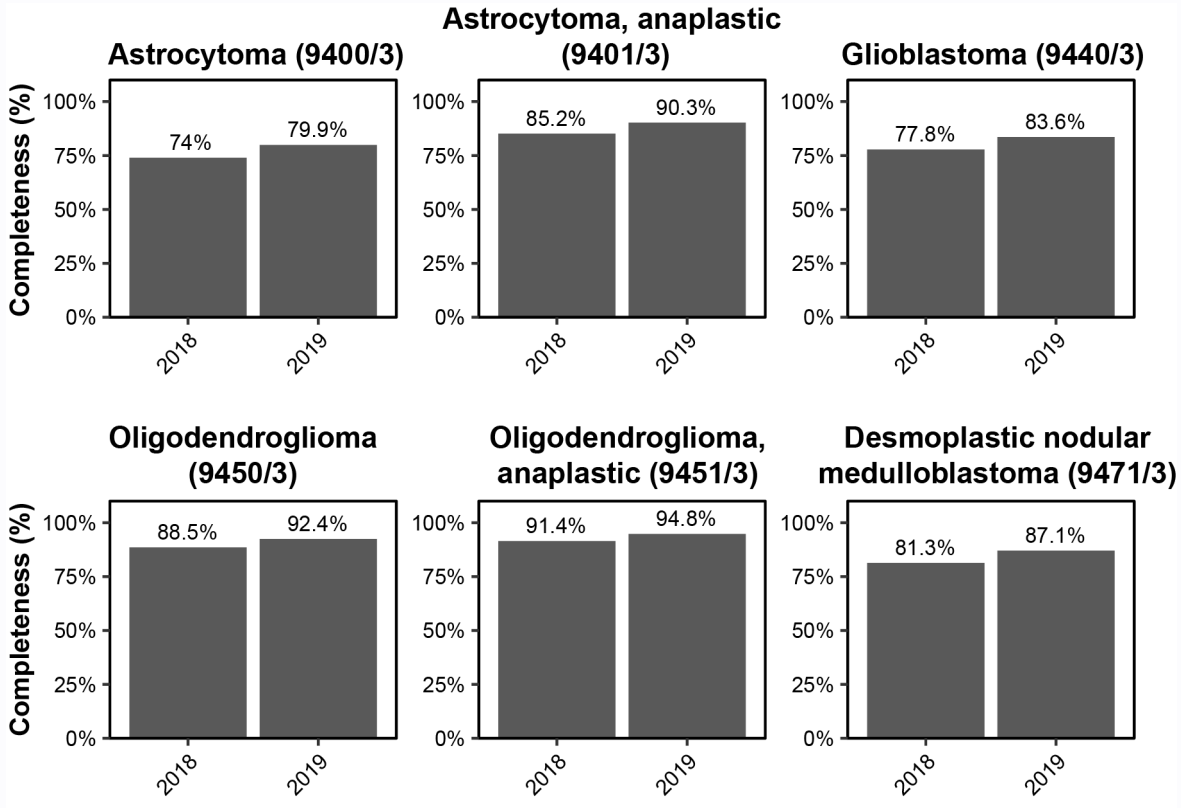
Louis et al, Neuro Oncology 2021

Uptake of these new guidelines

- May vary by geographic location and type of medical facility
- Patient may wish to have pathology reviewed-
  for example, older pathology report may say “glioma, Not otherwise specified”

- Currently survival estimates (CBTRUS, SEER) are based on older guidelines as entry to tumor registries of new biomarkers takes years

Completeness of the Brain Molecular Marker Variable by Year at Diagnosis by ICD-O-3 Code, CBTRUS Statistical Report: US Cancer Statistics - NPCR and SEER, 2018-2019



Survival

Overall Survival

- There were 84,264 deaths attributed to **malignant** brain and other CNS tumors between 2015 and 2019. This represents an average annual mortality rate of 4.41 per 100,000 population and an average of 16,853 deaths per year.

- The five-year relative survival rate following diagnosis of a **malignant** brain and other CNS tumor was 35.7%, for a **non-malignant** brain and other CNS tumors the five-year relative survival rate was 91.8%.

CAVEATS

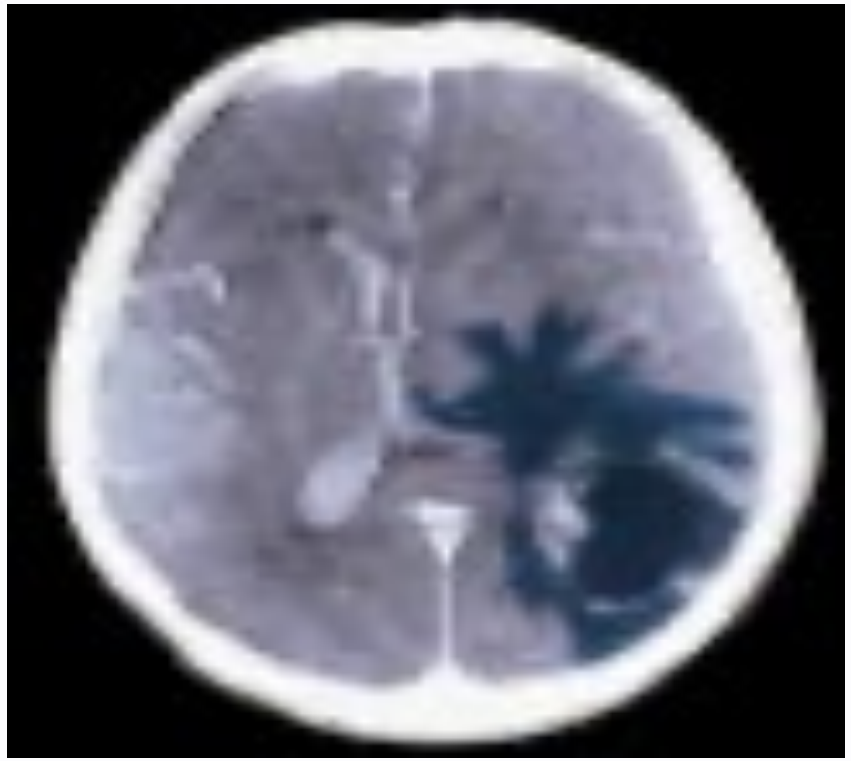
- Within the **malignant** group, expected survival time varies widely thus it is important to further define subtype to better estimated expected lifespan.

- Within the **non-malignant group**, reported survival times may be more applicable to persons undergoing surgical treatment rather than all persons with this diagnosis

Not all gliomas are the same!!

Life expectancy estimates may vary widely (decades) by specifics of diagnosis (and treatment received)-

EXAMPLE

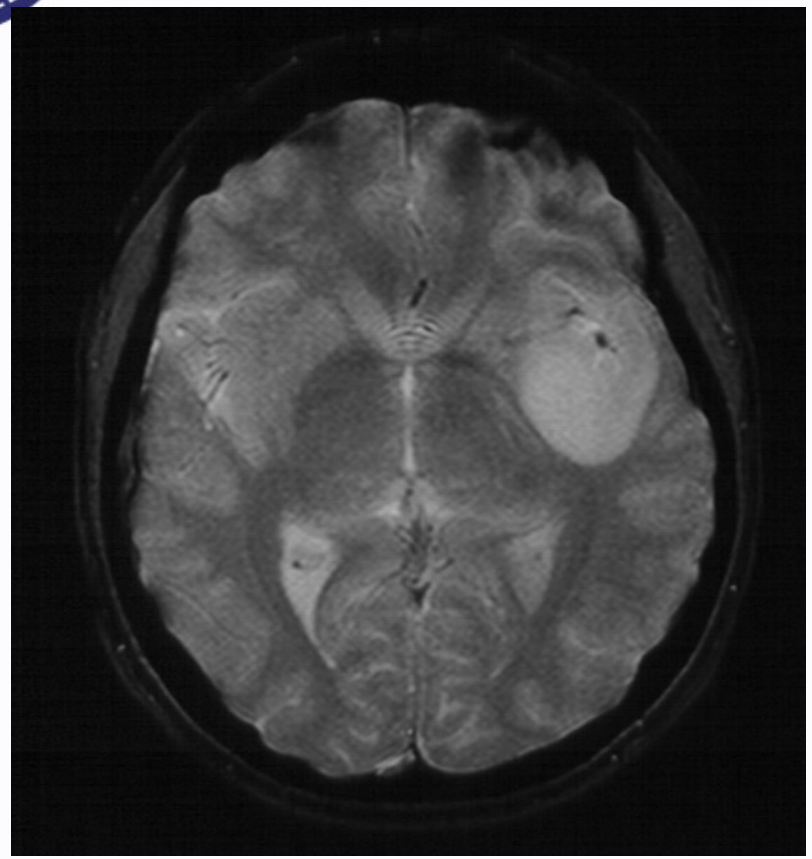


80 year old male,
Slow change in personality and memory
Surgery revealed glioblastoma, patient survived for two years

Glioblastoma-CBTRUS survival estimates

	Age	N	1 year	5 years	10 years
Glioblastoma	0-14	1,102	57.1 (54.1-60.0)	19.9 (17.4-22.5)	16.6 (14.1-19.2)
	15-39	6,467	76.8 (75.7-77.8)	26.6 (25.4-27.8)	18.6 (17.4-19.8)
	40+	117,076	40.6 (40.4-40.9)	5.6 (5.5-5.8)	3.4 (3.2-3.5)
	All ages	124,645	42.7 (42.4-43.0)	6.9 (6.7-7.1)	4.3 (4.2-4.5)

EXAMPLE



37 year old female, otherwise healthy, with sudden onset seizure

Treated with surgery, alive and well 25 years later

Oligodendroglioma-CBTRUS survival estimates

	Age	N	1 year	5 years	10 years
Oligodendroglioma	0-14	272	97.4 (94.6-98.8)	94.3 (90.6-96.5)	92.2 (87.8-95.1)
	15-39	3,934	98.6 (98.2-99.0)	92.5 (91.5-93.4)	78.5 (76.7-80.2)
	40+	5,445	92.5 (91.7-93.2)	77.6 (76.3-78.9)	64.0 (62.1-65.7)
	All ages	9,651	95.2 (94.7-95.6)	84.2 (83.4-85.1)	70.9 (69.6-72.1)

The majority of oligodendroglioma patients are alive more than two decades after their diagnosis

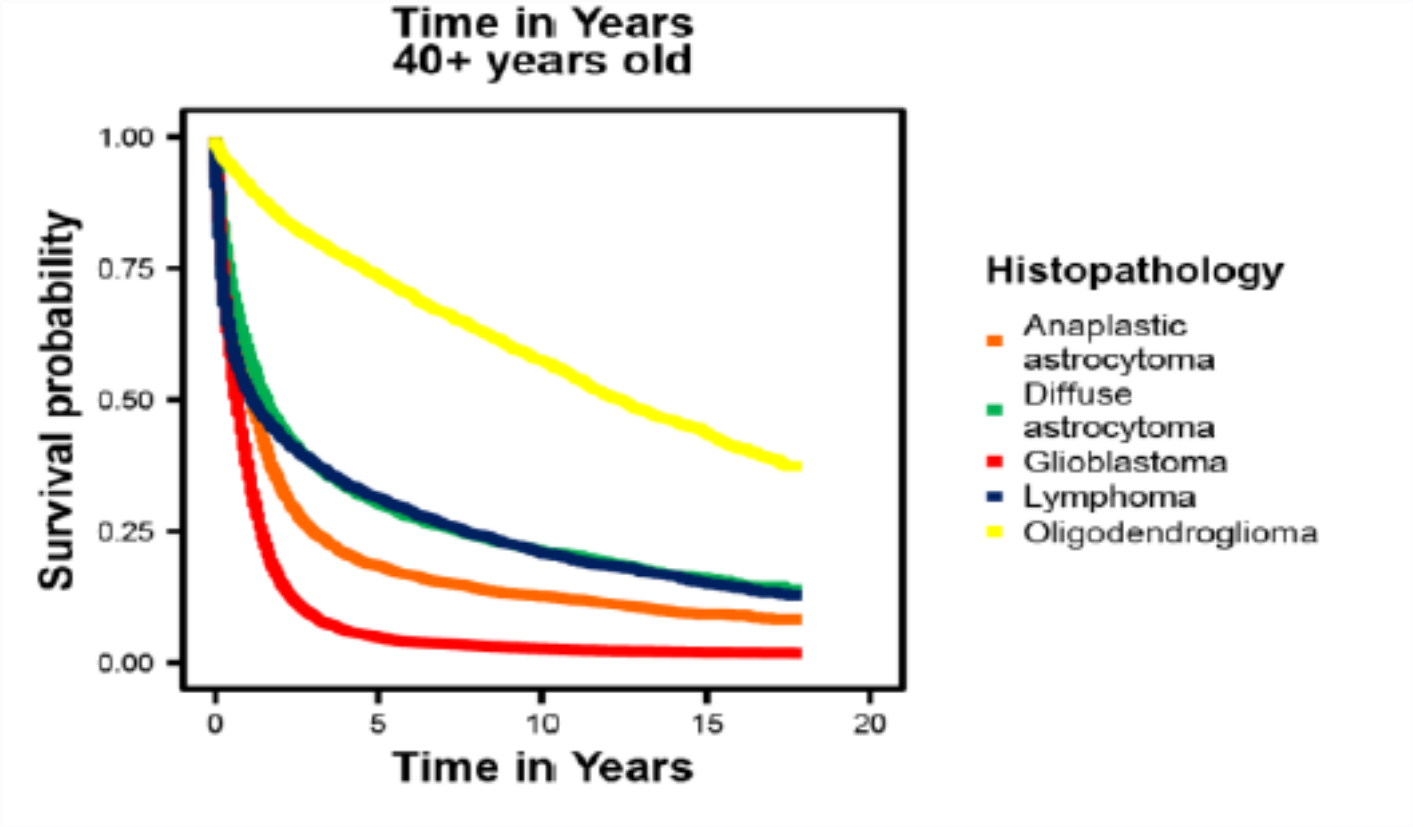


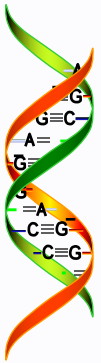
Figure 1. A) Kaplan-Meier Survival Curves for the Five Most Common Histopathologies within Age Group at Diagnosis (Ages 0-14, 15-39 and 40+ Years) and B) Hazard Ratios And 95% Confidence Intervals for Sex, Age at Diagnosis, Race, and Ethnicity for the Five Most Common Histopathologies Overall, National, Data provided by CDC's National Program of Cancer Registries, 2001-2018

Glioma Biomarkers

- Discovery lags behind other cancers
- But likely to play a role in the future in terms of response to treatment and outcome

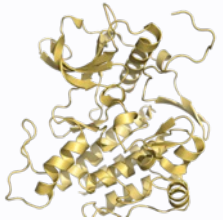
Cancer Biomarkers, genetic variants, and survival

Leukemia
Lung cancer
Sarcoma
Breast cancer
Melanoma

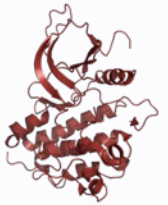


Oncogene discovery

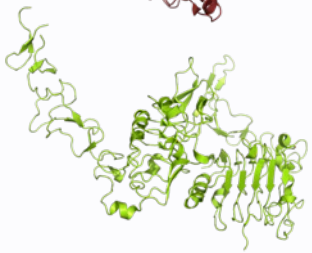
KIT
(Imatinib)



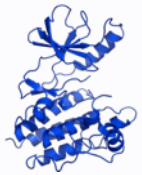
EGFR
(Erlotinib)



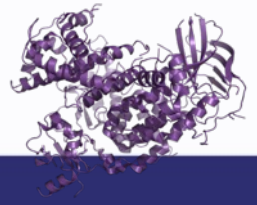
HER2
(Trastuzumab)



BRAF
(Vemurafenib)

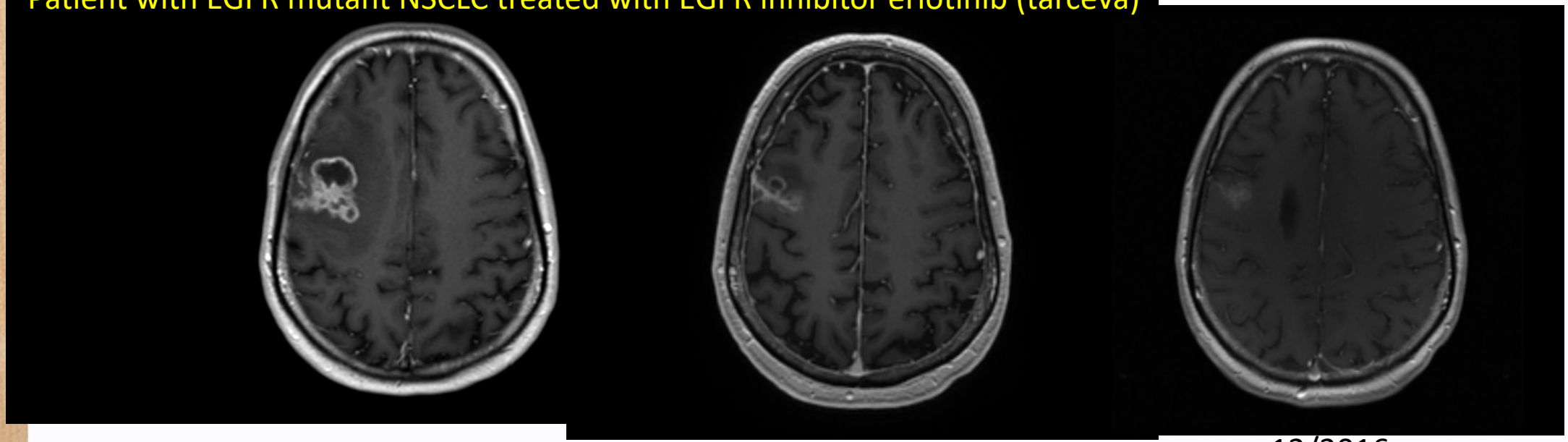


PIK3CA
(BEZ235)



TAKING A PAGE FROM OTHER CANCERS EX. LUNG-GENETIC VARIANTS COME INTO PLAY!

Patient with EGFR mutant NSCLC treated with EGFR inhibitor erlotinib (tarceva)



12/2015 2/2016 12/2016

Non-Malignant Brain Tumors

Asymptomatic Non-Malignant Brain Tumors Relatively Common

ORIGINAL ARTICLE

N Engl J Med 2007;357:1821-8.

Incidental Findings on Brain MRI in the General Population

Meike W. Vernooij, M.D., M. Arfan Ikram, M.D., Hervé L. Tanghe, M.D., Arnaud J.P.E. Vincent, M.D., Albert Hofman, M.D., Gabriel P. Krestin, M.D., Wiro J. Niessen, Ph.D., Monique M.B. Breteler, M.D., and Aad van der Lugt, M.D.

- Rotterdam Study

2000 Adults undergoing a brain MRI

Mean age 63.3 years

N Engl J Med 2007;357:1821-8.

Table 1. Incidental Findings on 2000 MRI Scans.*

Finding	No. (%)
Asymptomatic brain infarct†	145 (7.2)
Lacunar infarct	112 (5.6)
Cortical infarct	41 (2.0)
Primary tumors, benign	31 (1.6)
Meningioma	18 (0.9)
Vestibular schwannoma	4 (0.2)
Intracranial lipoma‡	2 (0.1)
Trigeminal schwannoma	1 (<0.1)
Pituitary adenoma	6 (0.3)
Primary tumors, malignant§	1 (<0.1)
Other findings	
Aneurysm	35 (1.8)
Cavernous angioma	7 (0.4)
Metastases	1 (<0.1)
Subdural hematoma	1 (<0.1)
Arachnoid cyst¶	22 (1.1)
Type I Chiari malformation‖	18 (0.9)
Major-vessel stenosis**	9 (0.5)
Dermoid cyst of lateral orbital rim	1 (<0.1)
Fibrous dysplasia	1 (<0.1)

Meningioma

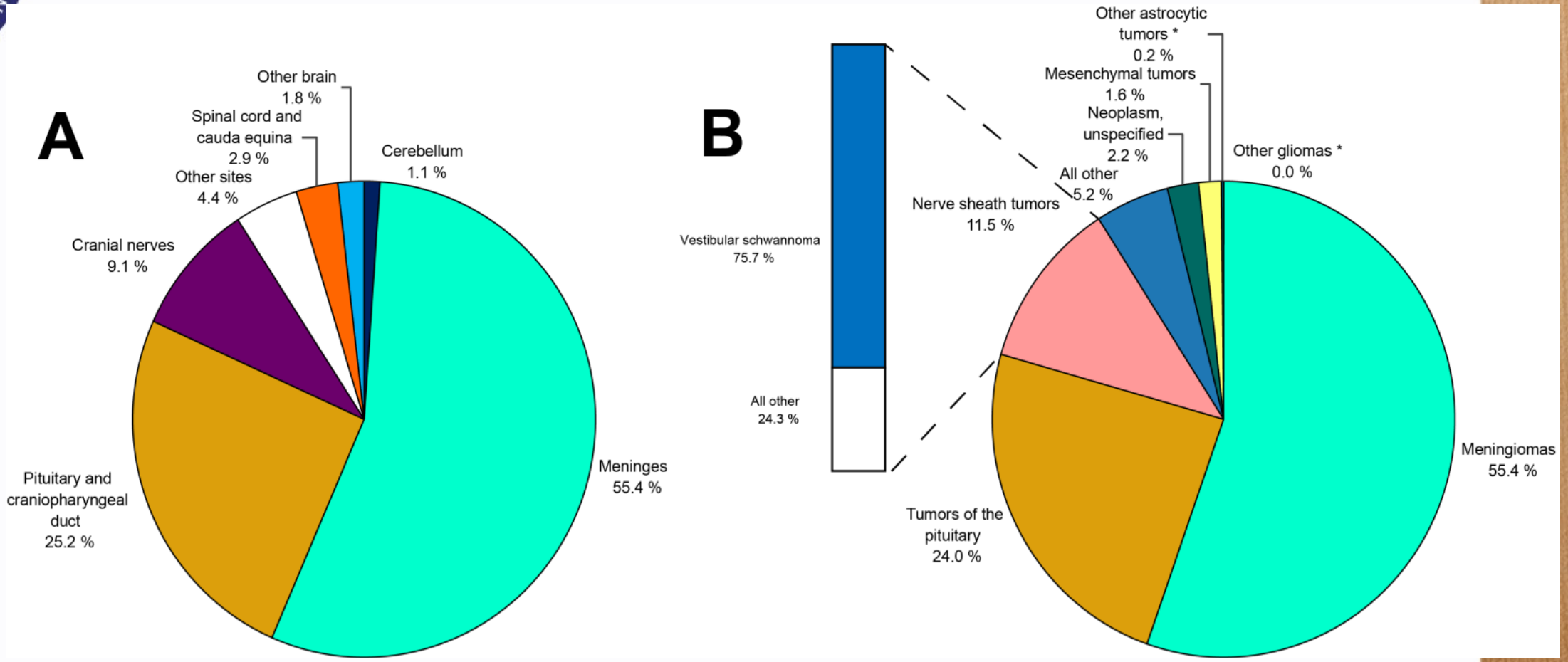
Most Common Non-Malignant Primary Brain Tumor

Many will never require intervention or affect lifespan

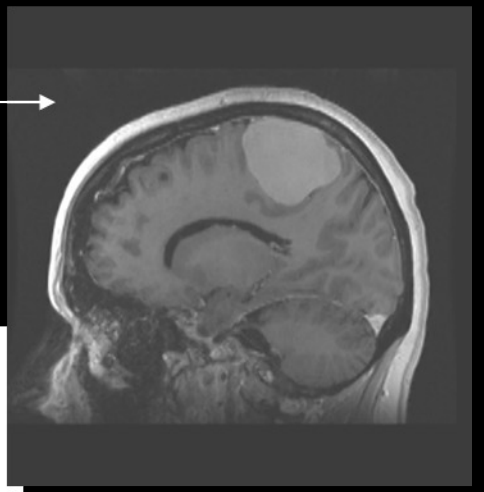
Need for Treatment associated with

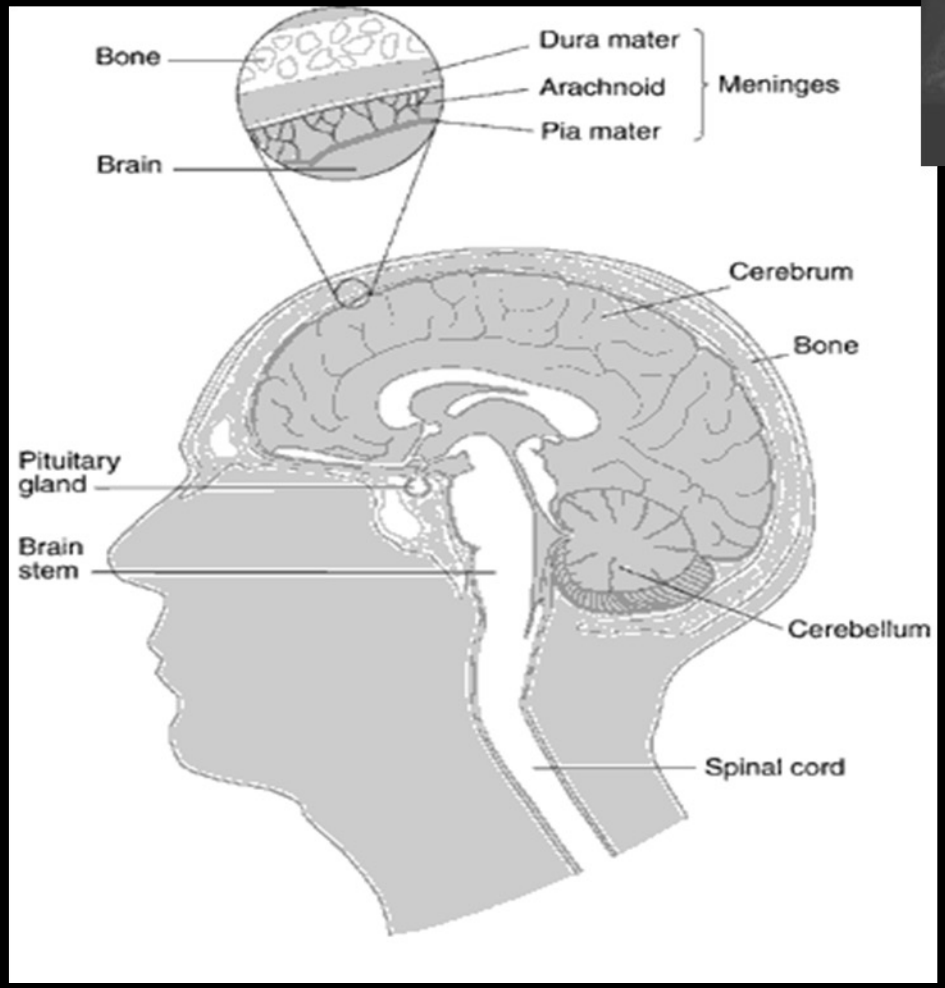
- **Presence of Symptoms**
- **Location**
- **Size**
- **Growth**
- **Patient age/condition**
- **Patient's preference**

Figure 1. Distribution[a] of All Non-Malignant Primary Brain and Other Central Nervous System Tumors (Five-Year Total=319,447; Annual Average Cases=63,887), by A) Site and B) Histopathology, CBTRUS Statistical Report: US Cancer Statistics - NPCR and SEER, 2015-2019



What is a Meningioma?



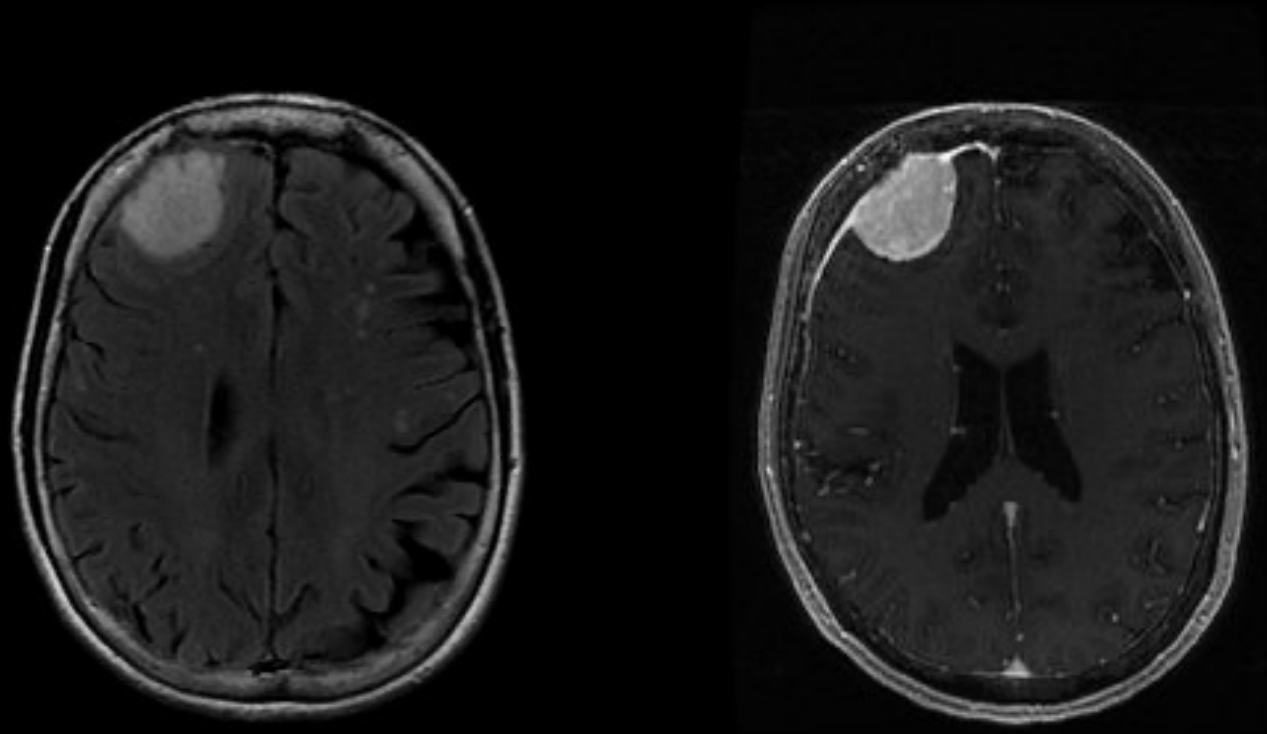


TREATMENT OPTIONS

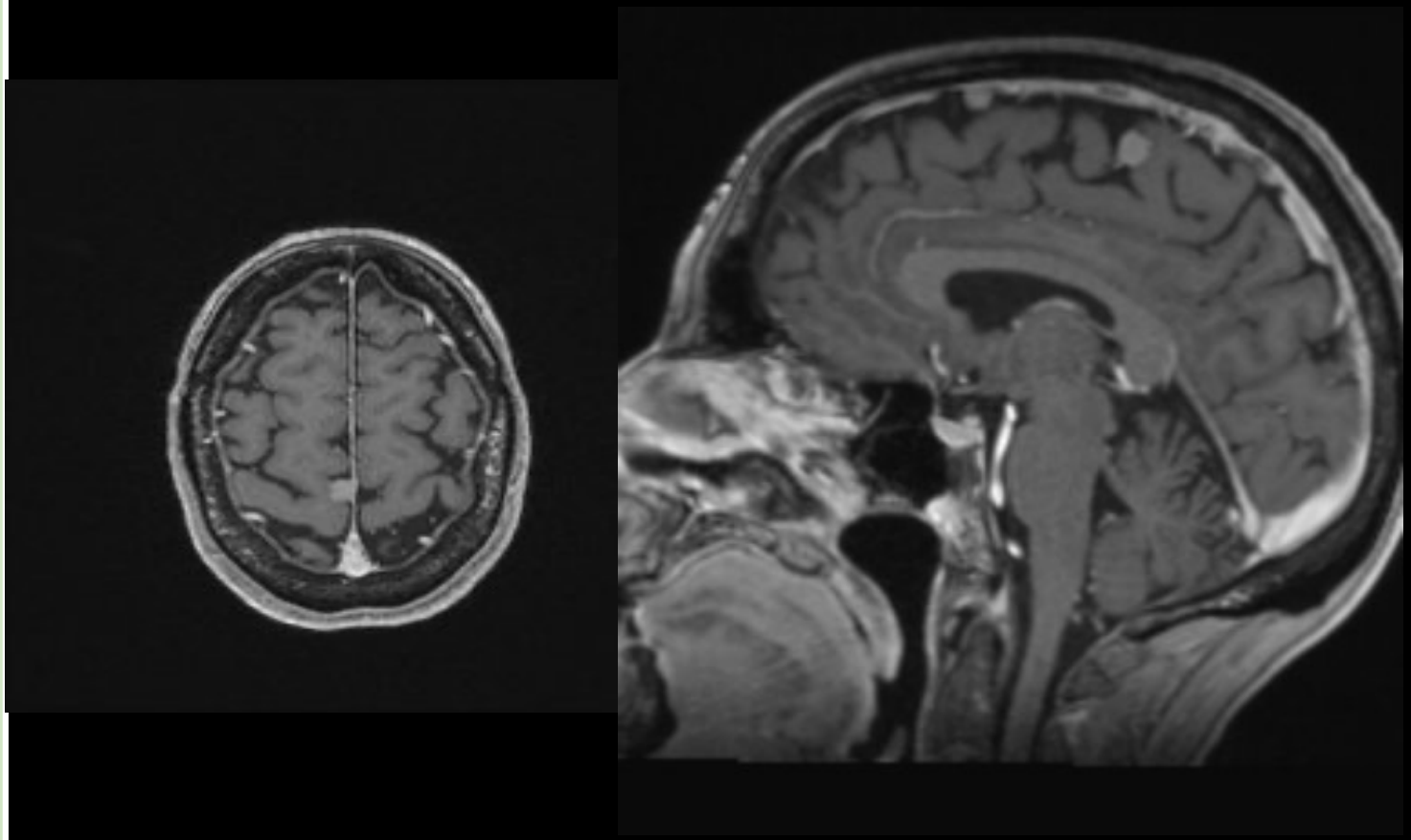
- Watch and Wait (observation)
- Neurosurgery
- Radiotherapy (focused)-initially or if recurrence noted

- Chemotherapy/Immunotherapy only in instances of refractory disease-just as for other brain tumors, tumor genetics are important!

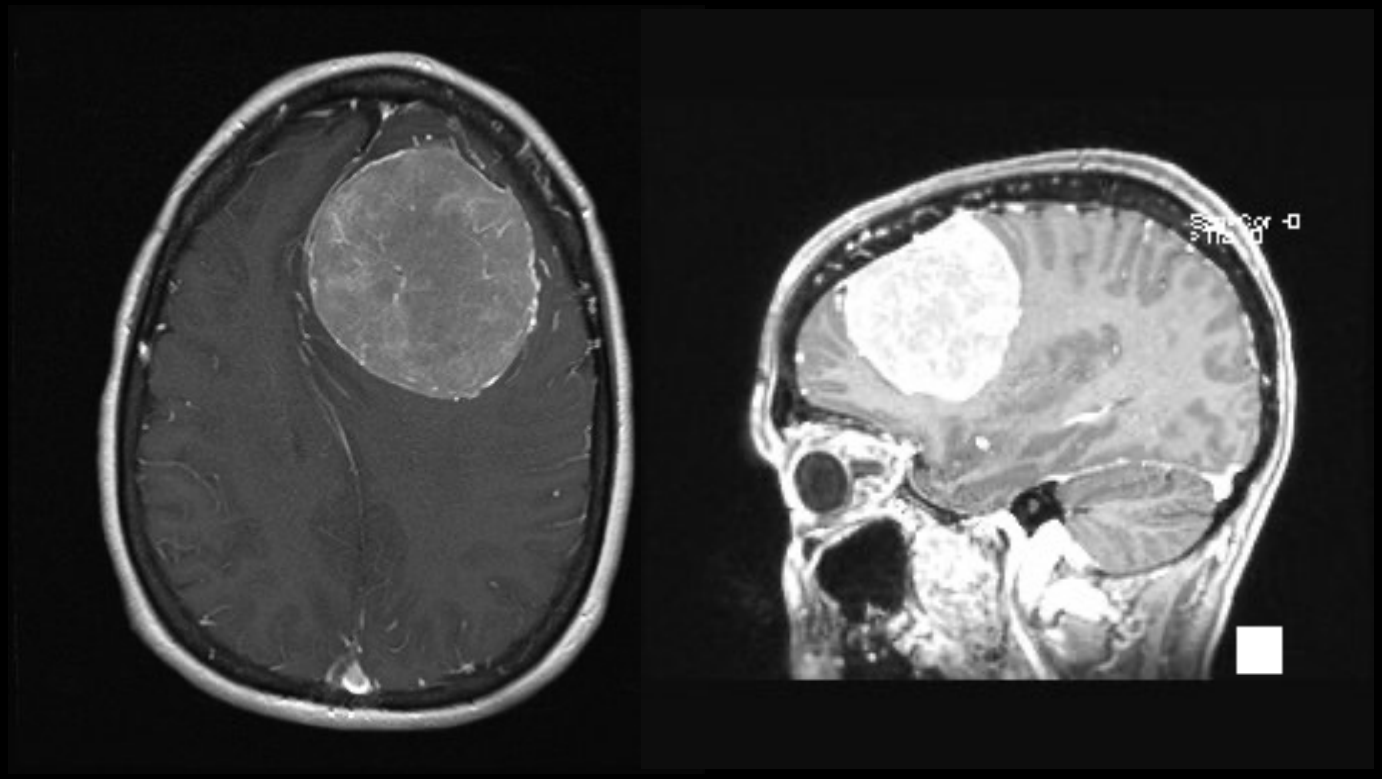
Example 1: Symptomatic? Fainting spell while exercising- hx of cancer- resected and doing well 11 years later



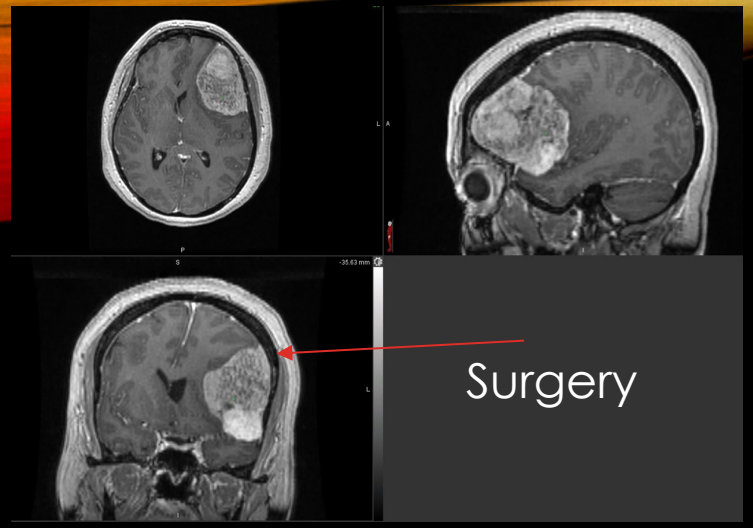
Example 2: Asymptomatic-discovered after fall on Harborcruise-conservative management

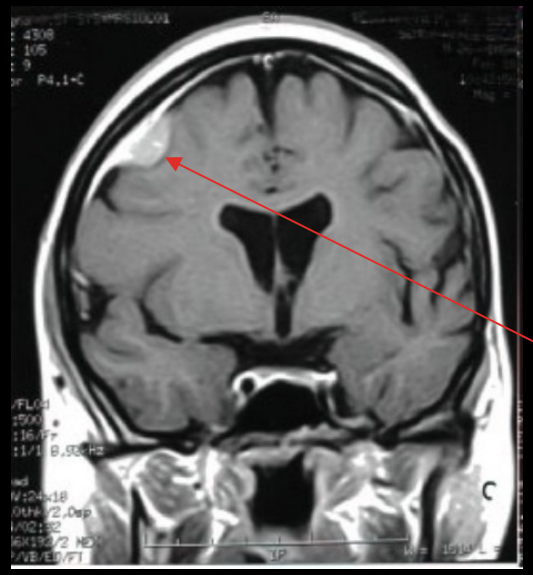


Example 3:
Symptomatic
-Seizure while driving
-Large
-Resected and doing well



OBSERVATION VERSUS INTERVENTION





- Size
- Location
- MRI characteristics
- Symptoms?
- Change in Size
- Patient preference
- General Health/Age

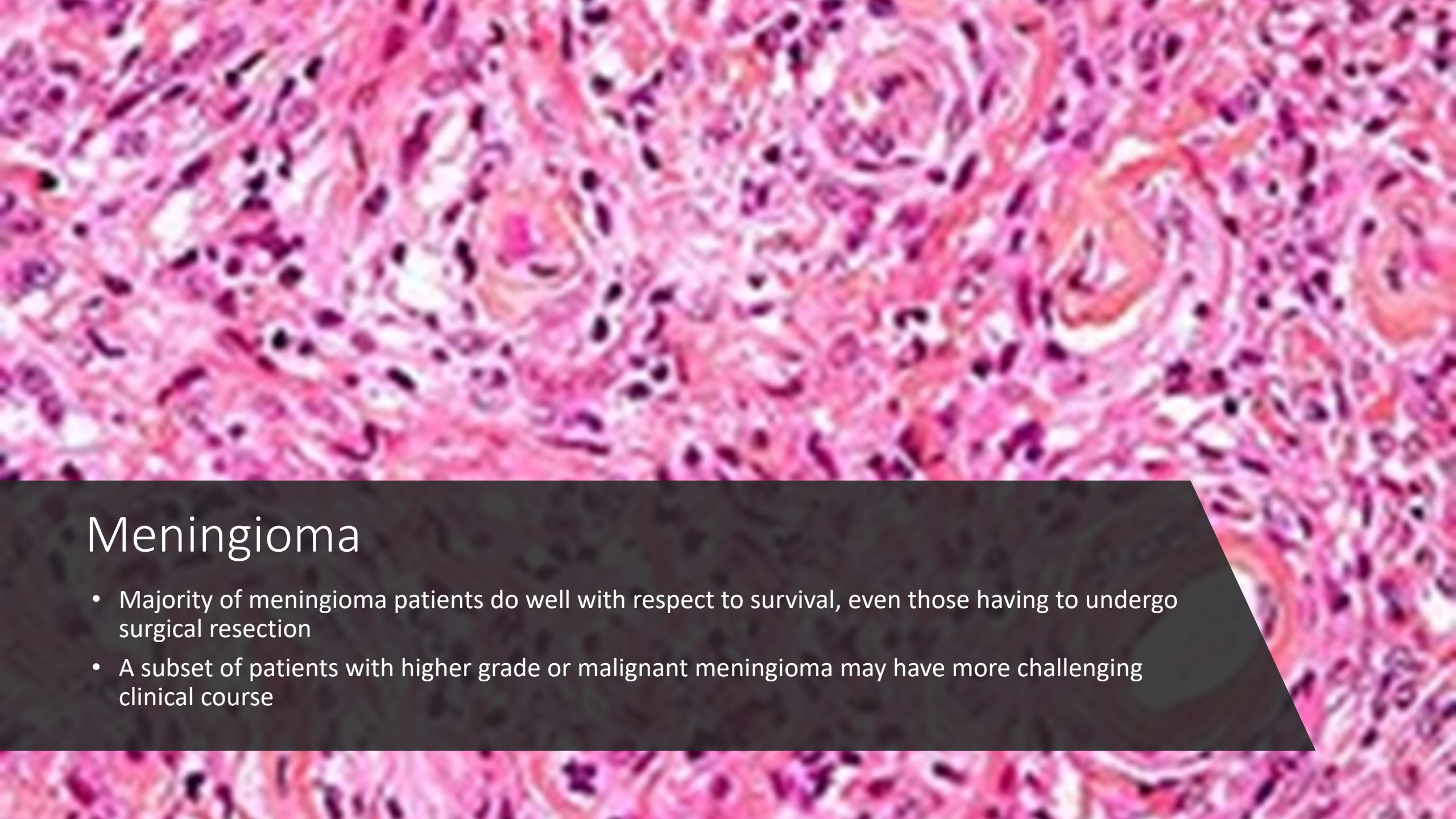
Meningioma

- Meningioma the most frequently reported brain and other CNS tumor, accounting for 40% of tumors overall.
- Non-malignant meningioma account for 99.0% of reported meningiomas.
- Of meningioma with documented WHO grade (82.2%), 80.1% of meningioma were WHO grade I, 18.3% were WHO grade II, and 1.5% were WHO grade III.
- Ten-year relative survival for malignant meningioma was 60%. Age had a large effect on survival after diagnosis with malignant meningioma: 10-year relative survival was 78% for the population ages 20-44 years, and 38.5% for ages 75+ years.
- Ten-year relative survival for non-malignant meningioma was 83.4%. Age had a large effect on survival after diagnosis with non-malignant meningioma: 10-year relative survival was 93.2% in children 0–14, 95% in AYA 15-39, and 82.5% in adults 40+ years old.

Meningioma Survival (CBTRUS Table 10)

Histopathology	Age Groups (years)	All				Malignant[a]				Non-Malignant[b]			
		N[c]	1-Year RS (95% CI)	5-Year RS (95% CI)	10-Year RS (95% CI)	N[d]	1-Year RS (95% CI)	5-Year RS (95% CI)	10-Year RS (95% CI)	N[c]	1-Year RS (95% CI)	5-Year RS (95% CI)	10-Year RS (95% CI)
Meningiomas	0-14	683	97.8 (96.3-98.7)	95.6 (93.6-97.0)	91.7 (88.6-94.0)	59	89.8 (78.6-95.3)	79.0 (65.9-87.5)	73.7 (59.1-83.8)	635	98.6 (97.2-99.3)	96.8 (94.9-98.1)	93.2 (90.1-95.3)
	15-39	23,524	98.8 (98.6-98.9)	97.0 (96.7-97.2)	94.7 (94.3-95.1)	422	93.9 (91.0-95.8)	84.2 (80.0-87.5)	79.0 (74.0-83.1)	23,200	98.8 (98.7-99.0)	97.2 (96.9-97.4)	95.0 (94.6-95.4)
	40+	357,071	92.8 (92.7-92.9)	87.3 (87.1-87.4)	82.2 (81.9-82.5)	4,644	83.2 (82.0-84.3)	65.2 (63.4-66.8)	57.9 (55.7-60.0)	353,421	92.9 (92.8-93.0)	87.5 (87.3-87.7)	82.5 (82.2-82.8)
	All ages	381,278	93.2 (93.1-93.3)	87.9 (87.7-88.1)	83.1 (82.8-83.4)	5,125	84.2 (83.0-85.2)	67.0 (65.4-68.6)	60.0 (57.9-61.9)	377,256	93.3 (93.2-93.4)	88.2 (88.0-88.4)	83.4 (83.1-83.7)

[a] *Assigned behavior code of /3 (see **Table 2**).*
[b] *Assigned behavior code of /0 or /1 (see **Table 2**).*
[c] *Total number of cases that occurred within the included NPCR and SEER registries between 2004 and 2018.*
[d] *Total number of cases that occurred within the included NPCR and SEER registries between 2001 and 2018.*

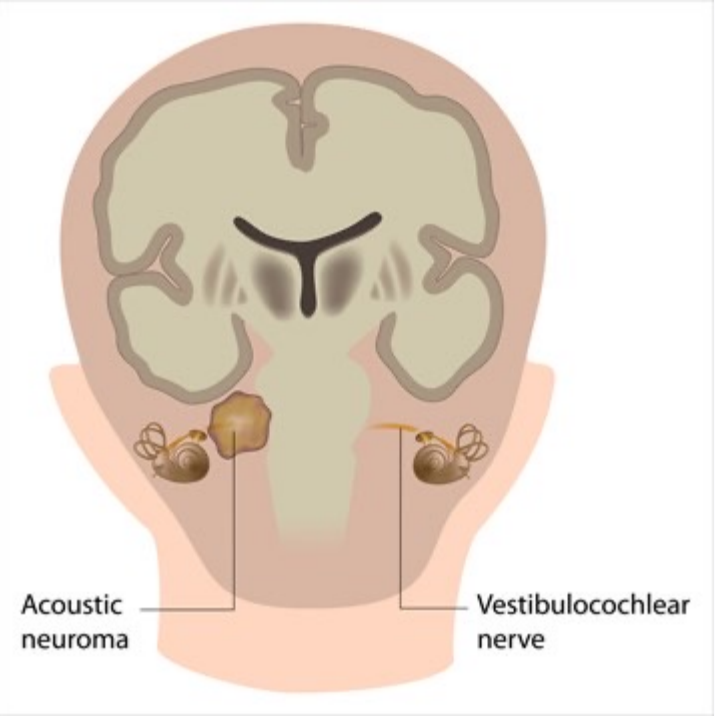


Meningioma

- Majority of meningioma patients do well with respect to survival, even those having to undergo surgical resection
- A subset of patients with higher grade or malignant meningioma may have more challenging clinical course

What is an Acoustic Neuroma?

- Acoustic Neuroma (AN) is a tumor of the nerve (called the vestibulocochlear or eighth cranial nerve) that connects the ear to the brain. AN comes from an overproduction of the cells that normally wrap around nerve fibers to help support and insulate nerves.



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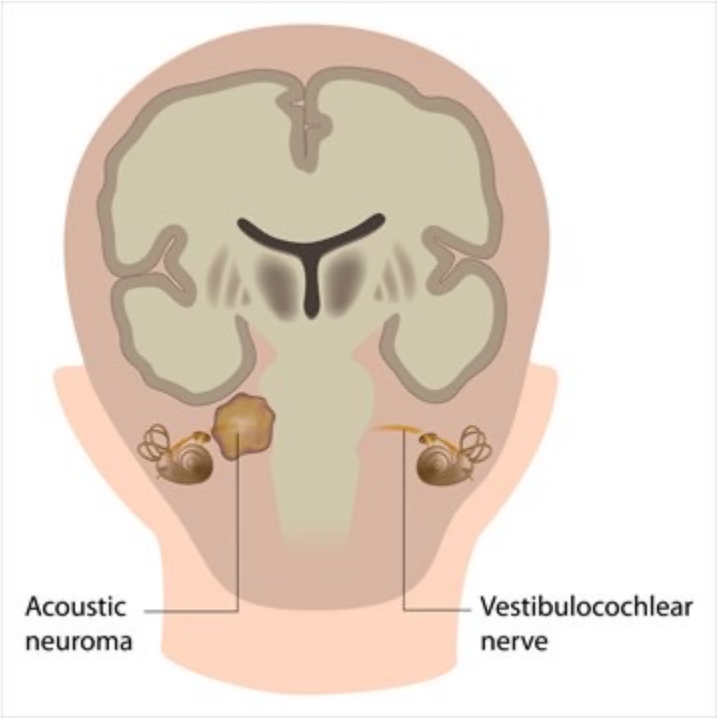
How many people are diagnosed with AN?

- Reporting of AN to cancer registries began in 2004 in the United States



How Do Patients Select a Treatment?

Treatment selection is based on

- Tumor Size and Location
- Tumor Growth Rate
- Hearing Status
- Symptoms
- Patient's age and medical condition
- NF2
- Patient and Surgeon Preference

Survival

Overall good survival rates that are similar to meningioma

Conclusions

- Primary brain tumors come in all sizes and shapes
- Survival/Life expectancy varies widely
- Life expectancy of majority of persons with non-malignant brain tumors are not expected to vary by diagnosis
- Details of tumor type, biomarkers, genetic variants of import especially for persons with malignant tumors.
- Current national statistics re survival do not yet fully incorporate biomarker/genetic data and are focused on persons who undergo surgery.
- Access to life insurance a key financial and quality of life concern for brain tumor patients (particularly young persons who are in the midst of their family, work, and life pursuits)

Thank you!

Questions?