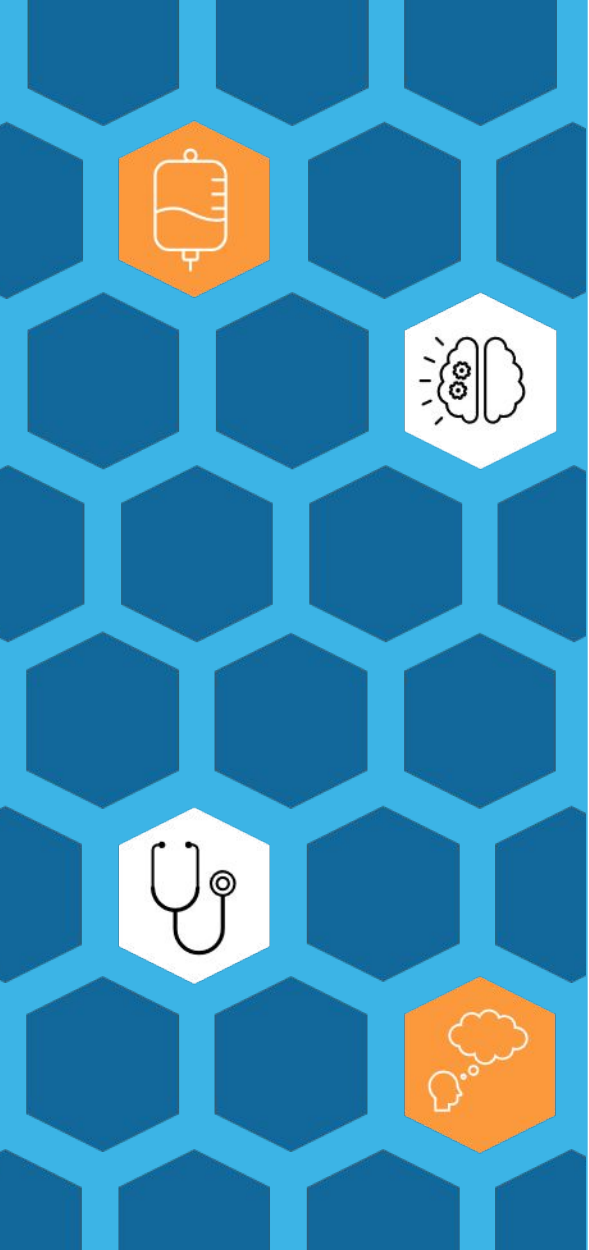




Neuropsychology

Neuropsychiatry: A Comprehensive Update

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Dana-Farber
Cancer Institute

Disclosures

Neither I nor my spouse have a relevant financial relationship with a commercial interest to disclose.

Learning objectives

Describe the key neuropsychiatric symptoms associated with:

- Primary brain tumors
- Metastatic brain tumors
- Leptomeningeal disease
- Paraneoplastic syndromes.

Integrate neuropsychiatric findings into recommendations during oncology and neurology consultations.

Neuro-oncologic Illnesses

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graph TD; A[Neuro-oncologic Illnesses] --> B[Primary brain tumors]; A --> C[Metastatic brain tumors]; A --> D[Leptomeningeal metastases]; A --> E[Paraneoplastic syndromes];
```

**Primary brain
tumors**

**Metastatic
brain tumors**

**Leptomeningeal
metastases**

**Paraneoplastic
syndromes**

Neuro-oncologic Illnesses

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Primary brain tumors

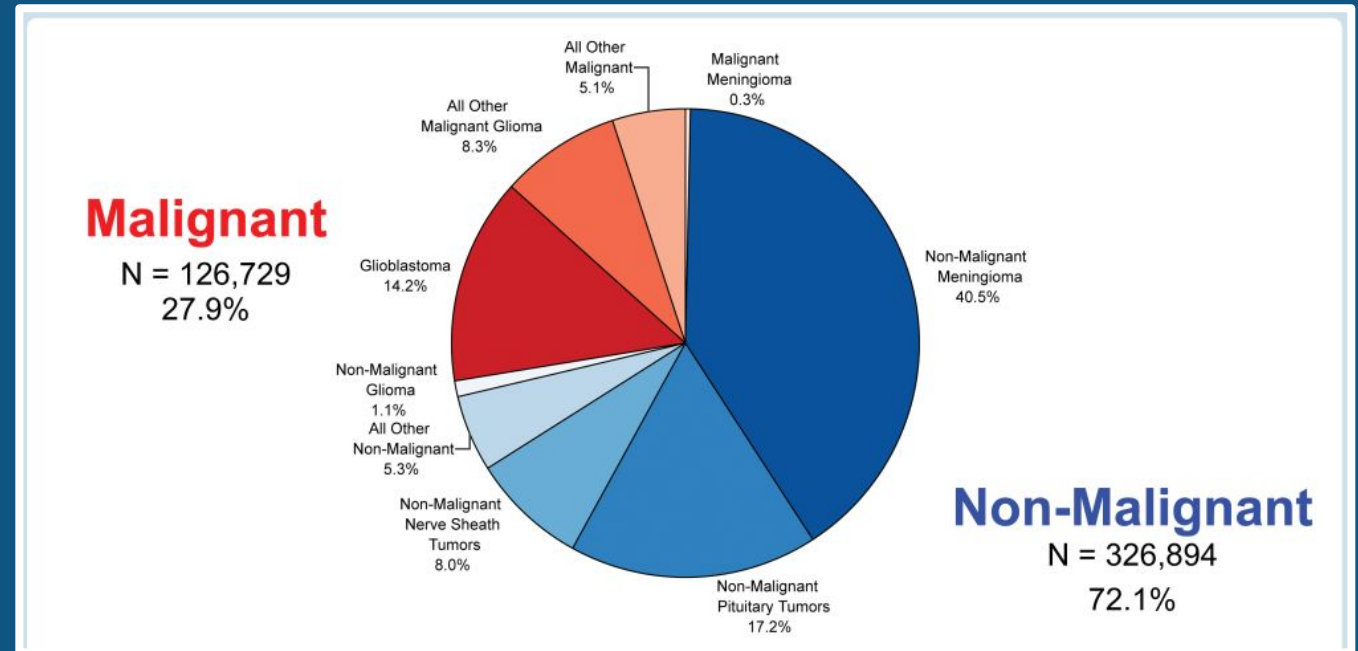
Metastatic brain tumors

Leptomeningeal metastases

Paraneoplastic syndromes

Primary Brain Tumors

- Significant heterogeneity
- Characterized by:
 - Location within CNS
 - Histology: cell line of origin
 - Behavior: malignant vs non-malignant
 - Genotype and biomarkers



Ostrom, 2023

Primary Brain Tumors

Clinical symptoms caused by:

- Direct infiltration and displacement of brain tissue
- Mass effect
- Increased intracranial pressure
- Disruption in brain connectivity
- Seizures
- Treatment side effects
- Psychological distress

Ostrom, 2023

Brain Tumor Symptomatology

Most common symptoms among patients with gliomas at specific phases of treatment:

Diagnosis	
Cognitive Deficits	36%
Seizures	35%
Headache	31%
Dizziness	24%
Motor Deficits	22%

Treatment	
Seizures	37%
Nausea/Vomiting	23%
Cognitive Deficits	18%
Fatigue	14%

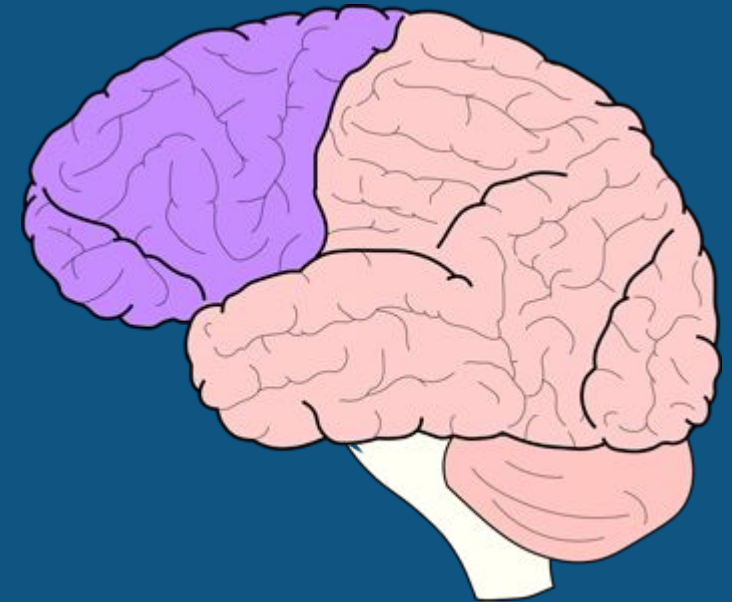
End-of-Life	
Drowsiness	81%
Fatigue	50%
Seizures	45%
Cognitive Deficits	44%
Aphasia	44%

Ijzerman-Korevaar, 2018

Primary Brain Tumors

Frontal Lobe Tumors:

- Most common location
- Significant neuropsychiatric effect burden:
 - Apathy, abulia, akinetic mutism
 - Executive dysfunction
 - Personality changes
 - Irritability, emotional lability
 - Disinhibition



Ostrom, 2023. Image credit: <https://www.brainframe-idks.com/brain/facts-lobes.htm>

Primary Brain Tumors

Temporal Lobe Tumors:

- Second most common location
- Commonly associated with neuropsychiatric symptoms
- Presentation may be similar to frontal lobe tumors due to tumor infiltration across lobes and/or interactions between white-matter tracts connecting brain regions.



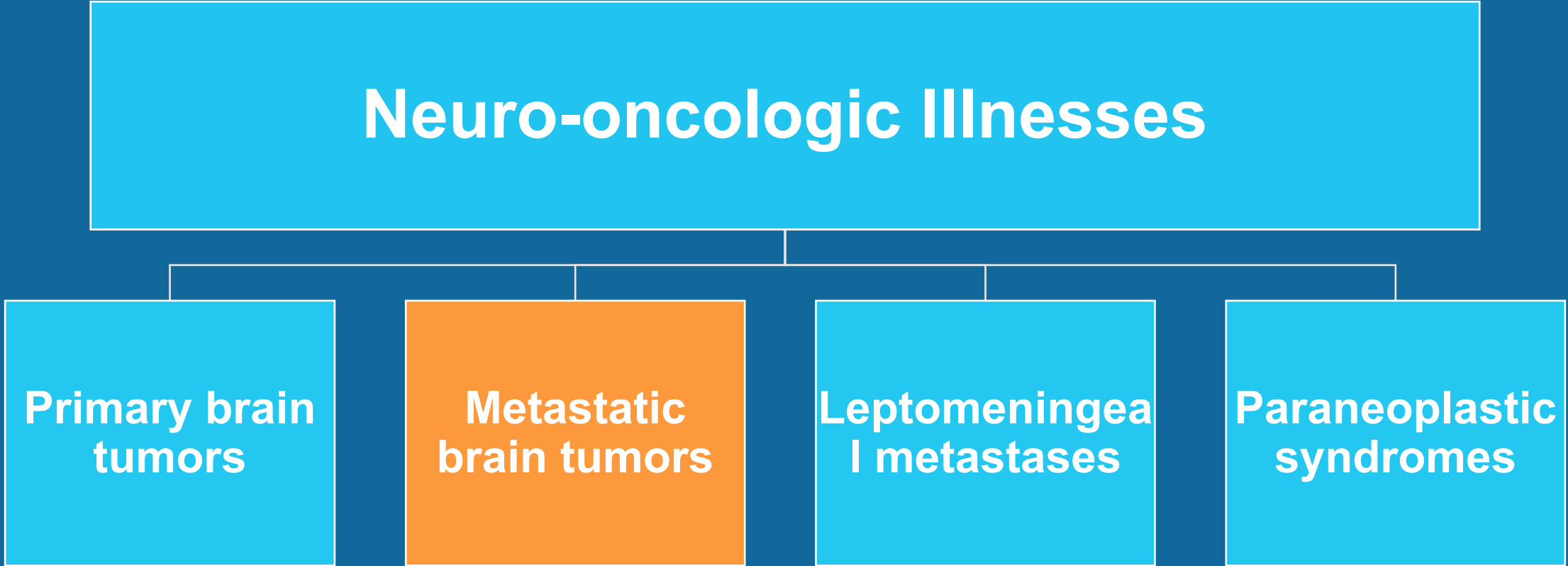
Ostrom, 2023. Image credit: <https://www.brainframe-idks.com/brain/facts-lobes.htm>

Primary Brain Tumors

Psychiatric symptoms in patients with brain tumors:

- Depression
- Fatigue
- Sleep disturbances
- Cognitive deficits

Neuro-oncologic Illnesses



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graph TD; A[Neuro-oncologic Illnesses] --> B[Primary brain tumors]; A --> C[Metastatic brain tumors]; A --> D[Leptomeningeal metastases]; A --> E[Paraneoplastic syndromes];
```

Primary brain tumors

Metastatic brain tumors

Leptomeningeal metastases

Paraneoplastic syndromes

Metastatic Brain Tumors

- Potential consequence of almost any cancer
- Significantly more common than primary brain tumors
 - 10x more common than primary malignant brain tumors
 - Potentially as many as 40% of patients with cancer will have metastatic spread to the brain

Nayak, 2012; Lamba, 2021; Fink, 2013; Patchell, 1990

Metastatic Brain Tumors

- Incidence is increasing

- Improved imaging modalities
- Development of chemotherapies that control systemic illness, prolonging overall survival
- Clinical trials often exclude patients with brain metastases
- Brain as "sanctuary" for cancer

Nayak, 2012; Lamba, 2021; Fink, 2013; Patchell, 1990

Brain Metastases Pose Major Impact on a Patient's Course

High mortality
rates

Potential neurologic
symptoms or
disability

Higher risk for
psychiatric
symptoms

Cognitive
changes

Changes in
overall cancer
treatment plan

Exclusion from
most clinical trials

Nayak, 2012; Lamba, 2021; Fink, 2013; Patchell, 1990

Metastatic Brain Tumors

- Presenting symptoms driven by similar factors compared to primary tumors
- **Common presenting symptoms:**
 - Headache, seizure, focal neurologic signs or symptoms, cognitive and behavioral changes, gait disturbance
 - Neuropsychiatric symptoms vary based on location

Nayak, 2012; Lamba, 2021; Fink, 2013; Patchell, 1990

Metastatic Brain Tumors

- Significant difference from primary tumors:
 - Brain metastases are often multifocal
 - Symptoms may not localize, patient may present with variety of symptoms simultaneously

Nayak, 2012; Lamba, 2021; Fink, 2013; Patchell, 1990

Metastatic Brain Tumors

Destination of metastases within the brain:

- Location of spread within the brain corresponds to relative blood flow in the brain:
 - Cerebrum: 65-80%: Frontal lobe (30% total) > parietal lobe (15%) > temporal lobe (10%) > occipital lobe (10%)
 - Cerebellum: 15%
 - Brainstem: 5%
- Increasing evidence suggesting primary tumor type is relevant to distribution of metastases

Nayak, 2012; Schroeder, 2020

Metastatic Brain Tumors

Origin of metastatic brain tumors

- Virtually any cancer type can metastasize to the brain
- Most common primary tumors that spread to the brain:
 - Lung cancer: 39-50%
 - Breast cancer: 13-30%
 - Melanoma: 6-11%
 - Renal cell carcinoma: 6%
 - Gastrointestinal cancer: 3-7%
- Identity of primary tumor may be unknown, including after biopsy

Nayak, 2012; Ostrom, 2021; Giordana, 2000

Neuro-oncologic Illnesses

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**Primary brain
tumors**

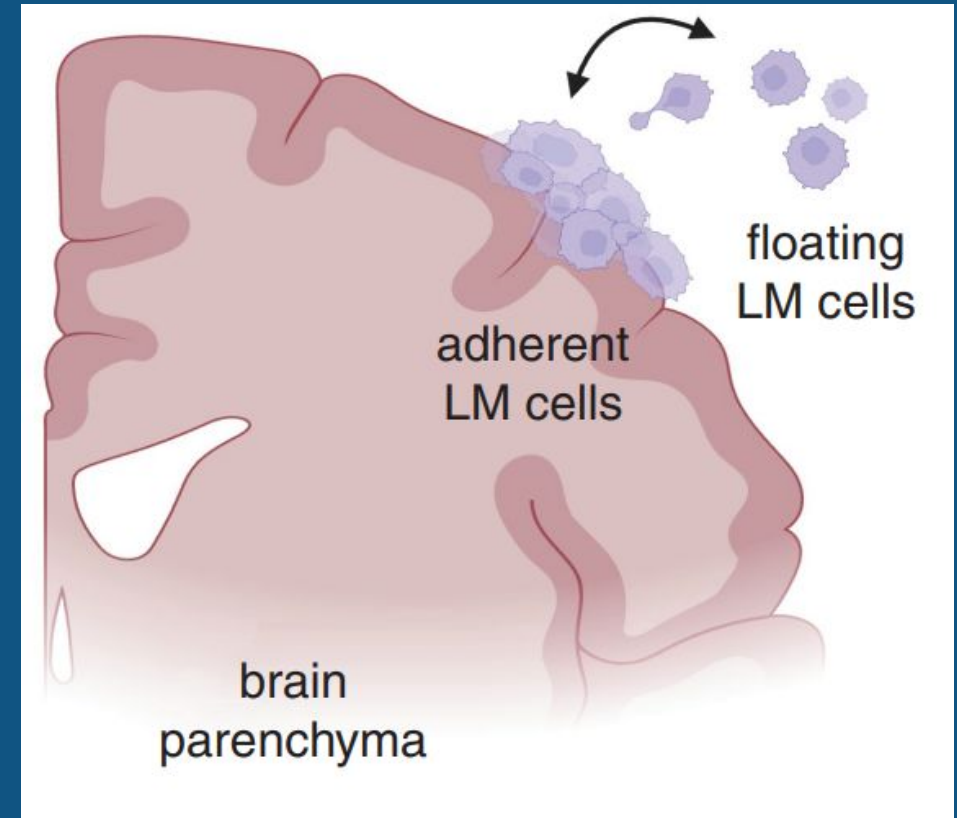
**Metastatic
brain tumors**

**Leptomeningeal
metastases**

**Paraneoplastic
syndromes**

Leptomeningeal metastases

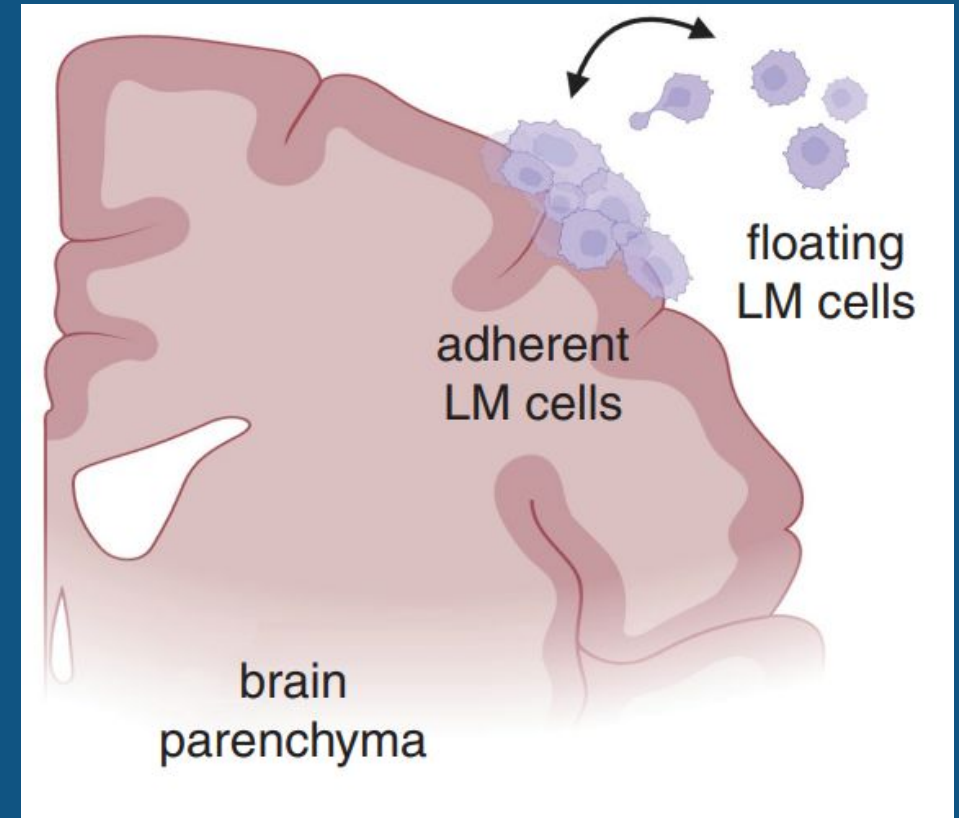
- Tumor cells disseminate and grow within the leptomeninges
- Potential modes of entry:
 - Via choroid plexus
 - Direct seeding from brain or dural metastases
 - Perineural invasion



Wilcox, 2024; Lamba, 2021

Leptomeningeal metastases

- Disruption in CNS functioning:
 - Adherent plaques form:
 - Brain surface
 - Spinal cord surface
 - Exiting cranial or spinal nerves
 - Disruptions in blood-brain and blood-CSF barriers
 - Alterations in CSF microenvironment



Wilcox, 2024; Lamba, 2021

Leptomeningeal metastases

- Associated symptoms secondary to:
 - Increased intracranial pressure
 - Meningeal irritation
 - Cranial Nerve VI, VII, and VIII dysfunction
 - Spinal nerve dysfunction
 - Dermatomal sensory loss
 - Radicular pain
 - Bowel and bladder dysfunction
 - Limb weakness

Lamba, 2021 Seute, 2005; Balm, 1996; Wassertrom, 1982; Clarke, 2010

Leptomeningeal metastases

- Potential complication for nearly any cancer type
 - More common in: Lung, Breast, Melanoma
- Often late manifestation of cancer, associated with:
 - 60-70% of patients with LM demonstrate progressive systemic disease
 - 25-40% concurrent parenchymal metastasis

Lamba, 2021 Seute, 2005; Balm, 1996; Wassertrom, 1982; Clarke, 2010

Leptomeningeal metastases

- Incidence is increasing with improvements in systemic disease control and treatments that poorly penetrate the blood-brain barrier
 - Lead to brain “sanctuary” or “reservoir” for tumor cells

Lamba, 2021 Seute, 2005; Balm, 1996; Wassertrom, 1982; Clarke, 2010

Leptomeningeal metastases

- **Poor prognosis:** average survival 2-4 months, despite treatment
 - 2005 prospective study: median survival 1.3 months following LMD diagnosis in SCLC patients

Lamba, 2021 Seute, 2005; Balm, 1996; Wassertrom, 1982; Clarke, 2010

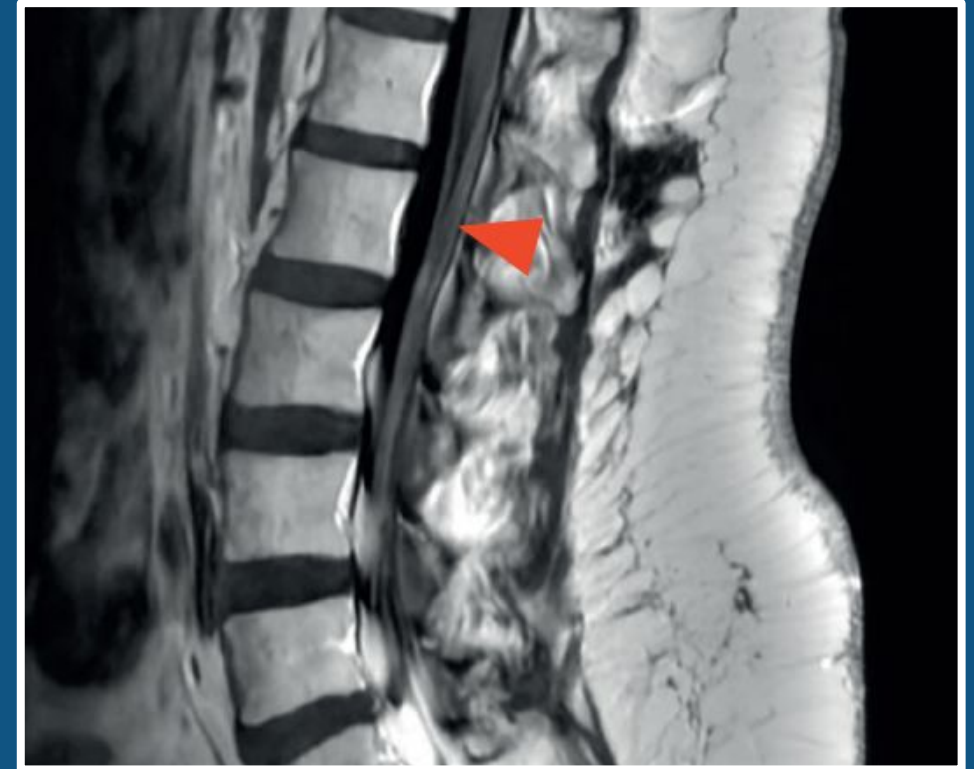
Leptomeningeal metastases

- **Diagnostic work-up**

- Brain MRI
- CSF studies

- **Treatment options**

- Radiation therapy
- Intrathecal chemotherapy
- Tyrosine kinase inhibitors
- Steroids
- CSF diversion



Wilcox, 2024: "Smooth widespread enhancement of the conus medullaris and cauda equina (arrowhead) on MRI lumbar spine sagittal T1 post-contrast images"

Neuro-oncologic Illnesses

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**Primary brain
tumors**

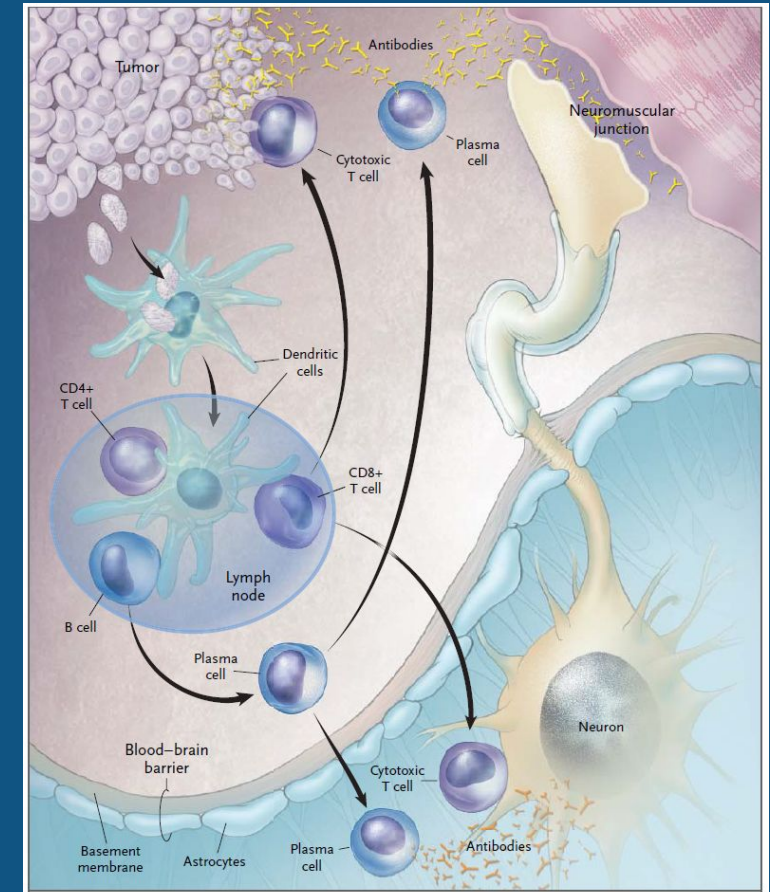
**Metastatic
brain tumors**

**Leptomeningeal
metastases**

**Paraneoplastic
syndromes**

Paraneoplastic Neurologic Syndromes

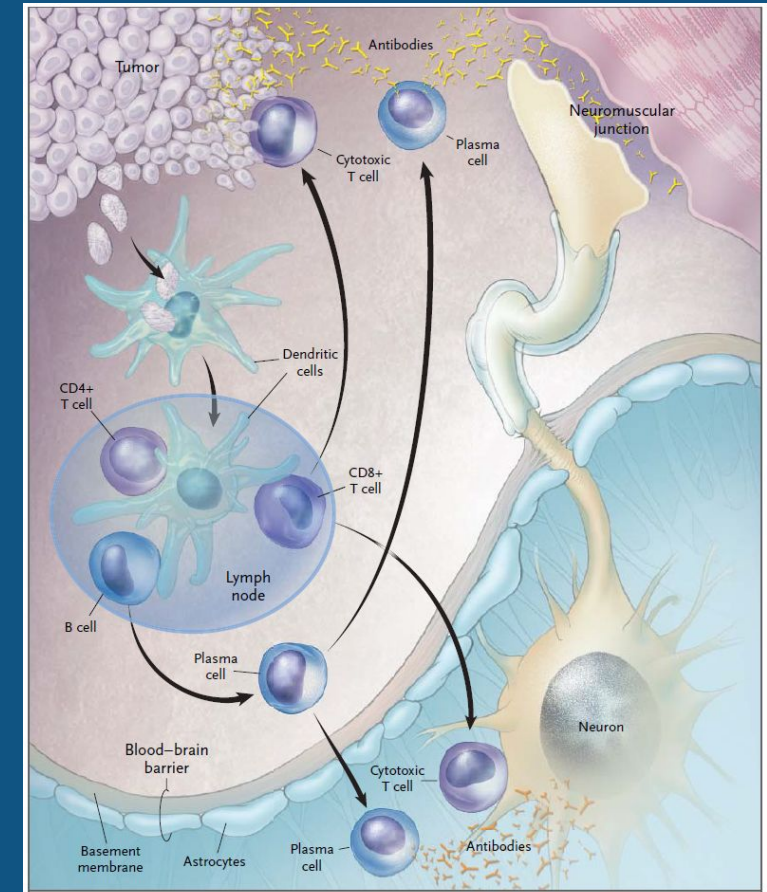
- Complex clinical syndromes secondary to immune-mediated effects:
 - Autoantibody response against antigens expressed by the tumor.
 - **Onconeural antibodies**
- Cause remote neurological effects not related to tumor, metastases, or other comorbidities



Darnell and Posner, 2003; Rosenfeld, 2012; Gratiwol, 2018; Pelosof, 2010; Corsini, 2016

Paraneoplastic Neurologic Syndromes

- Commonly present prior to cancer diagnosis (60-70%)
 - May present years prior to formal diagnosis
- Specific autoantibodies are associated with specific cancer type
 - May aid in identification of primary tumor
- Characterized by antigen target location
 - Intracellular antigens
 - Cell surface/synaptic-targeted antigens



Binks, 2022; Tung, 2021

Paraneoplastic Neurologic Syndromes

- Can be diagnostically challenging, mimics other conditions
- Presentation varies based on specific antibodies and their targets
- Often nonspecific and non-focal presenting symptoms
 - Ataxia, vision changes, seizures

Darnell and Posner, 2003; Rosenfeld, 2012; Gratiwol, 2018; Pelosof, 2010; Corsini, 2016

Paraneoplastic Neurologic Syndromes

- **Neuropsychiatric symptoms:**
 - **Affective symptoms:** Depression, mood lability, irritability
 - **Psychosis:** Paranoia, visual and auditory hallucinations
 - **Cognitive deficits:** Memory dysfunction

Darnell and Posner, 2003; Rosenfeld, 2012; Gratiwol, 2018; Pelosof, 2010; Corsini, 2016

Paraneoplastic Neurologic Syndromes

Diagnostic work-up

- Studies: EEG, MRI, or CSF analysis
- Consider paraneoplastic process in setting of acute onset of neurologic or psychiatric symptoms

Treatment

- Treat underlying cancer
- Immunotherapy
- Plasmapheresis, steroids, IVIG, rituximab

Darnell and Posner, 2003; Rosenfeld, 2012; Gratiwol, 2018; Pelosof, 2010; Corsini, 2016

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Thank you

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