# Leptomeningeal metastases

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# EPIDEMIOLOGY

- 5% of pts with metastatic solid cancer
- Autopsy studies : 19%
- Co-existing brain mets in 50-80% of pts

Kesari S. Neurol Clin 2003;21:25-66 / Posner JB. Adv Neurol 1978;19:579-92 / Clarke JL. Neurology 2010;74:1449-54 / LM = Leptomeningeal Metastases.

# EPIDEMIOLOGY

- Breast cancer (12-35%, ILC, HER2+)
- Lung cancer (10-26%, EGFR/ALK)
- Melanoma (5-25%)
- GI malignancies (4-14%)
- Cancer of unknown primary (1-7%)
- Primary brain tumors can infiltrate the leptomeninges

Kesari S. Neurol Clin 2003;21:25-66 / Lamovec J. J Surg Oncol 1991;48:28-33 / Saito R. J Neurooncol 2003;61:227 / ILC = Invasive Lobular Carcinoma / GI = Gastro-Intestinal.

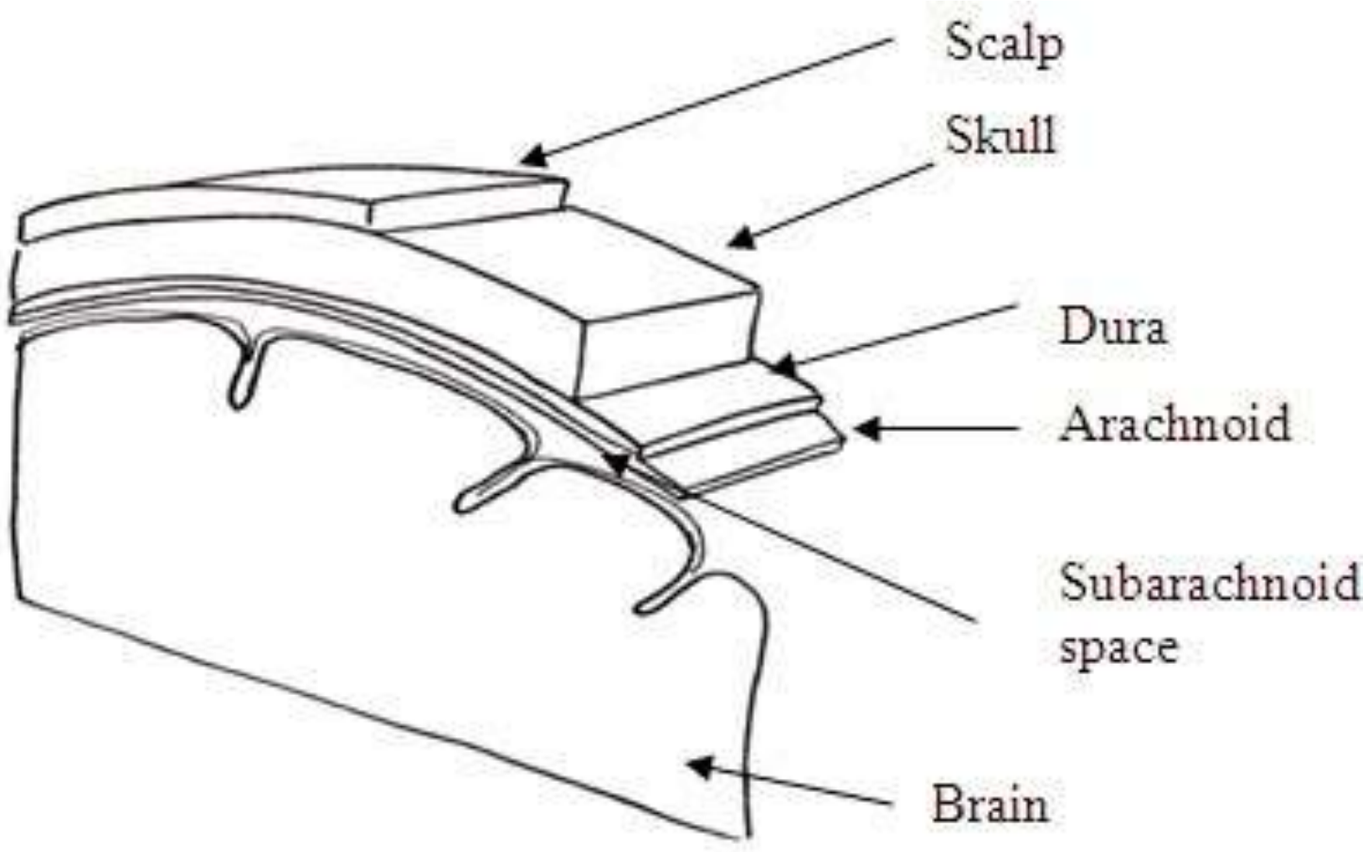
# EPIDEMIOLOGY

Occurence may be influenced by treatments

- Long-term survivors of HER2-positive MBC
- Piecemeal surgical resection of brain mets

Bendell JC. Cancer 2003;97:2972-7 / Ahn JH. J Neurosurg 2008;116:984-93 / MBC = Metastatic Breast Cancer.

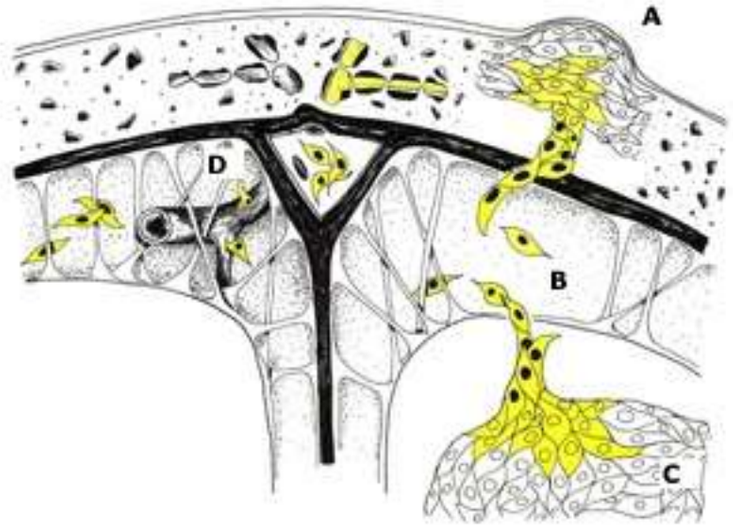
# PATHOPHYSIOLOGY



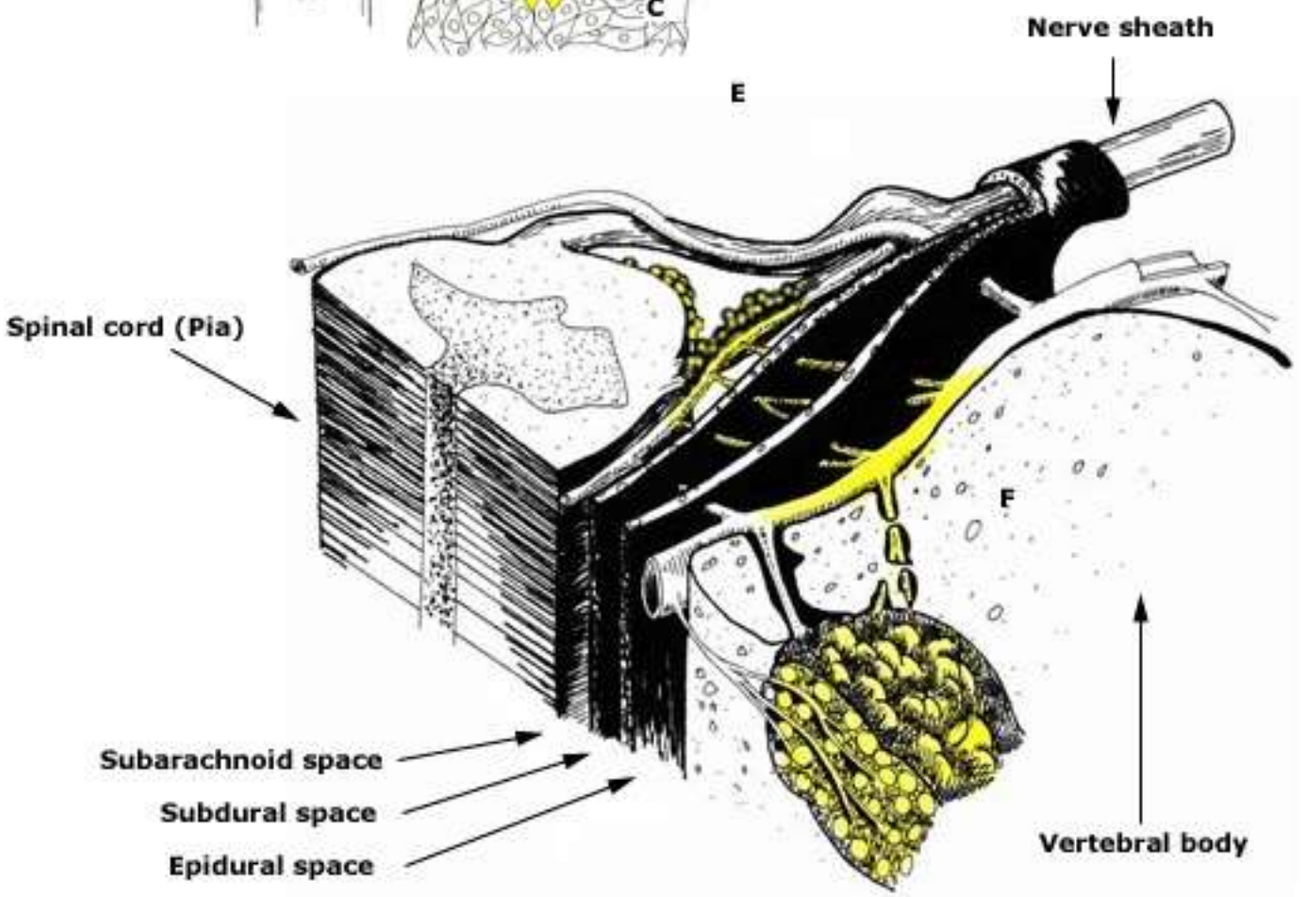

Spread of malignant cells throughout the subarachnoid space

University Hospital Southampton. NHS.

# PATHOPHYSIOLOGY




1. Hematogenous spread
2. Lymphatic spread
3. Direct extension




A: skull; B: subarachnoid space; C: brain; D: sagittal sinus; E: blood vessels; F: nerve sheaths

# PATHOPHYSIOLOGY

Most common sites

- Base of the brain (posterior fossa)
- Sylvian fissures
- Cauda equina

Relatively slow flow of CSF in these areas

Kesari S. Neurol Clin 2003;21:25-66 / CSF = CerebroSpinal Fluid.

# CLINICAL FEATURES

1. Mass effect (hydrocephalus or increased ICP)

2. Invasion of the brain parenchyma or cranial nerve

3. Disruption of the BBB

Kesari S. Neurol Clin 2003;21:25-66 / ICP = IntraCranial Pressure / BBB = Blood-Brain Barrier.

# CLINICAL FEATURES

Headache (39%)

Nausea (25%)

Seizure (25%)

Leg weakness (21%)

Cerebellar dysfunction (17%)

Altered mental status (16%)

Diplopia (14%)

Facial weakness (13%)

Clarke JL. Neurology 2010;74:1449-54.

# NEUROIMAGING STUDIES

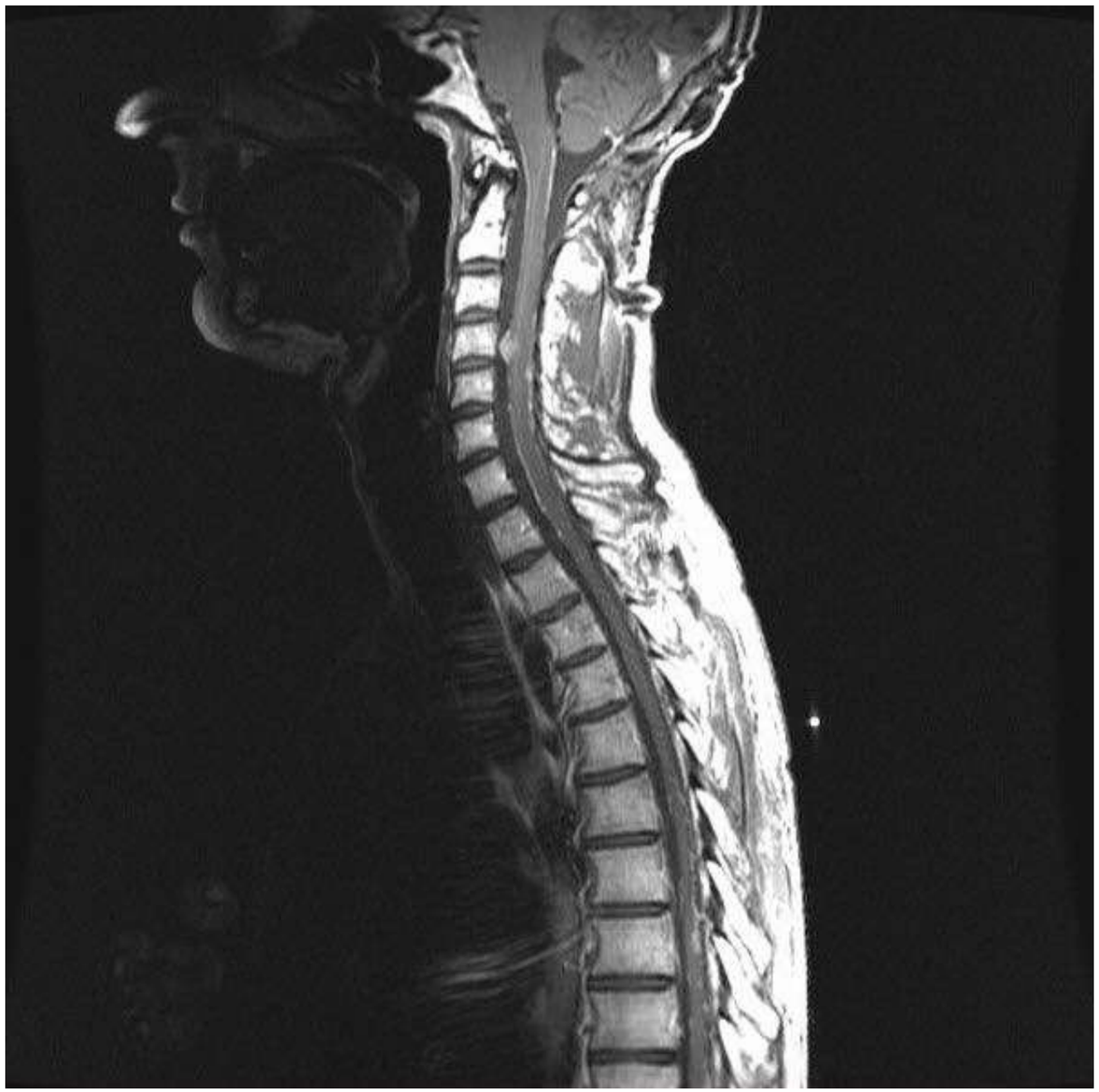
MRI of the brain and the spine

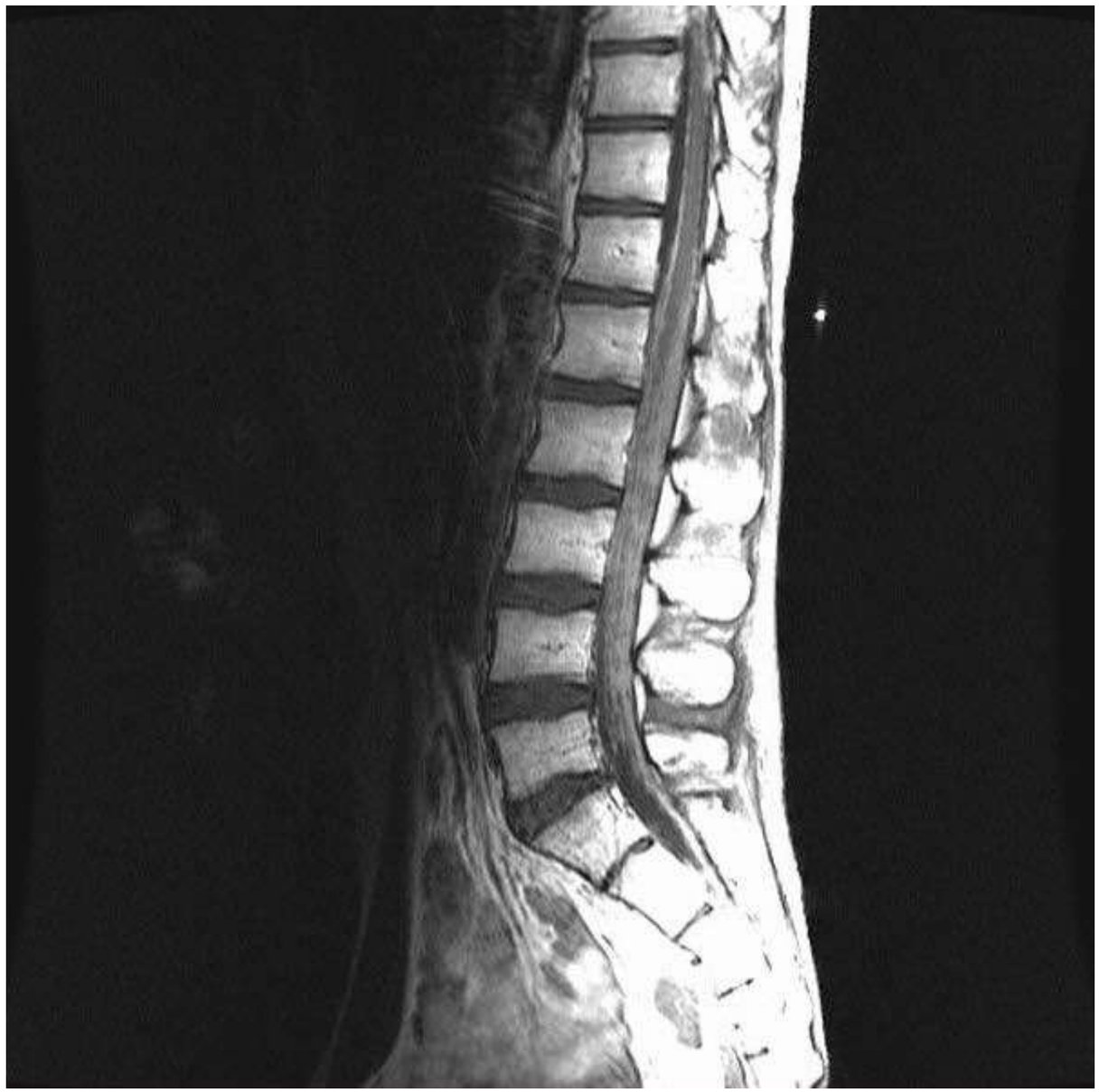
- Sensitivity ≈ 75%
- Less specific than cytology

Before lumbar puncture !

Straathof CS. J Neurol 1999;246:810-4 / Chamberlain MC. J Neuro Oncol 1995;23:233-8 /
MRI = Magnetic Resonance Imaging.

# NEUROIMAGING STUDIES





Yen PY. Medscape 2012.

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# DIFFERENTIAL DIAGNOSIS

**INFECTIONS**

Opportunistic (tuberculosis, cryptococcus)

Meningitis (bacterial or viral)

Lyme disease

West Nile virus

**AUTOIMMUNE**

Vasculitis

Sarcoidosis

Granulomatosis (Wegener's)

Langerhans cell histiocytosis

Bell's palsy

**ARTIFACT**

Post-radiotherapy

Post-lumbar puncture

Intracranial hypovolemia

Intracranial hypotension

Enhancing meningeal blood vessels

Mokri B. Curr Neurol Neurosci 2001;1:109-17 / Olsan AD. AJR 2003;181:591-2 / Hsia AW Neurology 2003;60:1694-6 / Ducray F. Neuro Oncol 2008;10:1035-9.

# CEREBROSPINAL FLUID

↑ opening pressure (> 200 mmHg)

↑ lymphocytosis or eosinophilia

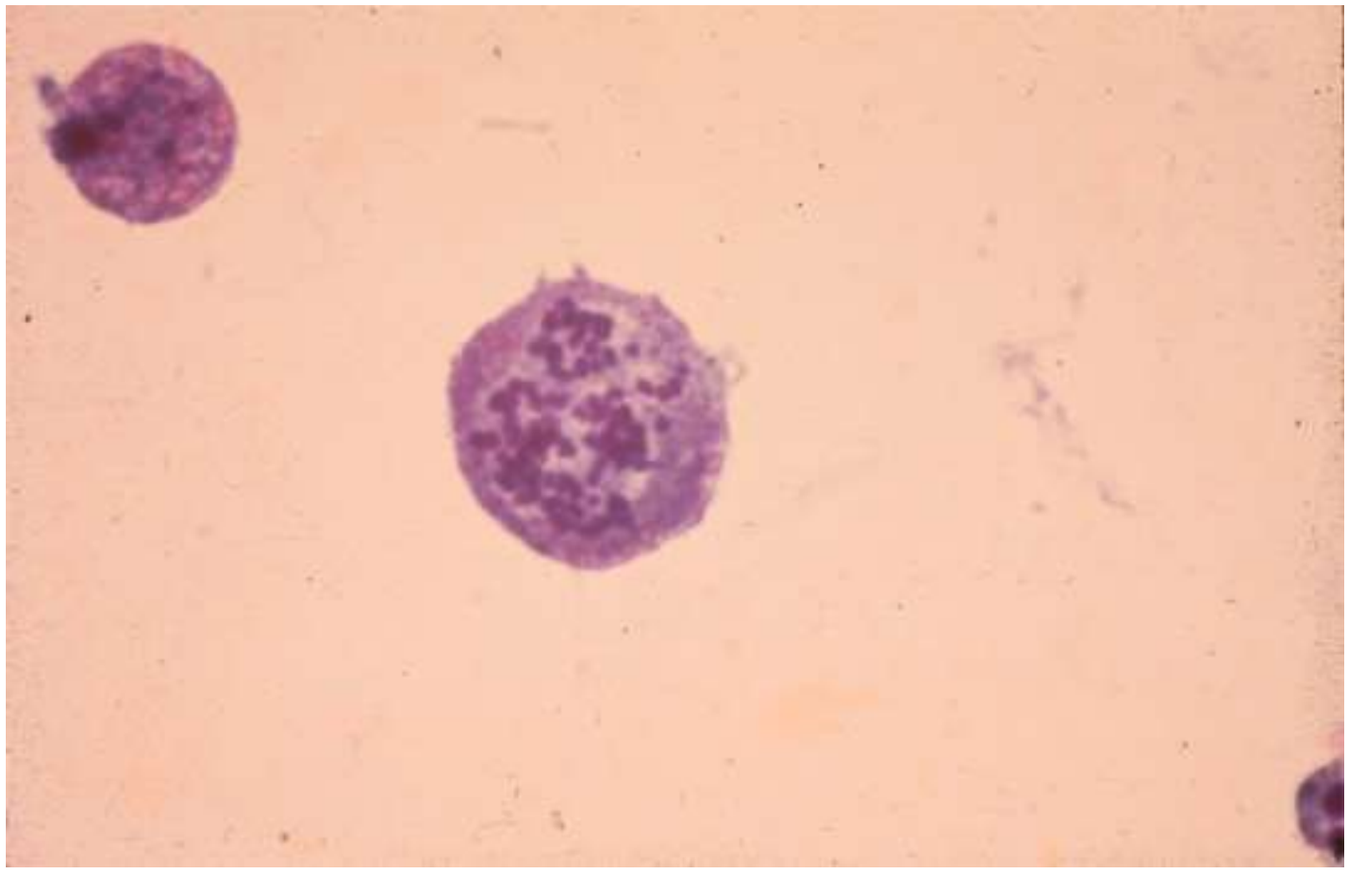
↕ protein concentration (> 38 mg/dL)

↓ glucose concentration (CSF:serum < 0.6)

Clarke JL. Neurology 2010;74:1449-54.

# CEREBROSPINAL FLUID

## Cytology



Sensitivity ≈ 70% / Specificity ≈ 100%

Glantz MJ. Cancer 1998;82:733-9 / Chamberlain MC. Neuro Oncol 2001;3:42.

# CEREBROSPINAL FLUID

To minimize false-negative results

- ≥ 10 mL of CSF should be withdrawn
- Immediate fixation in ethanol-based agent
- Puncture closest to the site of symptoms

Glantz MJ. Cancer 1998;82:733-9 / Chamberlain MC. Neuro Oncol 2001;3:42.

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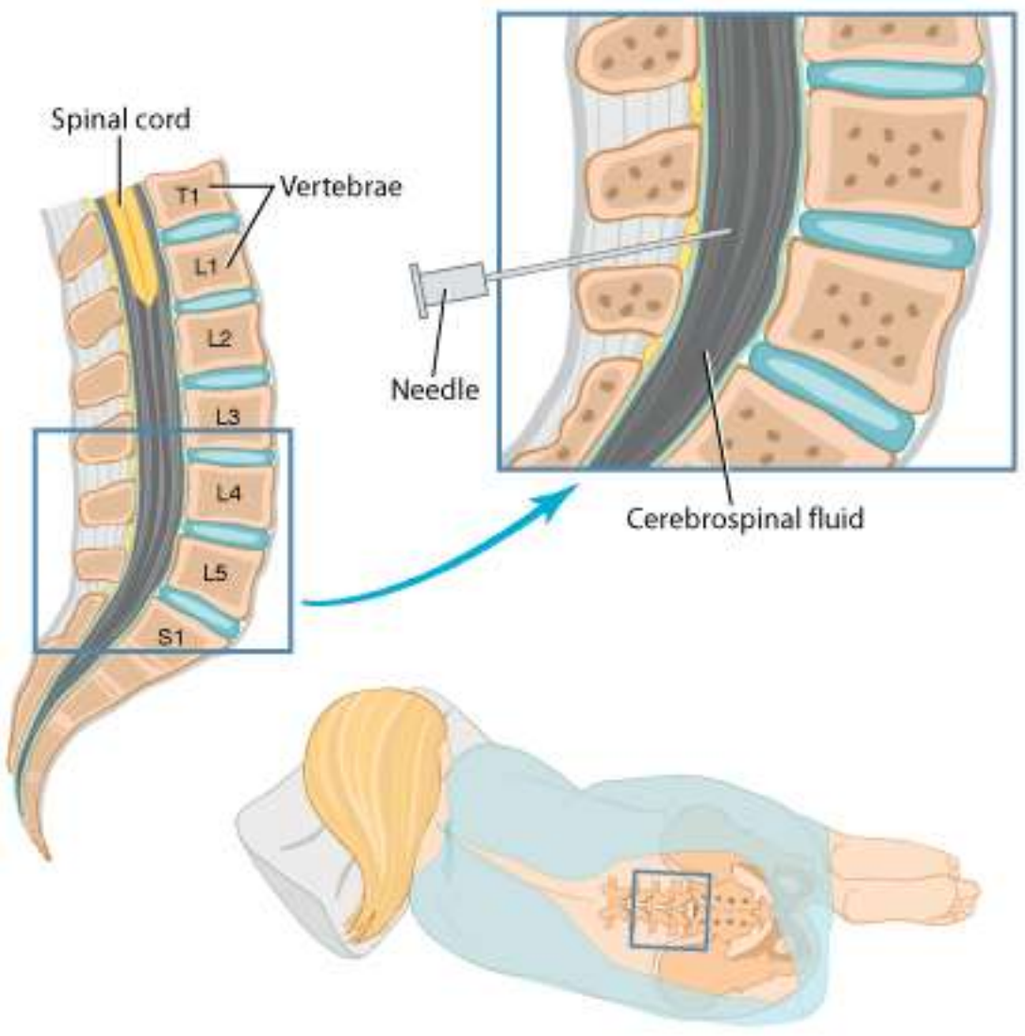
# CEREBROSPINAL FLUID

| Number of samples | Rates of positive cytology |
|---|---|
| 1 | 71 % |
| 2 | 86 % |
| 3 | 90 % |
| > 3 | 98 % |

Glantz MJ. Cancer 1998;82:733-9.

# CEREBROSPINAL FLUID




CSF cytology remains negative in 10% of pts with unequivocal LM

A typical MRI in the appropriate clinical setting is sufficient for the diagnosis

Glantz MJ. Cancer 1998;82:733-9 / Chamberlain MC. Neuro Oncol 2001;3:42.

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# TREATMENT

## Goals of treatments

- Stabilizing or improving neurologic function
- Prolonging survival
- Palliating symptoms

# PROGNOSIS

| | **mOS (months)** |
|---|---|
| Untreated | 1.0 |
| Treated, non-responding | 2.0 |
| Treated, responding | |
| Melanoma | 4.0 |
| Non-small cell lung cancer | 6.0 |
| AIDS-related lymphoma | 6.0 |
| Breast | 7.5 |
| Non-AIDS-related lymphoma | 10.0 |

Adapted from Chamberlain MC. J Neurooncol 1998;37:271-84.

# TREATMENT

| Poor-risk | Good-risk |
|---|---|
| KPS < 60 | KPS ≥ 60 |
| Multiple, fixed neurologic deficits | Minimal or no fixed neurologic deficits |
| Extensive systemic cancer without good treatment options | Effective systemic treatment of cancer possible |
| Encephalopathy or bulky CNS disease | |

NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016; KPS = Karnofsky Performance Status; CNS = Central Nervous System.

# POOR-RISK PATIENTS

**Palliative approach**

- Targeted RT : no whole-neuraxis irradiation
- Corticosteroids : increased ICP
- Anticonvulsants : seizures, no prophylactic use
- VP shunting : hydrocephalus

NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016 / RT = Radiation Therapy / VP = VentriculoPeritoneal.

# TREATMENT

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NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016.

# GOOD-RISK PATIENTS

**Aggressive approach**

1. Control of ICP

2. Control of CSF flow

NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016.

# CONTROL OF INCREASED ICP

- Dexamethasone 8 mg bid

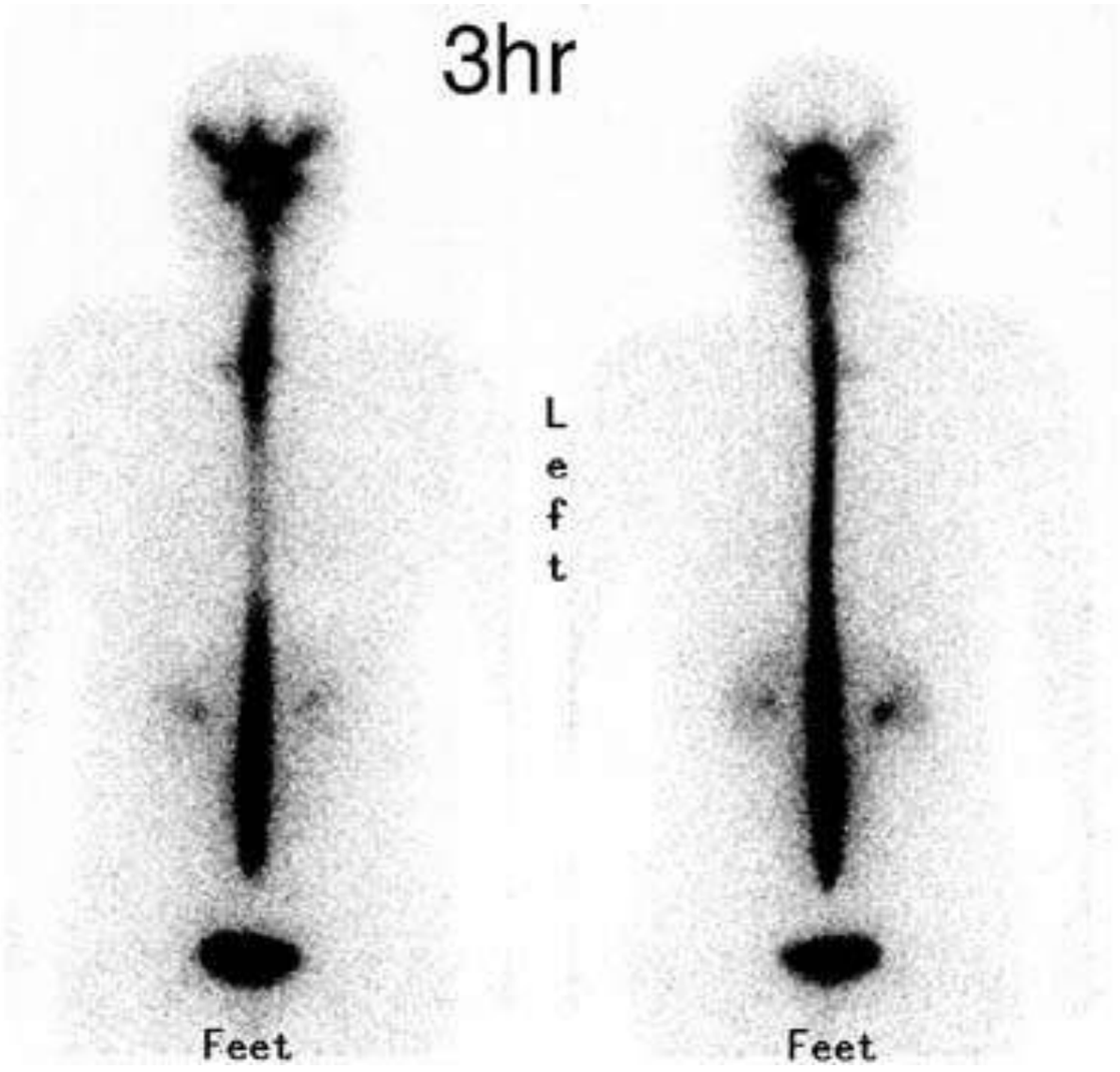
- VP shunting

NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016.

# CONTROL OF CSF FLOW

Radionuclide CSF flow study

Flow abnormalities in 2/3 of pts




Chamberlain MC. J Neurooncol 1998;38(2-3):135-40.

# CSF FLOW OBSTRUCTION

- Greater risk of chemo accumulation
- Predict poor survival
- Treatment = RT to areas of obstruction

Chamberlain MC. J Neurooncol 1998;38(2-3):135-40.

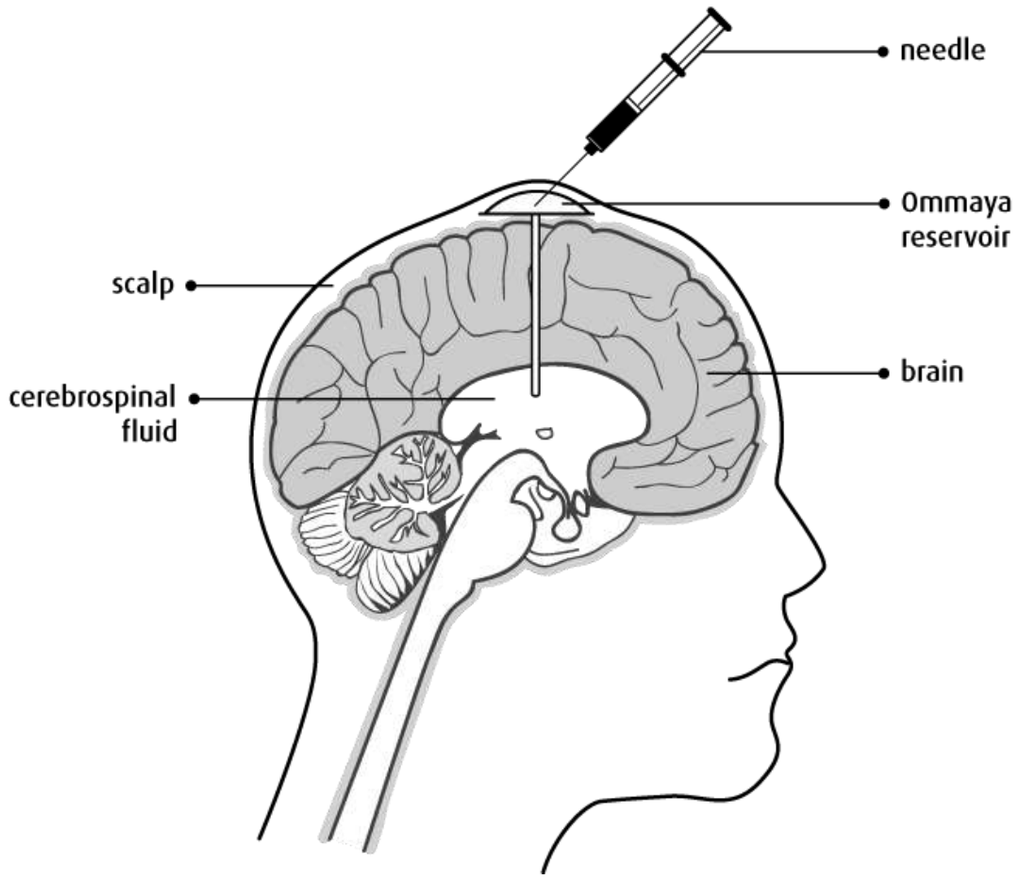
# NORMAL CSF FLOW

1. Intrathecal chemotherapy
2. Systemic chemotherapy
3. Targeted therapies

NCCN Guidelines. Central Nervous System Cancers. NCCN.org. Version 1.2016.

# INTRATHECAL CHEMO

- Ventricular cathether (Ommaya device)




- Lumbar puncture

Canadian Cancer Society. www.cancer.ca.

# VI VERSUS LI CHEMO

| VI | LI |
|---|---|
| Safe injection | Risk of epidural or subdural injection |
| Uniform drug distribution | Unpredictable ventricular drug concentration |
| Catheter-related complications | Multiple LP |
| Survival benefit (observational data) for VI compared w/ LI chemo | |

Larson SM. J Nucl Med 1971;12:555 / Shapiro WR. N Engl J Med 1975;293:161 / Hitchins RN. J Clin Oncol 1987;5(10):1655 / VI = Ventricular Injection / LI = Lumbar Injection / LP = Lumbar Puncture.

# INTRATHECAL CHEMO

- MTX
- (Liposomal cytarabine)
- (Thiotepa)

Gleissner B and Chamberlain MC. Lancet Neurol 2006;5:443-52 / MTX = Methotrexate.

# IT MTX

- Dose : 12 mg + Leucovorin rescue
- Induction : BIW for 4 weeks
- Consolidation : QW for 4 weeks
- Maintenance : QMT maximum 6 months

Siegal T. Neurology 1994;44:1463-9 / BIW = twice a week / QW = once a week / QMT = every month.

# IT MTX

## Toxicity

- Myelosuppression (platelet > 50.000/microL)
- Aseptic meningitis
- Leukoencephalopathy
- Transverse myelopathy

Siegal T. Neurology 1994;44:1463-9.

# IT LIPOSOMAL CYTARABINE

- Dose : 50 mg
- Induction : every 2 weeks for 4 weeks
- Consolidation : every 4 weeks for 6 months
- Versus MTX (2 small studies)
  - Same PFS and OS
  - ↑ chemical meningitis

Beauchesne P. Lancet Oncol 2010;11:871-9.

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# SYSTEMIC CHEMO

- High-dose MTX (8 g/m$^2$)

  + Leucovorin rescue

  + hydratation

  + urinary alkalinization

- Capecitabine

Glantz MJ. J Clin Oncol 1998;16:1561-7 / Giglio P. J Neurooncol 2003;65(2):167-72.

# COMPARISONS

| TREATMENTS | ORR | mOS (range) |
|---|---|---|
| IT chemo | 27 % | 14w (7-35) |
| RT | 20 % | 11w (7-13) |
| IT chemo + RT | 34 % | 13w (4-18) |
| Intensified treatments | 62 % | 17w (12-30) |

Gleissner B and Chamberlain MC. Lancet Neurol 2006;5:443-52.

# TARGETED THERAPIES

- EGFR TKI (osimertinib) in mutated NSCLC
- ALK TKI (alectinib) in mutated NSCLC
- BRAF TKI (dabrafenib) in mutated melanoma
- Intrathecal trastuzumab in HER2+ BC
- Intrathecal IL13Rα2-targeted CAR T cells in GBM

Ou SH. J Clin Oncol 2016;34:661-8 / Simeone E. J Med Case Rep 2012;6:131 / Oliveira M. Breast Cancer Res Treat 2011;127:841-4 / Brown CE. NEJM 2016;375:2561-9 / TKI = Tyrosine Kinase Inhibitors / NSCLC = Non Small Cell Lung Cancers / CPI = CheckPoint Inhibitors / CAR = Chimeric Antigen Receptor / GBM = GlioBlastoma Multiforme.

# THANK YOU.

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