An Update on Leptomeningeal Metastasis

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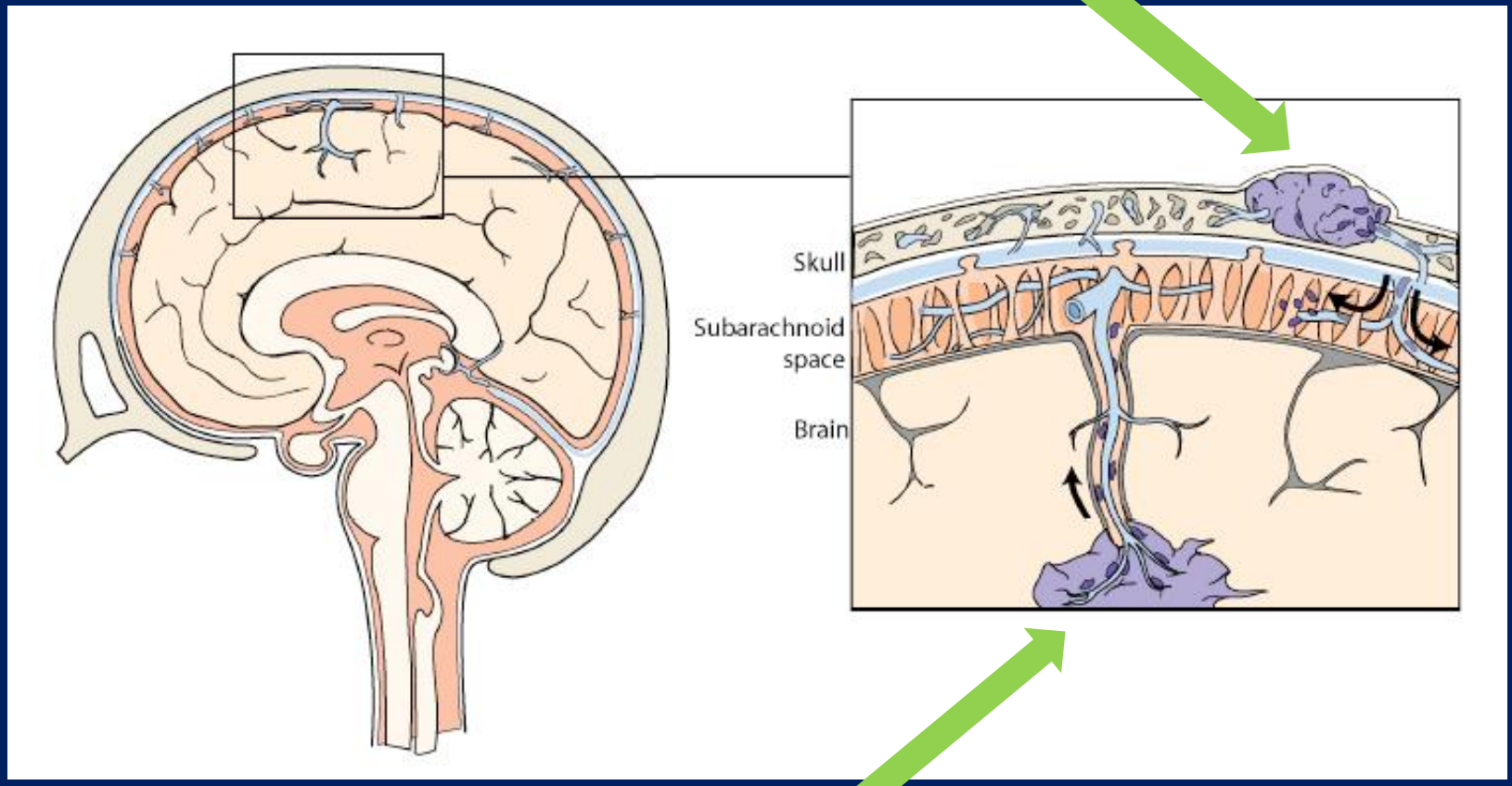
Leptomeningeal Metastasis

- Overall incidence in cancer pts: 3-8%
  - Leukemia, NHL
  - Breast, lung, melanoma
  - Any histology possible
- Usually occurs in disseminated disease
  - Risk increased with brain mets
  - Posterior fossa craniotomy: 40% incidence
- Increasing incidence of isolated LM met?
  - Breast, NHL
  - Sanctuary site?

Pathogenesis: Direct Extension

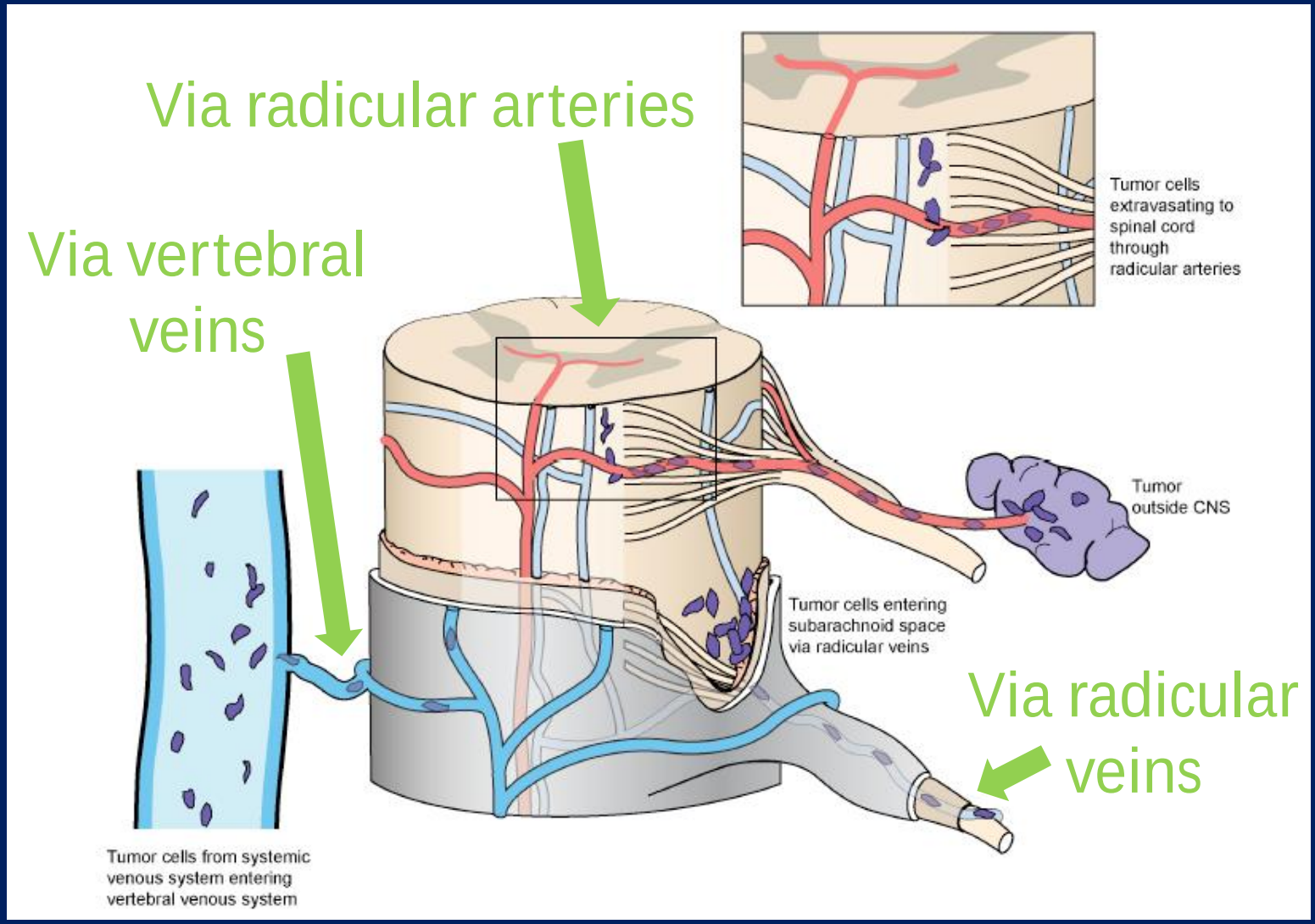
From skull mets



From parenchymal mets

LM DeAngelis and JB Posner, Neurologic Complications of Cancer, 2009

Pathogenesis: Perivascular Spread



LM DeAngelis and JB Posner, Neurologic Complications of Cancer, 2009

Pathogenesis

- Most common sites involved:
  - Basal cisterns
  - Dorsal aspect of spinal cord
  - Cauda equina
- Microscopic evidence often present even if no gross evidence of disease

Retrospective Series From MSKCC

- All cases diagnosed from 2002-2004
- Total N = 187
  - Solid tumors: N = 150
  - Hematopoietic tumors: N = 37
- 73% women
- Median age 56, median KPS 70
- 89% with active systemic disease at LM Dx
- Current or prior brain mets in 70% of solid tumor pts, 11% of hematopoietic tumor pts

Distribution of Histologies: Solid Tumors (N = 150)

Histology	% of Patients
Breast	43%
Lung	31%
GI	7%
Melanoma	6%
Other	9%
Unknown	3%

- NSCLC 91%
- SCLC 9%

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- SCLC 9%

- Esophageal 45%
- Gastric 45%
- Colon 9%

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Breast	43%
Lung	31%
GI	7%
Melanoma	6%
Other	9%
Unknown	3%

- Head & Neck (4)
- Bladder (2)
- Ovarian (2)
- Endometrial (1)
- Prostate (1)
- Sarcoma (1)
- Germ Cell (1)
- Neuroendocrine (1)

Distribution of Histologies, Hematopoietic Tumors (N = 37)

Histology	% of Patients
Lymphoma	57%
Leukemia	41%
Multiple Myeloma	3%

Clinical Characteristics

- Multifocal signs/symptoms
- Signs > symptoms
- 3 main compartments
  - Cerebral
  - Posterior fossa / cranial nerves
  - Spinal cord and roots
- May present only with hydrocephalus or elevated ICP
- Incidental Dx rare: only 2% of recent series

Cerebral Signs/Symptoms

Symptoms	%	Signs	%
Headache	39%	Altered mental status	16%
Dizziness	4%	Seizures	3%
Confusion	12%	Hemiparesis	2%
Fatigue	2%	Pyramidal signs NOS	4%
Gait difficulty	4%	Homonymous hemianopsia	3%
Aphasia	4%	Papilledema	2%

Posterior Fossa/CN Signs/Sx

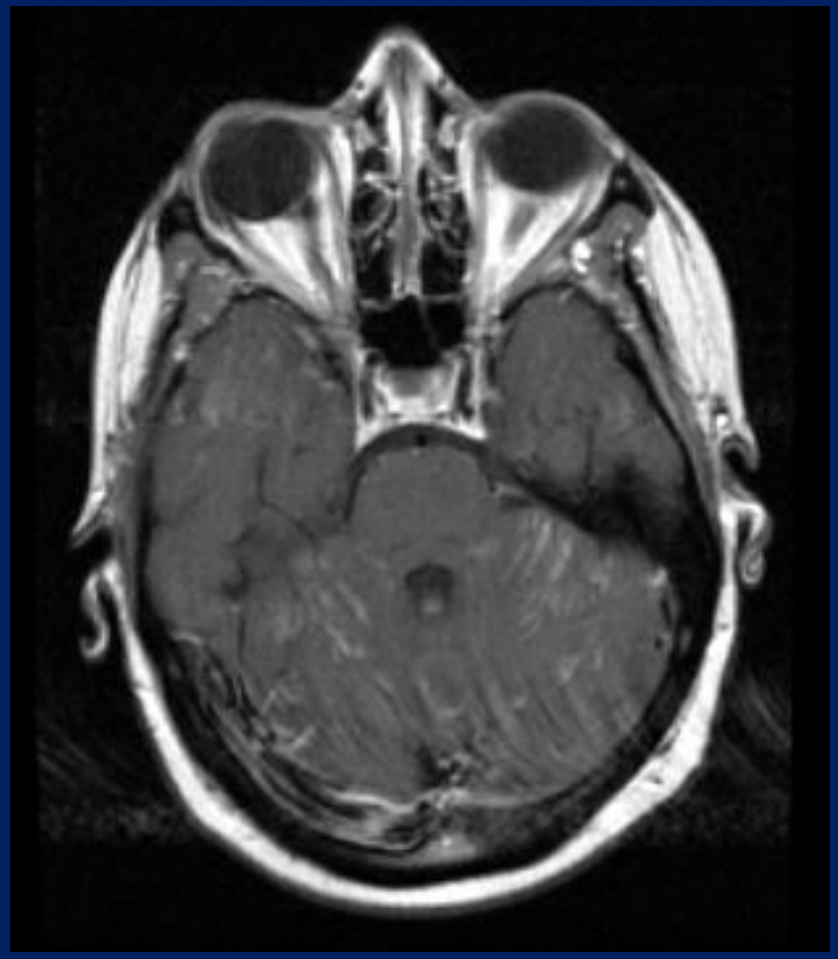
Symptoms	%	Signs	%
Vision loss	3%	Loss of visual acuity	2%
Diplopia	14%	Ocular muscle paresis	15%
Facial numbness	6%	Facial numbness	5%
Facial weakness	8%	Facial weakness	13%
Hearing loss	4%	Loss of hearing	4%
Dysarthria/Dysphagia	5%	Dysarthria/Dysphagia	4%
Cerebellar symptoms	17%	Cerebellar signs	17%
Nausea/Vomiting	25%		
Meningeal irritation	2%		

Spinal Cord/Nerve Root Signs/Sx

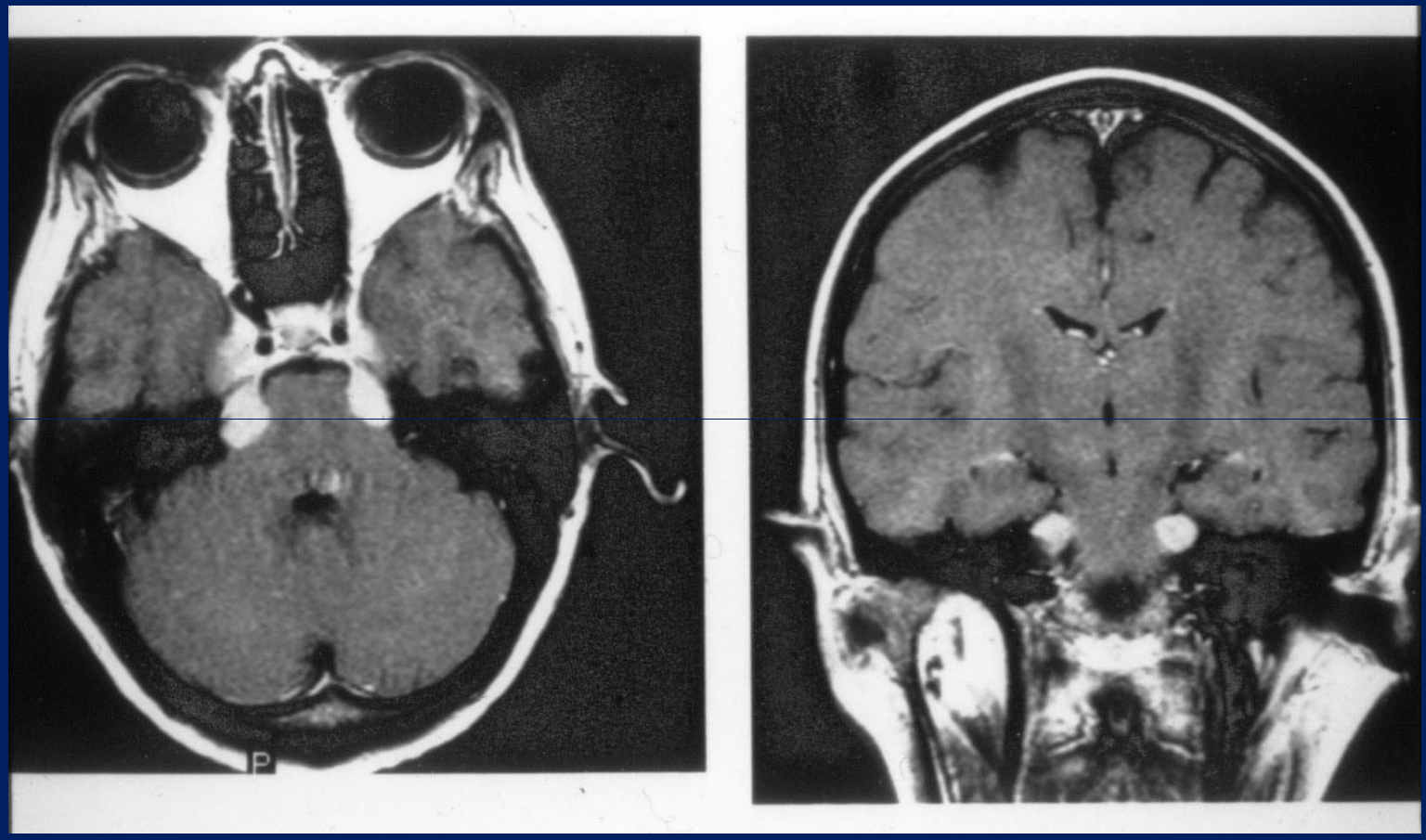
Symptoms	%	Signs	%
Back pain	12%	Arm weakness	5%
Arm pain	1%	Arm numbness	2%
Leg pain	3%	Leg weakness	21%
Bowel/bladder	5%	Leg numbness	12%
		Loss of reflexes	4%

Diagnosis: Imaging

- MRI +/- gad
- Do imaging before LP
- Image entire neuraxis (brain + total spine)
- Look for hydrocephalus
- If definitive: CSF not necessary

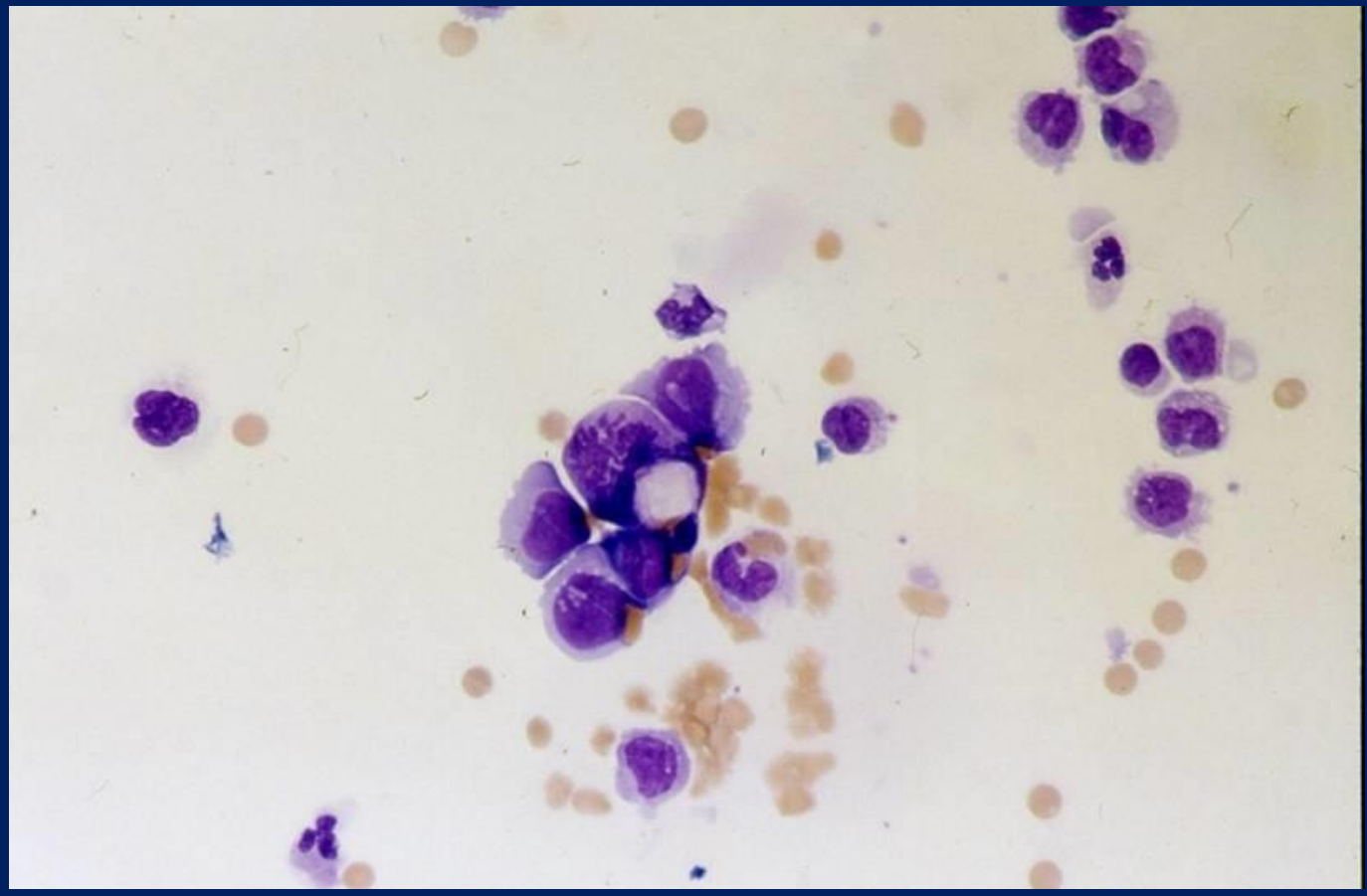


LM Metastases: NHL



LM Metastases: Melanoma

Diagnosis: CSF

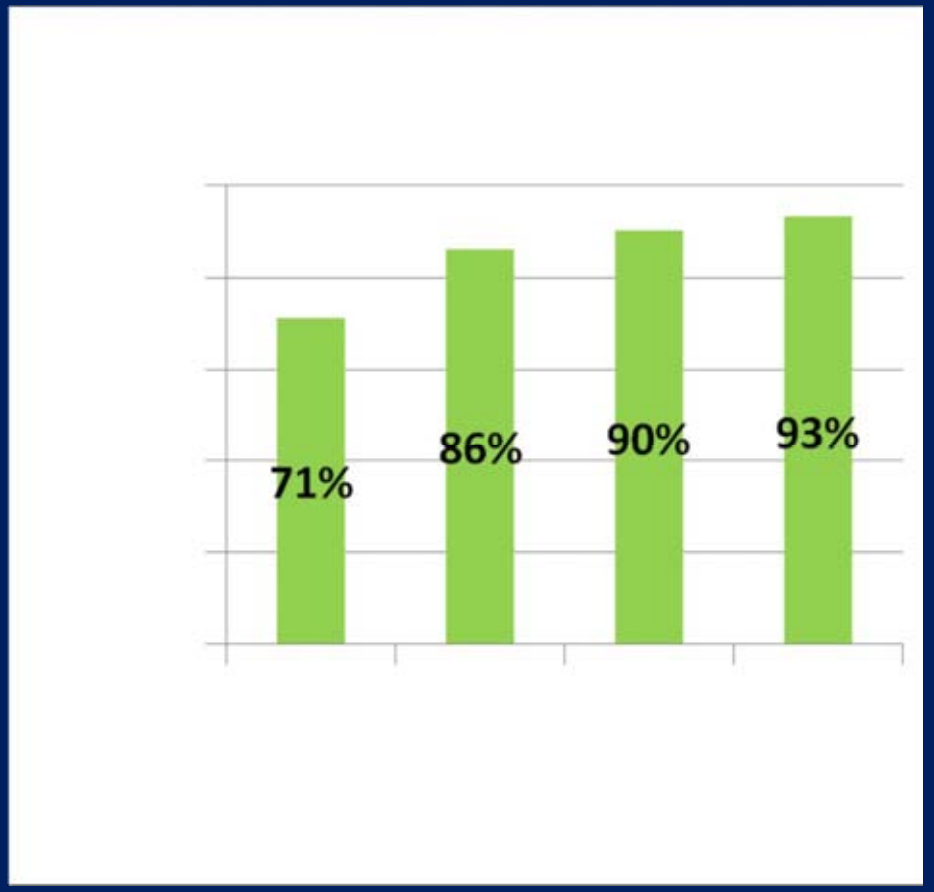


Positive CSF cytology via LP is gold standard

Picture courtesy of http://commons.wikimedia.org/wiki/File:Leptomeningeal_metastasis.jpg

Diagnosis: CSF

- Cytology sensitivity imperfect
- Other findings:
  - Protein often ↑
  - Glucose ↓
  - WBC often ↑
  - Opening pressure often ↑ (when done)
  - 5% normal
- Flow cytometry can be helpful



Glantz, et al. Cancer 1998;82(4):733-39.

Diagnosis: CSF

	All pts	Solid Tumors	Hematopoietic Tumors
Leukocytes			
# measured	80	51	29
> 5 / mm2	64%	57%	76%
Protein			
# measured	82	53	29
> 50 mg/dl	59%	62%	52%
Glucose			
# measured	81	52	29
< 40 mg/dl	31%	38%	17%
Opening Pressure			
# measured	32	25	7
> 20 cm H2O	50%	56%	29%

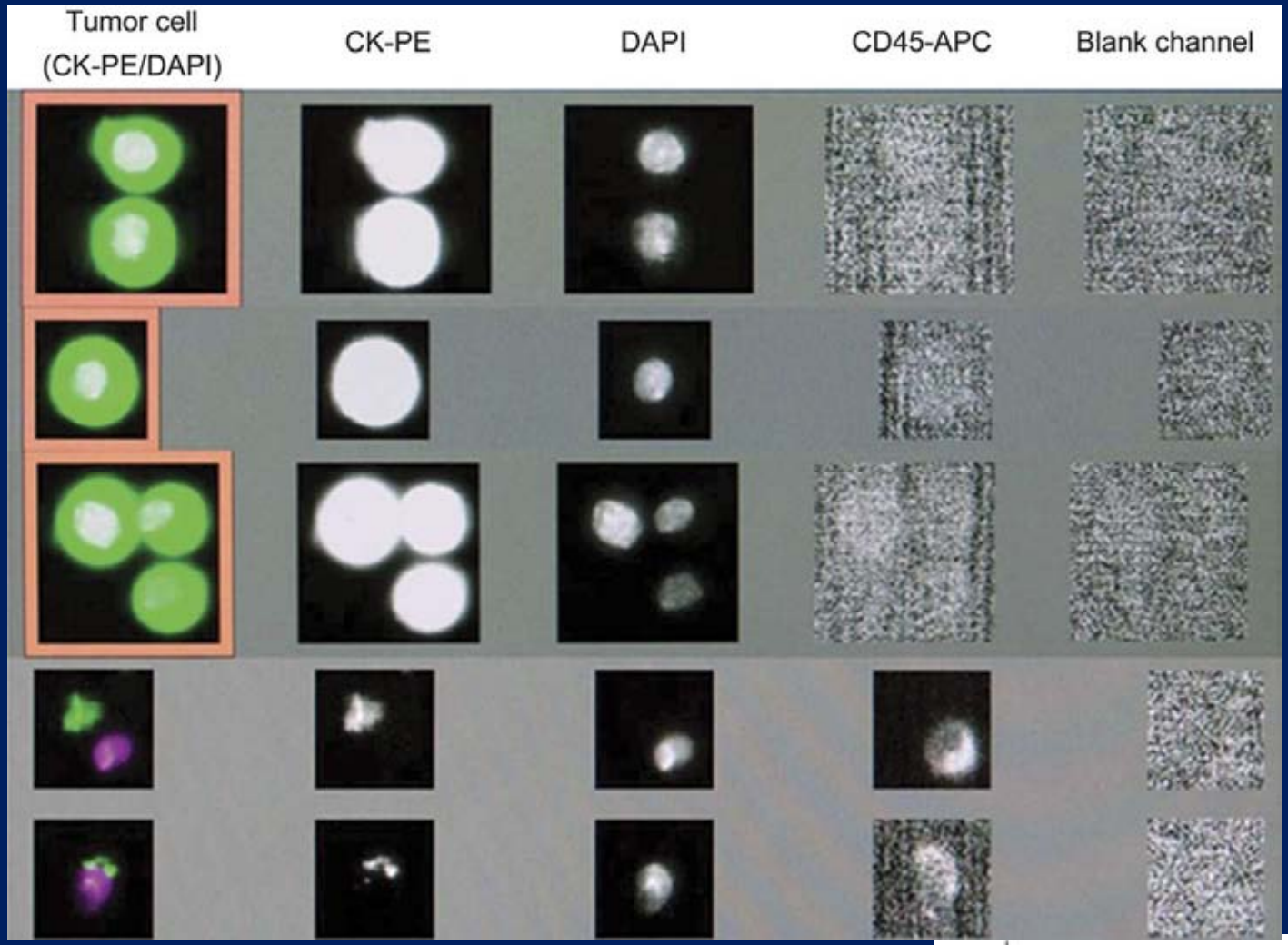
Diagnosis: CSF

- Assessment for tumor markers can be helpful:

Marker	Associated Tumor(s)
CEA	GI, lung
AFP	Germ cell
hCG	Germ cell
CA125	Ovarian
CA 15-3	Breast
CA 19-9	AdenoCA, biliary disease
Melanin	Melanoma
Beta-2 microglobulin	Leukemia/lymphoma

- Usually looking for > 1% of serum level

CSF analysis utilizing the CellTracks Analyzer II system
The first 3 rows examples of circulating tumor cells (CTCs)



Nayak L et al. Neurology 2013;80:1598

AMERICAN ACADEMY OF NEUROLOGY

Treatment Goals

- Prolong life
  - Curable?
    - NHL
    - Leukemia
- Reverse symptoms
  - Pain
  - Neurologic disability
- Preserve neurologic function

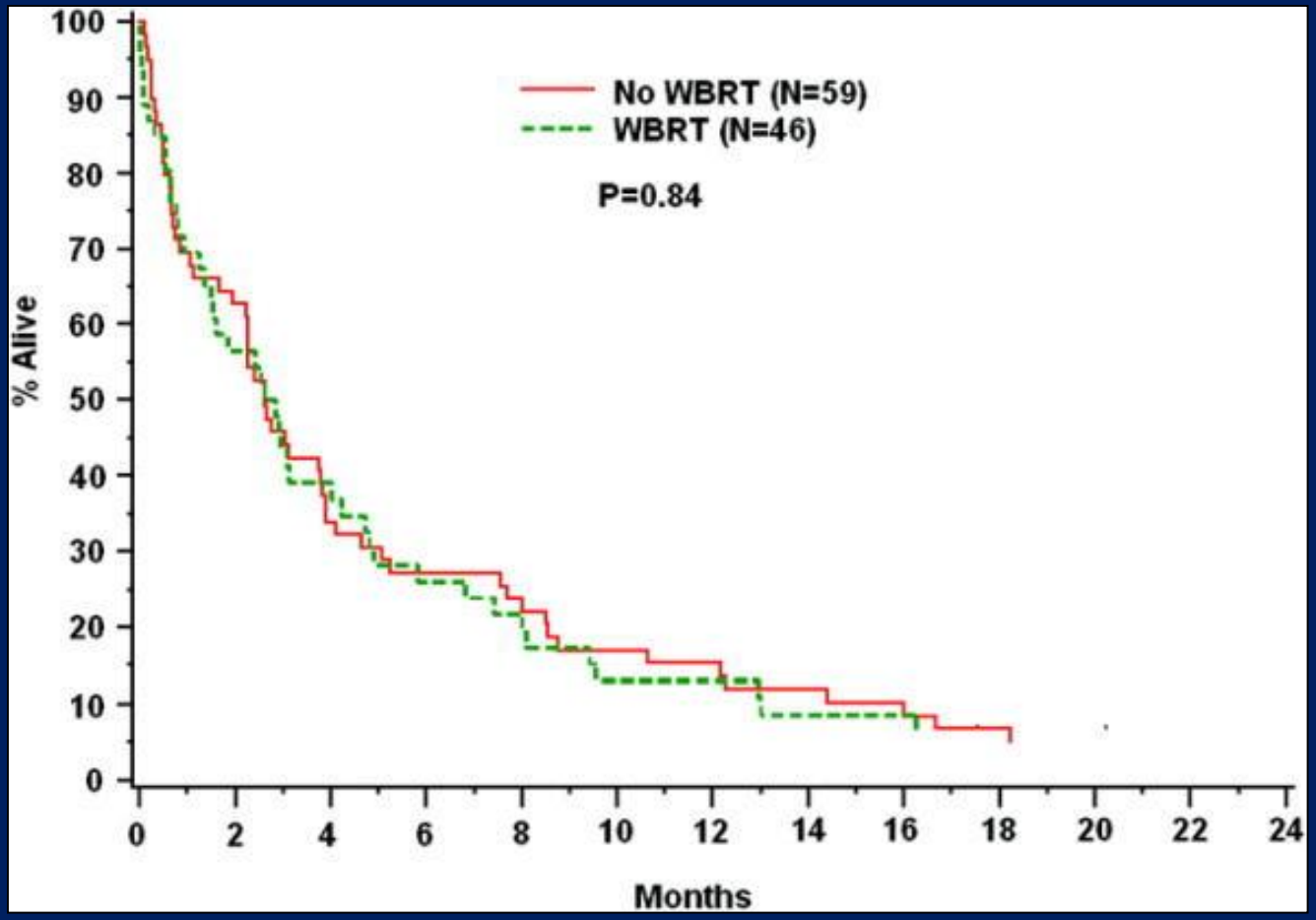
Treatment of LM Metastasis

- Radiotherapy
- Chemotherapy
  - Intrathecal
  - Systemic
- Surgery
- Regardless of tumor Rx decision, should provide supportive/symptomatic care

Radiotherapy for LM Metastasis

- Palliative but no impact on survival?
- Symptomatic site – even if radiographically negative
  - 30 Gy in 10 fractions
- Neuraxis RT too toxic and ineffective
- Areas of bulky disease
  - Prophylactic?
- Control symptoms
  - Pain relief
- Neurologic recovery limited
  - Leukemia, NHL and breast cancer

Survival by whole brain radiotherapy (WBRT)



Leptomeningeal Metastasis from Non-small Cell Lung Cancer: Survival and the Impact of Whole Brain Radiotherapy Morris,et al JThoracic Oncol 7(2):382, 2012

Treatment: IT Chemotherapy

- Delivery of drug into subarachnoid space
  - Via LP/Ommaya reservoir
  - Fixed dose
- 4 drugs used routinely used:
  - Methotrexate (MTX)
  - Cytarabine (ara-C)
  - Liposomal cytarabine (“DepoCyt”)
  - Thiotepa

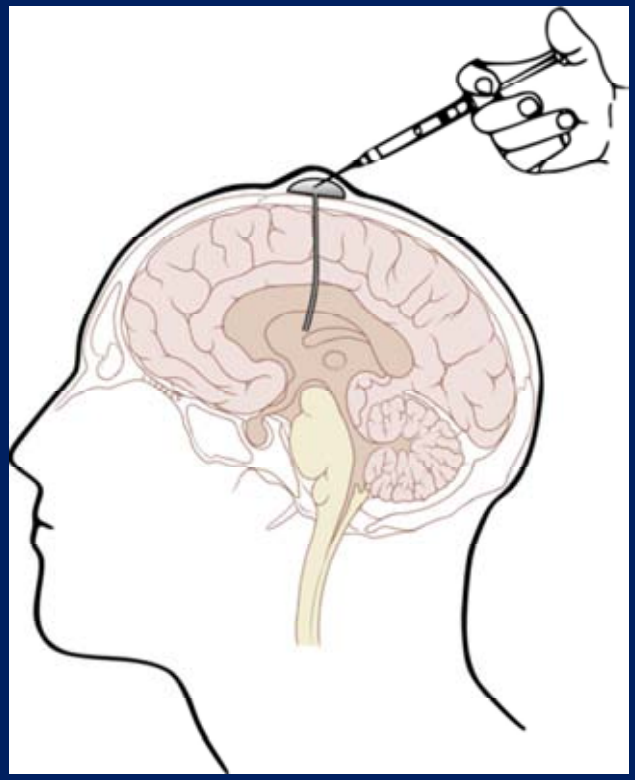


Diagram courtesy of Patrick L. Lynch, obtained from commons.wikimedia.org/wiki/File:Ommaya_01.png

Treatment: IT Chemotherapy

Pros:

- Assures drug into CSF
- Reduces systemic side effects

Cons:

- Surgery: placement of Ommaya
- Limited drug penetration into bulky disease
- Drug distribution dependent on CSF flow
- Poor flow = short survival due to high disease burden

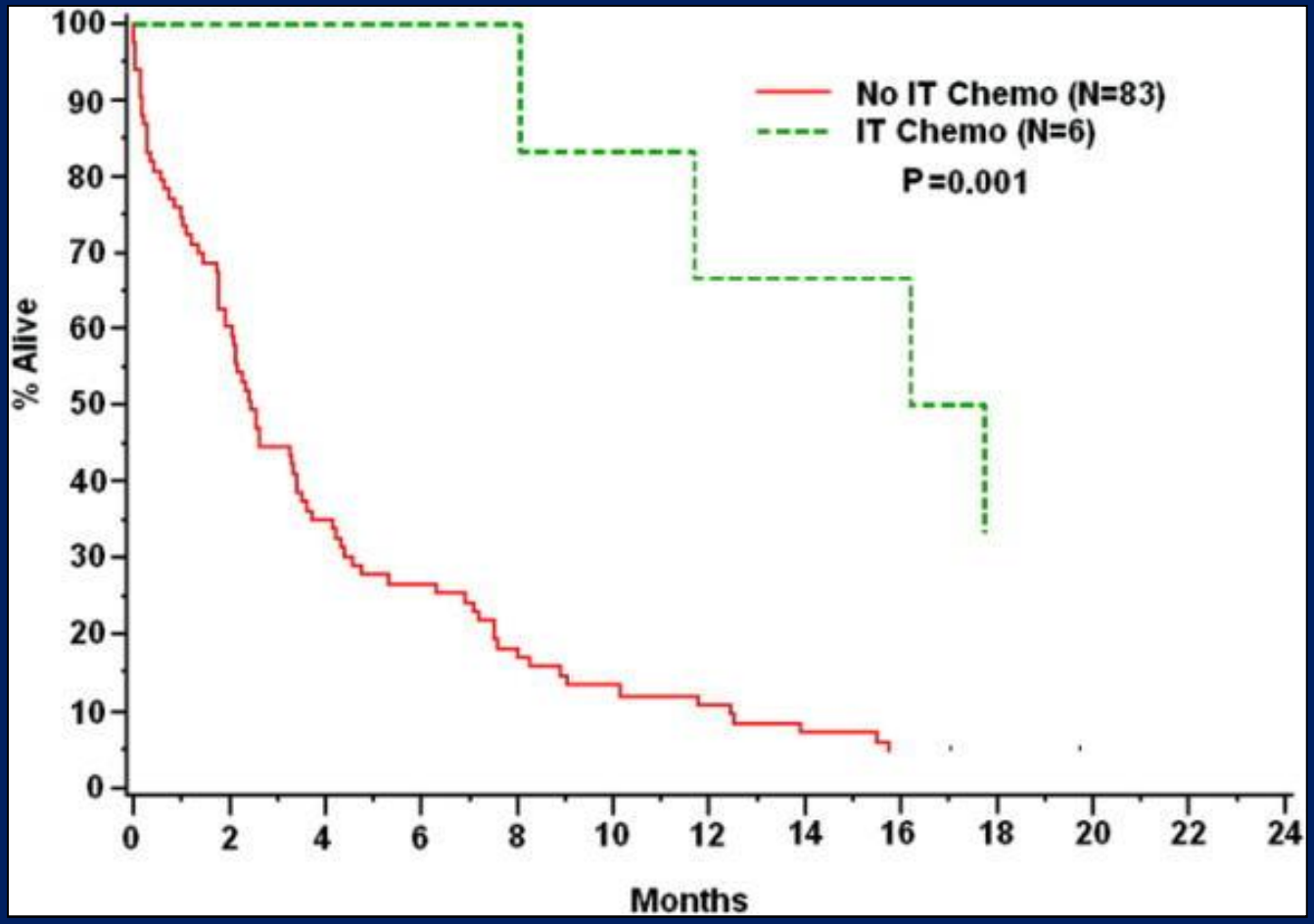
Treatment: IT Chemotherapy

Study	Description	Treatment Arms*	Median Survival	Signif
Hitchins, et al.	44 pts	MTX MTX + ara-C	12 wks 7 wks	P = 0.084
Grossman, et al.	52 pts	MTX Thiotepa	15.9 wks 14.1 wks	P = 0.36
Glantz, et al.	61 pts	MTX Depocyt	11.1 wks 15.0 wks	P = 0.15
Boogerd, et al.	35 pts (100% breast)	MTX No IT Rx	18.3 wks 30.3 wks	P = 0.32

*RT + systemic Rx also allowed ad lib in all studies

Hitchins JCO 1987; Grossman, JCO 1993; Glantz, CCR 1999; Boogerd, Eur J Cancer 2004

Survival by intrathecal (IT) chemotherapy

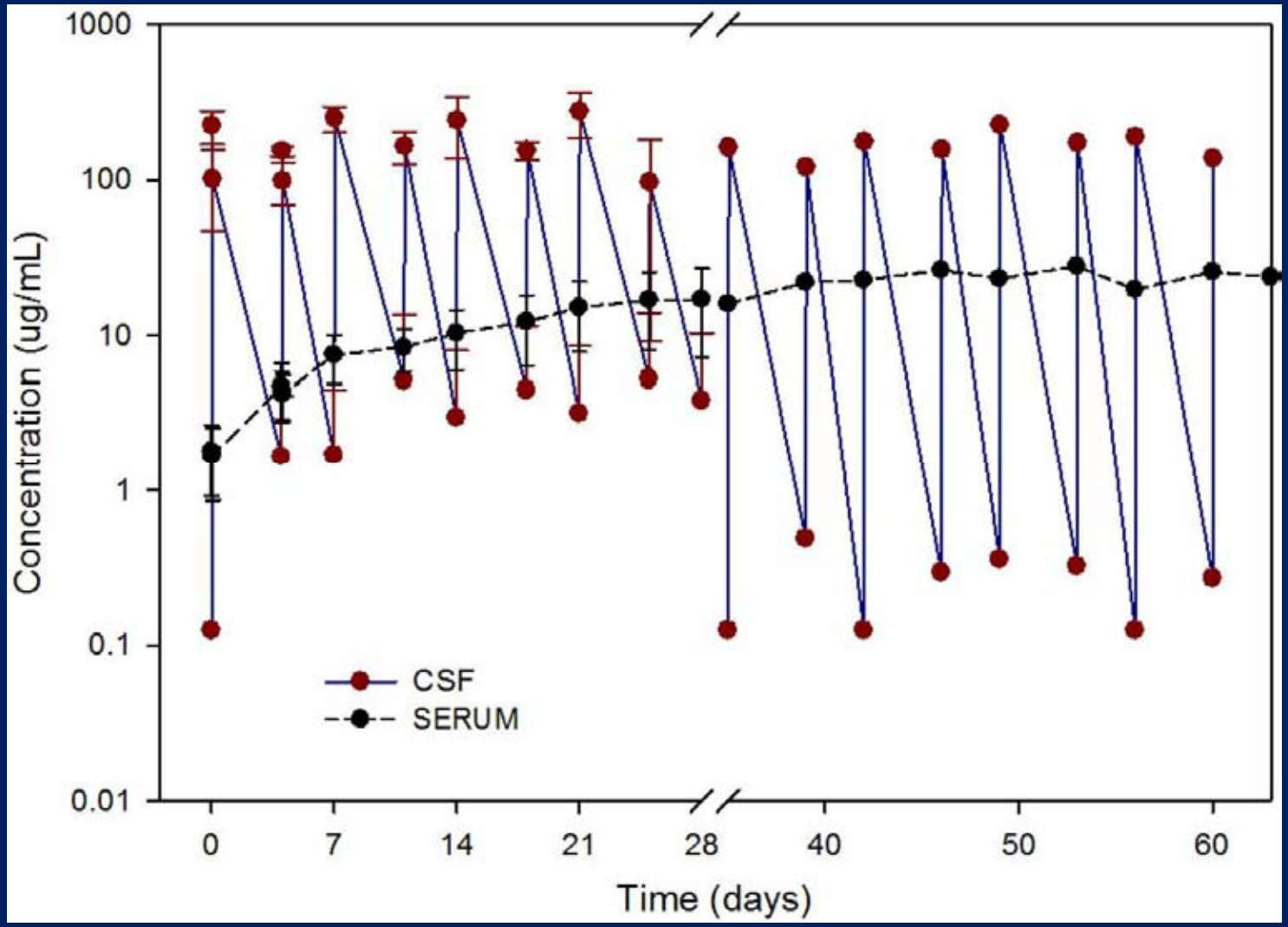


Leptomeningeal Metastasis from Non-small Cell Lung Cancer: Survival and the Impact of Whole Brain Radiotherapy Morris et al J Thoracic Oncol 7(2):382, 2012.

IT Chemotherapy

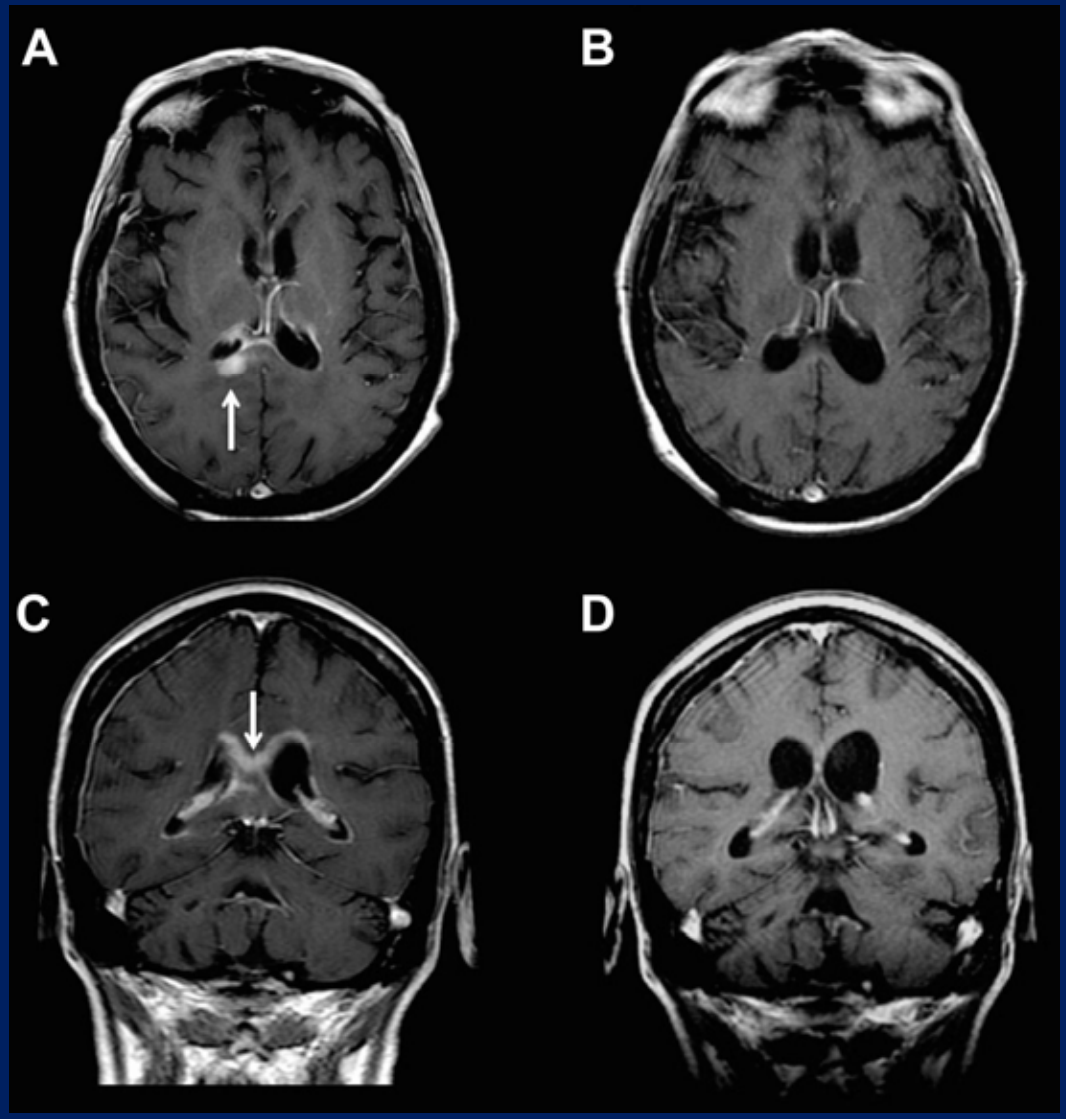
- Conventional drugs have limited spectrum of anti-tumor activity
  - Poor disease control
  - Best for hematopoietic tumors
- Newer agents
  - Topotecan and others – in trial setting
  - Monoclonal Ab
    - Rituximab – CD20+ heme malignancies
    - Trastuzumab - HER2+ breast cancer

Rituximab concentrations in CSF and serum



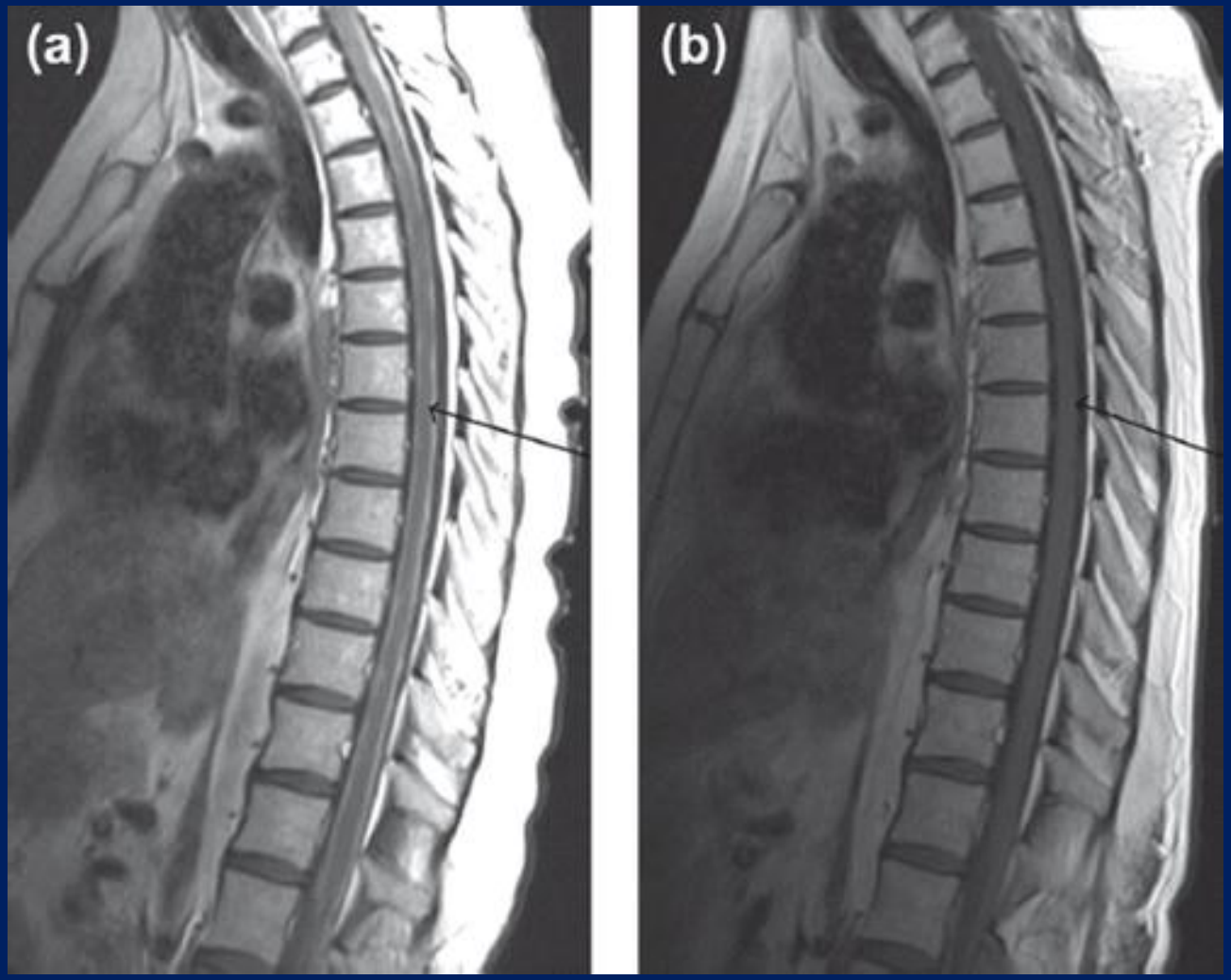
Rubenstein J L et al. Blood 2013;121:745-751

Parenchymal response in refractory CNS lymphoma after IT rituximab plus MTX



Rubenstein J L et al. Blood 2013;121:745-751

Response to IT Trastuzumab



Martens et al Acta Oncol 52:175,2013

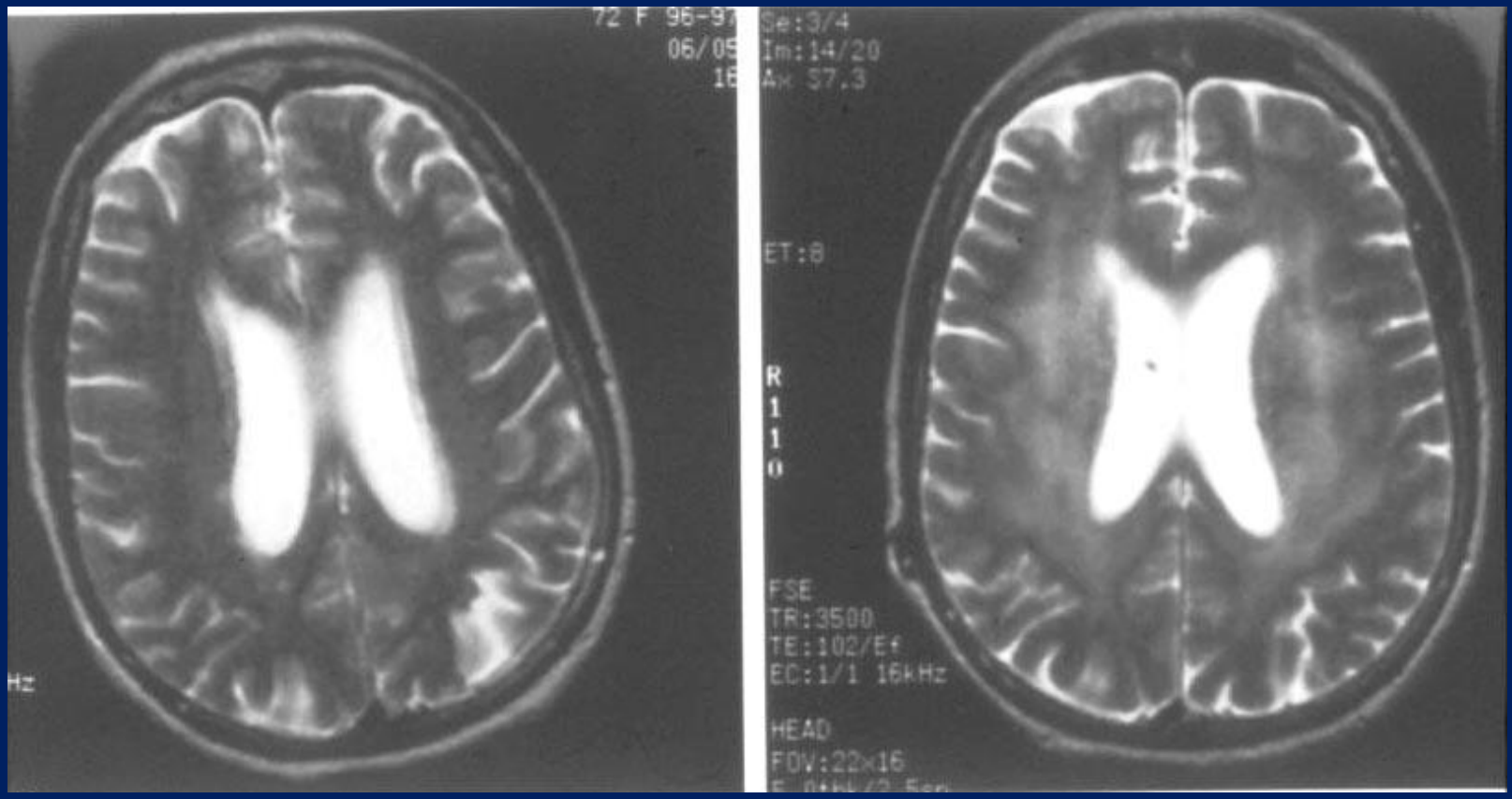
Intrathecal Chemotherapy

- Can be effective
- Can be sufficient
  - Positive cytology
  - Minimal/no neurologic symptoms
- Improves survival (breast, heme malignancies)
- Std drugs ineffective for bulky disease
  - Monoclonal Ab?
- Rarely reverses neurologic deficits

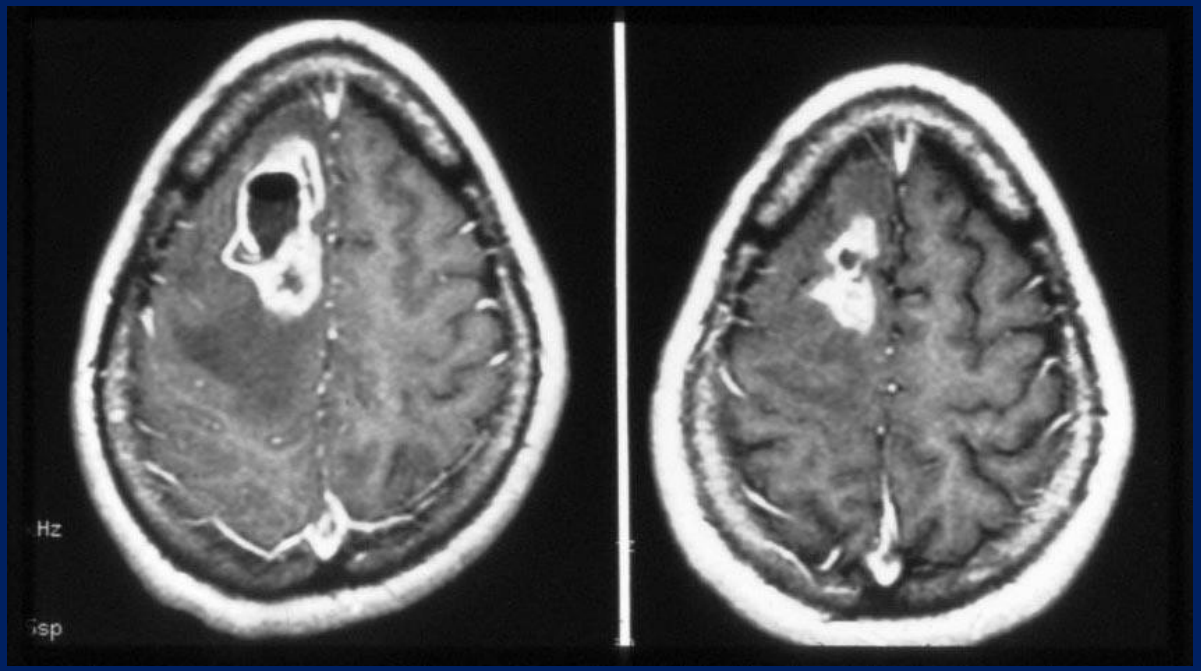
Toxicity

- Diffuse leukoencephalopathy
  - Enhanced with combination of WBRT and IT drug
- Ommaya problems: infection, clogging
- Focal leukoencephalopathy/sterile abscess
  - Misplaced Ommaya reservoir
  - Leakage of chemotherapy
    - Ventricular obstruction
    - Elevated ICP
  - Resolves spontaneously

Leukoencephalopathy After IT Drug Alone



Focal Leukoencephalopathy



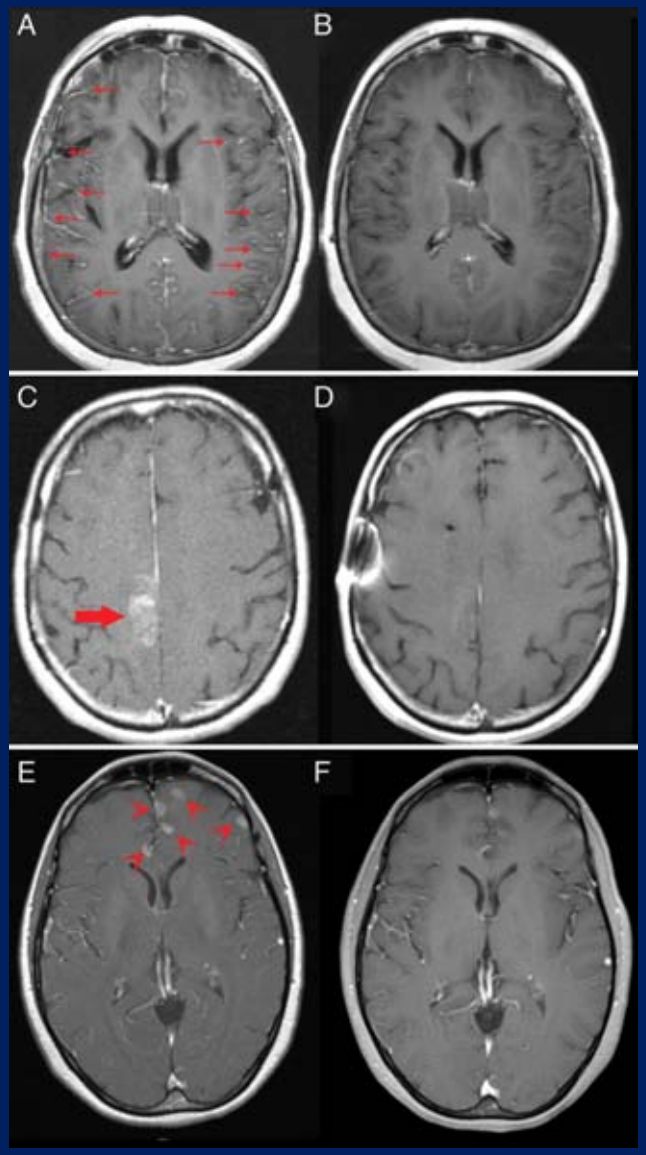
Systemic Chemotherapy: Pro

- Addresses systemic disease
- Drug distribution in CSF more uniform than IT
- Drug penetrates into bulky lesions via vascular distribution
  - BBB more permeable in lesions seen on MRI
- Choice of drug based on primary
  - Increases spectrum of anti-tumor activity
- Successful example with primary BT
  - Medulloblastoma
  - Breast Ca: prolongs survival Rudnicka et al JNO, 2007

Systemic Chemotherapy: Con

- BBB is important
  - Tumor cells floating in CSF
  - Microscopic disease not visualized
  - Tumor cells penetrating neural structures
- Most drugs don't penetrate CNS well
  - HD (MTX, ara-C) or lipophilic
    - Capecitabine, thiotepa, temozolomide
- Highly resistant disease with few new drug options at time of LM

Response to pulsatile erlotinib: CNS Mets



Grommes C et al. Neuro Oncol 2011;13:1364

Neuro-Oncology

Surgery for LM Metastasis

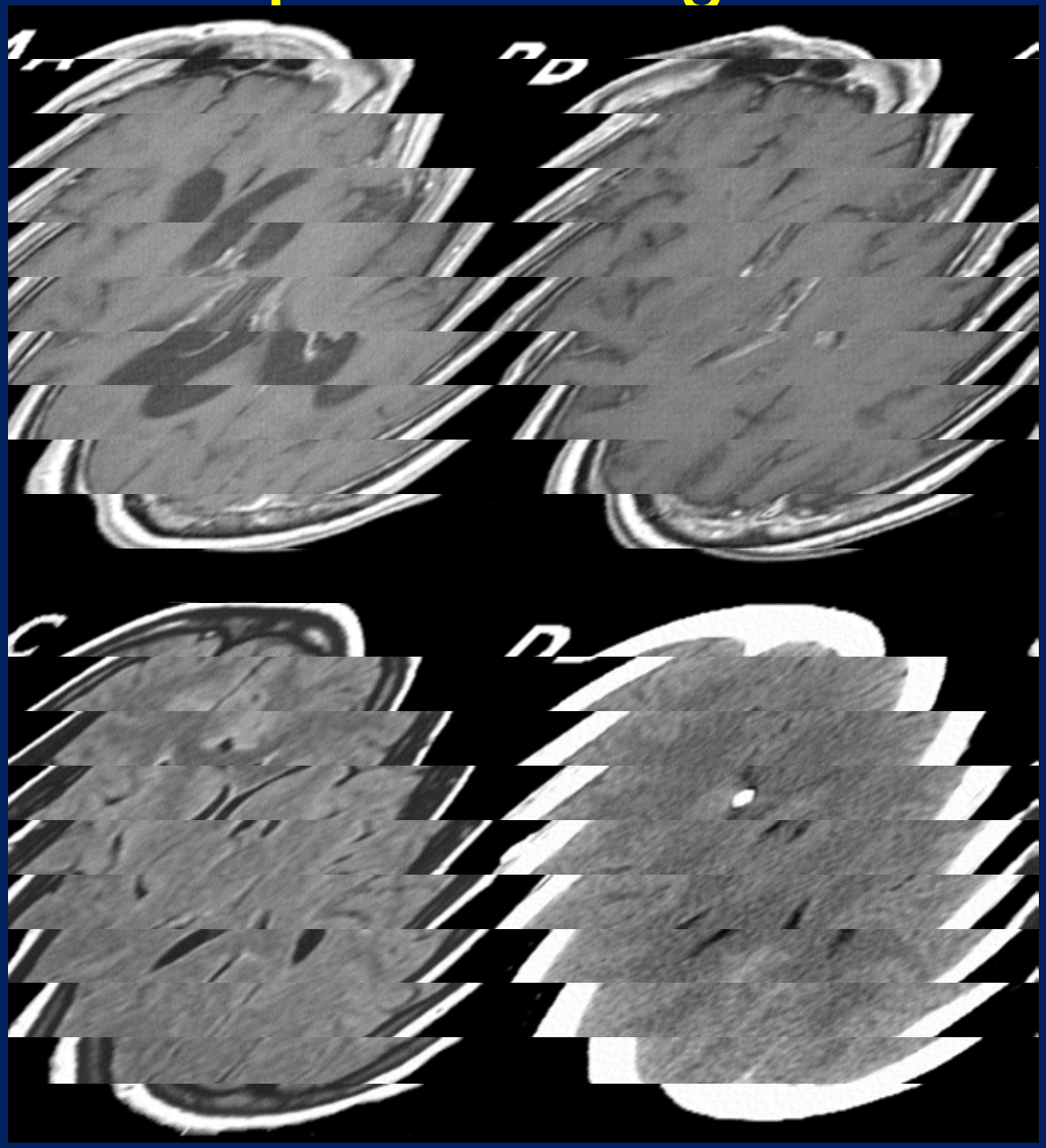
- Rare biopsy for diagnosis
- Ventriculoperitoneal shunt
  - Elevated ICP: under-recognized
  - Hydrocephalus may or may not be present
  - Need for VPS determined by symptoms
    - Headache, n/v, ataxia, confusion, lethargy
  - Underutilized: *single most common mistake*

Shunt for Leptomeningeal Mets

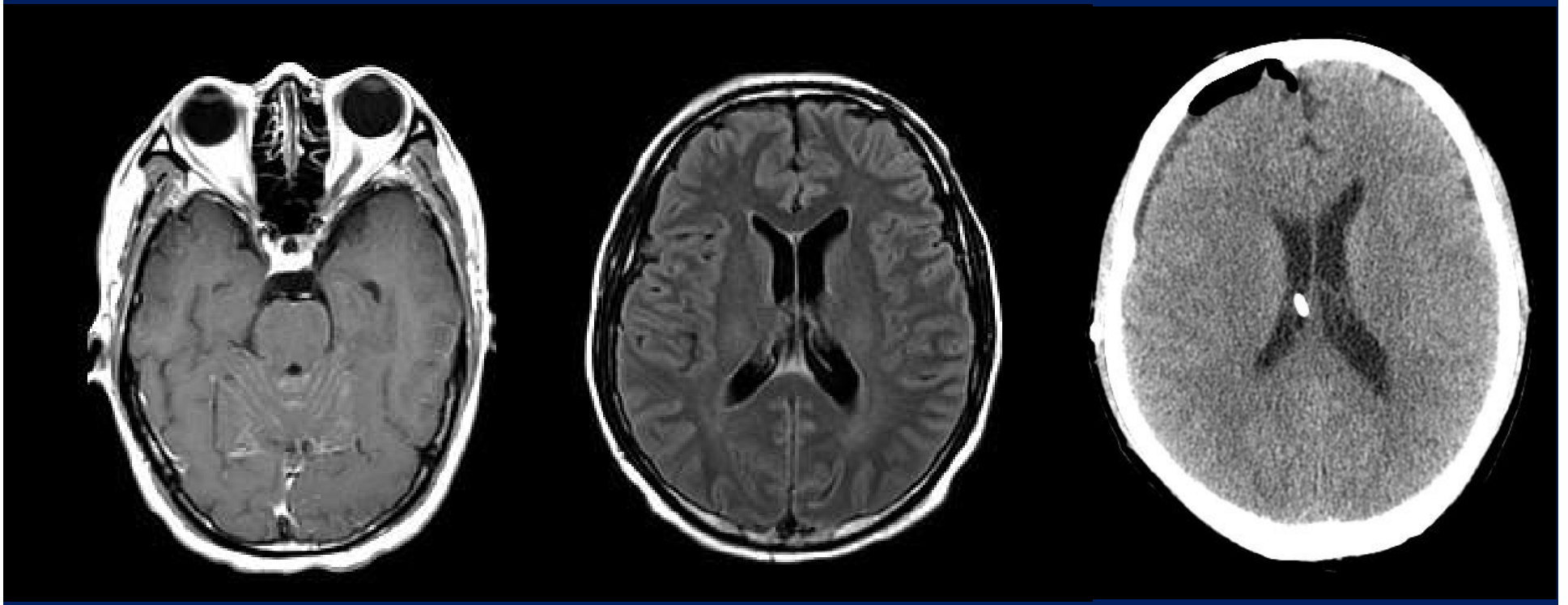
- 1995-2003 review
  - 37/640 (6%) pts with LM had VPS
- ICH documented in 35; 2 post-op CSF leak
- Clinical improvement in 27 (77%)
- Median OS 2 mo (2 days-3.6 yr) post-VPS
- Prior or concurrent brain mets: worse survival

Omuro et al Neurology 2005;64:1625

ICH in Leptomeningeal Mets



NSCLC LM with OP of 550mm



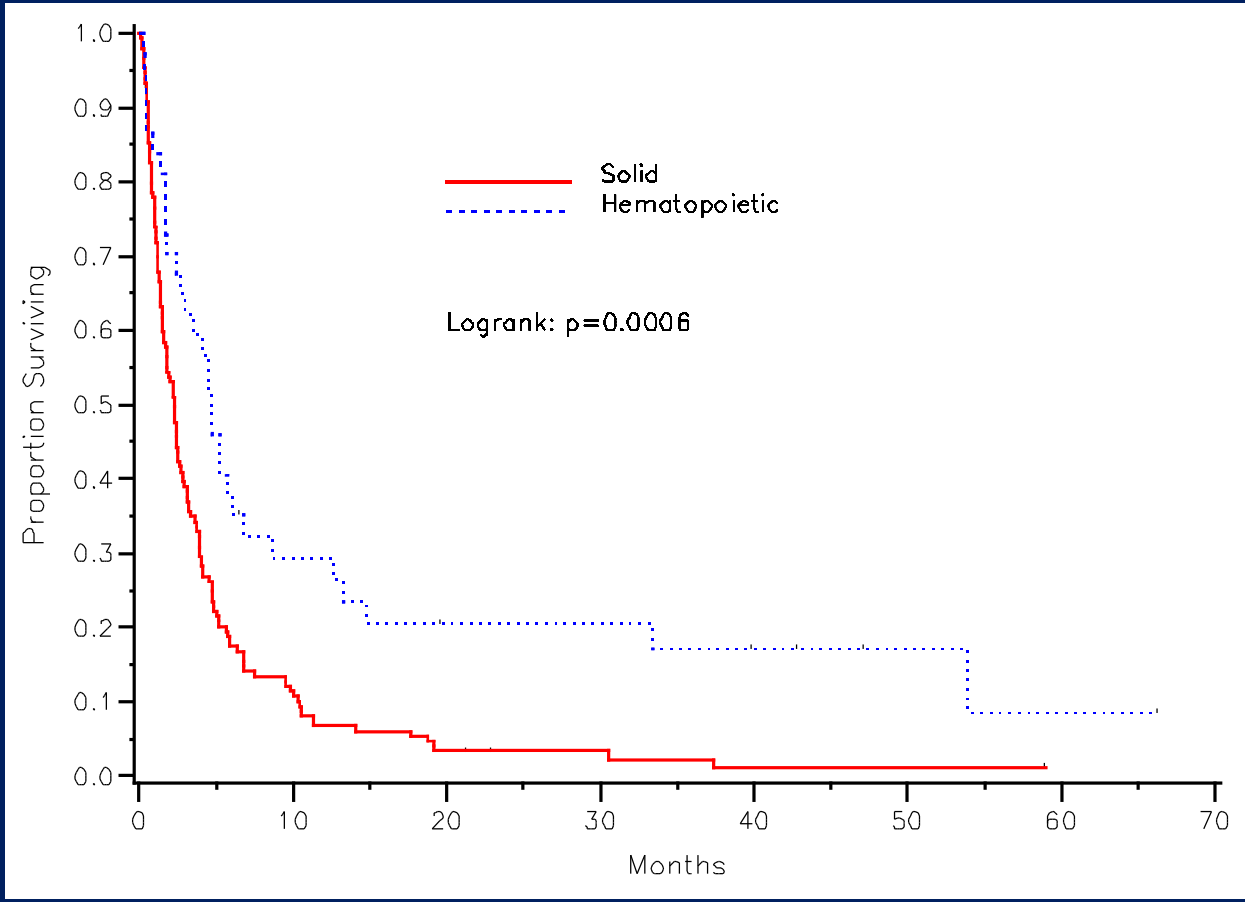
Shunt for LM Metastasis

- Complicates IT chemotherapy
  - Can't use Ommaya
  - On/off valve ineffective
  - Programmable valves problematic
    - Paramagnetic
    - Requires resetting after every MRI
- Follow VPS with IT chemo via LP: suboptimal
- Best to use systemic chemotherapy

Prognosis

- Despite advances in diagnosis/treatment, prognosis remains poor
- Median survival: weeks in most
  - A minority can have long survival
- Patients die from LM and not systemic tumor
  - Unlike brain mets
- Hematopoietic tumors do better than solid tumors

Prognosis (MSKCC cohort)



Median OS:

Solid
2.3 mo

Heme
4.7 mo

Summary

- Despite advances in cancer therapeutics, LM remains a late-stage complication that is difficult to diagnose and treat
- Prevention with agents that penetrate CNS at initial cancer diagnosis ?
- Prognosis is poor despite aggressive therapy
  - Systemic chemo and novel IT drugs hopeful
- Elevated ICP (+/- hydrocephalus) is under-diagnosed in LM and should be treated