

# Neoplastic Meningitis:

A Clear Indication For  
Intensive Hospice and Palliative Care

Richard Stephenson MD

Chief Medical Officer

Hospice & Palliative CareCenter

[Dick.Stephenson@hospicecarecenter.org](mailto:Dick.Stephenson@hospicecarecenter.org)

336.768.3972

# Introduction

- My understanding has always been...
  - A rare but ominous development in cancer patients.
- But, 2 recent admissions to KBR and another to home care...
- Rare? What's up?
- The KBR admissions were young women with Breast CA
  - Both very challenging for us
  - Both with very complex symptom management
  - Both with profound psychosocial & spiritual implications

# Objectives

- Review definition, epidemiology, pathogenesis and diagnosis
- Understand prognostic variables
- Explore treatment options
- Anticipate the need for intensive symptom management

# 1<sup>st</sup> Case at KBR

- CH – 42 y/o WF presented to FMC with headache and neck rigidity, found leptomeningeal metastases (LM) as first site of recurrence < 1 year after original diagnosis
- Long and difficult course at FMC
- Transferred to KBR
  - Long and difficult course at KBR
  - Celebrated 43<sup>rd</sup> birthday with us
- Relentless neurologic progression
  - Pain, numbness, paralysis
- 2 young children
- Ultimately, incrementally required sedation for comfort

## 2<sup>nd</sup> Case at KBR

- JJ - 32 y/o AAF presented to FMC with HA, N/V and abdominal pain. Found to have liver metastases and in the hospital quickly developed cervical neck pain and persistent N/V and LM diagnosed.
- Long and difficult course at FMC
- Transferred to KBR
  - Long and difficult course at KBR
  - Celebrated 33<sup>rd</sup> birthday with us
- Relentless neurologic progression
  - Pain, HA, N/V, numbness, paralysis, blindness
- 2 young children
- Ultimately, incrementally, required sedation for comfort

# Terminology

## ● Neoplastic meningitis

- the development of meningitis due to the infiltration of the subarachnoid space with cancer cells. Any kind of neoplasia, including leukemia and lymphoma

## ● Carcinomatous meningitis

- Due to a carcinoma (solid tumors), doesn't include leukemia and lymphoma

## ● **Leptomeningeal metastases (LM)**

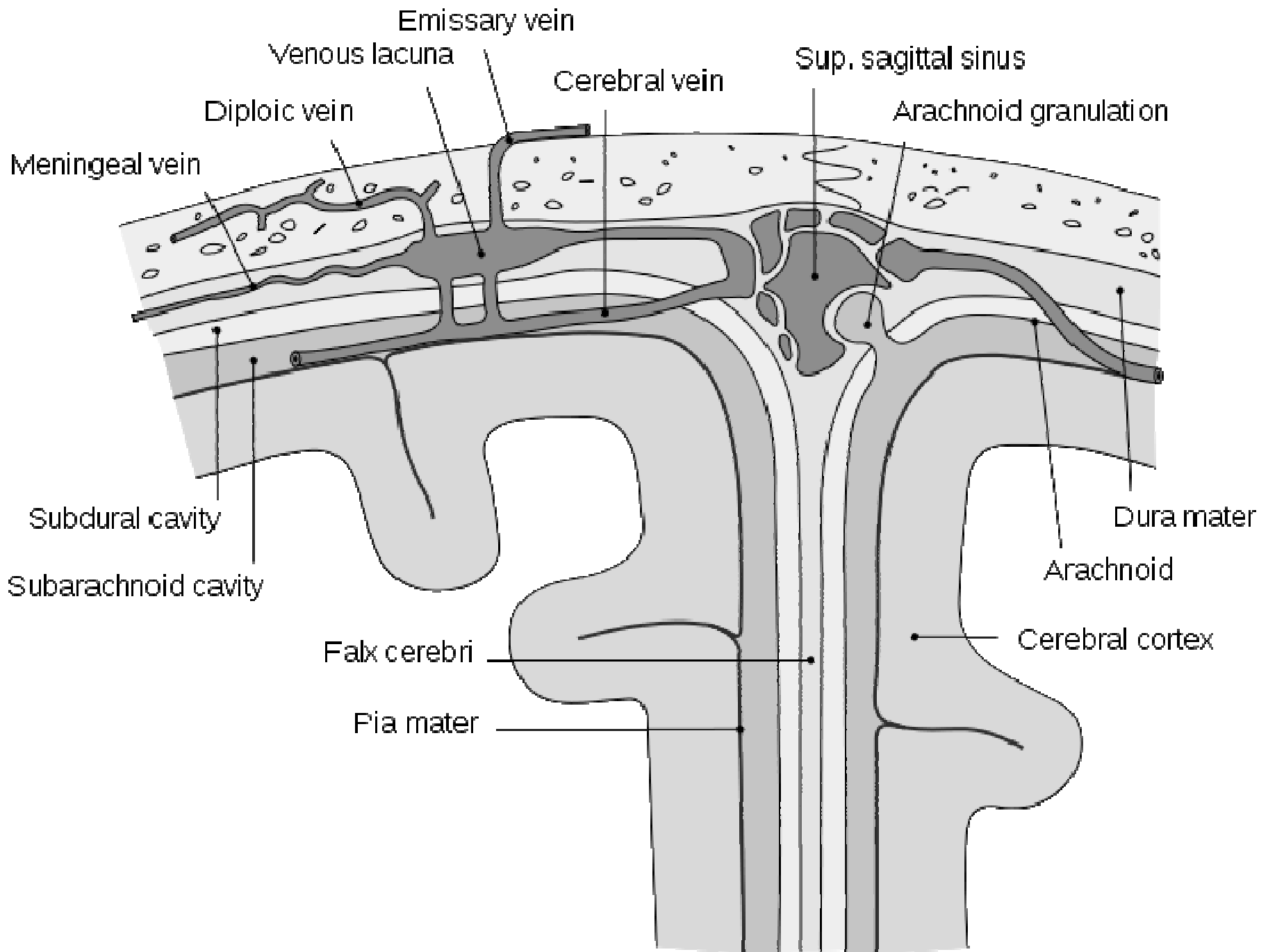
- Leptomeninges – arachnoid membrane and pia mater
- Now seems to be the preferred term

## ● Other terminology...

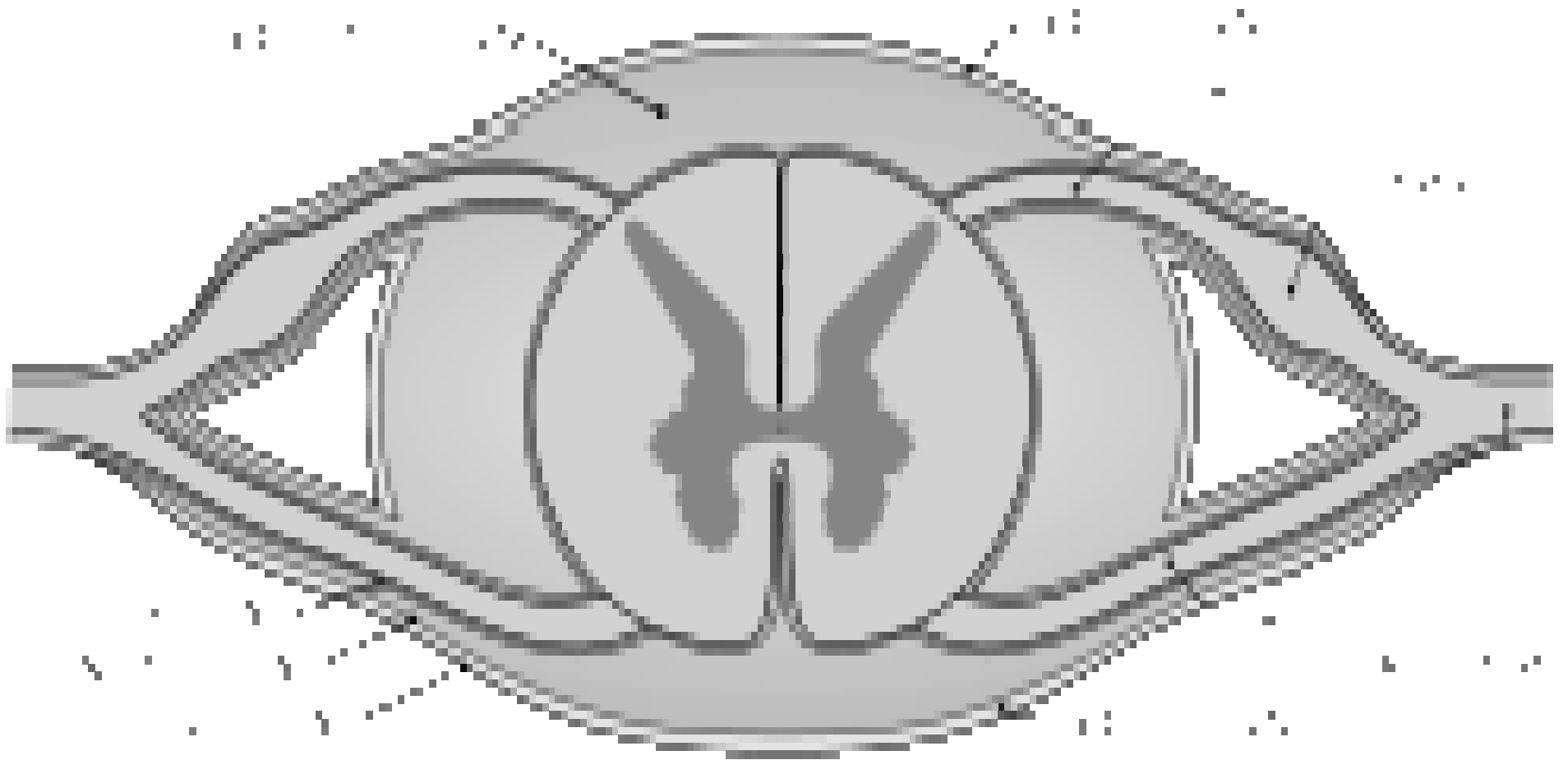
## ● Leptomeningeal carcinomatosis, meningeal carcinomatosis

# Pathogenesis

- Hematogenous dissemination to the meninges or
- Direct extension from para-meningeal or bony contiguous structures (bone, skull or vertebrae, regional lymph nodes or soft tissues) or
- Retrograde growth along spinal and/or cranial nerve roots
- Once in...
- Carried by bulk flow of CSF to basal cisterns and cauda equina where they settle 2<sup>o</sup> gravity and slow flow
  - Which is why cranial and spinal nerve symptoms are so common







# Incidence

- Seems to be happening more often!
  - Greater awareness of the condition by oncologists
    - Higher index of suspicion & look for it
  - Improved diagnostic methods
  - Longer survival among patients with systemic malignancies...more time to develop
  - Larger molecule chemotherapies (that don't cross Blood Brain Barrier)
- Occurs in ~ 5% of all cancers
  - 4 to 8% solid tumors; 5 to 15% leukemia and lymphomas (1000KBR 40%CA 5% LM = 50 pts/year?)

# Tumor Types

from Chamberlain review article

- Melanoma and SCLC have strongest propensity for LM, up to 25%
- Breast – 2 to 5% of all patients with metastatic breast CA
- Based on frequency of each cancer
- \*Accept in Korea
  - Gastric

Primary CA	% Total
Breast	27-50
Lung	22-36
AdenoCA	50-56
SqcellCA	26-36
SCLC	13-14
Melanoma	12
GU	5
Head & N	2
Unkn 1 <sup>0</sup>	2

# Clinical Features

- Classically presents with pleomorphic findings in 3 domains of neurologic function
  - Cerebral (15-50%)
    - Headache and mental status changes
    - Followed by confusion, cognitive impairment, seizures, and hemiparesis
  - Cranial nerve dysfunction (35-50%)
    - Diplopia (VI, III, IV), trigeminal sensory or motor, cochlear dysfunction, and optic neuropathy
      - Cranial Nerve VI is most commonly involved? Why?
      - Name that Nerve!
  - Spinal (60-70%) –LEs > UEs
    - Weakness, dermatomal sensory loss, pain in the neck, back, or in radicular patterns
    - Classic nuchal rigidity only 15-20% (**CH**)

# Symptoms\* of (Breast) Meningeal Carcinomatosis

from Gauthier et al

Headache	34%
Cranial nerve symptoms	25
Cerebellar signs	24
Nausea and vomiting	23
Visual disturbance	22
Radicular pain	21
Glascow coma scale < 15	21
Paresthesia	19
Meningismis	12
Motor deficit	11
Dysarthria	2

\* Symptoms on presentation!

# Symptoms of (Gastric) Leptomeningeal Carcinomatosis

from Oh et al.

Cerebral Symptoms		Cranial Symptoms	
Headache	85%	Diplopia	6%
N & V	59	Hearing loss	4
Dizziness	24	Facial palsy	2
Mental Change	22	Ptosis	2
Seizure	19	Spinal Symptoms	
Gait	4	Weakness	11
Dysarthria	4	Paresthesia	4
Psychosis	2	Back pain	2

# Diagnosis

- Usually presents in patients with widespread disease – 70% (JJ)
  - May present after disease free interval – 20%
  - Sole site of relapsed DZ with increasing frequency (CH)
  - Occasionally in absence of systemic DZ – 5%
- Symptoms sometimes for weeks or months (JJ&CH)
- May seem benign or stable (CH was being treated for migraine and JJ for vertigo 2<sup>o</sup> viral illness)
- Once recognized often progresses rapidly
- High index of suspicion with multifocal Neurologic dysfunction

# Diagnostic Testing

## ● Gadolinium enhanced MRI

- If Lumbar Puncture is done first may cause false (+) MRI
- Neither CH or JJ could have MRI because of metal in expandable breast implants

## ● Examination of CSF

- Cytology maybe false (-) ~ 10-30%
- Clinical suspicion, + MRI, and CSF signs but negative cytology may be enough for Dx and Rx

## ● CSF flow study

- Neither of our patients had this, rarely done locally?

## ● Meningeal biopsy



73Y,M,1612822  
Scan:6  
SI:110  
Pos:-59.2  
Dbl Obl  
Ec:1

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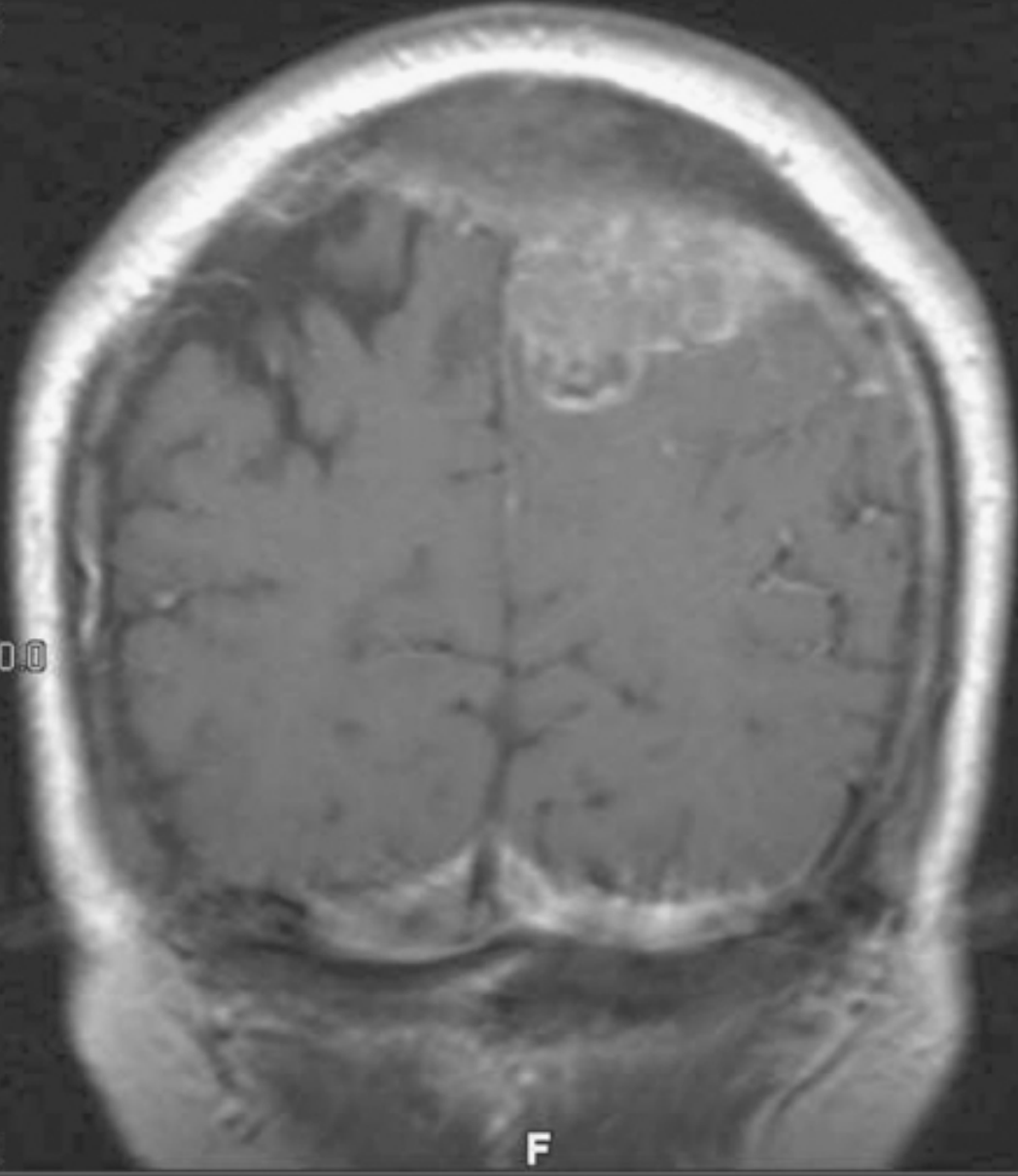
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**Table 56F-3 -- Diagnostic Tests for Leptomeningeal Metastases**

<b>TEST</b>	<b>MEASUREMENT</b>	<b>POSITIVE FINDINGS</b>
Lumbar puncture	Lymphocytic pleocytosis	>70%
	Elevated opening pressure	50%
	Elevated protein	75%
	Reduced glucose	30%–40%
	Cytology after 1 lumbar puncture	50%
	Cytology after 3 lumbar punctures	90% (< 100%)
	CSF markers	Variable
	Immunohistochemistry	Variable
	PCR	Variable
Brain MRI	Meningeal enhancement	>50%
	Enlarged ventricles	<50%
Spine MRI/myelogram	Subarachnoid masses	<25%
	Meningeal enhancement	>50%

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

From Bradley: Neurology in Clinical Practice, 5<sup>th</sup> ed.

**Table 56F-5 -- Differential Diagnosis of Leptomeningeal Metastasis**

<b>NEOPLASTIC</b>
Parenchymal metastases Dural metastases Castleman's disease*
<b>INFECTIONS</b>
Bacterial/viral meningitis Fungal infections, including cryptococcus Lyme disease Neurocysticercosis Tuberculosis
<b>GRANULOMATOUS DISORDERS</b>
Histiocytosis Sarcoidosis Wegener's granulomatosis
<b>INFLAMMATORY DISORDERS</b>
Multiple sclerosis Paraneoplastic encephalomyelitis Relapsing polychondritis Rheumatoid nodules Vasculitis (including granulomatous angiitis)

From Bradley: Neurology in Clinical Practice, 5th ed.

\* "benign" CNS lymphoma associated with HIV

# Prognosis of LM

- Bad...ominous...grave...terminal
- Median survival untreated patients is 4-6 weeks
  - **Death from progression of neurologic dysfunction**
- Treatment is intended to improve or stabilize neurologic status, maintain neurologic QOL, and prolong survival
- Fixed neurologic deficits rarely improve, but progression may be halted in some patients, and median survival can be increased to 4-6 months
  - Only pain-related Nx Sx improve; confusion, Cr Ns, ataxia, weakness minimally improve or stabilize
- Breast CA (of solid tumors) responds best
  - MLOSurvival 6 mos; 11-25% 1 year survival
- Who to treat?

# Bad Prognostic Signs (bad to worst)

- Generally accepted that patients do poorly with:
- Poor performance status
- Multiple fixed neurologic deficits
- Bulky CNS disease (1/3 of patients)
- Coexistent carcinomatous encephalopathy
- CSF flow abnormalities (1/3 of patients)
- Widely metastatic aggressive cancers
  - 75% have progressive systemic cancer

# Neoplastic Meningitis-Related Prognostic Significance of the Karnovsky Performance Status

Chamberlain et al. *Arch Neurol.* 2009;66(1):74-78.

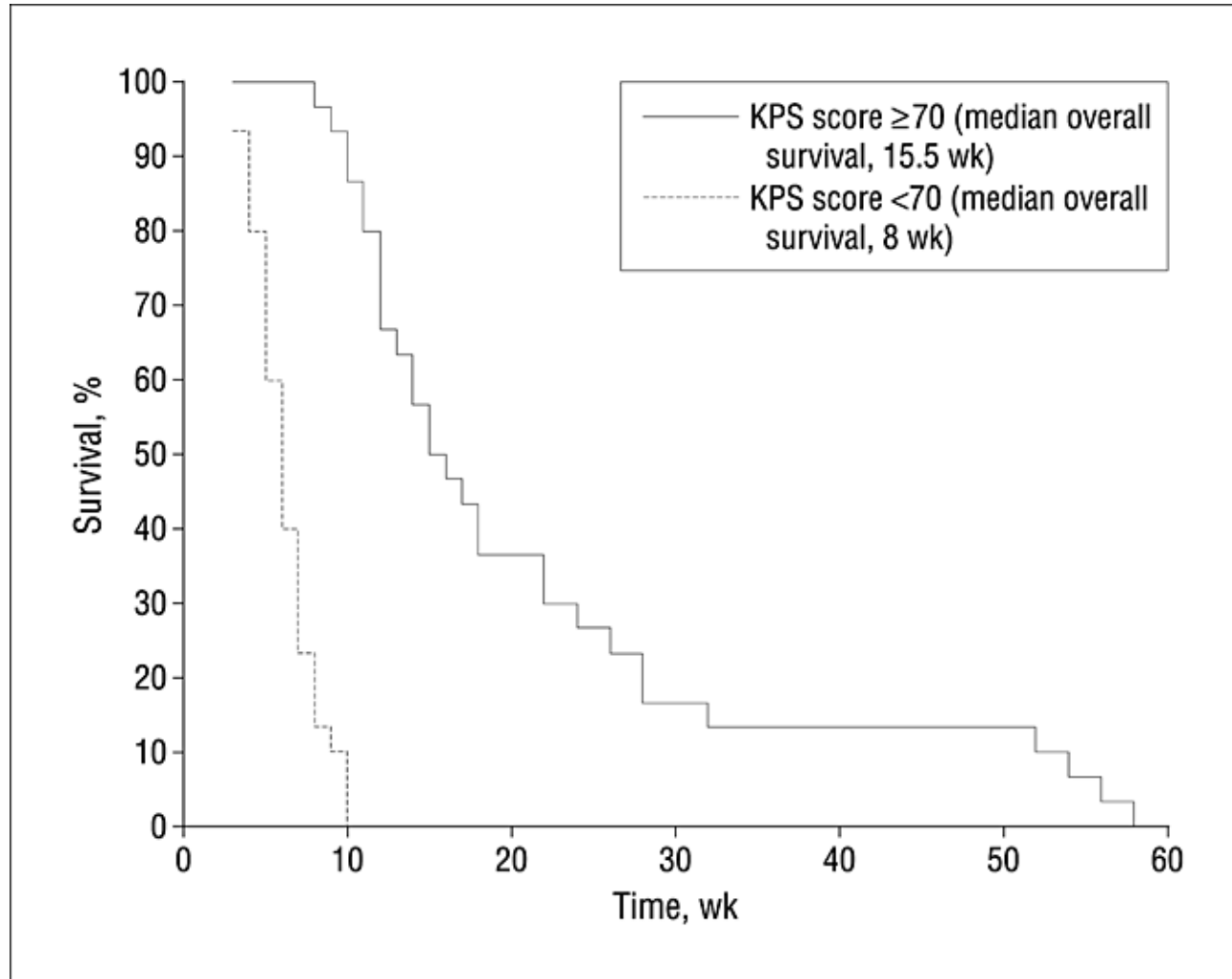
- KPS is easy to determine
- How about in patients matched for all the other bad prognostic signs?
- KPS < 70 vs. KPS > 70 matched for:
  - Age, 1<sup>o</sup> tumor site, site of NM (Cr Ns or cord), treatment (RT and chemo; systemic and intraventricular), CSF compartmentalization, encephalopathy, and bulky CNS disease



# Karnofsky Score

Karnofsky Score (KS)	Definition
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

# Survival in patients with neoplastic meningitis by Karnofsky performance status (KPS) score



Chamberlain, M. C. et al. Arch Neurol 2009;66:74-78.

# Conclusions

- A low Karnofsky performance score predicts poor survival in patients with NM
- Patients with low Karnofsky performance score may best be served by offering supportive care.
- Both CH and JJ were, “on the cusp” at 60-70%

# Survival of Breast Cancer Patients With Meningeal Carcinomatosis

Gauthier et al. *Ann Onc adv acc* 4/10

- Most common cause of nonhematologic MC
- Review of 91 Breast CA patients 2000-2007
- Report clinical and biologic features
- Determine significant prognostic features for response to therapy
- Develop and propose a prognostic score

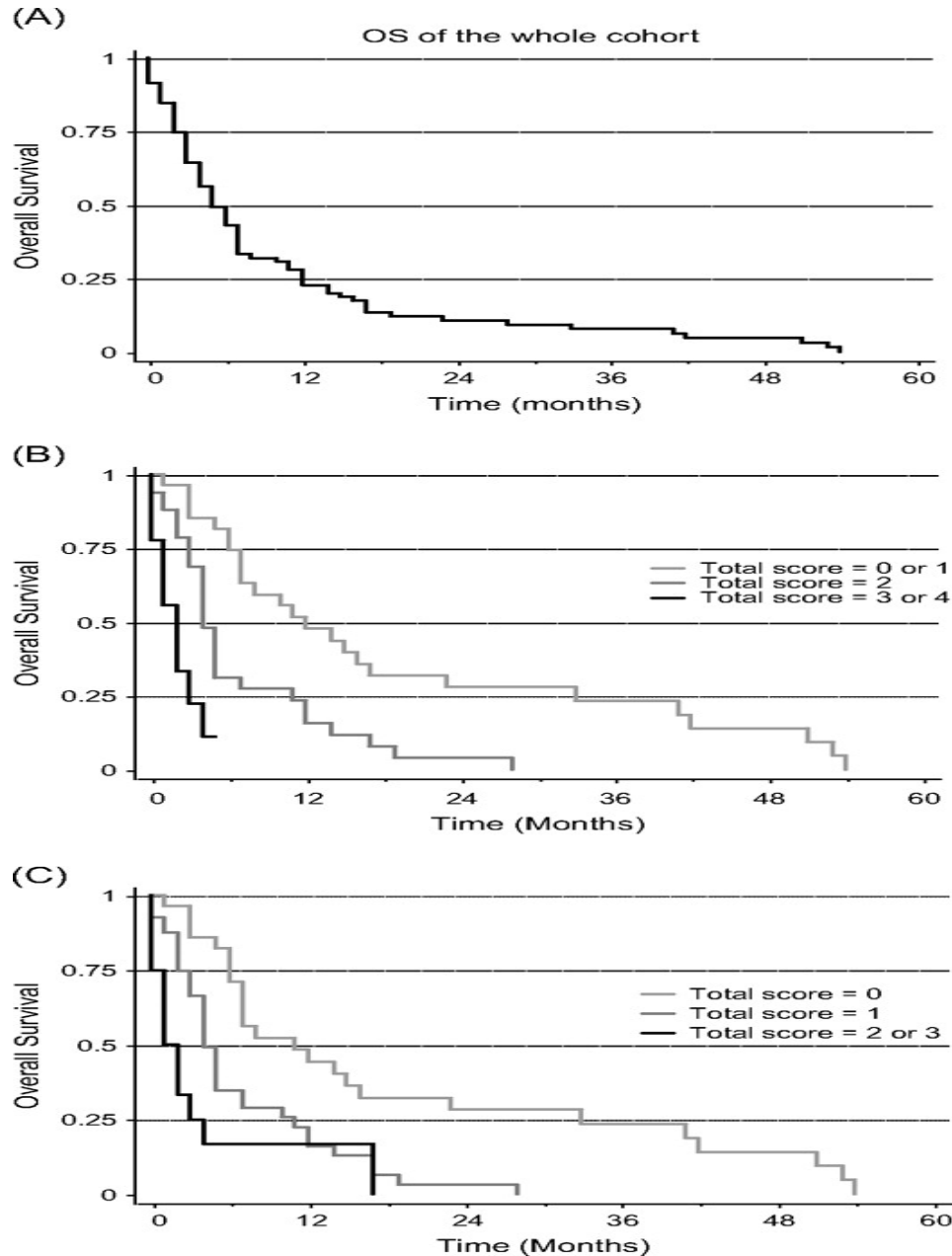
# Results

- Multivariate statistical analysis of prognostic features
- 4 features associated with poor survival
  1. Poor performance status (ECOG 3-4)
  2. Number of prior chemotherapy regimens (>3)
  3. Negative hormone receptor status
  4. High Cyfra 21-1 levels (Br Ca tumor marker)

## ECOG PERFORMANCE STATUS SCALE

ECOG (Zubrod)	Karnofsky	Definitions
0	100	Asymptomatic
1	80-90	Symptomatic, fully ambulatory
2	60-70	Symptomatic, in bed less than 50% of the day
3	40-50	Symptomatic, in bed more than 50% of the day, but not bedridden
4	20-30	Bedridden

**(A–C) Overall survival (OS) and prognostic scores.**



B. ECOG 3-4 = 1  
 HR(+) = 0; (-) = 1  
 CT > 3 lines = 1  
 Cyfra high = 1

C. Eliminated Cyfra  
 (not widely done)

**Both CH and JJ  
 Score = 2 and died  
 at ~ 12 weeks.**  
 Gauthier H et al. Ann Oncol  
 2010;annonc.mdq232

# Treatment

- Despite 3 decades of effort
- Treatment options remain limited
  1. Need to treat entire neuraxis
  2. Close proximity of tumor to neural structures
  3. Limit RT and CT because of neurotoxicity
  4. Blood-CSF Barrier
  5. Intrinsic resistance of solid tumors
  6. Routine presence of other sites of metastatic disease
- 1/3 opt out; 1/3 too sick; 1/3 treated



# Treatment Overview

## ● Surgery

- Occasional meningeal Bx for Dx
- Placement of intraventricular (Ommaya) reservoir for CSF access
- CSF diversionary procedures (V-P shunt)

## ● Radiation

- Focused
- Whole brain
- Spinal

## ● Chemotherapy

- Intrathecal
- Systemic

# Treatment Complications

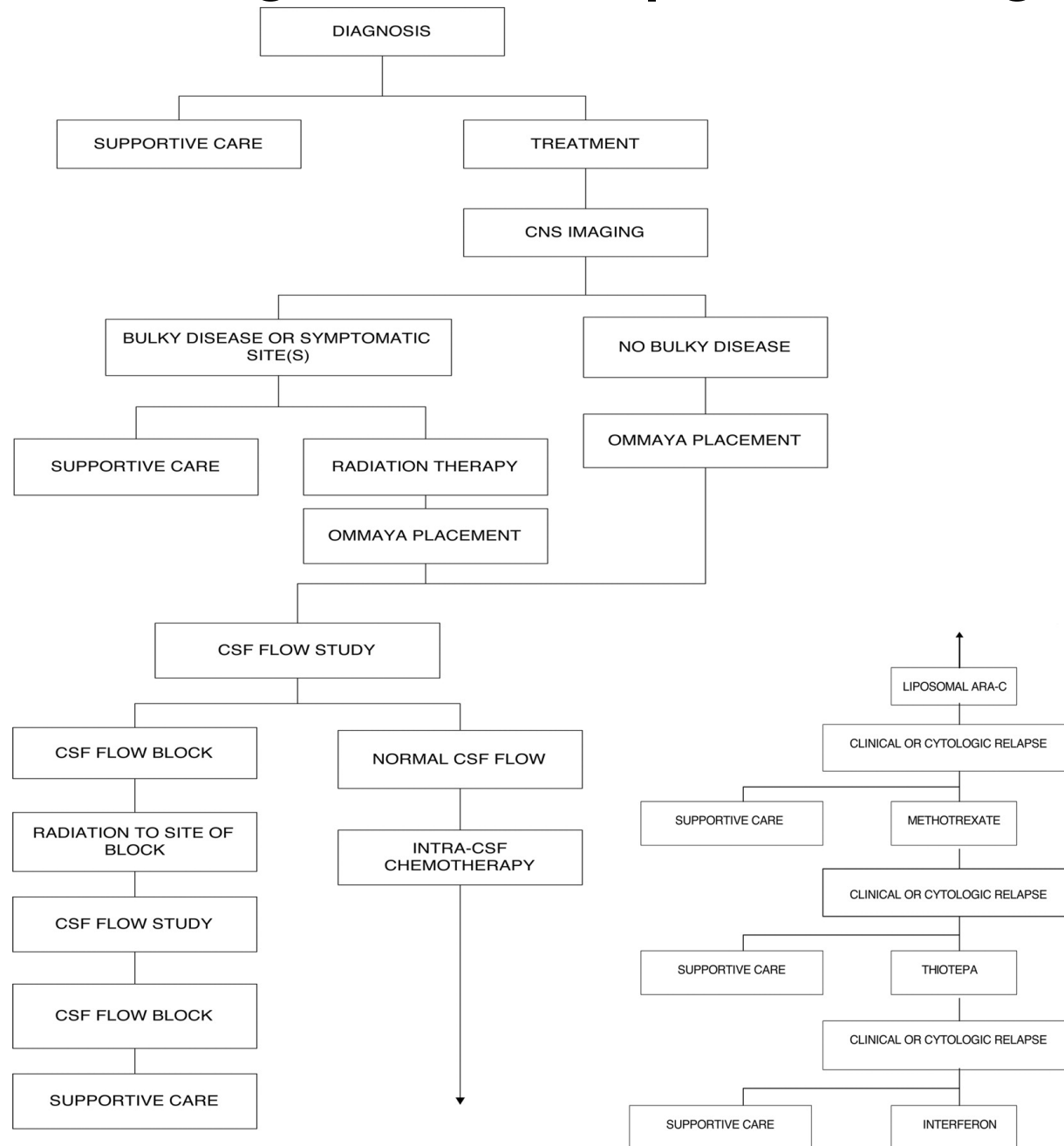
- Ommaya reservoir
  - 1% hemorrhage; 5% infection
- Impaired CSF flow due to obstruction
  - Chemo may cause seizures, arachnoiditis (N/V and MS changes)
- Aseptic meningitis
- Necrotizing leukoencephalopathy
  - Most common with IT Mtx following RT
  - Progressive dementia, debility and death
- Transverse myelitis
  - IT Chemo + RT cord

**Table 56F-6 -- Treatment of Leptomeningeal Metastases**

		Radiation therapy to sites of symptomatic and bulky disease
		Methotrexate (10 mg twice weekly) + leucovorin
		Thiotepa (10 mg twice weekly)
		Cytarabine (50 mg twice weekly)
		Cytarabine (DepoCyt) (50 mg every 2 weeks)
		Systemic chemotherapy (e.g., high-dose methotrexate)
		Optimal treatment of systemic disease

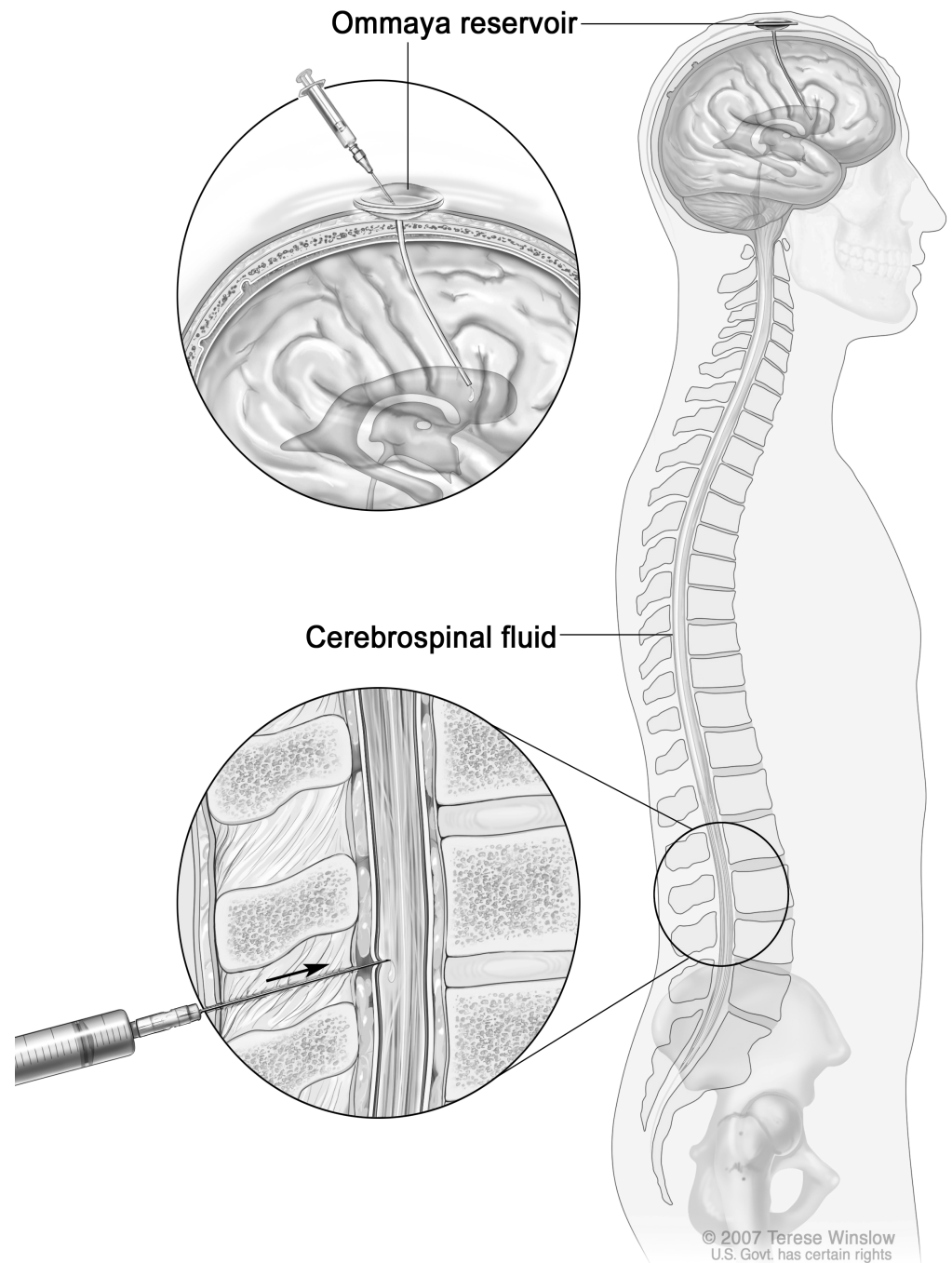
From Bradley: Neurology in Clinical Practice, 5th ed.

# Figure 1. Treatment algorithm of neoplastic meningitis

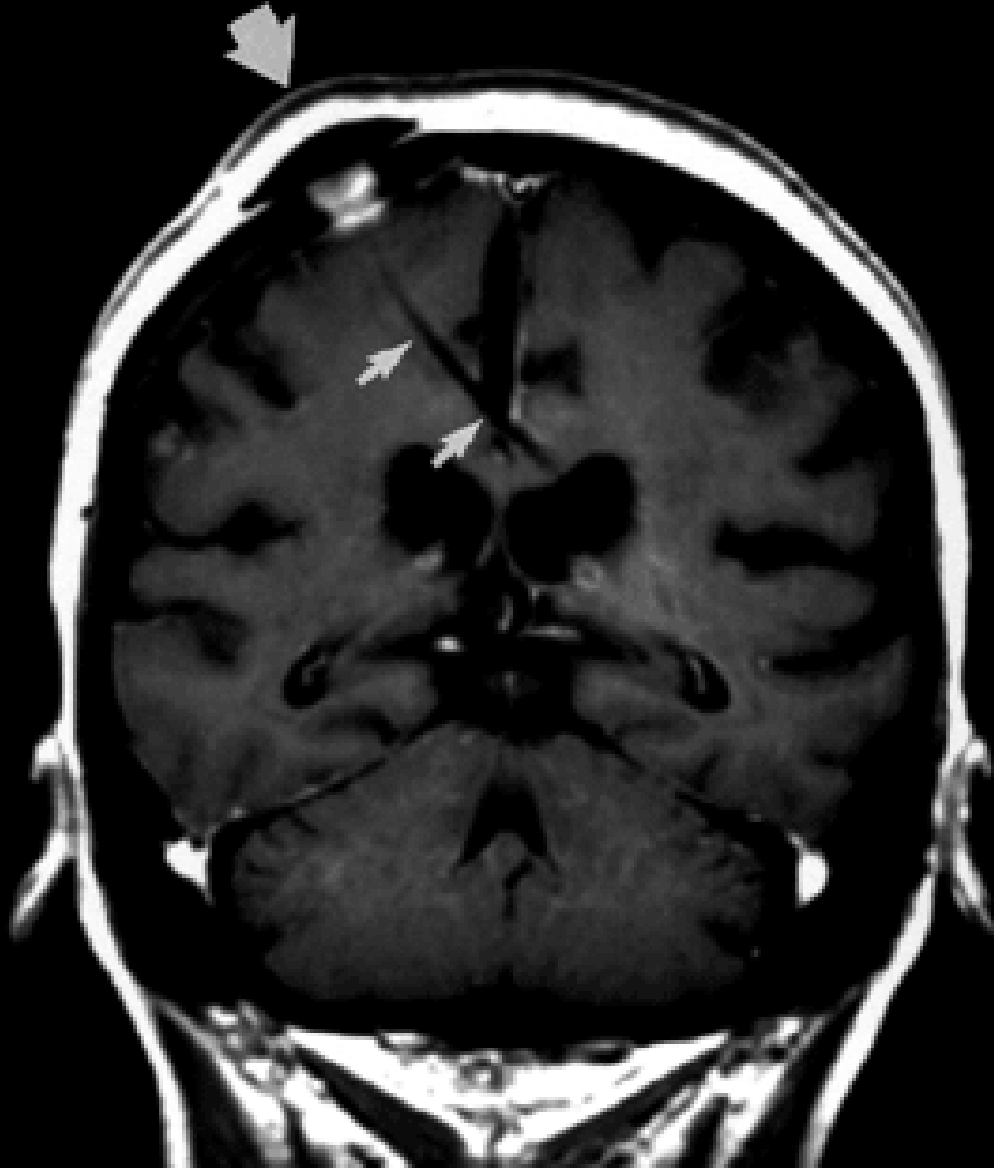


# Ommaya Reservoir

- Vs. LP
- Repeated access
- Better tolerated
  - But a procedure
- LP admin 10% leak
- Improved drug distribution
- Side port to convert to shunt if necessary



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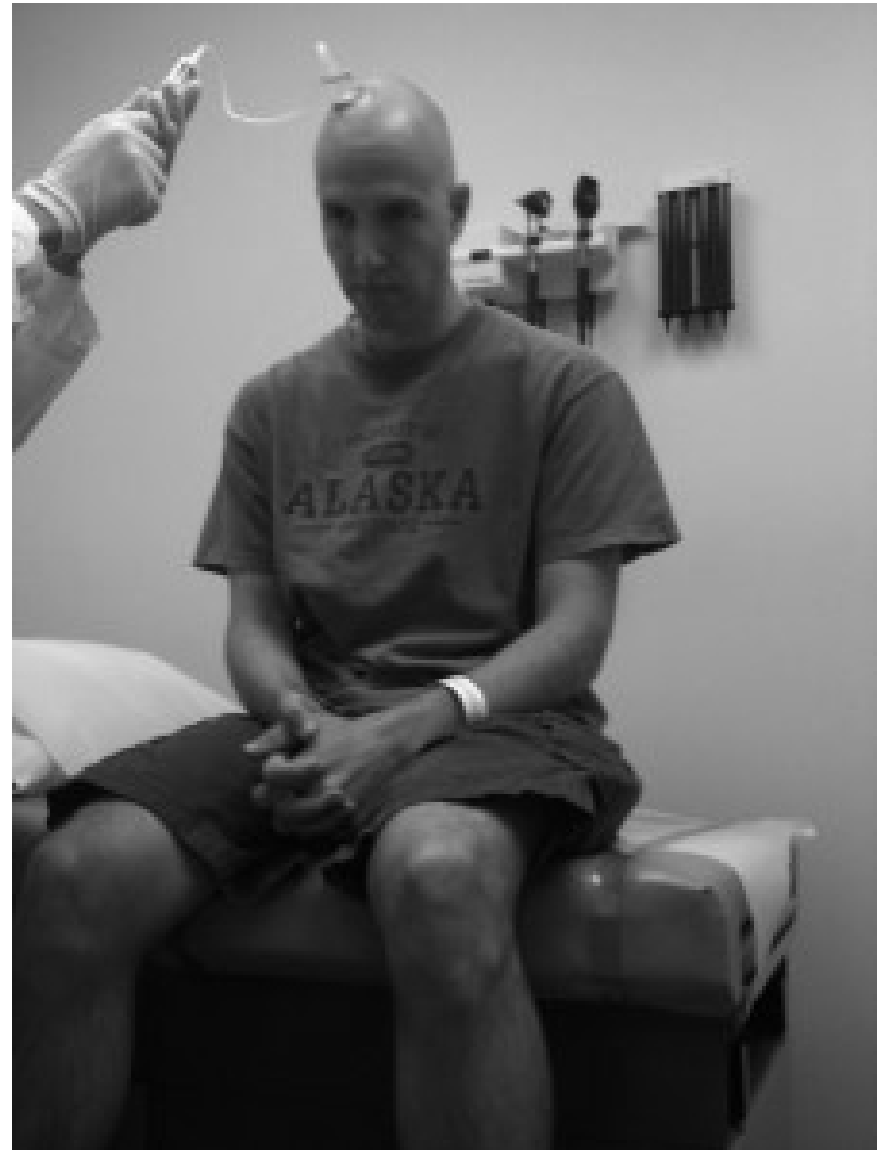


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SE | 1  
TR | 100  
TE | 14  
Tc | 50.00  
4.00 | 2  
Fov | 254.00  
R: 204.4746

TR | 100  
FW | 28.5  
TE | 14  
Tc | 50.00  
4.00 | 2  
Fov | 254.00  
R: 204.4746

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# Experimental Therapies

- New chemotherapeutic agents
- Intrathecal biologic agents, antibodies, and immunoconjugates
- Radioisotopes and radioimmunoconjugates
- Intensive systemic chemotherapy
  - High-dose Mtx with rescue
- Gene therapy



# Intensive Hospice & Palliative Care

- All treatments are palliative!
- No patients are cured of LM!
- All will die! Some of progressive systemic disease but
- Most with progressive neurologic dysfunction with many if not most of the symptoms noted earlier!
- Patients appropriate for aggressive treatment also need aggressive Sx Rx and comprehensive, holistic PC
- All others should get intensive H & PC
- What does that mean?
  - There is no literature to tell us what to expect and what to do RE SxRx and best supportive care
  - H/O and PC texts
  - H/O or PC journals
- Let's write that article!

# Symptoms in Patients Dying of (Breast) Meningeal Carcinomatosis

Services MS et al. *J Impt Stuff* 2010

(from Gauthier  
et al)

<b>Headache</b>	<b>34%</b>	<b>100%</b>
<b>Cranial nerve symptoms</b>	<b>25</b>	<b>100</b>
<b>Cerebellar signs</b>	<b>24</b>	<b>100</b>
<b>Nausea and vomiting</b>	<b>23</b>	<b>100</b>
<b>Visual disturbance</b>	<b>22</b>	<b>100</b>
<b>Radicular pain</b>	<b>21</b>	<b>100</b>
<b>Glascow coma scale &lt; 15</b>	<b>21</b>	<b>100</b>
<b>Paresthesia</b>	<b>19</b>	<b>100</b>
<b>Meningismis</b>	<b>12</b>	<b>100</b>
<b>Motor deficit</b>	<b>11</b>	<b>100</b>
<b>Dysarthria</b>	<b>2</b>	<b>100</b>

# Challenges in Intensive Symptom Management of Leptomeningeal Metastases

Services MS et al. *J Impt Stuff* 2010

- Reporting on our recent series of patients (n=2)
  - We can find more patients (PHO/FMC record review?)
- Severe Headache
  - Steroids, opioids, and complementary therapies
- Radicular pain
  - Steroids, opioids (methadone), gabapentin (or other anticonvulsants (keppra?), ketamine, muscle relaxants (benzos and baclofen)
  - Complementary therapies (PT, massage, guided imagery)
- Nausea & Vomiting
  - Steroids, anticholinergics (cochlear involvement), target every receptor if refractory (haloperidol, ondansetron, antihistamines, anticholinergics, cannabinoids)

# Refractory Pain

- Opioid dosing
- Opioid rotation
  - Fentanyl and methadone
- Maximal adjuvant therapy (neuropathic)
  - Anticonvulsants, antidepressants
  - Ketorolac (Toradol)
  - Ketamine
- Psychosocial and spiritual therapies
- Total sedation

# Use That Ommaya?

- **Intraventricular Administration of Morphine for Control of Intractable Cancer Pain in 90 Patients.** Karavelis et al
- Neurosurgery. 39(1):57-62, July 1996.
- No recent literature
- “We haven’t done that in years.” R Rauck

# Once Daily Administration of Morphine

	Mean	Median	Minimum	Maximum
Age (yr)	57	58	23	80
Pain duration (mo)	10	6	0.5	120
Duration of reservoir use (d)	95	46	1	1362
Morphine dose (mg)	1	1	0.25	4
Quality of analgesia (%)	78	90	0 <sup>a</sup>	100
Duration of analgesia (h)	22	24	0 <sup>a</sup>	72

<sup>a</sup> Complications.

**Theoretically – does it make sense to consider intraventricular administration of other medications using Ommaya reservoir already in place? Need a consultant!**

- Seizures –
  - Keppra, phenytoin, steroids, benzos, midazolam
- Constipation – paresis + opioids
  - Broad spectrum oral agents, MNTX, disimpaction
- Psychosis – hallucinations, delusions, paranoia
  - Haldol, Thorazine, minimize steroids
- Paresis, paresthesia, paralysis – I
  - Intensive personal care
  - Bed, mattress
- Senses - visual (to blind), auditory (to deaf)
  - CH could no longer read; JJ could no longer see
- Anxiety
  - Long-acting benzos, companionship
- Physical space
  - Bed, Mattress
  - Quiet, dark/light, room for PCG(s)

## ● Depression

- Ritalin, Remeron, Effexor
- Complementary, counseling, pastoral care

## ● Social

- Institutionalized for Sx Rx and personal care needs
- Loss of roles
- Counseling, pastoral care, social support

## ● Spiritual

- Fatal + suffering
- Losses
- Profound existential suffering

● JJ - “Why am I still here?!!”

● “I thought I’d wake up dead and in heaven!”

● “Let me go! Don’t be selfish, let me go!”

● Incremental, palliative sedation



# Great Teachers

- CH and JJ
- Medical students
- WE ALL learned so much
- Paybacks...
- A devastating complication with an ominous prognosis and high likelihood of intensive symptom management
- We can do a better job

# Comments & Questions

## Selected References

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