

# Metastasi al SNC da neoplasie della mammella : raccomandazioni di trattamento

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# **BRAIN METASTASES: EPIDEMIOLOGY**

- The most common intracranial tumors, outnumbering primary brain tumors
- Frequency: 20-40% of patients with cancer, being symptomatic during life in 60-75%
- Increasing incidence over time due to improved detection by MRI in asymptomatic patients, better treatment of systemic disease, and aging population

**Table 1.** Incidence of brain metastases among patients with HER2+ breast cancer

Study	Design	No. of patients with metastatic breast cancer	Incidence of CNS metastases (%)	Median survival from CNS diagnosis (mo)
Bendell et al. (6)	Retrospective chart review, all patients initiating trastuzumab between 1998 and 2000	122	34	13
Altaha et al. (29)	Retrospective chart review, patients with HER2-positive breast cancer diagnosed between 1998 and 2003	31	48	Not reported
Clayton et al. (30)	Retrospective chart review, all patients initiating trastuzumab between 1999 and 2002	93	25	5-6
Stemmler et al. (28)	Retrospective chart review, all patients who had received trastuzumab between 2000 and 2004	136	30.9	13
Yau et al. (27)	Retrospective chart review, all patients who had received trastuzumab between 1999 and 2003	87	30 (at 1 y)	9

*Lin and Winer*

Clin Cancer Res 2007;13(6) March 15, 2007

# BRAIN METASTASES

## *Major favorable prognostic factors*

- High performance status (KPS  $\geq$  70 or WHO grade 0-1).
- Absence of systemic metastases (solitary brain metastasis) and controlled primary tumor.
- Age  $\leq$  60-65 years.
- Single lesion

## *Minor favorable prognostic factors*

- Good neurocognitive function.
- Breast primary tumor.
- Metachronous presentation ( $>$  12 months).

Gaspar et al, 1997  
Sperduto et al, 2008-2010

# SURGERY FOR SINGLE BRAIN METASTASIS

- Three phase III studies have compared surgical resection + WBRT to WBRT alone.
- The American (*Patchell et al, 1990*) and the Dutch (*Vecht et al, 1993*) studies, including mainly patients with controlled or limited systemic disease, have reported a significant survival advantage for surgery + WBRT over WBRT alone (7-10 versus 3-6 mos).
- The Canadian study (*Mintz et al, 1996*), including mainly patients with active systemic disease and lower performance status, did not show any difference between the two treatment arms.
- In selected patients with recurrent metastasis surgery allows palliation of symptoms and improvement of survival

# STEREOTACTIC RADIOSURGERY FOR SINGLE BRAIN METASTASIS

- Local tumor control (shrinkage or no growth) in 80-90% of patients, with median survival of 7-12 months.
- Results after radiosurgery comparable to those after surgery, but lack of randomized studies.
- The addition of radiosurgery to WBRT (“boost”) significantly improves survival (6.9 vs 4.9 months).

*Linskey et al, 2010*

# WBRT ALONE

- Treatment of choice for patients with single or multiple lesions not amenable to surgery or radiosurgery, especially those with an active systemic disease.
- Survival between 3 and 6 months in two thirds of patients with a neurological improvement after steroids and WBRT.
- Tumor volume reduction associated with improved cognitive function and survival.
- Different fractionation schedules comparable → standard treatment 30 Gy in 10 fractions.
- Supportive care alone as an alternative for non-ambulatory patients

*Eichler and Loeffler, 2007*  
*Barnes et al, 2010*

# CAN WBRT BE AVOIDED AFTER COMPLETE RESECTION OR RADIOSURGERY ?

## *Arguments in favour of adjuvant WBRT*

- WBRT destroys microscopic metastatic deposits at original tumor site or at distant intracranial locations.
- Recurrent brain metastases present most commonly with symptomatic neurological deficit and/or neurocognitive decline (*Regine et al , 2002*)
- When adjuvant WBRT is omitted , there is an increased need for salvage treatments and it is not clearly defined their value in reversing the neurological symptoms and signs



# CAN WBRT BE AVOIDED AFTER COMPLETE RESECTION OR RADIOSURGERY ?

## *Arguments against adjuvant WBRT*

- MRI has increased the chance of detecting small lesions.
- Hypofractionated treatments (i.e. 30 Gy /10 fractions ) can be ineffective (especially in radioresistant tumors).
- Hypofractionated treatments carry a considerable risk of late neurotoxicity in long surviving patients ( $\geq 1$  year).
- Treatments at progression (WBRT, radiosurgery, surgery) are effective.

## WBRT AFTER COMPLETE SURGERY

American phase III study (Patchell et al, 1998):

- Adjuvant WBRT significantly reduces local and distant CNS relapses (18% versus 70%) without improving overall survival and functionally independent survival.
- Adjuvant WBRT decreases the rate of death from neurological causes (44% vs 14%).

MD Anderson retrospective study (McPherson et al, 2010):

adjuvant WBRT not a significant independent predictor of survival in the multivariate analysis

# WBRT IN CONJUNCTION WITH RADIOSURGERY

Japanese phase III study (Aoyama et al, 2006) :

- Adjuvant WBRT improves local control and reduces the risk of new distant brain metastases without influencing overall survival.
- No difference in the risk of death from neurological causes.

Multi-institutional American retrospective study (Sneed et al, 2002) :

- median survival 15.2 months after adjuvant WBRT vs 14 months after observation (RPA Class I)
- median survival 8.2 months after adjuvant WBRT vs 7.0 months after observation (RPA Class II)

# Adjuvant Whole Brain Radiotherapy versus Observation after Radiosurgery or Surgical Resection of 1-3 Cerebral Metastases: Results of the EORTC 22952-26001 Study

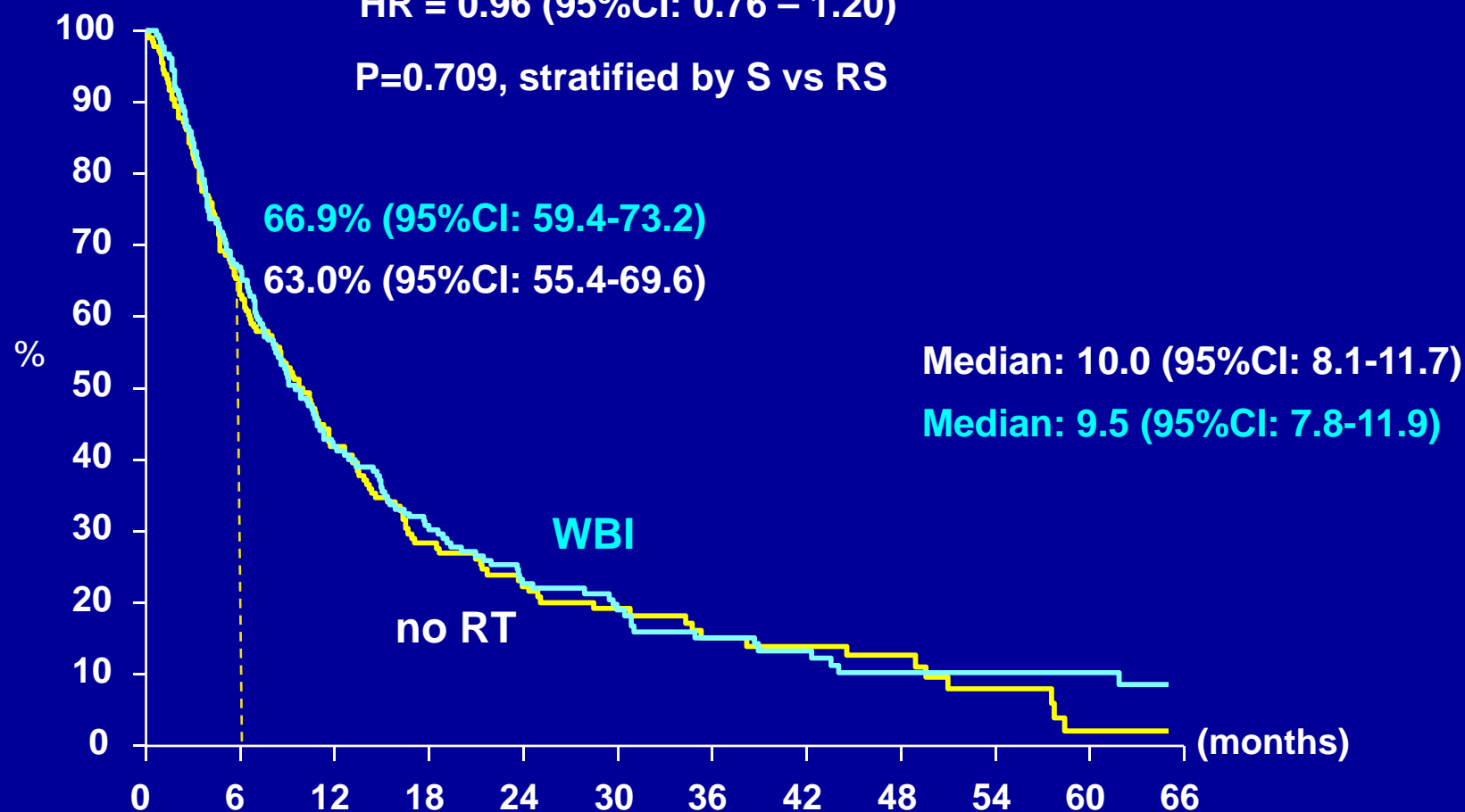
**M. Kocher<sup>2</sup>, R. Soffiatti<sup>1</sup>, M.U. Abacioglu<sup>3</sup>, S. Villa<sup>4</sup>, F. Fauchon<sup>5</sup>, B.G. Baumert<sup>6</sup>, L. Fariselli<sup>7</sup>, T. Tzuk-Shina<sup>8</sup>, L. Collette<sup>9</sup>, R.P. Mueller<sup>2</sup>**

<sup>1</sup>University of Torino, Torino, Italy; <sup>2</sup>University of Cologne, Koeln, Germany; <sup>3</sup>Marmara University Hospital, Istanbul, Turkey; <sup>4</sup>Hospital Germans Trias i Pujol ICO, Barcelona, Spain; <sup>5</sup>Centre Haute Énergie, Nice, France; <sup>6</sup>Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands; <sup>7</sup>Istituto Nazionale Neurologico Carlo Besta, Milano, Italy; <sup>8</sup>Rambam Health Care Campus Oncology Institute, Haifa, Israel; <sup>9</sup>EORTC Headquarters, Brussels, Belgium.

# Primary endpoint: Survival with $PS \leq 2$ (ITT)

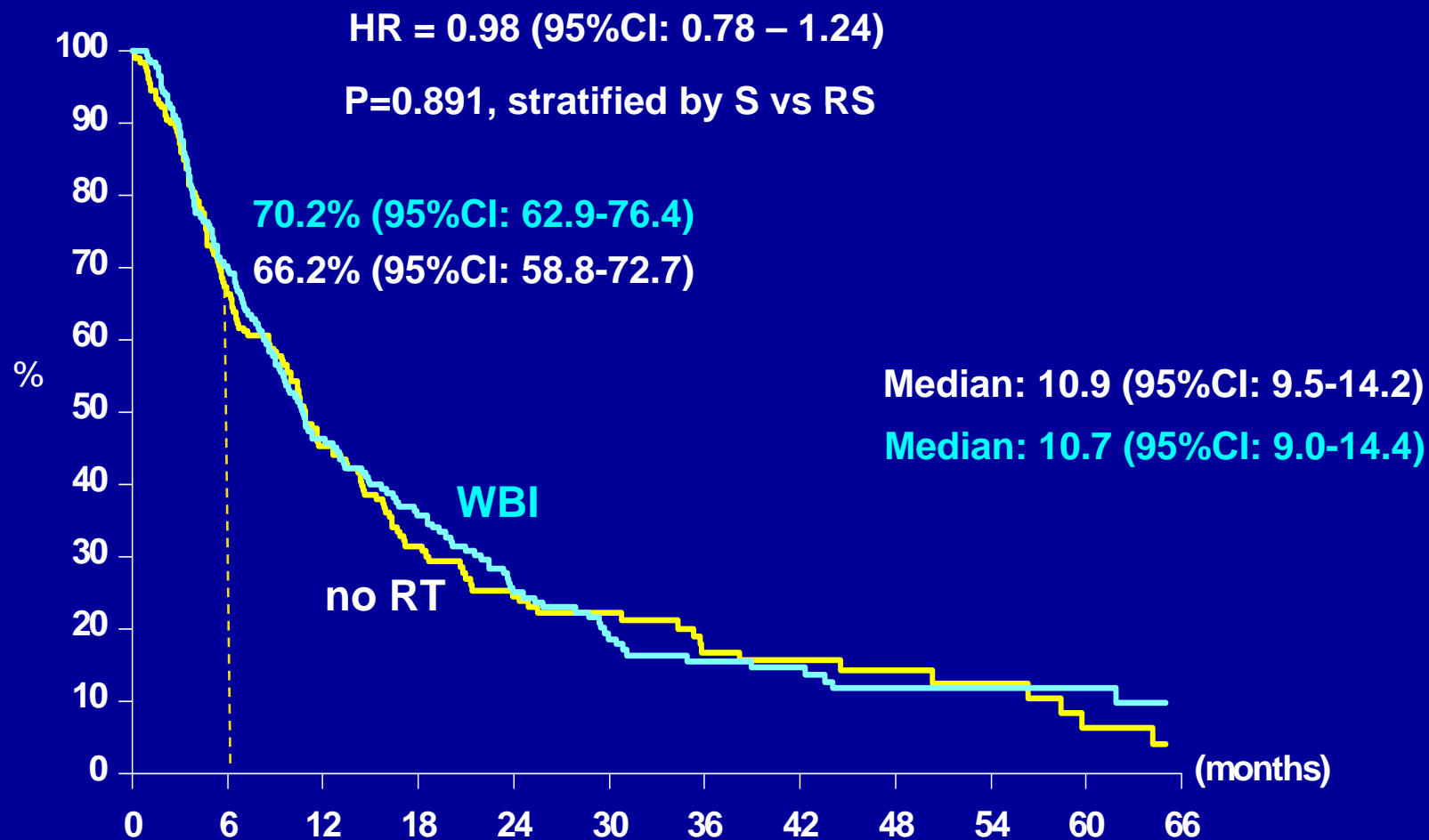
HR = 0.96 (95%CI: 0.76 – 1.20)

P=0.709, stratified by S vs RS



<u>O</u>	<u>N</u>	Number of patients at risk :										Treatment	
149	179	112	71	41	29	19	14	11	8	5	1		no RT
152	180	118	73	52	34	25	17	13	10	9	7		WBI

# Overall Survival (ITT)



O	N	Number of patients at risk :										Treatment
143	179	117	75	44	31	22	15	12	9	7	3	no RT
149	180	124	80	61	38	25	18	15	11	9	7	WBI

# Progression status

	No RT (N=179)	WBI (N=180)	Total (N=359)
All progressions, site of first progression:	160 (89.4)	143 (79.4)	303 (84.4)
<i>Intracranial</i>	<i>81 (45.3)</i>	<i>50 (27.8)</i>	<i>131 (36.5)</i>
<i>Extracranial</i>	<i>60 (33.5)</i>	<i>83 (46.1)</i>	<i>143 (39.8)</i>
<i>Both</i>	<i>19 (10.6)</i>	<i>10 (5.6)</i>	<i>29 (8.1)</i>

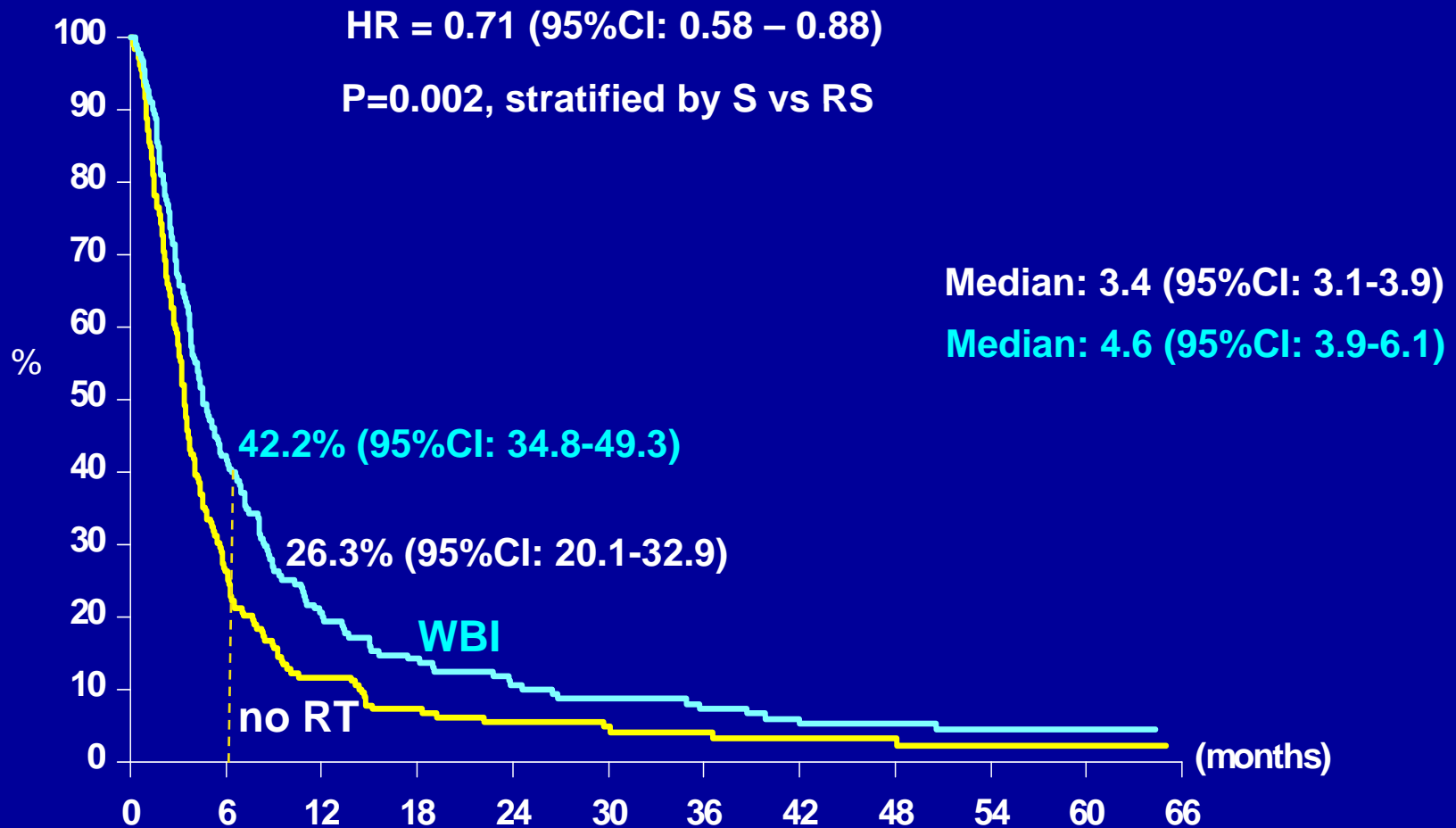
All Intracranial Progressions, site:	No RT (N=139)	WBI (N=87)	Total (N=226)
<i>New sites</i>	<i>60* (43.2)</i>	<i>44** (50.6)</i>	<i>104 (46.0)</i>
<i>Previous sites</i>	<i>54 (38.8)</i>	<i>31 (35.6)</i>	<i>85 (37.6)</i>
<i>Both</i>	<i>19 (13.7)</i>	<i>7 (8.0)</i>	<i>26 (11.5)</i>
<i>Unknown</i>	<i>6 (4.3)</i>	<i>5 (5.7)</i>	<i>11 (4.9)</i>

All Extracranial Progressions, site:	No RT (N=115)	WBI (N=119)	Total (N=234)
<i>Primary tumor</i>	<i>31 (27.0)</i>	<i>26 (21.8)</i>	<i>57 (24.4)</i>
<i>Other metastases</i>	<i>75 (65.2)</i>	<i>82 (68.9)</i>	<i>157 (67.1)</i>
<i>Both</i>	<i>4 (3.5)</i>	<i>2 (1.7)</i>	<i>6 (2.6)</i>
<i>Unknown</i>	<i>5 (4.3)</i>	<i>9 (7.6)</i>	<i>14 (6.0)</i>

\* 4 pts with leptomeningeal dissemination

\*\* 4 pts with leptomeningeal dissemination

# Progression Free Survival (ITT)



O	N	Number of patients at risk :										Treatment
174	179	47	21	13	10	6	5	4	3	2	2	no RT
167	180	75	36	24	17	14	11	8	8	5	3	WBI



## **WBRT MAY NEGATIVELY IMPACT HEALTH-RELATED QUALITY OF LIFE (HRQL)**

- Increasing interest for HRQL as an endpoint for treatment comparisons in many cancer types, especially in advanced stages (Bottomley et al, 2005)
- No data available so far regarding the impact of adjuvant WBRT on HRQL of patients with brain metastases.
- After PCI for SCLC significant, but reversible, short-term (3 months) negative impact on selected HRQL scales, such as fatigue, hair loss, or cognitive functioning (Slotman et al, 2009).

EORTC 22952-26001

Quality of Life results of an EORTC phase III  
randomized trial of adjuvant Whole Brain  
Radiotherapy versus Observation after Radio  
surgery or Surgical Resection of 1-3 Cerebral  
Metastases of solid tumors

HRQoL results

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G. Baumert<sup>6</sup>, L. Fariselli<sup>7</sup>, R. P. Mueller<sup>2</sup>, G. Tridello<sup>8</sup>, A. Bottomley<sup>8</sup>

ON BEHALF OF EORTC RADIOTHERAPY AND BRAIN TUMOUR GROUP STUDY GROUPS

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2.University of Cologne, Radiation Oncology, Koeln, Germany – 3.Marmara University Hospital,  
Radiation Oncology, Istanbul, Turkey – 4.Hospital Germans Trias i Pujol, ICO, Radiation Oncology,

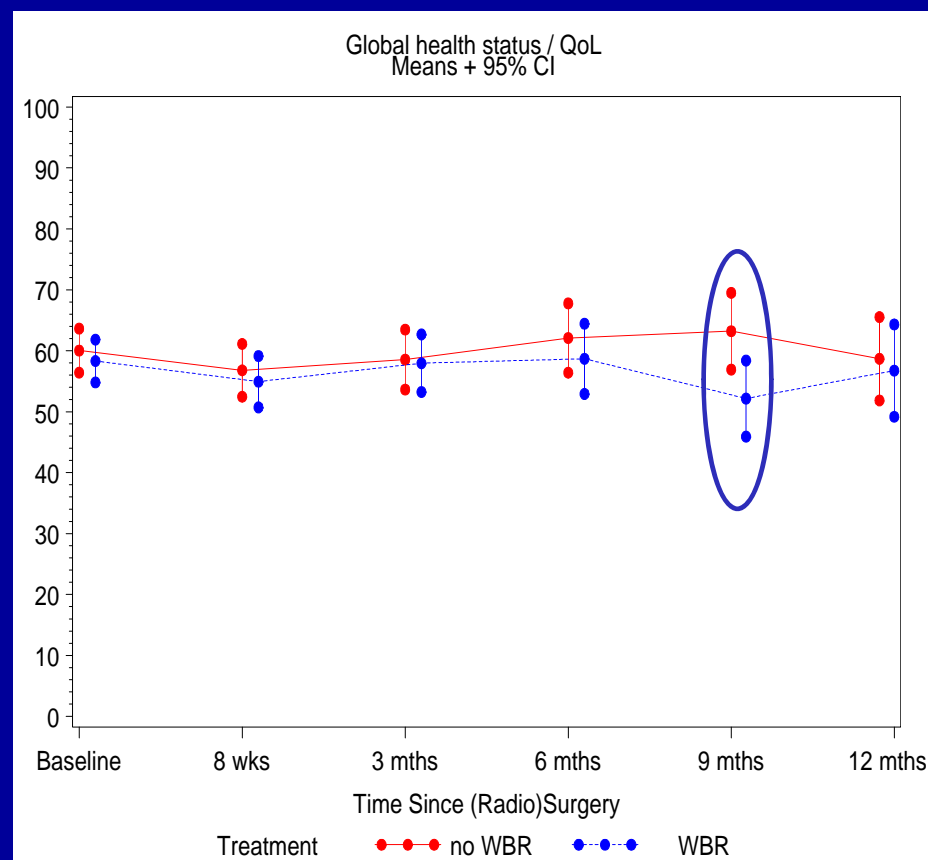
Barcelona, Spain – 5.Centre Haute Energie, Nice, France – 6.Radiation-Oncology (MAASTRO),

Maastricht University Medical Centre (MUMC), GROW (School for Oncology), Maastricht,  
Netherlands – 7.Fondazione Istituto Neurologico “Carlo Besta”, Milano – 8.EORTC Headquarters,  
Brussels, Belgium

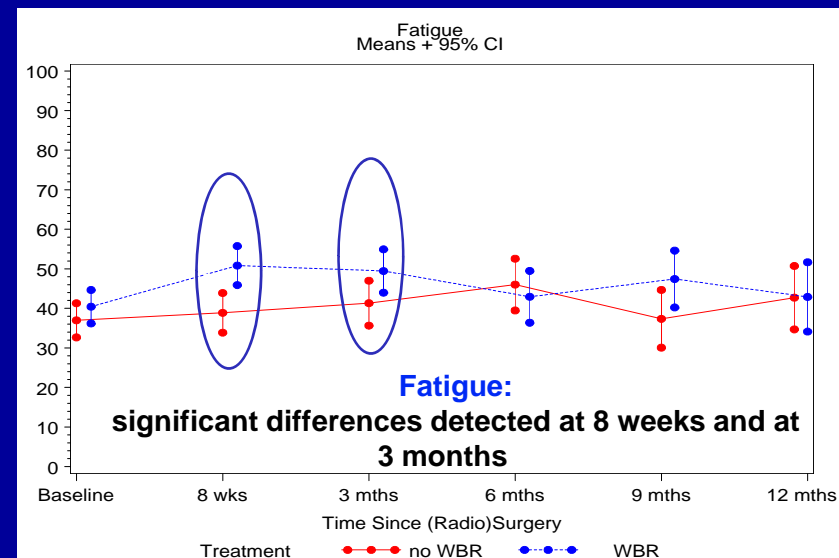
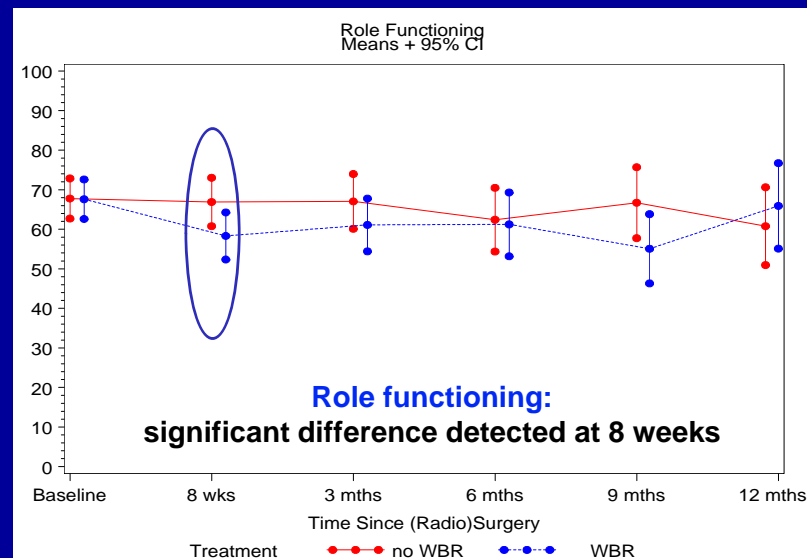
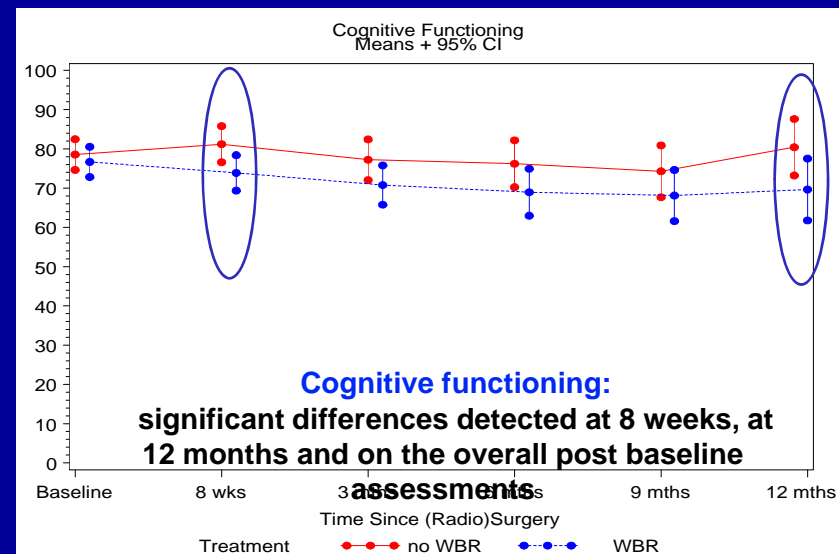
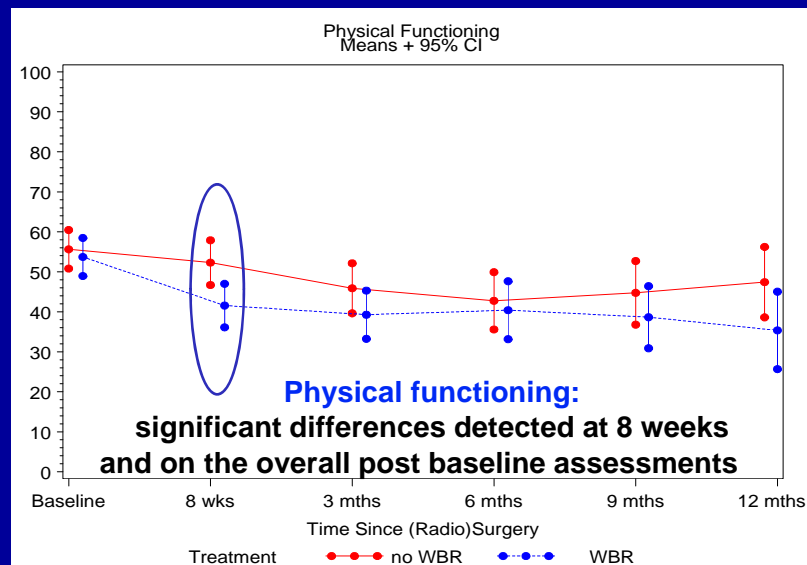
ASCO 2010, submitted

# Results: Global health status / QoL

Timepoint	WBI Estimate (Std.Err.)	No WBI Estimate (Std.Err.)	Treatment difference p-value
<b>Baseline</b>	<b>58.3 (1.8)</b>	<b>60.0 (1.8)</b>	<b>0.5</b>
<b>8 wks</b>	<b>54.9 (2.1)</b>	<b>56.8 (2.2)</b>	<b>0.5</b>
<b>3 mths</b>	<b>58.0 (2.4)</b>	<b>58.6 (2.5)</b>	<b>0.9</b>
<b>6 mths</b>	<b>58.7 (2.9)</b>	<b>62.1 (2.9)</b>	<b>0.4</b>
<b>9 mths</b>	<b>52.2 (3.2)</b>	<b>63.2 (3.2)</b>	<b>0.01</b>
<b>12 mths</b>	<b>56.8 (3.9)</b>	<b>58.7 (3.5)</b>	<b>0.7</b>
<b>Overall post baseline</b>			<b>0.1</b>



# Results: secondary QoL endpoints



## **WBRT MAY NEGATIVELY AFFECT COGNITIVE FUNCTIONS**

- Dementia occurs predominantly with large size fractions (4-6 Gy) that are not used anymore
- The true incidence of subtle cognitive deficits in long-term survivors (>1 year), when using conventional regimens (30 Gy, 10 fractions), is unknown.
- Long-term survivors frequently develop overtime changes on MRI, such as cortical atrophy, hyperintensity of the white matter in T<sub>2</sub>/FLAIR images, hydrocephalus, but the incidence of clinical concomitants has not been studied.

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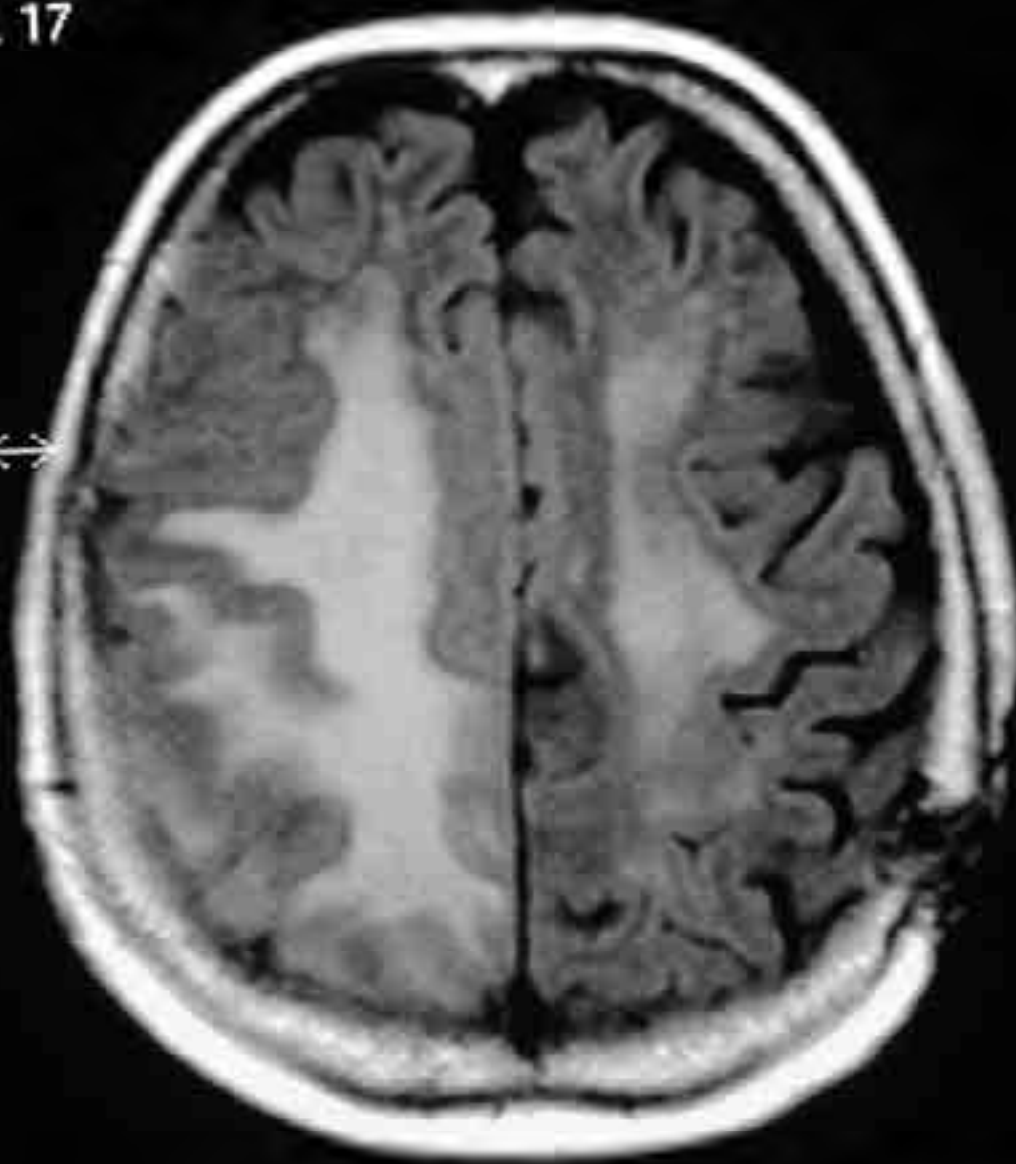
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## EARLY COGNITIVE DECLINE AFTER WBRT

- Early neurocognitive decline can occur within the first 1-4 months (Li et al, 2007; Welzel et al, 2008; Chang et al, 2009)
- Verbal and short-term memory recall (mediated by hippocampus) are affected (Chang et al, 2009; Sun et al, 2010)
- Unknown whether this early decline in memory is associated with long-term and/or permanent decline (Aoyama et al, 2007; Sun et al, 2010)

# **NEW APPROACHES TO AVOID COGNITIVE DYSFUNCTIONS AFTER WBRT**

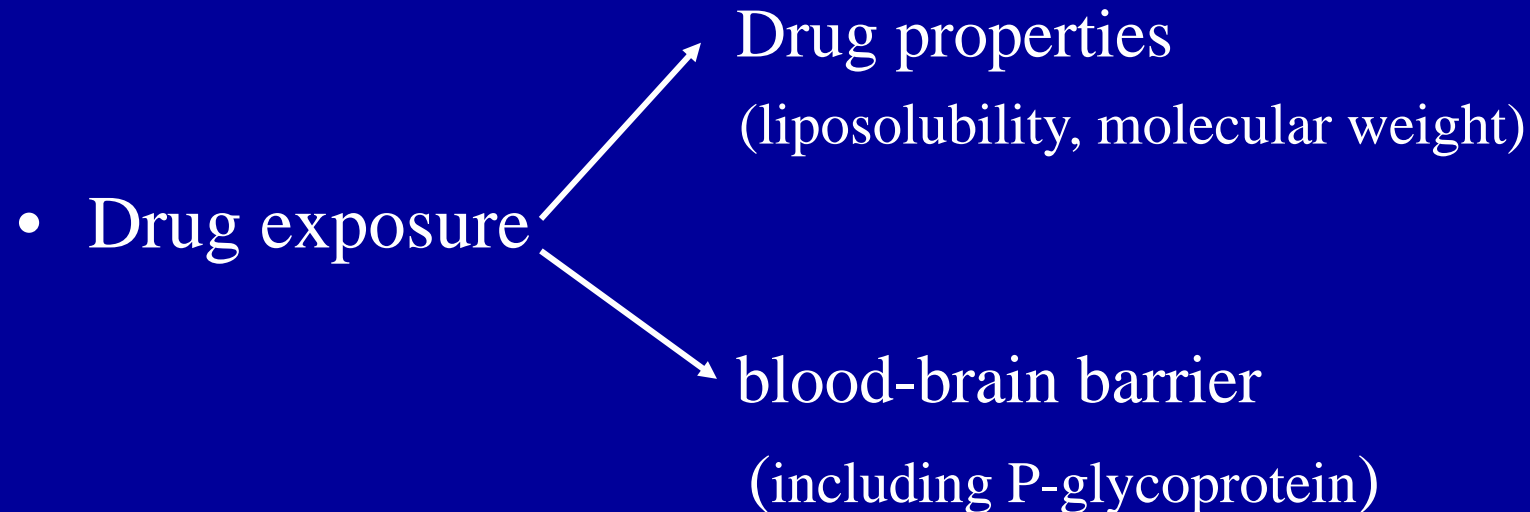
- Hippocampus avoidance with intensity modulated radiotherapy (Ghia et al, 2007; Gutierrez et al, 2007; Gondi et al, 2010; Hsu et al, 2010)
- Use of “protective” drugs (memantine) (ongoing RTOG trial)
- Identification of subgroups of patients at higher risk of developing cognitive deficits

Soffietti et al, 2008  
Gondi et al, 2010



# Chemotherapy of brain metastases: factors influencing the efficacy

- Sensitivity of neoplastic cells



**TABLE 6.2. Brain capillary permeability of chemotherapeutic agents<sup>a</sup>**

High	Intermediate		Low
●Nimustine	●Temozolomide	●Etoposide/Teniposide	●Doxorubicin
●Carmustine	●Cytarabine	●Cisplatin/Carboplatin <sup>b</sup>	●Vincristine
●Lomustine	●Topotecan	●Irinotecan <sup>b</sup>	●Taxanes
●Procarbazine	●Hydroxyurea	●Bleomycin	●Gemcitabine <sup>b</sup>
●Thiotepa		●Methotrexate	●Proteins (e.g., interferon-alpha, Trastuzumab)

<sup>a</sup> Information based on Refs. 9, 14, 15, 24, 39, 53, 54, 69, 73, 74, 79, 108, 110, and 111.

<sup>b</sup> These relationships were surmised based on physical size and hydrophobicity of these drugs.

# LESSONS FROM CLINICAL STUDIES

- Response rates of brain metastases reflect the sensitivity of the primary tumor: relatively high response rates in SCLC (30-80%), intermediate rates in breast cancer (30-50%) and NSCLC (10-30%) and low rates in melanoma (10-15%)
- Higher response rates are observed in newly-diagnosed chemotherapy-naïve patients
- Response in the brain does not always parallel that in the extracranial sites
- It is still uncertain if the response to chemotherapy of brain metastases from mostly chemosensitive tumors is of the same order of that observed after radiotherapy

# ASSOCIATION OF CHEMOTHERAPY AND RADIOTHERAPY

Few randomized studies have compared chemotherapy (temozolomide, topotecan) plus WBRT with chemotherapy or WBRT alone (in patients with metastases from SCLC, NSCLC, breast cancer and melanoma )

*As a general conclusion:* even in case of higher response rate and/or longer progression-free survival after combined treatment → overall survival not different

Eichler and Loeffler, 2007

Soffietti et al, 2008

## Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer

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**Abstract** **Purpose:** Brain metastases develop in one third of patients with advanced HER2+ breast cancer. Effective therapy for patients with central nervous system (CNS) progression after cranial radiation is extremely limited and represents a major clinical challenge. Lapatinib, an epidermal growth factor receptor/HER2 inhibitor, was associated with regressions of CNS lesions in a small phase 2 trial. The current study was done to further evaluate the CNS activity of lapatinib. The study was later amended to allow patients who progressed on lapatinib the option of receiving lapatinib plus capecitabine.

**Experimental Design:** Eligible patients had HER2+ breast cancer, progressive brain metastases, prior trastuzumab, and cranial radiotherapy. The primary end point was CNS objective response, defined as  $\geq 50\%$  volumetric reduction of CNS lesion(s) in the absence of increasing steroid use, progressive neurologic signs and symptoms, or progressive extra-CNS disease.

**Results:** Two-hundred and forty-two patients entered the study. CNS objective responses to lapatinib were observed in 6% of patients. In an exploratory analysis, 21% of patients experienced a  $\geq 20\%$  volumetric reduction in their CNS lesions. An association was observed between volumetric reduction and improvement in progression-free survival and neurologic signs and symptoms. Of the 50 evaluable patients who entered the lapatinib plus capecitabine extension, 20% experienced a CNS objective response and 40% experienced a  $\geq 20\%$  volumetric reduction in their CNS lesions.

**Conclusions:** This study confirms the modest CNS antitumor activity of lapatinib. Additional responses were observed with the combination of lapatinib and capecitabine. Further studies of lapatinib-based regimens for CNS metastases from HER2+ breast cancer are warranted.

## Targeted therapies for brain metastases from breast cancer

- lapatinib + capecitabine
- lapatinib and WBRT
- pan-erb B receptor inhibitors (CI-1033)
- bevacizumab alone
- bevacizumab + cytotoxic agents
- bevacizumab + lapatinib
- vorinostat



**Cancer Therapy: Clinical**

## Bevacizumab Safety in Patients with Central Nervous System Metastases

Benjamin Besse<sup>1</sup>, Susan F. Lasserre<sup>2</sup>, P  ter Compton<sup>1</sup>, Jane Huang<sup>2</sup>,  
Stella Augustus<sup>2</sup>, and Ulrich Peter Roh  <sup>2</sup>

### Abstract

**Purpose:** Patients with central nervous system (CNS) metastases were excluded from bevacizumab trials following a case of fatal cerebral hemorrhage in a patient with hepatocellular carcinoma in 1997. Safety information for bevacizumab-treated patients with CNS metastases was reviewed to determine whether general exclusion of these patients from bevacizumab treatment is still justified.

**Experimental Design:** A retrospective exploratory analysis was conducted using datasets from 13 randomized controlled phase II/III trials (dataset A), two open-label single-arm safety trials (dataset B), and two prospective studies including patients with treated CNS metastases (dataset C). In datasets A and B, known CNS metastasis was an exclusion criterion; patients with CNS metastasis had unrecognized CNS metastases at study entry or developed them during the trial. All reported cerebral hemorrhage grades in patients with CNS metastases were quantified.

**Results:** In dataset A, occult brain metastases were identified in 187 of 8,443 patients (91 in bevacizumab arms and 96 in non-bevacizumab arms). Three bevacizumab-treated patients (3.3%) developed grade 4 cerebral hemorrhage, whereas one control-arm patient (1.0%) developed grade 5 cerebral hemorrhage. In dataset B, 321 of 4,382 patients had initially occult CNS metastases, in whom two grade 1 and one grade 3 cerebral hemorrhage (0.9%) were reported. In 131 patients with treated CNS metastases in dataset C, one bevacizumab-treated patient (0.8%) developed grade 2 cerebral hemorrhage.

**Conclusions:** In this selected population, patients with CNS metastases are at similar risk of developing cerebral hemorrhage, independent of bevacizumab therapy. Consequently, such patients with CNS metastases from advanced/metastatic breast cancer, non-small cell lung carcinoma, and renal and colorectal cancer should not be generally excluded from bevacizumab therapy or clinical trials. *Clin Cancer Res*; 16(1): 269-78.   2010 AACR.

# ANTIEPILEPTIC DRUGS AND CHEMOTHERAPY

- Several antiepileptic drugs (phenobarbital, phenytoin, carbamazepine) are metabolized by the cytochrome P450
- These drugs may accelerate the metabolism of chemotherapeutic agents that are metabolized by cytochrome P450, such as paclitaxel, CPT-11, vinorelbine, cyclophosphamide, ifosfamide, doxorubicin, etoposide, teniposide, vinca alkaloids, thus reducing their efficacy
- Molecular agents such as TK inhibitors (gefitinib, erlotinib, imatinib) are metabolized through the P450 → interactions
- Non-inducing antiepileptic drugs (valproate, gabapentin, topiramate, levetiracetam, lamotrigine) must be chosen for patients with epileptic seizures



# NEOPLASTIC MENINGITIS (NM)

- A disease of the entire neuraxis, characterized by invasion of the leptomeninges/cerebrospinal fluid (CSF) by cancer cells
- Increasing incidence due to improvements in diagnosis (MRI) and outcome of cancer patients because of more effective treatment of the systemic disease
- Still underestimated

# INCIDENCE BY TUMOR TYPE

- 7-15% of patients with non-Hodgkin's lymphoma
- 5-15% of patients with leukemias
- 4-15% of patients with solid tumors
- Up to 10% of patients with primary brain tumors

# INCIDENCE OF CARCINOMATOUS MENINGITIS BY PRIMARY TUMOR SITE

- Breast → 12 - 43%
- Lung → 10 - 26% \*
- Melanoma → 17 - 25%
- Gastrointestinal → 4 - 14%
- Other primary → rare
- Unknown primary → 1 - 7%

\* Both small and non-small cell cancer

# NATURAL HISTORY OF CARCINOMATOUS MENINGITIS

- Coexistent active systemic disease > 70 %
- Absent/ stable systemic disease 20 %
- First sign of neoplastic disease 5-10 %
- Concomitant brain metastases 50-60%

# CLINICAL FEATURES

- Clinically, neoplastic meningitis (NM) is a multifocal disease that may involve the entire neuraxis at different levels: brain, cranial nerves, spinal cord and spinal roots.
- The key feature is therefore the coexistence of multifocal signs and symptoms

# CLINICAL FEATURES

- At an early stage, when isolated neurological symptoms develop, the diagnosis is difficult
- Conversely, due to the dramatic evolution of signs and symptoms, when the clinical picture is clear, many patients are not candidate for treatment

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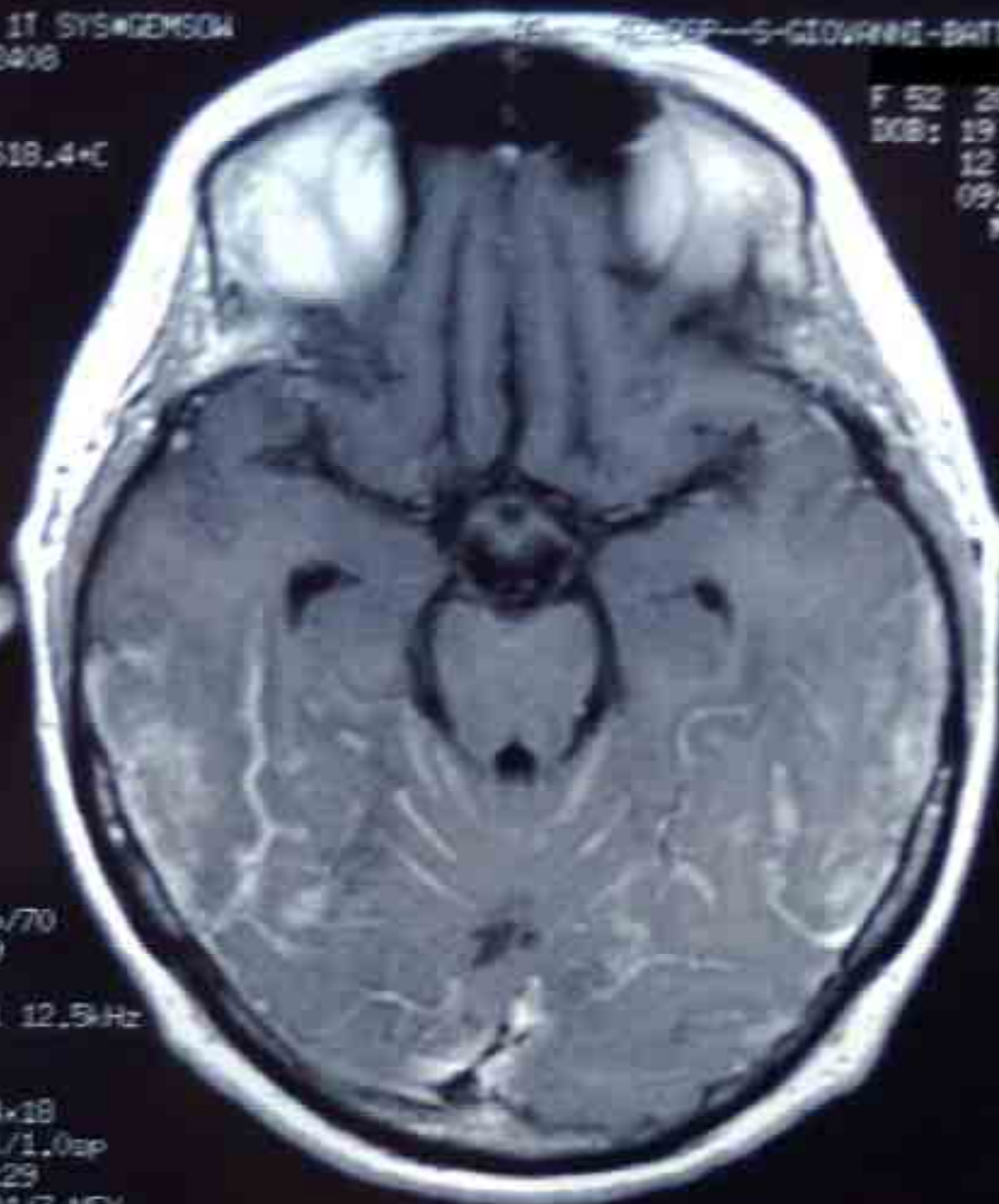
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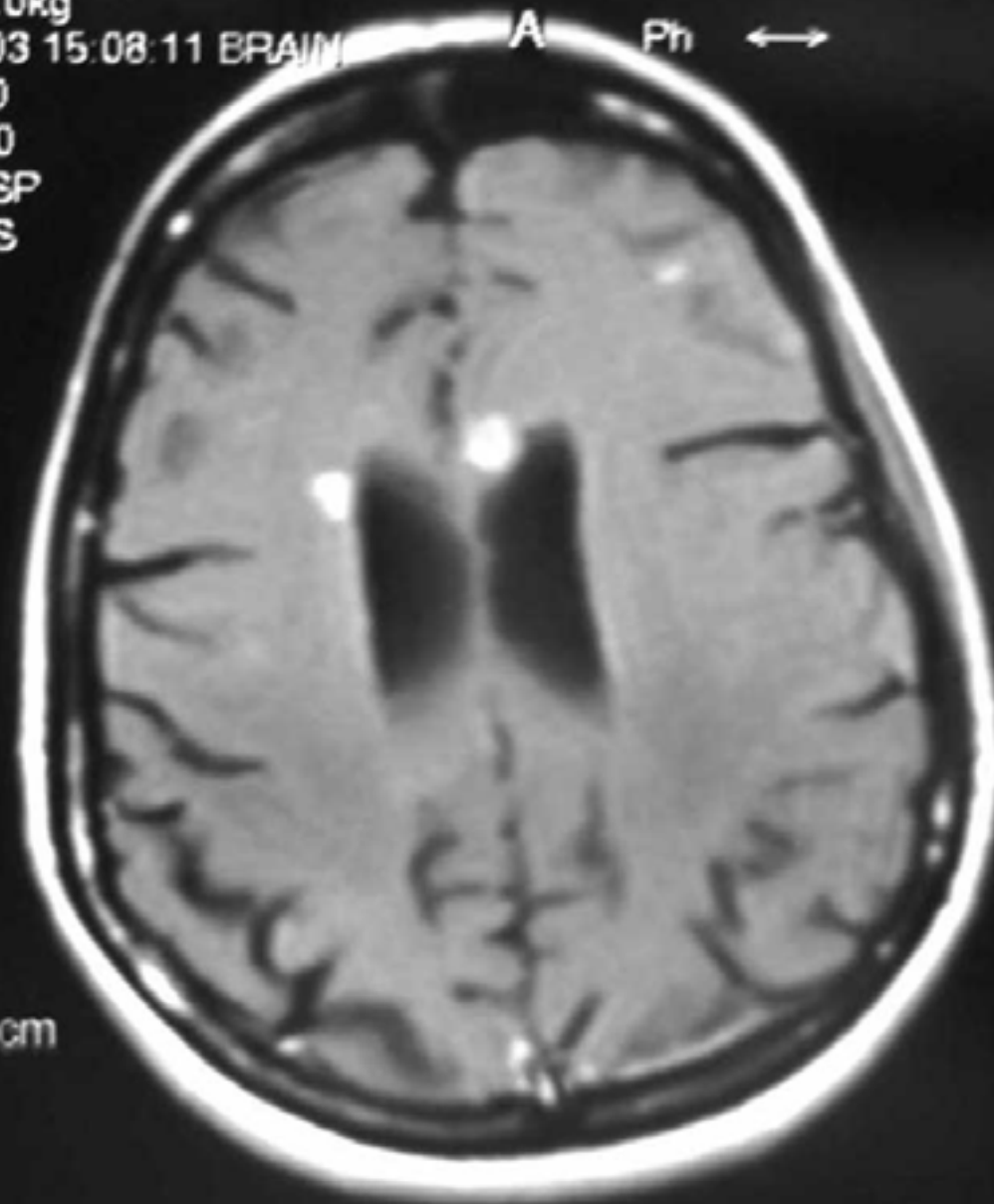
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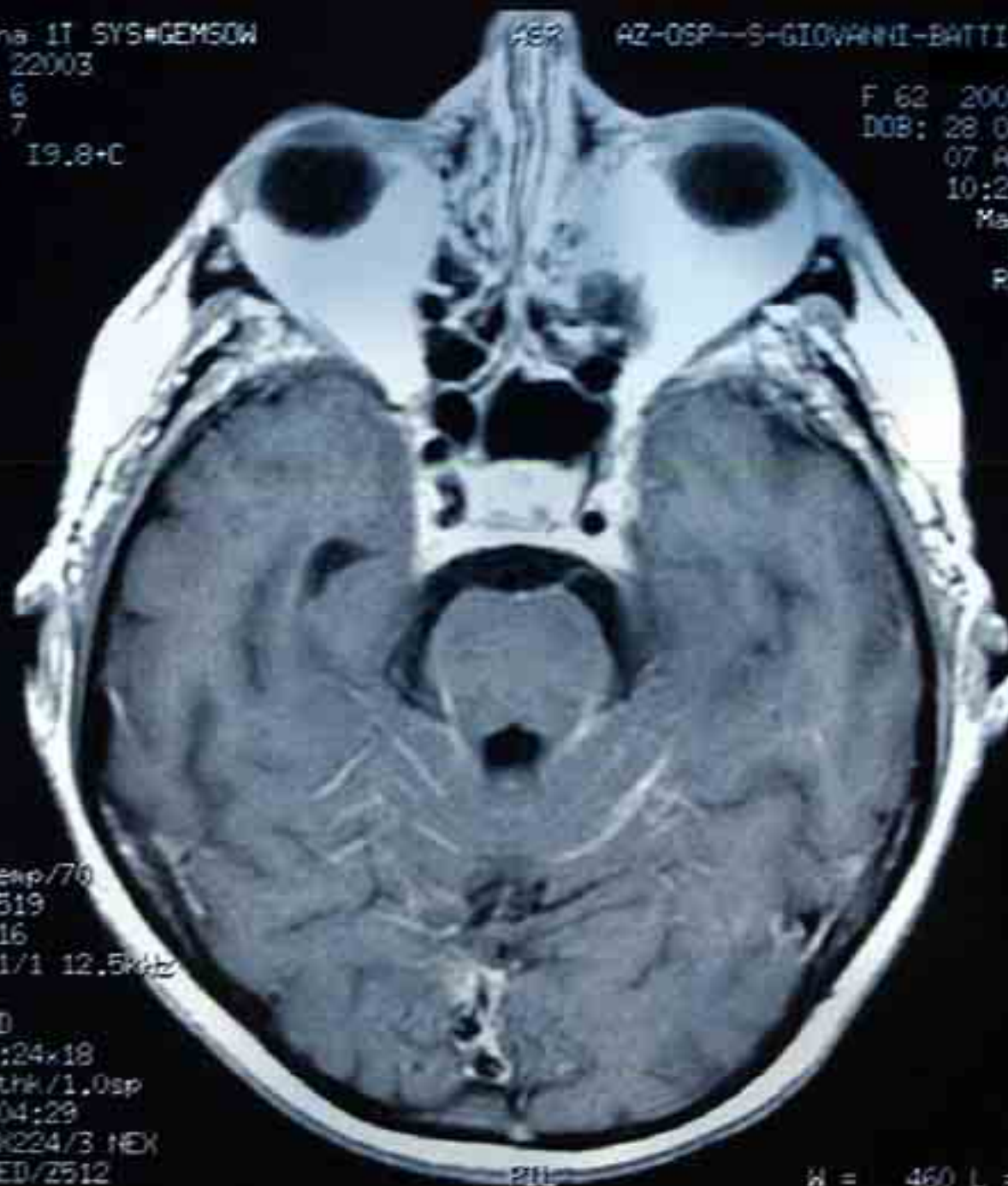
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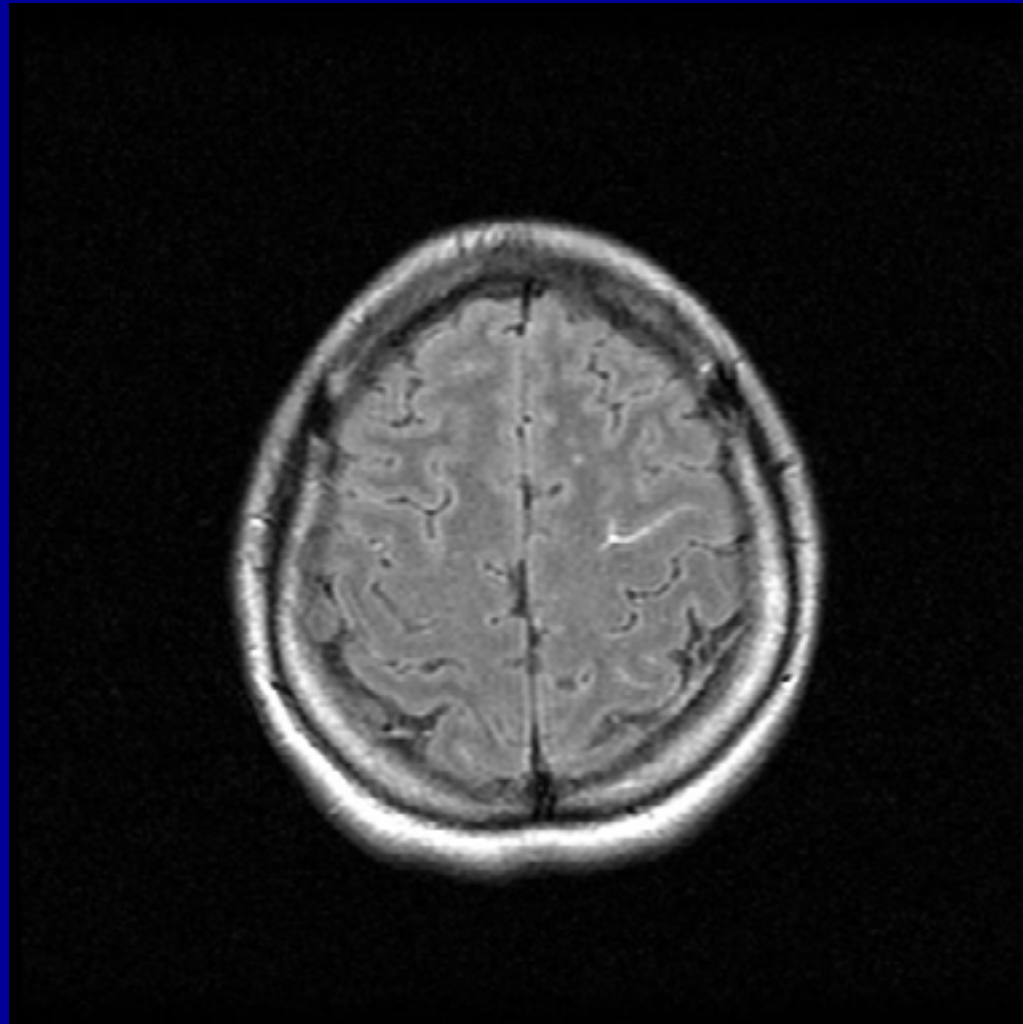
R  
I

t1wexp/70  
TR:519  
TE:16  
EC:1/1 12.5kHz

HEAD  
FOV:24x18  
5.0thk/1.0sp  
20/04:29  
256K224/3 HEX  
VB/ED/2512



W = 460 L = 25





## CSF ANALYSIS

- Single most useful test for diagnosing NM and monitoring treatment
- Abnormal CSF in nearly all patients with NM, regardless of the results of CSF cytology
- Variable CSF content of proteins, glucose and malignant cells at different levels of the neuraxis
- Volume of CSF critical (optimal 10 ml)

## CSF ANALYSIS

- Initial lumbar CSF cytology positive in 55% of patients, increasing to 80% after a second CFS examination
- No advantage with more than two CSF examinations
- Overall, at least 20% of patients with ultimately negative cytology

**Table 2** Comparison of diagnostic tools

	Diagnostic tool		Overall, count (%)	Hematopoietic, count (%)	Solid, count (%)	p Value
	Cytology	MRI				
Cytology and MRI (seg $\geq 1$ ), n = 93	+	+	45 (48)	12 (36)	33 (55)	0.08
	—	+	14 (15)	4 (12)	10 (17)	
	+	—	34 (37)	17 (52)	17 (28)	
Cytology and full MRI n, =48	+	+	26 (54)	6 (46)	20 (57)	0.42
	—	+	10 (21)	2 (15)	8 (23)	
	+	—	12 (25)	5 (38)	7 (20)	

Clarke et al, Neurology 2010

# DIAGNOSIS OF NEOPLASTIC MENINGITIS (NM)

- Pathologically defined NM: Patients with positive CSF cytology regardless of neuroimaging findings
- Clinically defined NM: Patients with negative CSF cytology, but pathologically proven cancer in the history and a clinical syndrome suggesting NM with corroborating neuroimaging findings

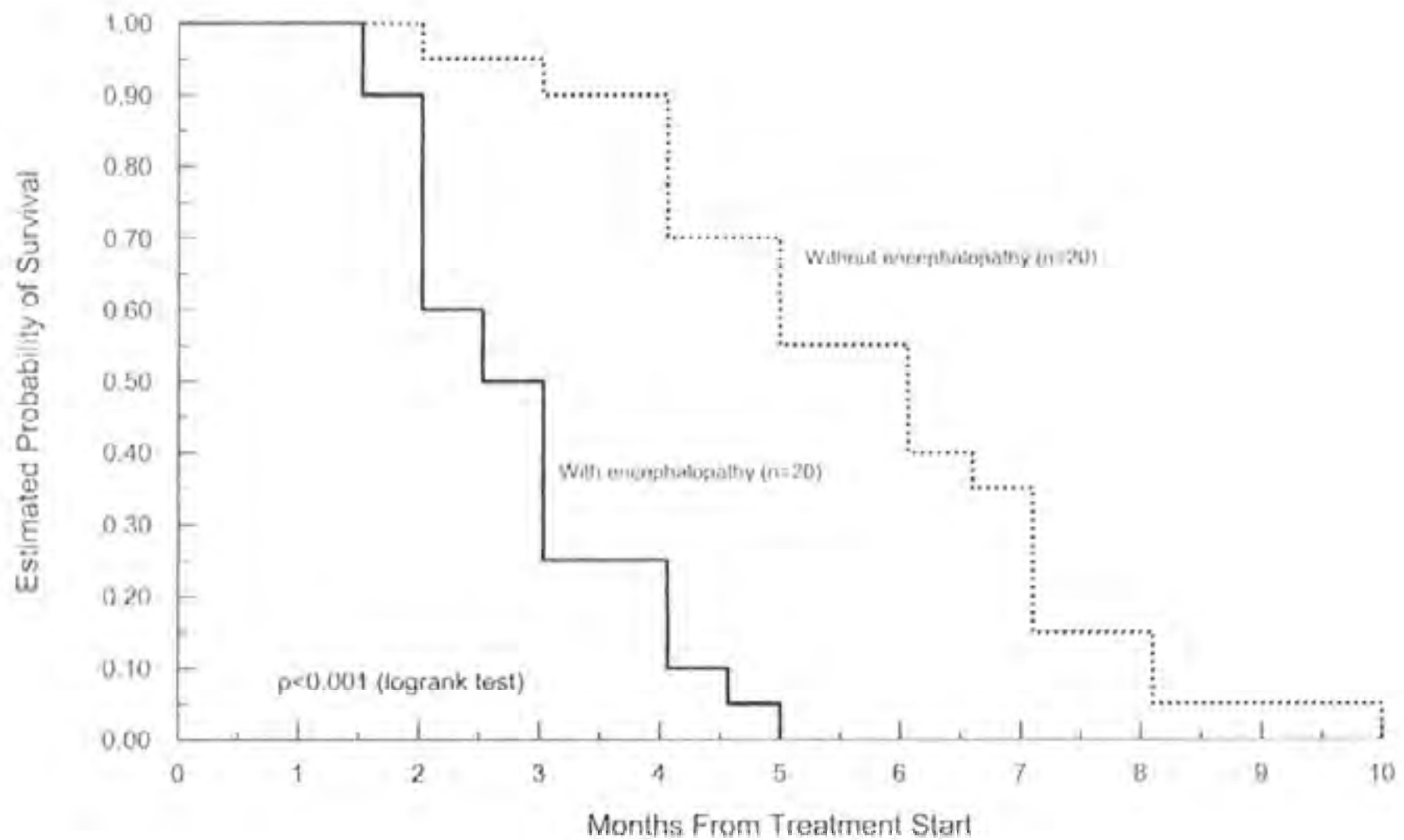
*Chamberlain, 2000*



**Table 2.** Prognosis by Tumor Histology<sup>20,52,56,57</sup>

Tumor Histology	Median Survival (months)	Range (months)
Breast (N = 32) <sup>20</sup>	7.5	1.5-16
Non-small-cell lung cancer (N = 32) <sup>56</sup>	5	1-12
Melanoma (N = 16) <sup>52</sup>	4	2-8
High-grade glioma (N = 20) <sup>57</sup>	3.5	1-6





Chamberlain et al, 2004

# **TREATMENT AND PROGNOSIS OF NEOPLASTIC MENINGITIS: GENERAL CONCEPTS**

- The majority of patients are not candidates for aggressive therapy, as NM presents at an advanced stage of the cancer history: these patients are best offered supportive care only
- A subset of patients may benefit from aggressive therapy
- Overall survival after treatments is 2-6 months
- The main objective of treatment is to palliate CNS symptoms/signs, thereby improving the patient's quality of life



# Frequency, patterns of care and outcome of neoplastic meningitis (NM) from solid tumors in the Regione Piemonte, Italy: a prospective survey from a cancer network

Roberta Rudà

Division of Neuro-Oncology,

Department of Neuroscience and Oncology, University  
and San Giovanni Battista Hospital, Turin, Italy

*ASCO, 2010*  
*SNO, 2010*

• **Polo del Nord-Ovest:**

**Aosta 3**

**Ciriè 2**

**Ivrea 1**

**Chivasso 1**

• **Polo di Torino:**

**Molinette 36**

**CTO-Neurochirurgia 3**

**Cottolengo 2**

**Martini 1**

**San Luigi 1**

**Moncalieri 1**

**Carmagnola 1**

• **Polo del Nord-Est:**

**Verbania 2**

**Novara 1**

**Borgomanero 1**

• **Polo del Sud-Ovest:**

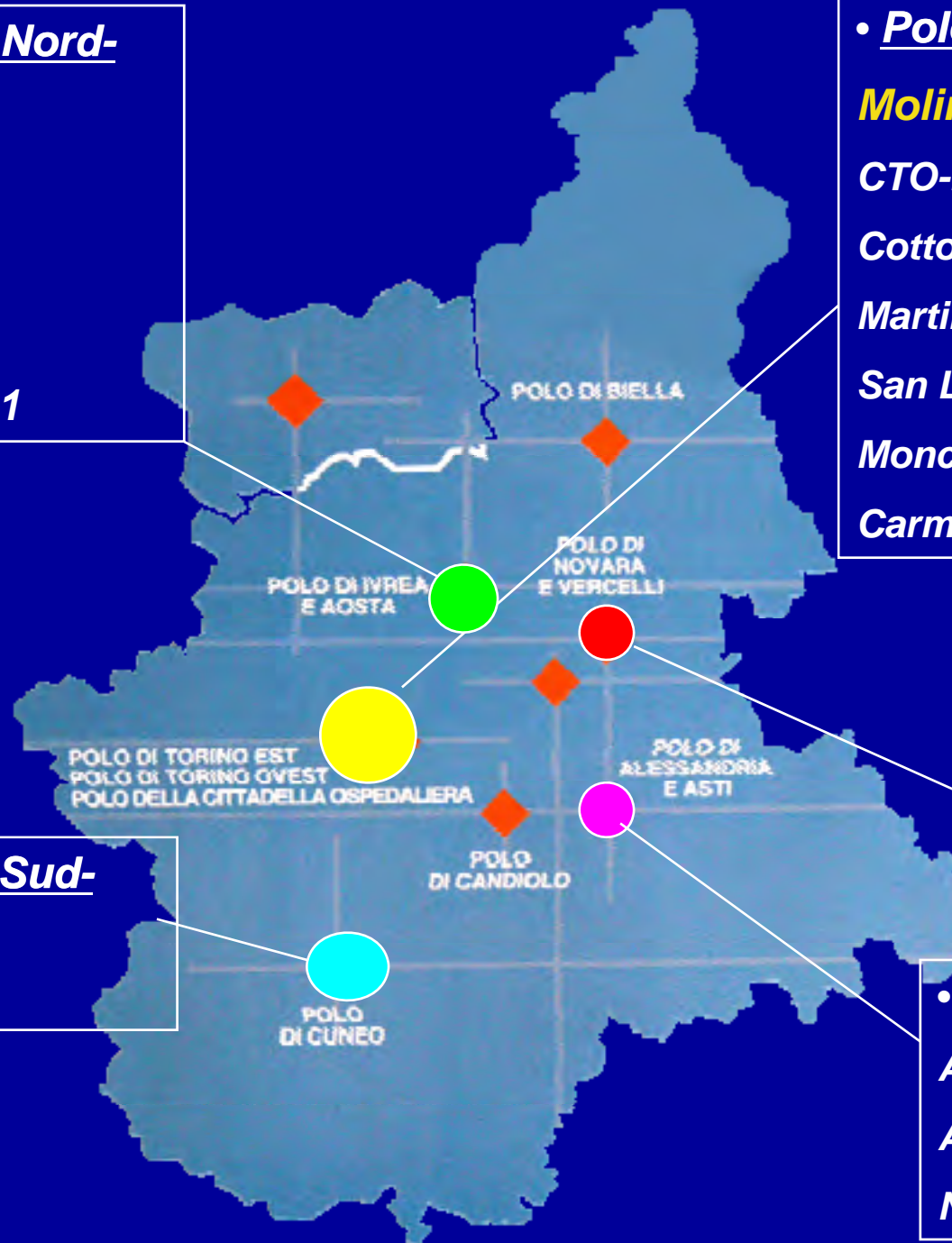
**Cuneo 5**

• **Polo del Sud-Est:**

**Alessandria 2**

**Asti 2**

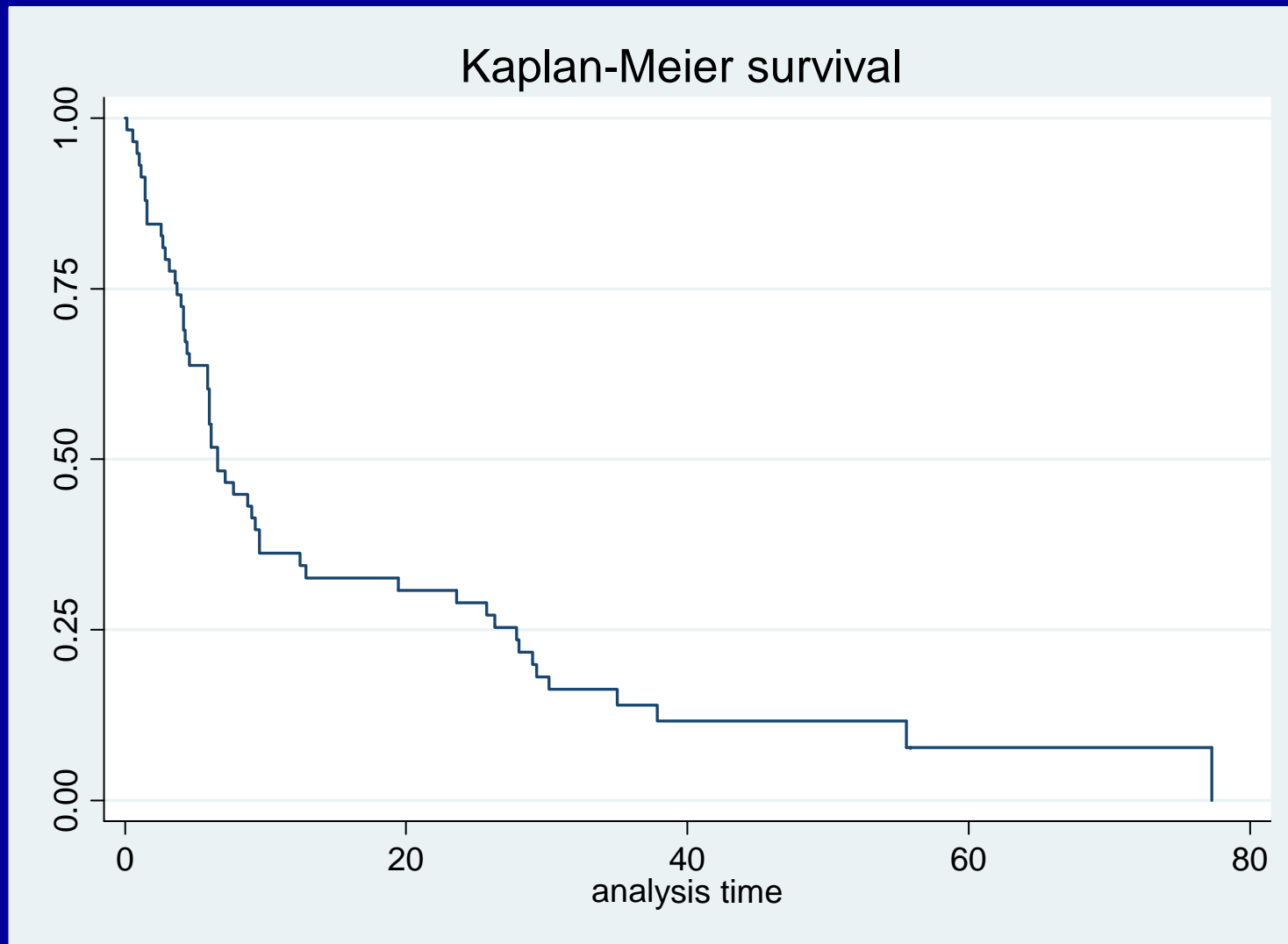
**Novi Ligure 3**



**(1/1/2008-31/12/2008)**



- **Enrolled patients: 68**
- Confirmed cases: 59 (9 false positives)
- Females: 44                      Males: 24
- Median age: 59                      Range: 38 - 80



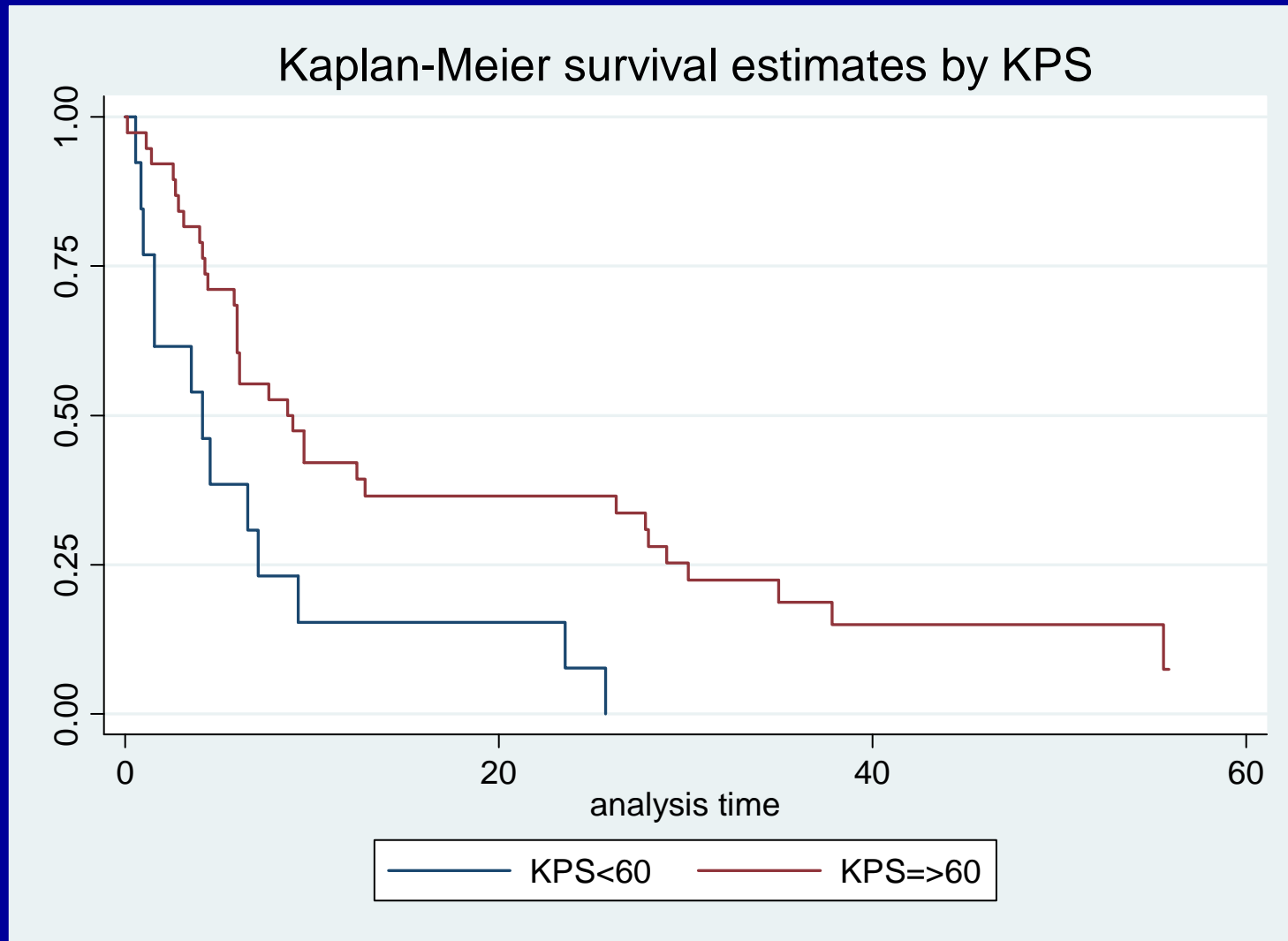
*Median survival time = 6.8 weeks*

*Survival at 6 months: 27.6%*

*Survival at 12 months: 5.2%*

# Factors affecting outcome

- High Karnofsky score ( $<60$  vs  $\geq 60$ ) was the sole factor associated with longer survival in both univariate and multivariate analysis
- Normal CSF glucose level showed a positive trend toward better survival
- Age ( $<60$  vs  $\geq 60$ ), sex, tumor type (breast vs lung vs other) and CSF cytology (positive vs negative) did not influence survival



$P < 0.0042$

*Median survival time (KPS<60) = 4.1 weeks*

*Median survival time (KPS $\geq$ 60) = 8.7 weeks*



## *Radiotherapy*

---

Focal radiotherapy should be administered to areas of bulky or symptomatic tumor [21, Class III].

Craniospinal radiotherapy is generally not recommended because of the high associated morbidity (predominantly myelosuppression) and lack of curative potential.

Radiotherapy is the most effective method to relieve symptoms, particularly painful radiculopathy; however, significant neurologic improvement is uncommon.

**Standard procedure** The standard course of treatment is to give a total of 30 Gy in 10 fractions. This can be given whether the patient is receiving treatment to the skull base (cranial neuropathy), whole brain (hydrocephalus or focal seizures), or the lumbosacral spine (cauda equina syndrome).

**Contraindications** Prior radiotherapy in the same region. (Retreatment may be possible if a significant interval, usually at least 1 year, has elapsed since the prior treatment.)

**Complications** Fatigue, alopecia, dermatitis, myelosuppression (particularly with spine radiotherapy), Lhermitte's sign. Patients with prolonged survival are at risk for delayed radiation encephalopathy or myelopathy.

**Cost/cost effectiveness** About \$10,000; no studies available on cost effectiveness.

# **CHEMOTHERAPY OF NEOPLASTIC MENINGITIS :**

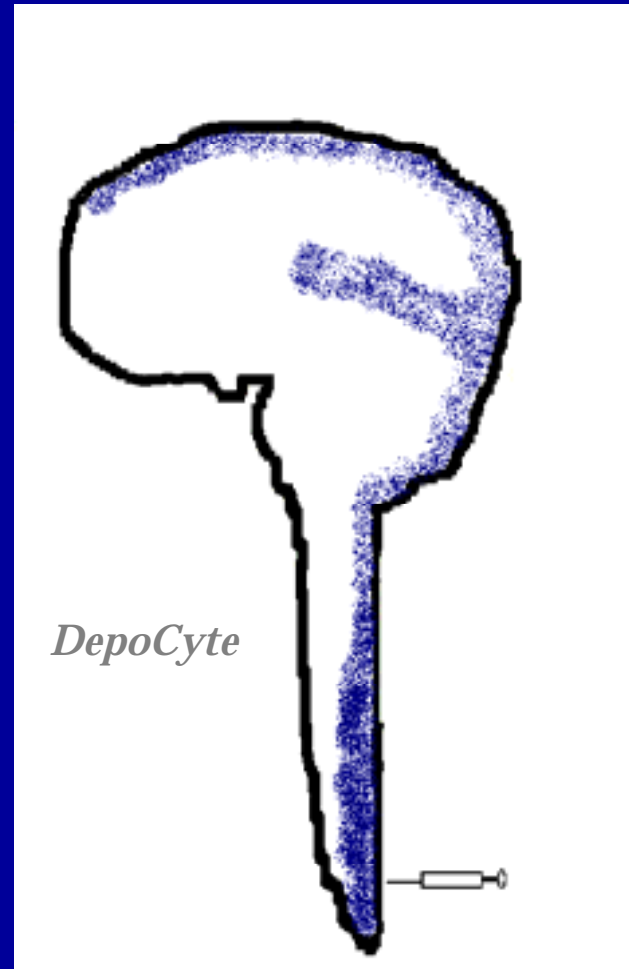
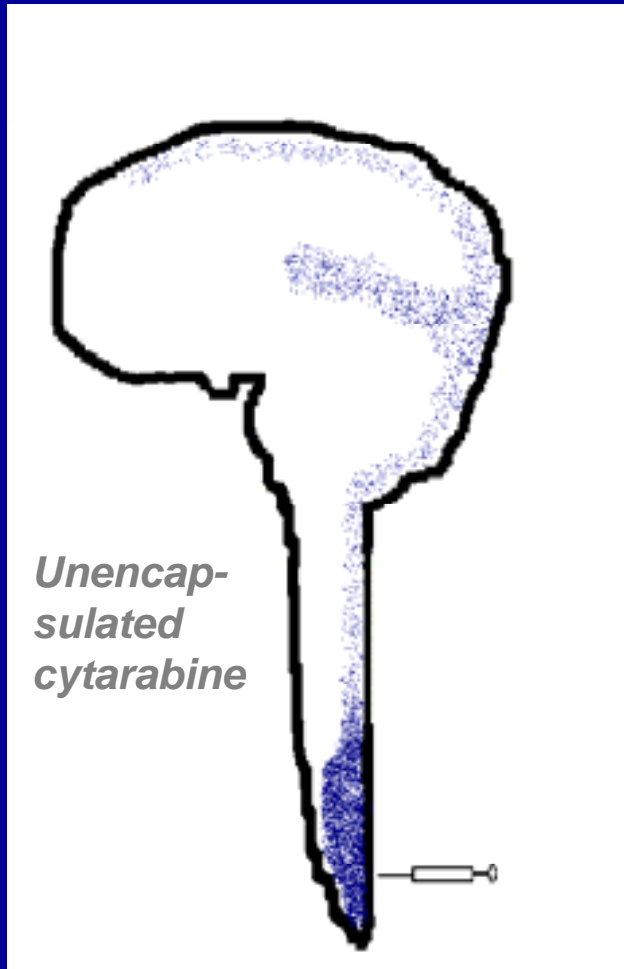
## **Major problems**

- The majority of patients have already received multiple prior systemic therapies
- Poor penetration of systemically administered drugs from blood to CSF (except for high dose methotrexate, cytarabine, thiotepa)
- Short intra-CSF half-life of intrathecally administered agents
- Limited penetration from CSF into thickened meninges and the superficial CNS tissue
- Physical obstruction to uniform distribution of drug through the CSF pathways produced by meningeal deposits

# **NEOPLASTIC MENINGITIS: INTRATHECAL CHEMOTHERAPY**

- Intrathecal chemotherapy is still the mainstay of treatment for leptomeningeal disease. The 3 agents most commonly used are methotrexate, cytarabine and thio-TEPA
- Methotrexate and cytarabine are active against leukemia and lymphoma. Methotrexate and thiotepa are active against breast cancer, but none of these agents have intrinsic activity against lung cancer or melanoma
- A modest advantage of Depocyte (liposomal encapsulated cytarabine) over standard cytarabine and methotrexate has been reported

# DEPOCYTE IMPROVES THE DISTRIBUTION OF FREE CYTARABINE IN THE CSF WHEN ADMINISTERED BY INJECTION INTO THE LUMBAR SAC



# **NEOPLASTIC MENINGITIS: SYSTEMIC CHEMOTHERAPY**

- Active drugs are high-dose intravenous methotrexate, cytarabine and thio-TEPA
- Some authors contend this therapy may be sufficient, and obviate the need for intra-CSF chemotherapy in the subset of patients with chemosensitive tumors (breast cancer, lymphomas)
- Hormonal therapy (Tamoxifen, etc) for breast and prostate cancer

## New drugs for intrathecal chemotherapy : ongoing studies in breast cancer patients

- Mafosfamide
- Trastuzumab

## New drugs for systemic chemotherapy : ongoing studies in breast cancer patients

- Capecitabine
- Temozolomide
- Bevacizumab

## Systemic + intrathecal chemotherapy : ongoing studies in breast cancer patients

- Capecitabine + Depocyte
- Lapatinib + Depocyte
- High dose MTX + Depocyte

## Radiotherapy + intrathecal chemotherapy

- WBRT + Depocyte

# Clinical Research Challenges

- Treatment of established disease
  - Early diagnosis for early treatment
  - Need for CSF markers
  - More effective drugs
  - Choice of endpoints



# Clinical Research Challenges

- Prophylaxis
  - Rationale:
    - minimal disease setting
    - minimal CSF flow abnormalities
  - Problems:
    - rarely isolated site of relapse
    - Need for well defined risk factors
  - Hypothesis:
    - High risk patients with breast cancer are good candidates?

*Soffietti R, Akerley W, Jensen RL, et al. Semin Oncol. 2009; 36(4 Suppl 2):S55-68.*