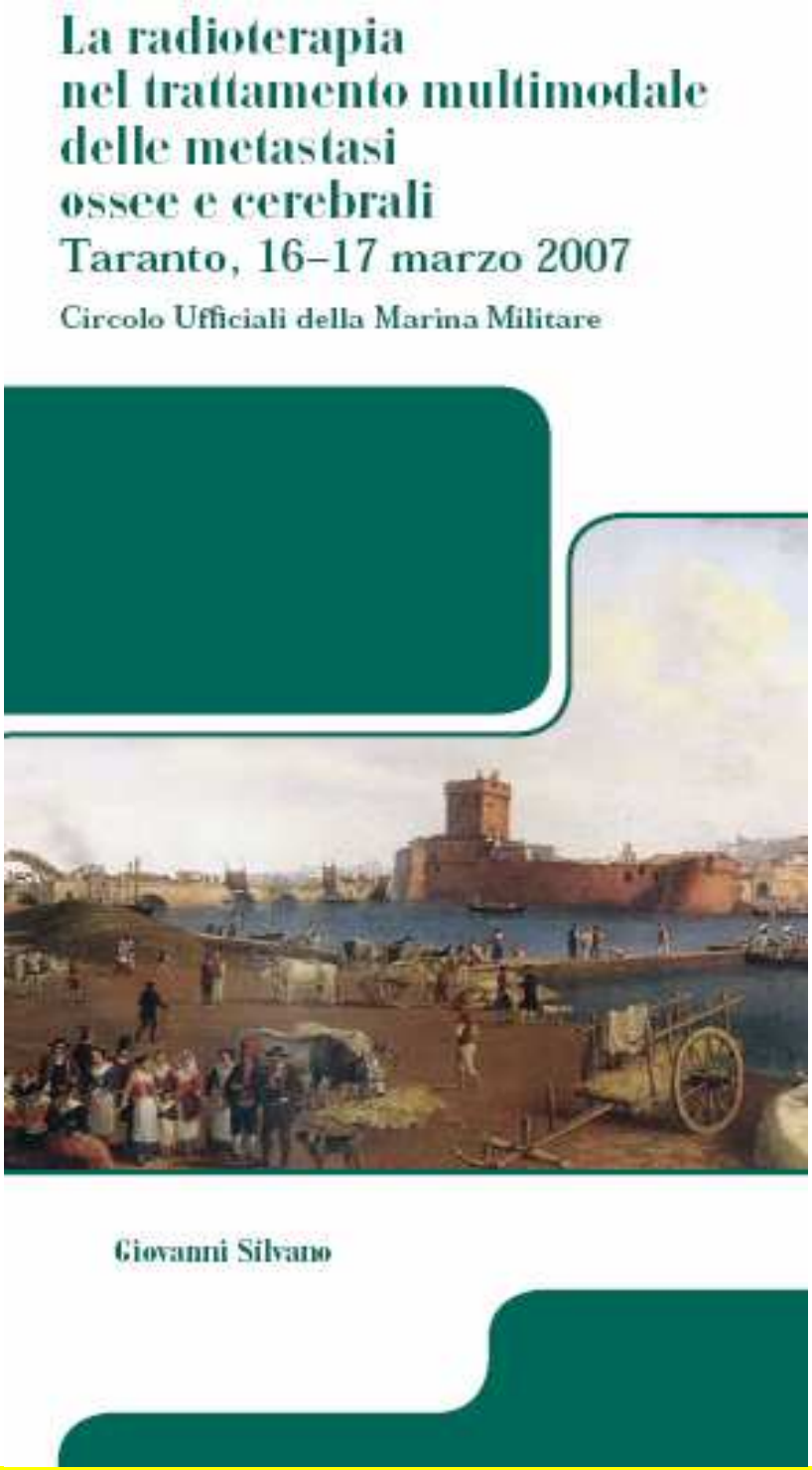
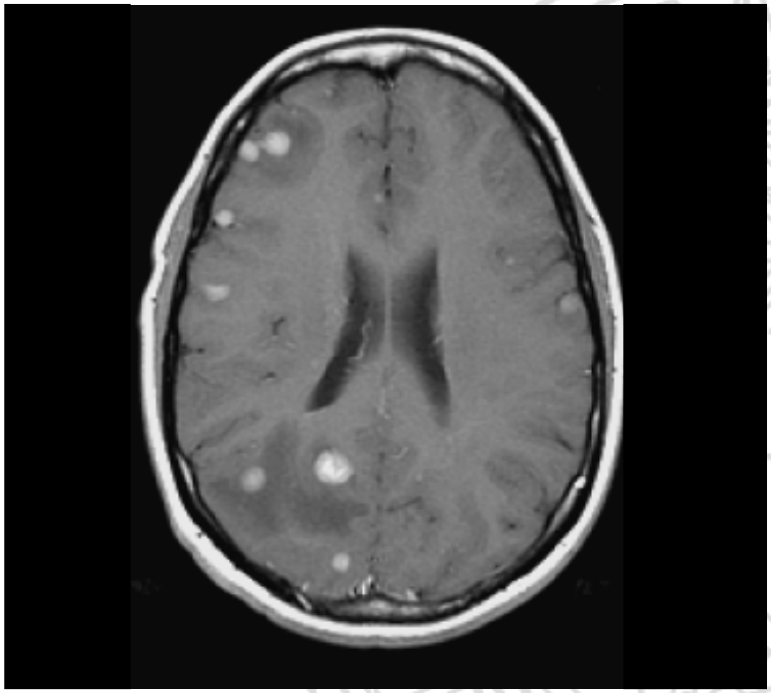
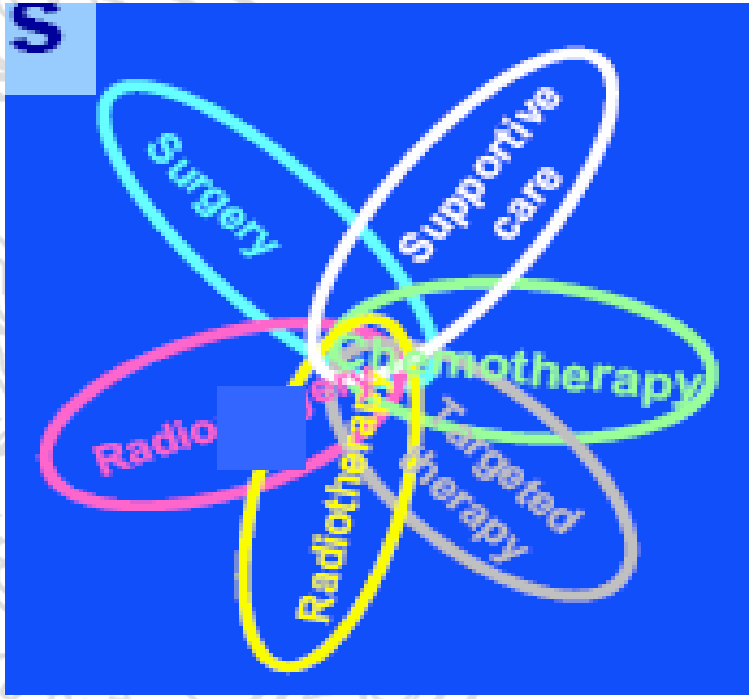


Metastasi cerebrali
La Radioterapia: tecnica, frazionamento, radiosensibilizzanti

Brain Metastases

Radiation Therapy of multiple brain metastases



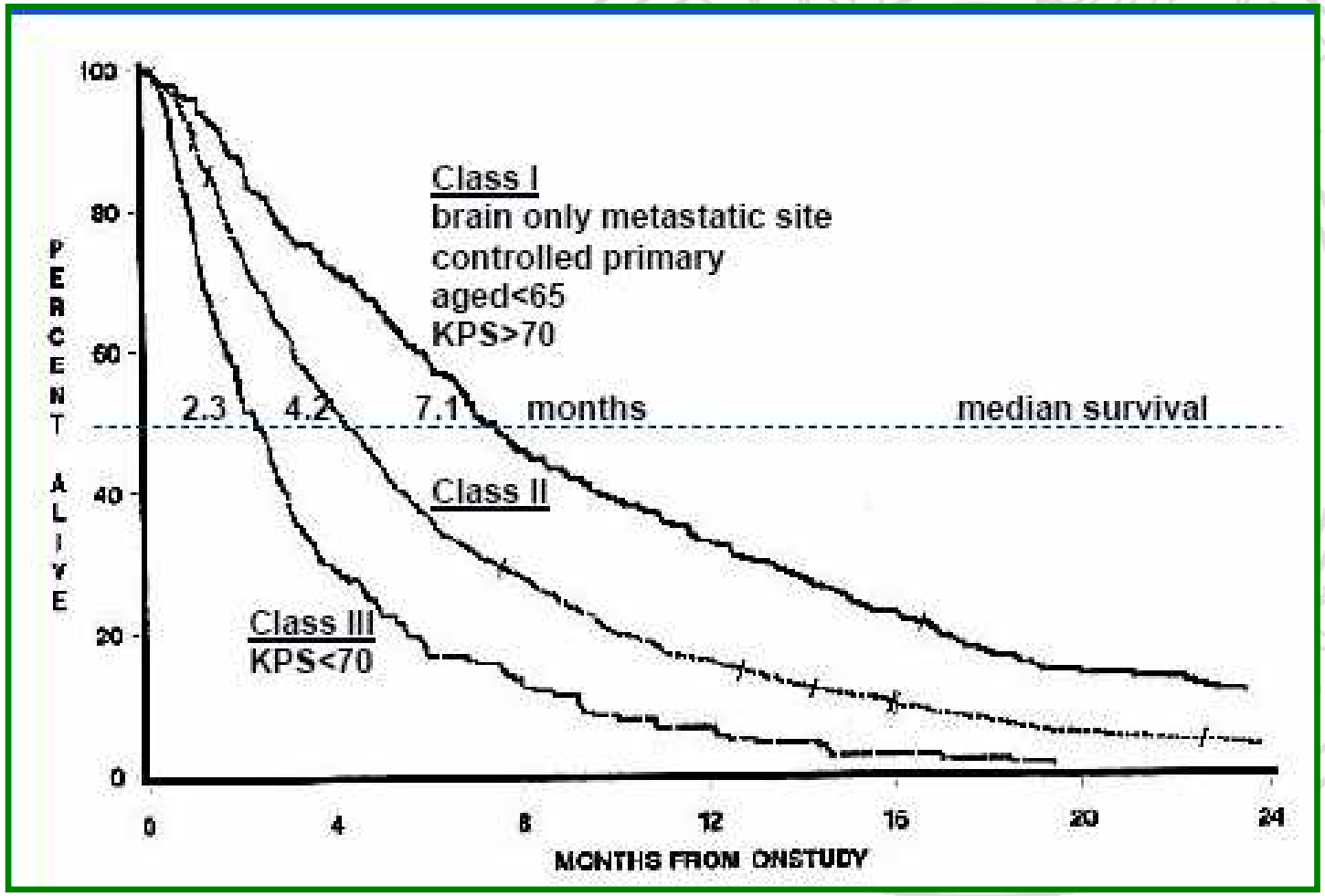


Is treatment appropriate?

- **Survival**
- **QoL**

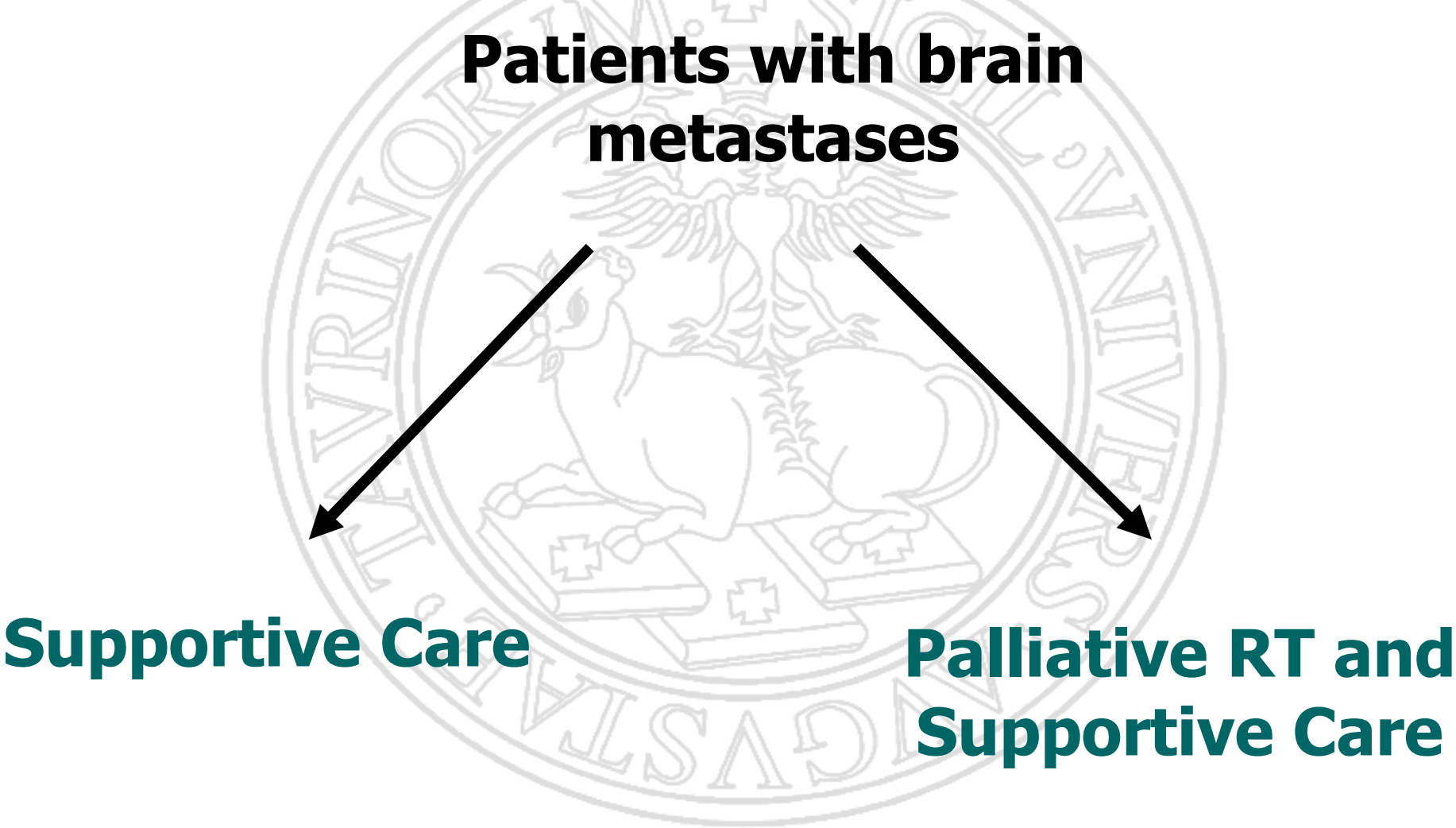
Brain Metastases

Survival by RPA prognostic class



Gaspar et al,1997

Multiple Brain Metastases



WBI for Multiple Brain Metastases

No data regarding

- Tumor response

- Intracranial Progression-free duration

- Quality of life

- Toxicity

WBI plus supportive care*

Median Survival 14 wks

Improvement in PS 61%

p value not stated

Supportive care*

Median Survival 10 wks

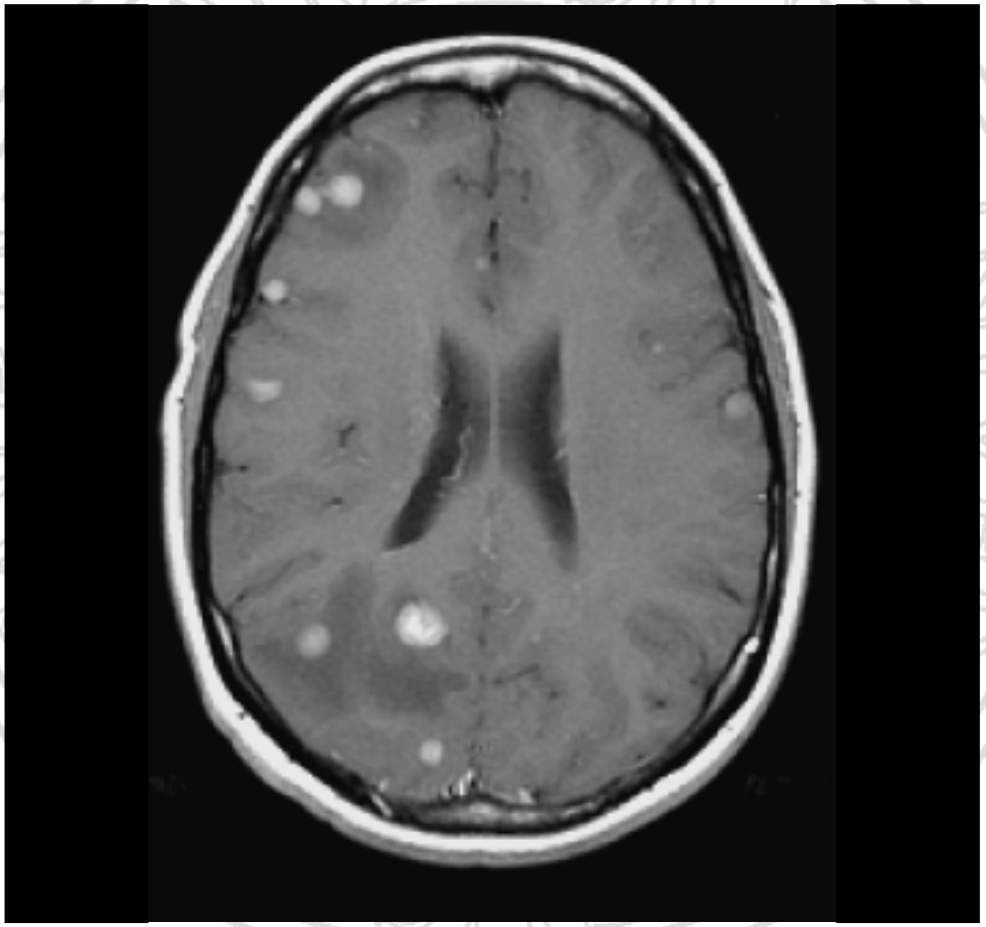
Improvement in PS 63%

* Oral prednisone

Horton, 1971

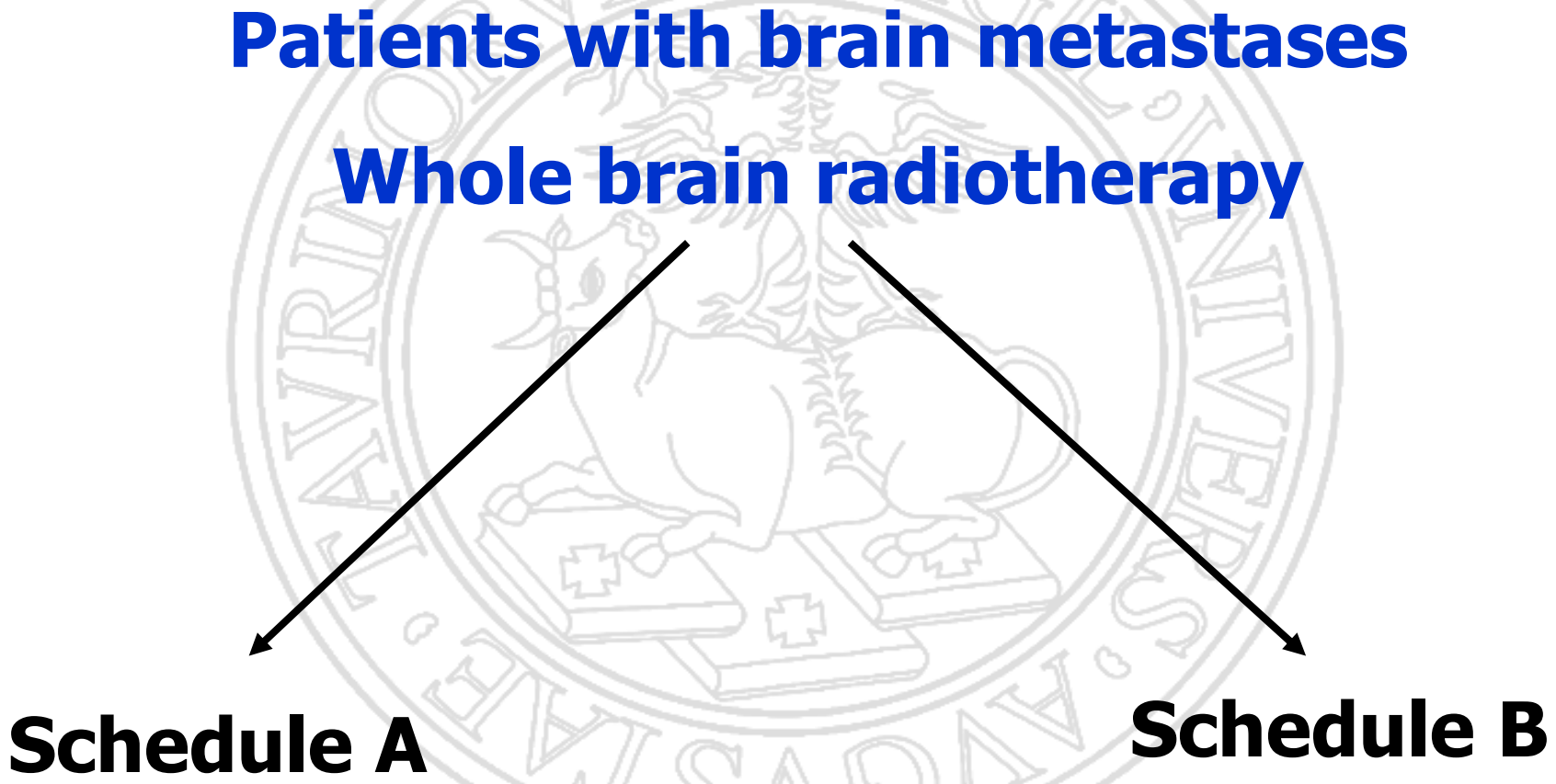
Multiple Brain Metastases

Whole Brain Radiotherapy



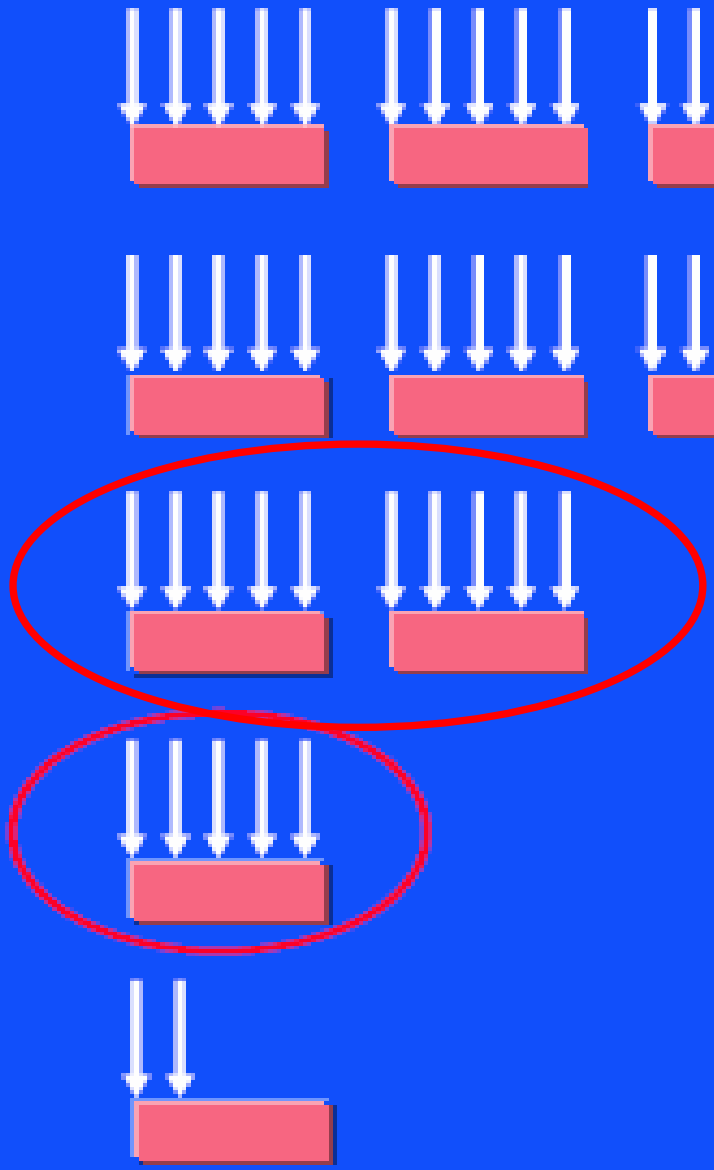
Brain metastases and Radiotherapy

Randomized trials



Radiotherapy in brain metastases

Palliative whole brain RT



4 weeks
(40Gy 20 fractions)

3 weeks
(30 - 40Gy 15 fractions)

2 weeks
(30Gy 10 fractions)

1 weeks
(20Gy 5 fractions)

2 days
(12Gy 1 fraction)

Royal College of Radiologists

Brain metastases trial

Patients with symptomatic brain metastases

544 pts (533 eligible)

WBI 30 Gy/10fr

WBI 12 Gy/2fr

Priestman et al., Clin.Oncol, 1996

Royal College brain metastases trial

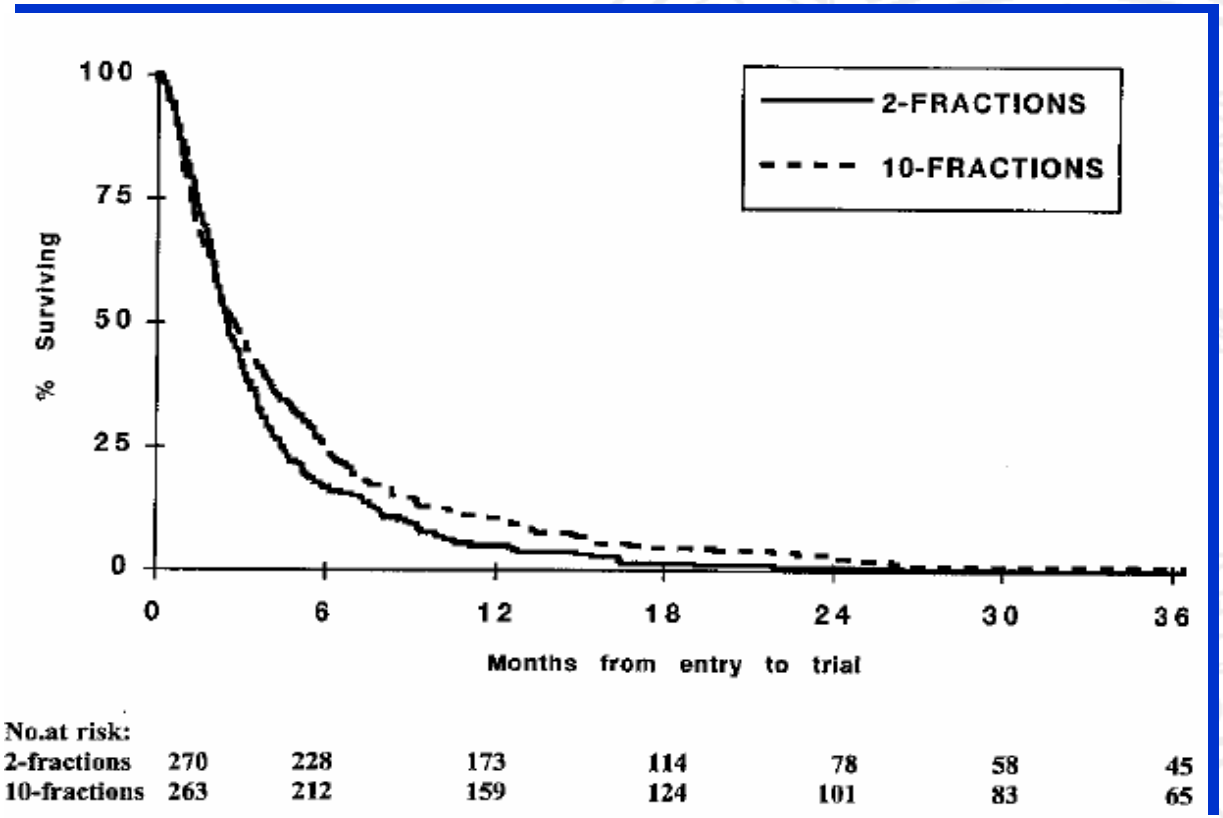
Characteristics of the 533 eligible patients

Factor	Grouping	2 fractions (n=270): no. patients (%)	10 fractions (n=263): no. patients (%)
Primary tumour	Bronchus small cell	52 (19)	51 (19)
	Bronchus other	109 (40)	98 (37)
	Breast	55 (20)	46 (18)
	Other	32 (12)	57 (22)
	Not known	22 (8)	11 (4)
Sex	Male	130 (48)	139 (53)
	Female	140 (52)	124 (47)
Age[a]	≤60 years	133 (49)	133 (51)
	>60 years	137 (51)	130 (49)
Extent	Solitary	106 (39)	106 (40)
	Multiple	149 (55)	148 (56)
	Not known	15 (6)	9 (3)
Dexamethasone	≤8 mg daily	80 (30)	103 (39)
	>8 mg daily	174 (64)	151 (57)
	Not known	16 (6)	9 (3)
Performance status (WHO)	0	22 (8)	24 (9)
	1	81 (30)	66 (25)
	2	68 (25)	86 (32)
	3	78 (29)	73 (28)
	Not known	21 (8)	14 (5)
Neurological status (MRC)	0	63 (23)	62 (24)
	1	69 (26)	64 (24)
	2	80 (30)	89 (34)
	3	31 (11)	35 (13)
	Not known	27 (10)	13 (5)

The two treatment groups were well balanced with respect to patients' characteristics

Priestman et al., Clin.Oncol, 1996

Royal College brain metastases trial



Analysis of the survival curves showed a marginal advantage for ten fractions ($p = 0.04$).

The 3-month and 6-month survival rates were 42% and **17%** respectively for the two fractions treatment and 48% and **25 %** respectively for the ten-fractions regimen

Priestman et al., Clin.Oncol, 1996

Royal College brain metastases trial

Analysis of prognostic factors for survival

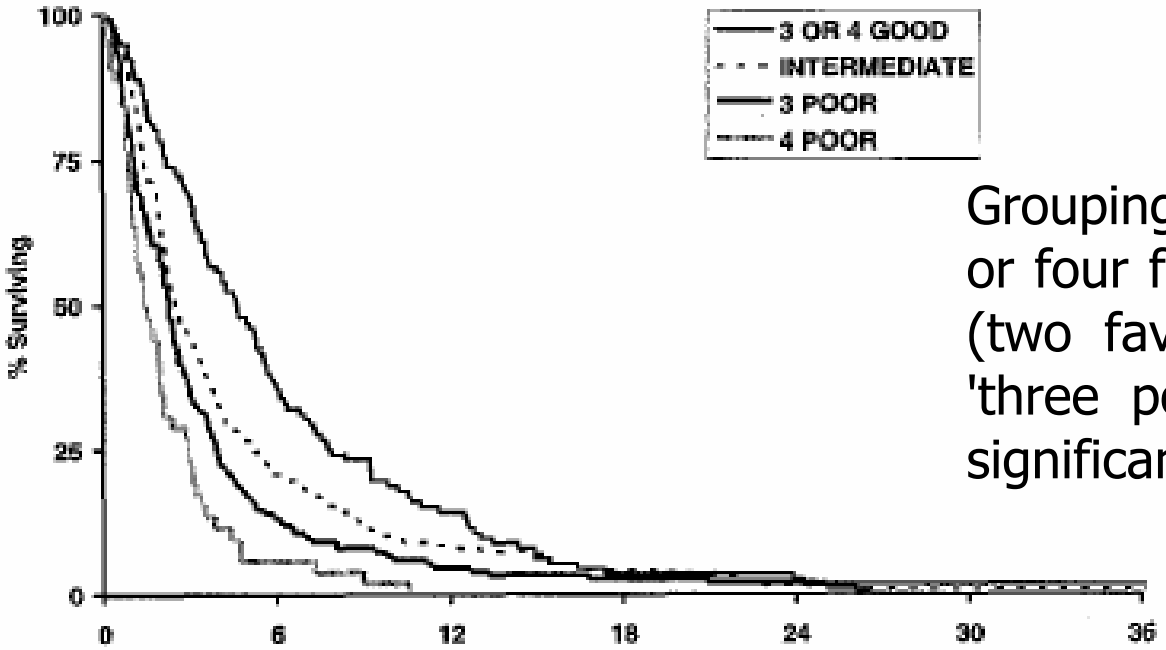
- age (p=0.008)
- site of the primary tumour (p=0.002)
- extent of cerebral disease (p = 0.008)
- dosage of dexamethasone at the time of entry into the trial (p = 0.001)
- WHO performance status (p<0.0001)

Factor	Grouping	Coefficient β	χ^2	*P*-value	Risk ratio
Performance status	0, 1, 2 vs 3	0.3990	14.42	0.0001	1.49
Primary tumour	Breast vs rest	0.3248	7.70	0.006	1.38
Dexamethasone	≤8 mg vs >8 mg	0.2827	8.48	0.004	1.33
Treatment	2 vs 10 fractions	−0.2052	4.81	0.028	0.81
Age	≤60 vs >60 yr	0.1985	4.37	0.037	1.22

Priestman et al., Clin.Oncol, 1996

Royal College brain metastases trial

Survival by prognostic groups



No.at risk:

3 or 4 Good	117	41	16	4	3	2	1
Intermediate	187	39	16	8	2	1	1
3 Poor	150	20	7	4	3	0	0
4 Poor	52	3	0	0	0	0	0

Grouping the patients into 'good risk' (three or four favourable factors), 'intermediate risk' (two favourable, two unfavourable factors), 'three poor', or 'four poor' factors revealed significant differences in survival ($p<0.0001$)

Priestman et al., Clin.Oncol, 1996

Clinical Oncology (1996) 8:308–315

Clinical Oncology

Original Article

Final Results of the Royal College of Radiologists' Trial Comparing Two Different Radiotherapy Schedules in the Treatment of Cerebral Metastases

T. J. Priestman[1], J. Dunn[2], M. Brada[3], R. Rampling[4] and P. G. Baker[2]

[1]New Cross Hospital, Wolverhampton, [2]CRC Trials Unit, Queen Elizabeth Hospital, Birmingham, [3]Royal Marsden Hospital, Sutton and [4]Beatson Oncology Centre, Western Infirmary, Glasgow, UK

These results suggest that **any increase in survival due to longer radiotherapy treatment is confined to good prognosis patients**, but, for the majority, there is no advantage and the value of radiotherapy for these patients relates purely to the possibility of control or relief of distressing symptoms.

Priestman et al., Clin.Oncol, 1996

Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 33, No. 2, pp. 349–355, 1995

0360-3016/95 $9.50 + .00

0360-3016(95)00121-2

● *Clinical Original Contribution*

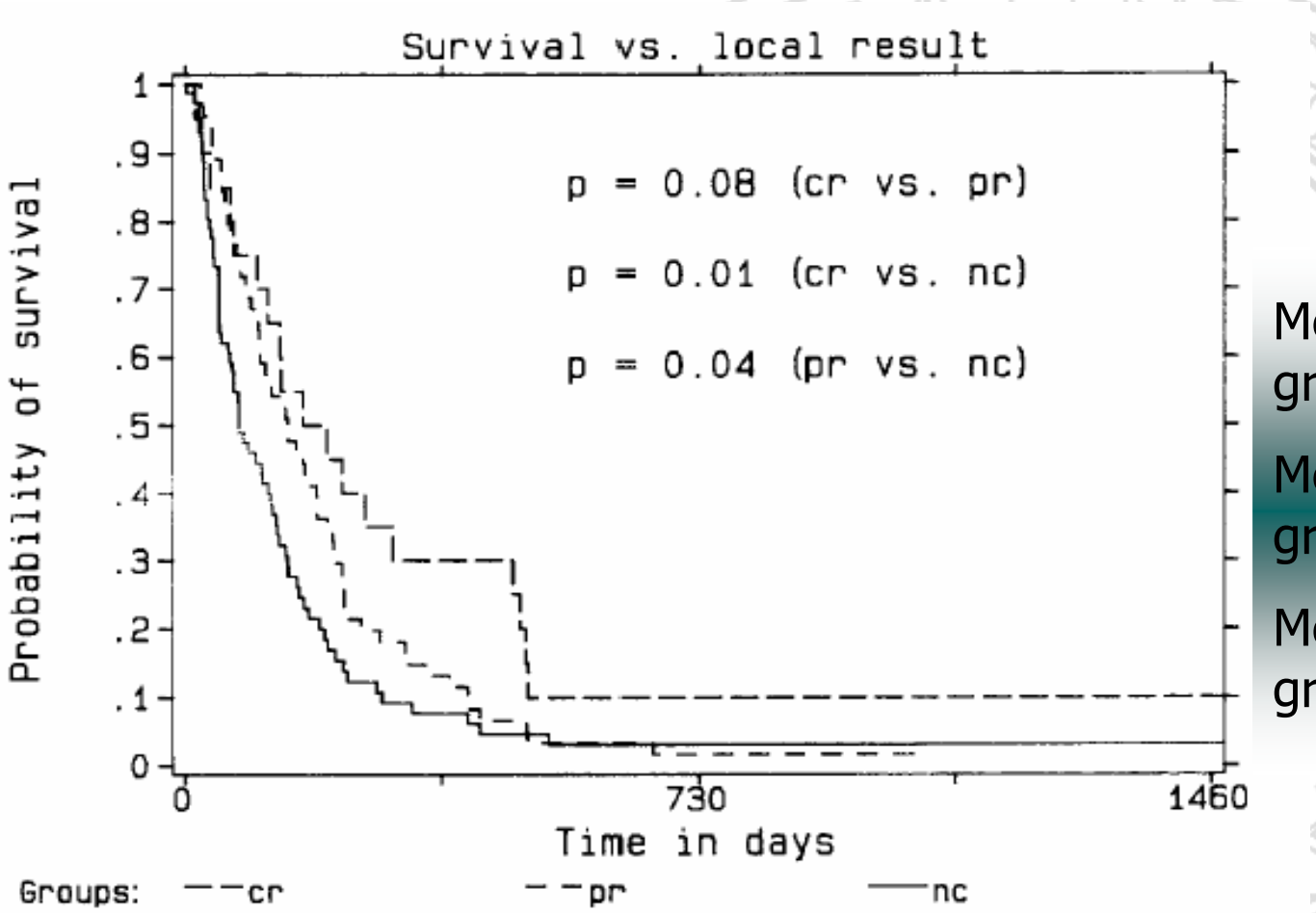
RELATION BETWEEN LOCAL RESULT AND TOTAL DOSE OF RADIOTHERAPY FOR BRAIN METASTASES

CARSTEN NIEDER, M.D.,* WERNER BERBERICH, M.D.,† URSULA NESTLE, M.D.,*
MARCUS NIEWALD, M.D.,* KARIN WALTER, M.D.* AND KLAUS SCHNABEL, M.D.*

*Department of Radiotherapy, University Hospital of the Saarland, Homburg/Saar, Germany and
†Department of Radiotherapy, St. Marien Hospital, Amberg, Germany

- A retrospective analysis of 164 pts treated with a standard regimen of 30 Gy/10fr was performed to find factors correlating with the local results
- To compare 39 pts treated with a total dose of 40-60 Gy with patients treated with the standard regimen 30 Gy/10fr

Response to radiotherapy and survival for brain metastases



Median survival 6 mo in the CR group

Median survival 4 mo in the PR group

Median survival 2.4 mo in the SD group

Relation between local result and total dose of RT for brain metastases

- The retrospective analysis showed a dependence of the local result after RT on two parameters:

- diameter of brain mets

- tumor histology (SCLC and adenoca more radiosensitive than squamous cell carcinoma)

- **The Local Response (CR or PR) was**

  48%-52% after 30 Gy

  77% after 40-60 Gy ($p \leq 0.05$)

- Survival was not significantly different

Pergamon

Int. J. Radiation Oncology Biol. Phys., Vol. 33, No. 2, pp. 349–355, 1995

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†Department of Radiotherapy, St. Marien Hospital, Amberg, Germany

Conclusion: This study suggests that there is a rationale for dose escalation in the treatment of brain metastases with radiotherapy, when local control is the aim. However, it seems questionable whether an improvement in survival results.

RTOG brain metastases trials

Patients with brain metastases

WBI

20 Gy in 5 fractions	1 week
30 Gy in 10 fractions	
30 Gy in 15 fractions	
37.5 Gy in 15 fractions	
40 Gy in 15 fractions	
40 Gy in 20 fractions	4 weeks

WBI for Multiple Brain Metastases

- **WBI is the conventional treatment for most patients with brain mets (except radioresistant tumors, i.e. melanoma)**

- **No specific dose or radiation schedule has been found to be superior (from 20 Gy over 1 week to 50 Gy over 5 weeks)**

  Typical radiation schedule: 30 Gy/10 fr or 37.5 Gy/15 fr (RTOG)

- **Some risk (>10%) of significant neurocognitive impairment and radiologic findings in long-term survivors (> 9 months)**

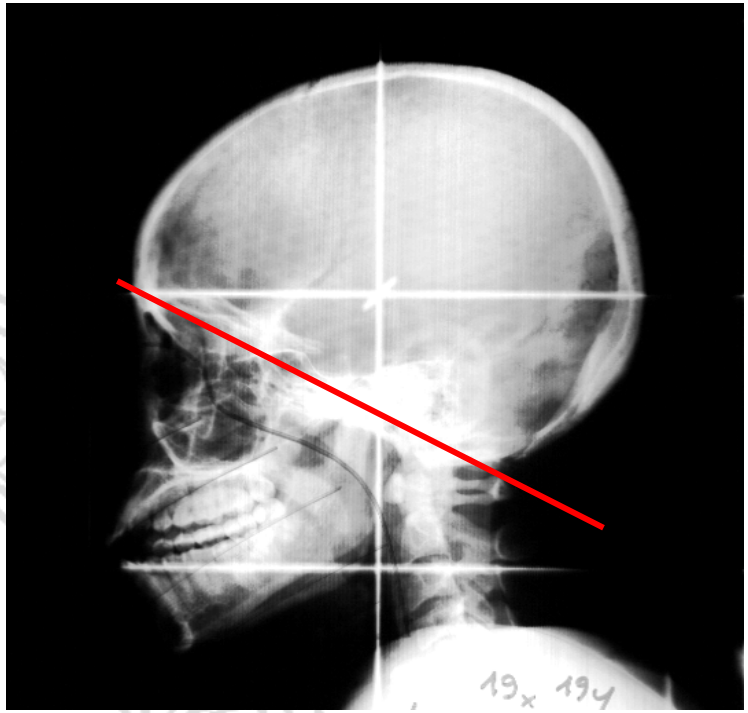
  Potentially safer schedules in patients with a likelihood of surviving more than 9 months

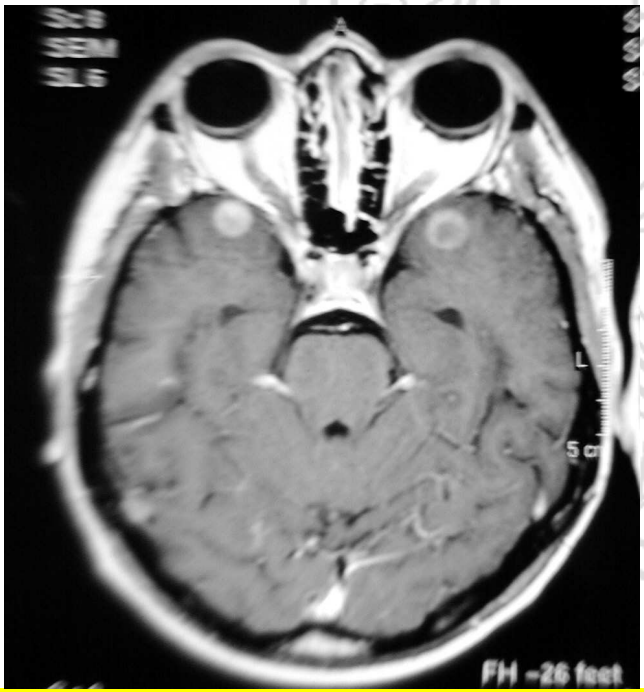
Good RT technique also for palliation

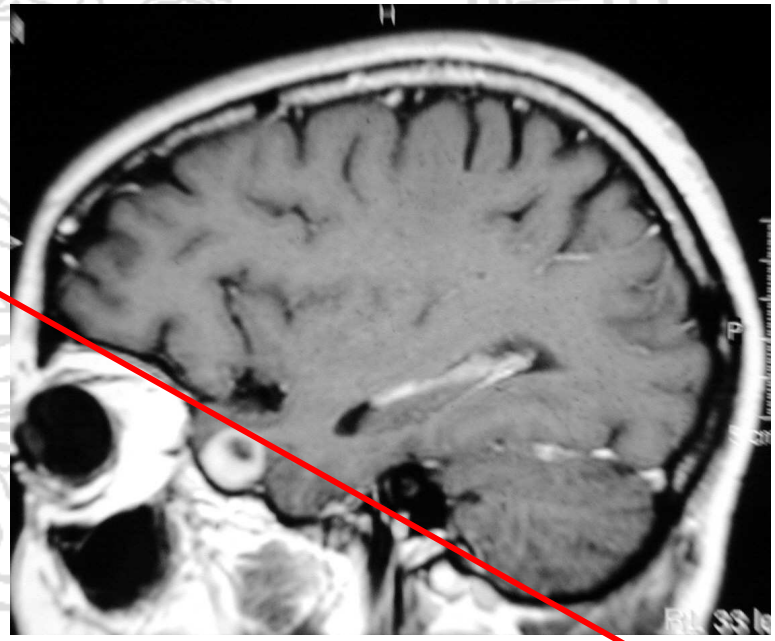
Technical considerations:

Modern conventional CNS RT:

- conformal
- conventional fraction size







PHYSICS CONTRIBUTION

THE ROLE OF CT SIMULATION IN WHOLE-BRAIN IRRADIATION

STEPHAN GRIPP, M.D., ROLF DOEKER, M.D., MICHAEL GLAG, M.D., PETRA VOGELSANG, BURCKHARDT BANNACH, M.S., THORSTEN DOLL, M.S., KLAUS MUSKALLA, PH.D., AND GERD SCHMITT, M.D.

Klinik für Strahlentherapie und Radiogische Onkologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

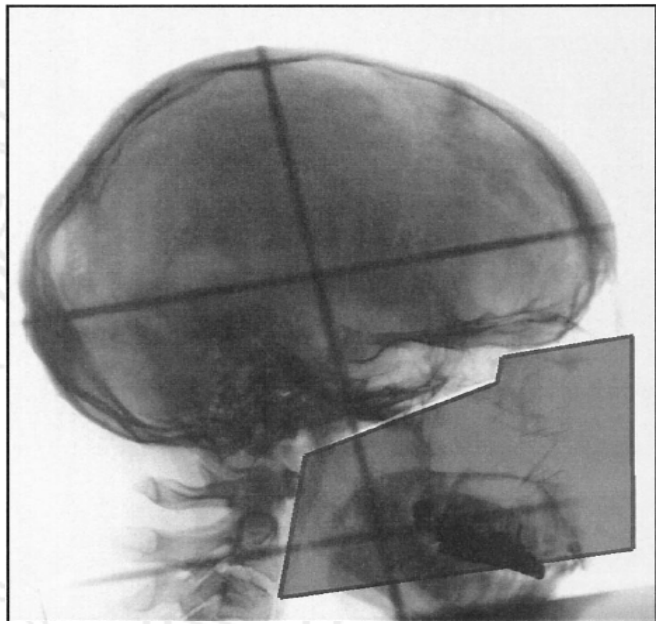
To evaluate the potential benefits of CT simulation in WBI comparing field-shaping based on 3D CT simulation to conventional 2D simulation.

Int. J. Radiation Oncology Biol. Phys.,

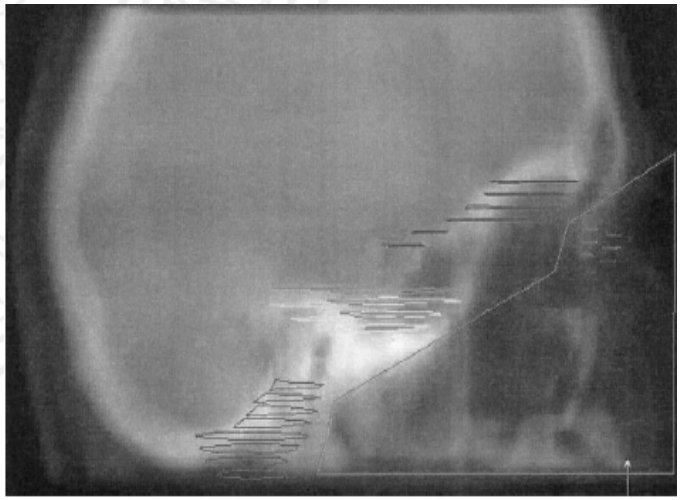
Role of CT simulation in WBI

- CT head scans were obtained from 20 patients.
- Conventional 2D planning was obtained by drawing the block contours on digitally reconstructed radiographs (DRR) as in conventional simulation
- 3D-planning was obtained by contouring target volume on the CT slices.

To assess the adequacy of margins, the minimal distance from the field edge to the contoured organ was measured for both planning situations at six sites (the subfrontal region (midline), both ocular lenses, both temporal lobes, and the medulla)



Portal design in WBI by conventional simulation



3D block shaping in 3D-planning

RESULTS

In conventional planning using DRR

- major geographic mismatches (< -3 mm) occurred in the subfrontal region
- minor mismatches (-3 to 0 mm) predominantly occurred in the contralateral lens (21%), ipsilateral lens (10%), and subfrontal region (9%).
- close margins (0–5 mm) were most frequently noted at the contralateral lens (49%), ipsilateral lens (35%), and the subfrontal region (28%).

In 3D planning

- mismatches were not found.
- close margins were inevitable at the ipsilateral lens (5%), subfrontal region (30%), and contralateral lens (70%).

PHYSICS CONTRIBUTION

THE ROLE OF CT SIMULATION IN WHOLE-BRAIN IRRADIATION

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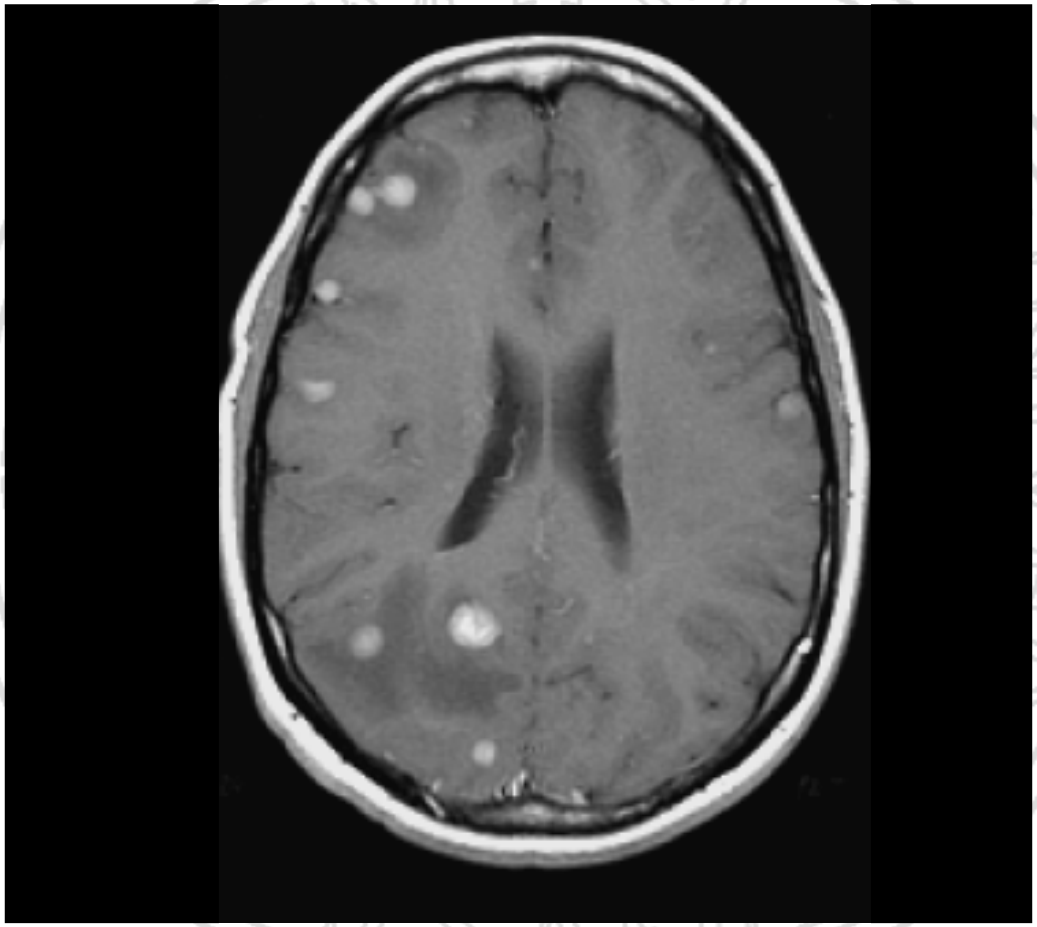
Klinik für Strahlentherapie und Radiogische Onkologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

CT simulation in WBI is significantly superior to conventional simulation with respect to complete coverage of the target volume and protection of the eye lenses

Int. J. Radiation Oncology Biol. Phys.,

Multiple Brain Metastases

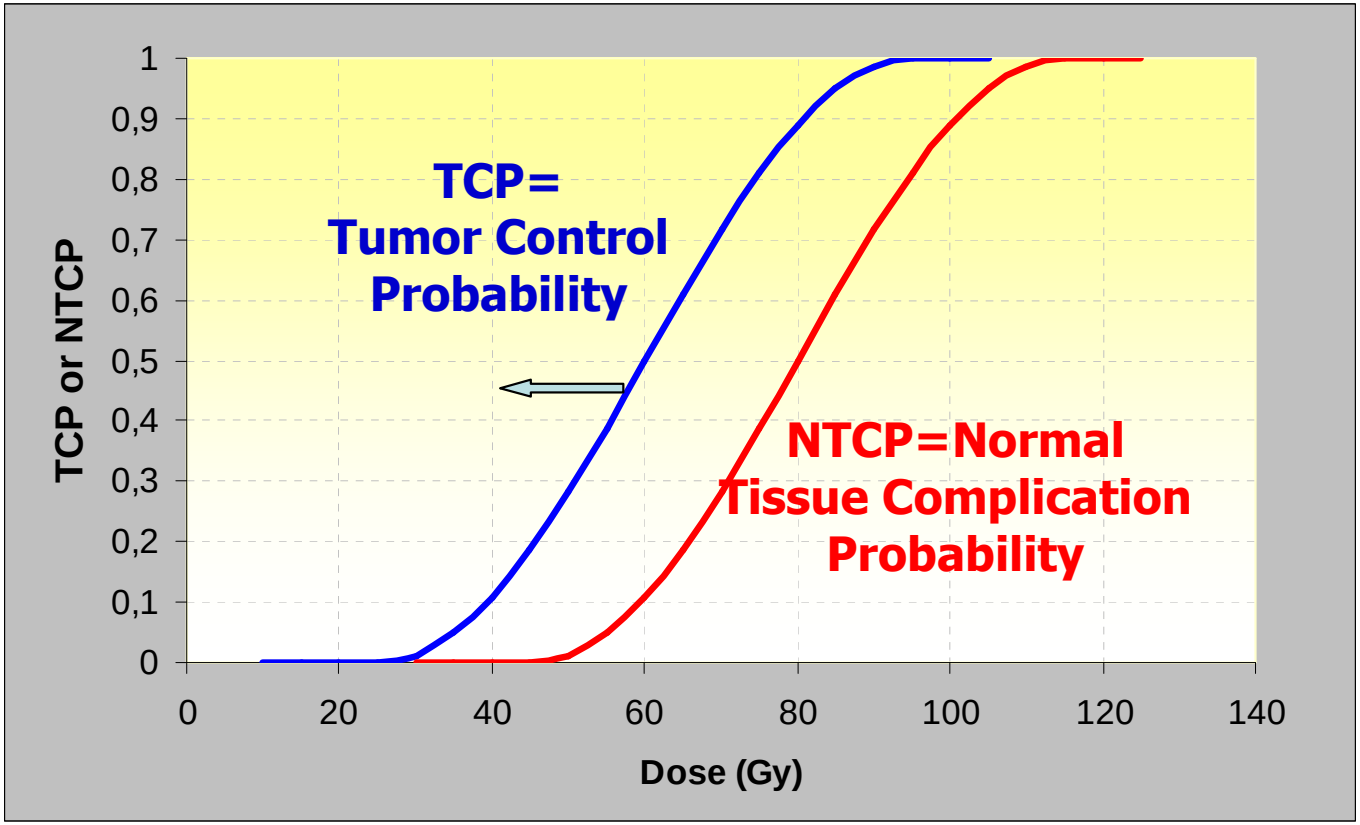
Whole Brain Radiotherapy



Can we improve the efficacy of RT?

Improvement of therapeutic index by radiosensitization

(shift of TCP curve to the left)



Randomized studies of WBI with "radiosensitizers"

Study	Study arms	N. of pts (eval)	Overall Median Survival	Overall Surv at 6 months	Response Rates
De Angelis.	30 Gy/10fr+lonidamine 30 Gy/10fr	31(19) 27 (20)	4.0 5.4	NR	37% 55%
Eyre	30 Gy/10fr+metronidazole 30 Gy/10fr	(57) (54)	2.8 3.2	14 13	27% 24%
Komarnicky	30Gy/6fr+misonidazole 30Gy/6fr 30Gy/10fr+misonidazole 30 Gy/10fr	220 (195) 216 (200) 211 (190) 212 (193)	3.1 4.1 3.9 4.5	68 83 65 72	
Phillips	37.5Gy/15fr+BrdUrd 37.5Gy/15fr	35 (34) 37 (36)	4.3 6.12	12 20	63% of 22pts 50% of 24pts

No significant difference

NSCLC→Brain (RTOG 0320)
Solitary or oligometastases (1-3)

- Stratifications:
  - PS: 0/1 v 2
  - Extracranial status: "controlled" vs active
- Targeted N = 381

  - To detect a 50% improvement in median survival (5.8 to 8.7 months)

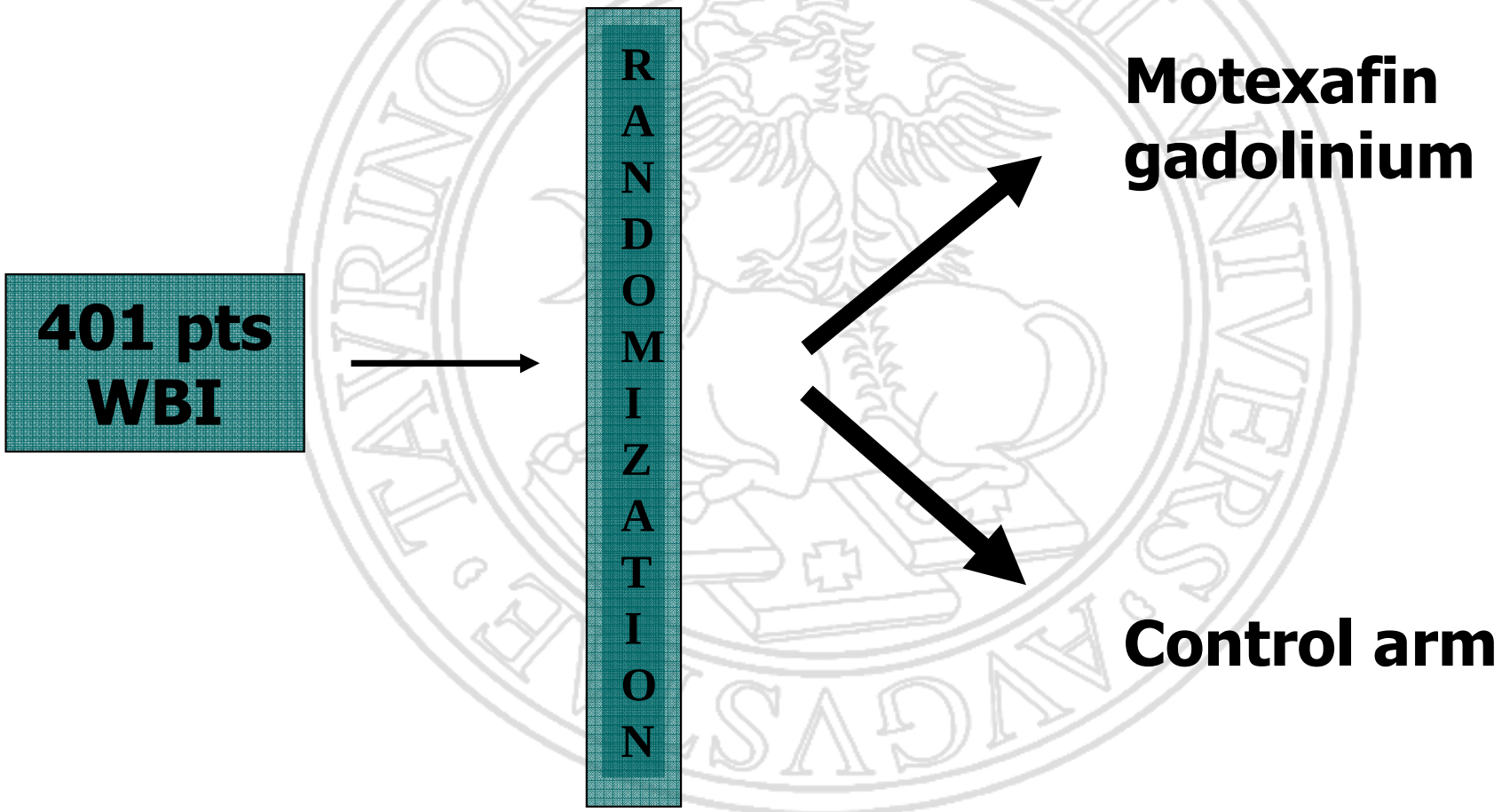
New radiosensitizing agents in brain mets: Motexafin Gadolinium

- Porphyrin-like macrocyclic compounds
- Motexafin gadolinium is selectively taken up and retained in tumor cells to a greater degree than in normal tissues
- Inside the tumor cell, it generates reactive oxygen species and oxidizes various intracellular reducing metabolites, inhibiting systems that normally protect cells against oxidative stress (inhibition of DNA repair, lower threshold for apoptosis)

Radiosensitizing agents in brain mets: Motexafin Gadolinium

Study	Patients	Comments
Carde, 2001	Phase I-II trial; WBI 30 Gy+Motexafin from 0.3 to 8.4 mg/kg/d x 10; 39 phase I and 22 phase II pts	Selective MR localization seen; drug well tolerated; Median Survival 4.7 months
Mehta, 2003	Phase III trial; WBI 30 Gy ± Motexafin; 5.5 mg/kg/d x 10 Well balanced arms; 401 pts	Median Survival 5.2 vs 4.9 months; Median Time to neurologic progression improved for NSCLC

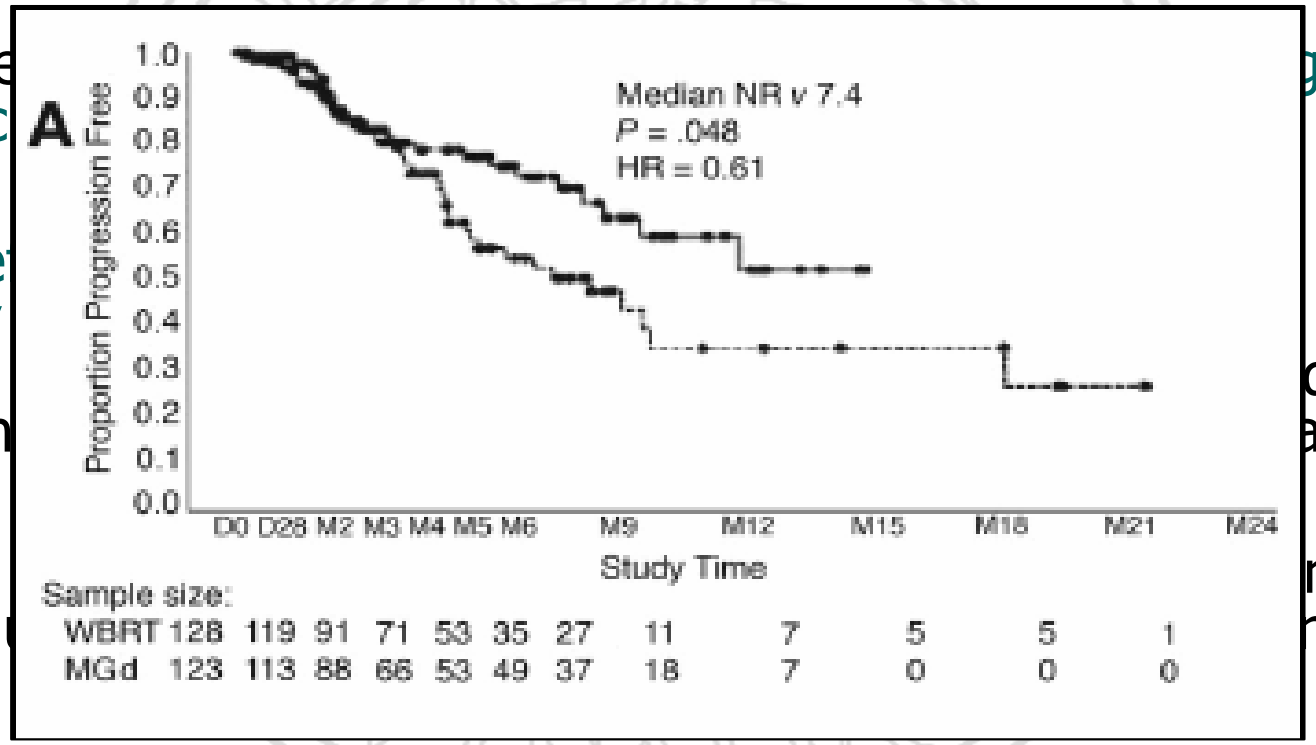
Randomized Phase III Trial of Motexafin Gadolinium for Patients with Brain Metastases



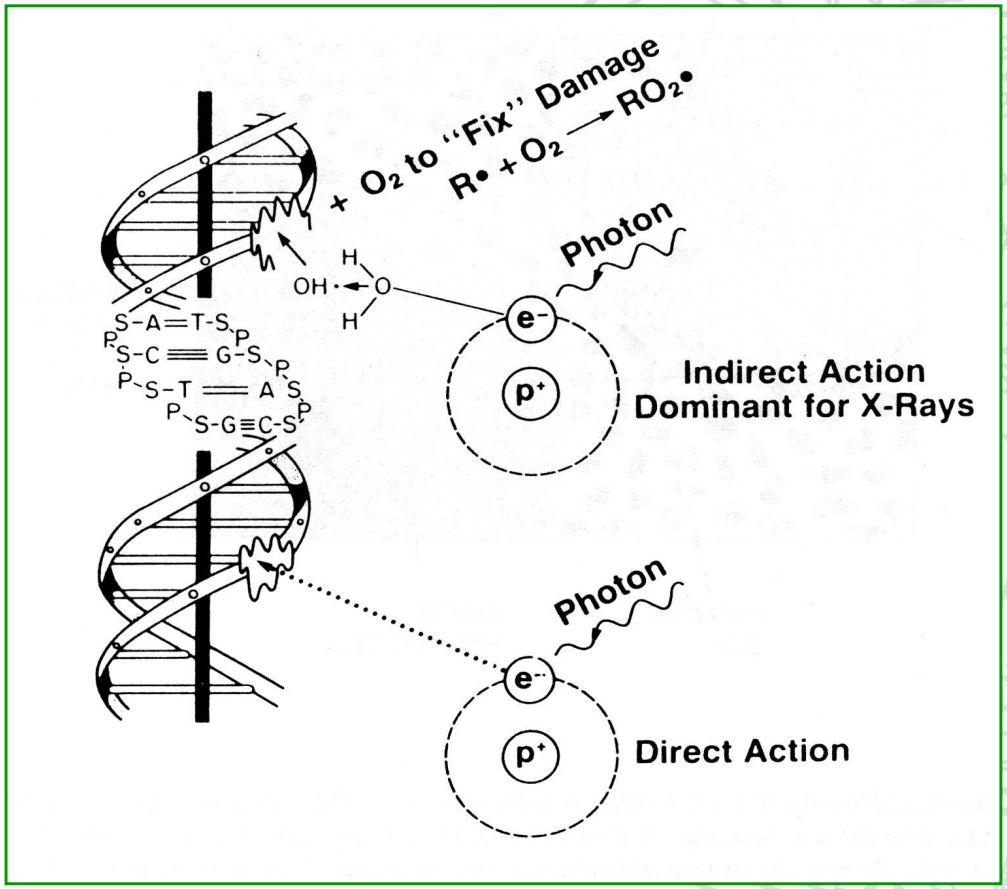
Mehta,2003

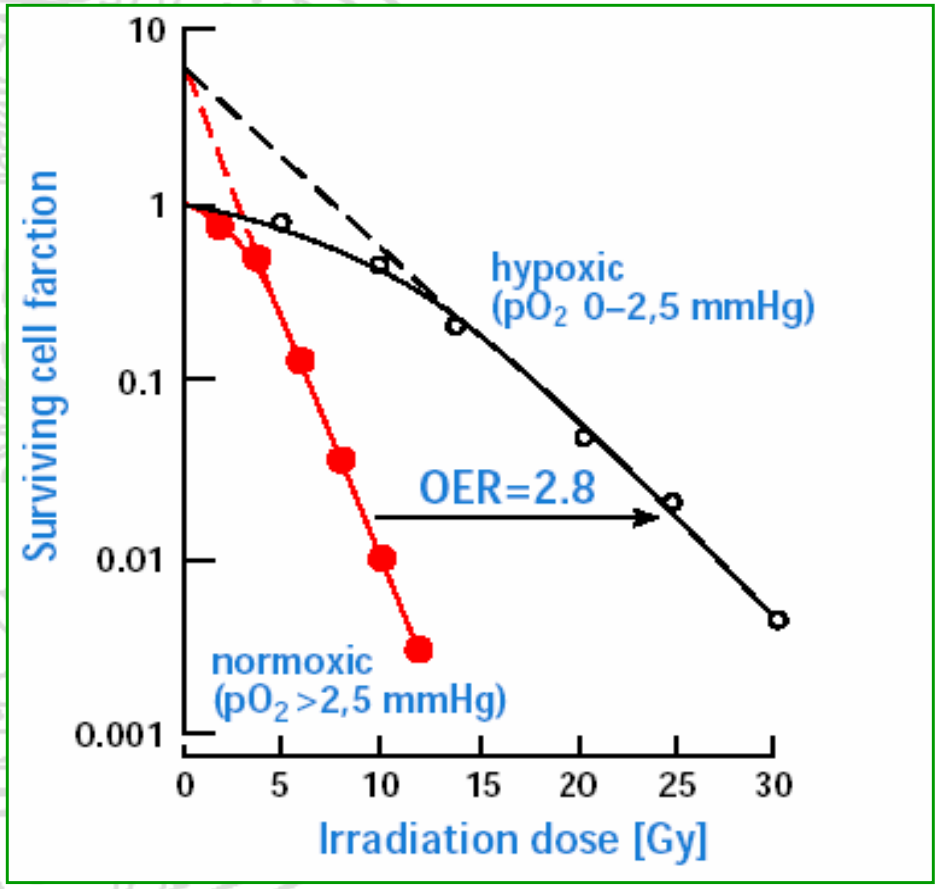
Randomized Phase III Trial of Motexafin Gadolinium for Patients with Brain Metastases

- Overall the study was negative, with no benefit in either end points
- ..but Mote ged time to neurologic
- The benef on several secondary lung cancer pts (52% d executive function in alone
- Adverse manageable (Skin and nts)
- Phase III trial in NSCLC ongoing



Influence of Tissue Oxygenation on Radiosensitivity

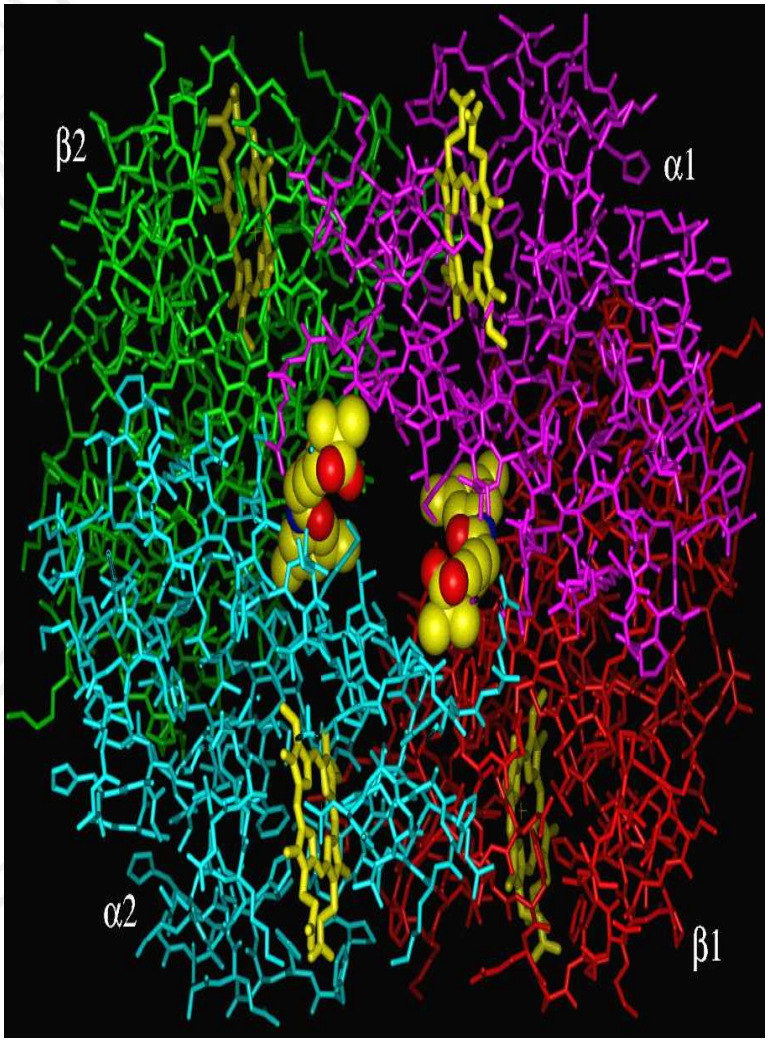




Efaproxiral (RSR13)

Well defined mechanism of Action

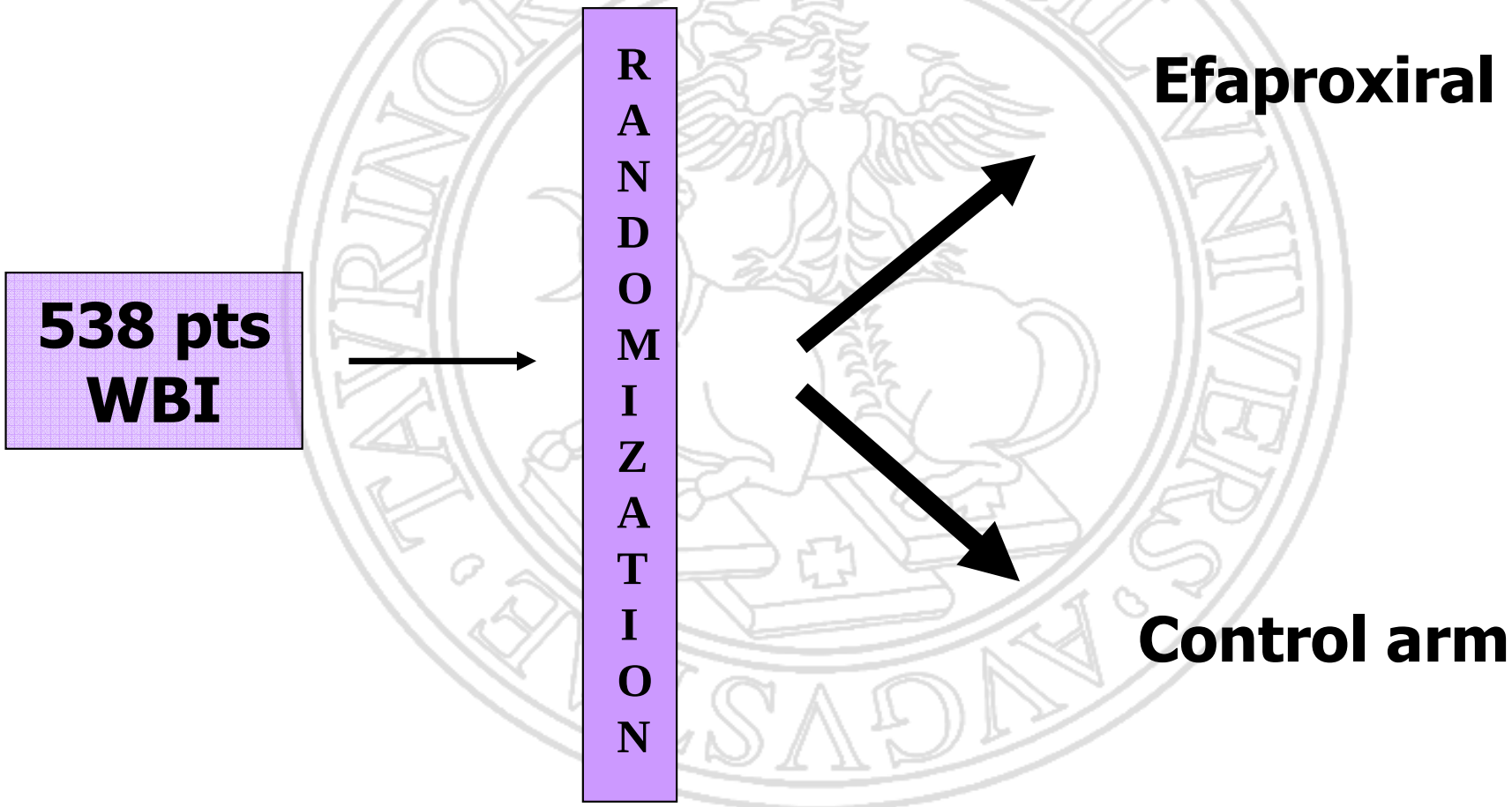
- Synthetic allosteric modifier of hemoglobin
- Decreases Hb affinity for O_2, increasing diffusion of O_2 to tissues
- No cytotoxic activity
- *In vivo* studies show reduction of hypoxic fraction in tumors after efaproxiral administration
- Increases tumor oxygenation during radiation therapy
- Need not penetrate tumor tissue for activity
- Need not cross blood brain barrier
- Rapid action and short half-life



Radiosensitizing agents in brain mets: Efaproxiral (RSR 13)

Study	Patients	Comments
Shaw, 2003	Phase II trial; WBI 30 Gy with 100 mg/kg efaproxiral; 69 pts	Median Survival 6.4 months; Grade 3-4 toxicities were hypoxia 10%, headache 10%, anemia 4%
Suh, 2003	Phase III trial; WBI 30 Gy ± efaproxiral 100 mg/kg/die; 538 pts	Median survival 5.3 months vs 4.5; improved survival in breast cancer subset

Phase III study of Efaproxiral as an adjunct to whole-brain Radiation therapy for brain Metastases



J.H. Suh,2003

Phase III Trial: WBRT +/- RSR-13

- 538 patients enrolled

WBRT and Supplemental O2 +/- RSR-13

No survival advantage: 5.3 vs 4.5 mo *(p=0.17)*

- In subset of 111 pts with breast cancer:
  - Control (n=52): 4.6 mo
  - RSR-13 (n=59): 8.7 mo

Pts with metastatic breast cancer to the brain also sustained a statistically significant increase in RR

A confirmatory phase III trial is underway

The ENRICH Study
ENRICH…..defined

ENhancing Whole Brain
Radiation Therapy
In Patients with Breast
Cancer and
Hypoxic Brain Metastases

The ENRICH Study

Objectives:

- Determine the effect of efaproxiral on primary and secondary endpoints in women with brain metastases from breast cancer receiving standard WBRT with supplemental oxygen
- Assess the safety of efaproxiral

End points:

Primary:

- Survival

Secondary:

- Response rate in the brain at 3 months
- KPS and neurologic signs and symptoms

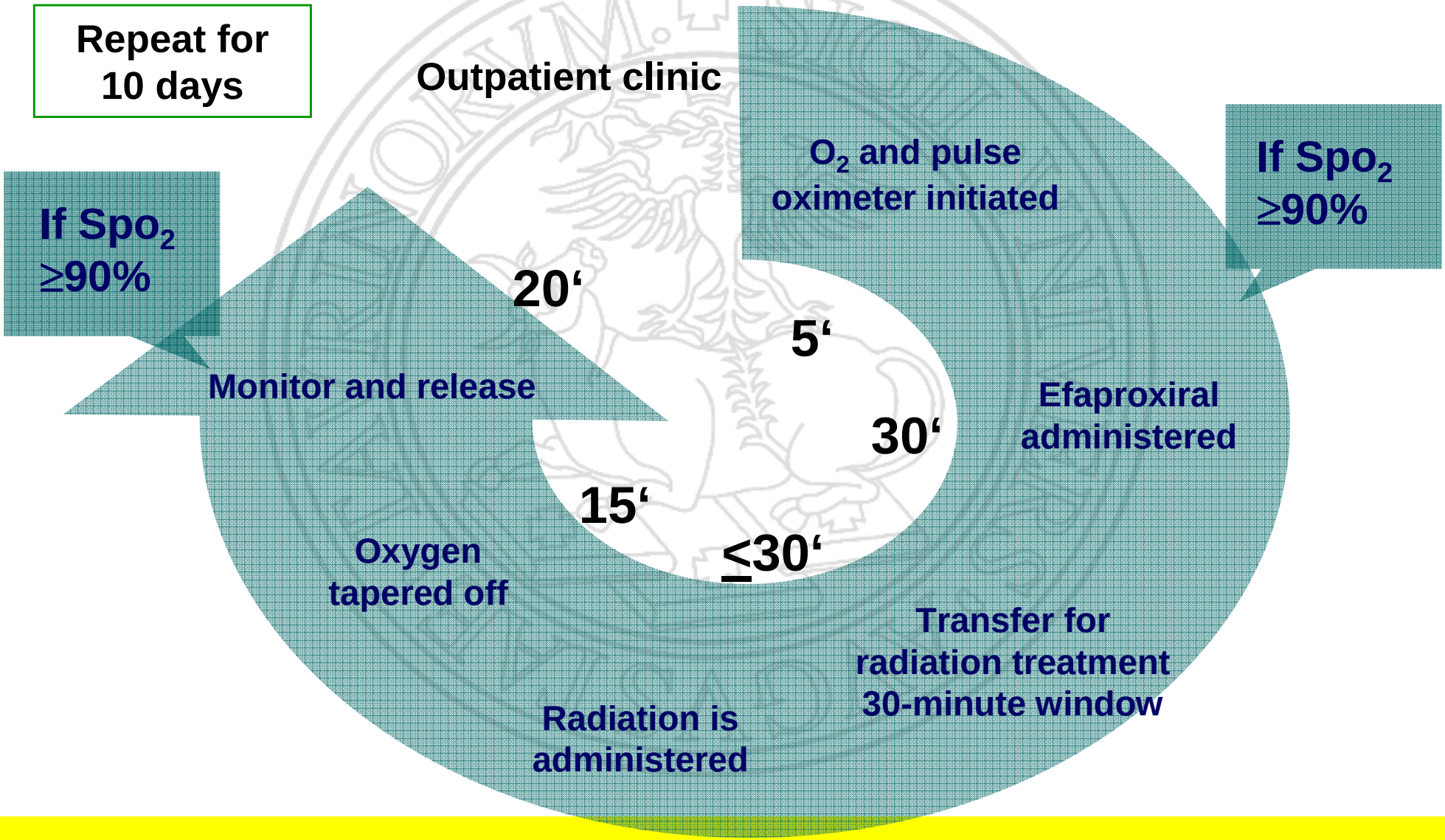
Mehta,2003

The ENRICH Study

- 360 eligible patients receiving a 2-week (10 fractions) course of WBRT (30.0 Gy/3.0 Gy fractions per day) with or without efaproxiral

- Patients are randomized 1:1 to:
  - Treatment Arm A: WBRT with efaproxiral (via a central venous access device) plus supplemental oxygen
  - Treatment Arm B: WBRT with supplemental oxygen, without a placebo

Efaproxiral Administration



Exclusion Criteria

- Active concurrent malignancy (except nonmelanoma skin cancer or in situ carcinoma of the cervix). If there is a history of prior malignancy, the patient must be disease-free for ≥5 years.
- The patient is a candidate for surgical resection and/or stereotactic radiosurgery as initial therapy for brain metastases.
- Planned concurrent systemic (cytotoxic and/or cytostatic) treatment for breast cancer and/or extracranial metastases during WBRT, with the exception of trastuzumab, hormonal, and/or corticosteroid therapy.
- Prior treatment for brain metastases (including external beam radiation therapy, brachytherapy, stereotactic radiosurgery, surgery, chemotherapy, and treatments with investigational drugs, biologics, or devices).
- Presence of leptomeningeal metastases.

Study Status

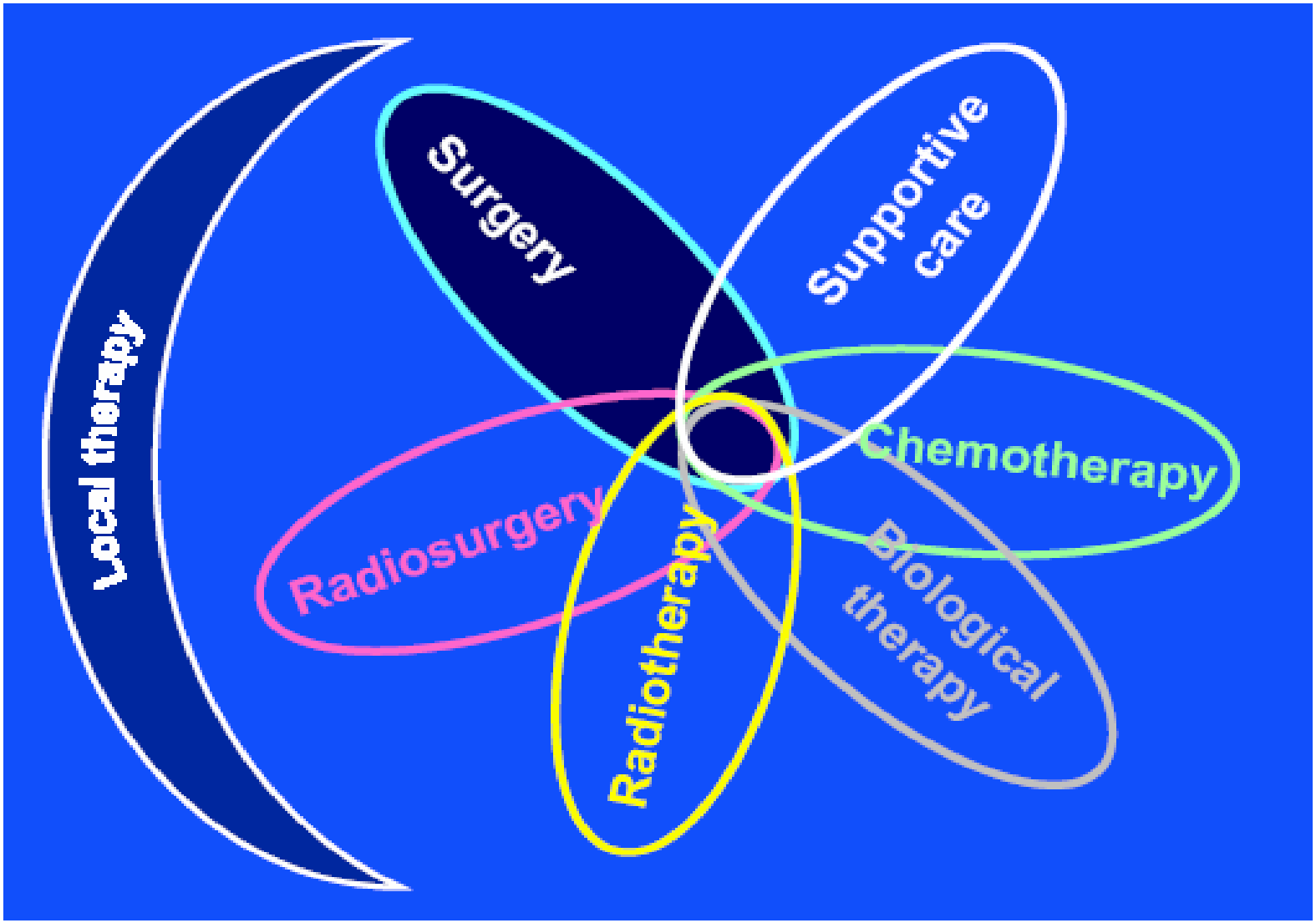
- Patient enrollment completed in August 2006, with a total of 368 patients enrolled at 78 medical centers
- Final analysis expected to occur in mid-2007

WBI and chemical modifiers of Radiation Therapy ("Radiosensitizers")

- Improvement of tumor response is a worthwhile aim in this population
- Regression of brain mets after WBI correlates with improved neurocognitive function and QoL (Level Ib)
- "Radiosensitizers" are not primary disease-specific

Solitary Brain Metastases

Oncological Management Options



Randomized studies of WBI plus SRS vs WBI alone in oligo (≤ 3) brain metastases

RTOG-9508: Phase III Trial

Enrollment: 1/96 - 6/01: N = 333 (2 pts excluded)

Arm 1: WBRT (37.5 Gy) + SRS: N = 164

≤ 2 cm	24 Gy
2.1 – 3.0 cm	18 Gy
3.1 – 4.0 cm	15 Gy

Arm 2: WBRT (37.5 Gy) alone: N = 167

- **Stratification**
  1. **Number of brain metastases (1 vs 2 - 3)**
  2. **Extracranial mets (none vs present)**

Andrews DW, et al. *Lancet* 2004

Randomized studies of WBI plus SRS vs WBI in oligo brain metastases

RTOG-9508: Subset Analysis

Survival Analyses	WBRT & SRS	WBRT	p-value
Overall	6.5 mo	5.7 mo.	0.13
Solitary brain met.	6.5 mo.	4.9 mo	0.04
1-3 mets & Age < 50	9.9 mo.	8.3 mo	0.04
1-3 mets & NSCLC	5.9 mo.	3.9 mo.	0.05
1-3 mets & RPA Class 1	11.6 mo.	9.6 mo.	0.05

Role of Adjuvant WBI

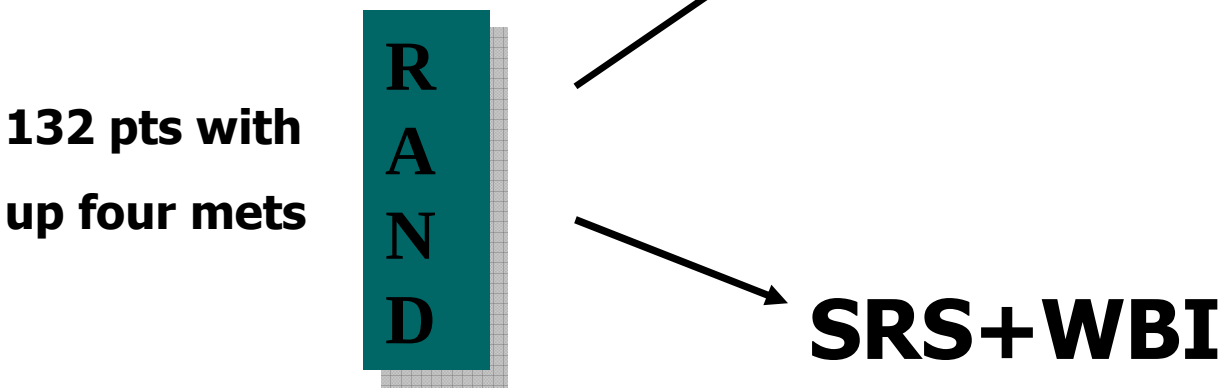
	Surgery (46)	Surgery + WBI (49)	
Recurrence:			
local	46%	10%	p<.001
in brain	37%	14%	p<.01
Time to recurrence:			
in brain (median)	26 wks	220 wks	
Neurologic death	44%	14%	p = .003
Survival (median)	43 wks	48 wks	p = .39

Patchell, 1998

Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

JAMA 2006;295:2483-2491

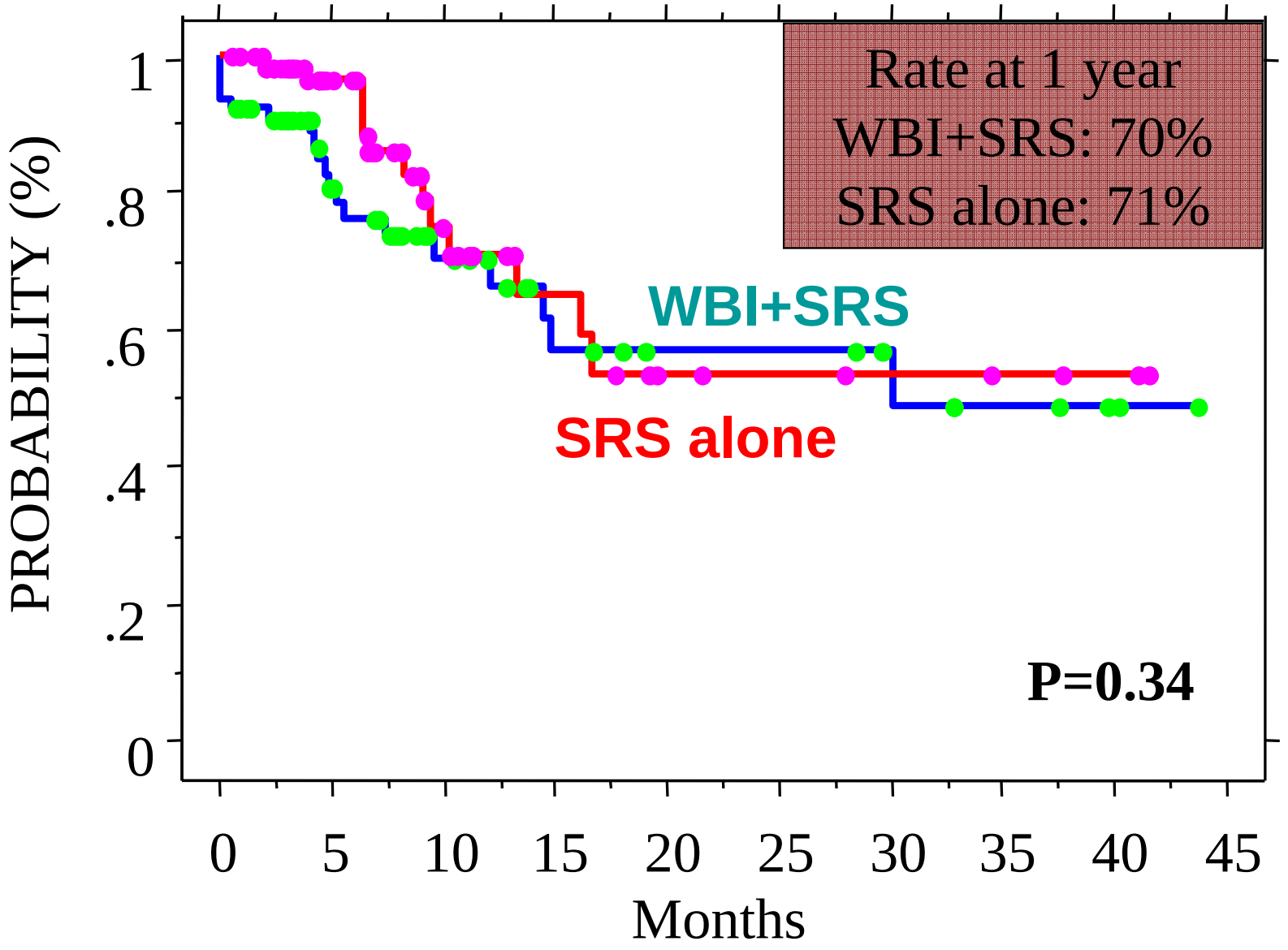


No Survival difference
(8.0 vs 7.5 mesi; *p=NS*)

Better intracranial desease control
(23.6% vs 53.2%; *p<0.001*)

No difference in neurocognitive outcome

Neurological Functional Preservation Rate (RPA class ≤ 2)

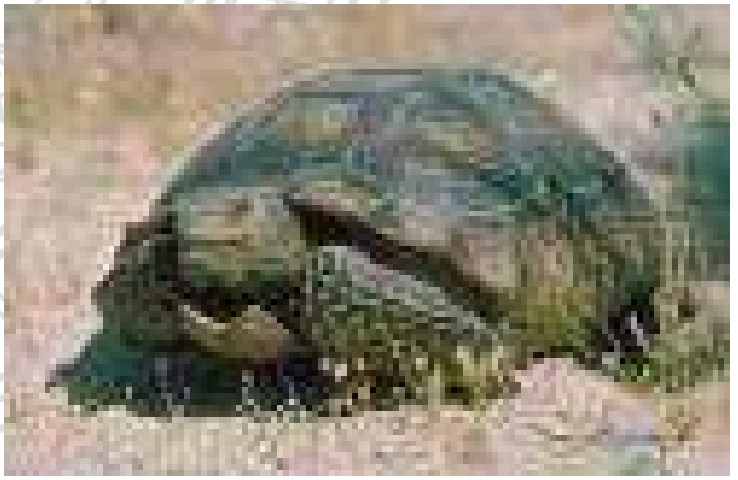


Aoyama, ASCO 2004

WBI and NCF/QOL

- WBRT is bad and should be delayed because that prevents neurocognitive deterioration and maintains quality of life

- Maybe so, probably not, because recurrence is worse for the brain



WBI and NCF/QOL

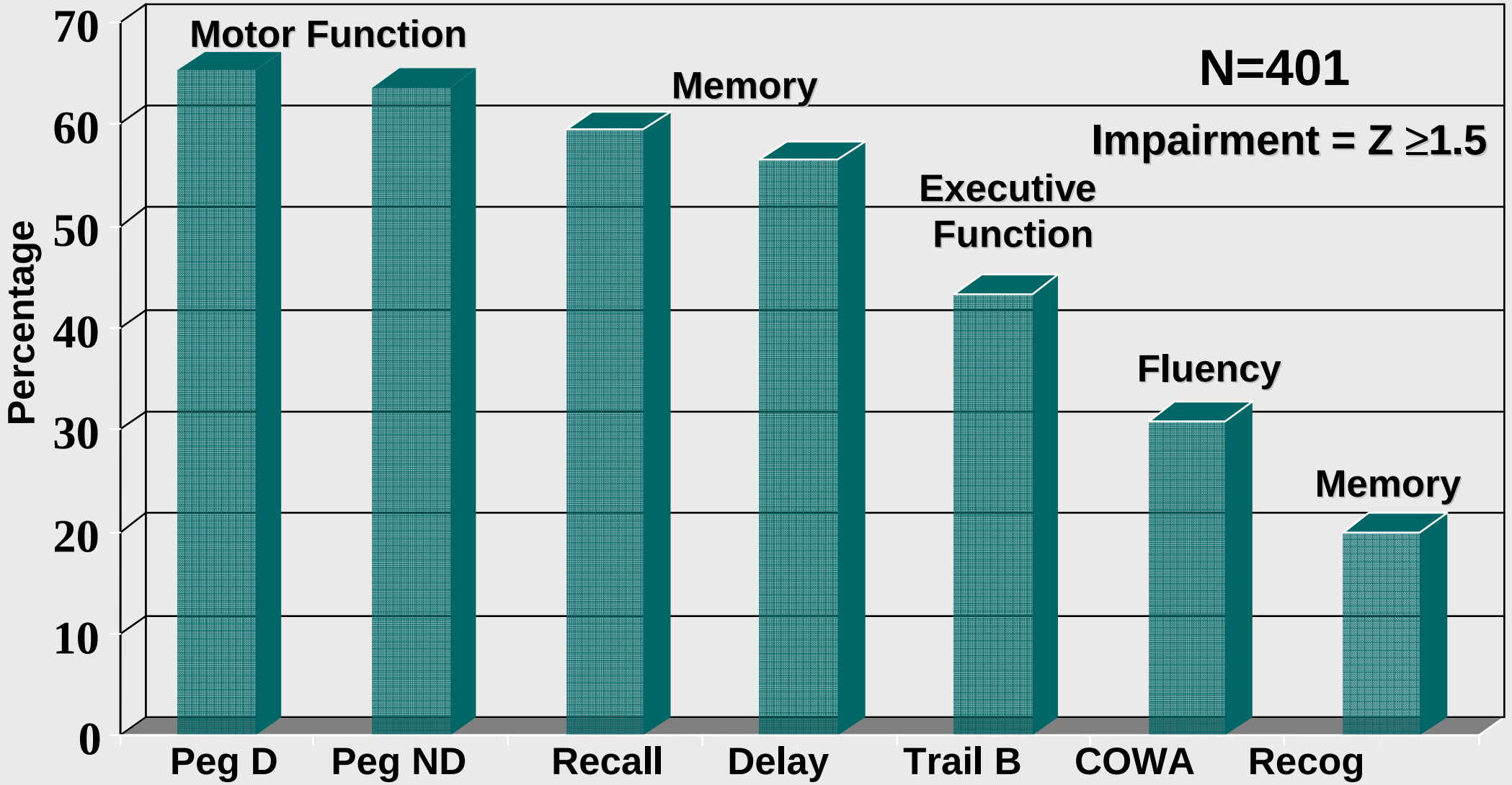
Dementia after WBI of brain metastases

Risk factors

- Treatment volume
- Fraction size >2 Gy
- Total dose: less important than fraction size
- Concurrent chemotherapy: possible
- Age: elderly patients (> 60 yrs) at higher risk

Patients Impaired at Presentation

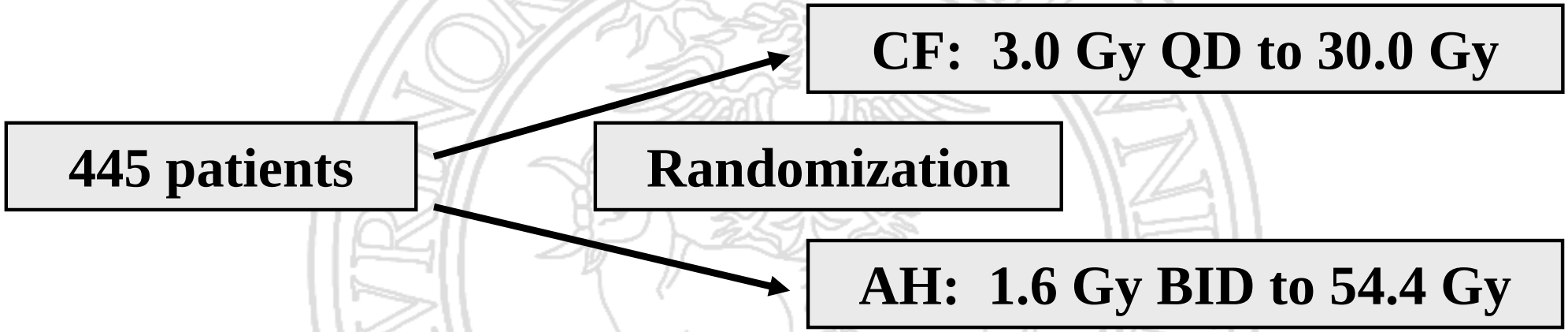
Brain mets patients have high rates of baseline deficits



Meyers CA, et al. *J Clin Oncol.* 2004

RTOG 91-04: Neurocognitive Outcome

- 445 patients accrued to RTOG 91-04.



- 359 patients had Mini-Mental Status Examinations (MMSE) performed before WBRT; and at 2 and 3 months

Tumor Control and MMSE Change

Uncontrolled tumor is *bad* for the brain.

Brain Mets	At 2 months Avg Change (N=91)	in MMSE	At 3 months Avg Change (N=23)	in MMSE
Controlled	**91%**	**-0.5**	**83%**	**-0.5**
Uncontrolled	**9%**	**-1.9**	**17%**	**-6.3**

***P*=0.02**

Regine, WF et al. IJROBP, 2001

WBI and NCF/QOL

What have we learned?

Radiation is not nearly as bad as the tumor is!!

Is It Rational to Withhold Whole Brain Radiotherapy?

EORTC
European Organisation for Research and Treatment of Cancer
1962-2002
40 years of excellence in developing new standards of cancer care

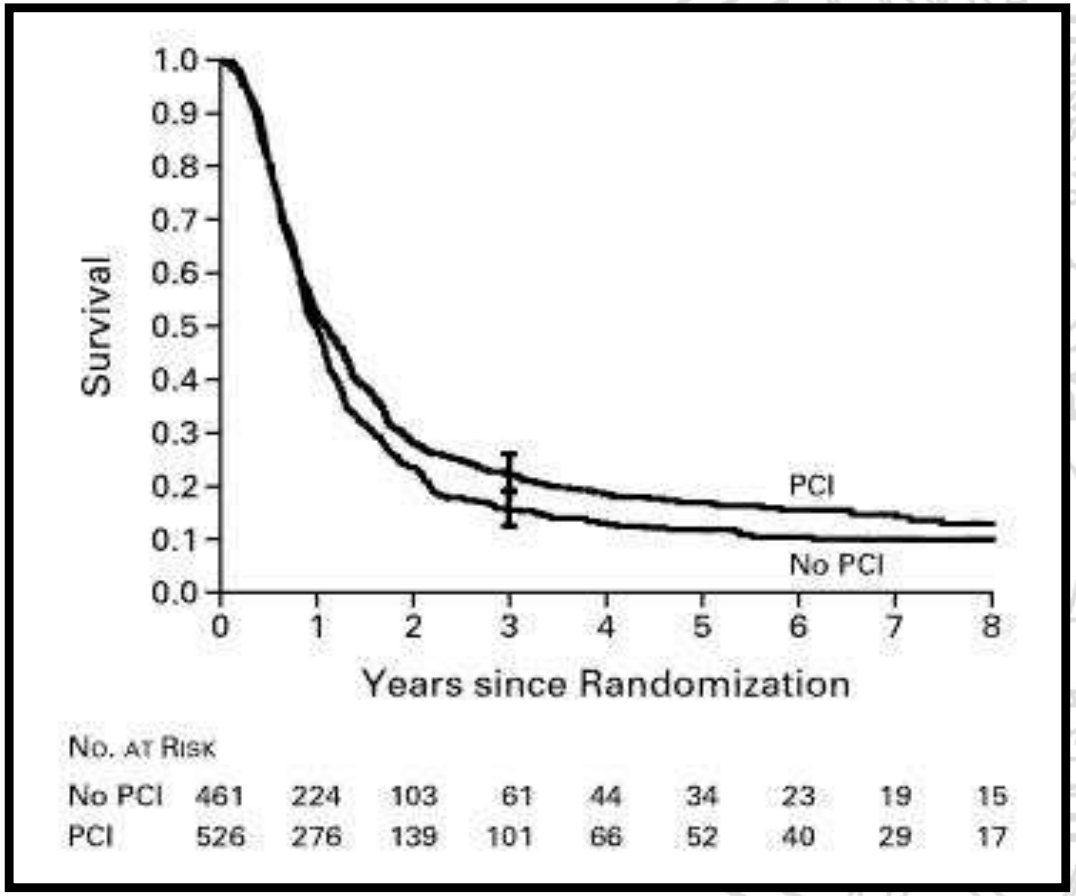
EORTC 22952-26001

No radiotherapy versus whole brain radiotherapy for 1 to 3 brain metastases from solid tumor after surgical resection or radiosurgery: a randomized Phase III trial

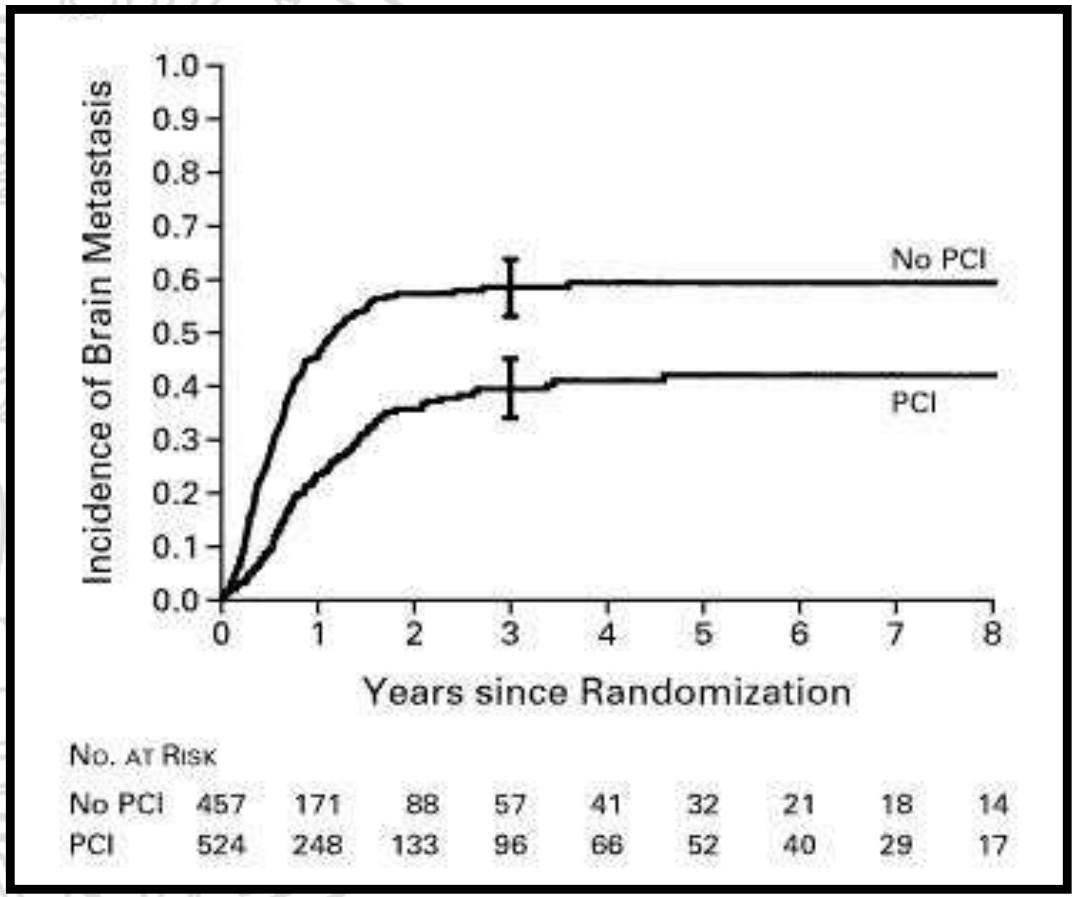
Role of WBI as prophylactic therapy

Meta-analysis of PCI in SCLC

Overall survival



Brain metastases



Auperin A NEJM 1999

Results of the meta-analysis of PCI in SCLC in complete remission

	No. of pts		Relative risk (95% CI)	P value	3-yr rate in the control group	Absolute benefit at 3 yr
	Treatment group	Control group				
OS	526	461	0.84 (0.73-0.97)	0.01	15.3%	+5.4%
DFS	526	461	0.75 (0.65-0.86)	<0.001	13.5%	+8.8%
Brain metastases	524	457	0.46 (0.38-0.57)	<0.001	58.6%	-25.3%

Auperin NEJM 1999

SCLC and Radiation therapy PCI

- The role of PCI now seems quite clearly indicated

- Dose, fractionation and timing require further clarification (PCI EULINT-EORTC trial, 25 Gy in 10 fr vs 36 Gy in 18 fr)

- Concerns on serious neurotoxicity mainly related to "old" hypofractionated schedules (prospective NCF evaluation as a part of prospective trials)

NSCLC and Radiation therapy PCI

- Brain mets are a relative common event in radically treated NSCLC patients
- PCI may reduce the incidence of brain mets, but there is no evidence of a survival benefit
- No data regarding whether radiotherapy regimen is superior, and the effect of PCI on QoL
- RTOG 0214, randomized trial, is ongoing

Carolan, 2005

Prophylactic Cranial Irradiation in the treatment of locally advanced NSCLC

Study	pts	PCI dose	Primary treatment	CNS failure (Obs vs PCI)	P value
Cox et al.	281	20 Gy	RT alone	13% vs 6%	0.038
Russell et al.	187	30 Gy	RT alone	19% vs 9%	0.010
Umsawasdi et al.	97	30 Gy	CT and RT or CT,RT, and surgery	27% vs 4%	0.002

Significantly lower risk for developing brain mets with PCI, but no difference in survival

Phase III randomized trial RTOG 0214

Conclusions

- Disease oriented studies in brain metastases

- Identification of patients at higher risk of developing brain mets (epidemiological studies, gene expression profiling)

- RT, with or without chemo, is still the treatment of choice for pts needing a palliation of neurological symptoms