UniversityHospital Zurich

MADRID 2014 ESMO congress

University of Zurich[UZH]

Brain Metastases – to treat or not to treat

Roger Stupp, MD
Professor and Director
Department of Oncology and Zurich Cancer Center

President

European Organisation for Research and Treatment of Cancer

EORTC *The future of cancer therapy*

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Disclosures

MADRID 2014 ESMO congress

Roger Stupp has served as an advisor to Roche/Genentech, Merck KGaA, MSD/Merck&Co.

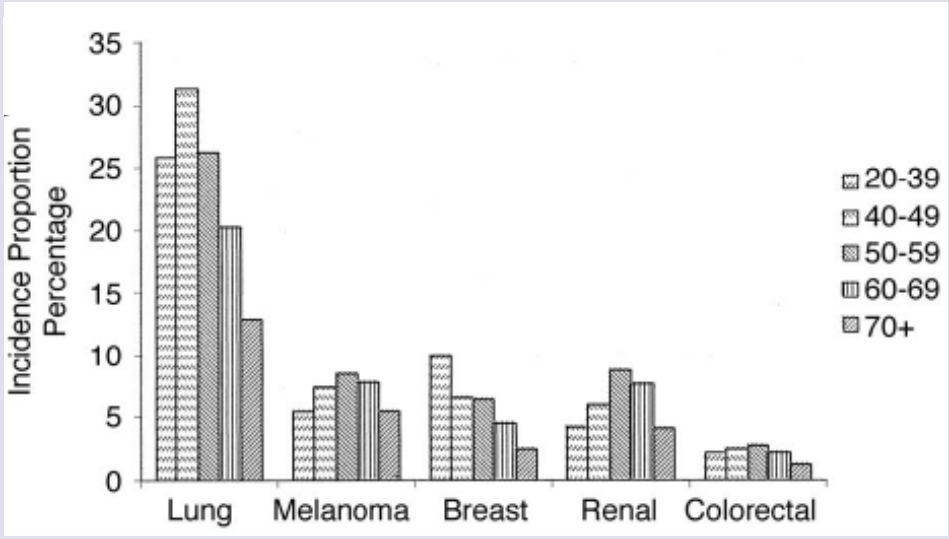
There a no potential conflicts of interest with regards to this presentation.

Acknowledgements

- Nicolas Andratschke, Zurich
- Michael Brada, Liverpool
- Enrico Francesci, Bologna
- Ricardo Soffietti, Torino
- Michael Weller, Zurich

Brain Mets: Incidence

- Occur in 10-30% of all adult cancers
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma



Barnholtz-Sloan… Sawaya RE. J Clin Oncol 22:2865-72, 2004

Definitions and Paradigms

- Metastasis: *"The spread of disease from one part of the body to another, as when cancer cells appear in parts of the body remote from the site of the primary tumor »*
- Metastases are commonly multiple
- Treatment is dictated by the histology and origin of the primary tumor

Definitions and Paradigms

- Metastatic disease dissemination requires a systemic therapy
- Mets in the brain respond just as well to systemic treatment than other mets (if the drug reaches its target, BBB!)

→ Conclusion:

- Brain mets are a manifestation of a primary tumor, not a diagnosis per se

Brain metastases

- Is a symptom and disease manifestation, not a diagnosis

→ Management & recommendations need to be disease specific

- **Literature (Pubmed Aug 2012 – July 2014): >150 publications on brain mets without specifying tumor type in title**

Challenges

Challenges of research in brain metastases

- Lack of preclinical models
- Little knowledge of biological predisposing factors
- Role of the blood-brain barrier
- Unique microenvironnment in the brain
  → sanctuary site (?)

- Exclusion of pts from clinical trials
- Risk of hemorrhage

<u>Incidence brain mets ↑</u>

- Improved systemic therapy
- Longer survival
- Better detection of occult metastases

Different biology ?

Melanoma: Concordance between extracranial and brain metastases

Molecular Profiling of Patient-Matched Brain and Extracranial Melanoma Metastases Implicates the PI3K Pathway as a Therapeutic Target

Guo Chen, Nitin Chakravarti, Kimberly Aardalen,, Alexander J. Lazar, Michael Tetzlaff, Bradley Wubberhorst, Sang-Bae Kim, Scott Kopetz, Alicia Ledoux, Y.N. Vashisht Gopal, Cristiano Goncalves Pereira, Wanleng Deng, Ju-Seog Lee, Katherine L. Nathanson, Kenneth D. Aldape, Victor G. Prieto, Darrin Stuart, and Michael A. Davies

Clin Cancer Res Published OnlineFirst May 6, 2014

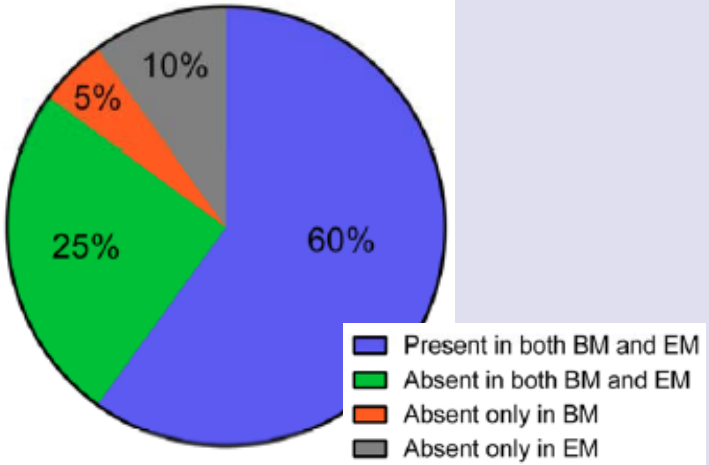
Sequenom analysis: 154 hotspot mutations

- 16 matched pairs
- 100% concordance

Gene expression profiling (25 pairs)

- Highly concordant expression

Immunohistochemistry: PTEN



Genes involved in formation of brain mets

Eichler .. & Jain. Nat. Rev. Clin. Oncol. 2011; 8: 344–356?

Genes	Function	Primary tumor type	Comments
COX2	Important in prostaglandin production, possibly leading to increased permeability of BBB	Breast	Inhibition suppresses penetration of an artificial BBB, and enhances brain-metastasis-free survival[78]
HBEGF	EGFR ligand—increases cell growth, motility, and invasiveness	Breast	Inhibition suppresses penetration of an artificial BBB, and enhances brain-metastasis-free survival[78]
ST6GALNAC5	Sialyltransferases catalyze the addition of sialic acid to gangliosides and glycoproteins, and cell-surface sialylation has been implicated in cell–cell interactions	Breast	Inhibition suppresses penetration of an artificial BBB, and enhances brain-metastasis-free survival[78]
HK2	Important in glucose metabolism, oxidative phosphorylation, and antiapoptosis	Breast	High *HK2* expression is associated with poor patient survival after craniotomy[140]
FOXC1	Transcription factor essential for mesoderm development; involved in brain development and brain tumorigenesis	Breast	Predicts poor overall survival in basal-like breast cancer, a higher incidence of brain metastasis and a shorter brain-metastasis-free survival in lymph-node-negative patients[141]
HER2	Receptor tyrosine kinase of the EGFR family	Breast	Overexpression increased the incidence of large brain metastases (>50 μm^2)[73]
LEF1	A transcriptional effector of the canonical WNT pathway	Lung	Part of a signature that predicts lung metastasis to the brain; knockdown inhibited brain metastasis, and decreased colony formation and invasion *in vitro*[142]
HOXB9	Belongs to the homeobox transcription factor gene family, which is critical for embryonic segmentation and limb patterning—a TCF4 target	Lung	Part of a signature that predicts lung metastasis to the brain; knockdown inhibited brain metastasis, and decreased colony formation and invasion *in vitro*[142]
CDH2, KIFC1, and FALZ3	N-cadherin is a calcium-dependent cell–cell adhesion molecule	Lung	Highly predictive of brain metastasis in early-stage and advanced-stage lung cancers—causal role is not clear[143]
STAT3	Important transcription factor in cellular signaling pathways	Melanoma	Reduction suppressed brain metastases—affected angiogenesis *in vivo* and cell invasion *in vitro*[144]
$\alpha_v\beta_3$	Important for sprouting endothelial cells, contributes to angiogenesis, supports invasion and metastasis	MDA-MB-453	Activated $\alpha_v\beta_3$ enhances brain metastatic tumor growth through continuous upregulation of VEGF, leading to increased angiogenesis and decreased hypoxia[54]
HDAC3, JAG2, NUMB, APH1B, HES4, and PSEN1	Notch signaling pathway genes that determine cell fates through communication with their environment	MDA-MB-453	Inactivation of Notch significantly inhibited migration and invasion[145]

VEGF & brain mets formation

VEGFA	Angiogenic growth factor	Breast	Increased in brain-metastatic clones, and VEGFR inhibition decreased brain tumor burden via a reduced number of blood vessels, decreased proliferation and increased apoptosis[52]
		Melanoma	Overexpression accelerated growth, accompanied by dilation of co-opted tumor vessels with concomitant induction of vascular permeability[48]
		Lung & colon	Decreased expression significantly decreased the incidence of brain metastases[51]

Real-time imaging reveals the single steps of brain metastasis formation

Yvonne Kienast[1,2], Louisa von Baumgarten[1], Martin Fuhrmann[2], Wolfgang E F Klinkert[4], Jochen Herms[2,5] & Frank Winkler[1,5]

NATURE MEDICINE VOLUME 16 | NUMBE

Brain metastasis frequently occurs in individuals with cancer and is often fatal. We used multiphoton laser scanning microscopy to image the single steps of metastasis formation in real time. Thus, it was possible to track the fate of individual metastasizing cancer cells *in vivo* in relation to blood vessels deep in the mouse brain over minutes to months. The essential steps in this model were arrest at vascular branch points, early extravasation, persistent close contacts to microvessels and perivascular growth by vessel cooption (melanoma) or early angiogenesis (lung cancer). Inefficient steps differed between the tumor types. Long-term dormancy was only observed for single perivascular cancer cells, some of which moved continuously. Vascular endothelial growth factor-A (VEGF-A) inhibition induced long-term dormancy of lung cancer micrometastases by preventing angiogenic growth to macrometastases. The ability to image the establishment of brain metastases *in vivo* provides new insights into their evolution and response to therapies.

Imaging model:

- Stepwise brain mets formation
- Interaction tumor cell by angiogenesis or vessel co-option
- VEGF inhibition → mets formation ↓

CNS metastasis from solid tumors

	Incidence Clinical (%)	Autopsy (%)	Median interval from diagnosis (months)	Range (months)
Lung cancer				
small cell	30-45	30-70	2.6	0-15
adenocarcinoma	24-30	50	2	0-66
squamous cell	30	40	0.2	0-31
Breast cancer	10-20	20-40	23	0-121
Melanoma	20-45	40-90	36	3-83
Renal cell cancer	20	20	39	19-119
Colon cancer	4	6-10	22	0-48

So maybe after all

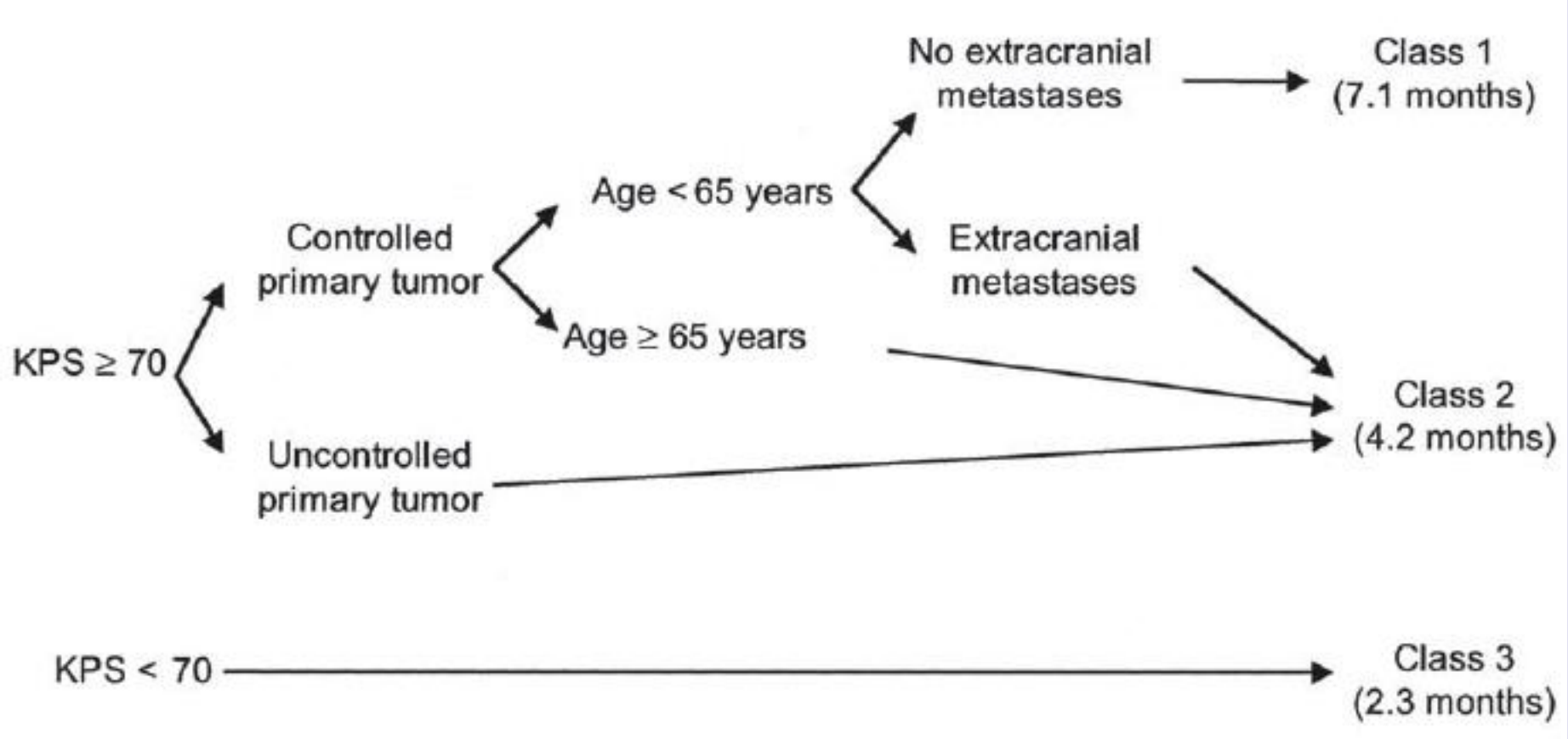
- Biology of CNS metastases not so different from visceral metastases

Why do we treat brain mets differently ? – Brain as a sanctuary !

- Blood-brain barrier
  - Disrupted for macroscopically overt mets (contrast enhancement !)
  - Intact for micrometastases
- Poor prognosis
  - Presence of [symptomatic !] CNS mets associated with advanced disease
  - Screening (MRI) allows detection of occult/silent mets → earlier diagnosis, lead time bias and stage migration

Prognosis – the individual and the median

RPA classification for brain mets

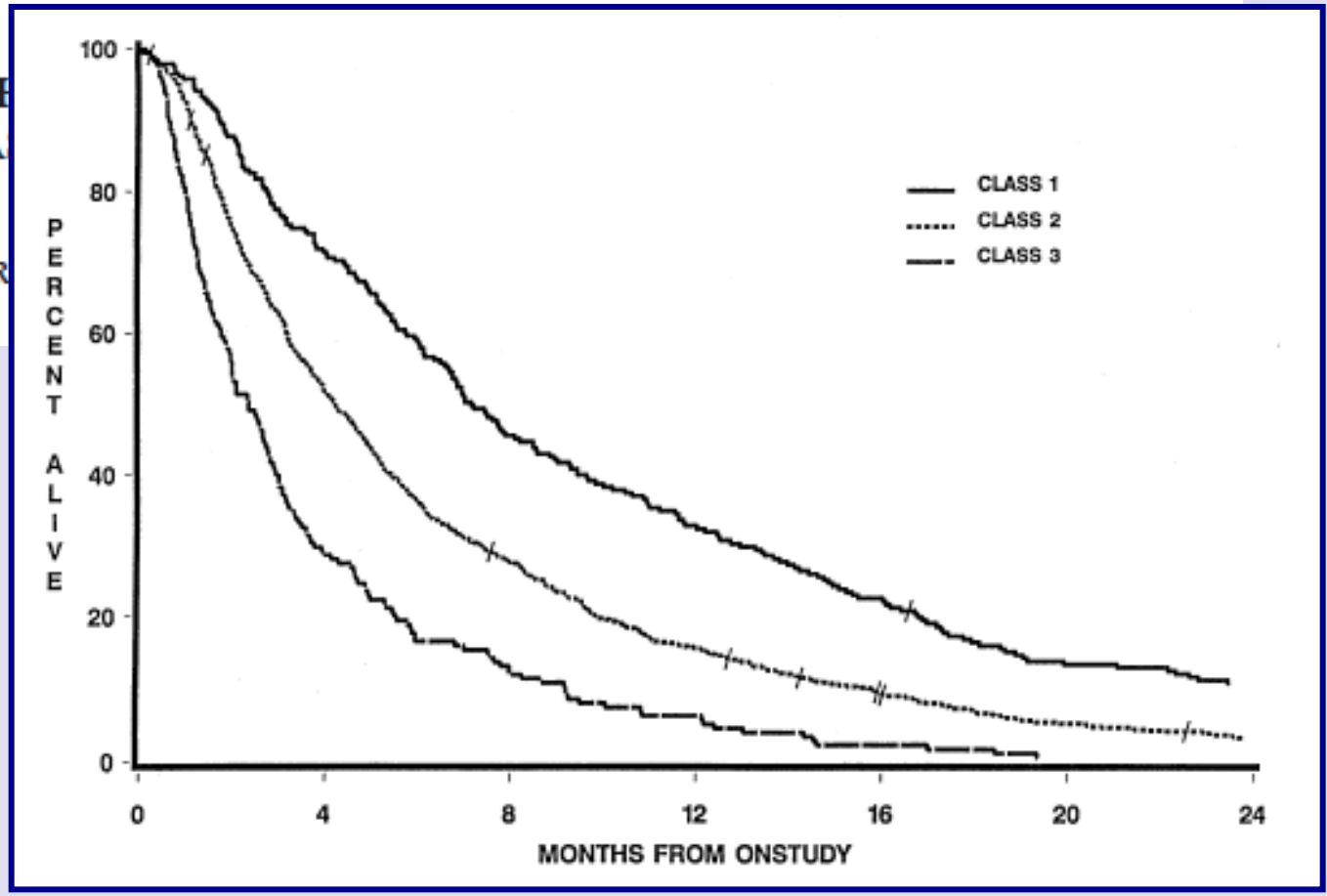


Brain mets: Prognostic Indices: RTOG RPA

RECURSIVE PARTITIONING ANALYSIS (RPA) OF PROGNOSTIC FACTORS IN THREE RADIATION THERAPY ONCOLOGY GROUP (RTOG)

VALIDATION OF TH
CLA

LAURIE E. GASPAR



Class 1:

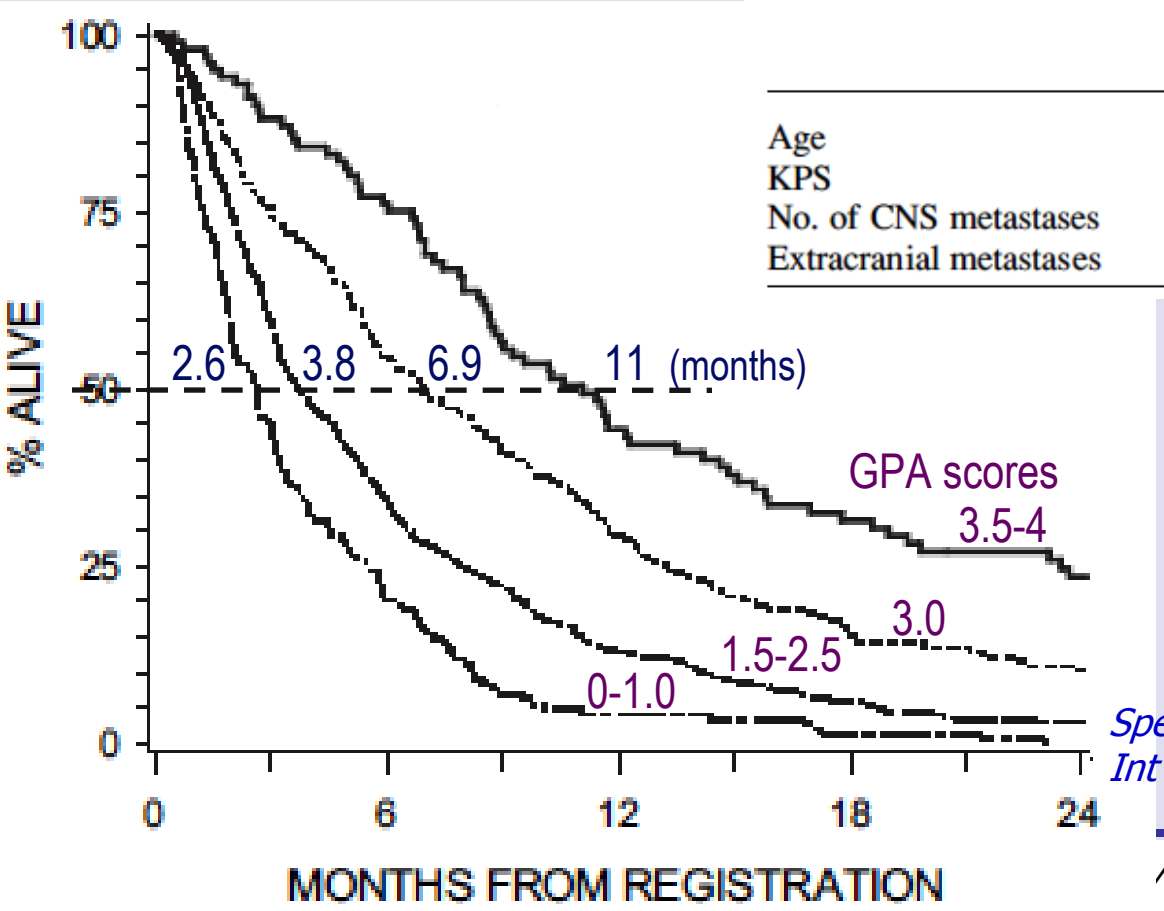
- KPS≥70%
- Age<65 yrs
- primary controlled,
- no other mets

Brain Mets: Prognosis

"Graded Prognostic Assessment"

Table 4. Graded Prognostic Assessment

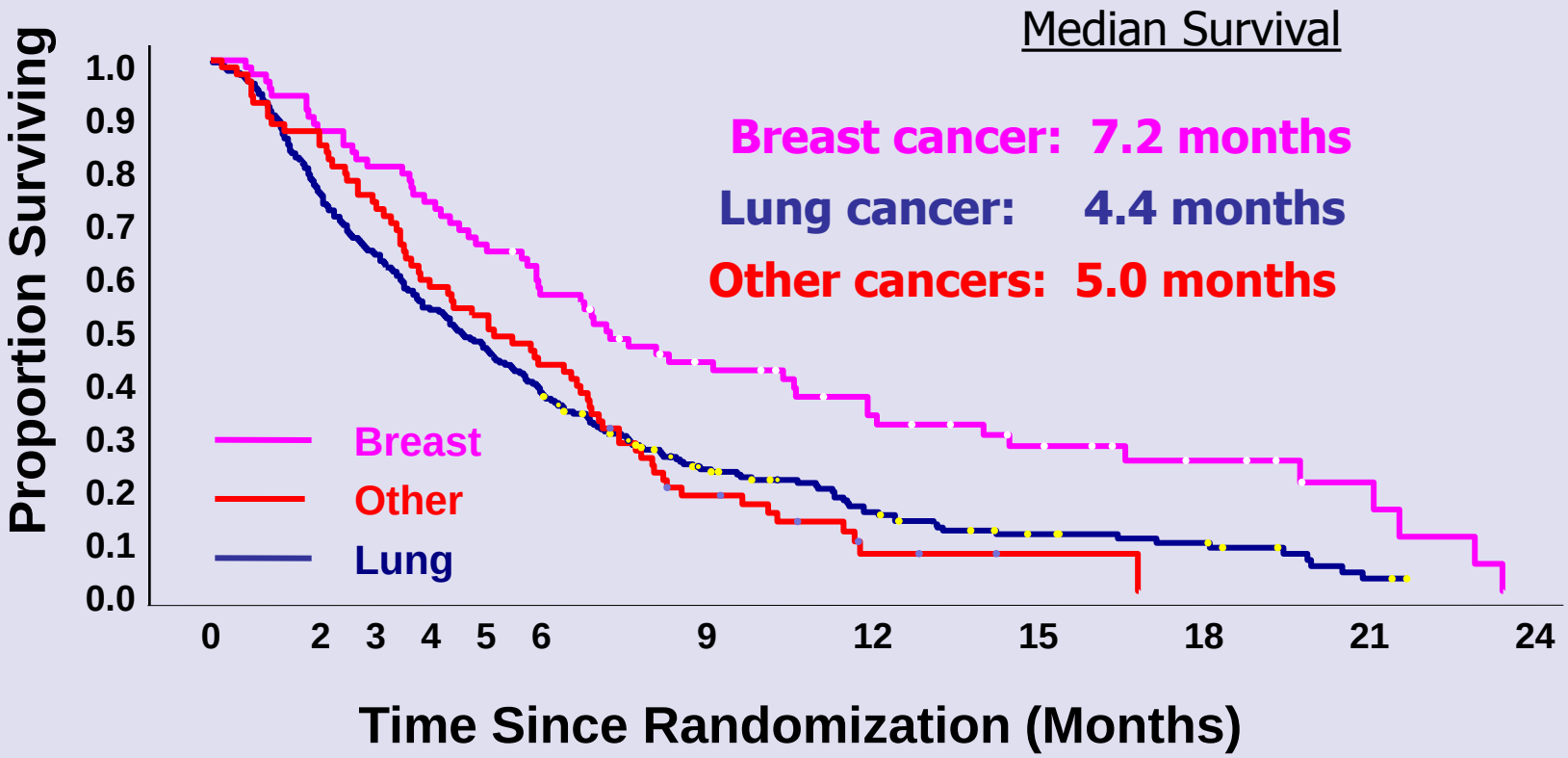
	Score		
	0	0.5	1.0
Age	>60	50–59	<50
KPS	<70	70–80	90–100
No. of CNS metastases	>3	2–3	1
Extracranial metastases	Present	—	None



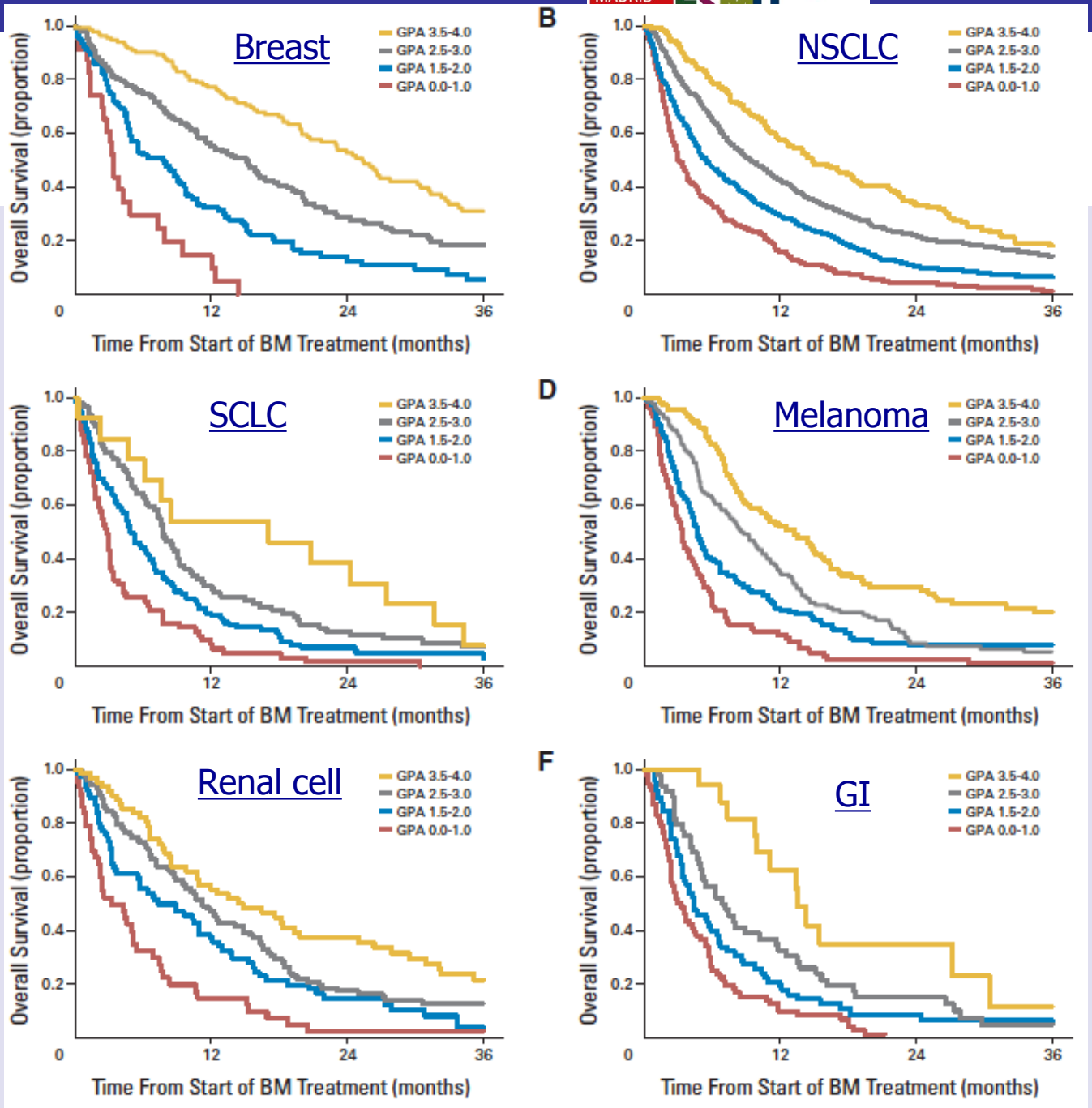
- Performance status
- Age
- No. of mets
- Extracranial disease

Sperduto et al for RTOG.
Int J Radi Oncol Biol Phys 2008; 70:510–514

Histology matters …!



Mehta MP, et al. J Clin Oncol. 2003;21:2529-2536.



Sperduto et al.
J Clin Oncol 2011; 30:419-425

Experts are inaccurate in prognostication

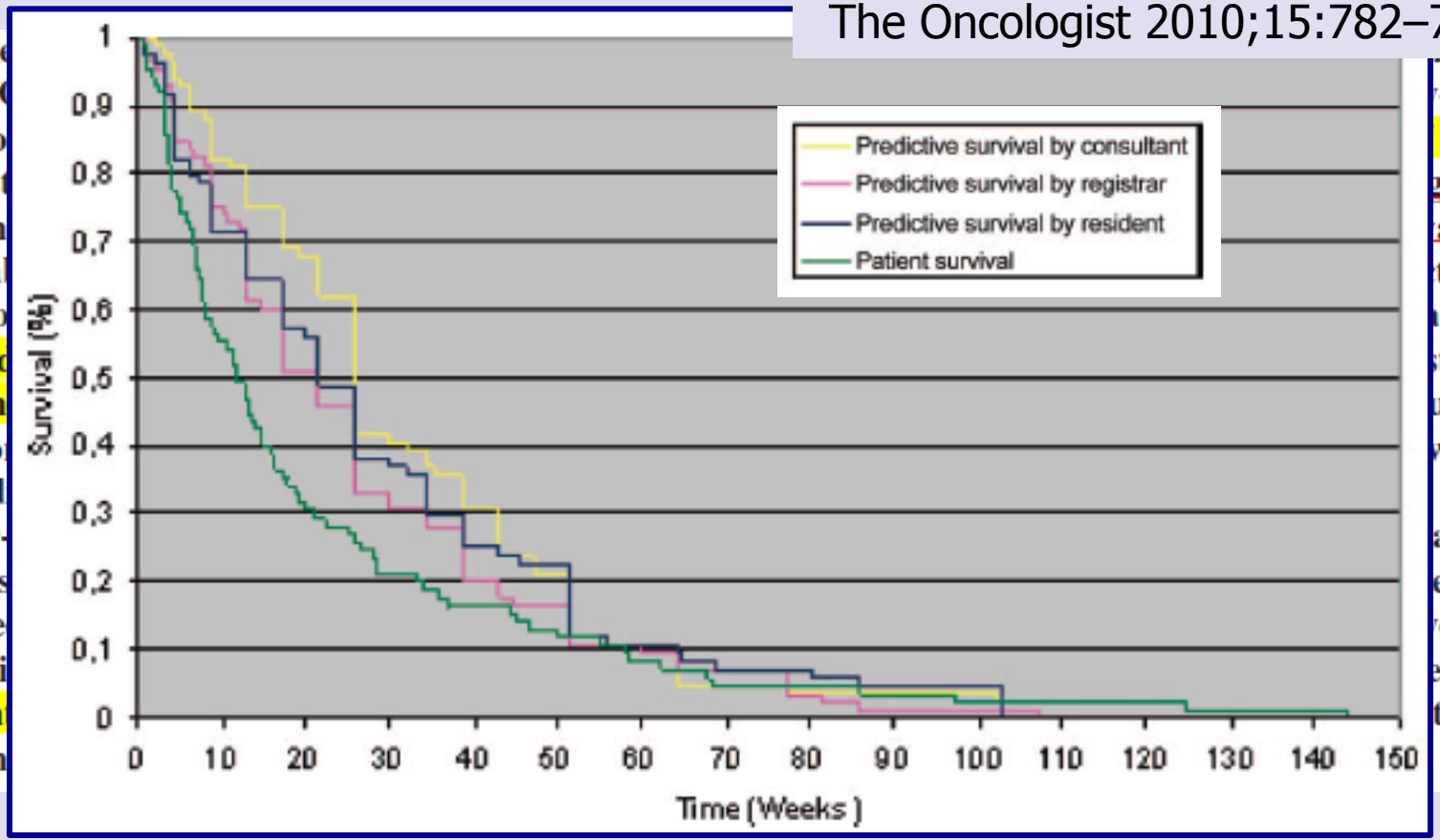
How Accurate Are Physicians in the Prediction of Patient Survival in Advanced Lung Cancer?

CHRISTELLE CLÉMENT-DUCHÊNE,[a] CHARLOTTE CARNIN,[a] FRANCIS GUILLEMIN,[b] YVES MARTINET[a]

The Oncologist 2010;15:782–789

Background. Be
cancer (NSCL
with a poor pro
is critical. Most
ancy >3 month
survival probal
lines. The aim o
clinicians' prec
(stages IIIB, an
quality of life o
Methods. At d
life data (QLQ-
doctors "forecas
cordance betwe
sessed with the i
Results. Eigh
years, 81.1% m

-up was
(range,
gistrars,
al time,
ted and
tus was
stimated
unction-
ween es-
ations to
ection in
estigate
es by cli-
t patient



Experts are inaccurate in prediction of survival

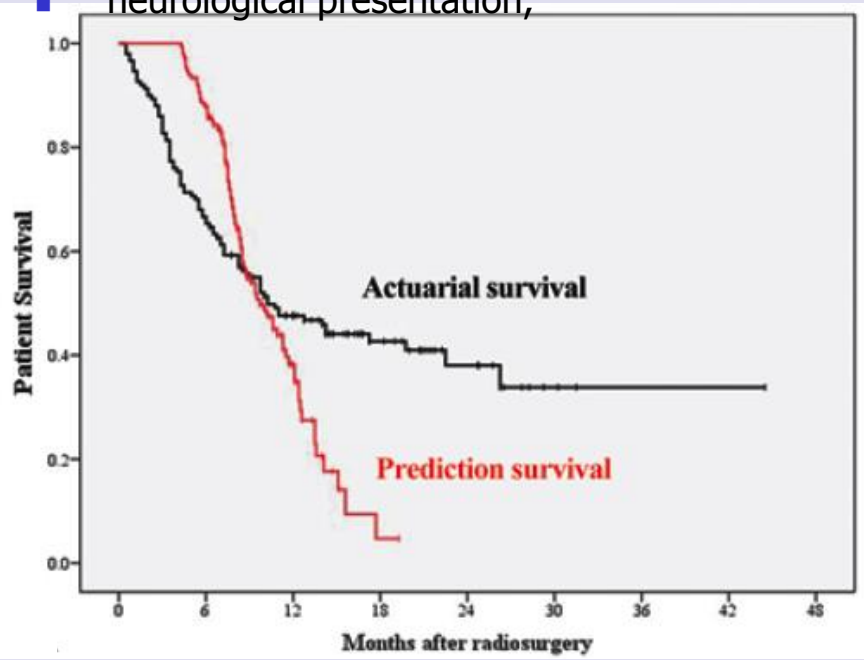
The accuracy of predicting survival in individual patients with cancer

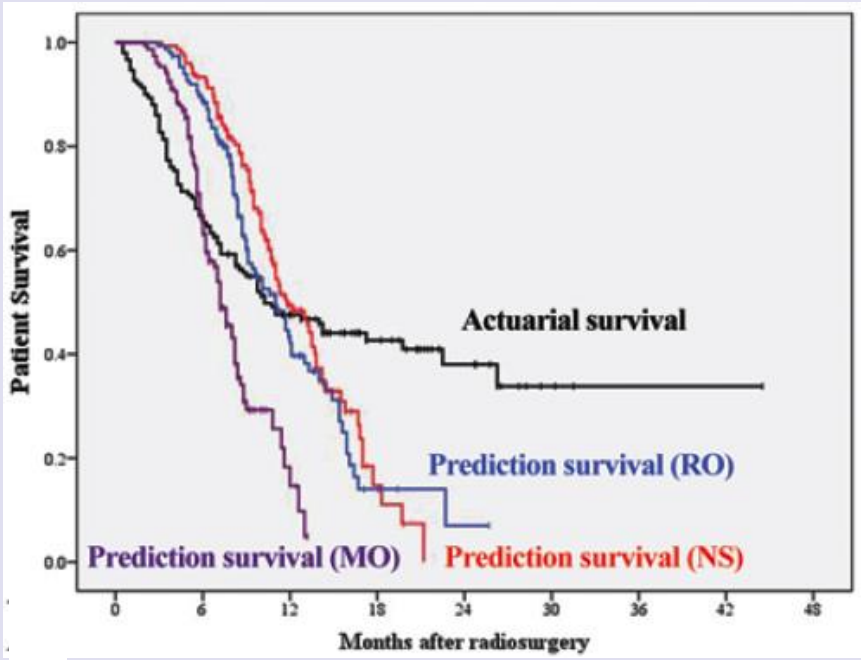
Kondziolka ... & Stupp. J Neurosurg 120:24–30, 2014

- 150 patients treated with SRS
- Estimate survival by 18 MD's

Clinical data available:

- cancer type
- number of brain metastases,
- neurological presentation,
- extracranial disease status,
- Karnofsky Performance Scale score,
- Recursive Partitioning Analysis class,
- prior whole-brain radiotherapy,
- synchronous or metachronous





Prognosis


© MARK ANDERSON
WWW.ANDERTOONS.COM
ANDERSON
"I said you had three months to live, and I meant it."

Why are we treating patients with brain metastases ?

Why are we treating patients with brain metastases ?

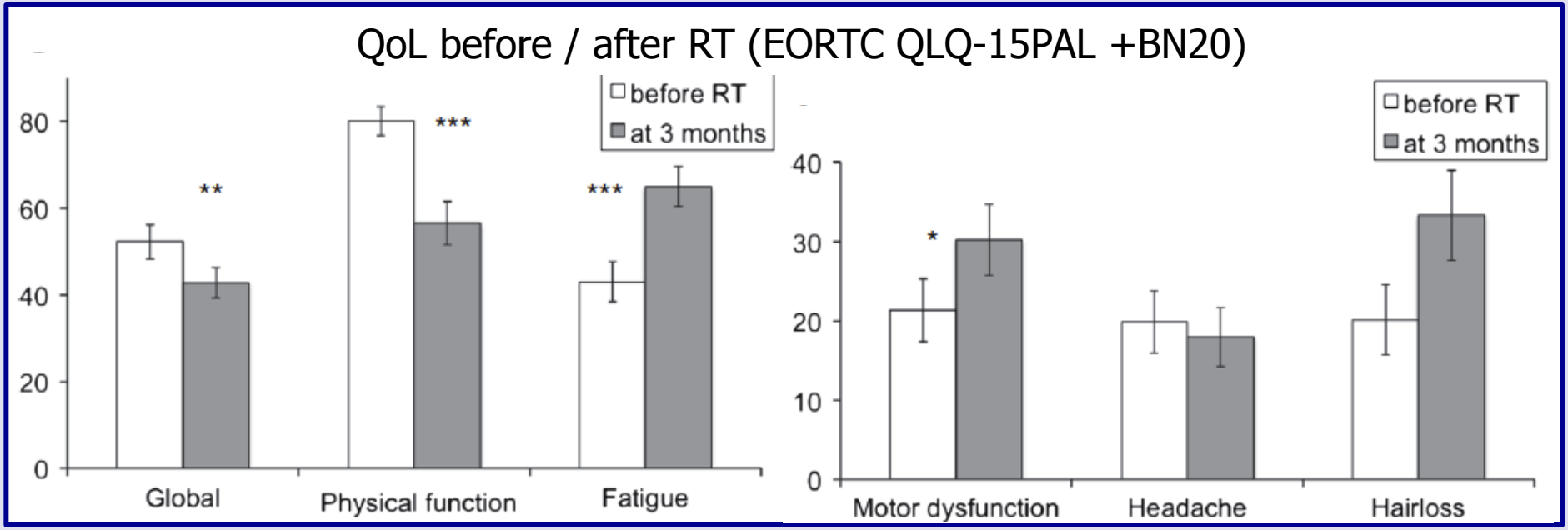
- Quality of life
- Avoidance of neurological progression
- Symptom control
  - prophylaxis

No improvement in QoL after WBRT

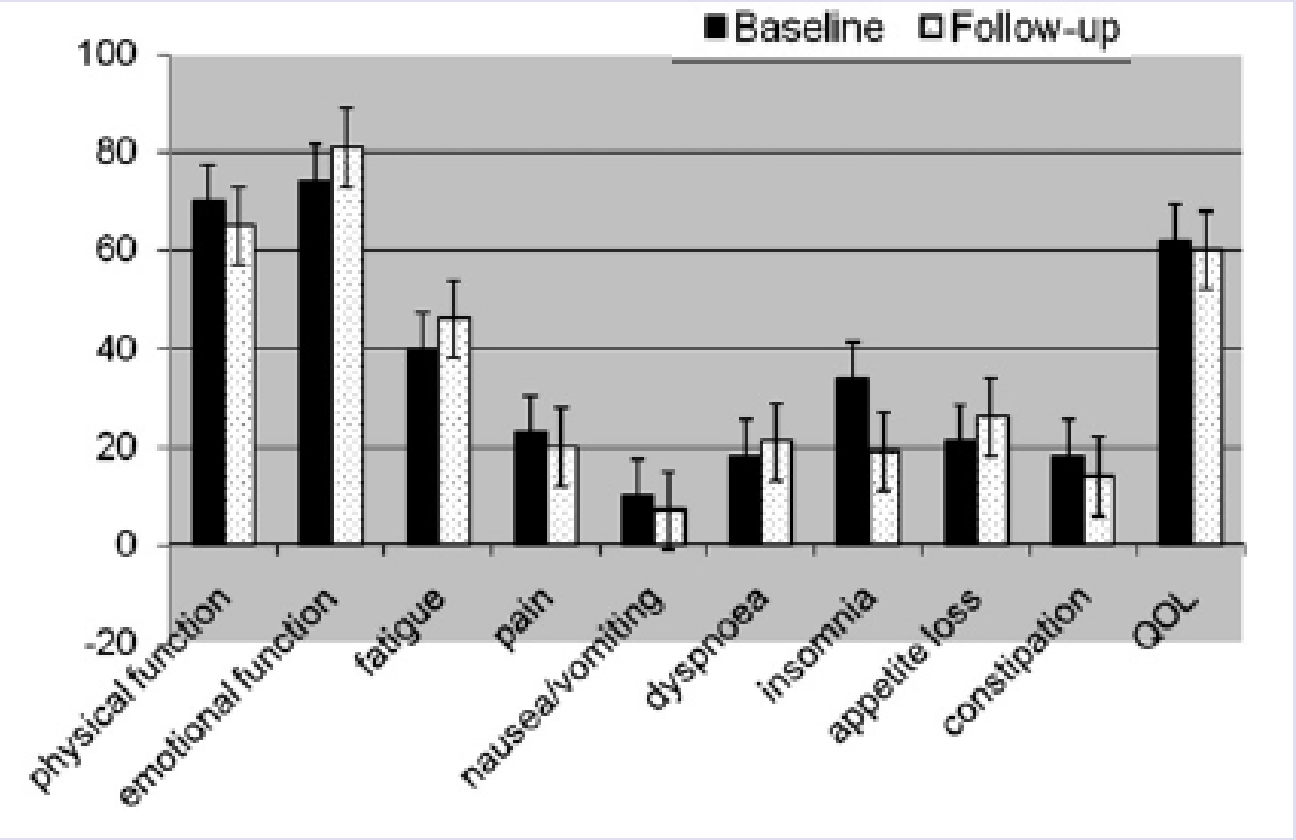
Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases

Steinmann et al. BMC Cancer 2012, 12:283

QoL before / after RT (EORTC QLQ-15PAL +BN20)



Quality of life after radiotherapy

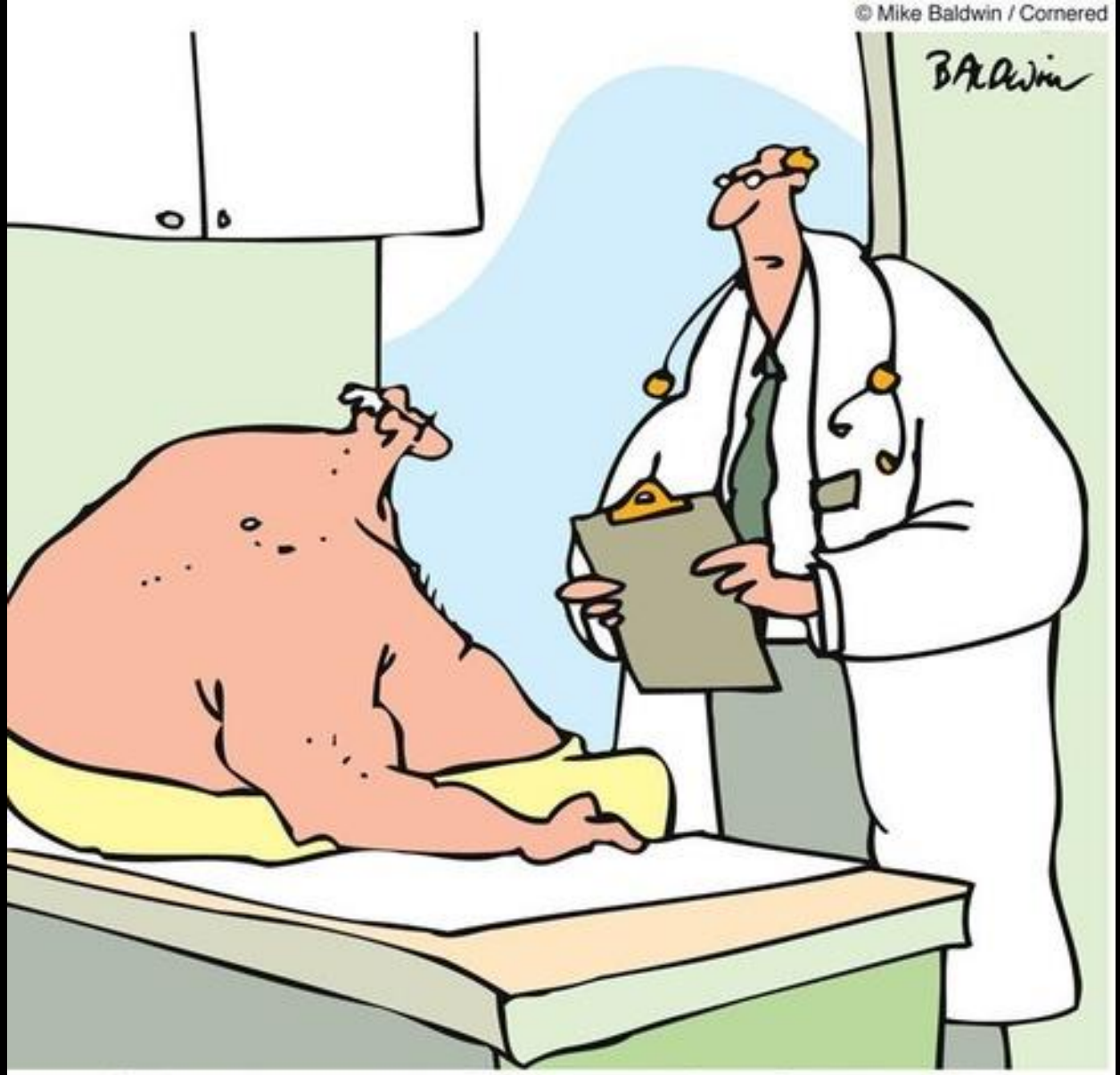


EORTC QLQ-C15-PAL scores

mean scores, 108 pts

- before
- 1 month after WBRT

Caissie et al. Int J Radiat Oncol Biol Phys. 2012 ;83:1238-45

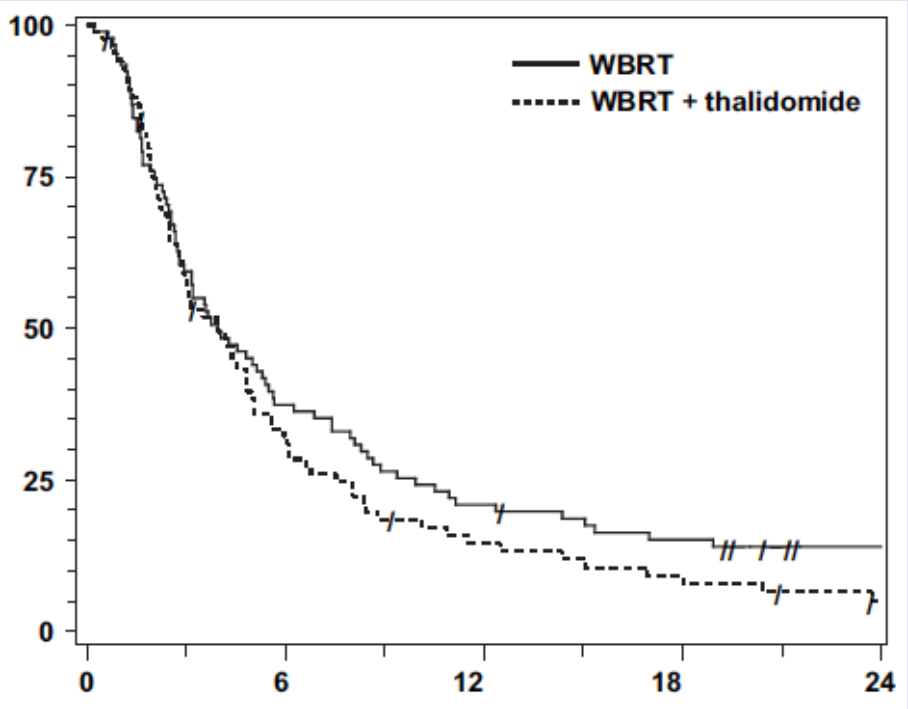


"You've got six months, but with aggressive treatment we can help make that seem much longer."

Short survival of most (!) brain mets pts receiving WBRT

A PHASE III STUDY OF CONVENTIONAL RADIATION THERAPY PLUS THALIDOMIDE VERSUS CONVENTIONAL RADIATION THERAPY FOR MULTIPLE BRAIN METASTASES (RTOG 0118)

- 183 pts randomized
  - RPA class 1 (25%)
    RPA class 2 (75%)
  - NSCLC 62%
  - >3 brain mets: 80%
- Median surv. 4 mo



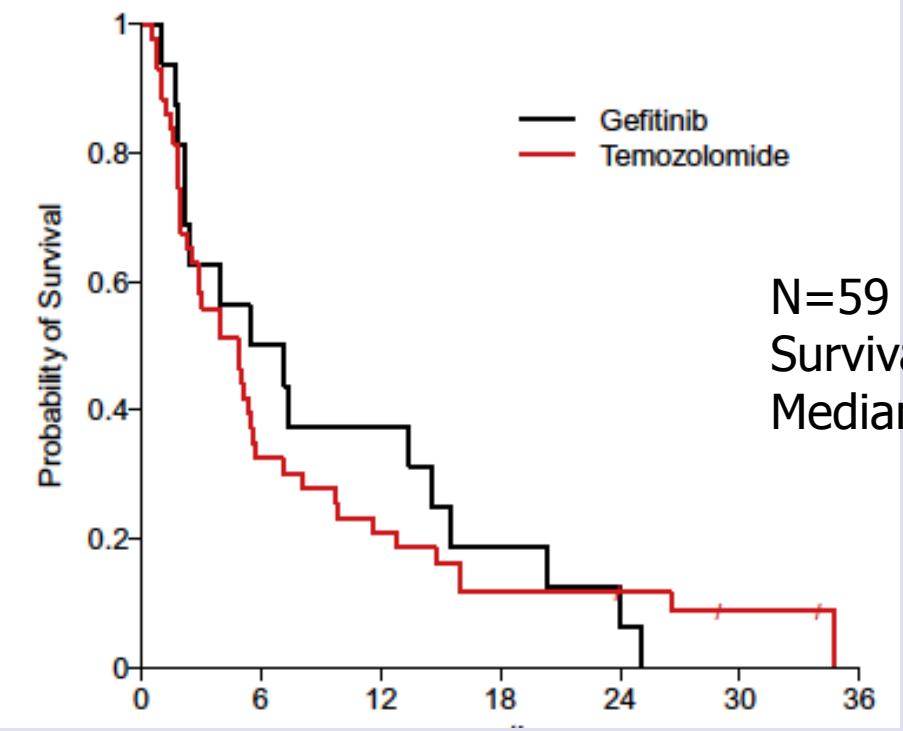
Knisely for RTOG: Int. J. Radiation Oncology Biol. Phys 2008:71; 79–86

Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03)

Gianfranco A. Pesce [a,], Dirk Klingbiel [b], Karin Ribi [c], Abderahim Zouhair [d], Roger von Moos [e], Marc Schlaeppi [f], Clemens B. Caspar [g], Natalie Fischer [h], Sandro Anchisi [i], Solange Peters [d], Richard Cathomas [e], Jürg Bernhard [c], Nina M. Kotrubczik [j], Giannicola D'Addario [f], Christiane Pilop [b], Damien C. Weber [k], Stephan Bodis [j], Miklos Pless [l], Michael Mayer [b], Roger Stupp [d]*

Europ. J Cancer 2012;48:377-84

EJC



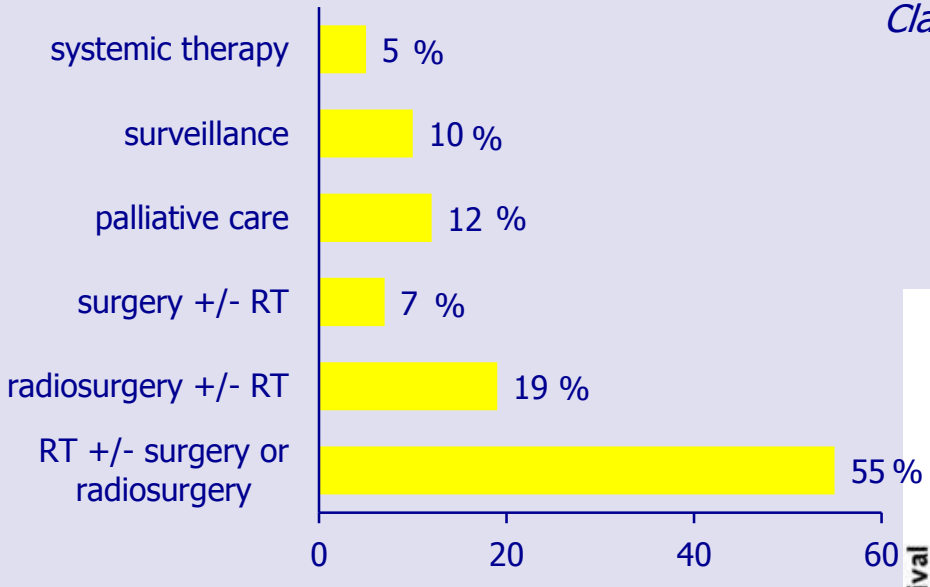
N=59 pts with NSCLC

Survival ≥ 3 months: 58.1% (95% CI 42.1–73.0%)

Median survival 5-6 months only !

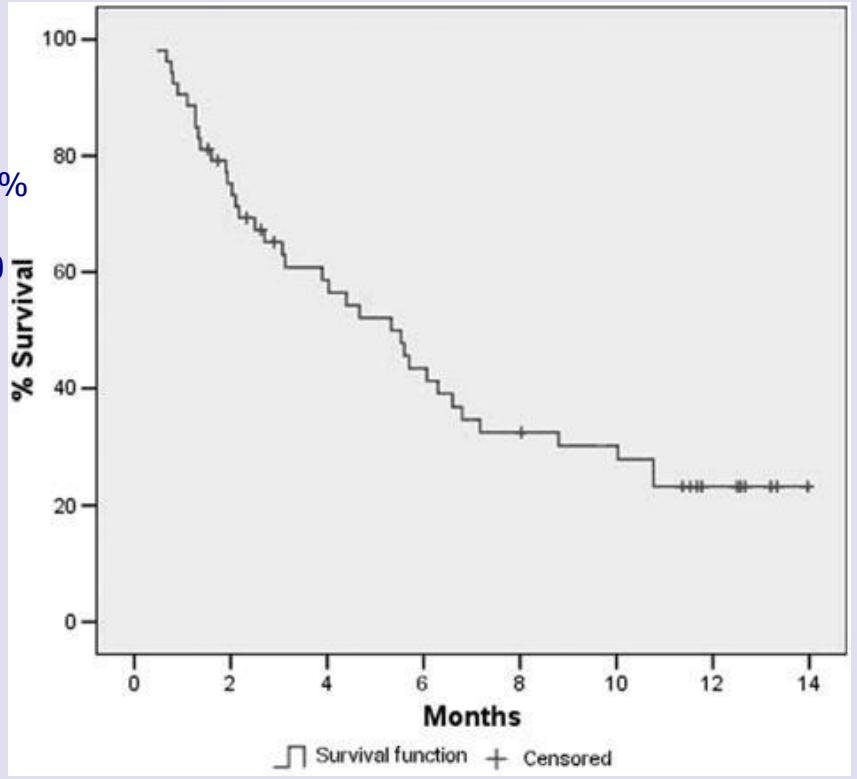
Management of brain metastases -

Audit of all pts with brain mets at a single cancer centre



Clarke, Brock & Brada. J Pall Med 2013; 16.836

Median survival 5.3 month
(95% CI 3.5–7.1)



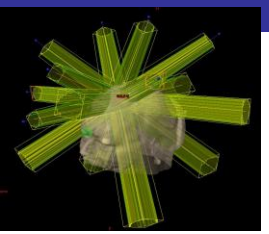
40% die within 3 month
22% no active anti-tumor therapy

Graph courtesy
M. Brada

Radiosurgery
useful or an expensive toy ?

- Linac-based stereotactic systems
  - Frame-based
  - Frame-less
- Gamma-Knife
- Cyber-Knife
- …

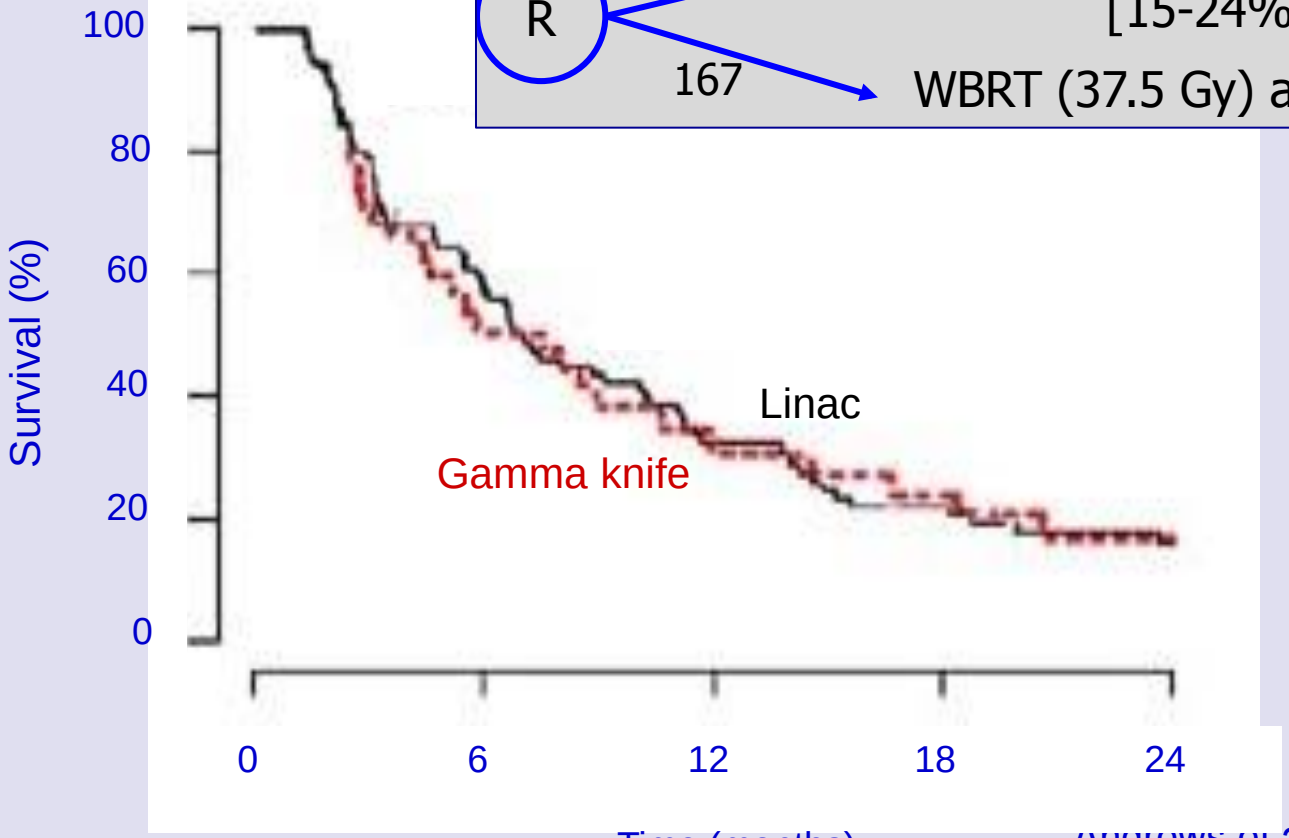
- Fractionated
- Single fraction



Survival:
Linac or Gamma Knife

R → 164 → WBRT (37.5 Gy) + SRS [15-24% did not receive SRS !!]

R → 167 → WBRT (37.5 Gy) alone



Andrews et al 2004 RTOG trial 9508

Availability of SRS → increased use (OR >12)

A Multi-institutional Study of Factors Influencing the Use of Stereotactic Radiosurgery for Brain Metastases

Hodgson et al. Int J Radiation Oncol Biol Phys 2013; 85:335-340

Purpose: Stereotactic radiosurgery (SRS) for brain metasta
nology with established guidelines regarding patient select
technically complex. We evaluated the extent to which lo
treatment of patients with brain metastases.

Methods and Materials: We identified 3030 patients w
therapy (WBRT) for brain metastases in 1 of 7 cancer cer
abstracted for a random sample of 973 patients. Logistic r
to identify factors associated with the use of SRS as a boos
or at any time following WBRT.

Results: Of 898 patients eligible for analysis, SRS was pro
time during the course of their disease and to 34 (3.8%) pati
multivariable analyses, factors significantly associated wit
WBRT were fewer brain metastases (odds ratio [OR] = 6
(OR = 3.49), age (OR = 0.97 per year of advancing ag
SRS program at the hospital where WBRT was given (OR
Similarly, availability of on-site SRS was the factor most p
time following WBRT (OR = 5.98). Among patients w
performance status, and no evidence of active extracran
40.3% of patients who received WBRT in a hospital tha
3.0% of patients who received WBRT at a hospital without

Explanatory variable	Adjusted OR (95% CI)	*P* value
Age (per y)	0.97 (0.94-0.99)	.043
Gender	-	NS
Male		
Female (referent)		
Marital status	-	NS
Married		
Other (referent)		
ECOG score	3.88 (0.51-29.57)	.191
0-2		
>2 (referent)		
No. of brain metastases	6.50 (2.18-19.39)	.001
1-3		
>3 (referent)		
Uncontrolled EC disease	3.49 (1.65-7.36)	.001
No		
Yes (referent)		
Surgery for brain metastase	0.65 (0.26-1.64)	.361
Yes		
No (referent)		
SRS on-site	12.34 (3.69-41.33)	<.001
Yes		
No (referent)		

Availability of SRS → increased use (OR >12)

A Multi-institutional Study of Factors Influencing the Use of Stereotactic Radiosurgery for Brain Metastases

Hodgson et al. Int J Radiation Oncol Biol Phys 2013; 85:335-340

Purpose: Stereotactic radiosurgery (SRS) for brain metasta
nology with established guidelines regarding patient select
technically complex. We evaluated the extent to which loc
treatment
Methods
therapy (W
abstracted
to identify
or at any t
Results: C
time durin
multivariat
WBRT were fewer brain metastases (odds ratio [OR] = 6
(OR = 3.49), age (OR = 0.97 per year of advancing ag
SRS program at the hospital where WBRT was given (OR
Similarly, availability of on-site SRS was the factor most
time following WBRT (OR = 5.98). Among patients w
performance status, and no evidence of active extracran
40.3% of patients who received WBRT in a hospital tha
3.0% of patients who received WBRT at a hospital without

- Availability of on-site SRS
- Fewer brain metastases
- Controlled extracranial disease
- Age

Explanatory variable	Adjusted OR (95% CI)	*P* value
	0.97 (0.94-0.99)	.043
	-	NS
	-	NS
	3.88 (0.51-29.57)	.191
ses	6.50 (2.18-19.39)	.001
1-3		
>3 (referent)		
Uncontrolled EC disease	3.49 (1.65-7.36)	.001
No		
Yes (referent)		
Surgery for brain metastase	0.65 (0.26-1.64)	.361
Yes		
No (referent)		
SRS on-site	12.34 (3.69-41.33)	<.001
Yes		
No (referent)		

Expectations

The NEW ENGLAND JOURNAL of MEDICINE

Overestimation of treatment benefit

Patients' Expectations about Effects of Chemotherapy for Advanced Cancer

Weeks ... Schrag: N Engl J Med 2012;367:1616-25

METHODS

We studied 1193 patients participating in the Cancer Care Outcomes Research and Surveillance (CanCORS) study (a national, prospective, observational cohort study) who were alive 4 months after diagnosis and received chemotherapy for newly diagnosed metastatic (stage IV) lung or colorectal cancer. We sought to characterize the prevalence of the expectation that chemotherapy might be curative and to identify the clinical, sociodemographic, and health-system factors associated with this expectation. Data were obtained from a patient survey by professional interviewers in addition to a comprehensive review of medical records.

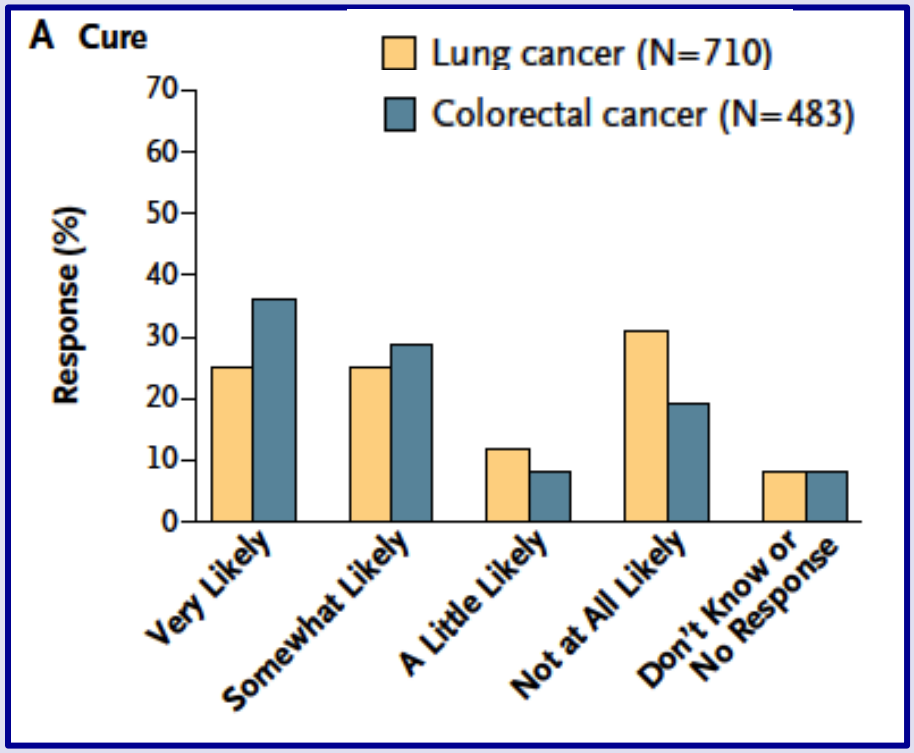
The NEW ENGLAND JOURNAL of MEDICINE

Overestimation of treatment benefit

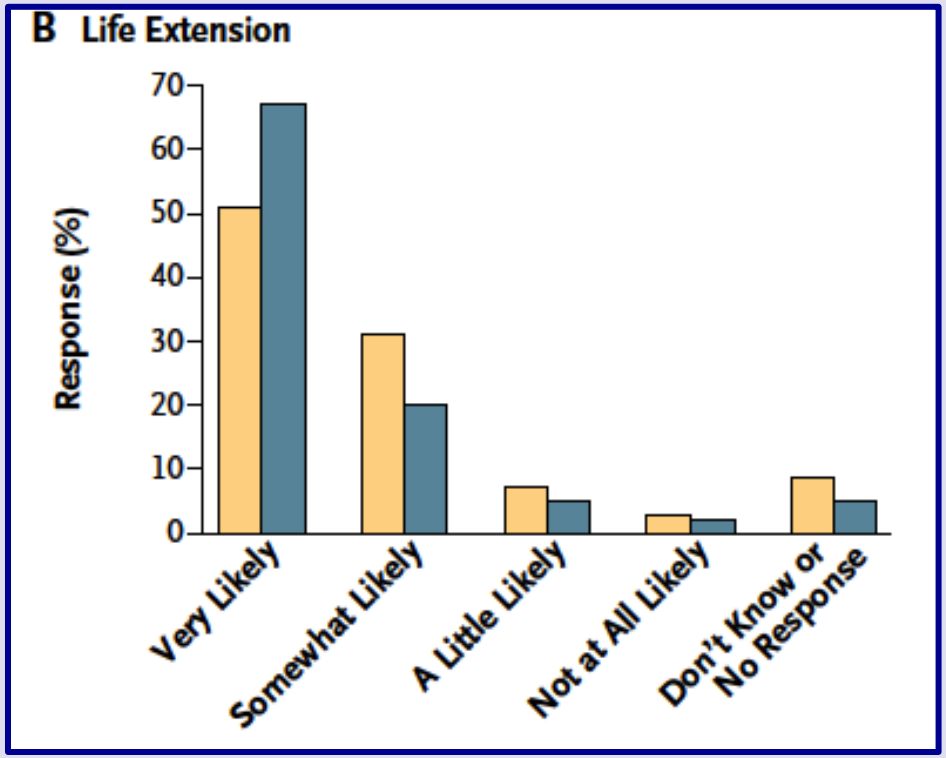
Patients' Expectations about Effects of Chemotherapy for Advanced Cancer

Weeks ... Schrag: N Engl J Med 2012;367:1616-25

Cure



Life Extension



The NEW ENGLAND JOURNAL of MEDICINE

Overestimation of treatment benefit

Patients' Expectations about Effects of Chemotherapy for Advanced Cancer

Weeks ... Schrag: N Engl J Med 2012;367:1616-25

METHODS

We studied 1193 patients participating in the Cancer Care Outcomes Research and

RESULTS

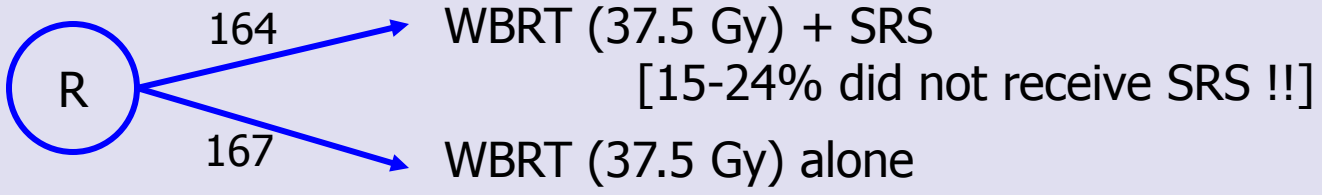
Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer. In multivariable logistic regression, the risk of reporting inaccurate beliefs about chemotherapy was higher among patients with colorectal cancer, as compared with those with lung cancer (odds ratio, 1.75; 95% confidence interval [CI], 1.29 to 2.37); among nonwhite and Hispanic patients, as compared with non-Hispanic white patients (odds ratio for Hispanic patients, 2.82; 95% CI, 1.51 to 5.27; odds ratio for black patients, 2.93; 95% CI, 1.80 to 4.78); and among patients who rated their communication with their physician very favorably, as compared with less favorably (odds ratio for highest third vs. lowest third, 1.90; 95% CI, 1.33 to 2.72). Educational level, functional status, and the patient's role in decision making were not associated with such inaccurate beliefs about chemotherapy.

Key Questions in brain metastases

1. **Is the primary tumor known ?**
   - *Work-up, histology, sensitivity to chemotherapy or targeted agents*
2. **Single vs multiple brain mets ?**
   - *Sugery vs radiosurgery vs WBRT*
3. **Is the systemic disease controlled or controllable ?**
   - *Systemic treatment needed ?*
4. **Do the brain mets cause symptoms ?**
   - *Symptomatic vs screening detection*
   - *Improvement after steroids ?*
5. **Goal of treatment and expected outcome ?**
   - *Improvement of general condition+ QoL*
   - *Prevention of complications*
   - *Cure of true solitary metastasis*

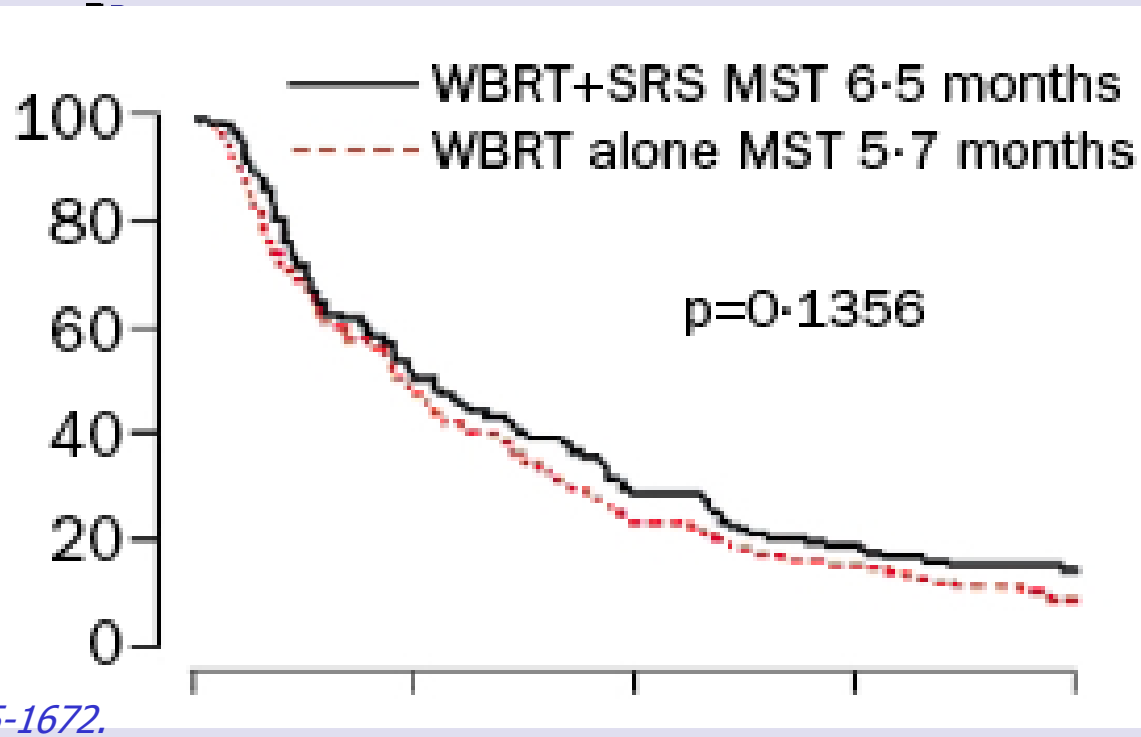
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

David W Andrews, Charles B Scott, Paul W Sperduto, Adam E Flanders, Laurie E Gaspar, Michael C Schell, Maria Werner-Wasik, William Demas, Janice Ryu, Jean-Paul Bahary, Luis Souhami, Marvin Rotman, Minesh P Mehta, Walter J Curran Jr



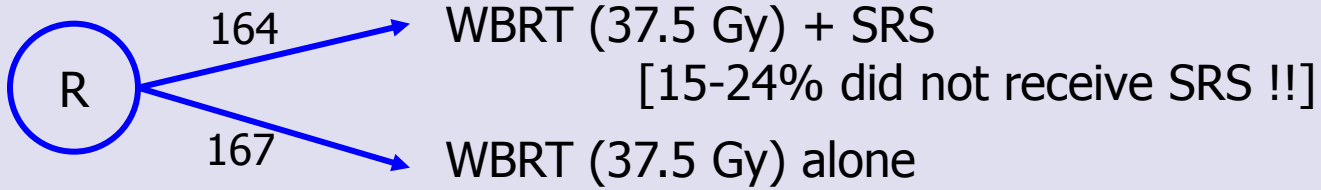
Stratification:

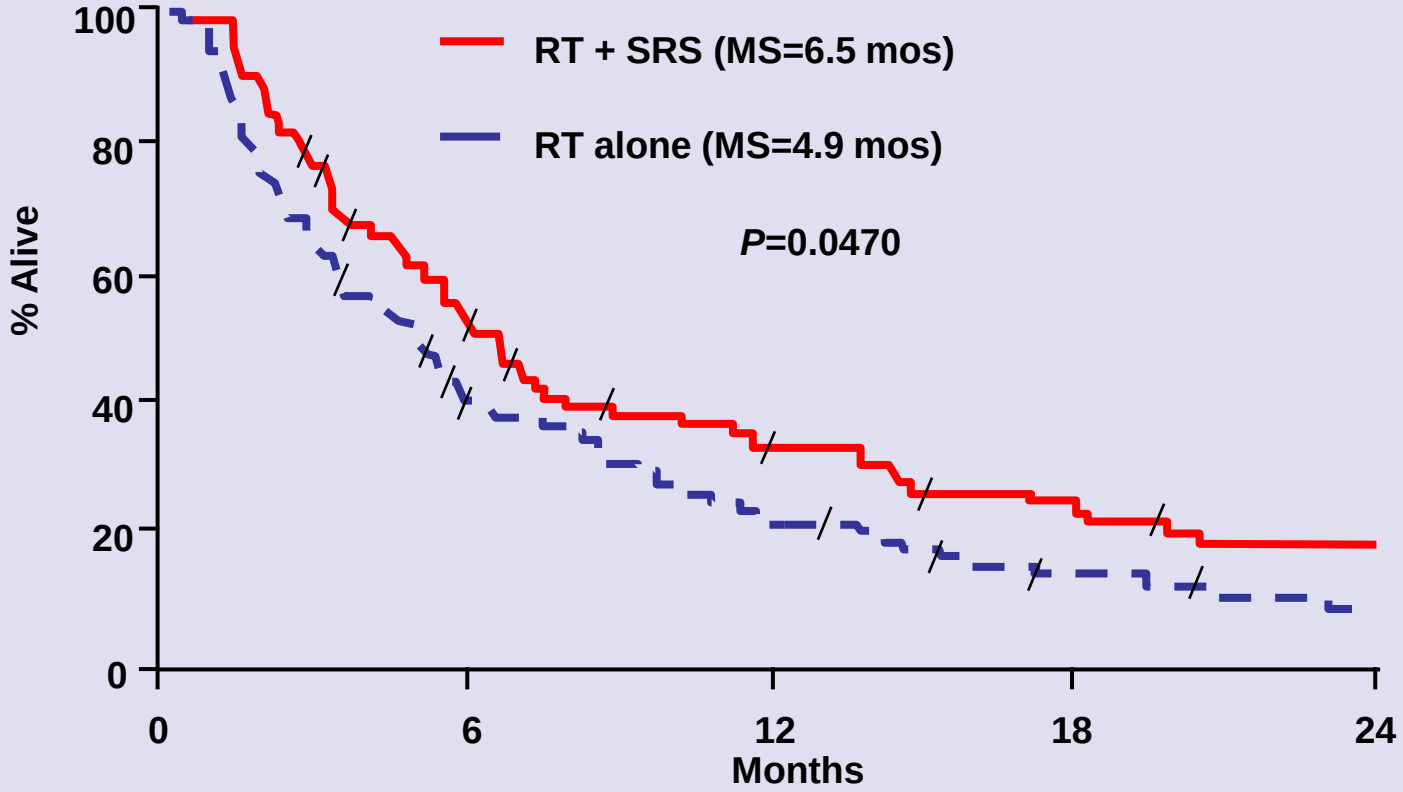
- Number of brain metastases:
  (1 vs 2 - 3)
- Extracranial mets
  (none vs present)



Andrews DW, et al. Lancet 2004;363:1665-1672.

RTOG9508: Subgroup analysis of single brain met (=56% of pts)





Andrews DW, et al. Lancet 2004;363:1665-1672

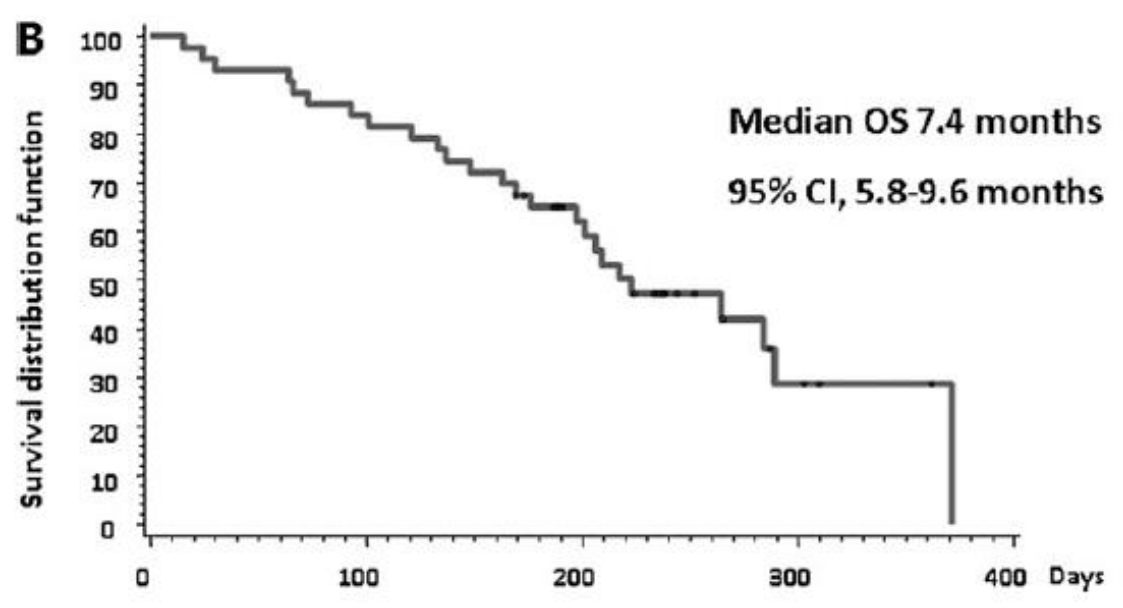
Initial Chemotherapy for NSCLC with brain metastases

- 44 pts with newly diagonsed NSCLC
  - Adeno-Ca 84%

- RR 35 %
  - Cerebral RR 42%
  - PD 26%; brain 14%, extracranial 19%

Treatment:

- CDDP/Pemetrexed x 2-4 cycles, followed by WBRT (received in 61% pts)

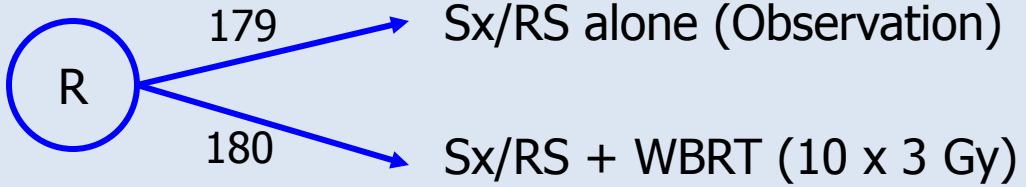


Barlesi et al.
Annals of Oncology 22: 2466–2470, 2011

Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

J Clin Oncol 2011; 29:134-141



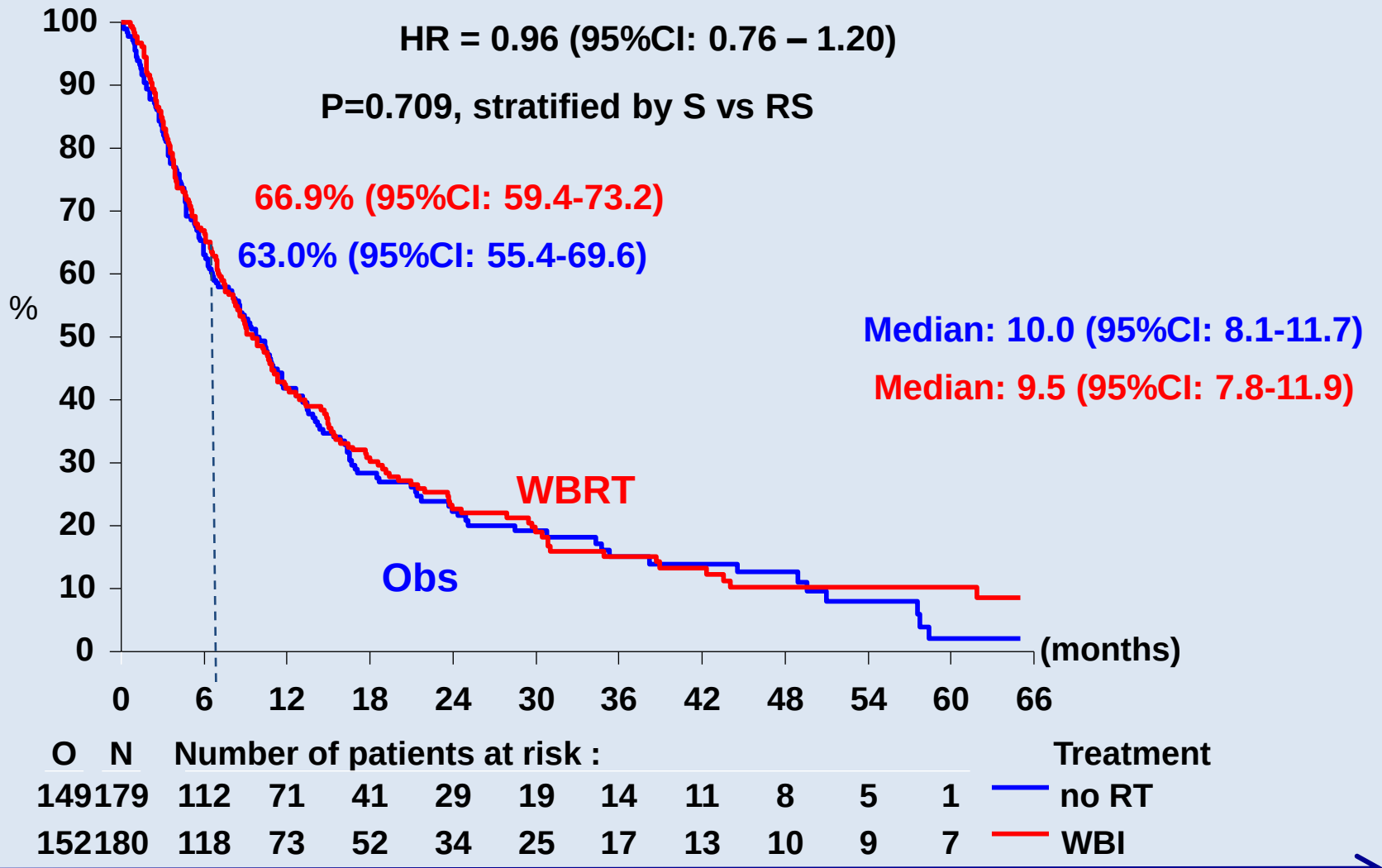
Progression

WBRT (n=60; 35% of all pts / 43% of PD pts

Patient Characteristics:

Lung Ca	53%
Breast	12%
Kidney, Melanoma, Colorectal each	8%

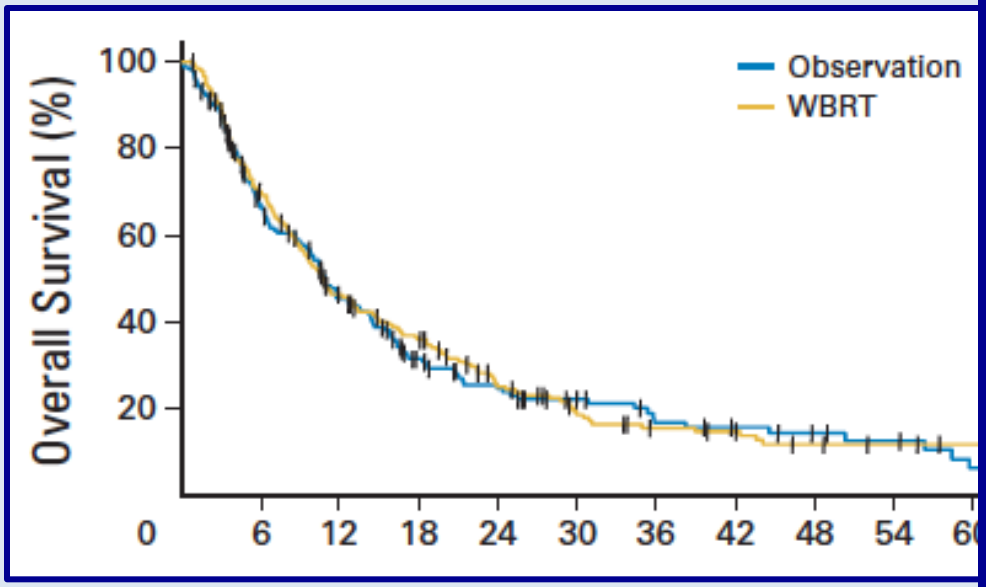
EORTC 22052-26001: 1° endpoint:
Survival with PS ≤ 2 (ITT)



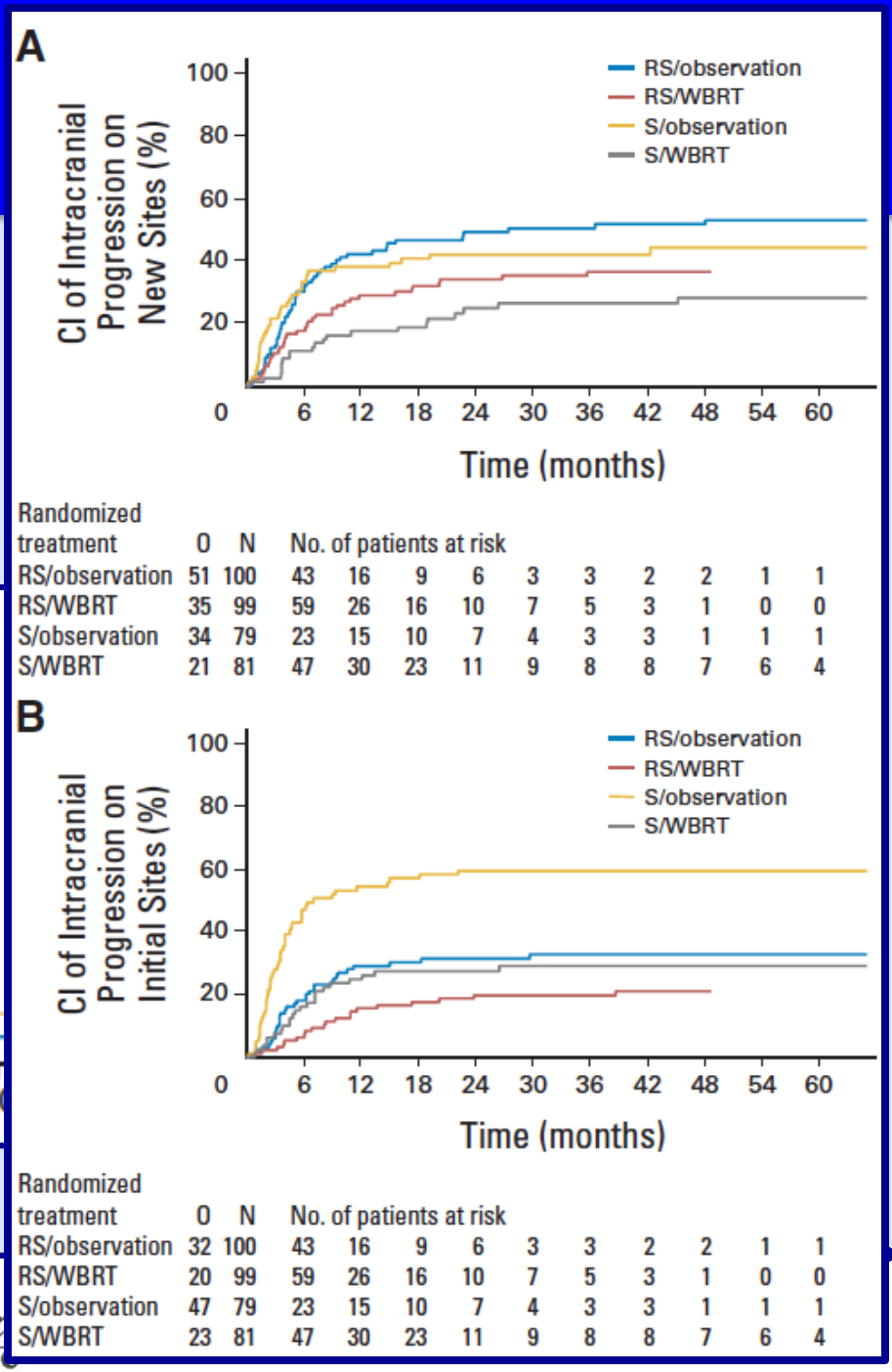
EORTC 22052-26001: Sx/RS ± WBRT

Secondary endpoints:

- Cummulative incidence of CNS progression
- Overall survival



Kocher, Soffietti et al. J Clin Oncol 2011; 29:134-141

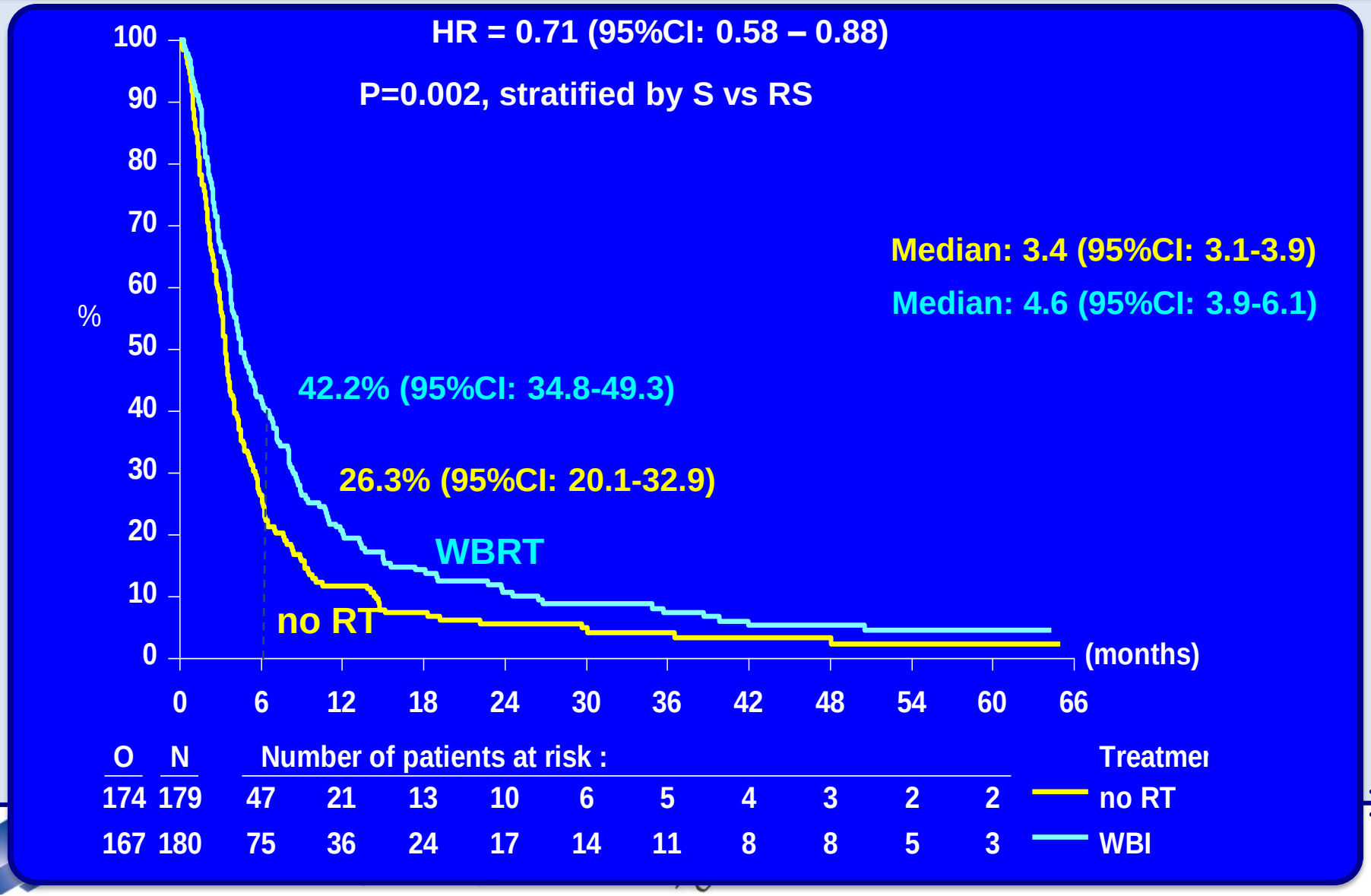


Randomized treatment	0	N	No. of patients at risk									
RS/observation	51	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	35	99	59	26	16	10	7	5	3	1	0	0
S/observation	34	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	21	81	47	30	23	11	9	8	8	7	6	4

Randomized treatment	0	N	No. of patients at risk									
RS/observation	32	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	20	99	59	26	16	10	7	5	3	1	0	0
S/observation	47	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	23	81	47	30	23	11	9	8	8	7	6	4

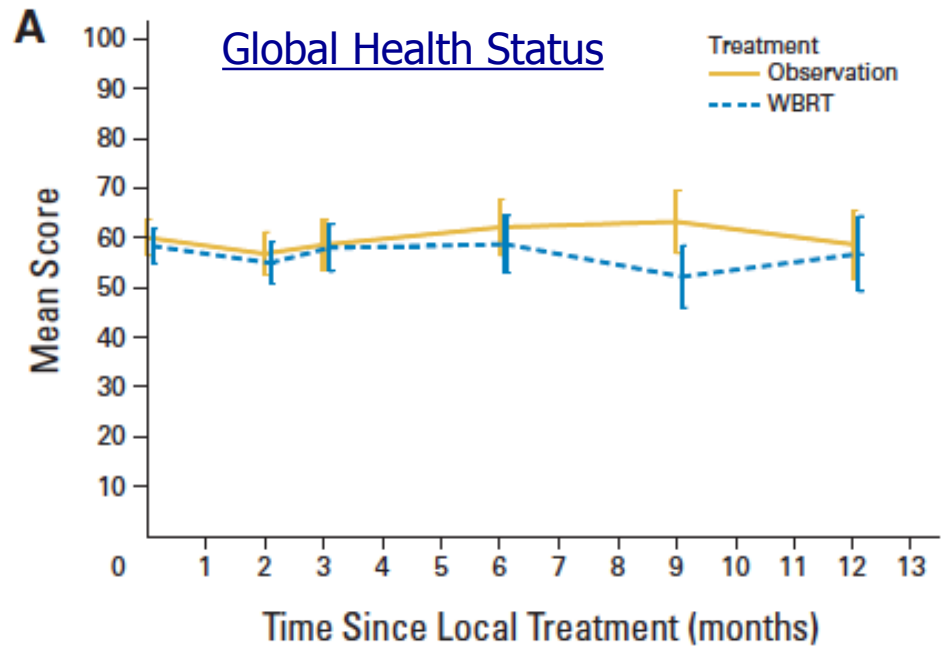
Progression Free Survival (ITT)

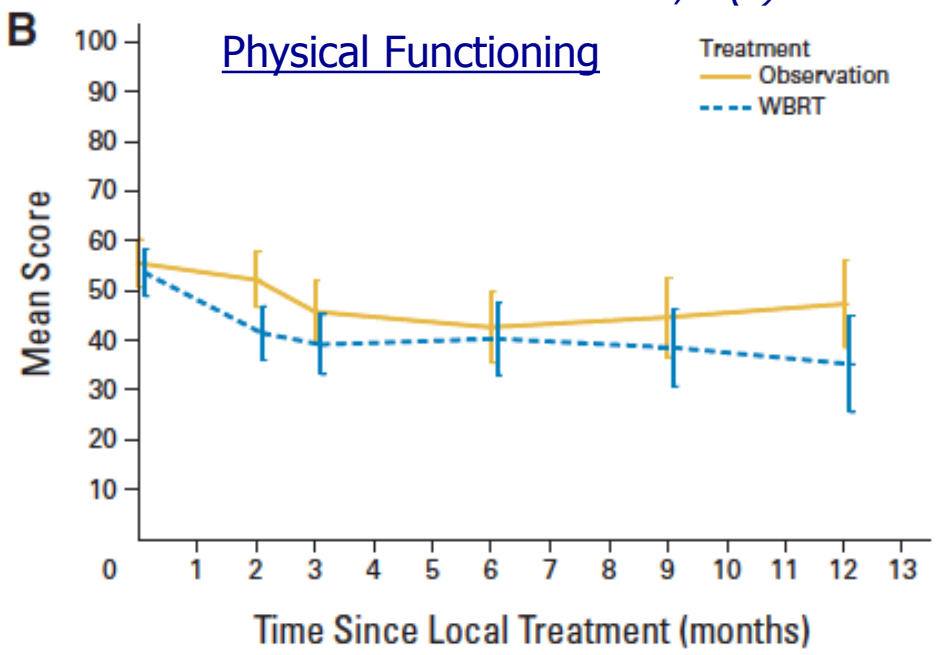
Kocher et al. J Clin Oncol 2011; 29:134-141

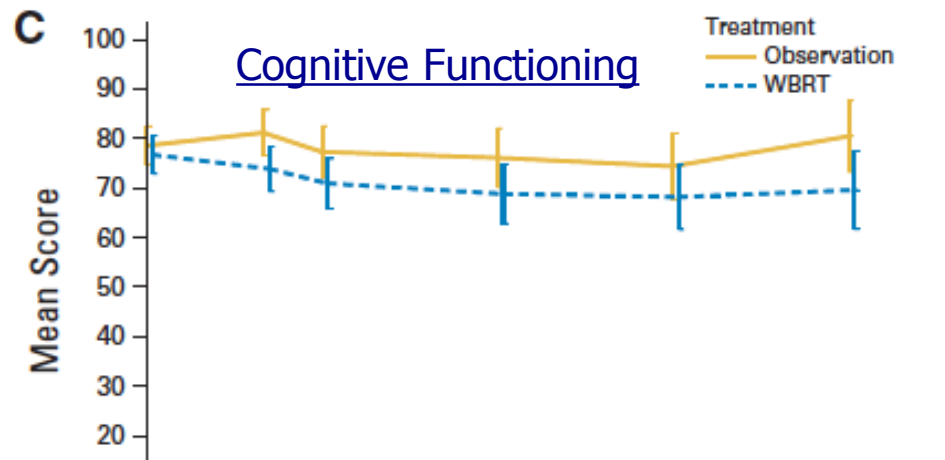


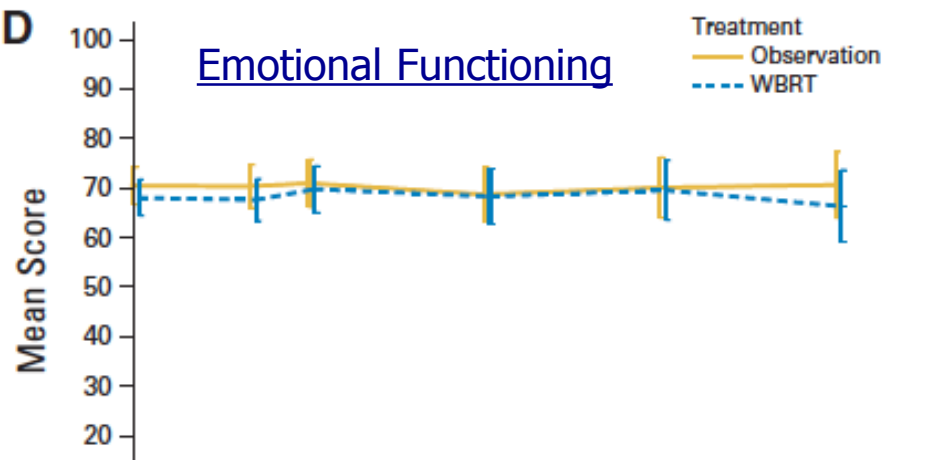
EORTC 22052-26001: Sx/RS ± WBRT
Global Health Status/ QoL

Soffietti et al. J Clin Oncol. 2013 Jan 1;31(1):65-72.









To treat or not to treat

- Brain metastases are not a diagnosis
- → Histology and molecular characteristics matter
- Management:
  - tumor extension local & distant
  - goals of therapy
- Visible mets: Blood brain barrier disrupted, treatment responses comparable to visceral mets
- Benefit of therapy overestimated,
  - asymptomatic multiple mets may not require therapy
  - Management may not need to be different from systemic disease
- Patient selection important

Brain Mets – Patient Cases

Sunday, 28. September 2014

11:45 - 12:45	**Type: Patient Cases** **Title: Response, neurological function and other objectives in the management of patients with brain metastases**	**Salamanca**
	Chair(s): Anthony Chalmers[1], Enrico Franceschi[2], Alexander Radbruch[3]; [1]Glasgow/UK, [2]Bologna/IT, [3] Heidelberg/DE	
11:45 - 11:55	**What type of radiotherapy is indicated in brain metastases?** Anthony Chalmers, Glasgow/UK	
11:55 - 12:05	**Systemic therapy instead or in addition to irradiation?** Enrico Franceschi, Bologna/IT	
12:05 - 12:15	**Challenges and pitfalls in radiological response assessment of brain metastases** Alexander Radbruch, Heidelberg/DE	
12:15 - 12:45	**Discussion**	


Savage Chickens
by Doug Savage
TO BE OR NOT TO BE?
HAMLET
PARAPHRASED BY CHICKENS
LIFE SUCKS, BUT THE ALTERNATIVE MIGHT SUCK MORE
©2007 BY DOUG SAVAGE
www.savagechickens.com