

con il Patrocinio dell'Associazione Italiana di Oncologia Medica



Progetto CANOA CARCINOMA MAMMARIO:

QUALI NOVITÀ PER IL 2013?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

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Negrar - Verona 22-23 marzo 2013
Ospedale Sacro Cuore - Don Calabria

Metastasi cerebrali

*Fattori associati alla
sopravvivenza*

Lucia Mentuccia

Oncologia Medica - Sora

Prognosis of patients with brain metastases from HER2-positive breast

Study	Time period	Number of patients	Median survival after CNS recurrence
Tham, et al	1970-1999	21	~3 months
Bendell, et al	1998-2000	42	13 months
Gori, et al	1999-2005	43	23 months
Stemmler, et al	2000-2004	42	13 months
Eichler, et al	2001-2005	30	17 months
Melisko, et al	1997-2007	35	23 months
Brufsky, et al	2003-2009	377	20.3 months

Prognosis of patients with brain metastases from triple-negative breast cancer

Study	Time period	Number of patients	Median survival after CNS recurrence
Dawood et al	1980-2006	42	2.9 months
Lin et al	2000-2006	53	4.9 months
Eichler et al	2001-2005	21	4.0 months
Nam et al	2001-2006	47	3.4 months

● *Clinical Investigation*

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

LAURIE GASPAR, M.D.,* CHARLES SCOTT, M.S.,[†] MARVIN ROTMAN, M.D.,[‡]
SUCHA ASBELL, M.D.,[§] THEODORE PHILLIPS, M.D.,[¶] TODD WASSERMAN, M.D.,[#]
W. GILLIES McKENNA, M.D., Ph.D.,** AND ROGER BYHARDT, M.D.^{††}

Database: 1200 pts from three RTOG brain metastases trials (1979-1993)

Prognostic groups by RPA

Class	Prognostic factors	Median survival, months
I	KPS $\geq$ 70 percent	7.1
	Age <65 years	
	Controlled primary site	
	No extracranial metastases	
III	KPS <70	2.3
II	All others	4.2

CLINICAL INVESTIGATION

Brain

**VALIDATION OF THE RTOG RECURSIVE PARTITIONING ANALYSIS (RPA)
CLASSIFICATION FOR BRAIN METASTASES**

LAURIE E. GASPAR, M.D.,* CHARLES SCOTT, PH.D.,[†] KEVIN MURRAY, M.D.,[‡] AND
WALTER CURRAN, M.D.[§]

- Phase III study
- 445 pts
- Only pts in RPA classes I and II were eligible

Survival by RPA stage

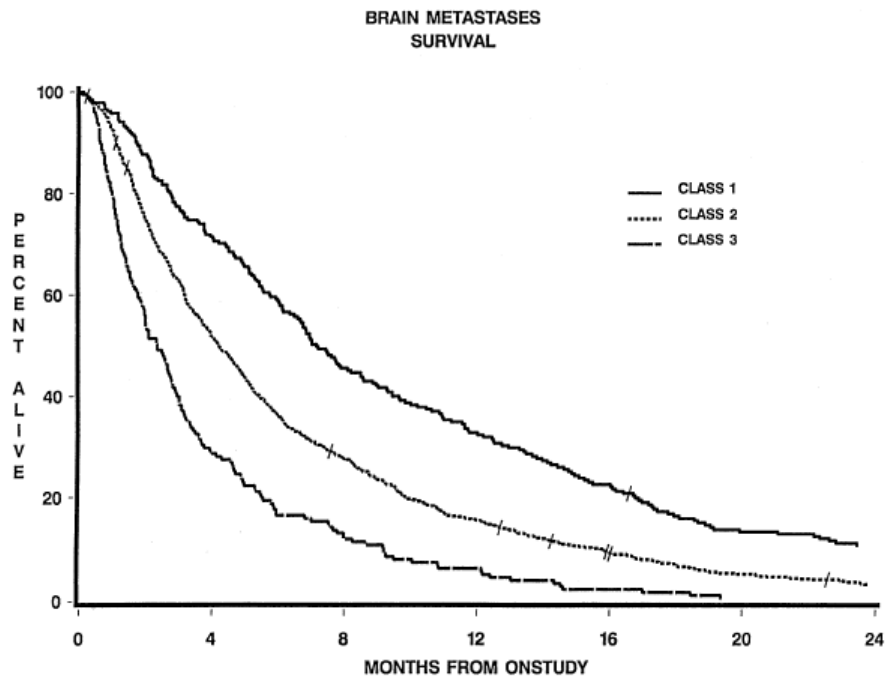


Fig. 2. Survival by RPA class from the RTOG database.

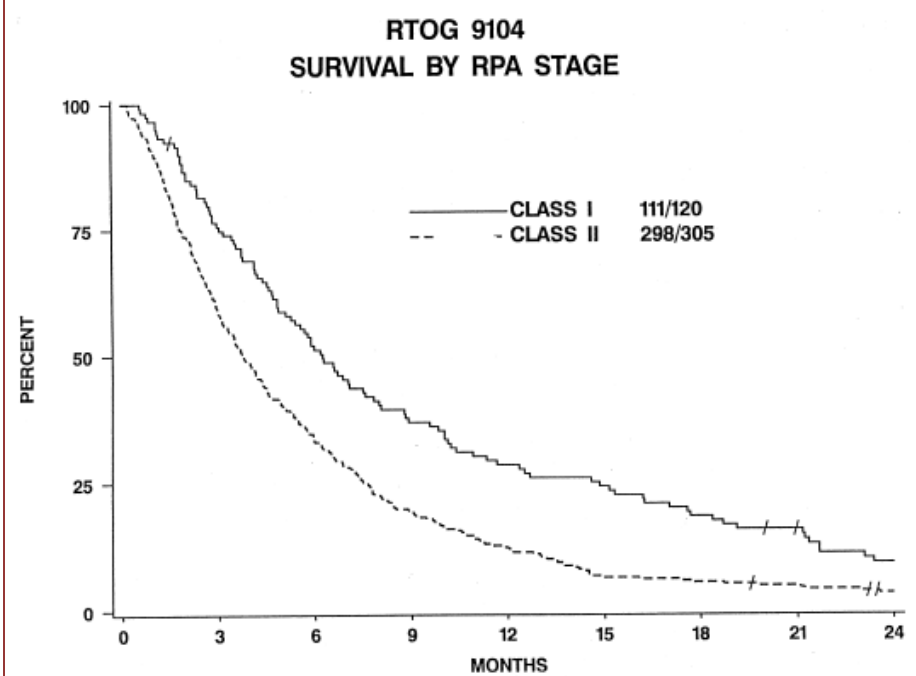


Fig. 3. Survival curves for RTOG 91-04 by RPA Class.

Gaspar L. et al, Int J Radiation Oncology, Vol 37, 1997

Gaspar L. et al, Int J Radiation Oncology, Vol 47, 2000

CLINICAL INVESTIGATION

Brain

**A NEW PROGNOSTIC INDEX AND COMPARISON TO THREE OTHER INDICES
FOR PATIENTS WITH BRAIN METASTASES: AN ANALYSIS
OF 1,960 PATIENTS IN THE RTOG DATABASE**

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AND WALTER CURRAN, M.D.^{||}

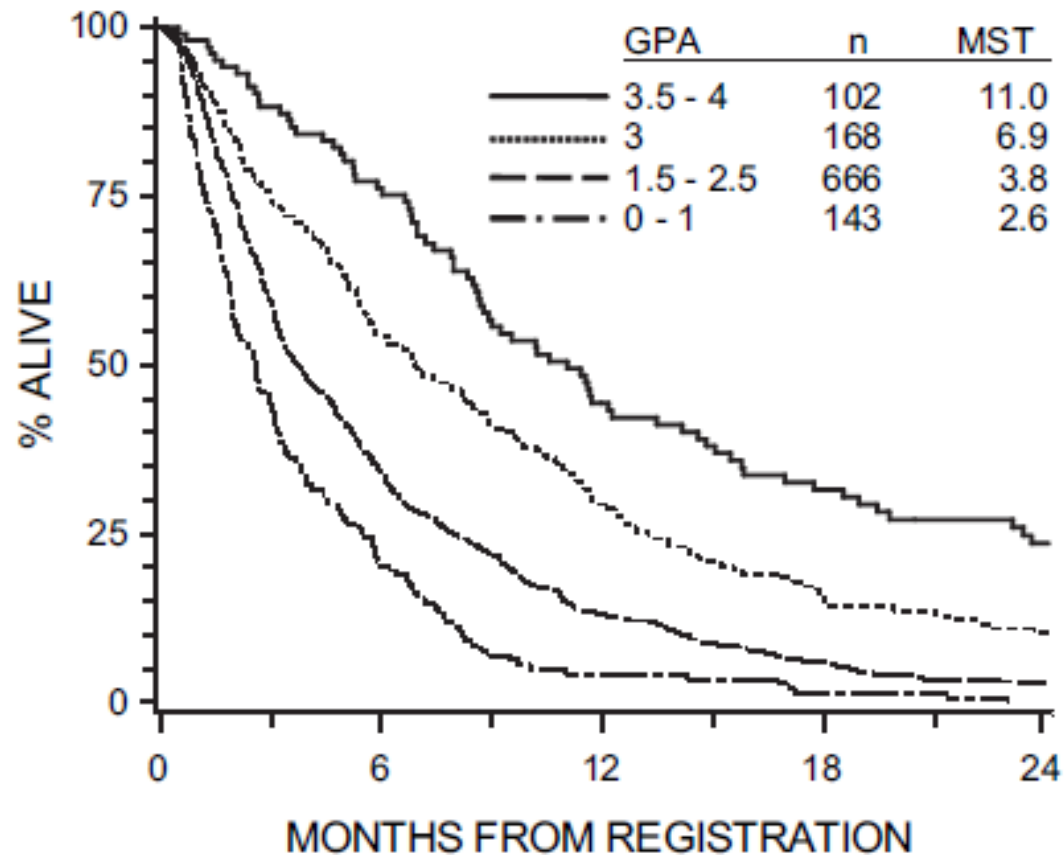
Database: 1960 pts from five randomized RTOG trials

Graded Prognostic Assessment (GPA)

	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

Graded Prognostic Assessment (GPA)

GRADED PROGNOSTIC ASSESSMENT



CLINICAL INVESTIGATION

Brain

**DIAGNOSIS-SPECIFIC PROGNOSTIC FACTORS, INDEXES, AND TREATMENT
OUTCOMES FOR PATIENTS WITH NEWLY DIAGNOSED BRAIN METASTASES:
A MULTI-INSTITUTIONAL ANALYSIS OF 4,259 PATIENTS**

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VERONICA CHIANG, M.D.,¶¶ JONATHAN KNISELY, M.D.,||| CHRISTINA MARIA SPERDUTO,##
AND MINESH MEHTA, M.D.||

Retrospective database: 5067 pts treated for BMs between 1985 and 2007

GPA and diagnosis

Table 2. Multivariate analysis of prognostic factors by diagnosis

Diagnosis	Significant prognostic factors (<i>n</i>)	Significance of prognostic factors (<i>p</i>)
NSCLC	4	Age (<i>p</i> <.0001); KPS (<i>p</i> <.0001); ECM (<i>p</i> = .0017); No. of BMs (<i>p</i> = .0007)
SCLC	4	KPS (<i>p</i> <.0001); age (<i>p</i> = .0031); ECM (<i>p</i> = .0184); No. of BMs (<i>p</i> = .0222)
Melanoma	2	KPS (<i>p</i> <.0001); No. of BMs (<i>p</i> <.0001)
RCC	2	KPS (<i>p</i> = .0003); No. of BMs (<i>p</i> = .0350)
→ Breast cancer	1	KPS (<i>p</i> <.0001)
GI cancer	1	KPS (<i>p</i> = .0035)

DS-GPA prognostic index

Table 3. Definition of diagnosis-specific graded prognostic assessment indexes for patients with newly diagnosed brain metastases

GPA of newly diagnosed BMs	Significant prognostic factors	GPA scoring criteria					
NSCLC/SCLC		0	0.5	1	—	—	
	Age	>60	50–60	<50	—	—	
	KPS	<70	70–80	90–100	—	—	
	ECM	Present	—	Absent	—	—	
	No. of BMs	>3	2–3	1	—	—	
Melanoma/ renal cell cancer		0	1	2	—	—	
	KPS	<70	70–80	90–100	—	—	
	No. of BMs	>3	2–3	1	—	—	
Breast/GI cancer		0	1	2	3	4	
	KPS	<70	70	80	90	100	



CLINICAL INVESTIGATION

Breast Cancer

EFFECT OF TUMOR SUBTYPE ON SURVIVAL AND THE GRADED PROGNOSTIC ASSESSMENT FOR PATIENTS WITH BREAST CANCER AND BRAIN METASTASES

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Retrospective database: 400 breast cancer pts treated for diagnosed brain metastases between 1993 and 2010

GPA and breast cancer

Table 2. Multivariate Cox regression model using Graded Prognostic Assessment (GPA) index categories

Factor	Level	Regression coefficient a.k.a. log hazard ratio (SE)	p Value	Hazard ratio (95% CI)
KPS	KPS ≤50			1.00
	KPS 60	−0.80 (0.37)	0.0295	0.45 (0.22, 0.92)
	KPS 70 or 80	−1.36 (0.30)	<0.0001	0.26 (0.14, 0.46)
	KPS 90 or 100	−1.94 (0.31)	<0.0001	0.14 (0.08, 0.26)
Genetic subtype*	Basal			1.00
	Luminal A	−0.69 (0.18)	0.0002	0.50 (0.35, 0.72)
	HER2	−0.96 (0.17)	<.0001	0.38 (0.28, 0.53)
	Luminal B	−1.06 (0.18)	<.0001	0.35 (0.25, 0.49)
Age (y)	≥60			1.00
	<60	−0.26 (0.14)	0.0640	0.77 (0.59, 1.02)

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; SE = standard error.

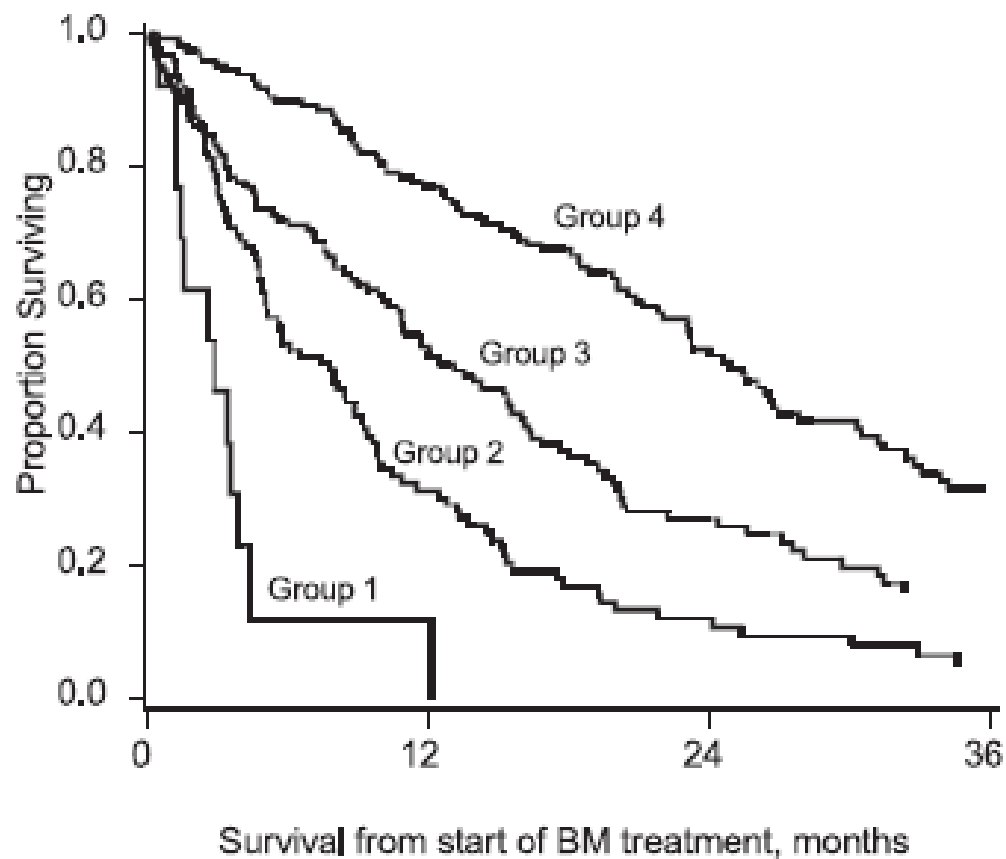
* Hazard ratio of HER2 positive and ER/PR positive to HER2 positive and ER/PR negative is 0.91 (95% confidence interval = 0.65, 1.28; $p = 0.6$).

GPA and breast cancer

Table 3. Graded Prognostic Assessment (GPA) index for women with breast cancer and brain metastases

Factor	0.0	0.5	1.0	1.5	2.0
→ KPS	≤50	60	70–80	90–100	–
→ Genetic subtype	Basal	–	Luminal A	HER2	Luminal B
→ Age (y)	≥60	<60	–	–	–

Abbreviation: KPS = Karnofsky performance status.



Group	Breast-GPA	N (%)	MST (months) (95% CI)	1 year OS (95% CI)	2 year OS (95% CI)	3 year OS (95% CI)
1	0.0 – 1.0	23 (6%)	3.4 (2.4, 4.9)	15 (4, 33)	0	0
2	1.5 – 2.0	104 (26%)	7.7 (4.8, 9.7)	32 (23, 41)	13 (6, 20)	6 (2, 13)
3	2.5 – 3.0	140 (35%)	15.1 (10.8, 17.9)	55 (46, 63)	29 (21, 37)	19 (11, 27)
4	3.5 – 4.0	133 (33%)	25.3 (20.4, 30.4)	77 (69, 84)	53 (43, 61)	31 (22, 40)

VOLUME 30 • NUMBER 4 • FEBRUARY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases

Paul W. Sperduto, Norbert Kased, David Roberge, Zhiyuan Xu, Ryan Shanley, Xianghua Luo, Penny K. Sneed, Samuel T. Chao, Robert J. Weil, John Suh, Amit Bhatt, Ashley W. Jensen, Paul D. Brown, Helen A. Shih, John Kirkpatrick, Laurie E. Gaspar, John B. Fiveash, Veronica Chiang, Jonathan P.S. Knisely, Christina Maria Sperduto, Nancy Lin, and Minesh Mehta

Retrospective database: 3940 pts with newly diagnosed brain metastases between 1995 and 2007

Breast –GPA index

Prognostic factor	GPA scoring criteria					Patient score
	0	0.5	1.0	1.5	2.0	
KPS	≤50	60	70-80	90-100	N/A	
Subtype	Basal	N/A	Luminal A	HER2	Luminal B	
Age, years	≥60	<60	N/A	N/A	N/A	
Sum total:						

Table 1. Median Survival Time for Patients With Brain Metastases by DS-GPA Score

Diagnosis	Overall		DS-GPA Score																p (log-rank)	
			0-1.0				1.5-2.0				2.5-3.0				3.5-4.0					
	Survival Time (months)		Survival Time																	
	Median	95% CI	No. of Patients	Median (months)	95% CI	No.	%	Median (months)	95% CI	No.	%	Median (months)	95% CI	No.	%	Median (months)	95% CI	No.		%
NSCLC	7.00	6.53 to 7.50	1,833	3.02	2.63 to 3.84	254	14	5.49	4.83 to 6.40	705	38	9.43	8.38 to 10.80	713	40	14.78	11.80 to 18.80	161	9	< .001
SCLC	4.90	4.30 to 6.20	281	2.79	1.83 to 3.12	65	23	4.90	4.04 to 6.51	119	42	7.67	6.27 to 9.13	84	30	17.05	4.70 to 27.43	13	5	< .001
Melanoma	6.74	5.90 to 7.56	481	3.38	2.53 to 4.27	84	17	4.70	4.07 to 5.39	150	31	8.77	6.74 to 10.77	135	28	13.23	9.13 to 15.64	112	23	< .001
RCC	9.63	7.66 to 10.91	286	3.27	2.04 to 5.10	43	15	7.29	3.73 to 10.91	76	27	11.27	8.80 to 14.80	104	36	14.77	9.73 to 19.79	63	22	< .001
Breast cancer	13.80	11.53 to 15.87	400	3.35	3.13 to 3.78	23	6	7.70	5.62 to 8.74	104	2	15.07	12.94 to 15.87	140	35	25.30	1.10 to 26.51	133	33	< .001
GI cancer	5.36	4.30 to 6.30	209	3.13	2.37 to 4.57	76	36	4.40	3.37 to 6.53	65	31	6.87	4.86 to 11.63	50	24	13.54	9.76 to 27.12	18	9	< .001
Other	6.37	5.22 to 7.49	450	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	7.16	6.83 to 7.52	3,940	3.10	2.83 to 3.45	545	16	5.40	4.90 to 5.89	1,219	35	9.63	8.74 to 10.58	1,226	35	16.73	14.65 to 18.80	500	14	< .001

Abbreviations: DS-GPA, diagnosis-specific Graded Prognostic Assessment; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small-cell lung cancer.

