

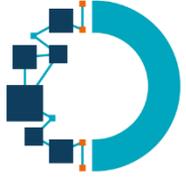
Radiothérapie cérébrale

Indications actuelles

24 Mai 2019

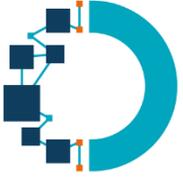
Angoulême

BERGER Antoine



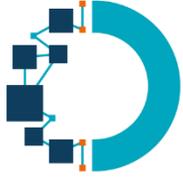
Liens d'intérêt

Aucun lien d'intérêt...



Limites actuelles

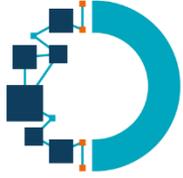
- La majorité de la littérature ne distingue pas ou peu l'histologie dans les essais relatifs à la prise en charge des métastases cérébrales



Objectif

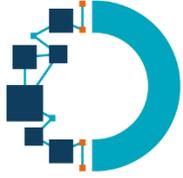
- De multiples présentations cliniques
- Des moyens thérapeutiques différents
- Un patient à prendre en charge...

- → traitement adapté :
 - Ne pas sur-traiter les patientes de mauvais pronostic
 - Ne pas sous-traiter les patients de pronostic favorable
 - Préserver la fonction (long survivant)



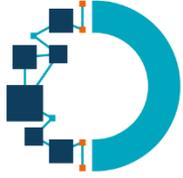
Présentation clinique

- Grande diversité : intègre :
 - Situation encéphalique
 - Situation extra-encéphalique
 - Données cliniques propres au patient
 - Données histologiques
 - Biologie moléculaire



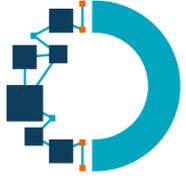
Situation encéphalique

- Selon l'atteinte encéphalique :
 - Atteinte :
 - Leptoméningée
 - Multiples > 3-4
 - Multiples < 3-4
 - Unique
 - Solitaire
- Territoires fonctionnels touchés :
 - Impact clinique
 - Potentiel de résécabilité



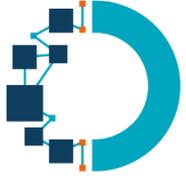
Situation extra encéphalique

- Selon le stade au diagnostic :
 - Méta synchrones:
 - Maladie extraencéphalique « opérable » vs « non opérable »
 - Méta asynchrones :
 - Métas asynchrones : maladie contrôlée ?
- Selon l'histologie :
 - Petites cellules
 - Non à petites cellules
 - BIOLOGIE?!.



Données cliniques du patient

- Comorbidités
- fonction neurologique
- Etat général global : OMS



Classes RPA RTOG (Gaspar 1997, validation en 2000 Gaspar)

Classification RPA et médianes de survie

	RPA I	RPA II	RPA III
Index de Karnofsky ≥ 70	≥ 70	≥ 70	< 70
Age	≤ 65 ans	> 65 ans	Indifférent
Tumeur primitive contrôlée	Oui	Non	Indifférent
Métastases extracrâniennes	Non	Oui	Indifférent
	Tous les facteurs	Ni RPA II ni RPA III	Un seul facteur

Médiane de survie globale

RPA I : 7.1 mois

RPA II : 4.2 mois

RPA III : 2.3 mois

Gaspar L et al. Int J Radiat Oncol Biol Phys 1997 ; 37 :745-751

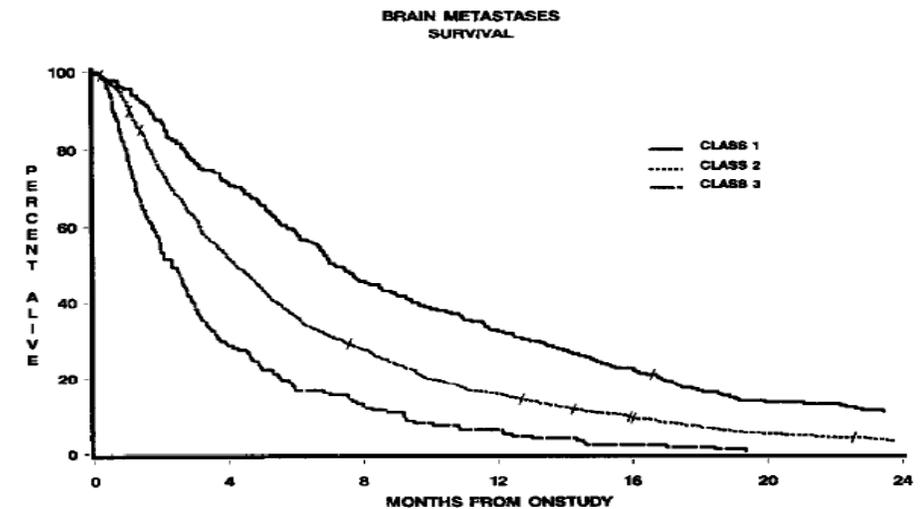
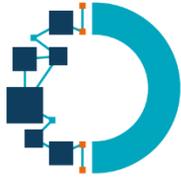


Fig. 3. Survival curves for Class I, II, III.

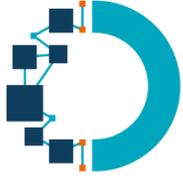


	Median survival (months)
RPA class 1	
KPS \geq 70, age <65 years, controlled primary tumour, no extracranial disease	7.1
Single metastasis	13.5
Multiple metastases	6.0
RPA class 2	
All other situations	4.2
Single metastasis	8.1
Multiple metastases	4.1
RPA class 3	
KPS <70	2.3

Survival results for overall RPA classes are from Radiation Therapy Oncology Group trials,⁷ and those for the single and multiple metastases subdivisions of class 1 and 2 are from Lutterbach et al.⁸ KPS=Karnofsky performance status score.

Table 1: Prognostic factors by RPA class

Gaspar L et al. Int J Radiat Oncol Biol Phys 1997 ; 37 :745-751



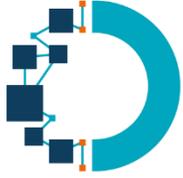
RPA corrigé (sous population IK>60)

Classification RPA corrigée et médianes de survie

	0	1
Index de Karnofsky	90% ou 100%	70% ou 80%
Métastases extra crânienne	Non	Oui
Tumeur primitive contrôlée	Oui	non

II-a : somme des 3 facteurs = 0 ou 1 Médiane de survie : 15.6 à 19.7 mois
II-b : somme des 3 facteurs = 2 Médiane de survie : 8.4 mois
II-c : somme des 3 facteurs = 3 ou 4 Médiane de survie : 5.2 à 3.5 mois

Yamamoto M, Int J Radiat Oncol Biol Phys 2012 ; 83, 5 :1399-1405.



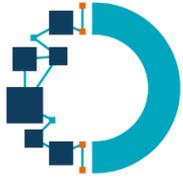
SIR

Classification SIR (Score Index for Radiosurgery)

	0	1	2
Age	<59	51-59	<51
Karnofsky	≤50	60-70	>70
Maladie systémique	Progression	Stable ou réponse partielle	Réponse complète ou absente
Volume de la lésion la plus importante	>13 cm ³	5-13 cm ³	<5 cm ³
Nombre de métastases	>2	1	1

Somme des valeurs de chaque paramètre : classe 1 (0-3), classe 2 (4-7), classe 3 (8-10).

Weltman E, Salvajoli JV, Brandt RA, de Moraes HR, Prisco FE, Cruz JC, *et al.*
Radiosurgery for brain metastases: a score index for predicting prognosis.
Int J Radiat Oncol Biol Phys 2000 ; 46 : 1155-61.



BSBM

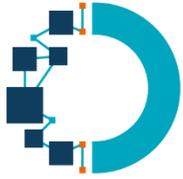
Classification BSBM (Basic Score for Brain Metastases)

Variable / Score	0	1
KPS	<80	80-100
Maladie métastatique extracérébrale	Oui	Non
Tumeur primitive contrôlée	Oui	Non
Total	0	3

Le score varie de 0 à 3 points. Plus le score est élevé, meilleure est la survie.

Lorenzoni J, Devriendt D, Massager N *et al.* : Radiosurgery for treatment of brain metastases : estimation of patient eligibility using three stratification systems.

Int J Radiat Oncol Biol Phys 2004 ; 60 : 218-224



GPA

Classification GPA.

Score GPA	0	0,5	1
Âge	>60 ans	50-59 ans	<50 ans
Karnofsky PS	<70	70-80	>80
Nombre de métastase cérébrale	>3	2-3	1
Métastase extra-cérébrale	oui	-	non

Sperduto PW, Berkey B, Gaspar LE, Mehta M et al., A new prognostic index and comparison to three other indices for patients with brain metastasis : an analysis of 1960 patients in the RTOG database. Int J Radiat Oncol Bio Phys 2008 ; 70 :510)4

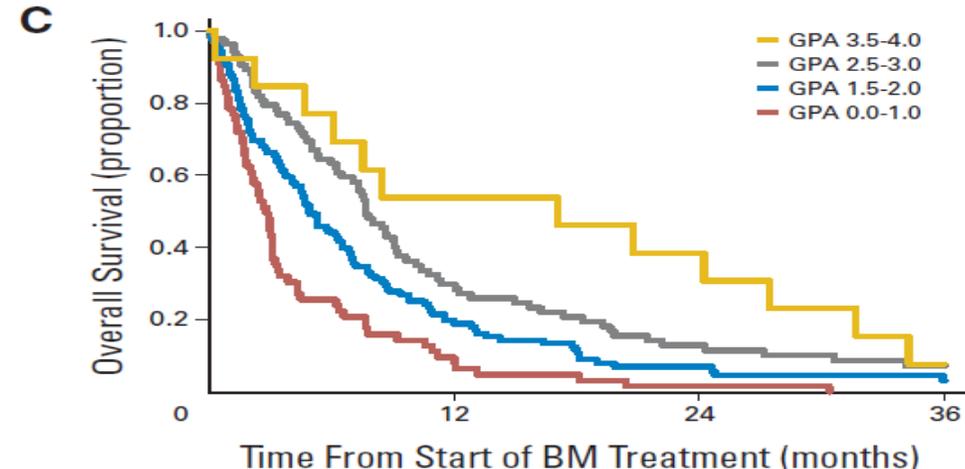
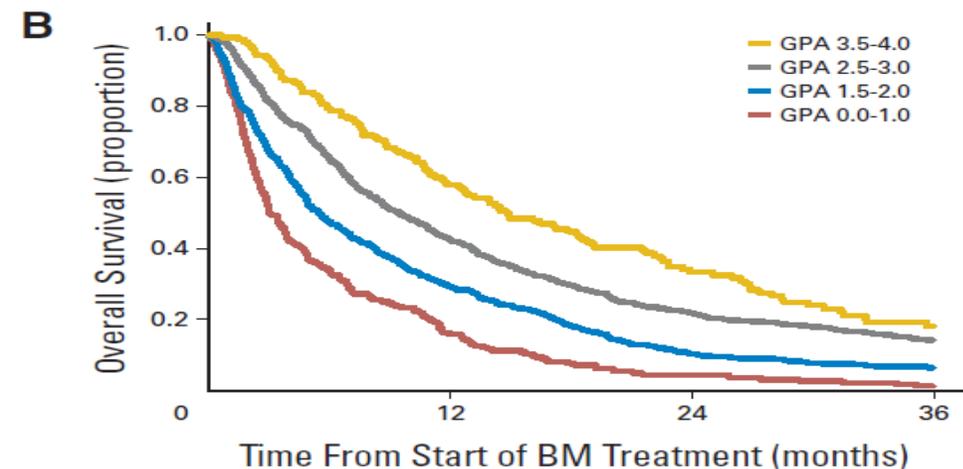


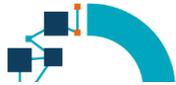
Classification DS-GPA

Sperduto PW, Kased N, roberge D, XuZ et al. Summary report on the graded prognostic assessment : an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases J Clin Oncol 2012 ;30(4) : 419.

	0	0,5	1
Age (années)	>60	50-60	<50
KPS	<70	70-80	90-100
ECM	Oui	-	Non
Nbre BM	>3	2-3	1
Total			

Score total	Survie médiane en mois
0-1,0	3,0
1,5-2,0	5,5
2,5-3,0	9,4
3,5-4,0	14,8





DS-GPA : Lung-molGPA

Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

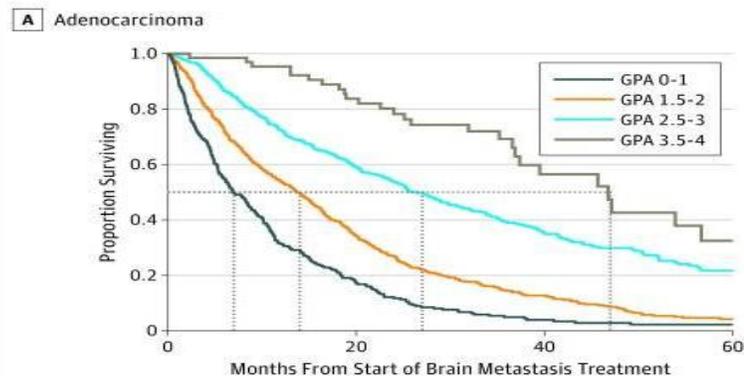
Prognostic Factor	GPA Scoring Criteria ^a			Patient Score ^b
	0	0.5	1.0	
Age, y	≥70	<70	NA	—
KPS	<70	80	90-100	—
ECM	Present		Absent	—
Brain metastases, No.	>4	1-4	NA	—
Gene status	<i>EGFR</i> neg/unk and <i>ALK</i> neg/unk	NA	<i>EGFR</i> pos or <i>ALK</i> pos	—
Total	NA	NA	NA	—

Abbreviations: DS, diagnosis-specific; ECM, extracranial metastases; GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; MS, median survival; NA, not applicable; neg/unk, negative or unknown; NSCLC, non-small-cell lung cancer; pos, positive.

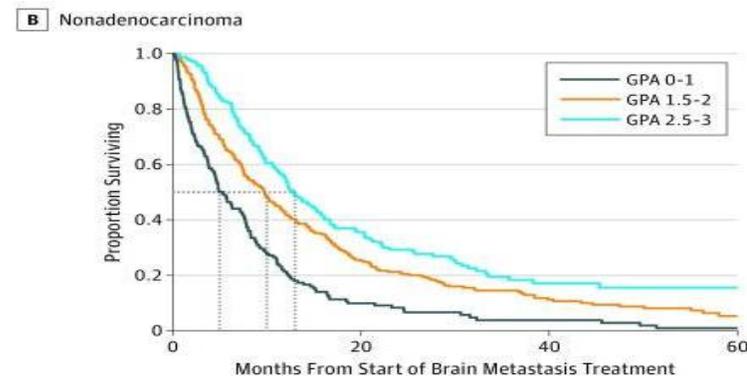
^a Adenocarcinoma MS in months by GPA: 0-1.0 6.9; 1.5-2.0, 13.7; 2.5-3.0 ,26.5;

and 3.5-4.0, 46.8; nonadenocarcinoma MS in months by GPA: 0-1.0, 5.3; 1.5-2.0, 9.8; 2.5-3.0, 12.8.

^b Evaluating clinician completes this column.



No. at risk	0	20	40	60
GPA 0-1	337	47	9	5
GPA 1.5-2	664	189	53	10
GPA 2.5-3	455	228	93	38
GPA 3.5-4	65	50	18	7



No. at risk	0	20	40	60
GPA 0-1	175	15	4	1
GPA 1.5-2	324	75	21	6
GPA 2.5-3	166	54	15	11

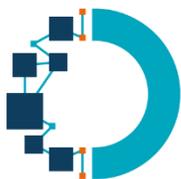
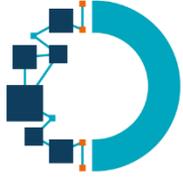


Table 1. Comparison of Historical and Recent Survival in Patients With NSCLC and Brain Metastases

Lung GPA Score	1985-2005		2006-2014			
	All NSCLC, DS-GPA		Nonadenocarcinoma NSCLC Lung-molGPA ^a		Adenocarcinoma NSCLC Lung-molGPA ^a	
	MS, mo	Patients, No. (%)	MS, mo	Patients, No. (%)	MS, mo	Patients, No. (%)
0.0-1.0	3.0	254 (14)	5.3	175 (26)	6.9	337 (22)
1.5-2.5	5.5	705 (38)	9.8	324 (49)	13.7	664 (44)
2.5-3.5	9.4	713 (40)	12.8	166 (25)	26.5	455 (30)
3.5-4.0	14.8	161 (9)		0	46.8	65 (4)
Overall	7.0	1833 (100)	9.2	665 (100)	15.2	1521 (100)

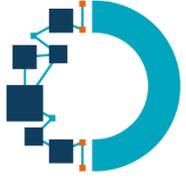
Abbreviations: DS, diagnosis-specific; GPA, graded prognostic assessment; MS, median survival; NSCLC, non-small-cell lung cancer.

^a The Lung-molGPA is the updated DS-GPA designed from the data in the present study.



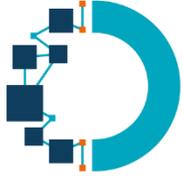
Quels moyens thérapeutiques ?

- Chirurgie
- Radiothérapie
 - WBRT (variante : WBRT avec épargne hippocampique (RTOG0933))
 - Radiochirurgie(SRS), RTE stéréo (SBRT)
- Chimiothérapie
- Association thérapeutique
- + soins de support



« dogmes »

- Barrière hémato-encéphalique
- CNS : sanctuaire de la maladie, inaccessible aux traitements généraux
- Maladie cérébrale jusqu'alors réservée aux traitements locaux.
 - Locaux stricts : Chir / radiochir
 - « locorégionaux » : EIT



Chirurgie: rationnel 3 essais randomisés

			Survie médiane	% de récidive/progression	Temps médian jusqu'à progression
Patchell 1990	G1 : WBRT (n=23) G2 : WBRT+ chir (n=25)	Unique 36 Gy en 12 fr. Histo multiple	G1 : 15 semaines G2 : 40 semaines P < 0.01	RL : G1 : 12/23 (52%) G2 : 5/25 (20%) p < 0.02 RLR G1 : 3/23 (13%) G2 5/25 (20%) NS	RL : G1: 21 semaines G2 > 59 semaines p < 0.0001
Mintz 1996	G1 : WBRT (n=43) G2 : WBRT+ chir (n=41)	Unique 30 Gy en 10 fr.	G1 : 6.3 mois <u>G2 : 5.6 mois</u> P = NS	NR	NR
Vecht 1993	G1 : WBRT (n=31) G2 : WBRT+ chir (n=32)	Unique 40 Gy en 20 fr. Histo multiple	G1 : 6 mois G2 : 10 mois P = 0.04	NR	NR

Méta unique : Chir Vs Chir + WBRT

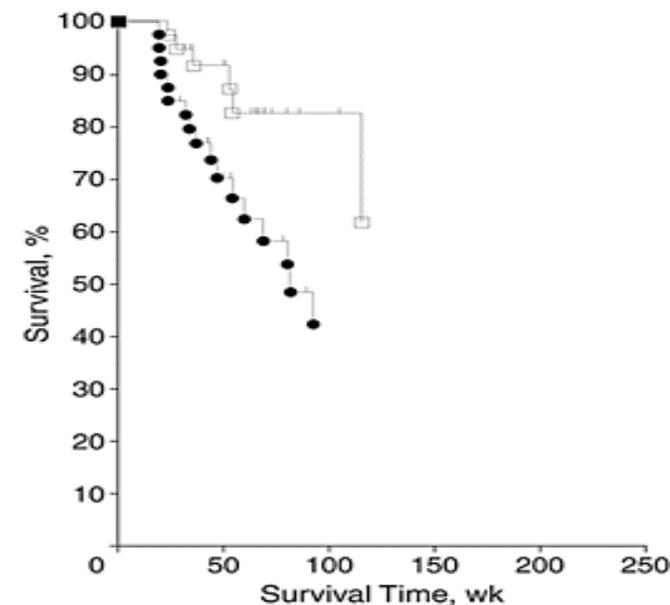
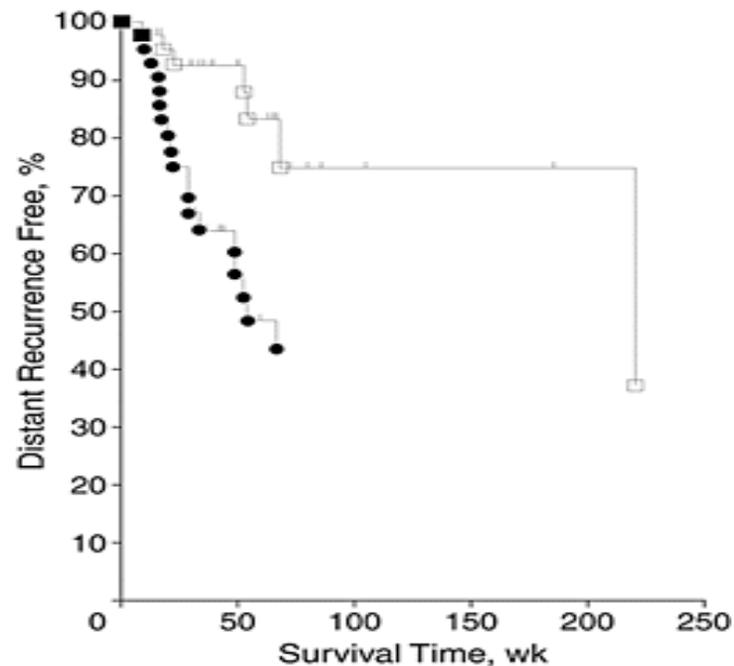
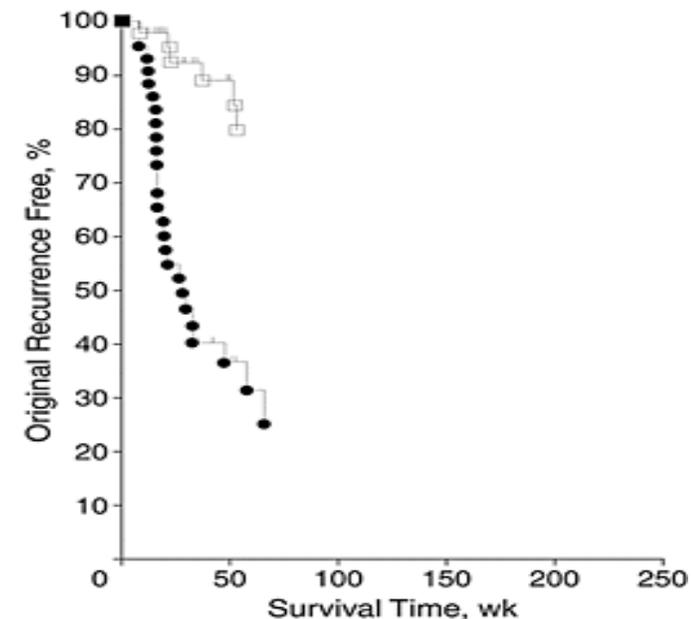
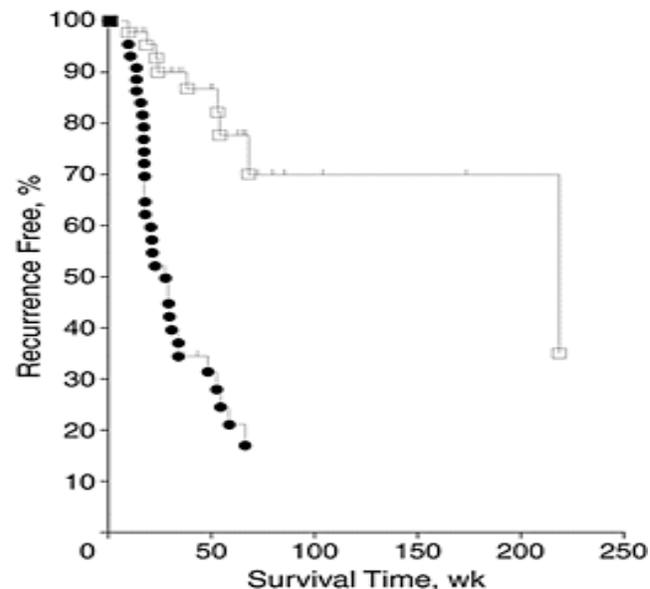
Table 4.—Location of Recurrence of Metastatic Cancer in the Brain

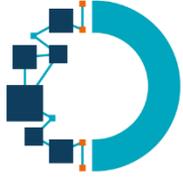
Recurrence	No. (%)	
	Observation Group (n = 46)	Radiation Group (n = 49)
None	14 (30)	40 (82)
Original only*	15 (33)	2 (4)
Original and distant†	6 (13)	3 (6)
Distant only	11 (24)	4 (8)

*A recurrence of the original brain metastasis is defined as the reappearance of metastasis in exactly the same site in the brain as the first metastasis.

†A distant brain recurrence is any recurrence not at the site of the original metastasis.

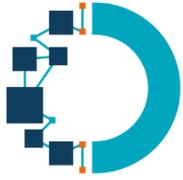
Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998 Nov 4;280(17):1485-1489.





Indications de la chirurgie

- Exerese à discuter de principe si « conditions de sécurité fonctionnelle satisfaisante » (yoo,2009)
 - →avis du chirurgien essentiel sur la faisabilité
- En intention « curatrice », possibilité d'accès à une chirurgie éveillée.
- En intention palliative : lié à l'impact fonctionnel (immédiat, attendu) ou au contexte (corticothérapie et immunothérapie?)
- Attitude de prise en charge combinée : « considérer chir et radiothérapie en concomitant »



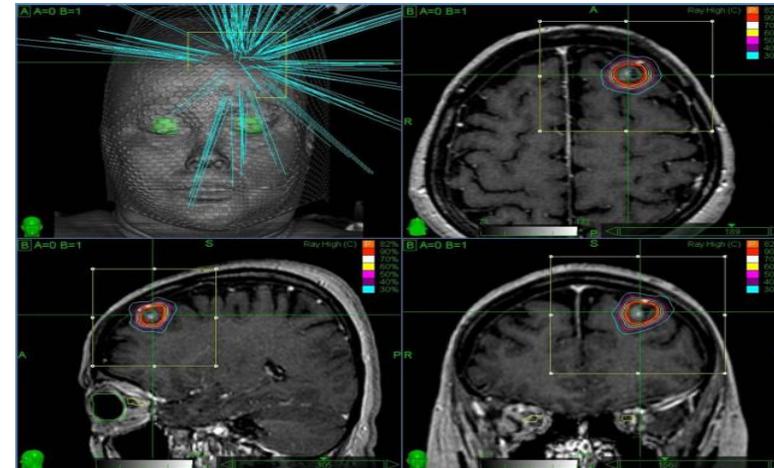
Pourquoi la radiochir (RTE Stéréo)?

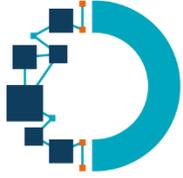
- Alternative à la chirurgie
- Impact de la dose sur le contrôle local
- Impact de l'épargne dosimétrique cérébrale sur la fonction neurologique à long terme



Inconvénients :

Impasse sur la maladie microscopique cérébrale





Definitions ...

- Radiochirurgie : radiothérapie stéréotaxique Dose Unique (SRS)
- Radiothérapie Stéréotaxique hypofractionnée (dose > 5 Gy) (SRT)

- Plusieurs techniques liées au matériel :
 - Gammaknife (Cobalt, cadre invasif)
 - Accélérateurs de particules « classiques » optimisés:
 - Système Novalis
 - Solution Varian
 - Solution Elekta
 - Accélérateurs stéréo « purs »:
 - Cyberknife (Accuray*)

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

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ORIGINAL REPORT

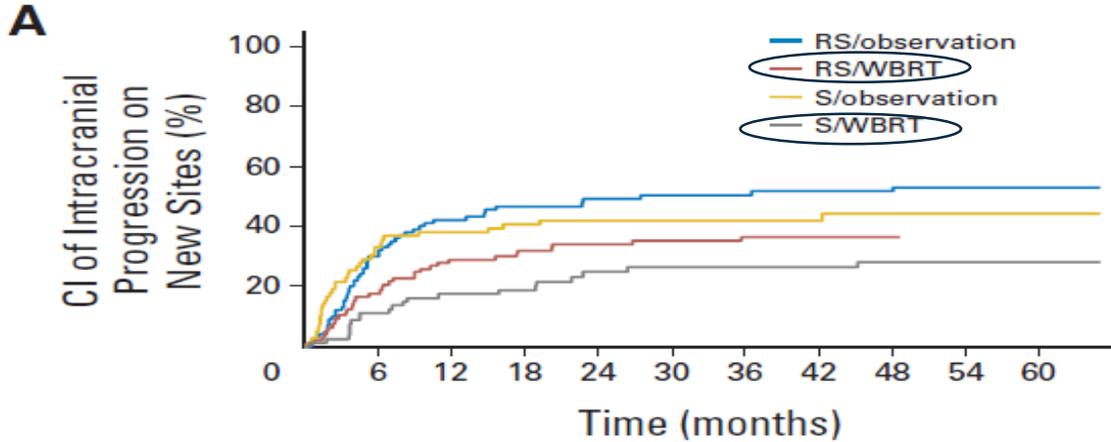
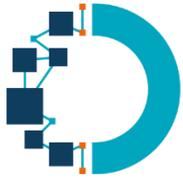
Table 1. Eligibility Criteria

Eligibility Criteria
Inclusion criteria
Age \geq 18 years
WHO performance status \leq 2
1-3 brain metastases
Radiosurgery: single metastasis \leq 3.5 cm, multiple metastases \leq 2.5 cm in diameter
Surgery: complete surgical resection
Radiosurgery: histologic confirmation of primary tumor or other metastases \leq 4 years ago, stereotactic biopsy of the brain metastasis otherwise
Stable systemic cancer for \geq 3 months and/or asymptomatic synchronous primary tumor without metastases outside the CNS or unknown primary tumor
Exclusion criteria
Brain metastasis of small-cell lung cancer, lymphoma, leukemia, myeloma, germ cell tumors
Brain stem metastases
Leptomeningeal metastases
Recurrent brain metastases after surgery and/or radiosurgery and/or brain irradiation
Inability to interrupt chemotherapy during whole-brain radiotherapy

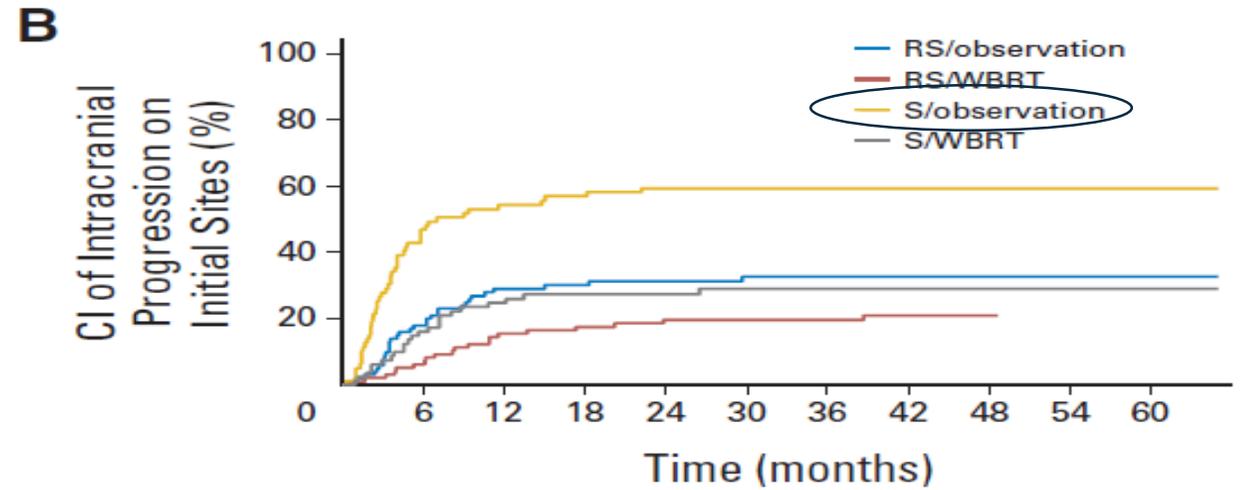
Table 2. Patient Demographics and Clinical Characteristics

Characteristic	Observation (n = 179)		WBRT (n = 180)		Total (N = 359)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	61		60		60	
Range	37-80		26-81		26-81	
Sex						
Male	122	68	113	63	235	65
Female	57	32	67	37	124	35
WHO performance status						
0	82	46	75	42	157	44
1	78	44	84	47	162	45
2	19	11	21	12	40	11
Neurologic status						
No deficit	97	54	97	54	194	54
Some deficit, useful work	52	29	54	30	106	30
Moderate impairment	29	16	29	16	58	16
Major impairment	1	1	0	0	1	0
Localization of primary tumor						
Lung (NSCLC)	93	52	97	54	190	53
Breast	20	11	22	12	42	12
Kidney	13	7	16	9	29	8
Colorectal	16	9	14	8	30	8
Melanoma	8	5	10	6	18	5
Other	15	8	12	7	27	8
CUP	14	8	9	5	23	6
Macroscopic tumor outside the brain						
Absent	89	50	79	44	168	47
Present	82	46	91	51	173	48
Unknown	8	4	10	6	18	5

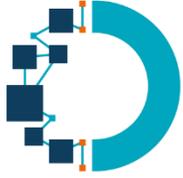
Abbreviations: WBRT, whole-brain radiotherapy; NSCLC, non-small-cell lung cancer; CUP, cancer of unknown primary tumor.



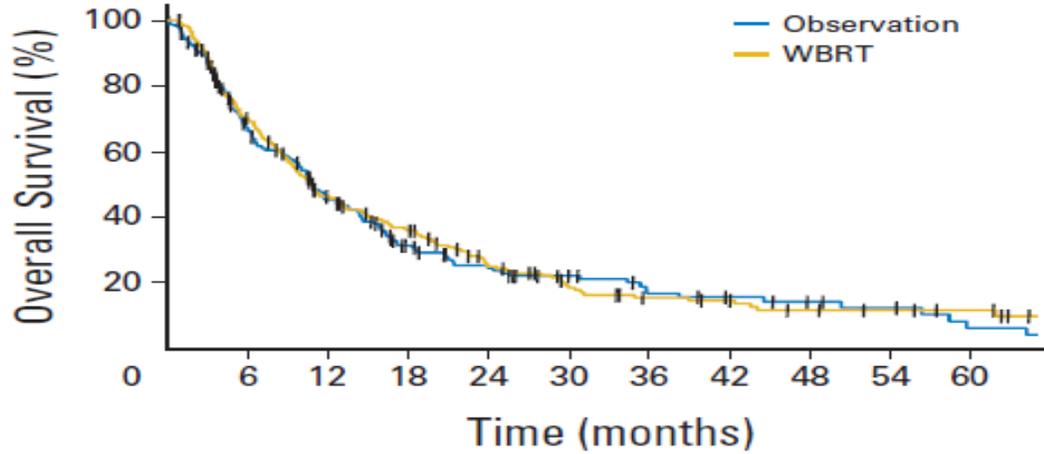
Randomized treatment	0	N	No. of patients at risk									
RS/observation	51	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	35	99	59	26	16	10	7	5	3	1	0	0
S/observation	34	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	21	81	47	30	23	11	9	8	8	7	6	4



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

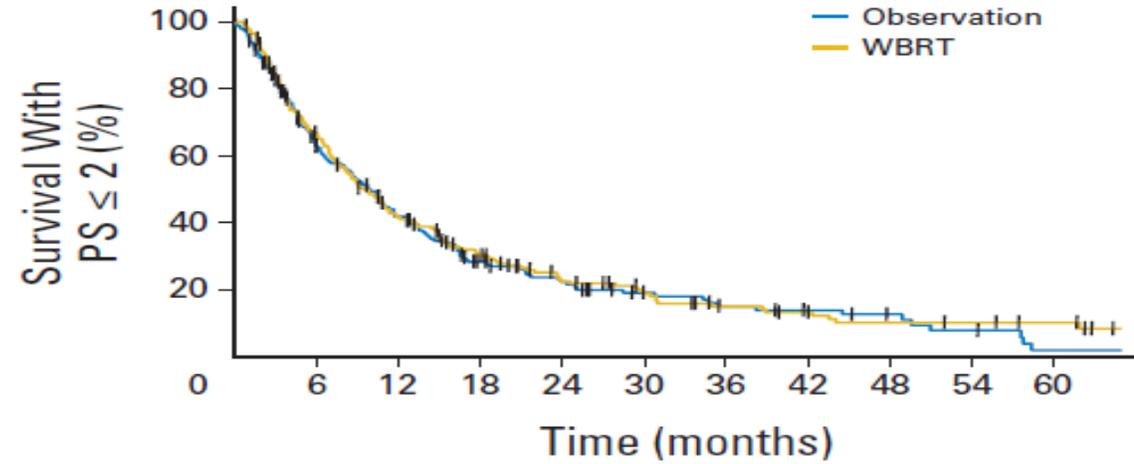


B



Randomized treatment	0	N	No. of patients at risk									
Observation	143	179	117	75	44	31	22	15	12	9	7	3
WBRT	149	180	124	80	61	38	25	18	15	11	9	7

A



Randomized treatment	0	N	No. of patients at risk									
Observation	149	179	112	71	41	29	19	14	11	8	5	1
WBRT	152	180	118	73	52	34	25	17	13	10	9	7

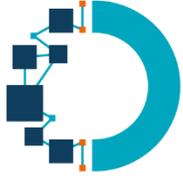


Table 5. Intracranial Progression and Salvage Therapy

Progression and Salvage Therapy	Observation			WBRT		
	No. of Patients	% of Patients Who Experienced Progression (n = 139)	% of Total Patients (n = 179)	No. of Patients	% of Patients Who Experienced Progression (n = 87)	% of Total Patients (n = 180)
Site of intracranial progression						
New sites	60	43	34	44	51	24
Initial sites	54	39	30	31	36	17
Both	19	14	11	7	8	4
Unknown	6	4	3	5	6	3
Salvage treatment						
WBRT	56	40	31	6	7	3
Radiosurgery	21	15	12	20	23	11
Surgery	11	8	6	3	3	2
Radiosurgery + WBRT	1	1	1			
Surgery + WBRT	3	2	2			

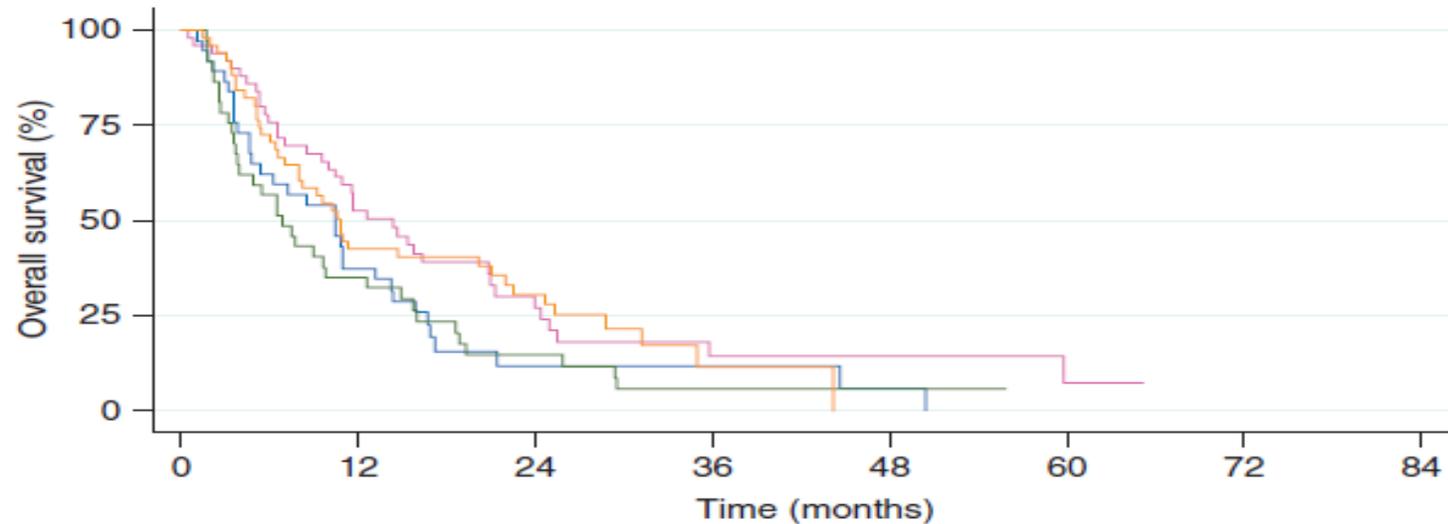
Abbreviation: WBRT, whole-brain radiotherapy.

Publication de QDV
mais cross-over
important

ORIGINAL ARTICLE

Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001

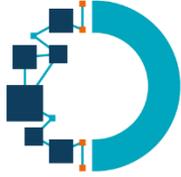
T. M. Churilla¹, E. Handorf¹, S. Collette², L. Collette², Y. Dong¹, A. A. Aizer³, M. Kocher⁴, R. Soffiatti⁵,
B. M. Alexander^{3†} & S. E. Weiss^{1*,†}



	Number at risk							
	0	12	24	36	48	60	72	84
No WBRT, GPA < 2.5	37	13	3	3	1	0	0	0
No WBRT, GPA ≥ 2.5	50	24	9	4	3	1	0	0
WBRT, GPA < 2.5	37	13	5	1	1	0	0	0
WBRT, GPA ≥ 2.5	51	20	12	2	0	0	0	0



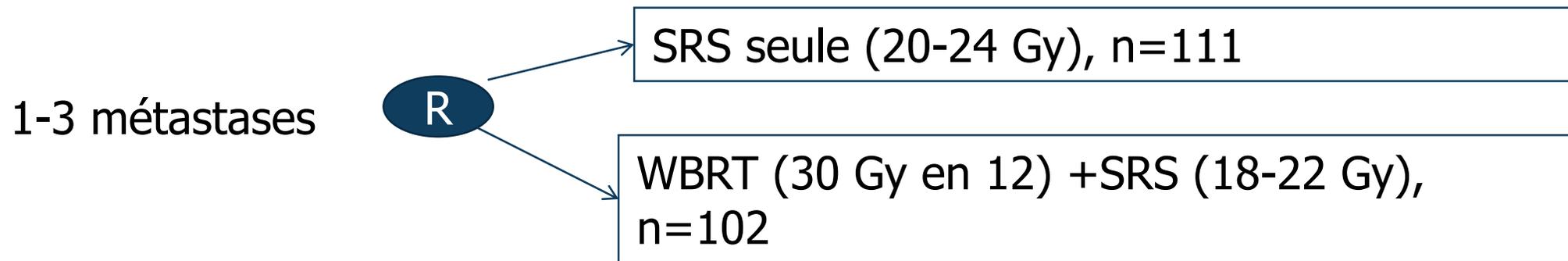
Figure 2. Overall survival among non-small-cell lung cancer (NSCLC) patients according to receipt of whole brain radiotherapy stratified by diagnosis-specific Graded Prognostic Assessment (GPA) score (per-protocol). NSCLC patients ($n = 175$) were stratified according to GPA scores of < 2.5 (unfavorable) and ≥ 2.5 (favorable).



Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases:

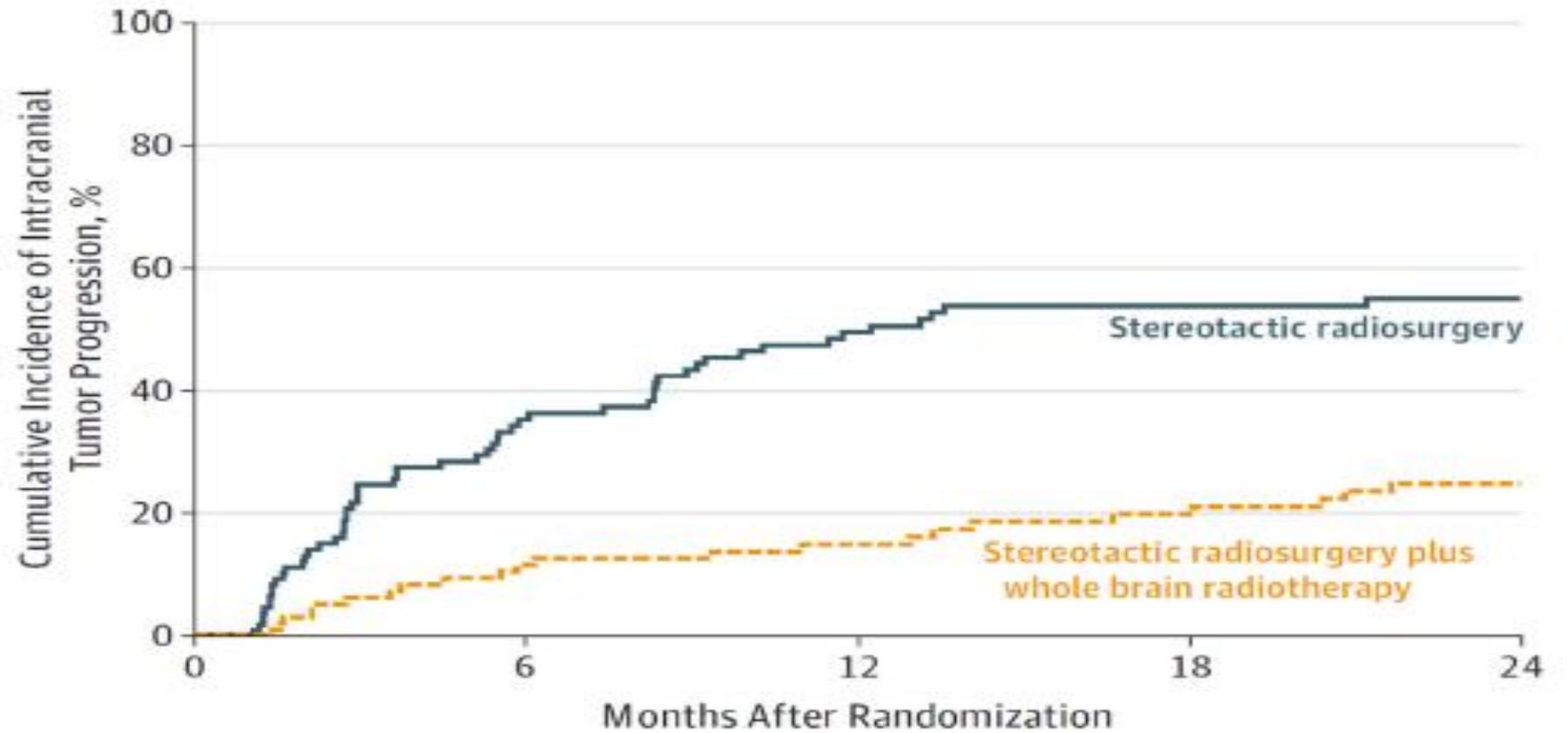
A Randomized Clinical Trial

Paul D. Brown, MD, Kurt Jaeckle, MD, Karla V. Ballman, PhD, Elana Farace, PhD, Jane H. Cerhan, PhD, S. Keith Anderson, MS, Xiomara W. Carrero, BS, Fred G. Barker II, MD, Richard Deming, MD, Stuart H. Burri, MD, Cynthia Ménard, MD, Caroline Chung, MD, Volker W. Stieber, MD, Bruce E. Pollock, MD, Evanthia Galanis, MD, Jan C. Buckner, MD, and Anthony L. Asher, MD



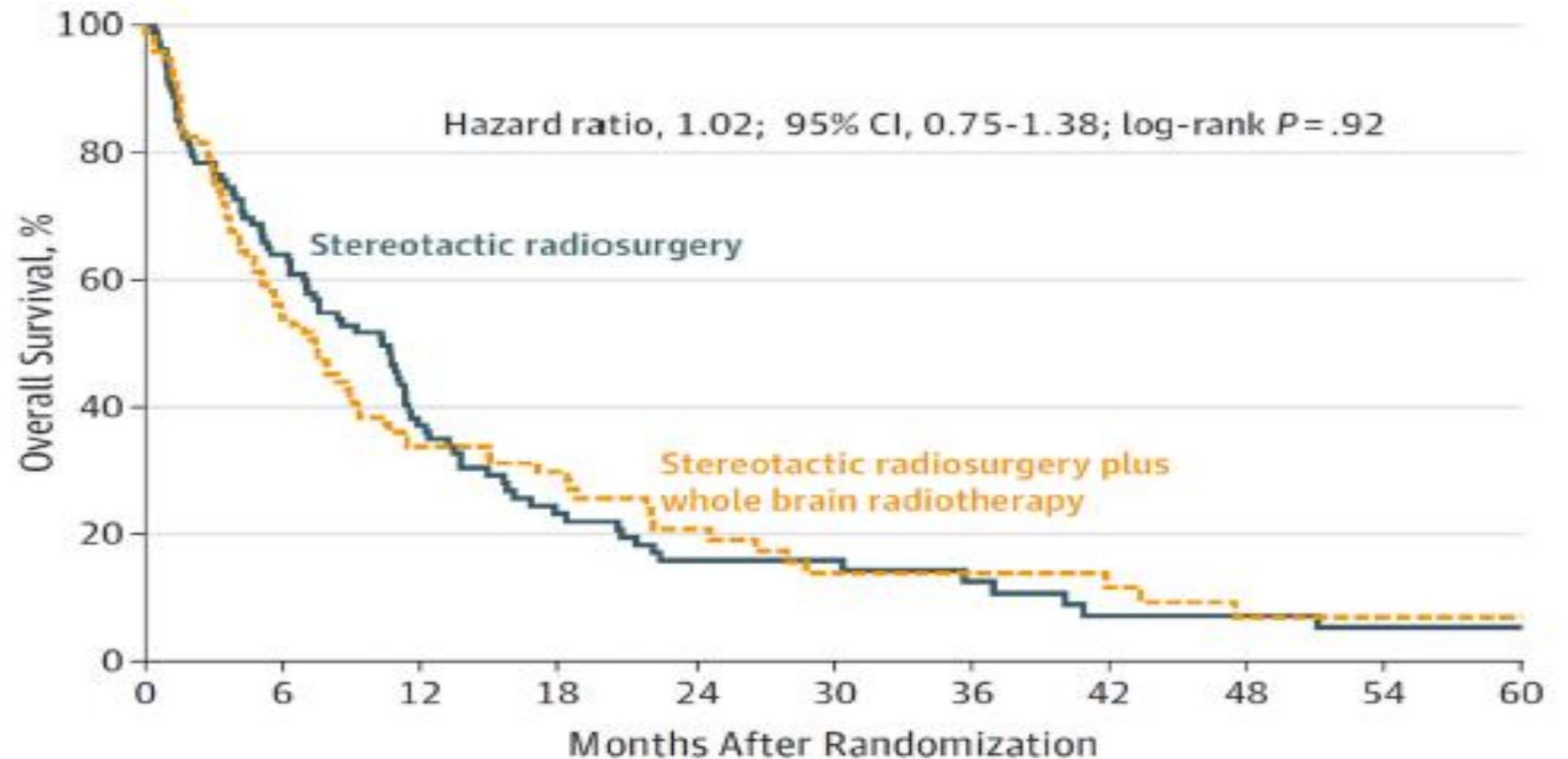
Objectif principal : détérioration cognitive à 3 mois

Objectifs secondaires : temps jusqu'à progression neuro, QDV, autonomie, cognition à long terme, SG



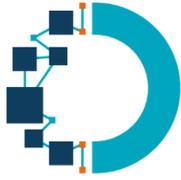
No. at risk

Stereotactic radiosurgery	111	35	12	5	1
Stereotactic radiosurgery plus whole brain radiotherapy	102	43	24	16	9



No. at risk

Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1



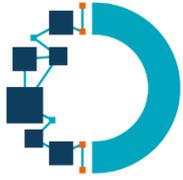
Patients Who Experienced Cognitive Deterioration by 3 Months and Difference Between Groups

	No. (%) of Participants		Mean Difference, % (95% CI)	P Value ^a
	SRS Alone (n = 63)	SRS Plus WBRT (n = 48)		
Change from baseline ^b				
HVLTR				
Immediate recall				
Deterioration	5 (8.2)	14 (30.4)	22.2 (5.4 to 39.1)	.004
No deterioration	56 (91.8)	32 (69.6)		
Delayed recall				
Deterioration	12 (19.7)	24 (51.1)	31.4 (12.1 to 50.7)	<.001
No deterioration	49 (80.3)	23 (48.9)		
Recognition				
Deterioration	14 (22.6)	19 (40.4)	17.8 (-1.5 to 37.2)	.06
No deterioration	48 (77.4)	28 (59.6)		
TMT-A time to complete				
Deterioration	10 (16.7)	14 (30.4)	13.8 (-4.4 to 32.0)	.11
No deterioration	50 (83.3)	32 (69.6)		
TMT-B time to complete				
Deterioration	11 (19.0)	16 (37.2)	18.2 (-1.4 to 37.9)	.07
No deterioration	47 (81.0)	27 (62.8)		
COWAT total				
Deterioration	1 (1.9)	8 (18.6)	16.7 (2.4 to 31.0)	.01
No deterioration	52 (98.1)	35 (81.4)		
GPS total seconds				
Deterioration	17 (29.3)	21 (47.7)	18.4 (-2.4 to 39.3)	.07
No deterioration	41 (70.7)	23 (52.3)		
Outcome for cognitive progression at 3 mo				
Stable	23 (36.5)	4 (8.3)	-28.2 (-44.2 to -12.2)	<.001
Progression	40 (63.5)	44 (91.7)		

Abbreviations: COWAT, Controlled Oral Word Association Test; GPS, Grooved Pegboard Test; HVLTR, Hopkins Verbal Learning Test-Revised; SRS, stereotactic radiosurgery; TMT, Trail Making Test; WBRT, whole brain radiotherapy.

^aBy Fisher exact test.

^bCognitive deterioration was defined as a decline of 1 SD in score from baseline.



Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Lancet Oncol 2014; 15: 387-95

Masaaki Yamamoto, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya*

Inclusions :

- 10 lésions maximum
- Toutes < 10 mL et axe < 3 cm
- Vtotal < 15 mL

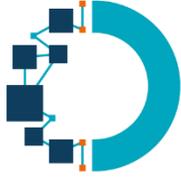
- KPS > 70
- Petites cellules inclus

Non infériorité

objectif principal : Survie globale

objectifs secondaires :

survie neurologique
détérioration neurologique
récidive 'locale'
récidive 'locorégionale'
récidive leptoméningée
leucoencéphalopathie
nouvelles RTE stéréo
WBRT de sauvetage
toxicité
fonctions cognitives



1194 patients dans 20 centres japonais:

- 3/4 de primitifs pulmonaires
- 60-70% de maladie « somatique » contrôlée
- Majorité de RPA II
- 70 % de patients asymptomatique sur le plan neuro

	Total (n=1194)	1 tumour (n=455)	2-4 tumours (n=531)	5-10 tumours (n=208)	p value
Tumour number					
Median (IQR)	2 (1-4)	1 (1-1)	2 (2-3)	6 (5-8)	--
Mean (SD)	3 (2)	1 (0)	3 (1)	7 (2)	--
Age, years					
Mean (SD)	65.8 (10.2)	65.9 (10.7)	65.8 (9.9)	65.4 (9.9)	0.55
Range	30-91	30-91	36-91	37-89	--
≥65	693 (58%)	270 (59%)	310 (58%)	113 (54%)	0.46
Sex					
Female	471 (39%)	177 (39%)	203 (38%)	91 (44%)	--
Male	723 (61%)	278 (61%)	328 (62%)	117 (56%)	--
Primary cancer					
Lung	912 (76%)	348 (76%)	400 (75%)	164 (79%)	--
Breast	123 (10%)	42 (9%)	57 (11%)	24 (12%)	--
GI tract	85 (7%)	35 (8%)	41 (8%)	9 (4%)	--
Kidney	36 (3%)	15 (3%)	19 (4%)	2 (1%)	--
Other	38 (3%)	15 (3%)	14 (3%)	9 (4%)	--
Extracerebral diseases					
Controlled	811 (68%)	325 (71%)	355 (67%)	131 (63%)	--
Not controlled	383 (32%)	130 (29%)	176 (33%)	77 (37%)	--
KPS					
≥80 points	1036 (87%)	395 (87%)	459 (86%)	182 (88%)	--
≤70 points	158 (13%)	60 (13%)	72 (14%)	26 (13%)	--
RPA class					
1	334 (28%)	134 (29%)	141 (27%)	59 (28%)	--
2	819 (69%)	304 (67%)	371 (70%)	144 (69%)	--
3	41 (3%)	17 (4%)	19 (4%)	5 (2%)	--
Neurological symptoms					
No	835 (70%)	335 (74%)	357 (67%)	143 (69%)	--
Yes	359 (30%)	120 (26%)	174 (33%)	65 (31%)	--
MMSE score					
Median (IQR)	28 (25-30)	28 (25-30)	28 (25-30)	28 (25-30)	0.66
Range	7-30	7-30	17-30	9-30	--
≥27 points	750 (63%)	279 (61%)	339 (64%)	132 (64%)	0.74
Cumulative tumour volume, mL					
Mean (SD)	2.84 (2.91)	2.27 (2.38)	3.07 (3.08)	3.54 (3.25)	<0.0001
Range	0.01-14.96	0.01-9.90	0.02-14.96	0.02-13.90	--
≥1.9 mL	601 (50%)	195 (43%)	279 (53%)	127 (61%)	<0.0001
Maximum diameter of the largest tumour (cm)					
Mean (SD)	1.63 (0.68)	1.60 (0.69)	1.66 (0.68)	1.62 (0.64)	0.49
Range	0.08-2.99	0.11-2.98	0.11-2.99	0.08-2.97	--
≥1.6 cm	600 (50%)	221 (49%)	273 (51%)	106 (51%)	0.65

Data are number (%), unless otherwise specified. Clinical characteristics were measured mainly on the day of stereotactic radiosurgery, or uncommonly on the day before. GI=gastrointestinal. KPS=Karnofsky performance status. RPA=recursive partitioning analysis. MMSE=Mini-Mental State Examination.

Table 1: Clinical characteristics of patients, measured immediately before stereotactic radiosurgery



Survie Globale

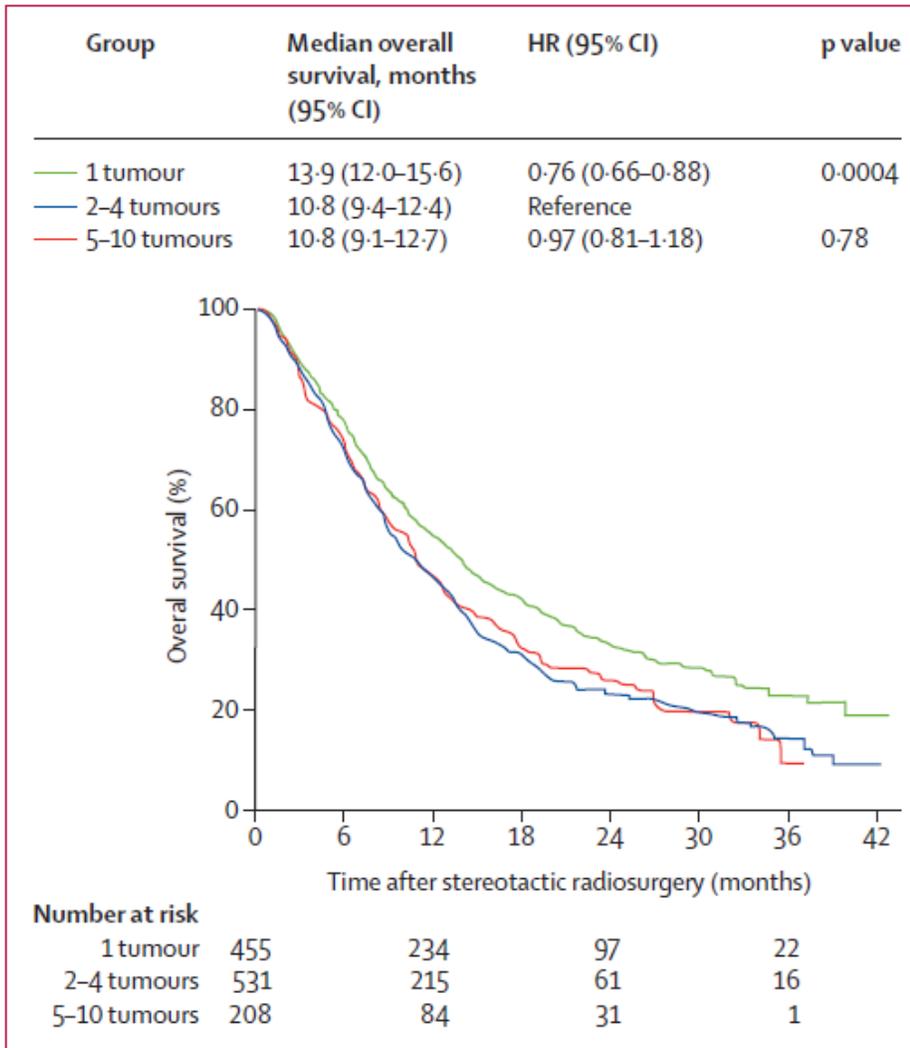
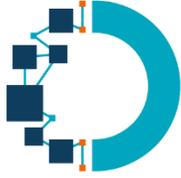


Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.



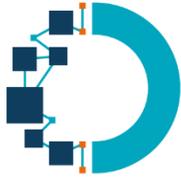
	Median overall survival, months (95% CI)				HR (95% CI); p value	
	Total (n=1194)	1 tumour (A) (n=455)	2-4 tumours (B) (n=531)	5-10 tumours (C) (n=208)	A vs B	B vs C
Lung	12.5 (11.2-13.4)	13.4 (11.7-15.5)	11.4 (9.5-13.1)	12.5 (10.3-14.9)	0.796 (0.671-0.945); p=0.0090	1.045 (0.842-1.297); p=0.69
Breast	14.8 (11.9-24.4)	27.2 (8.2-NE)	13.7 (10.9-23.6)	10.5 (5.2-NE)	0.761 (0.449-1.290); p=0.31	0.806 (0.441-1.475); p=0.48
GI tract	6.7 (5.7-8.7)	14.4 (6.7-18.2)	5.7 (4.7-7.9)	5.7 (1.5-7.9)	0.409 (0.244-0.685); p=0.0006	0.673 (0.306-1.484); p=0.33
Kidney	13.7 (6.0-17.0)	16.3 (6.0-NE)	13.7 (5.1-17.0)	3.8 (2.3-5.4)	0.511 (0.221-1.183); p=0.12	0.207 (0.040-1.082); p=0.10
Others	8.4 (6.1-10.3)	7.3 (3.3-24.3)	8.6 (1.0-14.8)	9.0 (2.9-27.3)	0.779 (0.335-1.811); p=0.56	1.263 (0.495-3.215); p=0.63

HR=hazard ratio. NE=not estimable. GI=gastrointestinal.

Table 3: Median overall survival for five primary cancer sites

Données évaluable sur poumon et sein.
Pas de données sur les autres primitifs (manque d'effectif)

Sur primitif pulmonaire : pas d'infériorité du bras 4-10 vs bras 2-4



	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)*	p value
Age, years (≥ 65 vs < 65)	1.412 (1.229–1.622)	< 0.0001	1.351 (1.174–1.554)	< 0.0001
Sex (male vs female)	1.427 (1.242–1.655)	< 0.0001	1.377 (1.179–1.608)	< 0.0001
KPS (≤ 70 vs ≥ 80)	2.079 (1.729–2.500)	< 0.0001	1.529 (1.240–1.886)	< 0.0001
Number of tumours				
2–4 vs 1	1.313 (1.131–1.525)	0.0001	1.328 (1.141–1.546)	0.0003
5–10 vs 2–4	0.974 (0.806–1.177)	0.78	0.993 (0.819–1.204)	0.94
Maximum diameter of largest tumour (≥ 1.6 cm vs < 1.6 cm)	1.431 (1.249–1.638)	< 0.0001	1.006 (0.771–1.314)	0.92
Cumulative tumour volume (≥ 1.9 mL vs < 1.9 mL)	1.503 (1.313–1.721)	< 0.0001	1.172 (0.899–1.530)	0.24
Primary tumour category				
Breast vs lung	0.743 (0.584–0.945)	0.014	0.881 (0.673–1.153)	0.36
GI vs lung	1.750 (1.373–2.231)	< 0.0001	1.407 (1.087–1.822)	0.0094
Renal cell vs lung	1.063 (0.718–1.573)	0.76	0.964 (0.648–1.434)	0.13
Others vs lung	1.572 (1.096–2.255)	0.021	1.333 (0.922–1.927)	0.86
Extracerebral disease status (not controlled vs controlled)	1.385 (1.200–1.589)	< 0.0001	1.272 (1.101–1.469)	0.0011
Neurological symptoms (yes vs no)	1.779 (1.541–2.053)	< 0.0001	1.334 (1.117–1.594)	0.0013

Clinical factors were measured before stereotactic surgery. HR=hazard ratio. KPS=Karnofsky performance status. GI=gastrointestinal. *HR adjusted for all clinical factors listed in this table.

Table 2: Clinical factors affecting survival after stereotactic radiosurgery

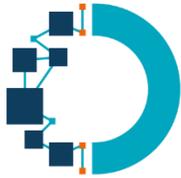
Pas de différence entre les trois bras

	Total (n=1194)	1 tumeur (A) (n=455)	2-4 tumeurs (B) (n=531)	5-10 tumeurs (C) (n=208)	p value (B vs C)
Died	850 (71%)	310 (68%)	392 (74%)	148 (71%)	0.46
Neurological death*	71 (8%)	32 (10%)	25 (6%)	14 (9%)	0.27
Deterioration of neurological function	146 (12%)	56 (12%)	62 (12%)	28 (13%)	0.53
Local recurrence†	138 (13%)	65 (16%)	54 (11%)	19 (10%)	0.78
New lesions‡	625 (58%)	199 (48%)	297 (63%)	129 (69%)	0.12
Leptomeningeal dissemination†	144 (13%)	48 (12%)	61 (13%)	35 (19%)	0.067
Leukoencephalopathy†	9 (1%)	3 (1%)	4 (1%)	2 (1%)	0.68
Salvage SRS procedures	459 (38%)	148 (33%)	221 (42%)	90 (43%)	0.74
1	256 (21%)	76 (17%)	129 (24%)	51 (25%)	0.92
2	113 (9%)	45 (1%)	47 (9%)	21 (10%)	
≥3	90 (8%)	27 (6%)	45 (8%)	18 (9%)	
Salvage WBRT	107 (9%)	36 (8%)	54 (10%)	17 (8%)	0.48
Salvage surgery	23 (2%)	12 (3%)	8 (2%)	3 (1%)	1.00
Systemic anticancer agents	861 (72%)	308 (68%)	387 (73%)	166 (70%)	0.059
Molecularly targeted agents	356 (30%)	123 (27%)	157 (30%)	76 (37%)	0.078

Data are number (%), unless otherwise specified. SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.
 *Percentages based on the number of patients who died. †Based on 1074 (90%) patients (414 [91%] in group A, 474 [89%] in group B, and 186 [89%] in group C; differences between proportions of patients with data, p=0.64), because MRI results were not available for 120 (10%) patients who had an early death or had remarkable deterioration of clinical state soon after stereotactic radiosurgery.

Table 4: Treatment outcomes after stereotactic radiosurgery

	Post-SRS cumulative rates (95% CI)			HR (95% CI)	p value
	6 months	12 months	24 months		
Neurological death*					
1 tumeur	0.9% (0-1.7)	4.2% (2.4-6.1)	7.0% (4.5-9.5)	1.17 (0.69-1.97)	0.56
2-4 tumeurs	0.4% (0-0.9)	1.7% (0.6-2.9)	5.3% (3.2-7.3)	Reference	NA
5-10 tumeurs	1.4% (0-3.1)	4.3% (1.6-7.1)	7.1% (3.3-11.0)	1.47 (0.76-2.85)	0.25
Deterioration of neurological function†					
1 tumeur	5.1% (3.0-7.1)	8.4% (5.8-10.9)	11.9% (8.8-15.0)	0.85 (0.59-1.22)	0.38
2-4 tumeurs	4.9% (3.1-6.7)	8.0% (5.7-10.4)	11.6% (8.8-14.5)	Reference	NA
5-10 tumeurs	5.2% (2.2-8.3)	8.7% (4.9-12.6)	13.0% (8.0-18.1)	1.15 (0.76-2.85)	0.54
Local recurrence‡§					
1 tumeur	6.5% (4.1-8.9)	12.7% (9.5-15.9)	15.5% (11.9-19.2)	1.15 (0.80-1.65)	0.45
2-4 tumeurs	3.0% (1.4-4.5)	7.0% (4.6-9.3)	12.1% (8.9-15.3)	Reference	NA
5-10 tumeurs	4.3% (1.4-7.3)	6.5% (2.9-10.1)	9.8% (5.1-14.6)	0.90 (0.53-1.53)	0.70
New lesions§					
1 tumeur	23.9% (19.8-28.0)	36.7% (32.0-41.4)	47.9% (43.0-53.0)	0.55 (0.46-0.66)	<0.0001
2-4 tumeurs	40.0% (35.5-44.4)	54.5% (50.0-59.0)	65.5% (60.9-70.1)	Reference	NA
5-10 tumeurs	45.9% (38.7-53.1)	63.8% (56.8-70.9)	72.0% (64.7-79.4)	1.22 (0.99-1.50)	0.067
Leptomeningeal dissemination§					
1 tumeur	3.6% (1.8-5.4)	7.1% (4.6-9.6)	11.0% (7.8-14.2)	0.71 (0.48-1.04)	0.087
2-4 tumeurs	5.1% (3.1-7.1)	8.8% (6.2-11.3)	13.2% (9.9-16.5)	Reference	NA
5-10 tumeurs	4.9% (1.8-8.0)	11.7% (6.9-16.4)	21.9% (15.0-28.7)	1.58 (1.04-2.40)	0.035
Leukoencephalopathy§					
1 tumeur	0.0%	1.1% (NE-2.4)	1.1% (NE-2.4)	0.55 (0.12-2.46)	0.43
2-4 tumeurs	0.0%	1.2% (0.0-2.4)	1.2% (0.0-2.4)	Reference	NA
5-10 tumeurs	0.0%	1.5% (NE-3.7)	1.5% (NE-3.7)	1.47 (0.27-8.13)	0.66
Repeat SRS					
1 tumeur	12.1% (9.1-15.1)	23.1% (19.3-27.1)	31.9% (27.5-36.4)	0.57 (0.46-0.71)	<0.0001
2-4 tumeurs	22.8% (19.3-26.4)	34.6% (30.5-38.6)	43.1% (38.7-47.5)	Reference	NA
5-10 tumeurs	23.1% (17.3-28.8)	38.3% (31.6-45.1)	45.4% (38.0-52.7)	1.12 (0.88-1.44)	0.36
Whole-brain radiotherapy					
1 tumeur	2.1% (0.8-3.5)	5.1% (3.1-7.1)	7.8% (5.2-10.4)	0.62 (0.41-0.95)	0.053
2-4 tumeurs	3.6% (2.0-5.2)	7.0% (4.9-9.3)	10.4% (7.6-13.1)	Reference	NA
5-10 tumeurs	1.4% (0-3.1)	5.4% (2.3-8.6)	9.1% (4.7-13.5)	0.78 (0.45-1.34)	0.36



	Total (n=1194)	1 tumour (A) (n=455)	2-4 tumours (B) (n=531)	5-10 tumours (C) (n=208)	p value (B vs C)
Treatment-related adverse events*					0.89†
None	1093 (92%)	422 (93%)	481 (91%)	190 (91%)	
Grade 1 and 2	69 (6%)	22 (5%)	36 (7%)	11 (5%)	..
Grade 3	20 (2%)	6 (1%)	10 (2%)	4 (2%)	..
Grade 4	8 (1%)	3 (1%)	3 (1%)	2 (1%)	..
Grade 5	4 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	..
Had MMSE at baseline	1132 (95%)	430 (95%)	504 (95%)	198 (95%)	..
Maintained neurocognitive function‡					
4 months after SRS	623/662 (94%)	243/256 (95%)	263/284 (93%)	117/122 (96%)	0.27
12 months after SRS	333/366 (91%)	141/154 (92%)	139/152 (91%)	53/60 (88%)	0.60
24 months after SRS	120/128 (94%)	55/60 (92%)	47/48 (98%)	18/20 (90%)	0.20
36 months after SRS	28/30 (93%)	14/15 (93%)	10/11 (91%)	4/4 (100%)	1.00

Data are number of patients with one or more adverse event (%), unless otherwise specified. MMSE=Mini-Mental State Examination. SRS= stereotactic radiosurgery. *Graded according to Common Terminology Criteria for Adverse Events, version 3.0.* †p value is for the number of patients with no adverse events versus the number with at least one or more grade 1-5 adverse event across all three tumour number groups. ‡Number of patients whose MMSE score did not decrease by 3 points or more from baseline (ie, same day or one day before or after SRS); percentages are based on the number of patients who completed MMSE at that timepoint.‡

Table 6: Adverse events and maintenance of neurocognitive function

Données de toxicités

STUDY PROTOCOL

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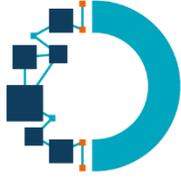


Whole brain radiotherapy versus stereotactic radiosurgery for 4–10 brain metastases: a phase III randomised multicentre trial

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North American Gamma Knife Consortium

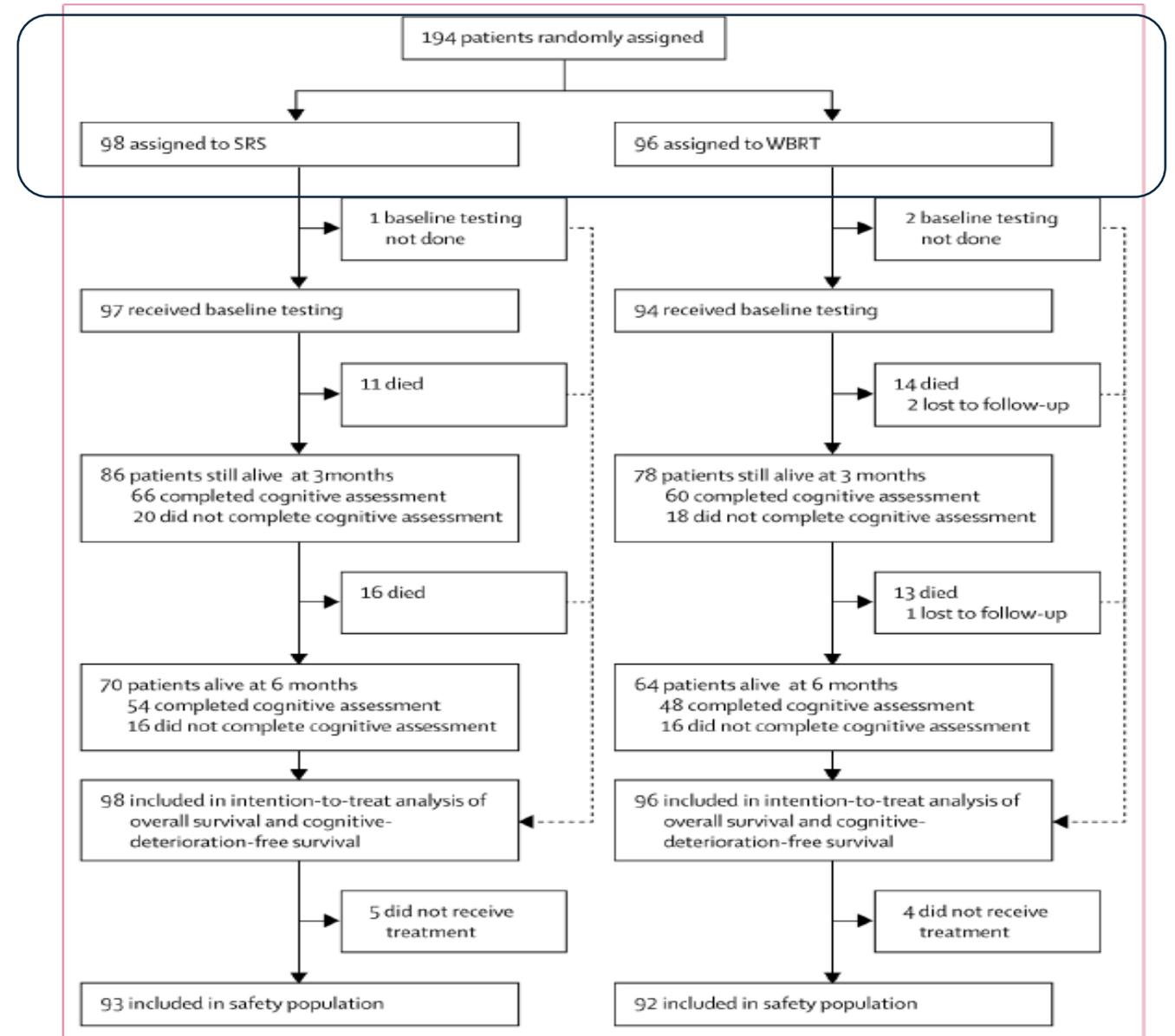
En cours de recrutement



Lancet Oncol. 2017 August ; 18(8): 1049–1060. doi:10.1016/S1470-2045(17)30441-2.

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial

Prof Paul D Brown, MD, Prof Karla V Ballman, PhD, Jane H Cerhan, PhD, S Keith Anderson, MS, Xiomara W Carrero, BS, Prof Anthony C Whitton, MD, Jeffrey Greenspoon, MD, Prof Ian F Parney, MD, Nadia N I Laack, MD, Jonathan B Ashman, MD, Prof Jean-Paul Bahary, MD, Prof Costas G Hadjipanayis, MD, James J Urbanic, MD, Fred G Barker II, MD, Elana Farace, PhD, Deepak Khuntia, MD, Prof Caterina Giannini, MD, Prof Jan C Buckner, MD, Prof Evanthia Galanis, MD, and David Roberge, MD



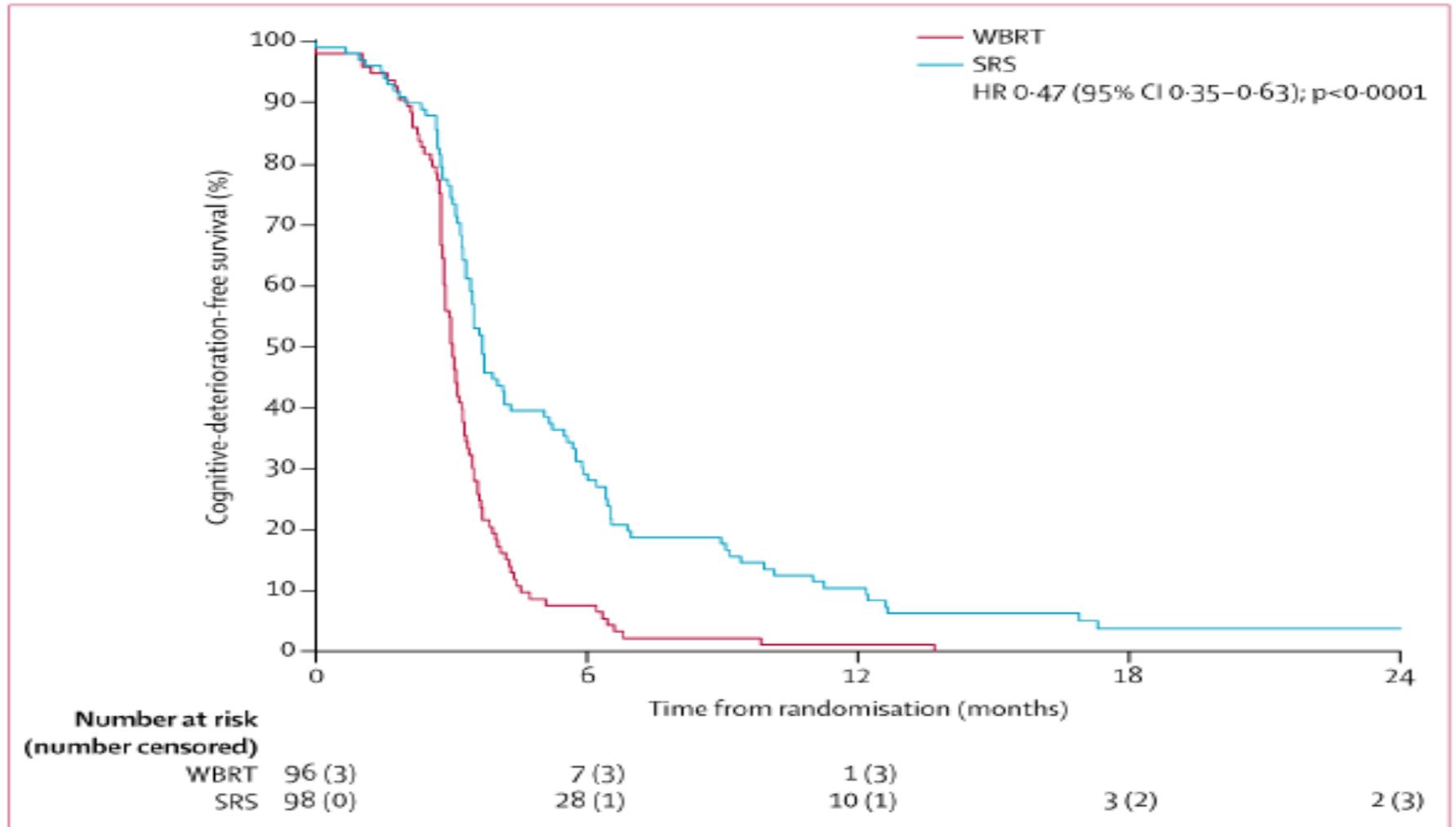
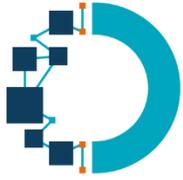


Figure 2. Cognitive-deterioration-free survival

WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

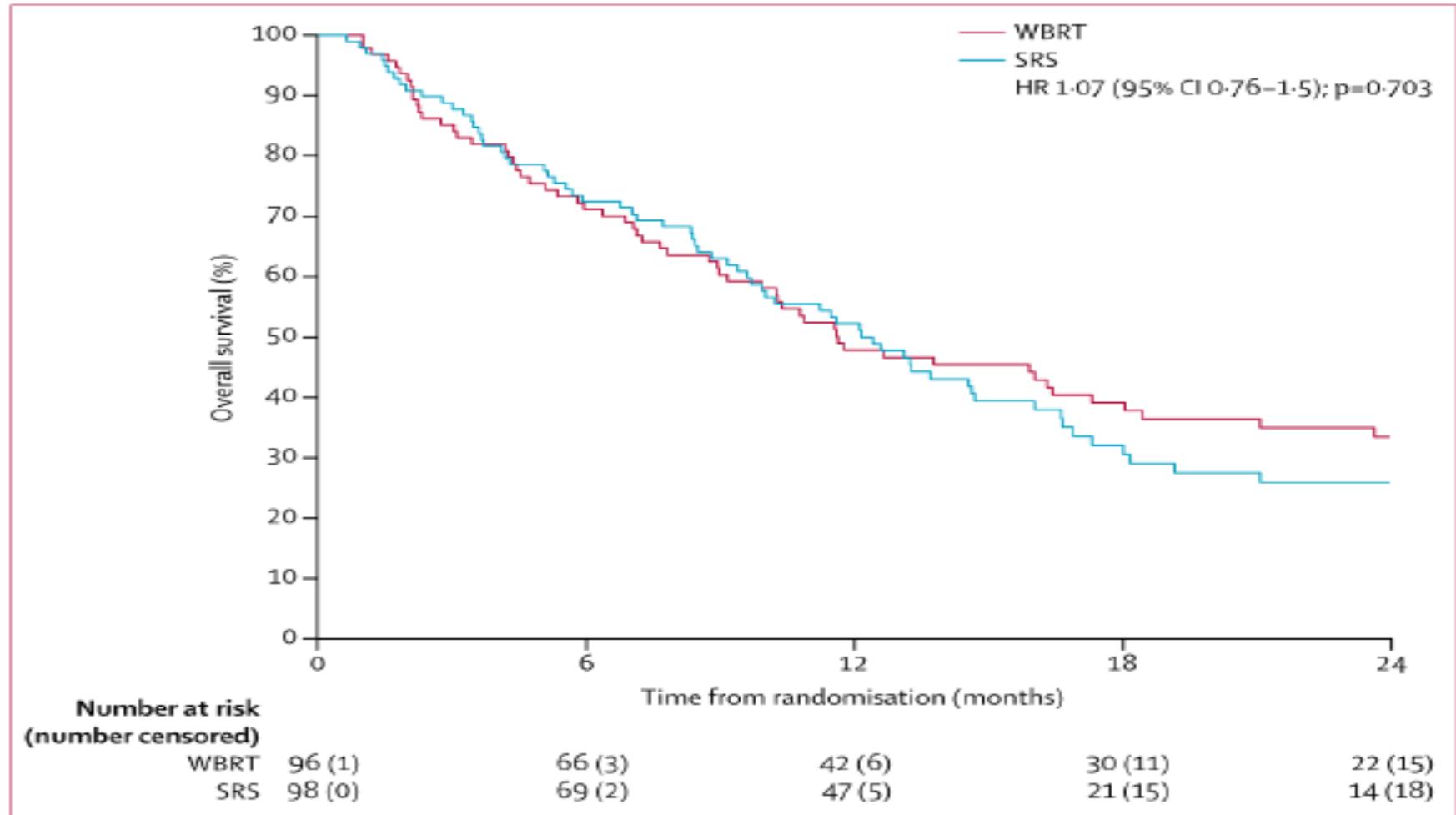
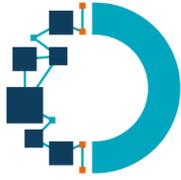
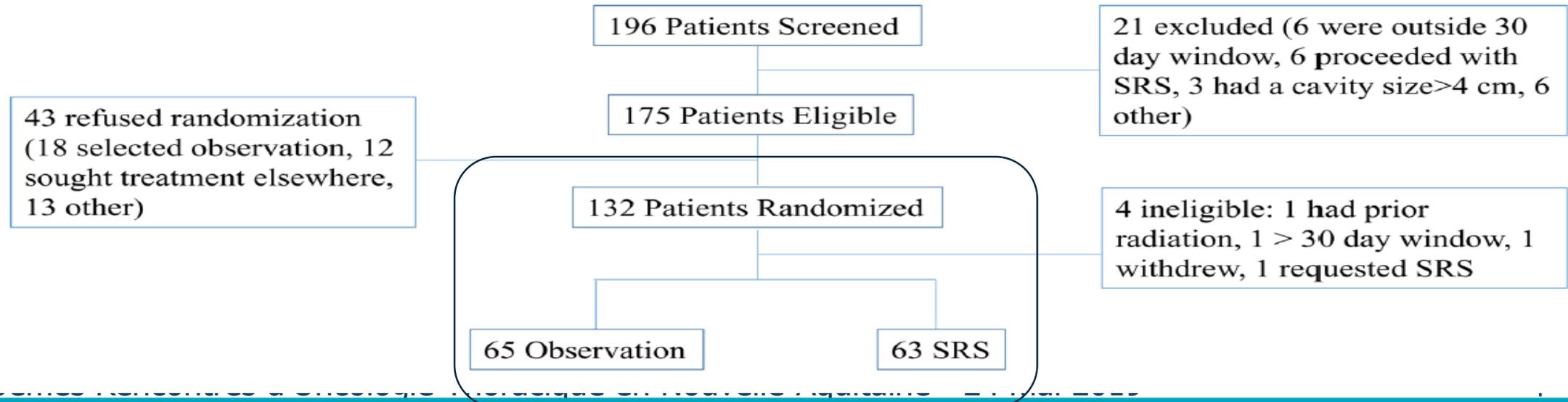


Figure 3. Overall survival

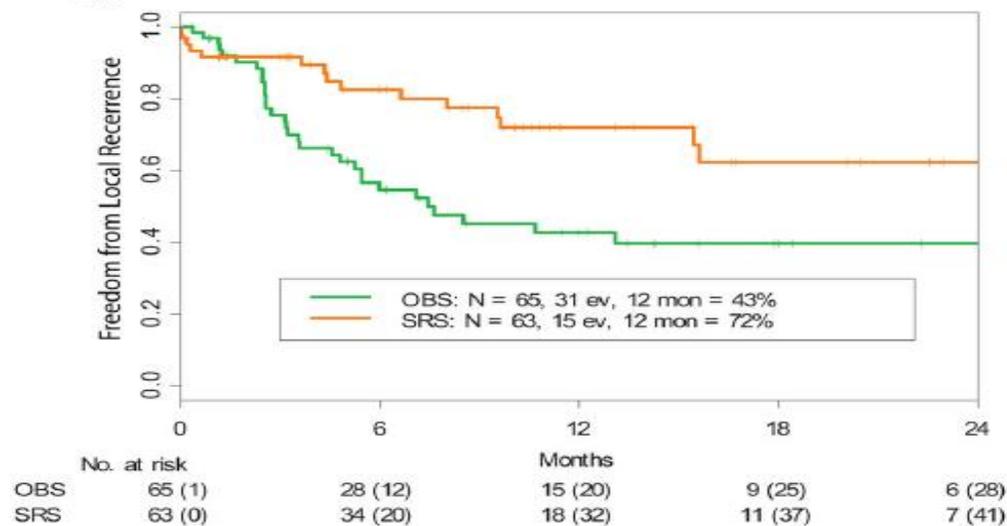
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

Prospective Randomized Trial of Post-operative Stereotactic Radiosurgery versus Observation for Completely Resected Brain Metastases

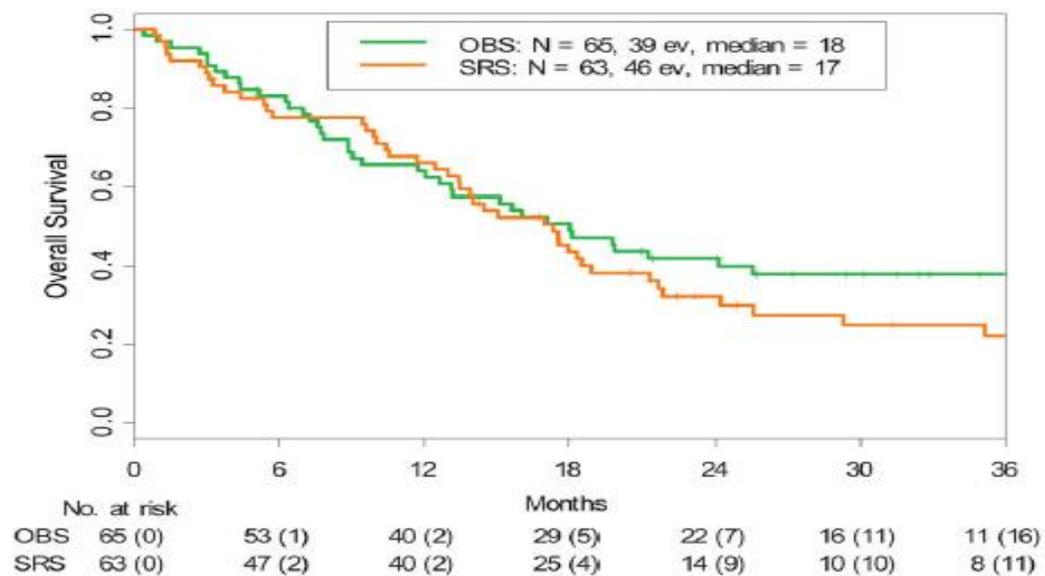
Anita Mahajan, M.D., Salmaan Ahmed, M.D., Mary Frances McAleer, M.D., Ph.D., Jeffrey S. Weinberg, M.D., Jing Li, M.D., Paul Brown, M.D., Stephen Settle, M.D., Sujit S. Prabhu, M.D., Frederick F. Lang, M.D., Nicholas Levine, M.D., Susan McGovern, M.D., Ph.D., Erik Sulman, M.D., Ph.D., Ian E. McCutcheon, M.D., Syed Azeem, M.D., Daniel Cahill, M.D., Ph.D., Claudio Tatsui, M.D., Amy B. Heimberger, M.D., Sherise Ferguson, M.D., Amol Ghia, M.D., Franco Demonte, M.D., Shaan Raza, M.D., Nandita Guha-Thakurta, M.D., James Yang, Ph.D., Raymond Sawaya, M.D., Kenneth R. Hess, Ph.D., and Ganesh Rao, M.D.



2A



2B



2C

