Management of brain metastases: Radiotherapy

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Disclosure

None

Which patients to treat?

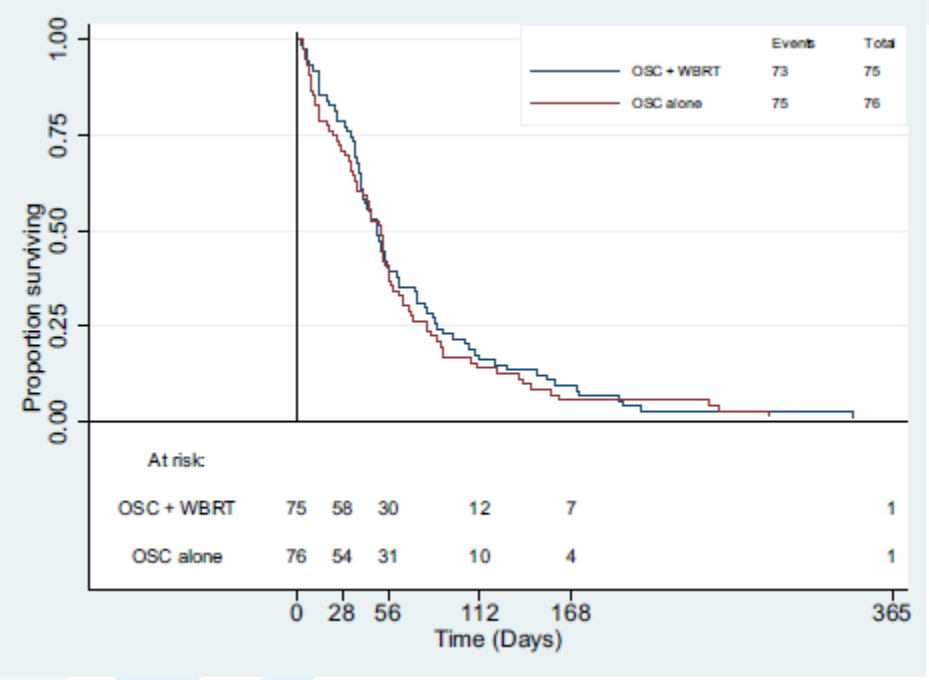
Table 1. Recursive partitioning analysis		Median survival	1-year OS
Class I:	Age <65 y, KPS ≥ 70, controlled primary tumor, no extracranial metastases	7.1 months	30 %
Class II:	All patients not in Class I or III	4.2 months	15 %
Class III:	KPS < 70	2.3 months	5 %

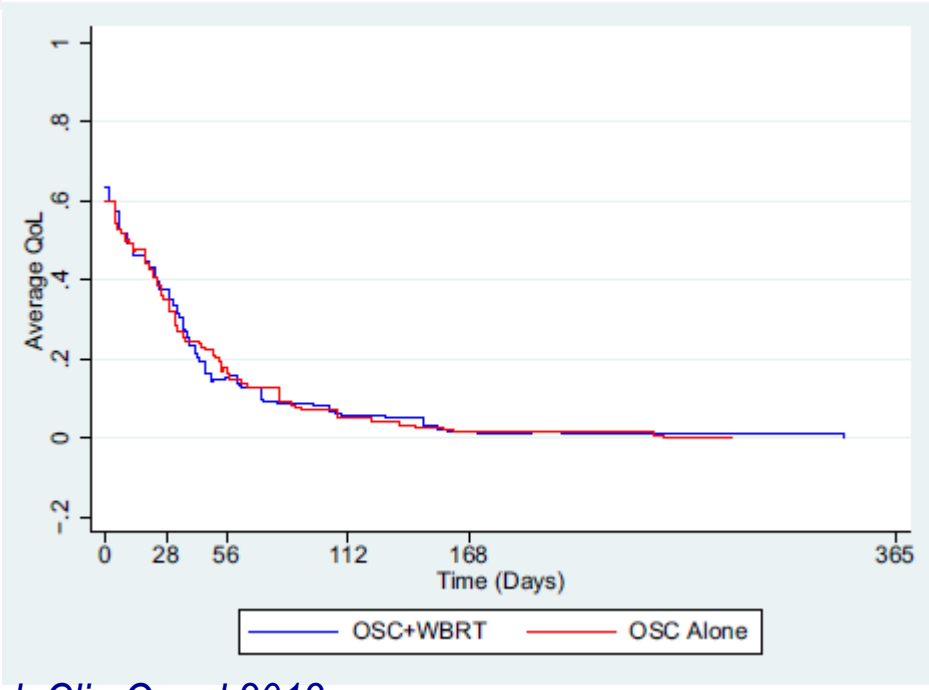
Abbreviation: KPS = Karnofsky Performance Status.

Sperduto et al. Int J Radiat Oncol Biol Phys 2008

Interim analysis QUARTZ phase III trial: WBRT vs. dexamethason in brain metastases from NSCLC

Characteristic		OSC + WBRT	OSC alone
Gender	Male	45 (60%)	46 (61%)
	Female	30 (40%)	30 (39%)
Recursive partitioning analysis	I	11 (15%)	1 (1%)
	II	28 (37%)	36 (47%)
	III	36 (48%)	39 (51%)





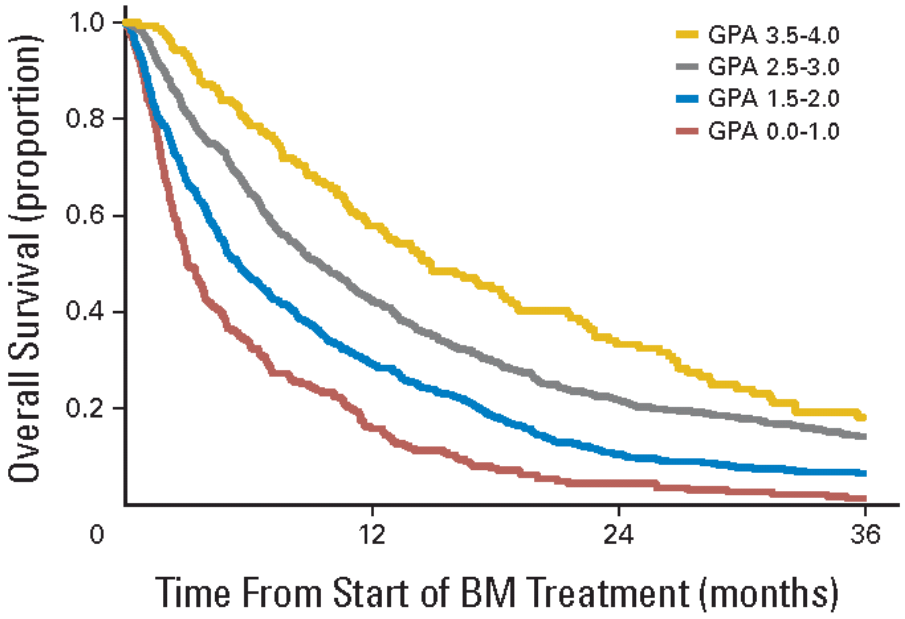
Langley RE et al. Clin Oncol 2013

Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)

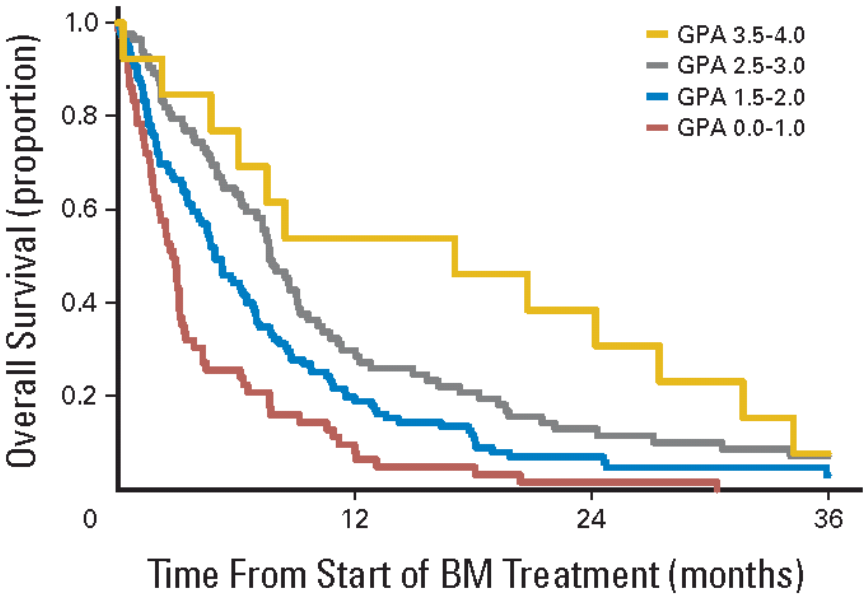
Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8



NSCLC



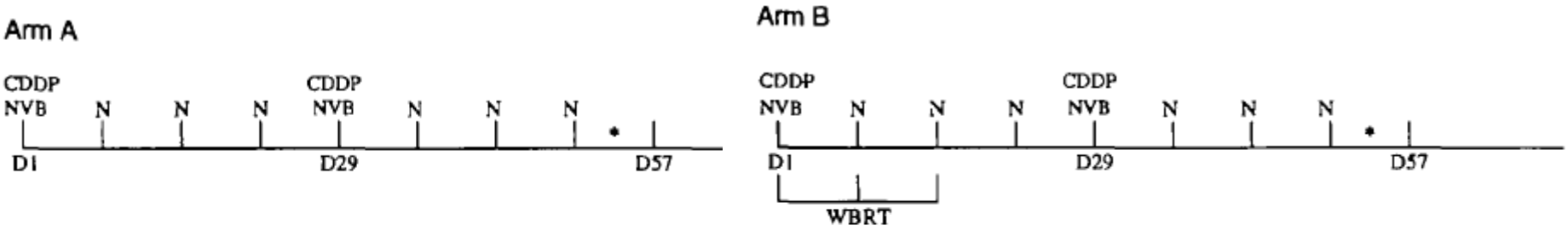
SCLC

Sperduto et al. J Clin Oncol 2012

Early vs. delayed WBRT and concurrent chemotherapy in NSCLC

n = 86

n = 85



* Response Evaluation (after 2-4 or 6 cycles)

if	Objective Response (intracranial and extracranial)	} Continue chemotherapy alone
if	No Objective Response (intracranial and extracranial)	} WBRT and stop chemotherapy
if	Intracranial SD or PD (but extracranial objective response)	} Chemotherapy and concurrent WBRT

27 %

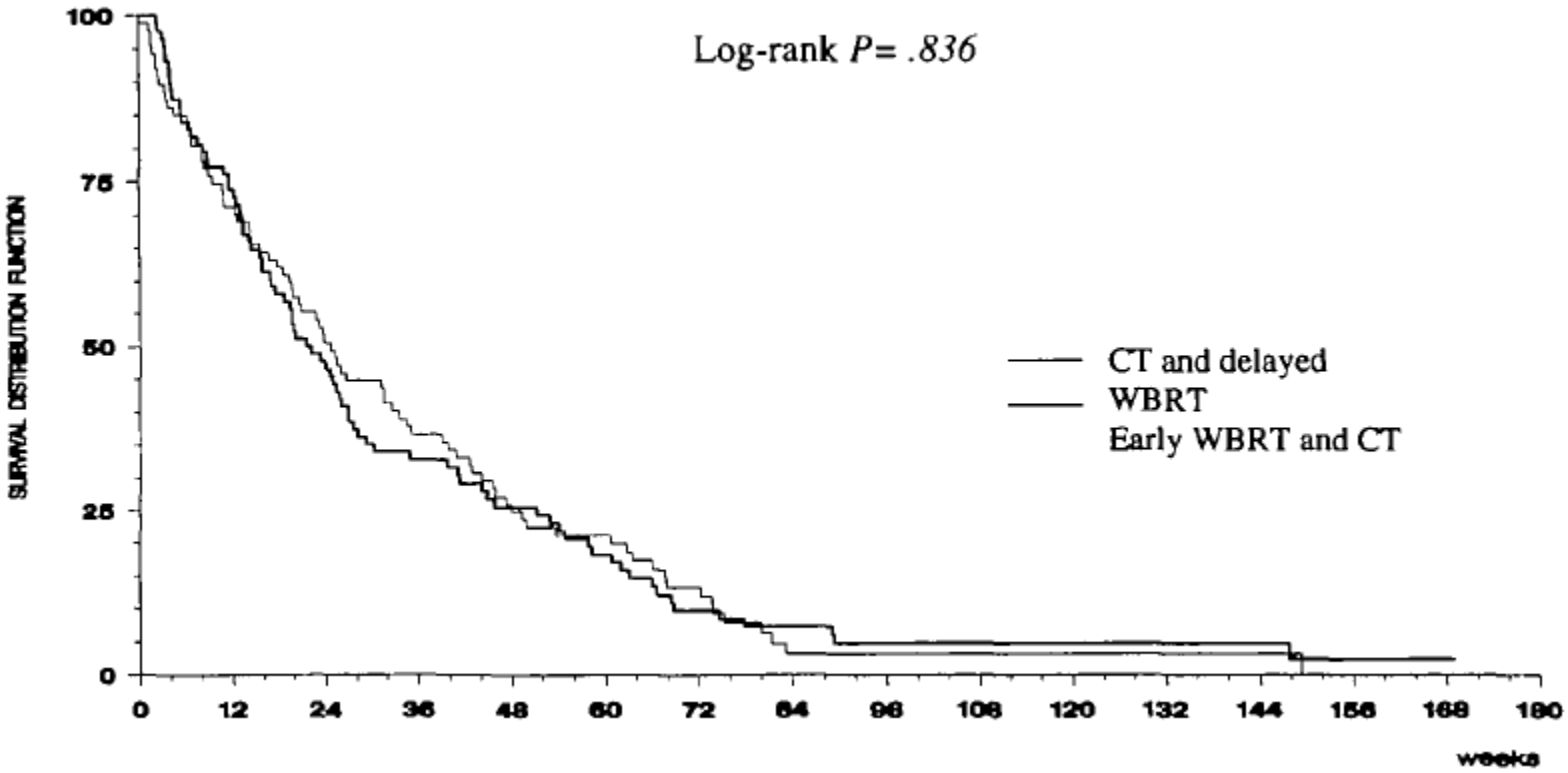
* Response Evaluation (after 2-4 or 6 cycles)

if	Objective Response	} Continue chemotherapy
if	SD or PD	} Stop chemotherapy

WBRT: 57/86 (66 %) patients

Robinet et al. Ann Oncol 2001

Early vs. delayed WBRT and concurrent chemotherapy in NSCLC



Robinet et al. Ann Oncol 2001

WBRT plus SRS vs. WBRT: Cochrane review

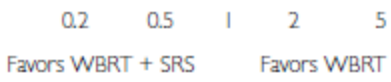
Outcome: 1 Overall survival

Study or subgroup	WBRT + SRS N	WBRT N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Andrews 2004	164	167	-0.18 (0.12)		92.8 %	0.84 [0.66, 1.06]
Kondziolka 1999	13	14	-0.52 (0.43)		7.2 %	0.59 [0.26, 1.38]
Total (95% CI)	**177**	**181**			**100.0 %**	**0.82 [0.65, 1.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 1.77 (P = 0.077)

Test for subgroup differences: Not applicable



Patil CG et al. Cochrane Collaboration 2012

WBRT plus SRS vs. WBRT: Cochrane review

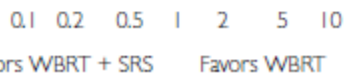
Outcome: 3 Local tumor control

Study or subgroup	WBRT + SRS N	WBRT N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Andrews 2004	164	167	-1.08 (0.44)		56.4 %	0.34 [0.14, 0.80]
Kondziolka 1999	13	14	-1.58 (0.5)		43.6 %	0.21 [0.08, 0.55]
Total (95% CI)	**177**	**181**			**100.0 %**	**0.27 [0.14, 0.52]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.56$, df = 1 (P = 0.45); $I^2 = 0.0\%$

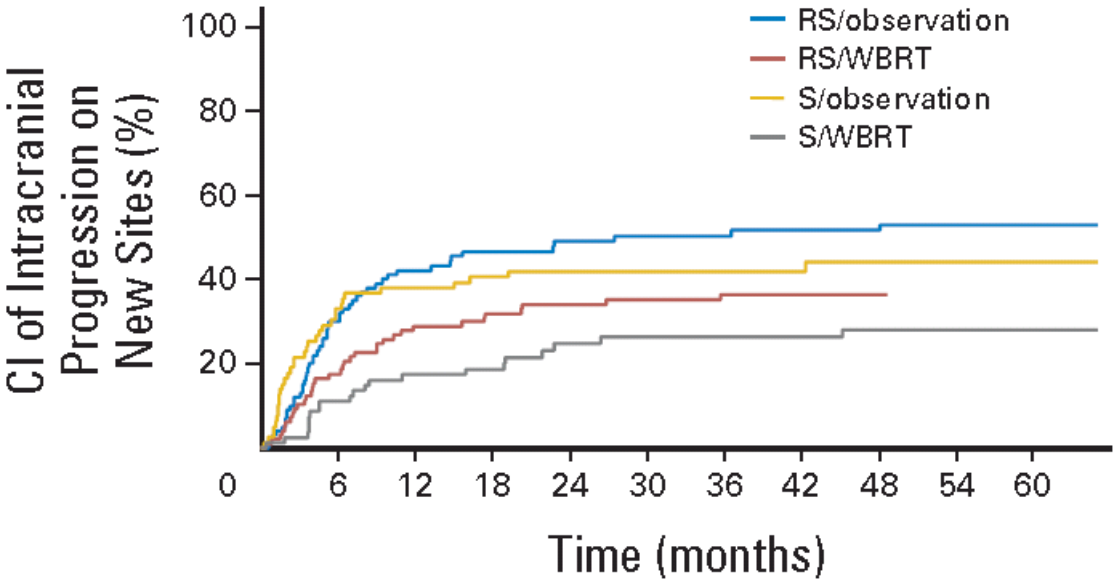
Test for overall effect: Z = 3.93 (P = 0.000085)

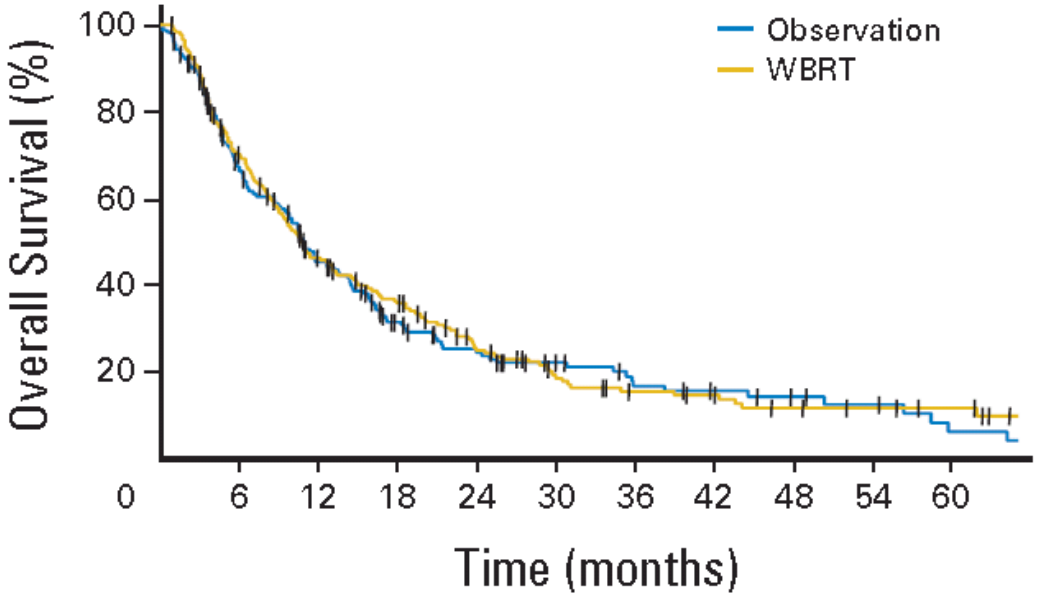
Test for subgroup differences: Not applicable



Patil CG et al. Cochrane Collaboration 2012

EORTC 22952-26001 Study





Kocher M et al. J Clin Oncol 20101

Radiosensitive subtypes of NSCLC

Table 2. Absolute recurrence rates by molecular subtype and for tyrosine kinase-activated tumors versus other tumors **after radiosurgery**

	EGFR mutant	ALK translocation	KRAS mutant	Other	ALL
By patient					
In-field	0/21 (0%)	0/9 (0%)	3/17 (18%)	6/32 (19%)	9/79 (11%)
Distant brain	9/21 (43%)	7/9 (78%)	10/17 (59%)	13/32 (41%)	39/79 (49%)
By lesion					
In-field	0/164 (0%)	0/61 (0%)	3/105 (3%)	10/139 (7%)	13/469 (3%)

	Tyrosine kinase-activated	Other	*P*
By patient			
In-field	0/30 (0%)	9/49 (18%)	0.01
Distant-brain	16/30 (53%)	23/49 (47%)	0.58
By lesion			
In-field	0/225 (0%)	13/244 (5%)	<0.001

EGFR mutation & ALK translocation: more radiosensitive

Johung CCR 2013

Clinical data: WBRT + erlotinib Toxicity

Table 1. Clinical trials of combination of erlotinib with WBRT in brain metastases from NSCLC

Trial	Year	Trial type	*N*	Treatment	Efficacy outcome	Safety outcomes
Lind et al.[33]	2009	Phase I single arm	11	WBRT:30 Gy/10 f Erlotinib:100 mg/d for four patients; 150 mg/d for seven patients(started 1 week before, and continued during WBRT and then maintenance)	Of seven patients with follow-up imaging,PRs in five and SD in two.	Grade 3–5 toxicities: interstitial lung disease (18%), acneiform rash (9%), fatigue (9%)
Olmez et al.[34]	2010	Retrospective analysis	8	WBRT:37.5 Gy/15 f, 40 Gy/20 f or 35 Gy/14 f Erlotinib:150 mg/d varied from 3 weeks to 12 months	Of six patients with follow-up evaluation: PR in three, SD in two and PD in one.	Grade 3–5 toxicities: liver function abnormalities (25%) thrombocytope-
Zhuang et al.[48]	2012	Phase II study	23	WBRT: 30 Gy /10 f; Erlotinib:150 mg/d till one month after WBRT.	ORR of brain: 95.7%. Median LPFS of brain: 9.0 months. Median PFS: 7.3 months.	Gra).
						No increase in neurotoxicity.
Welsh et al.[35]	2013	Phase II study	40	WBRT: 35 Gy/14f Erlotinib:150 mg/d 1 week before WBRT then concurrently with WBRT and maintenance.	ORR of brain: 86%; Median survival time :11.8 months.	Grade 3–5 toxicities: No increase in neurotoxicity; no patient experienced grade ≥ 4 toxicity, grade 3 rash: 3 patients.

PR: partial response; RR: response rate; RT: radiotherapy; SD: stable disease; ORR: Objective response rate; WBRT: whole-brain radiotherapy.

No increased neurotoxicity

Combination of WBRT & erlotinib is well-tolerated

Conclusions

- Select patients carefully!
- WBRT indicated in symptomatic patients with a life expectancy > 3 months
- In a symptomatic patients, WBRT may be deferred
- SRS superior local control than WBRT
- After SRS: no WBRT, but MRI Q 3 months
- EGFR mutated and ALK +: highly radiosensitive