Practical Consideration of Palliative Radiotherapy

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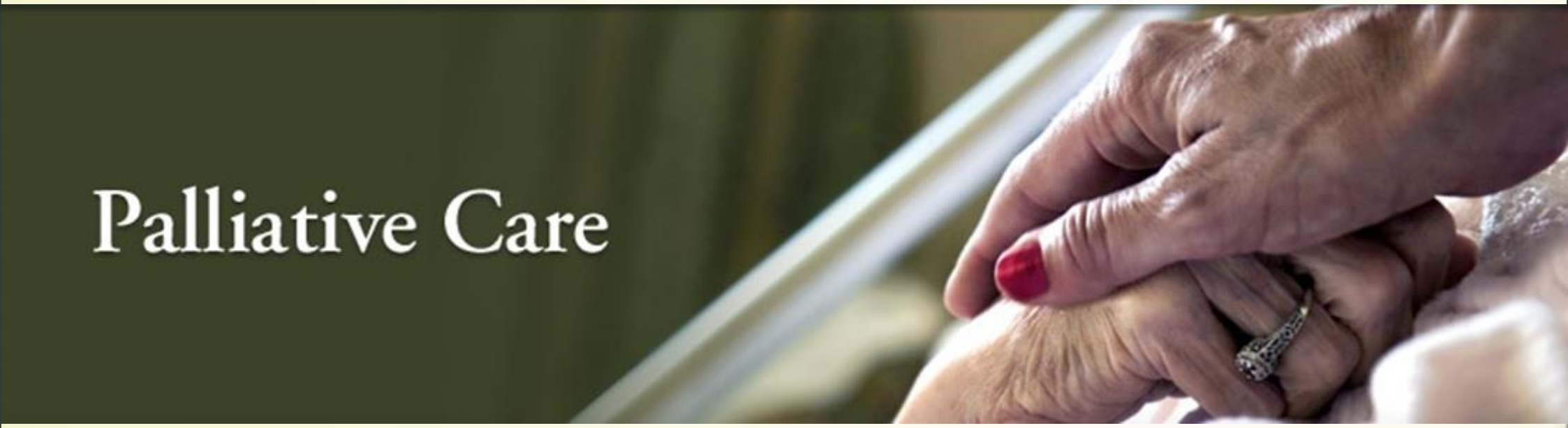
- Palliative radiotherapy (pRT)

. Goal: symptom relief at the site of primary tumor or metastatic lesions

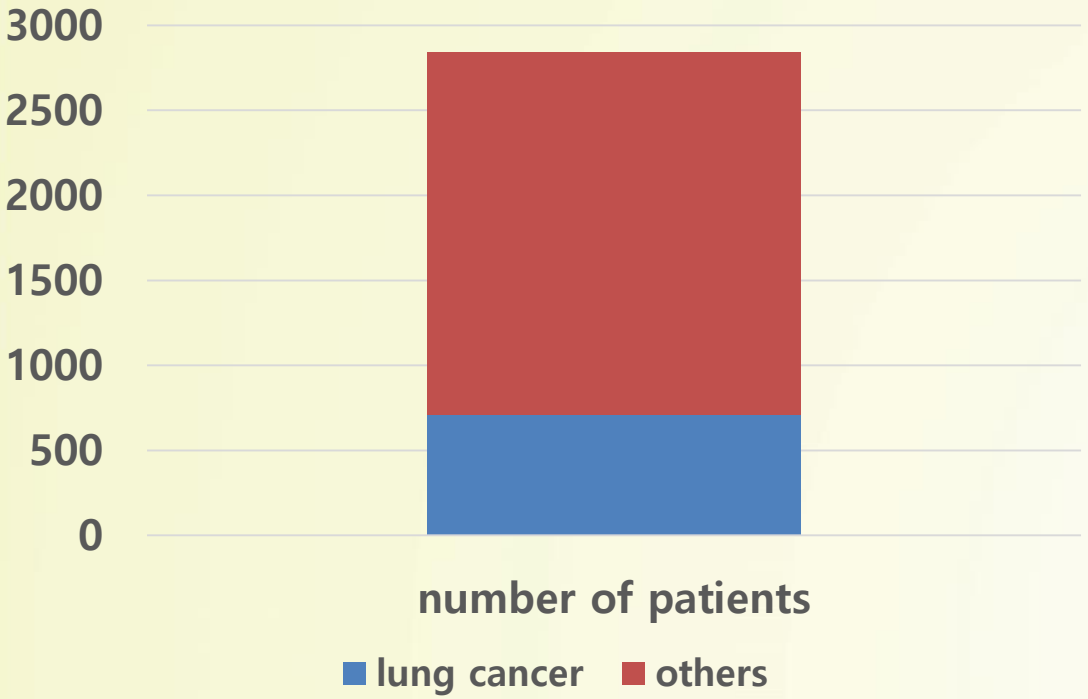
. Quick, inexpensive, effective for reducing symptoms of incurable cancer

* J Clin Oncol 2014;32:2913-9

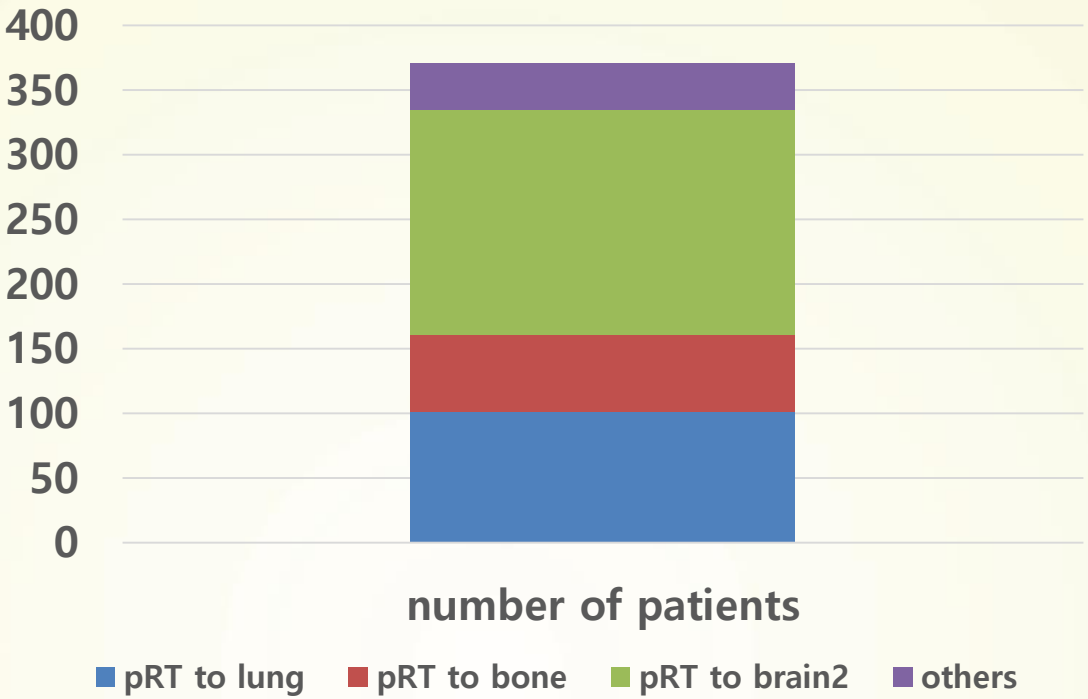
* BMJ 2018;360:k821



RT Patients (2017, CNUH)



pRT patients (lung cancer, CNUH)



Total 2941 pts

Lung cancer patients: 707 pts (24%)

- Palliative RT: 371 pts (52.4%)

. Lung: 101 pts (27.2%)

. Bone: 174 pts (46.9%)

. Brain: 60 pts (16.2%)

. Others: 36 pts (9.7%)

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- Airway obstruction, SVC syndrome, tumor bleeding

2. Palliative RT for Bone metastases

3. Palliative RT for Brain metastases

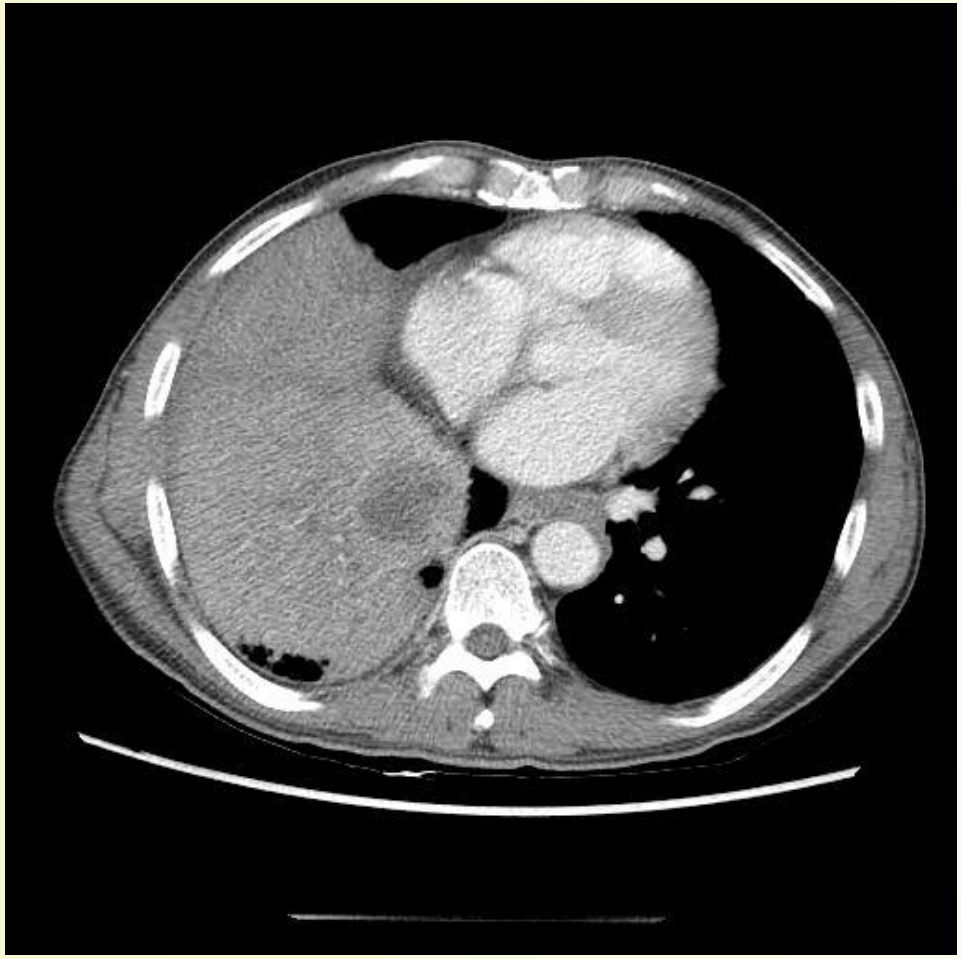
1. Palliative RT for Primary lung cancer

- Airway obstruction, SVC syndrome, tumor bleeding

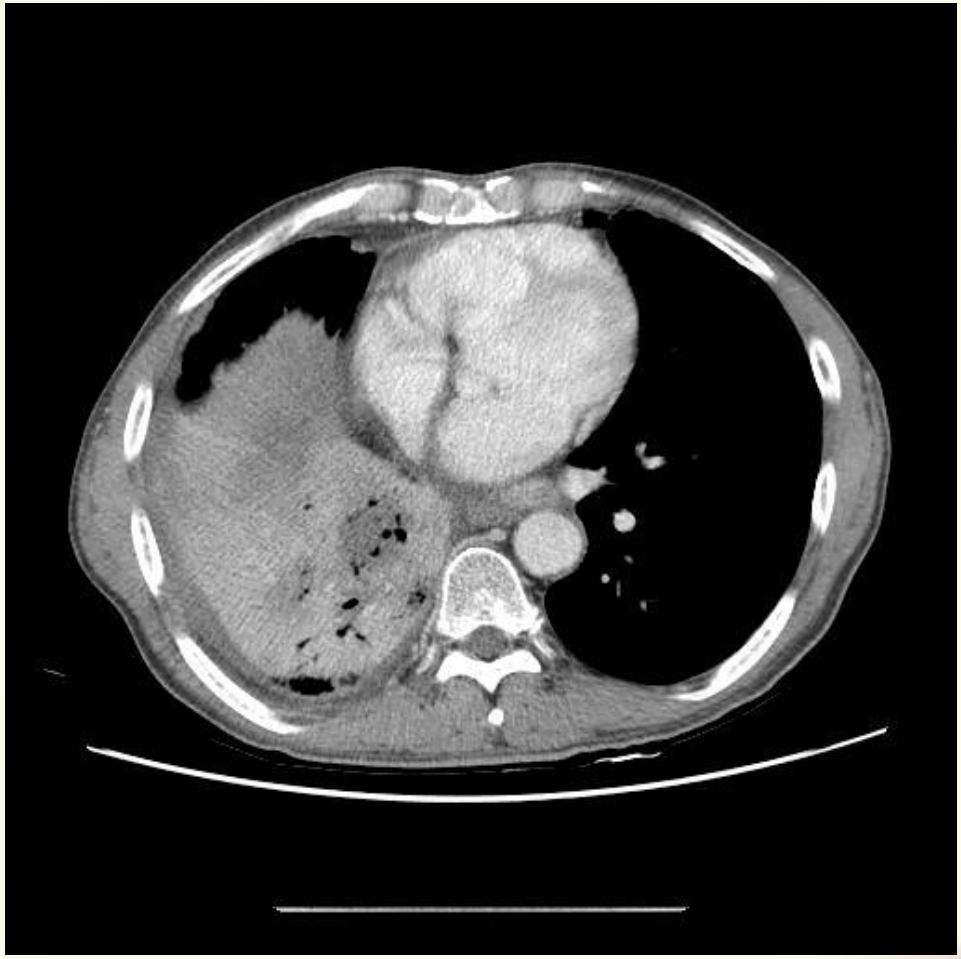
1. Airway obstruction : case

60/M, NSCLC (SQC), cT3N2M1a, PS: 2, dyspnea

Palliative RT (17.2.9-17.2.22)



2017.02.07

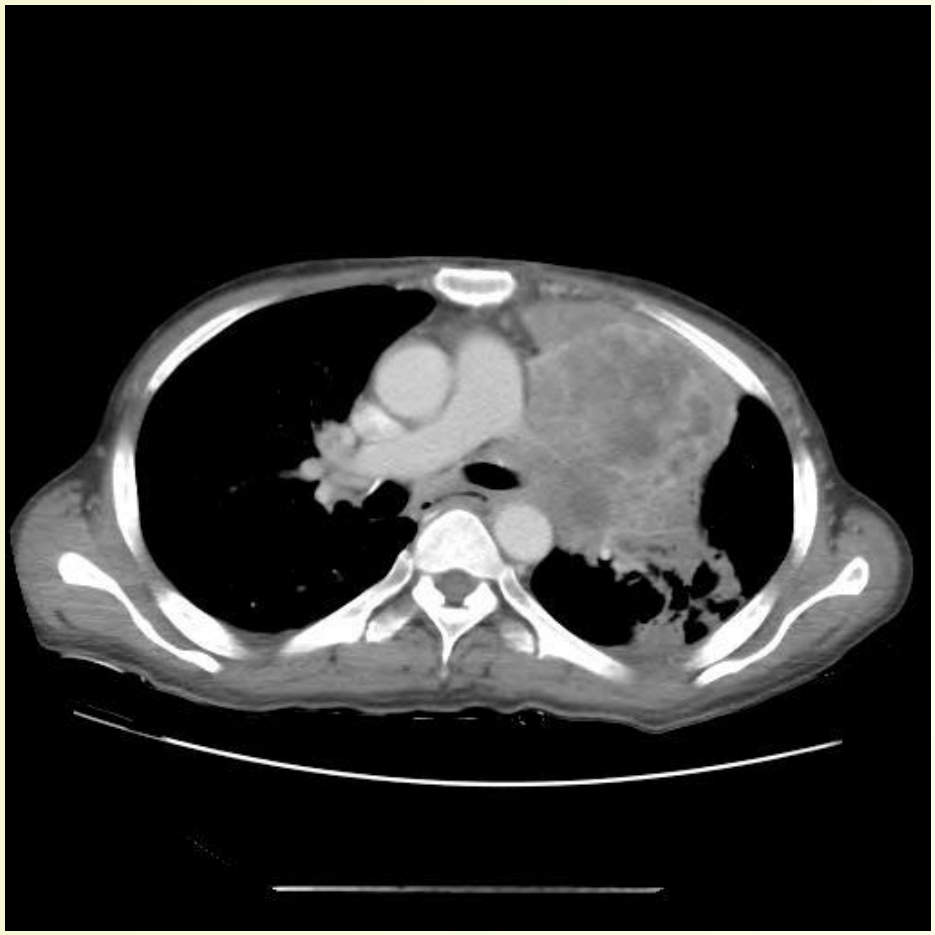


2017.04.11

1. Airway obstruction : case

60/M, NSCLC (SQC), cT4N1M0, PS: 2, dyspnea

Palliative RT (17.2.20-17.3.6)



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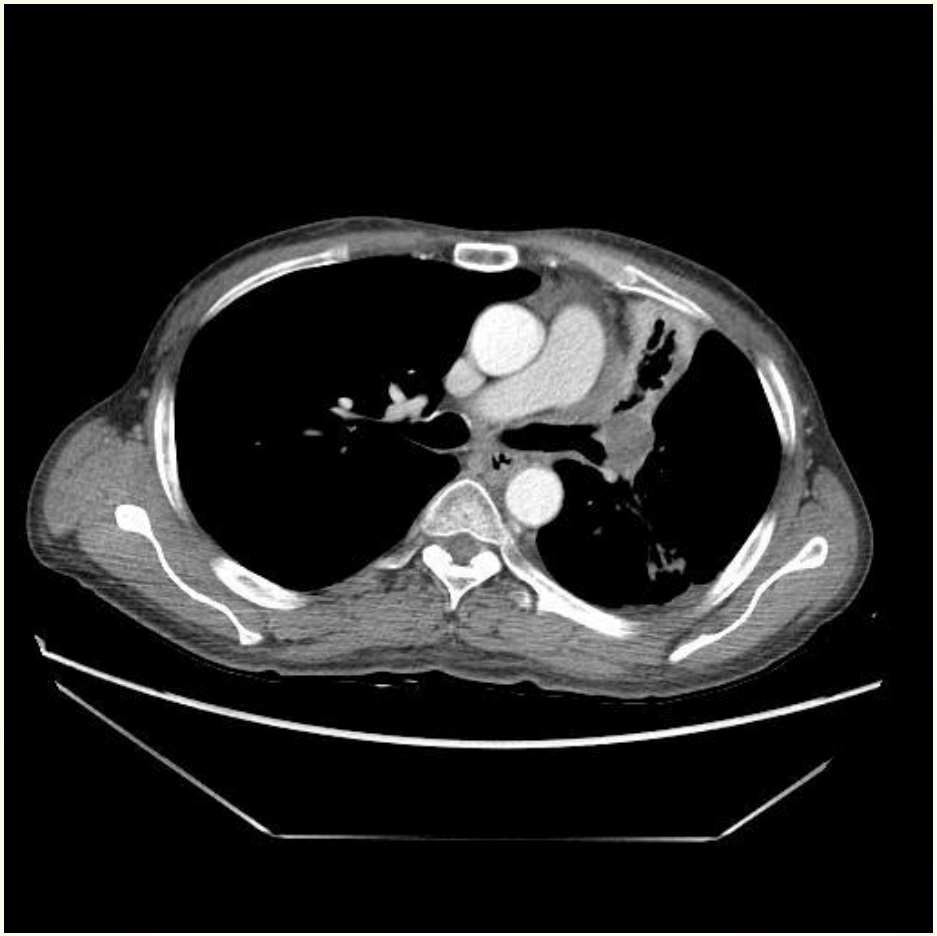


2017.04.15

1. Airway obstruction : case

56/M, SCLC, ED, cT4N3M1c, PS: 2, dyspnea

Palliative RT (17.5.15-17.5.19)

2017.05.08

2017.06.19

1. Airway obstruction : palliative RT

. dyspnea in 45-90% of patients with lung cancer

. cause of airway obstruction
; intrinsic compression by endobronchial tumor or extrinsic compression by tumor

. response rate of palliative RT: 80%

* Cancer Res Treat 2015;47(2):189-96

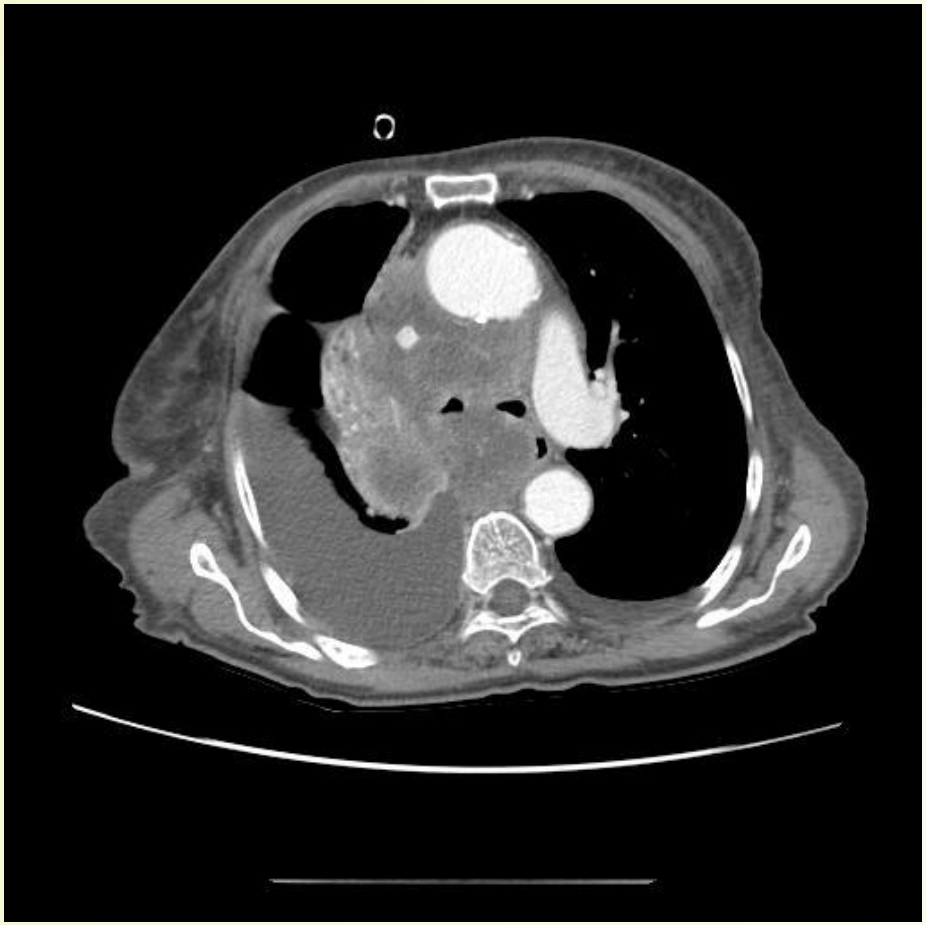
. duration of palliation: 50-80% of survival duration

* Br J Cancer 1992;65:934-41
* J Clin Oncol 2000;23:89-93
* Int J Clin Oncol 2002;7:284-8

1. SVC syndrome : case

81/M, lung cancer, cT4N3M1a, PS: 2, dyspnea, facial swelling

Palliative RT (17.12.26-18.1.5)



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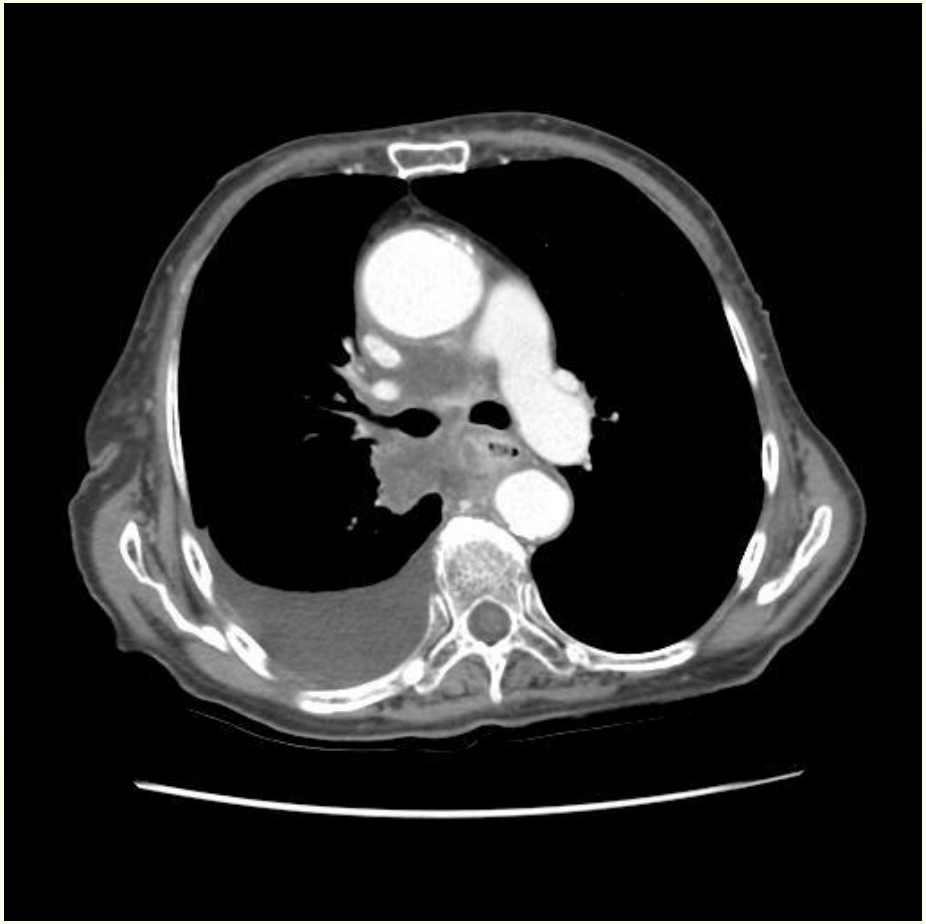
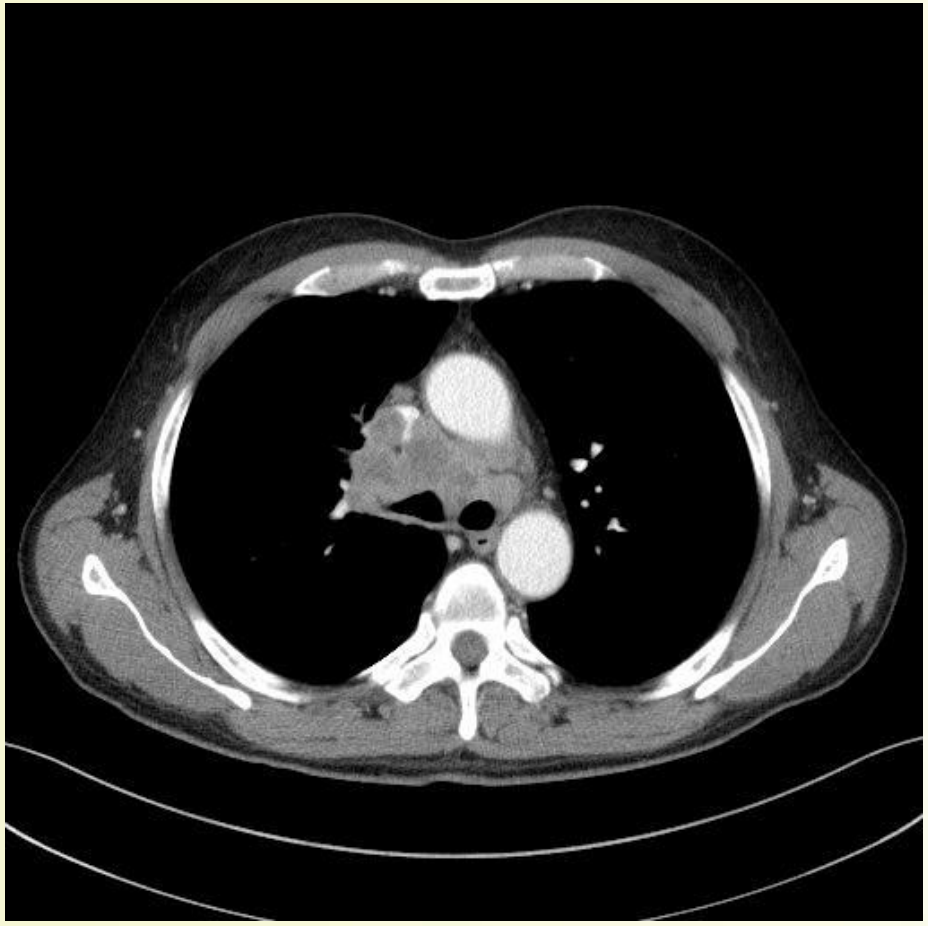


2018.02.26

1. SVC syndrome : case

59/M, SCLC, ED, cT4N3M1c, PS: 2, dyspnea, facial swelling

Palliative RT (17.11.8-17.11.14)



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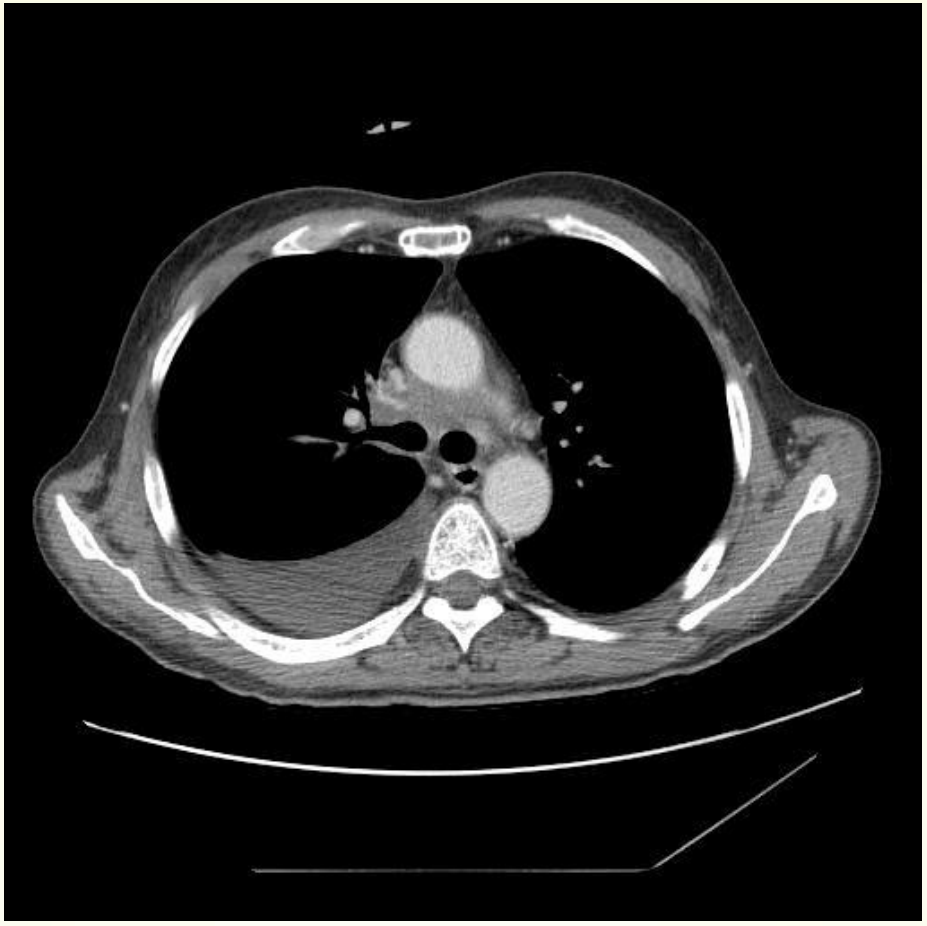


2017.12.16

1. SVC syndrome : palliative RT

. cancer related SVC syndrome
; NSCLC 50%, SCLC, 25%

. emergent RT is not necessary (stable, diagnosis is not established)

* Am J Med 1981;70(6):1169-74, J Clin Oncol 1986;4(5):716-21

. time to symptomatic relief
; 3 days – 30 days (78% SCLC, 63% NSCLC)

. duration of palliation: >30 days

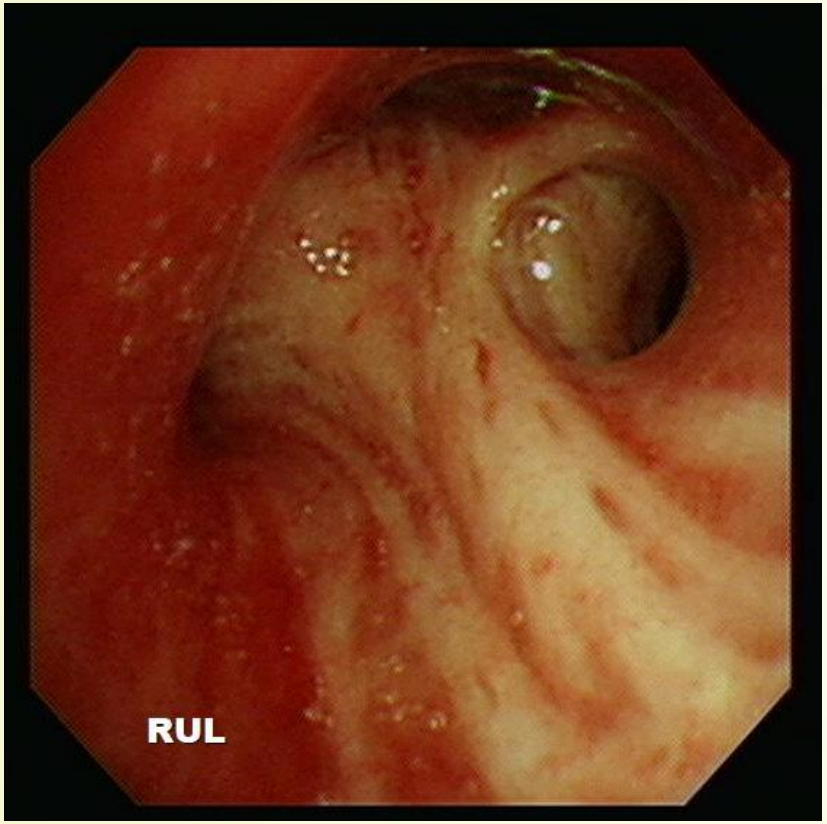
* Springerplus 2016;5:229

. intensive treatments (CCRT)
; no distant metastasis, good performance status

1. Tumor bleeding
: case

75/M, NSCLC (ADC), cT2aN2M1b, PS: 2, hemoptysis

Palliative RT (17.11.7-17.11.13)



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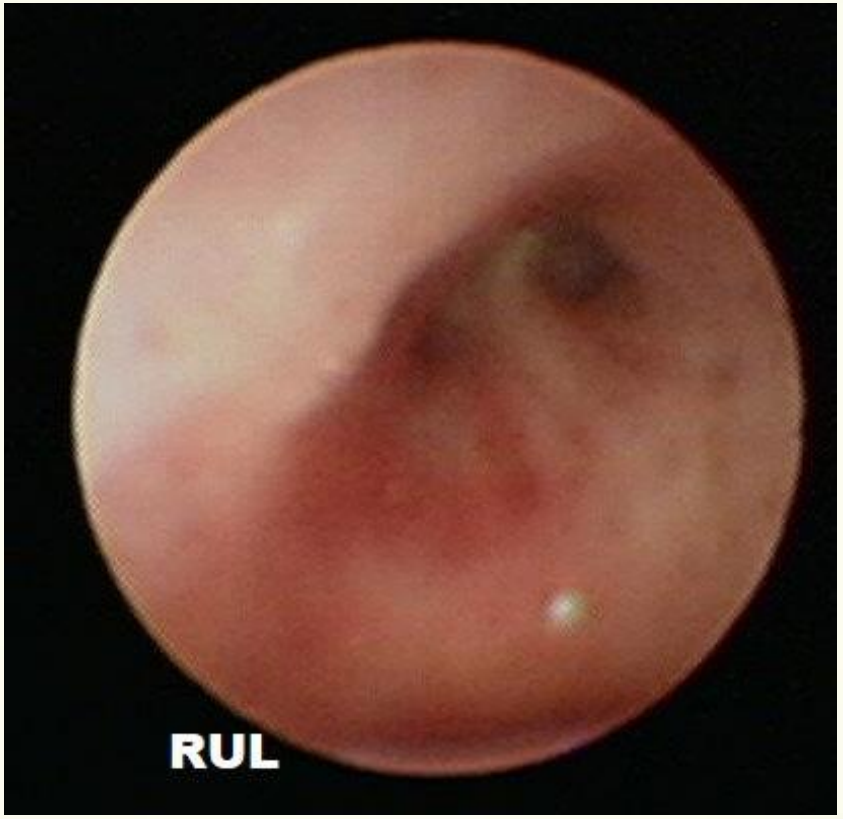
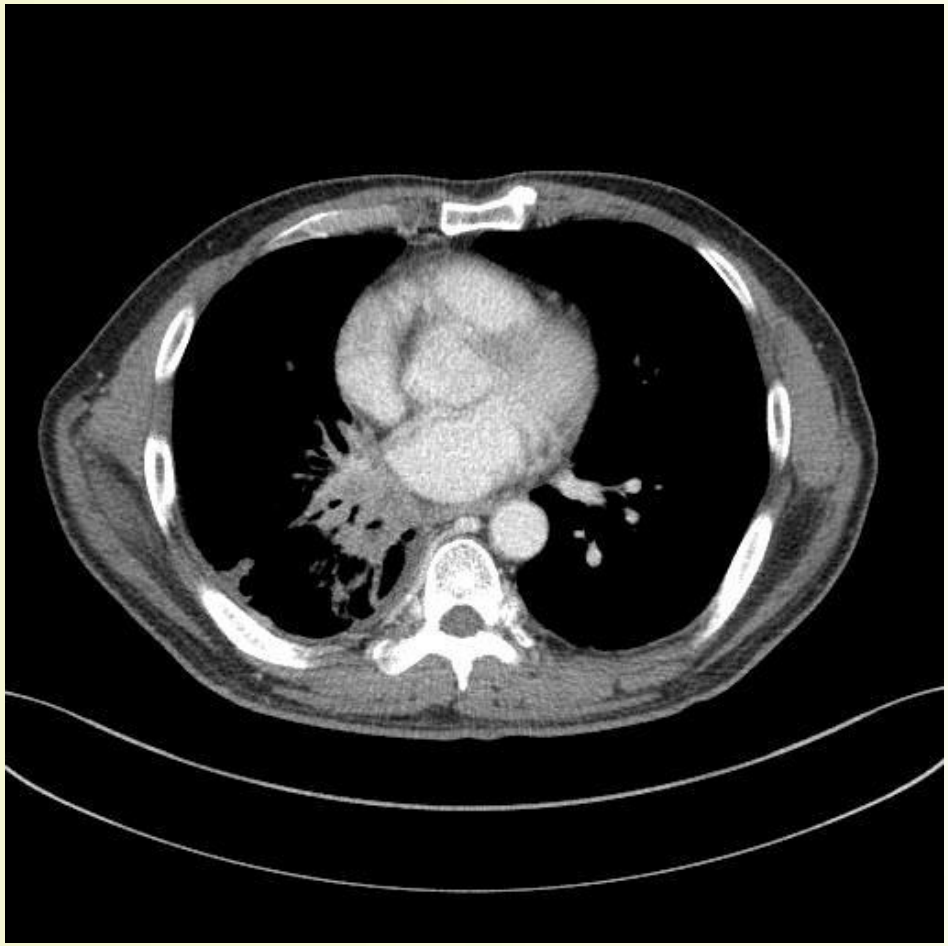


2018.03.27

1. Tumor bleeding : case

55/M, NSCLC (ADC), cT2aN2M1a, PS: 2, hemoptysis

Palliative RT (17.3.31-17.4.6)



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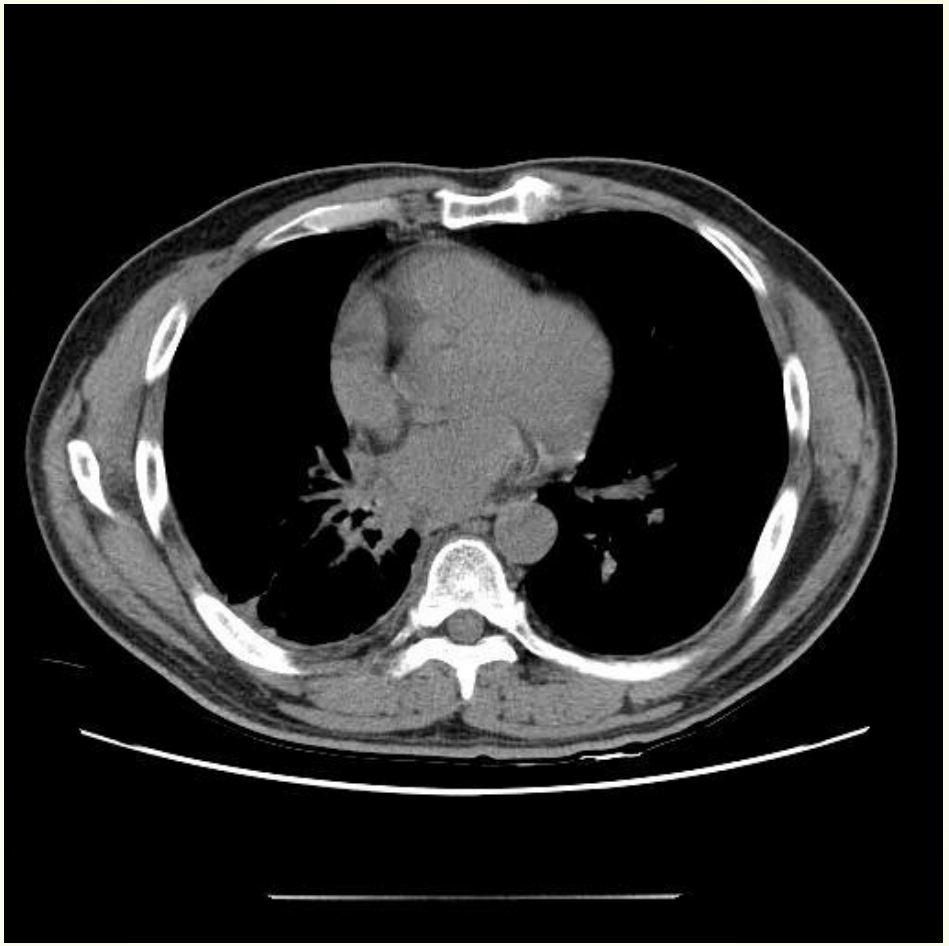


2017.04.26

1. Tumor bleeding
: palliative RT

. mechanism of hemostasis by RT
; unknown, thrombosis by increased tissue factor in PBMC

* Thromb Res 2007;120(6):857-64

. response rate
; 65-80%

. duration of palliation: 2 months

* Br J Cancer 1992;65(6):934-41
* Int J Radiat Oncol Biol Phys 2000;47:149-155

2. Palliative RT for Bone metastases

2. Bone metastases : introduction

- incidence: more than 100,000 people in US, annually

- 70% of patients with metastatic disease: breast, prostate
. 3~15%: GI malignancy

- median survival: months rather than years, depends on primary site
. lung ca.: 6 months vs. prostate, breast ca.: 2~4 years

- aim of treatment: to prevent deterioration of quality of life

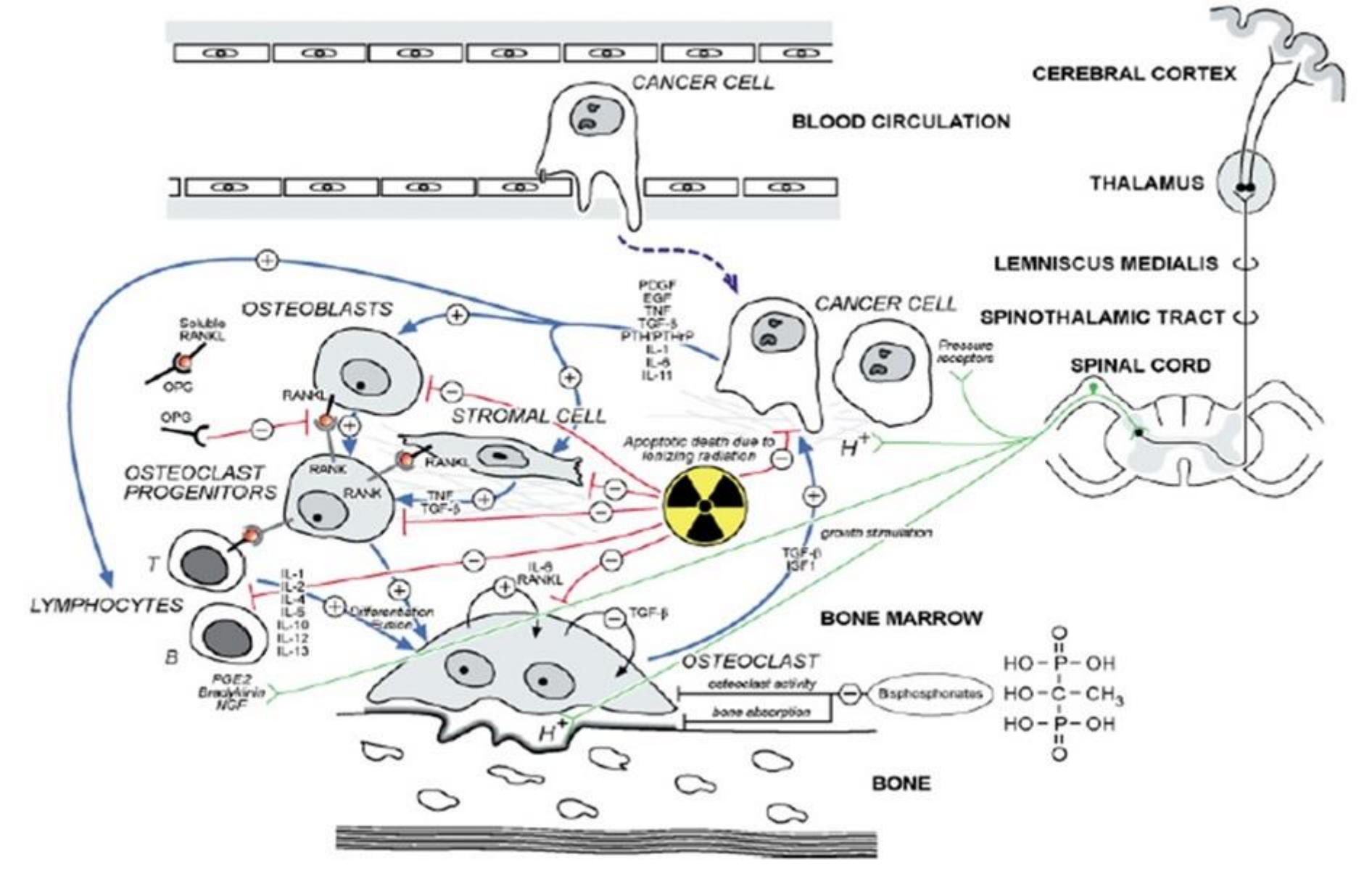
- axial skeleton: m/c site of bone metastasis (lumbar spine)
. appendicular skeleton: m/c site → proximal femur (weight bearing bones)

2. Bone metastases : introduction

INCIDENCE OF BONE METASTASES AT AUTOPSY
(ADAPTED FROM COLEMAN, 2001)

Primary tumour	Incidence of bone metastasis in advanced disease	Median time of survival (in months) after diagnosis of bone metastases
Myeloma	70-95%	24
Breast	65-75%	36
Prostate	65-75%	36
Thyroid	60%	48
Bladder	40%	6-9
Lung	30-40%	7
Hypernefroma	20-25%	12
Melanoma	14-45%	6

2. Bone metastases : introduction



2. Bone metastases : radiation therapy

- exact mechanism of action of EBRT: unknown
. substantial reduction in number of viable tumor cells
  → will result in shrinkage of tumor bulk
  → osteoblastic repair will partially restore integrity of bone

- analgesic effect of RT
. tumor shrinkage: unlikely to account for early period of pain relief
  ; d/t absence of dose response relationship
    . some of very low single doses (4 Gy): shown to cause pain relief
. no obvious relationship
  ; between radiosensitivity of primary tumor and response on pain

2. Bone metastases : radiation therapy

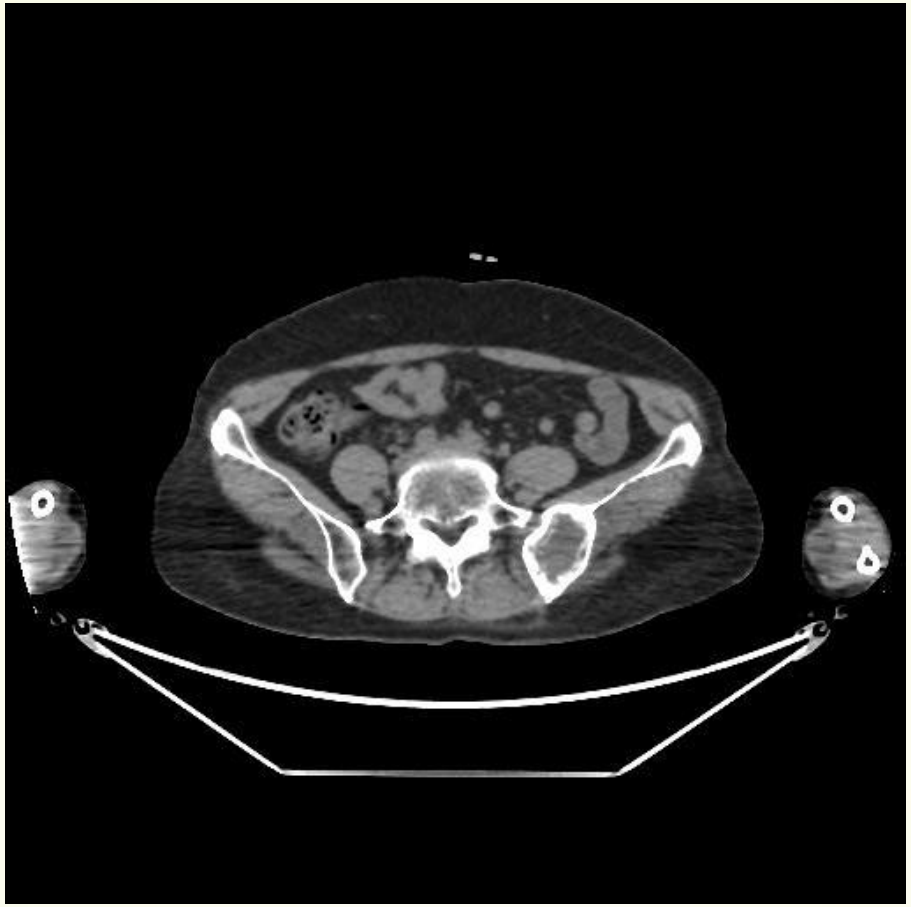
- some patients experience symptom relief within 24 hrs after RT
  → presence of early reacting, very sensitive cells, molecules

. inflammatory cells
  ; largely present in bone metastasis micro-environment
  ; reduction by ionizing radiation of inflammatory cells
    → inhibits the release of chemical pain mediators
    → probably responsible for rapid reaction seen in some patients

2. Bone metastases : case

60/F, NSCLC (ADC), cT1bN3M1c, PS: 1, Lt. pelvic pain
Palliative RT (17.5.10-17.5.23), erlotinib (17.6.22-)

2017.05.10

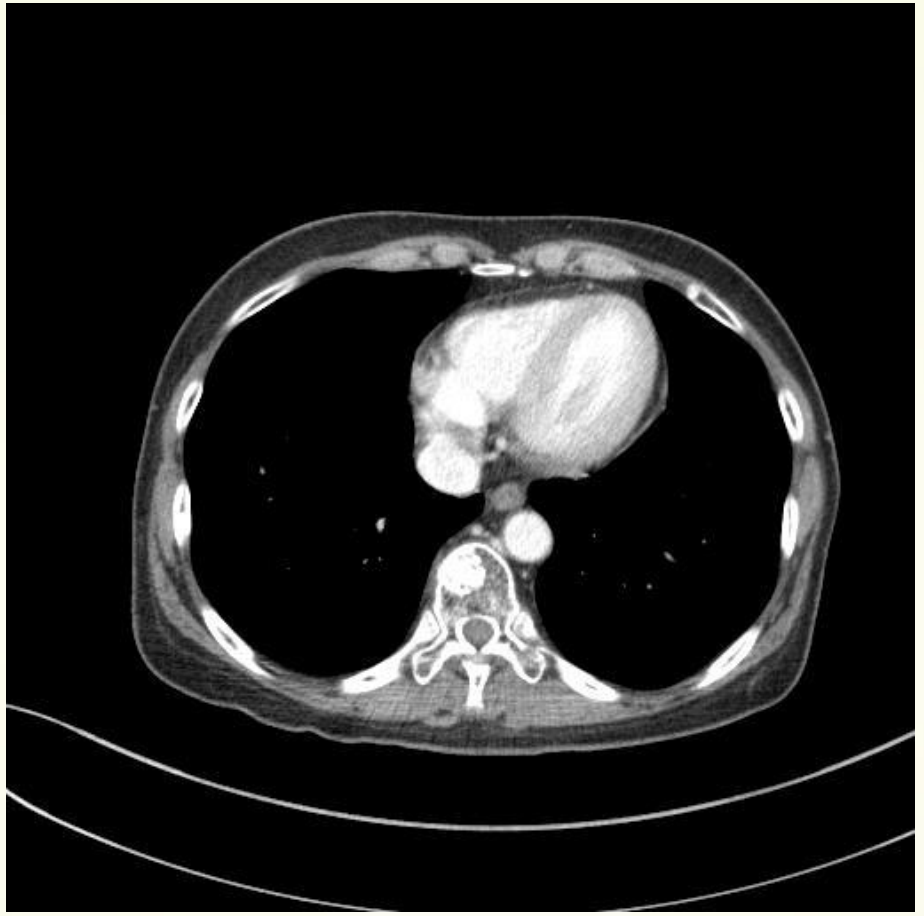


2018.01.29

2. Bone metastases : case

56/F, NSCLC (ADC), cT1bN2M1c, PS: 1, back pain
AP#4 (17.2.8-17.4.11), A#6 (17.5.2-17.10.12)
Palliative RT (17.8.21-17.9.1), G#12 (17.11.7-18.7.5)

2017.08.10



2018.06.26

2. Bone metastases : clinical consideration

1. Dutch trial (1999)
- 1,171 patients, randomized
. 8 Gy single fraction vs 24 Gy/6 fractions
. primary: breast (39%), prostate (23%), lung (25%)
. site: spine (36%), pelvis(30%)
. median pain score: 6.3 (using 11-point scale:0-10), minimum score: 2
. narcotic pain medication: about a half, previous system therapy: 53%

- result
. median survival rate: 30 weeks, no significant difference
. response: 71%, CR: 35%, no significant rates in response
(breast: 44%, prostate: 41%, lung: 21%)

	8Gy/1fx	24Gy/6fx	P value
pathologic fracture	4% (median 21 weeks)	2% (median 17 weeks)	<0.05
retreatment	25%	7%	<0.001

* Radiother Oncol 1999;52:101-109

2. Bone metastases : clinical consideration

2. RTOG study 9714, US, Canada (2005)

- limited patients: breast, prostate primaries, up to 3 painful bone mets

. 8 Gy single fraction vs 30 Gy/10 fractions

. minimum pain score: 5, >70% of patients had severe pain (pain score: 7-10)

. high narcotic pain medication (morphine, >60 mg/day)

- result

. median survival: 9.3 months, overall toxicity: low in both arms

. CR (17%), PR (49%): no significant rates in response

. complete pain & narcotic response (pain score:0, no narcotics use): 11%

	8Gy/1fx	30Gy/10fx	P value
pathologic fracture	5%	4%	NS
retreatment	18%	9%	<0.001

* J Natl Cancer Inst 2005;97:798-804

2. Bone metastases
: clinical consideration

- Dutch trial: only half had moderate range of pain (minimum: 2)
- RTOG trial: severe pain, high-dose narcotic medication (minimum: 5)

→ higher rate of CR (35% vs 17%), moderate pain score in Dutch trial

→ outcome is much better if patients are treated with palliative RT
earlier in the course of their bone metastases, rather than waiting until pain medication requirements are significant

2. Bone metastases : RT schedule

- Meta-analysis, 3435 patients were randomized in 11 trials

	single (8-10Gy)	multiple (5Gy x 3fx – 3Gy x 10fx)	*p*-value
CR	34% (497/1441)	32% (463/1435)	NS
overall response	60% (1059/1779)	59% (1038/1769)	NS
retreatment	21.5% (276/1240)	7.4% (91/1236)	<0.00001
pathologic fracture	3.0% (37/1240)	1.6% (20/1236)	0.0031
spinal cord compression	2.0% (21/1102)	1.4% (15/1104)	NS

* Cochrane Database Syst Rev 2004;(2):CD004721

2. Bone metastases : spinal cord compression

- Randomized trial, decompression + RT (30Gy/10fx) vs. RT alone (30Gy/10fx)
. 101 patients (early closed after interim analysis)
  ; decompression + RT (50 patients) vs. RT alone (51 patients)
. Eligibility: ≥18 years, confirmed by MRI, neurological sign, ≤48 hours of paraplegia

	decompression + RT	RT	*p*-value
Ability to walk (total)	84% (42/50)	57% (29/51)	0.001
Median duration of ambulation (total)	122 days	13 days	0.003
Ability to walk (ambulatory)	94% (32/34)	74% (26/35)	0.024
Median duration of ambulation (ambulatory)	153 days	54 days	0.024
Ability to walk (non-ambulatory)	62% (10/16)	19% (3/16)	0.012
Median duration of ambulation (non-ambulatory)	59 days	0 days	0.04

* Lancet 2005;366:643-648

2. Bone metastases : summary

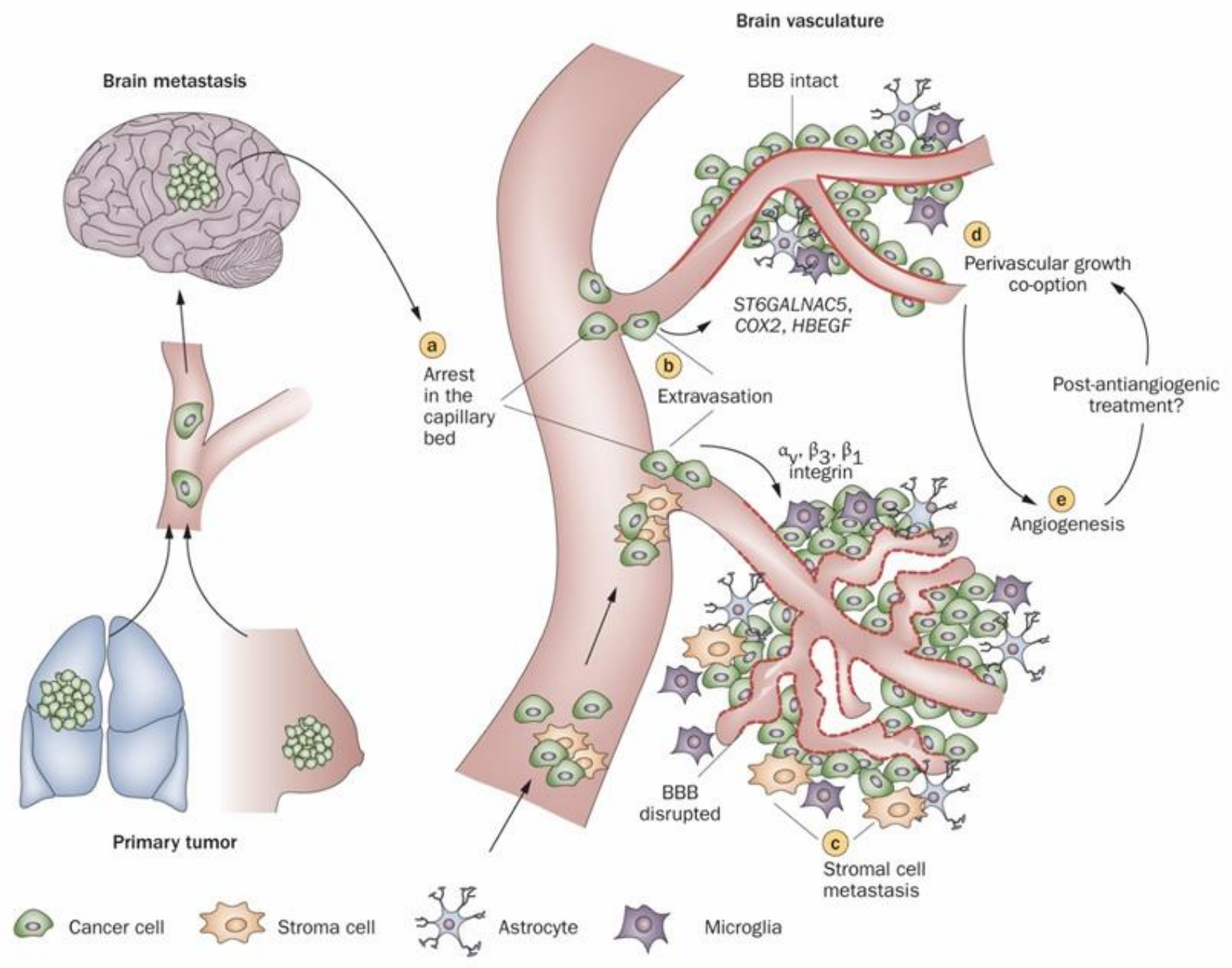
. When is the palliative RT needed to reduce pain for patients with bone mets?

; the earlier the palliative RT, the better the relief of pain

(overall response: ~70%, complete remission: ~35%)

3. Palliative RT for Brain metastases

3. Brain metastases : introduction



* Nat Rev Clin Oncol 2011;8(6):344-56

3. Brain metastases : introduction

- Brain metastases

. up to 30% of patients with cancer

. the most common primary: lung (50%)

* J Clin Oncol 1988;6:543–51

. options for local treatment

; surgery, stereotactic radiation therapy (SBRT), whole brain radiotherapy (WBRT)

. main prognostic factors

; KPS (≥70 vs. <70)

; age (<65 vs. ≥65 years)

; control of primary tumor

; absence of extracranial metastases

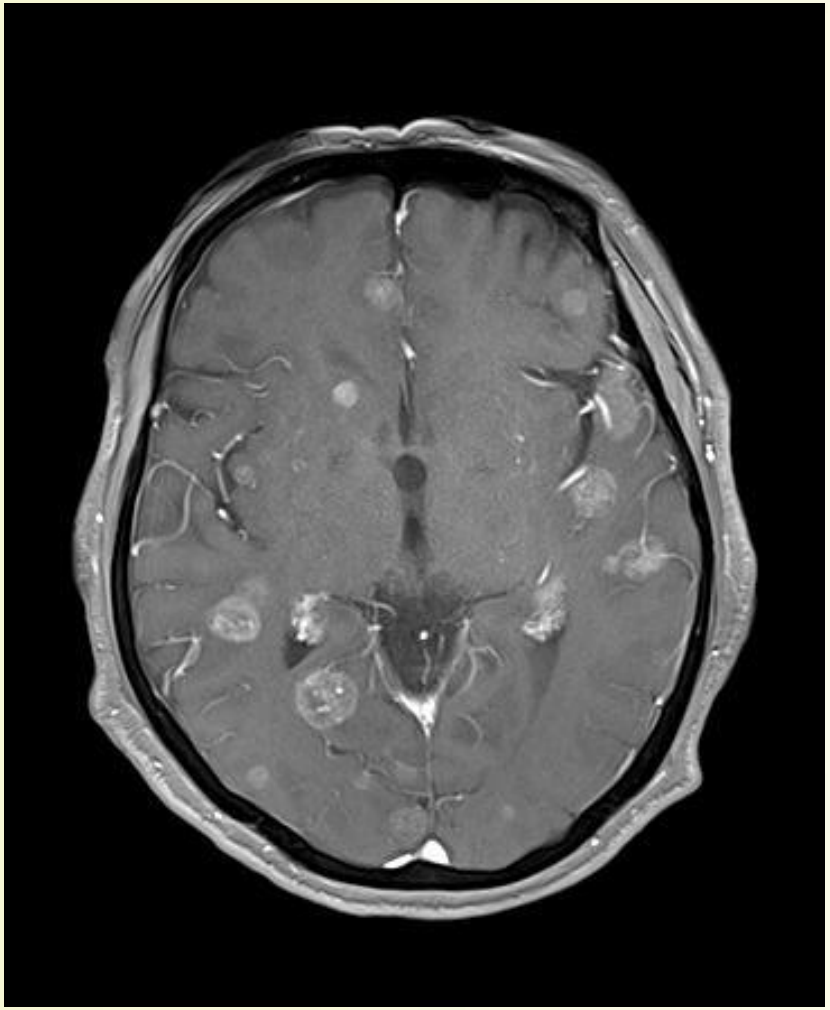
; number of brain lesions

class	characteristics	survival (months)
I	KPS≥70 Age<65 Mets to brain only	7.1
II	All others	4.2
III	KPS<70	2.3

* Int J Radiat Oncol Biol Phys 1997;37:745–51

3. Brain metastases : case

73/M, NSCLC (ADC), cT2aN3M1c, PS: 1, EGFR (+)
WBRT (17.5.22-17.6.2), osimertinib (17.6.28-18.5.30), gefitinib (18.6.25-)



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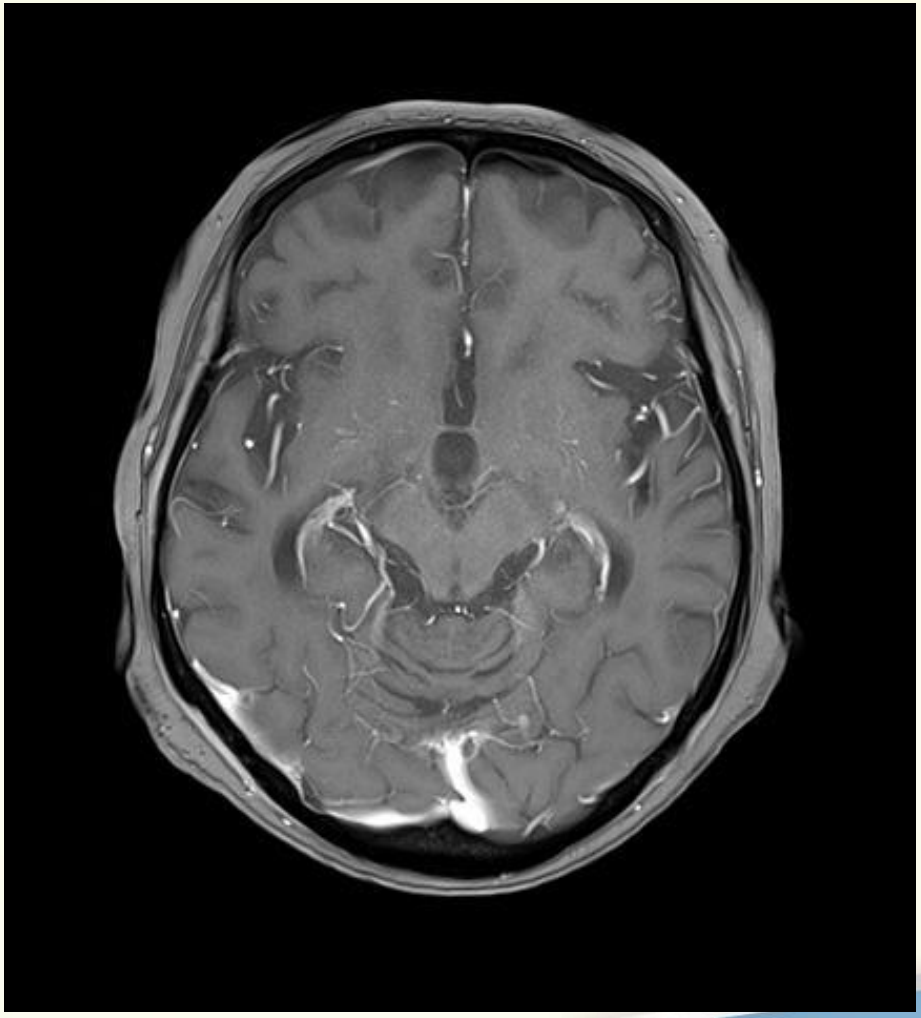

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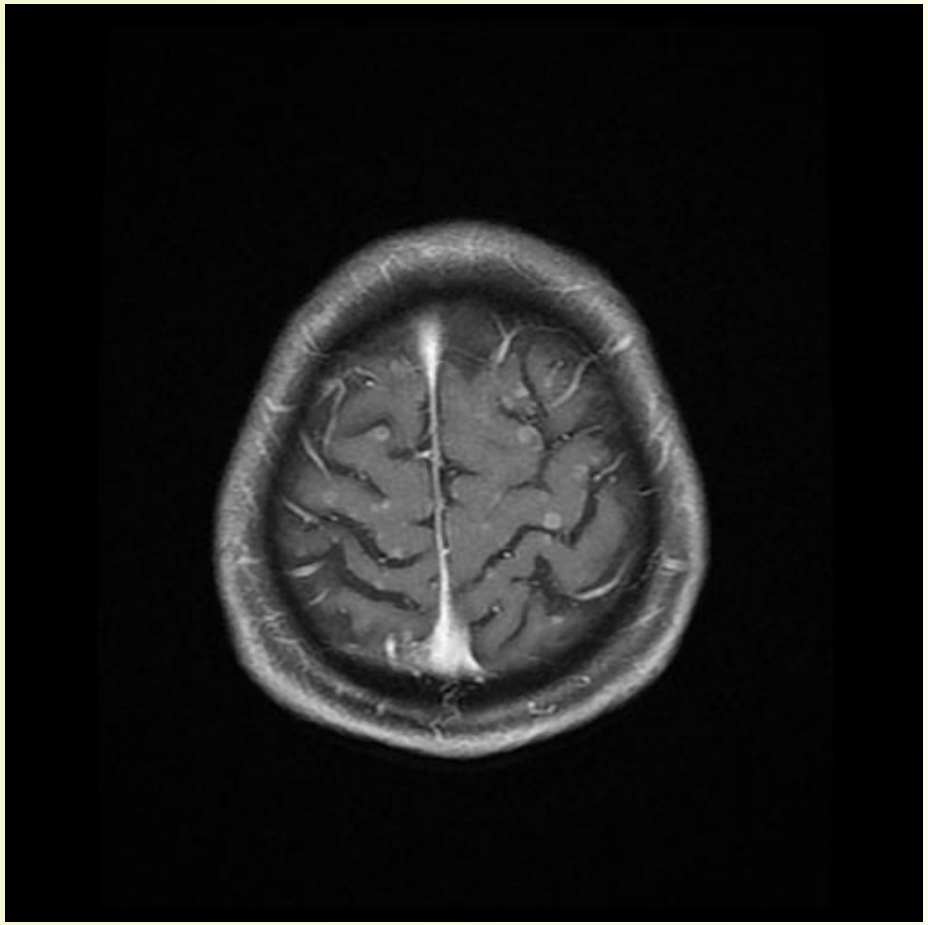
3. Brain metastases : case

74/M, NSCLC (ADC), cT4N3M1c, PS: 1, EGFR (+)
WBRT (17.12.26-18.1.9), afatinib (18.1.5-)



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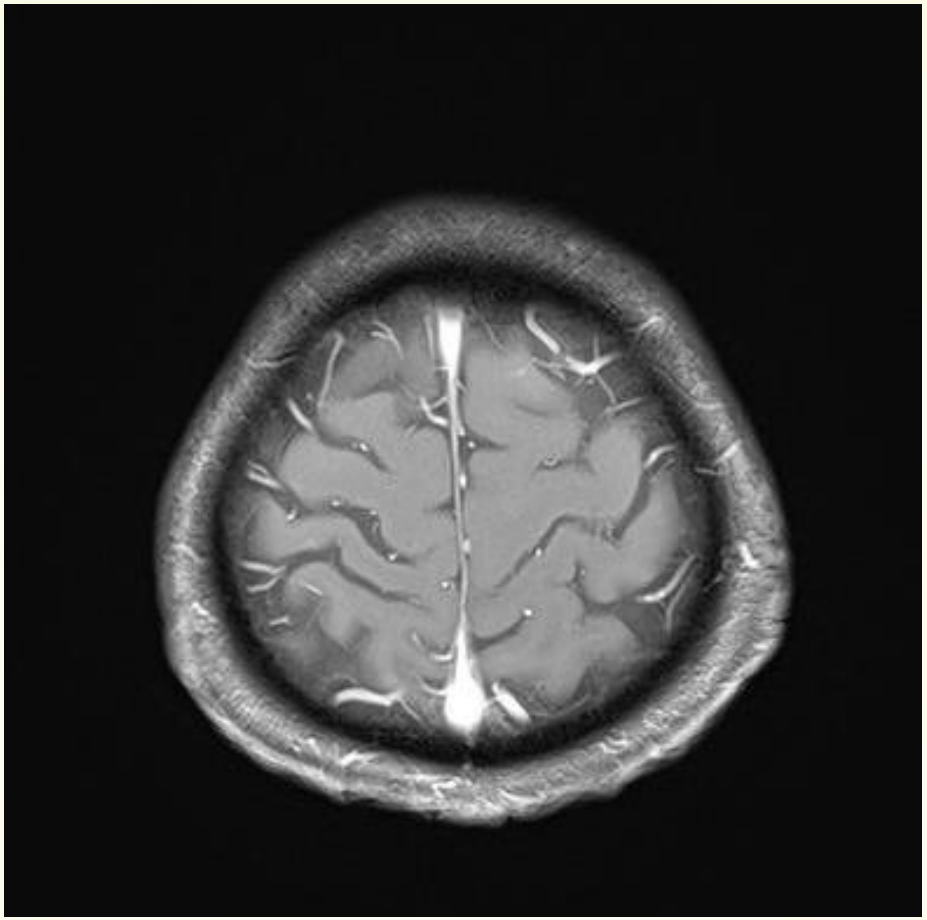

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3. Brain metastases : case

74/M, NSCLC (ADC), cT4N3M1c, PS: 1, EGFR (+)
WBRT (17.12.26-18.1.9), afatinib (18.1.5-)

2017.12.14

2018.03.14

3. Brain metastases : prognosis

- prognostic factors varied by primary tumor, 3940 patients, retrospective

. GPA (Graded Prognostic Assessment)

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

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	
No. of BM	> 3	2-3	1	
Sum total				

Median survival (months) by GPA: 0-1.0 – 3.4; 1.5-2.0 – 4.7; 2.5-3.0 – 8.8; 3.5-4.0 – 13.2

Breast cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	
Subtype	Basal	n/a	LumA	HER2	LumB	
Age, years	≥ 60	< 60	n/a	n/a	n/a	
Sum total						

Median survival (months) by GPA: 0-1.0 – 3.4; 1.5-2.0 – 7.7; 2.5-3.0 – 15.1; 3.5-4.0 – 25.3

Renal cell carcinoma

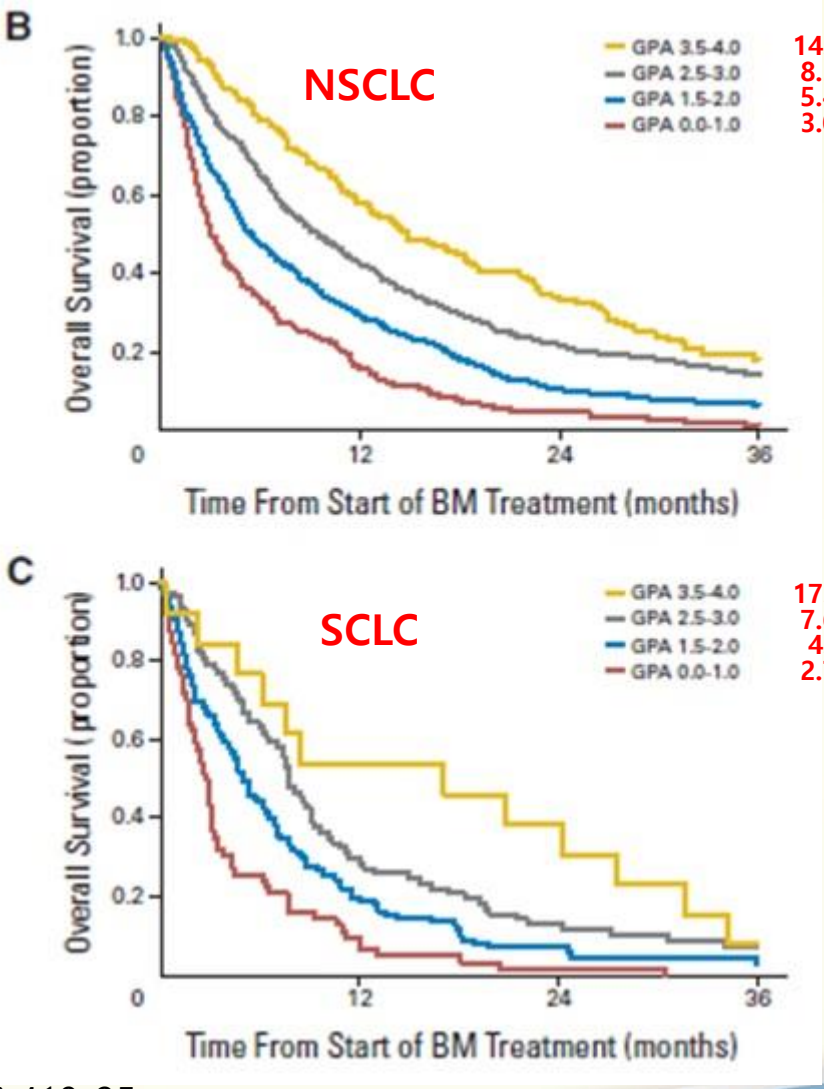
Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	
No. of BM	> 3	2-3	1	
Sum total				

Median survival (months) by GPA: 0-1.0 – 3.3; 1.5-2.0 – 7.3; 2.5-3.0 – 11.3; 3.5-4.0 – 14.8

GI cancers

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	

Median survival (months) by GPA: 0-1.0 – 3.1; 2.0 – 4.4; 3.0 – 6.9; 4.0 – 13.5



* J Clin Oncol 2012;30(4):419-25

3. Brain metastases : prognosis

- molecular marker-GPA

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	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* 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.

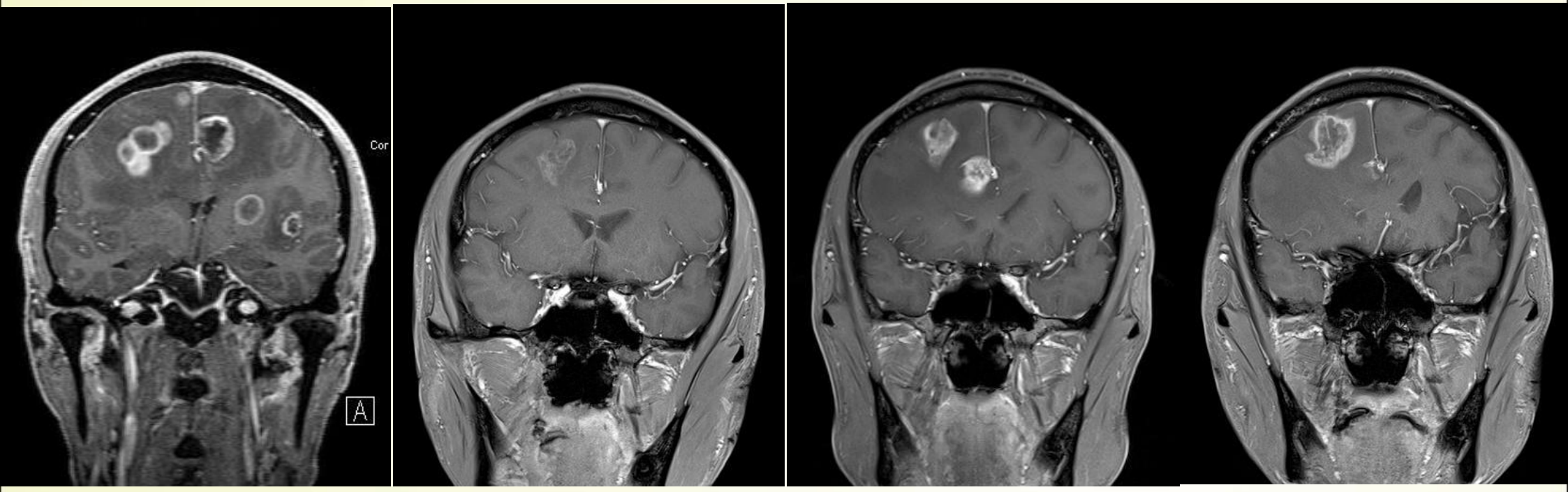
[a]Adenocarcinoma MS in months by GPA: 0-1.0 6.9; 1.5-2.0, 13.7; 2.5-3.0 ,26.5; and 3.5-4.0, 46.8; nonadenocarcinoma MS in months by GPA: 0-1.0, 5.3; 1.5-2.0, 9.8; 2.5-3.0, 12.8.

[b]Evaluating clinician completes this column.

* JAMA 2017;3(6):827-831

3. Brain metastases : case

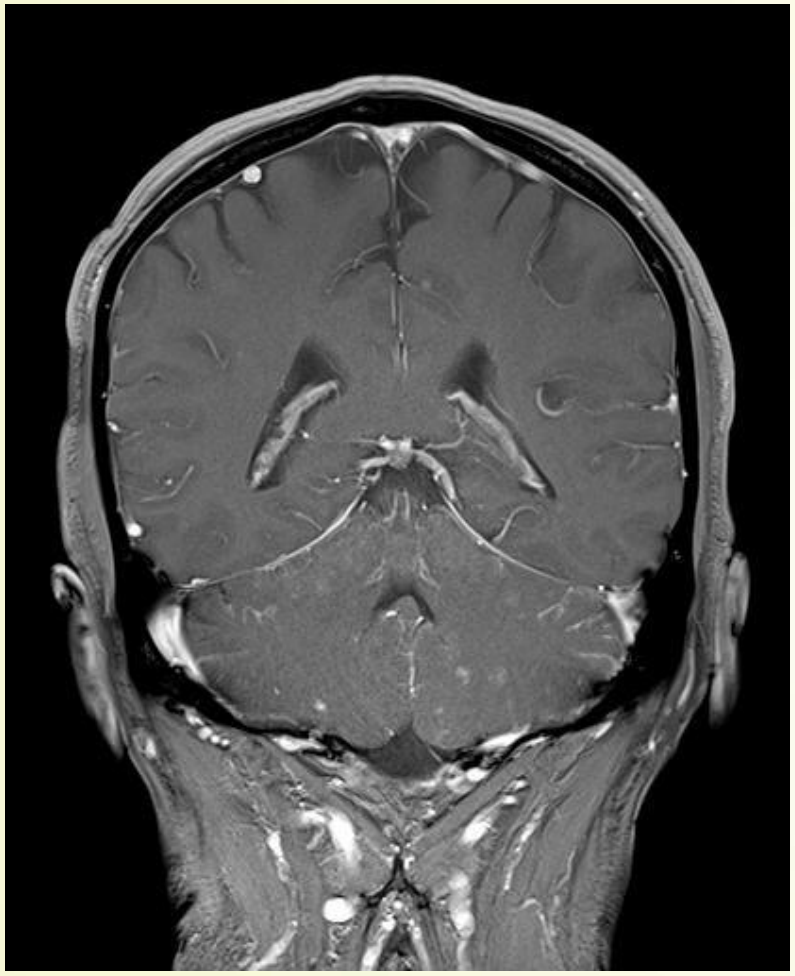
49/M, NSCLC (ADC), cT2bN2M1c, PS: 1, EGFR (+)
WBRT (16.6.15-16.6.28), afatinib (16.6.9-), GKS (17.6.1, 17.12.19)



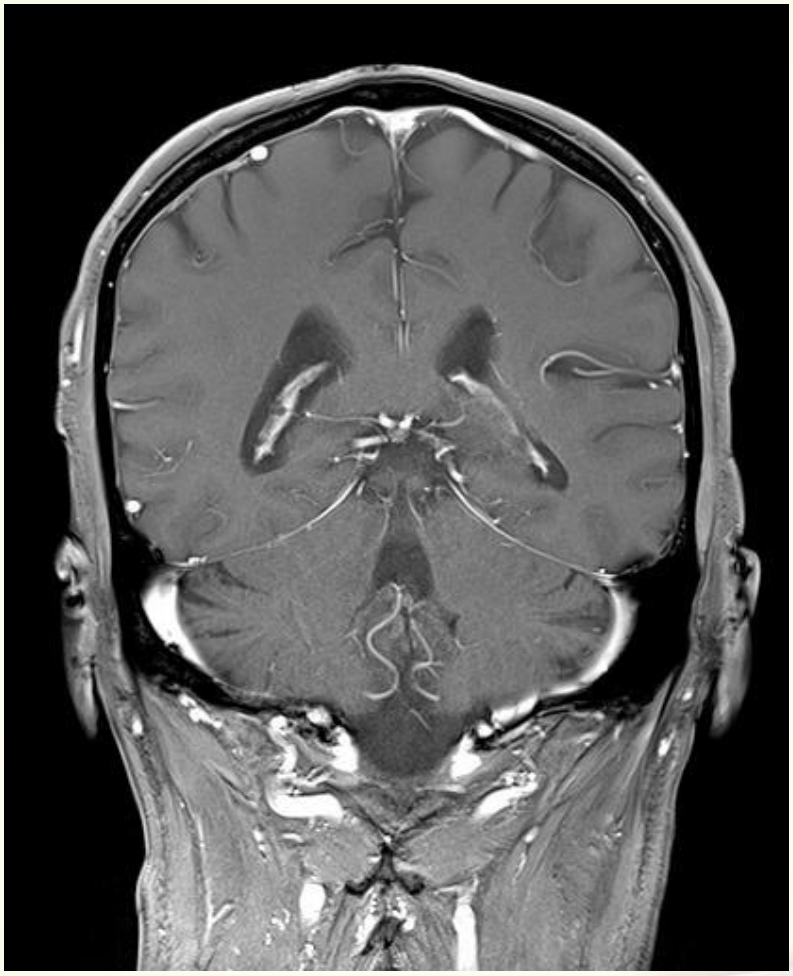
2016.6.3 2016.9.12 2017.5.17 2017.12.6

3. Brain metastases : case

57/M, NSCLC (ADC), cT2bN3M1c, PS: 1, ALK (+)
AP#4 (15.4.24-15.6.22), GKS (15.4.29), A#3 (15.7.13-15.9.7)
crizotinib (15.10.12-17.8.23), GKS (17.7.5), ceretinib (17.8.31-18.3.26), GKS (17.12.13)
WBRT (17.12.26-18.1.9), lorlatinib (18.4.27)



2018.3.23



2018.6.1

3. Brain metastases : targeted therapy

- Icotinib vs. WBRT (30Gy/10fx) in EGFR (+) NSCLC, phase III randomized, China
. intracranial PFS: Icotinib vs. WBRT (10.0 vs. 4.8 months, p = 0.014)
. ≥Gr3 toxicity: Icotinib vs. WBRT (8% vs. 38%)

	Intracranial response			Extracranial response			Overall response		
	Icotinib (n=85)	WBI (n=73)	p value	Icotinib (n=85)	WBI (n=73)	p value	Icotinib (n=85)	WBI (n=73)	p value
Complete remission	4 (5%)	3 (4%)	..	1 (1%)	0	..	1 (1%)	0	..
Partial response	51 (60%)	24 (33%)	..	43 (51%)	7 (10%)	..	56 (66%)	14 (19%)	..
Stable disease	17 (20%)	22 (30%)	..	23 (27%)	33 (45%)	..	10 (12%)	17 (23%)	..
Progressive disease	10 (12%)	17 (23%)	..	13 (15%)	23 (32%)	..	16 (19%)	36 (49%)	..
Not available	3 (4%)	7 (10%)	..	5 (6%)	10 (14%)	..	2 (2%)	6 (8%)	..
Objective response	55 (65%)	27 (37%)	0·001	44 (52%)	7 (10%)	<0·0001	57 (67%)	14 (19%)	<0·0001
Disease control	72 (85%)	49 (67%)	0·014	67 (79%)	40 (55%)	0·002	67 (79%)	31 (42%)	<0·0001

Data are n (%). Responses were graded according to the Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1. WBI=whole-brain irradiation. ..=data not available.

Table 2: **Proportion of the modified intention-to-treat population who achieved a response**

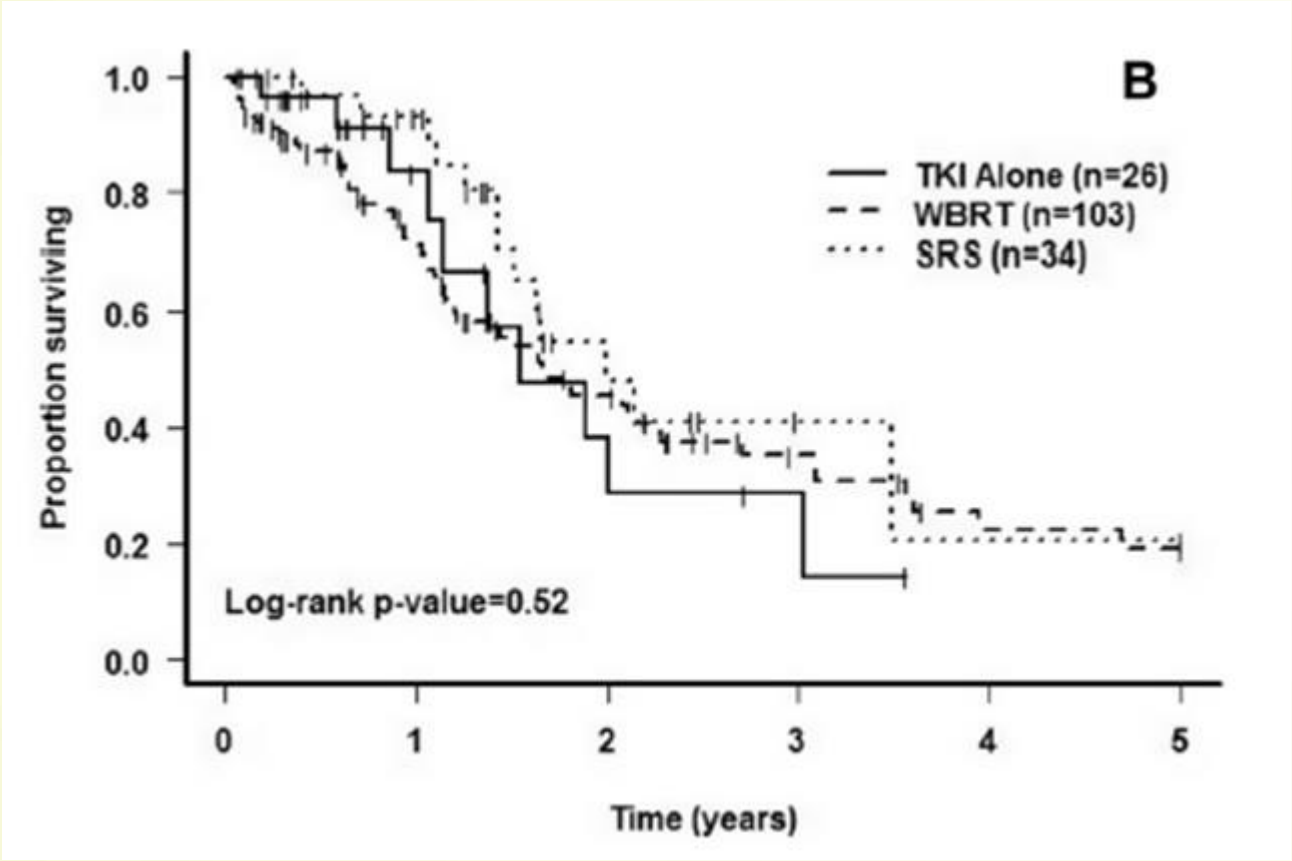
* Lancet Respir Med 2017 Jul 19. pii: S2213-2600(17)30262-X. doi: 10.1016/S2213-2600(17)30262-X. [Epub ahead of print]

3. Brain metastases : local modality

- EGFR-TKI vs. +WBRT vs. +SRS in EGFR (+) NSCLC, retrospective

. median OS: 19.9 vs. 23.9 vs. 18.5 months, p = 0.52

. intracranial progression: 73% vs. 38% vs. 71%, p = 0.0064

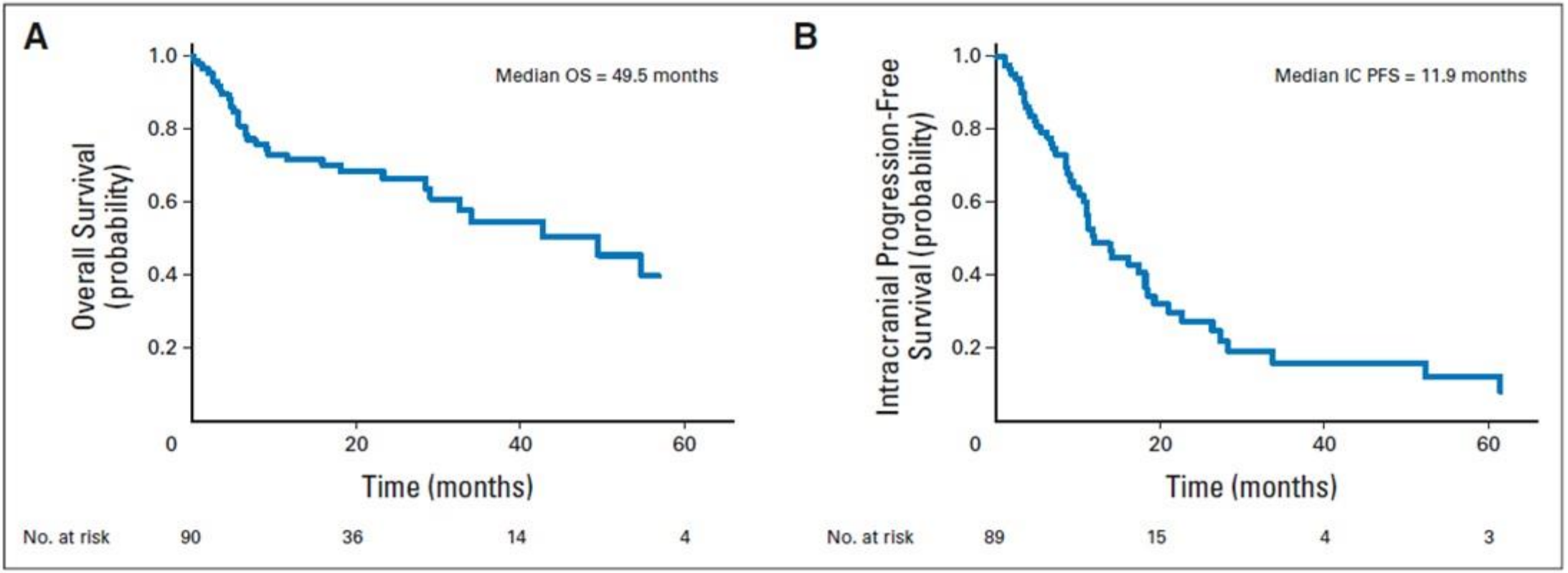


* Radiother Oncol 2017;123(2):195-202

3. Brain metastases : combination

- 90 pts with brain mets, ALK (+), retrospective, USA

. 84/90 pts: WBRT or SRS, 86/90 pts: ALK-TKI



* J Clin Oncol 2016;34(2):123-9

3. Brain metastases : sequence

- EGFR (+) NSCLC (ADC), retrospective

. upfront WBRT or SRS vs. EGFR-TKI

; median OS (34.1 vs. 19.4 months, p = 0.01)

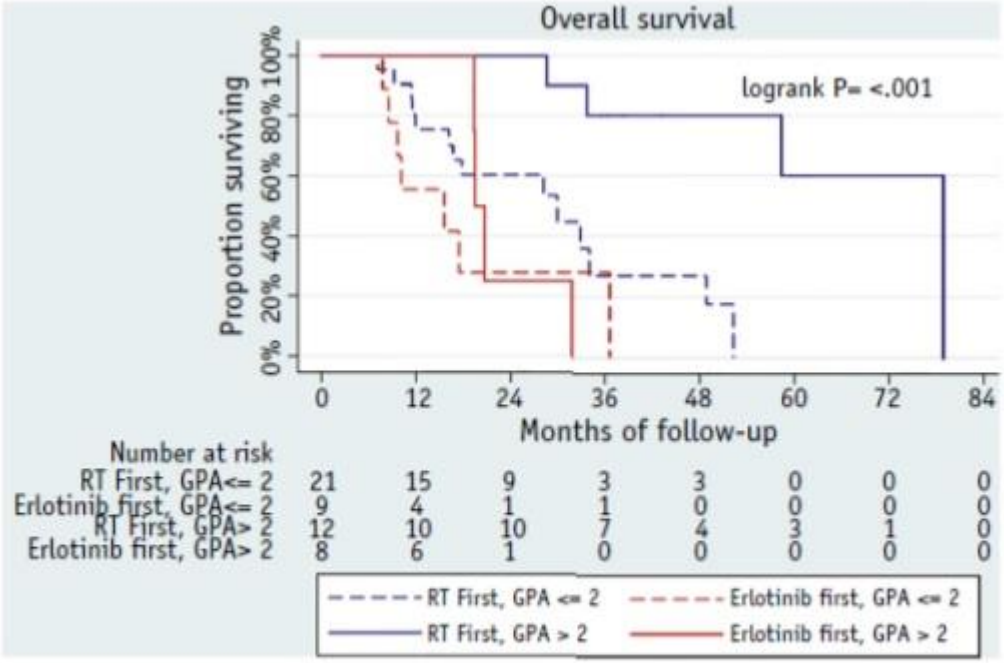


Fig. 3. Overall Survival of patients treated with upfront RT vs. upfront Erlotinib, stratified by disease specific GPA.

GPA >2

Median 78.9 vs. 19.5 months

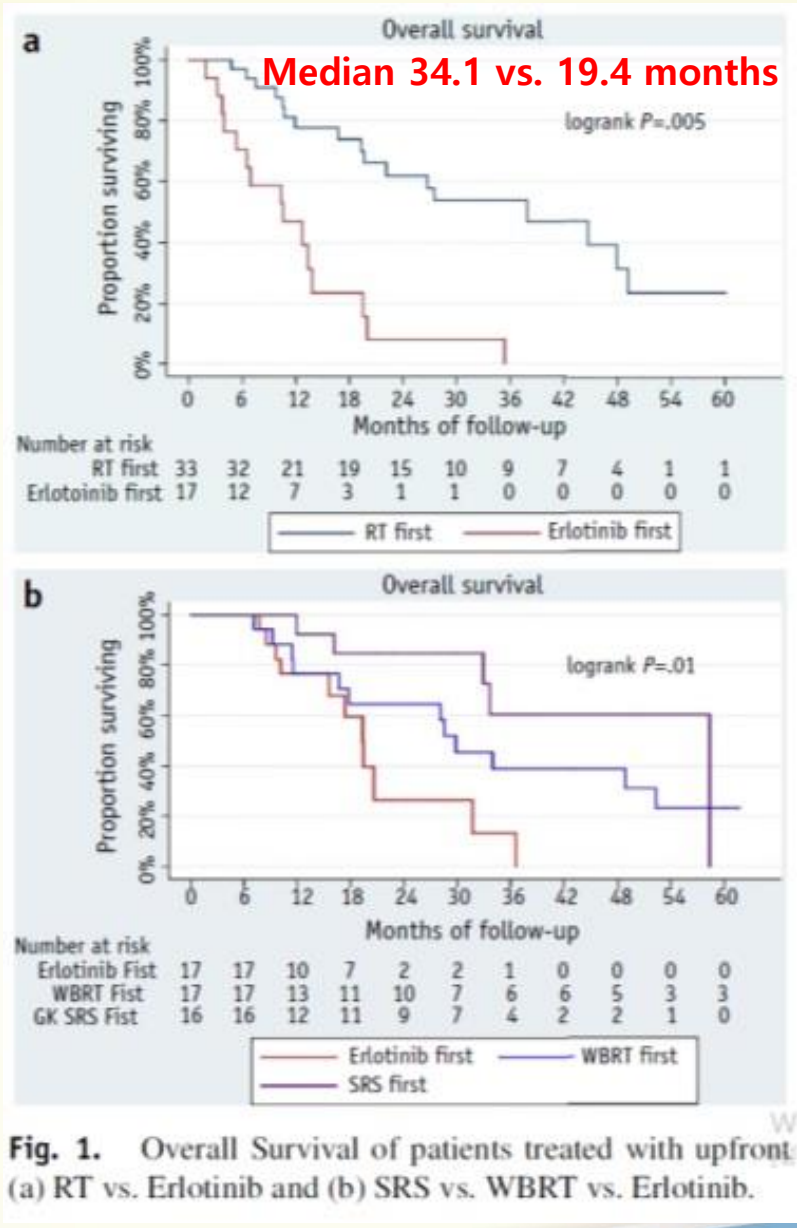


Fig. 1. Overall Survival of patients treated with upfront (a) RT vs. Erlotinib and (b) SRS vs. WBRT vs. Erlotinib.

* Int J Radiat Oncol Biol Phys 2016;95(2):673-679

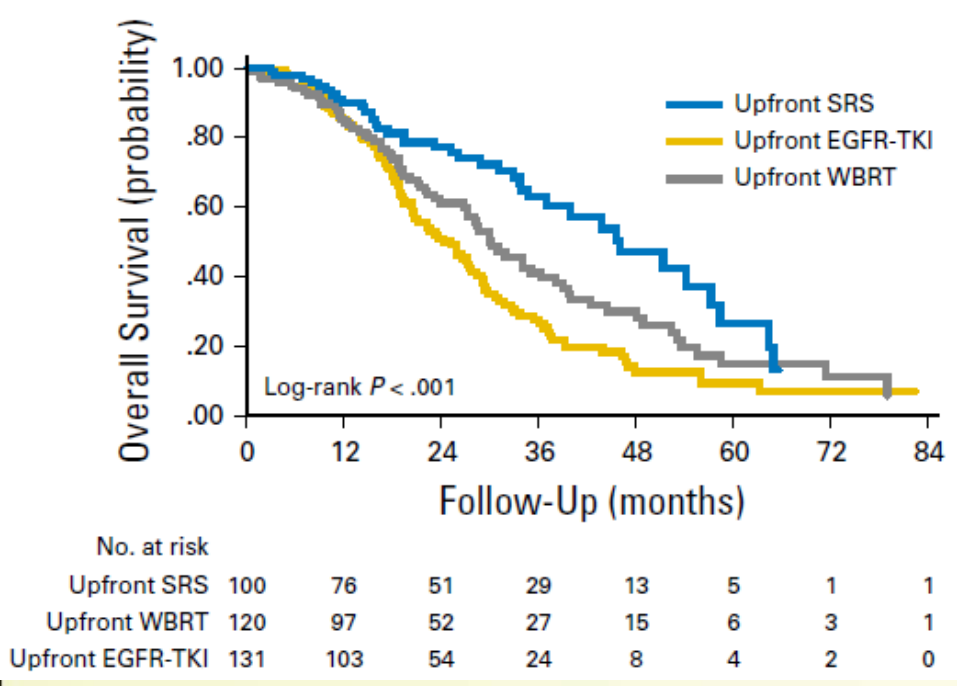
3. Brain metastases : sequence

- EGFR (+) NSCLC, multicenter, retrospective

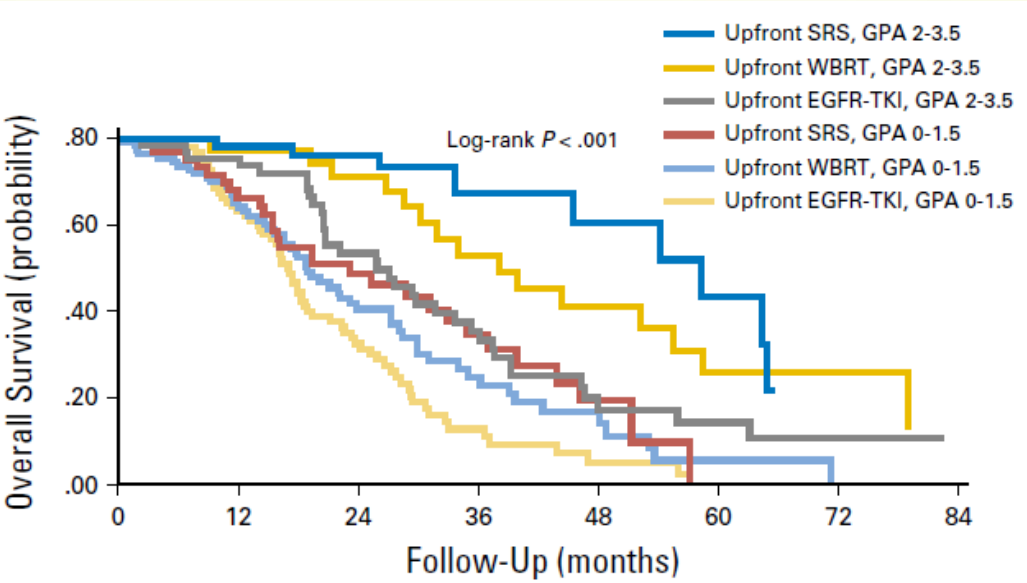
. upfront SRS vs. WBRT vs. EGFR-TKI

; median OS (46 vs. 30 vs. 25 months, $p < 0.01$)

; median OS, GPA 2-3.5 (64 vs. 52 vs. 32 months, $p < 0.01$)



No. at risk								
Upfront SRS	100	76	51	29	13	5	1	1
Upfront WBRT	120	97	52	27	15	6	3	1
Upfront EGFR-TKI	131	103	54	24	8	4	2	0



No. at risk								
Upfront SRS, GPA 2-3.5	48	40	30	18	9	5	1	1
Upfront WBRT, GPA 2-3.5	30	29	22	14	9	5	3	1
Upfront EGFR-TKI, GPA 2-3.5	53	45	28	17	6	4	2	0
Upfront SRS, GPA 0-1.5	52	36	21	11	4	0	0	0
Upfront WBRT, GPA 0-1.5	90	68	30	13	6	1	0	0
Upfront EGFR-TKI, GPA 0-1.5	78	58	26	7	2	0	0	0

* J Clin Oncol 2017;35(10):1070-7

3. Brain metastases : sequence

- EGFR-TKI concentration in CSF before and during WBRT

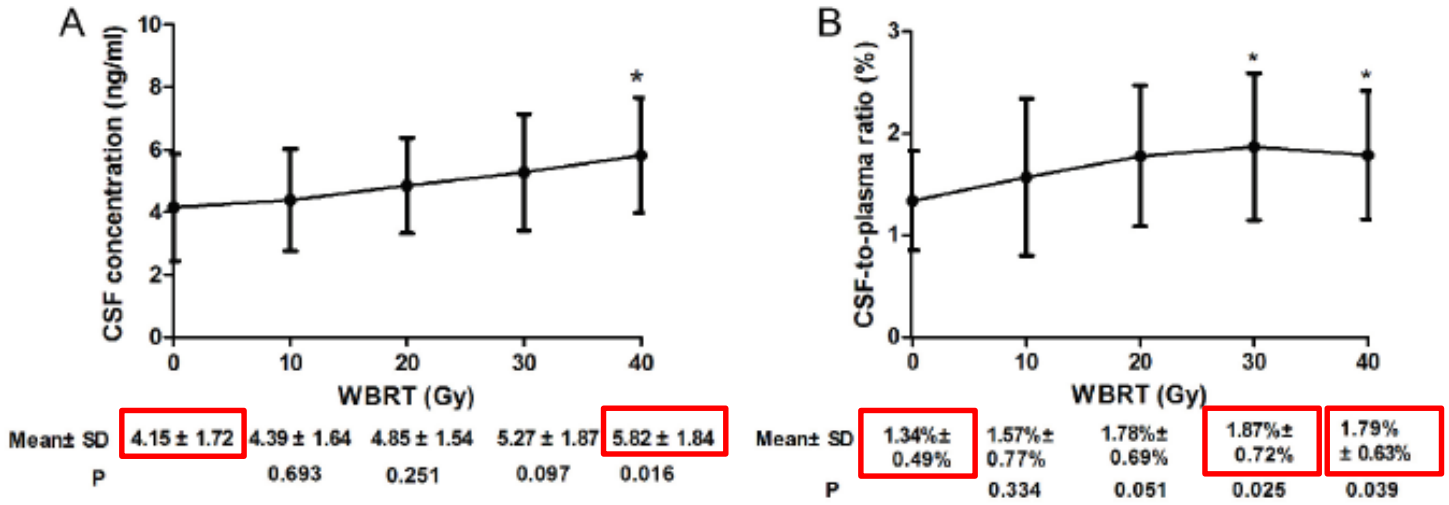


Figure 3: Gefitinib CSF concentration (A) and CSF-to-plasma ratio of gefitinib concentration (B) during WBRT compared with that of baseline (0 Gy). *$P < 0.05$.

* Oncotarget 2015;6:8366-76

3. Brain metastases : clinical consideration

- DS-GPA

Table 3 Median survival time (MST) in months, by treatment, GPA, and number of metastases

	WBRT		WBRT + SRS		
	n	MST (95% CI)	n	MST (95% CI)	*P* value
Overall	126	5.8 (4.7-6.8)	126	5.7 (4.6-8.6)	.21
GPA <3.5	104	5.4 (3.3-6.3)	101	5.0 (3.2-6.5)	.97
GPA 3.5-4.0	22	10.3 (5.3-19.4)	25	21.0 (10.5-36.0	.05
1 metastasis	73	5.0 (3.0-6.2)	70	6.6 (4.6-11.2)	.07
GPA <3.5	56	3.3 (2.2-5.3)	52	5.4 (3.4-6.6)	.16
GPA 3.5-4.0	17	11.4 (4.7-23.1)	18	21.0 (10.0-36.0)	.21
2-3 metastases	52	6.7 (5.7-9.1)	55	5.3 (2.7-9.0)	.92
GPA <3.5	47	6.5 (5.4-9.1)	48	4.0 (2.5-7.9)	.26
GPA 3.5-4.0	5	8.9 (2.4-14.6)	7	14.1 (1.7-36.0)	.10

Abbreviations: CI = confidence interval; GPA = graded prognostic assessment; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

* Int J Radiat Oncol Biol Phys 2014;90:528-531

3. Brain metastases
: hippocampus sparing

- Phase II, 113 patients single arm (hippocampus sparing)
. historical decline (WBRT) in 4 months memory: 30%
. hippocampus sparing WBRT in 4 months memory : 7%

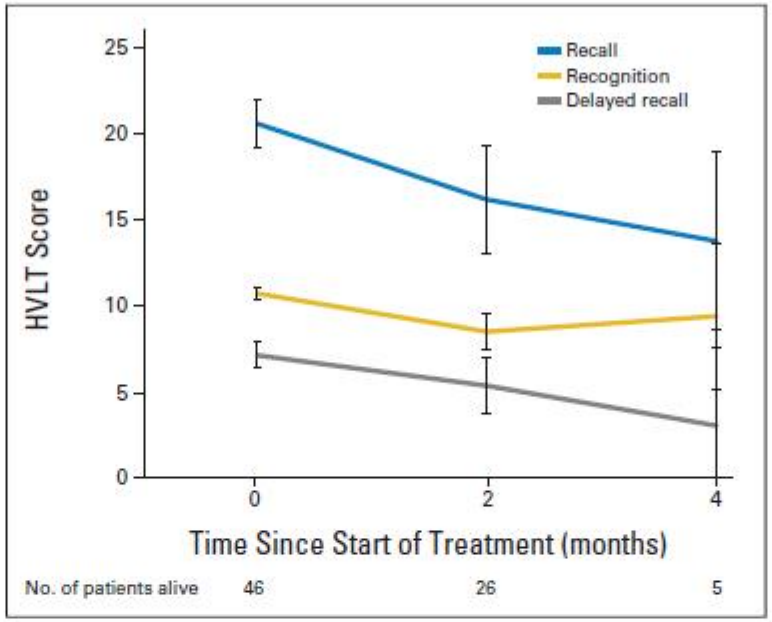


Fig 2. Hopkins Verbal Learning Test (HVLT) scores for 46 patients who had died by 6 months.

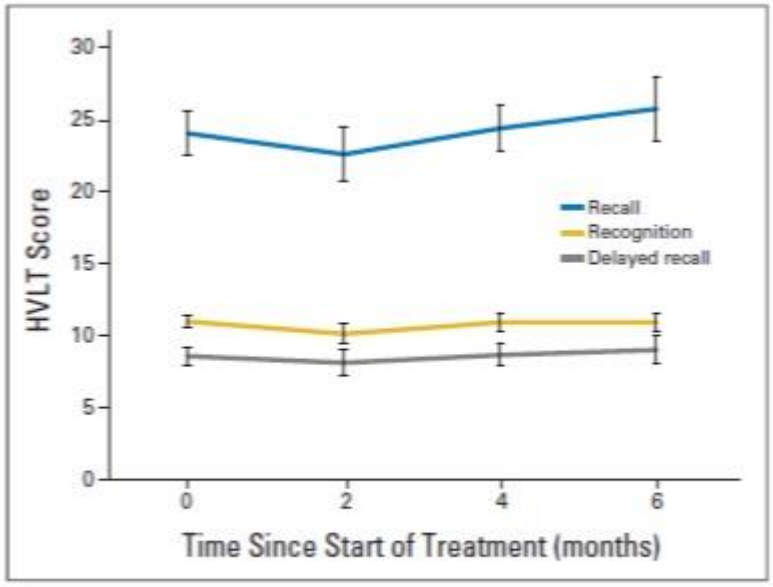
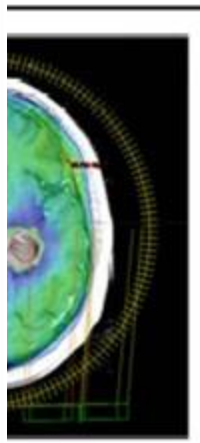


Fig 1. Hopkins Verbal Learning Test (HVLT) scores for 50 patients alive at 6 months.



ous dose coverage in the rest of

* J Clin Oncol 2014;32:3810-3816

3. Brain metastases : summary

. high incidence of brain metastases (50-60%)

. long survival treated with EGFR-TKI (OS: 15-20 months)

. long survival treated with ALK-TKI (OS: 49.5 months)

. Which patients with brain mets would be benefited from additional brain RT ?

; high intracranial control → survival

; molecular marker-GPA could be used as clinical predictor

(PS≤1, age<70, EGFR or ALK (+) → estimated OS: 2 years)

→ SBRT + EGFR-TKI + WBRT (hippocampus-sparing WBRT)

Management of acute side effects

Anatomical site	Side effects	Management	Supporting evidence
Bone	35% of patient in the first week after treatment to bone metastases experience a pain flare. This resolves within a median of 3 days	Oral dexamethasone 8 mg once daily before treatment and for 4 days after, possibly with oral proton pump inhibitor	Rate of flare significantly reduced with dexamethasone (26% *v* 35%, P=0.05) (RCT, 298 patients)
Lung	Cough after treatment is not well documented but common in practice	Routinely managed with medication (such as weak opioids)	Limited evidence supporting any specific intervention (SR, 326 patients, 9 studies)
Brain	Fatigue	Exercise, as possible, has been shown to reduce fatigue in cancer patients generally	Standardised mean difference in fatigue −0.27 (95% CI −0.37 to −0.17) with exercise (MA, 2648 patients, 38 trials). Small RCTs of psycho-stimulants show mixed results in cancer related fatigue (SR). No evidence in whole brain radiotherapy specifically
	Headache (32%)	Simple analgesia with dexamethasone 4 mg once daily if persistent	Recommendation based on routine palliative care prescribing
	Nausea and vomiting (10-16%)	Antiemetics (such as cyclizine) and dexamethasone if persistent	Recommendation based on routine palliative care prescribing
	Otitis externa (5%)	Otitis externa is often asymptomatic, steroid drops can be used if troublesome	No randomised evidence identified

* BMJ 2018;360:k821

The Doctor (1891, Luke Fildes)