

# Palliative RT for bone, CNS mets - when, where, and how?

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# Lung cancer

- Third most common form of cancer to spread to bone (30-40%).
- The majority of brain metastases originate from lung cancer (40-50%).
- Associated with significant morbidity & mortality, loss of functional independence, reduction in QoL.



# Treatment options

## Bone

RT  
(conventional RT, SBRT)

Surgery

Systemic therapy

Bisphosphonates

Pain control

Radionuclide therapy

## CNS

RT  
(WBRT, SRS)

Surgery

Systemic therapy

Symptomatic therapy



# Palliative RT to bone

- When?
- Where?
- How?



# When?

1. Local bone pain
2. Pathologic fracture
3. Spinal cord compression

→ Uncomplicated

→ Complicated



# How? Dose

- Conventional RT schedules

1. Single fraction (SF)

- 8 Gy/1 fx

2. Multiple fraction (MF)

- 30 Gy/10 fx, 24 Gy/6 fx, 20 Gy/5 fx



# How? Uncomplicated bone mets

- SF (8 Gy/1 fx) is recommended.

Pros

Same efficacy to MF  
Cost-effective  
Convenient

Cons

Higher retreatment rate  
SF 20% vs MF 8%

# How? Complicated bone mets

- MF schedule is considered appropriate.
- MF is also commonly prescribed after surgery.

# How? RT techniques

## 1. Conventional RT

- 2D RT & 3D-conformal RT (3D-CRT)

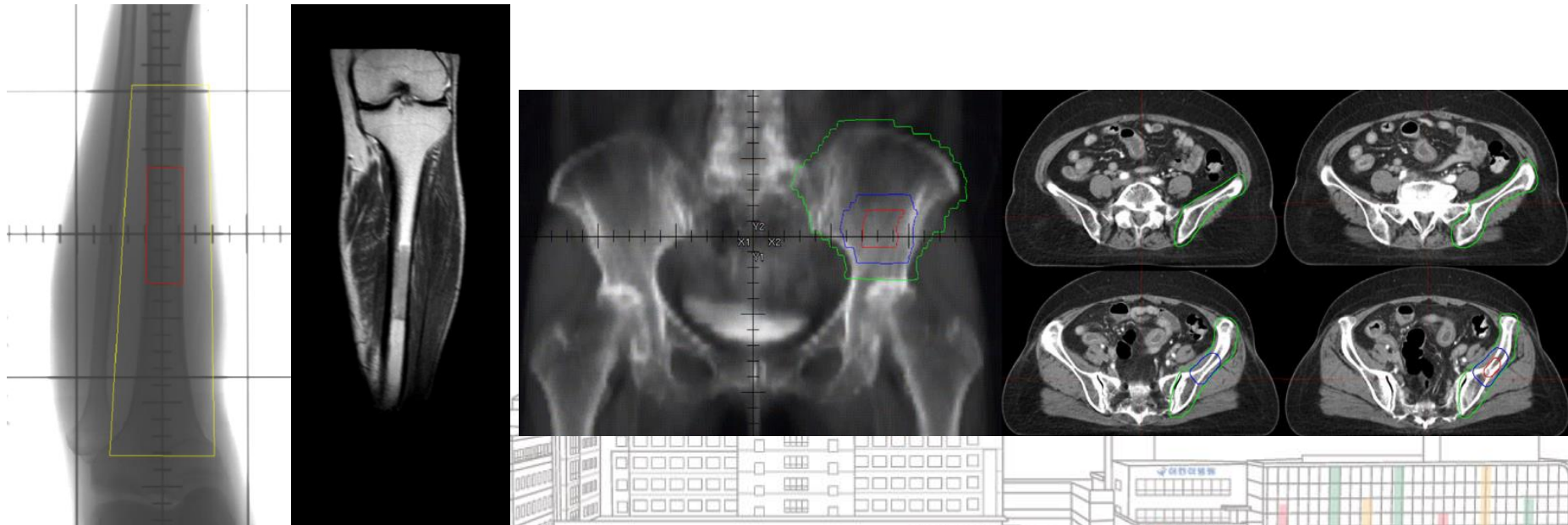
## 2. High-precision RT

- Intensity modulated RT (IMRT)
- Volumetric modulated arc therapy (VMAT)
- Tomotherapy
- Stereotactic body radiotherapy (SBRT)



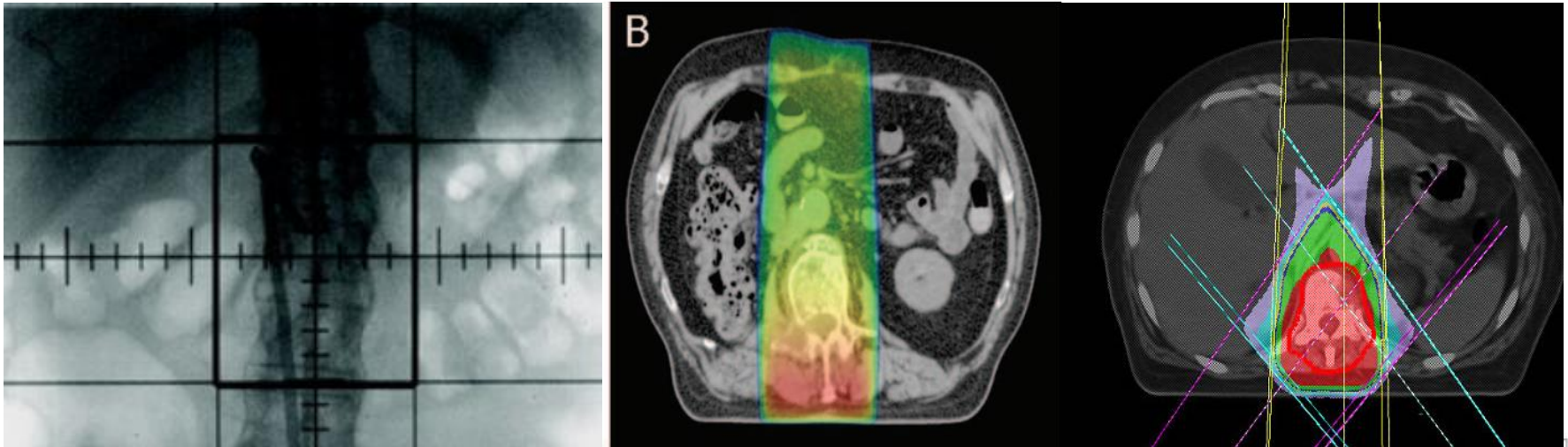
# Where? Conventional RT

- Treatment volume includes the radiographic abnormality with at least a 2 cm margin.



# Where? Conventional RT

- At least, involved vertebral body should be fully covered.



# How? RT techniques

## 1. Conventional RT

- 2D RT & 3D-conformal RT (3D-CRT)

## 2. High-precision RT

- Intensity modulated RT (IMRT)
- Volumetric modulated arc therapy (VMAT)
- Tomotherapy
- SBRT

Protect adjacent  
critical organs  
Dose escalation

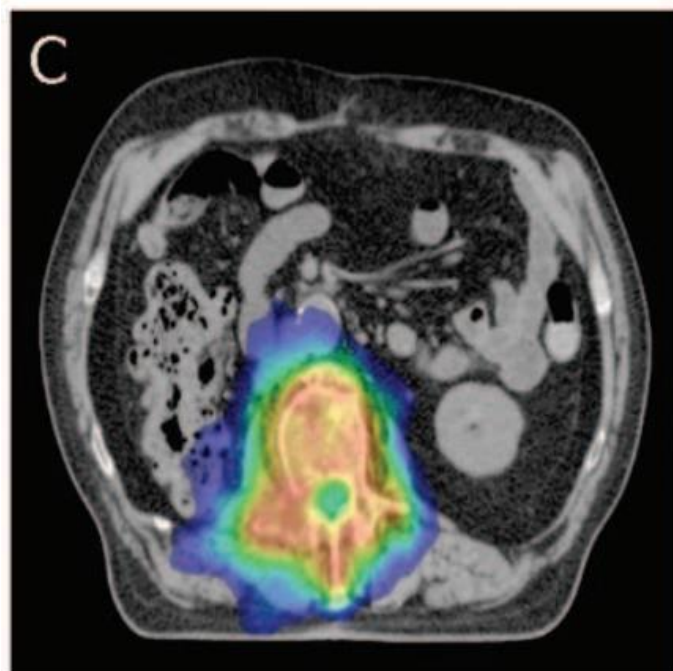


# Dose escalation

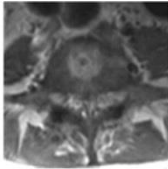
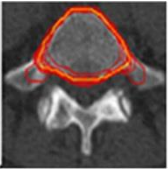
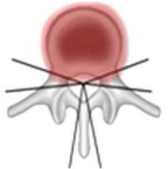
- Conventional RT: relapse rate of 50% at 1 year.
- Improving survival with stage IV disease.  
→ Demand for durable treatment that matches or exceeds survival.

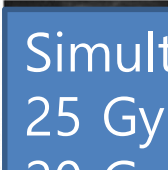
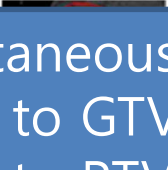
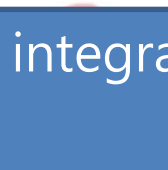


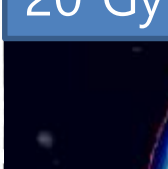


# How, Where? VMAT/SBRT

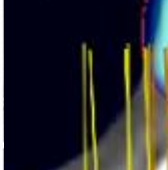
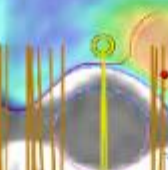
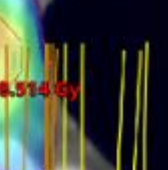


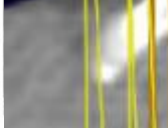


50 Gy/10 fx

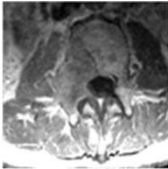
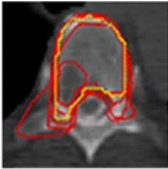
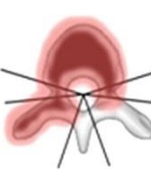
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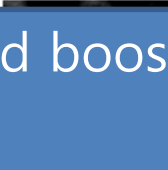
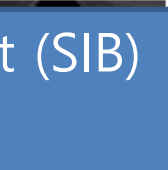

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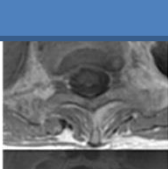
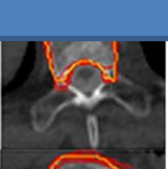
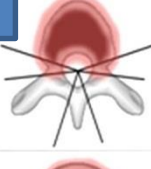
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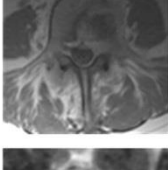
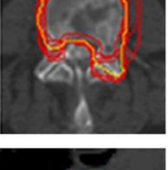
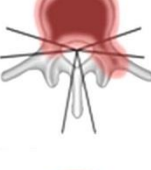
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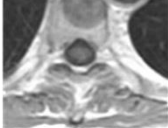


5   

6   

7   

8   

9   

10   

Simultaneous integrated boost (SIB)  
25 Gy to GTV  
20 Gy to PTV

# Spine SBRT

- Efficacy

Center	N	Dose	Median f/u (M)	Outcomes
Pittsburgh	500	Mean 20 Gy (12.5-25 Gy) Single fraction	21	Long-term pain control 86% Long-term tumor control 90%
MD Anderson	74	30 Gy/5 fx	21.3	1-year PFS 84%
MSKCC	811	Median 24 Gy (16-26 Gy) Single fraction	27	2-year cumulative incidence of local failure 3.1% - High dose to GTV (23.56 Gy): 2.1% - Low dose to GTV (17.09 cGy): 14%

# Spine SBRT

- Toxicity
  - Vertebral body fracture
    - Radiographic fracture: 6-39%
    - Symptomatic fractures need stabilization: 4-21%
  - Myelopathy: 0.6%
  - Peripheral neuropathy: 3-year 2.6%
  - Esophageal fistula, stenosis: G3-4 6%

# Case 1 T3 Thyroid Ca

46/F Stage IV poorly differentiated thyroid cancer  
Upper back pain for 1 month  
Multiple lung mets, new T3 mets

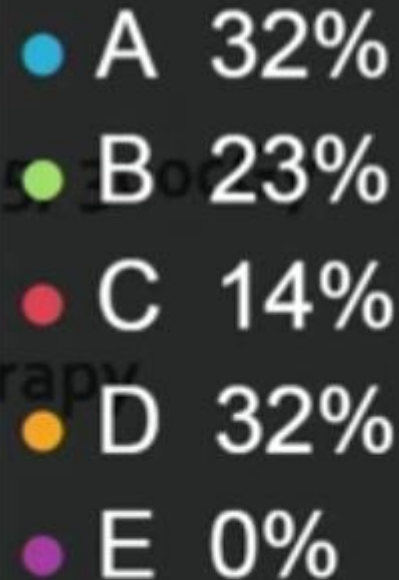


## Case 1

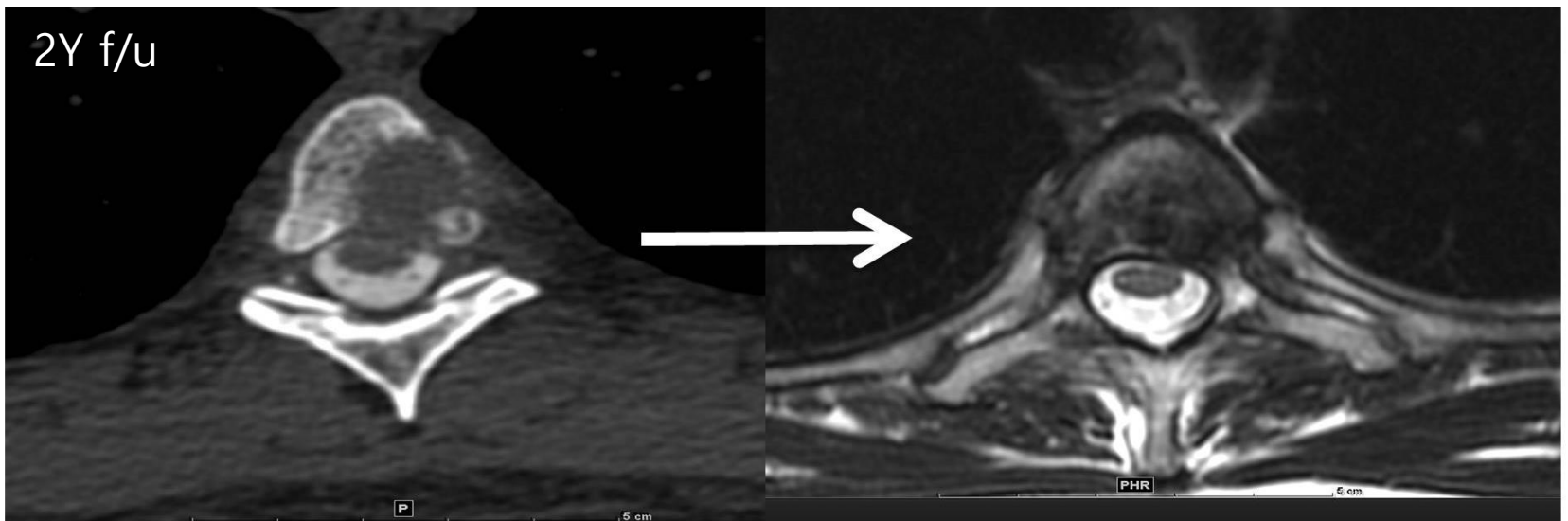
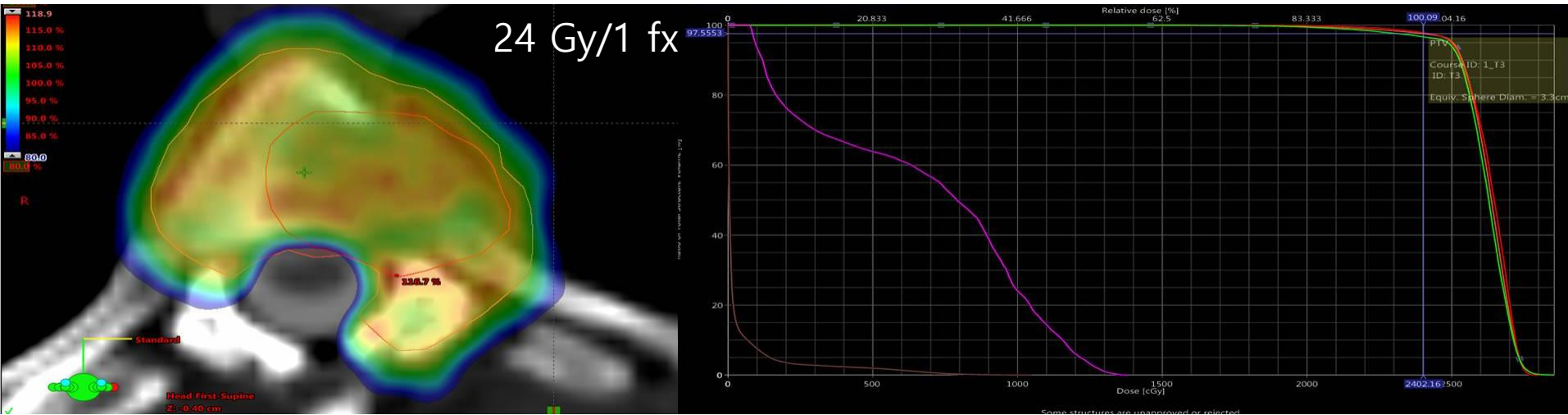
- Which of the following would you recommend?
  - a. Hypofractionation (900cGyx 3 or similar)
  - b. Single session radiosurgery (16-24 Gy x 1)
  - c. Conventional palliation (800cGyx 1, 400cGyx 5, 300cGyx 10 or similar)
  - d. Surgical decompression followed by radiotherapy
  - e. None of the above

## Case 1

- Which of the following would you recommend?
  - a. Hypofractionation (900cGy x 3 or similar)
  - b. Single session radiosurgery (16-24 Gy x 1)
  - c. Conventional palliation (800cGy x 1, 400cGy x 10 or similar)
  - d. Surgical decompression followed by radiotherapy
  - e. None of the above



# Palliative RT to bone



# Summary

- Uncomplicated bone mets
  - Conventional SF
- Complicated bone mets
  - Conventional MF
- For more durable symptom and local control, consider dose-escalated RT or SBRT.

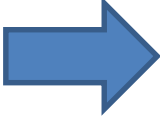


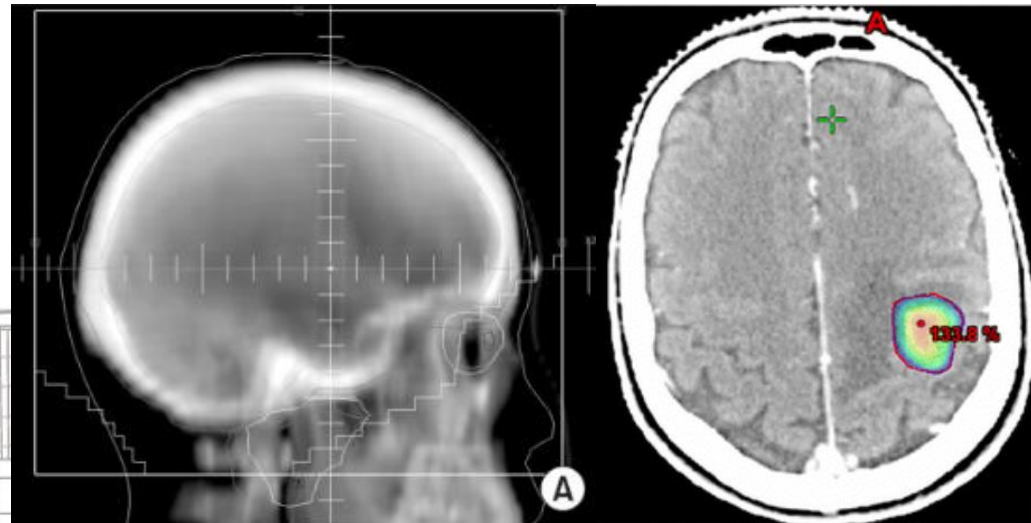
# Palliative RT to CNS

- When?
- Where?
- How?

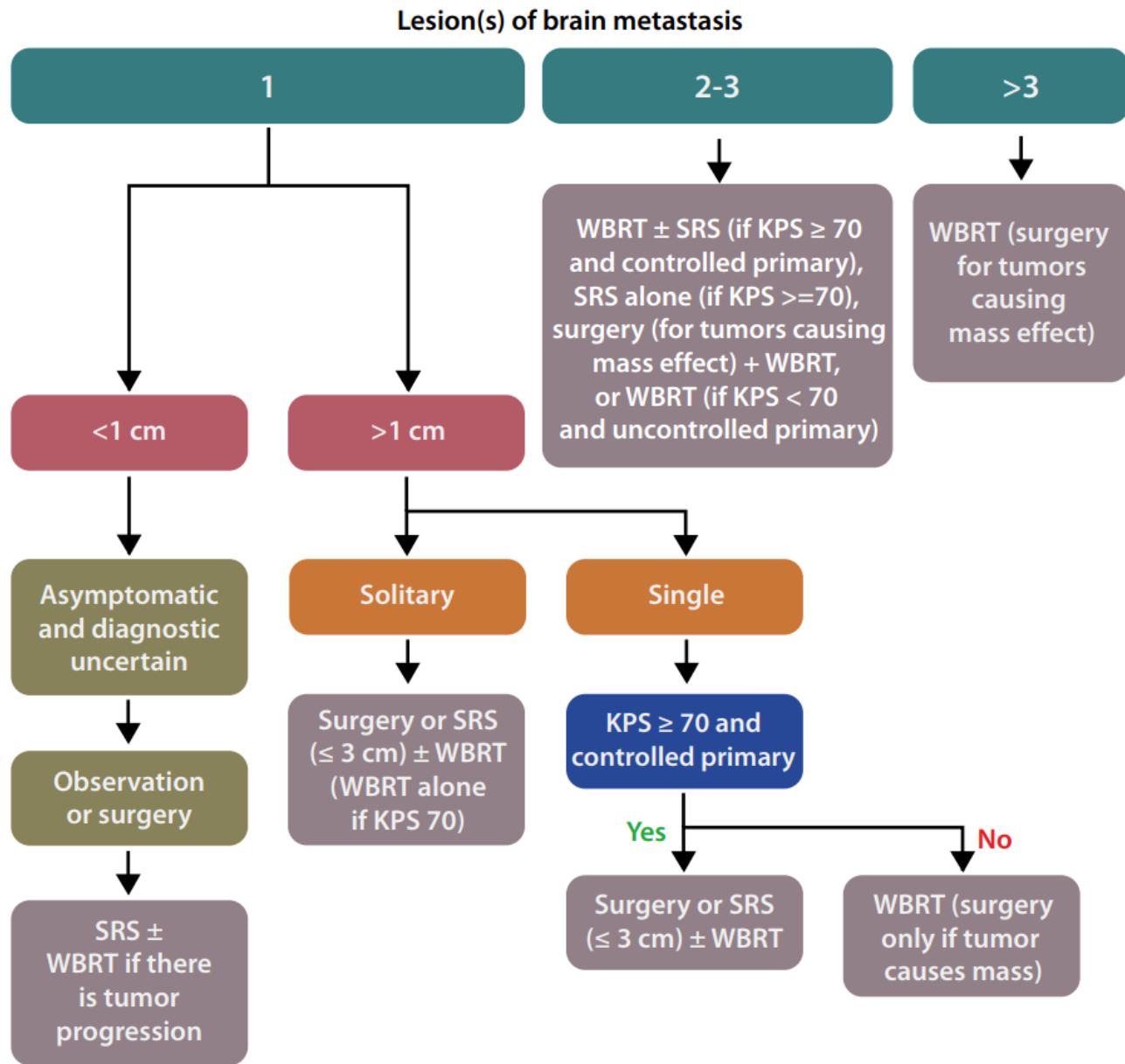


# Palliative RT to CNS - Brain

- When?
  - Where? 
  - How?
- Number(s) of mets
    - Whole brain RT (WBRT)
    - Stereotactic radiosurgery (SRS)



# When?



**Figure 1A.1** Proposed algorithm in the management of brain metastases.

Source: Chang EL, Lo S (2003) Diagnosis and management of central nervous system metastases from breast cancer. *Oncologist* 8:398–410



# When?



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## NCCN Guidelines Version 1.2019 Limited Brain Metastases

c"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation. (Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)

Newly diagnosed or  
stable systemic  
disease or  
Reasonable systemic  
treatment options  
exist<sup>e</sup>

SRS (preferred)<sup>g,h,i</sup>  
 or  
 WBRT<sup>g,h,j</sup>



# When? **Single brain mets**

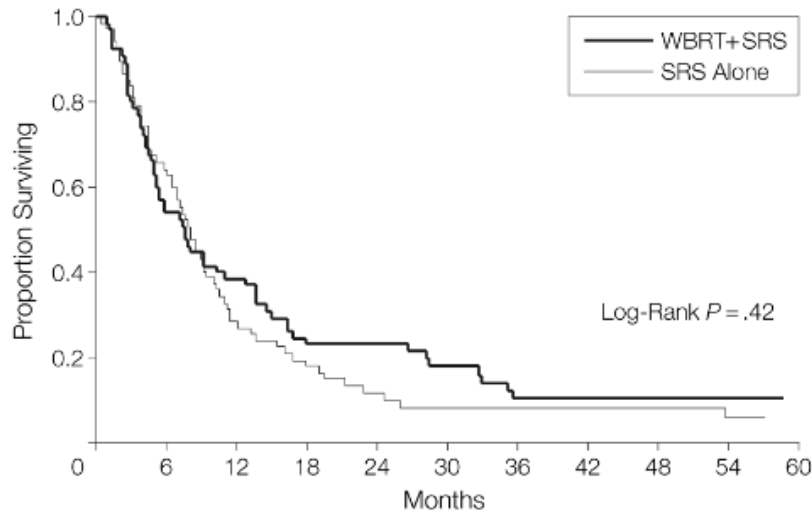
- WBRT+SRS vs. WBRT alone (RTOG 95-08)
  - Survival advantage in the WBRT + SRS for single brain mets (median survival time 6.5 vs 4.9 months,  $p=0.039$ )
  - WBRT + SRS should be standard treatment for patients with a single unresectable brain metastasis and considered for patients with 2-3 brain metastases.



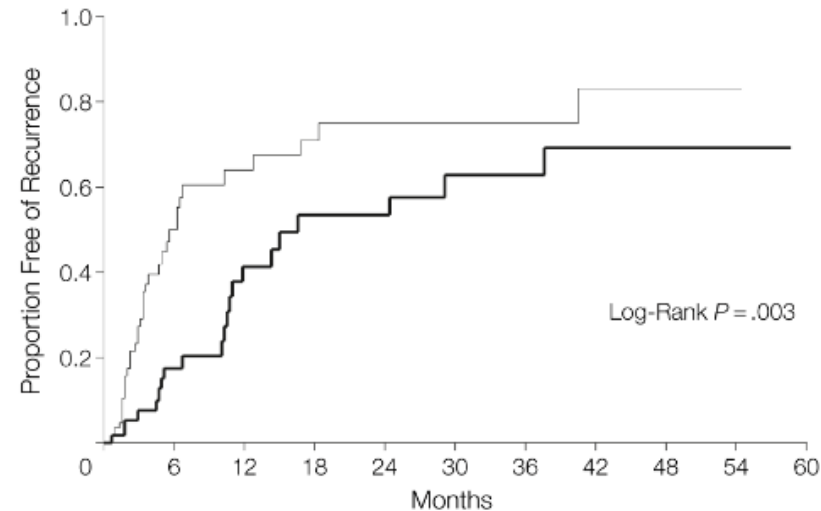
# When? Number $\leq 4$ & Size $\leq 3$ cm

- SRS alone vs. SRS+WBRT (JROSG 99-1)

Overall survival



Brain tumor recurrence



No. of Patients at Risk

WBRT+SRS	65	35	25	15	14	10	6	6	4	2
SRS Alone	67	43	19	12	7	5	5	5	5	2

No. of Patients at Risk

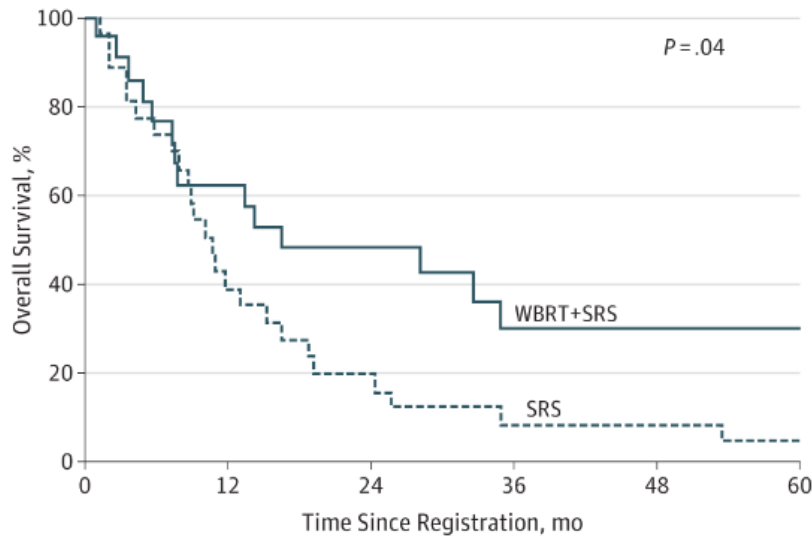
WBRT+SRS	60	29	16	12	11	7	6	5	3	2
SRS Alone	62	19	10	7	4	4	4	2	1	1



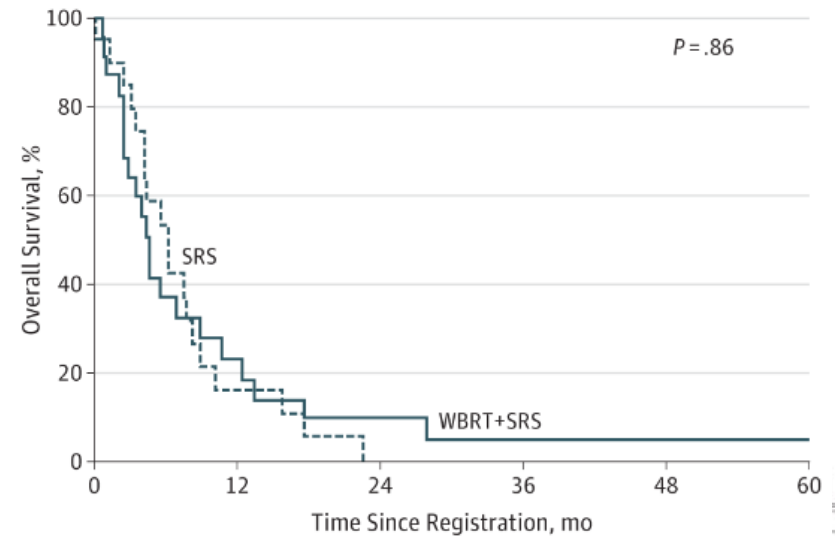
# When? Number $\leq 4$ & Size $\leq 3$ cm

- Secondary analysis in NSCLC (n=88)
  - Overall survival

**A** DS-GPA scores 2.5-4.0



**B** DS-GPA scores 0.5-2.0



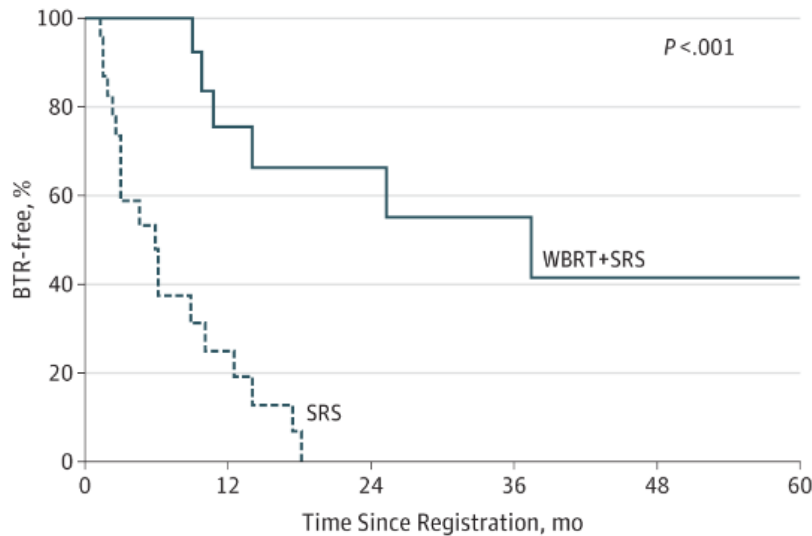
No. at risk

SRS	26	11	5	2	2	1	19	3	0	0	0	0
WBRT+SRS	21	13	9	5	5	5	22	5	2	1	1	1

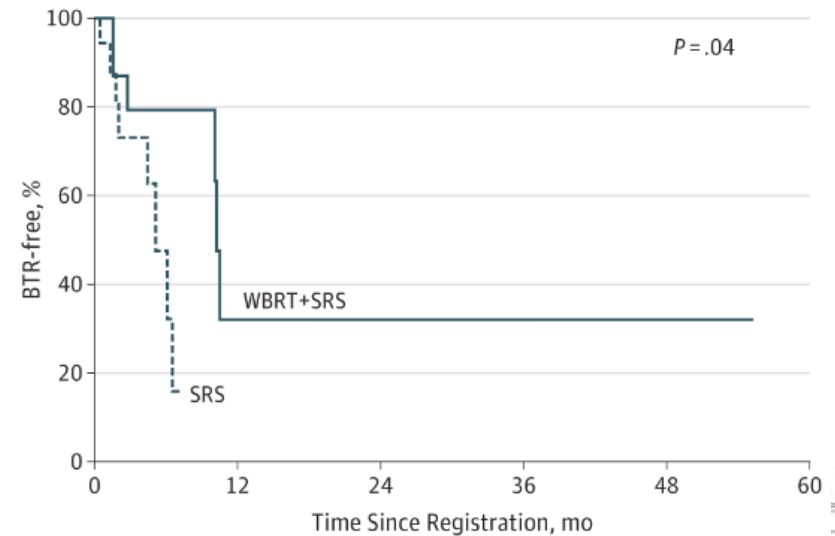
# When? **Number $\leq 4$ & Size $\leq 3$ cm**

- Secondary analysis in NSCLC (n=88)
  - Brain tumor recurrence-free survival

**A** DS-GPA scores 2.5-4.0



**B** DS-GPA scores 0.5-2.0



No. at risk

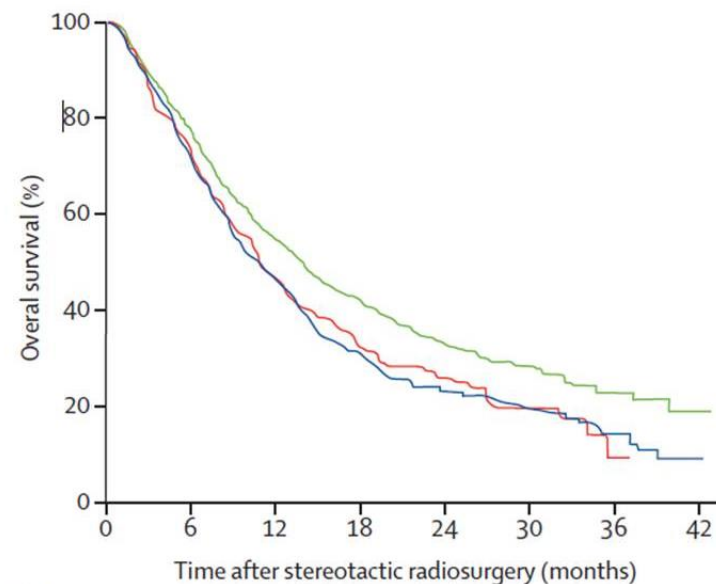
	0	12	24	36	48	60	0	12	24	36	48	60
SRS	24	4	0	0	0	0	17	0	0	0	0	0
WBRT+SRS	20	9	6	4	2	1	19	2	2	1	1	0

# When? Number >4

- SRS alone for 1-10 brain mets (JLGK0901)
  - 1194 patients
  - No difference in toxicity

→ SRS alone might be a suitable alternative for 5-10 brain metastases.

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13.9 (12.0-15.6)	0.76 (0.66-0.88)	0.0004
2-4 tumours	10.8 (9.4-12.4)	Reference	
5-10 tumours	10.8 (9.1-12.7)	0.97 (0.81-1.18)	0.78



Number at risk	0	6	12	18	24	30	36	42
1 tumour	455	234	97	22				
2-4 tumours	531	215	61	16				
5-10 tumours	208	84	31	1				

# Toxicity of WBRT

- Fatigue
- Somnolence
- Nausea, vomiting
- Alopecia
- Neurocognitive deterioration



# Neurocognitive function

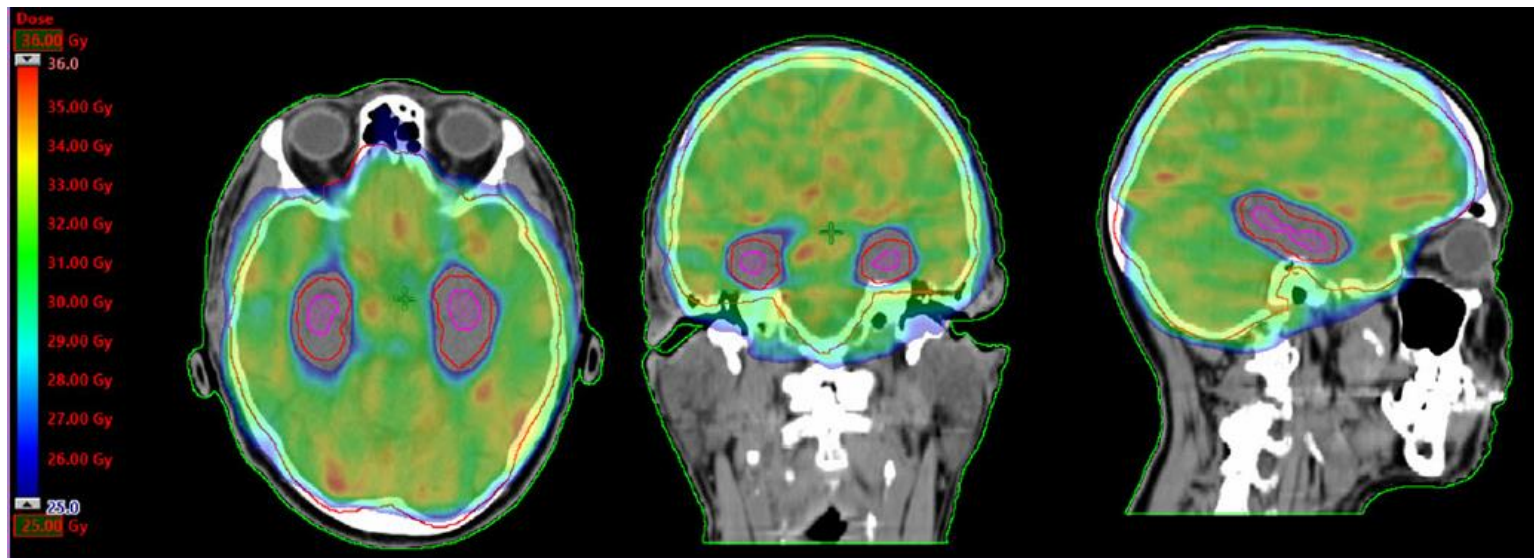
Table 2. Patients Who Experienced Cognitive Deterioration by 3 Months and Difference Between Groups

	No. (%) of Participants		Mean Difference, % (95% CI)	P Value <sup>a</sup>
	SRS Alone (n = 63)	SRS Plus WBRT (n = 48)		
Change from baseline <sup>b</sup>				
HVLt-R				
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)		



# New approaches

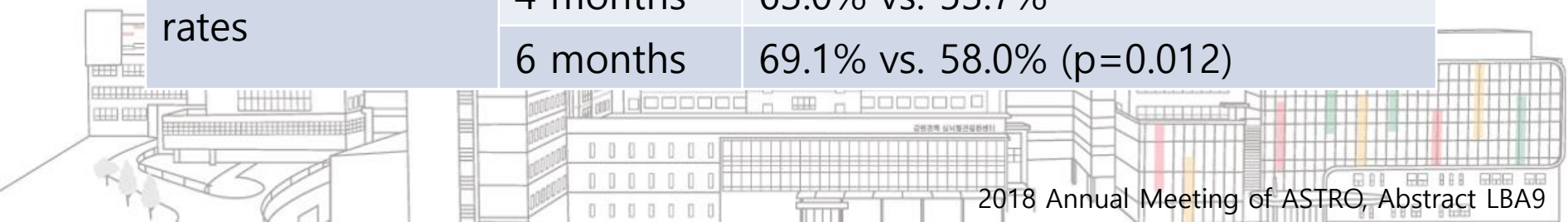
- Hippocampus-sparing WBRT



# Hippocampus-sparing WBRT

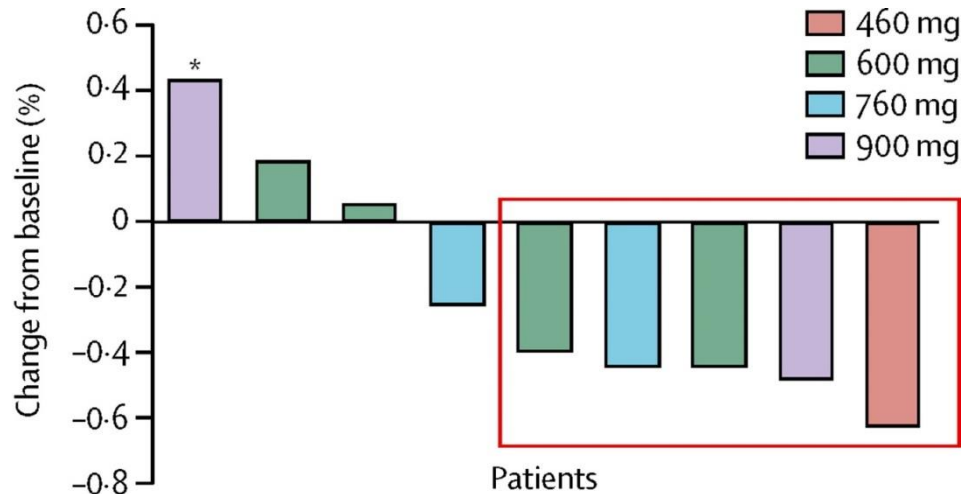
- Preliminary analysis of NRG Oncology CC001

N=518	WBRT vs. Hippocampus-sparing WBRT	
Enroll period	2016.01-2018.03	
Median f/u	6.1 months	
OS	HR 1.13 (95% CI 0.89-1.44, p=0.31)	
Intracranial PFS	HR 1.12 (95% CI 0.90-1.39, p=0.33)	
Neurocognitive function failure rates	2 months	12.8% vs. 11.2%
	4 months	63.0% vs. 53.7%
	6 months	69.1% vs. 58.0% (p=0.012)



# Potential role of targeted therapy

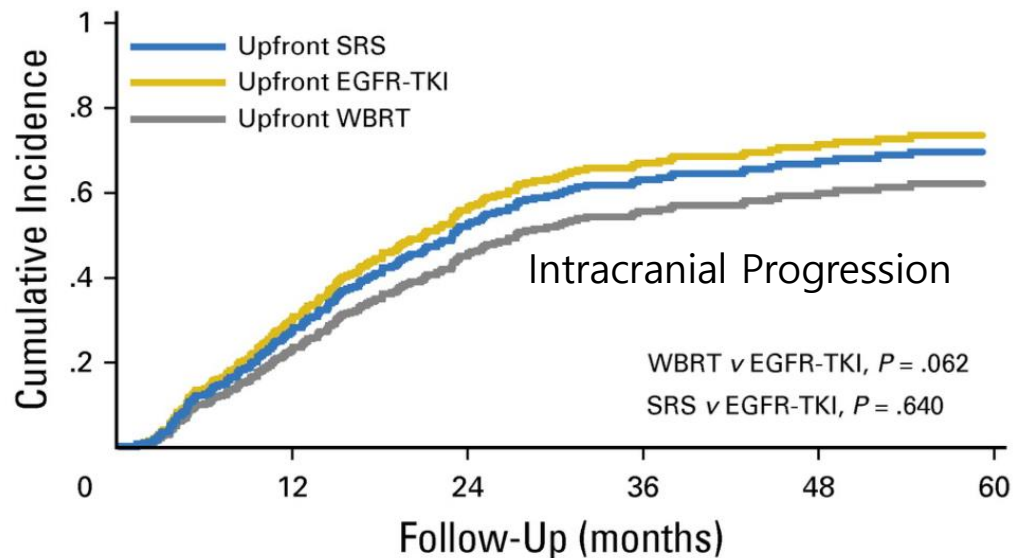
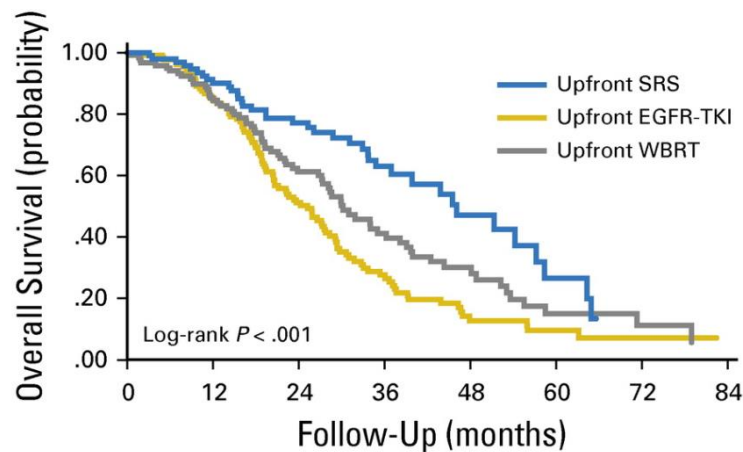
- Erlotinib
  - CNS objective response rate of 55% to 89%.
- Alectinib



Days on treatment 91+ 203+ 42 224+ 287+ 224+ 98+ 196+ 294+

# Potential role of targeted therapy

- In terms of intracranial control, WBRT works better.

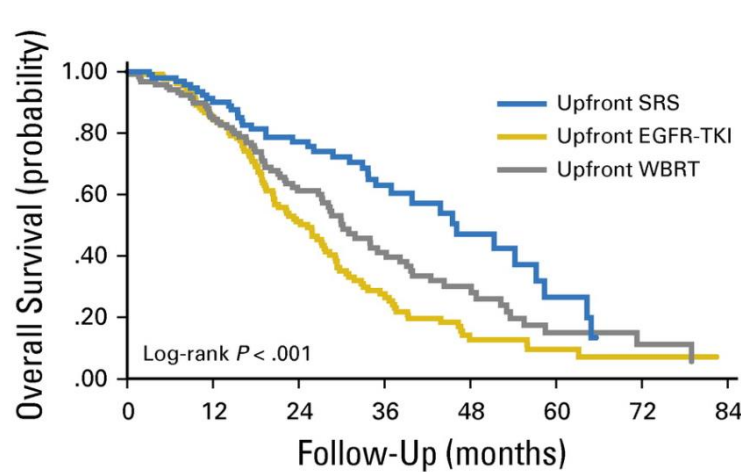


No. at risk

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

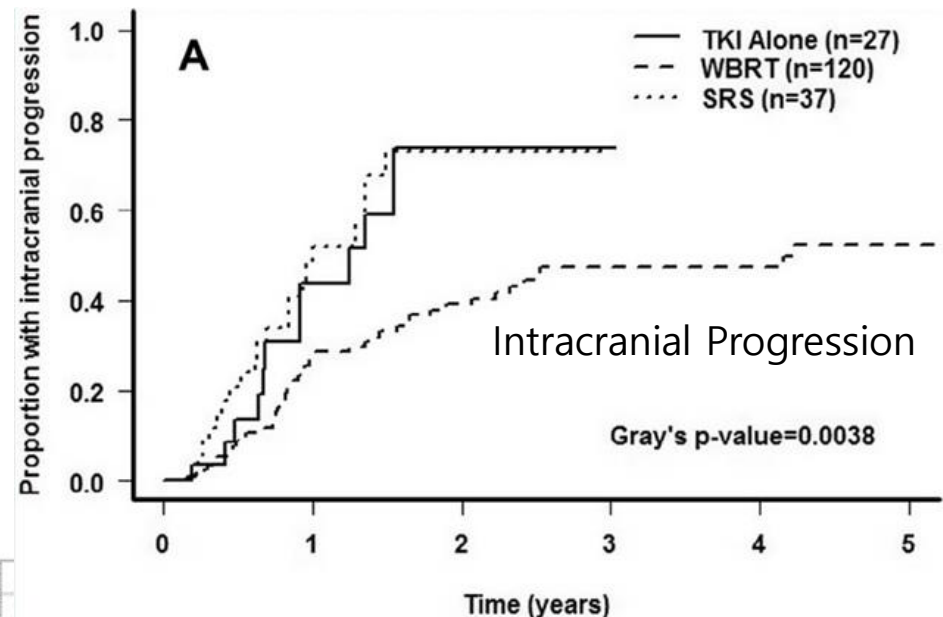
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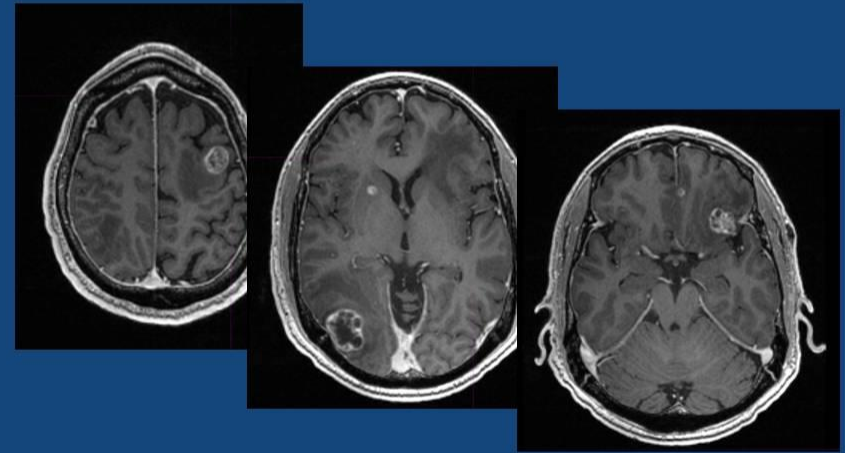
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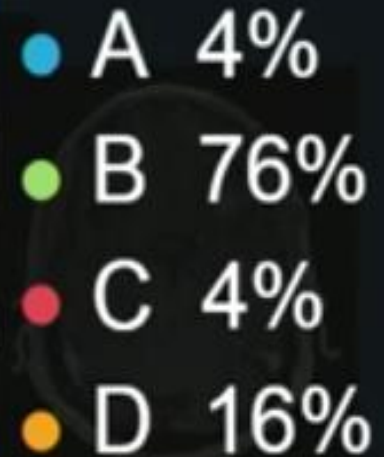


**Multiple Choice:** 73 y/o man, nonsmoker, KPS 90, new diagnosis metastatic EGFR mutant NSCLC with multiple brain metastases. Your management?

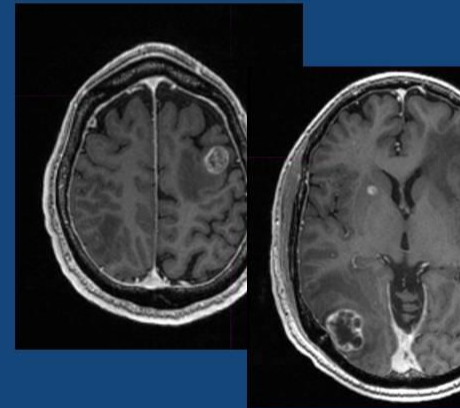
- A. WBRT
- B. EGFR inhibitor
- C. Immunotherapy
- D. SRS

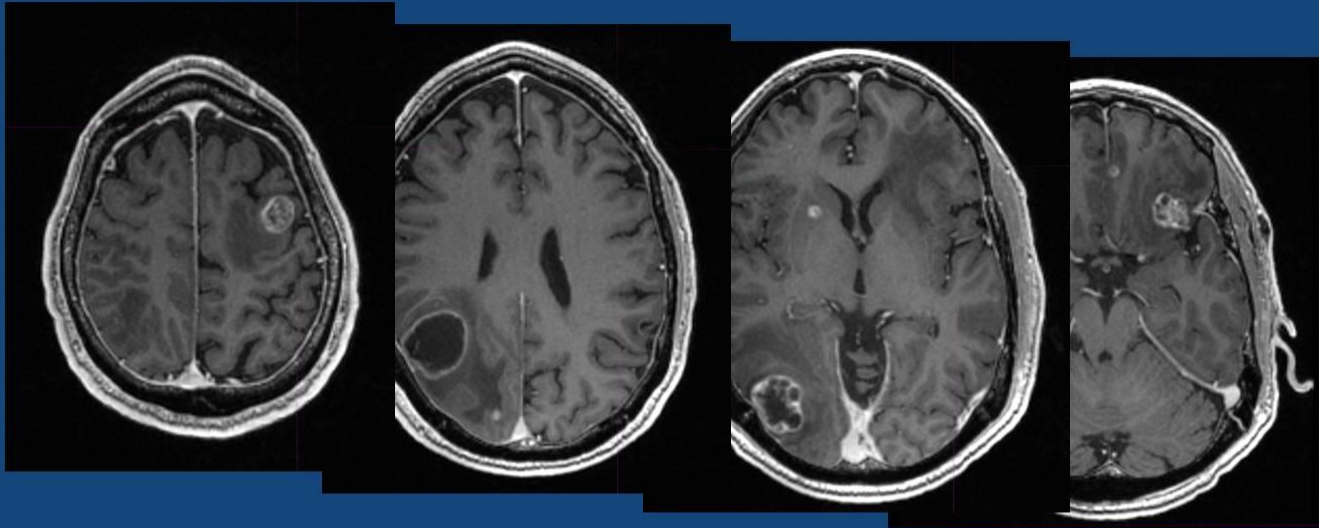


**Multiple Choice:** 73 y/o man, nonsmoker, KPS 2, diagnosis metastatic EGFR mutant NSCLC with multiple brain metastases. Your management is:



- A. WBRT
- B. EGFR inhibitor
- C. Immunotherapy
- D. SRS





73M with EGFR+ NSCLC & multiple brain metastases:  
- Treated first with EGFR inhibitor

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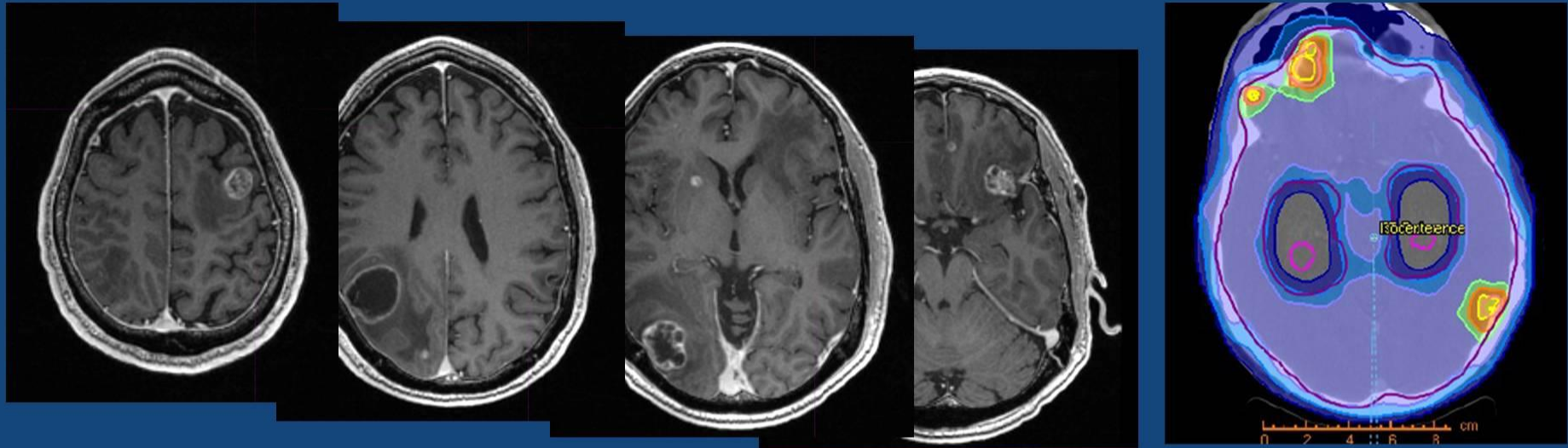
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73M with EGFR+ NSCLC & multiple brain metastases:

- Treated first with EGFR inhibitor
- At CNS progression, treated with HA-WBRT

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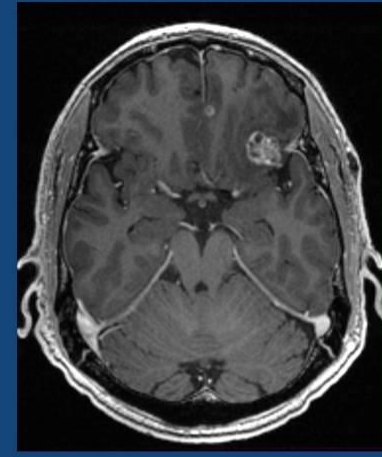
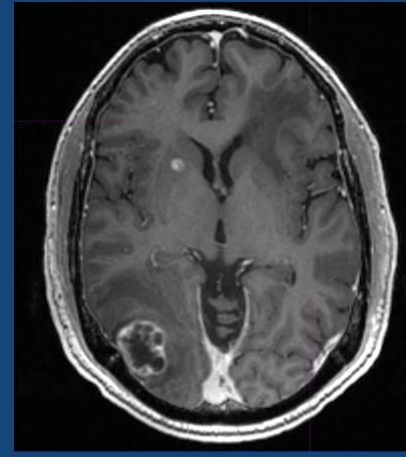
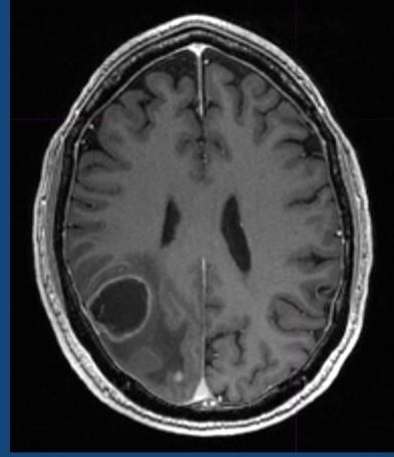
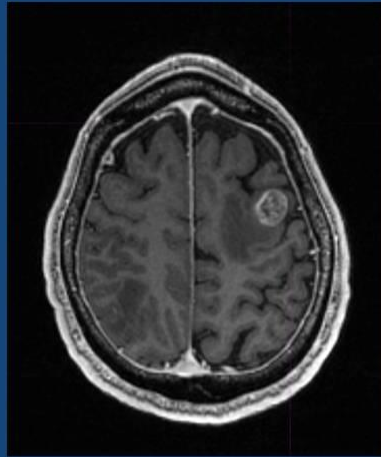
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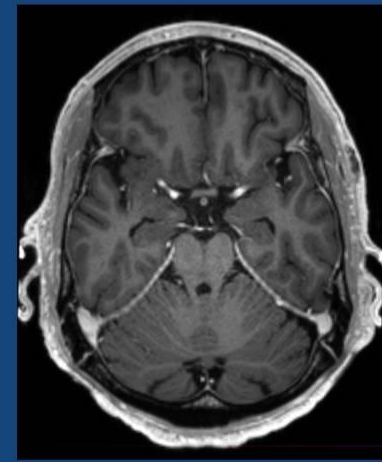
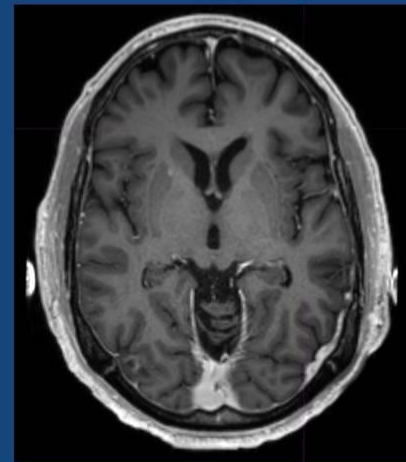
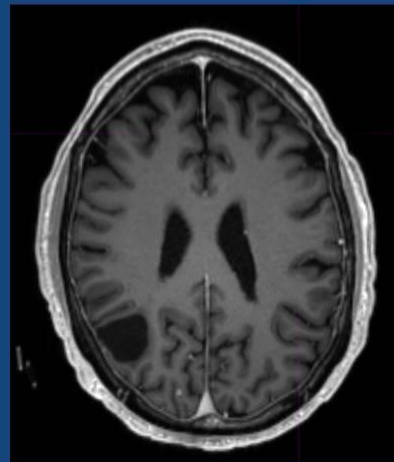
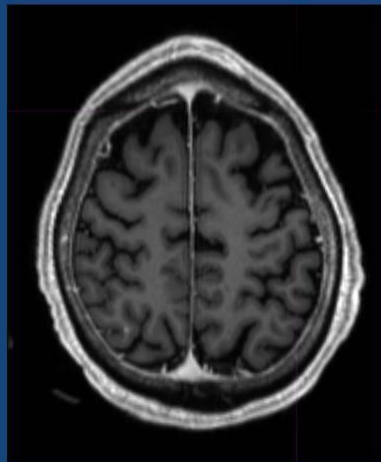
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Before HA-WBRT



6 months after  
HA-WBRT



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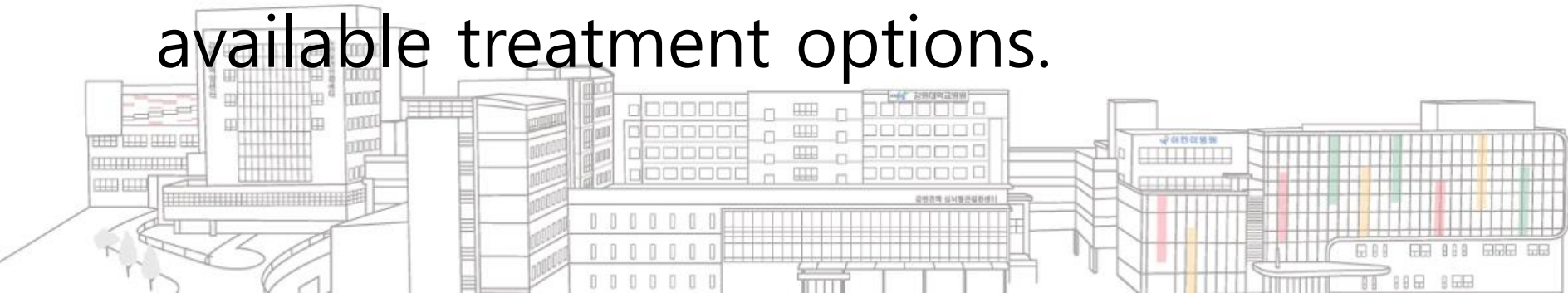


# Leptomeningeal seeding

- WBRT may be considered for extensive nodular or symptomatic linear LM or co-existing brain metastasis.
- Involved-field RT can be used to treat nodular disease and symptomatic spinal sites.
- Concomitant CNS directed RT and systemic or intra-CSF treatment should be avoided to prevent severe neurotoxicity.

# Summary

- WBRT cannot be entirely replaced by SRS and targeted agents.
- Consider patient factors (age, performance status, life expectancy), tumor factors (biology, disease status), previous treatment, and currently available treatment options.



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