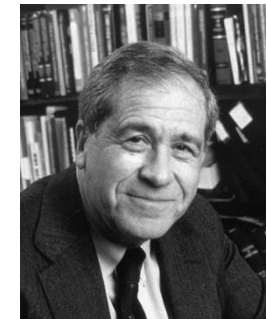


# Management of Oligometastatic Breast Cancer

Dr Suman Mallik

# Evolution of Breast Cancer Management



**Adjuvant therapies**  
**Bernard Fisher**  
**(1976)**

**SYSTEMIC DISEASE**  
**Hippocrates**  
**(400BC)**



**Galen**  
**(200 A.D)**

**Local disease**

**Valsalva**  
**(1704)**

**LeDran**  
**(1757)**

**Morgagni**  
**(1769)**

**Sylvius, Gendron**  
**(1730)**

**Astruc**  
**(1769)**

**Lymphatic Dissemination**

**Hunter (1772)**

**Barrier Function of Lymph Nodes**

**Virchow (1863)**

**Radical Mastectomy**  
**Halstead (1882)**

**Jerome Urban (1949)**

**Criteria of Operability**  
**Haagensen & Stout**  
**(1943)**

# Oligometastasis

- Metastases limited in number and extent and potentially amenable to definitive directed treatment.



S Hellman



R Weichselbaum

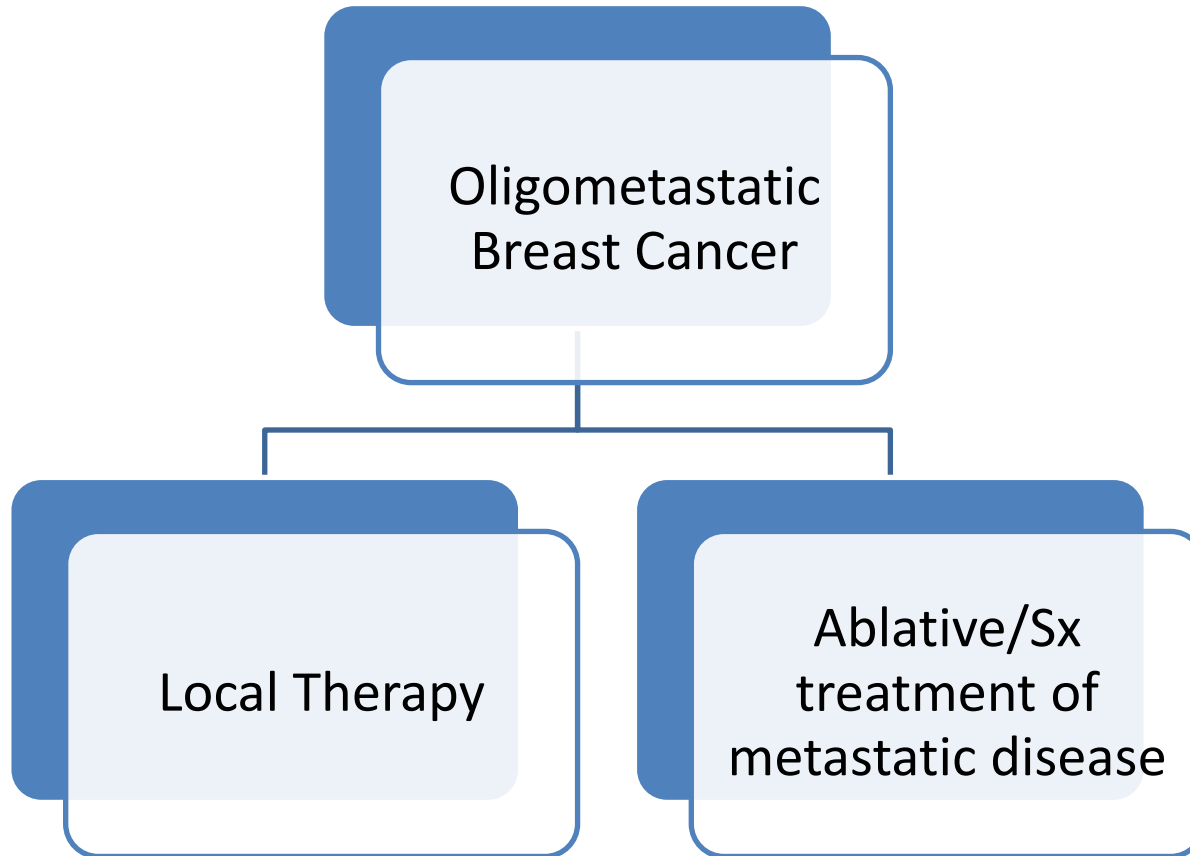
# Stage IV Breast Cancer: Epidemiology

- 10% Breast cancer present at stage IV at diagnosis. (Howlander SEER).
- 20-30% of early BC will experience distant metastatic relapse. (EBCTCG, Lancet 2005, 2012)
- “Potentially curable” stage IV estimated to be 1-10% of newly diagnosed metastatic BC. (Pagani, JNCI 2010)

# Are metastatic breast cancer curable?

- For select patient with limited metastases receive systemic therapy to sterilize occult metastatic disease and local ablative therapy/Sx to overt sites could be potentially curable.

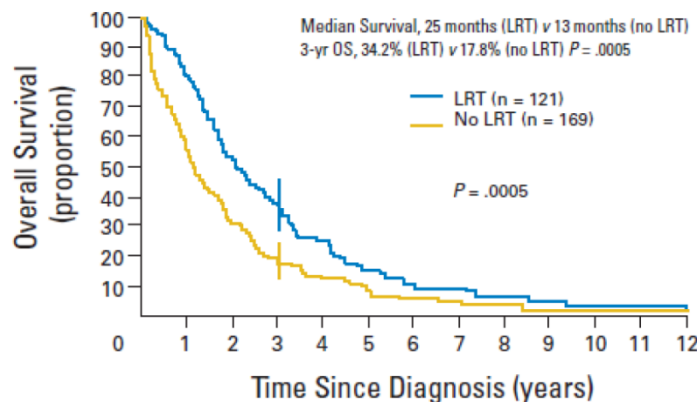
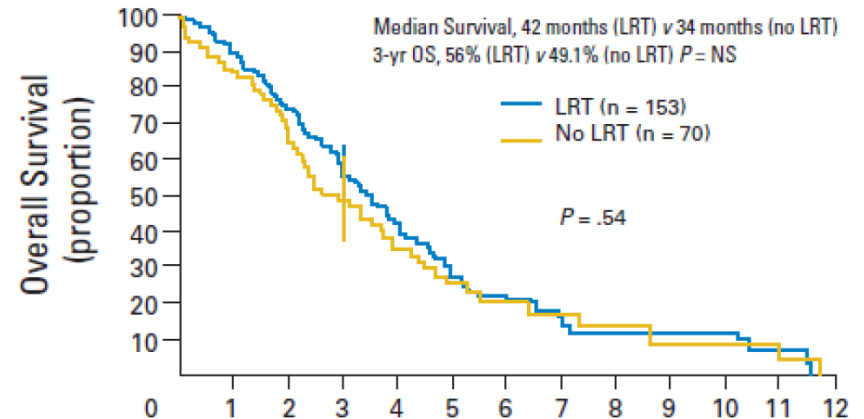
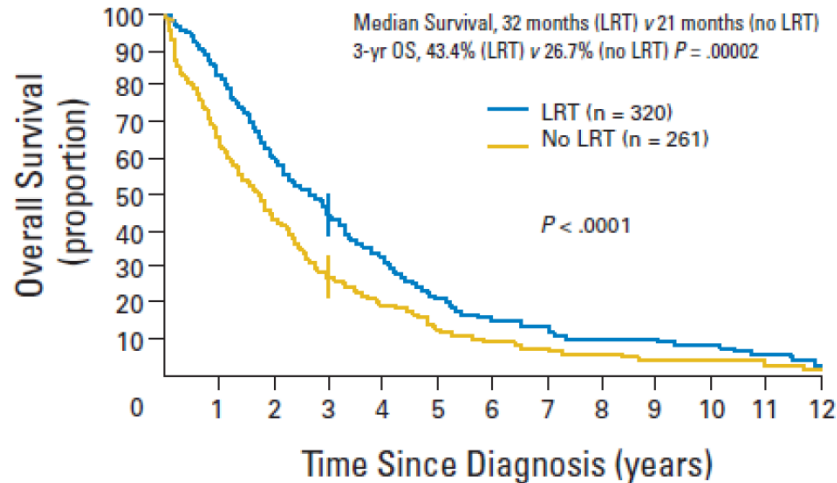
# Oligometastatic Breast Cancer



# Evidence of radical irradiation

- Salama JK, Milano MT. Radical irradiation of extracranial oligometastases. J Clin Oncol 2014;32:2902–12.
- Ahmed KA, Torres-Roca JF. Stereotactic body radiotherapy in the management of oligometastatic disease. Cancer Control. 2016;23:21–9.
- Chmura SJ, Winter K, Salama JK, Robinson CG, Pisansky TM, Borges V, et al. Phase I trial of stereotactic body radiation therapy (SBRT) to multiple metastatic sites: a NRG oncology study. Int J Radiat Oncol Biol Phys 2018;102:S68–9.

# Impact of local therapy in metastatic breast cancer

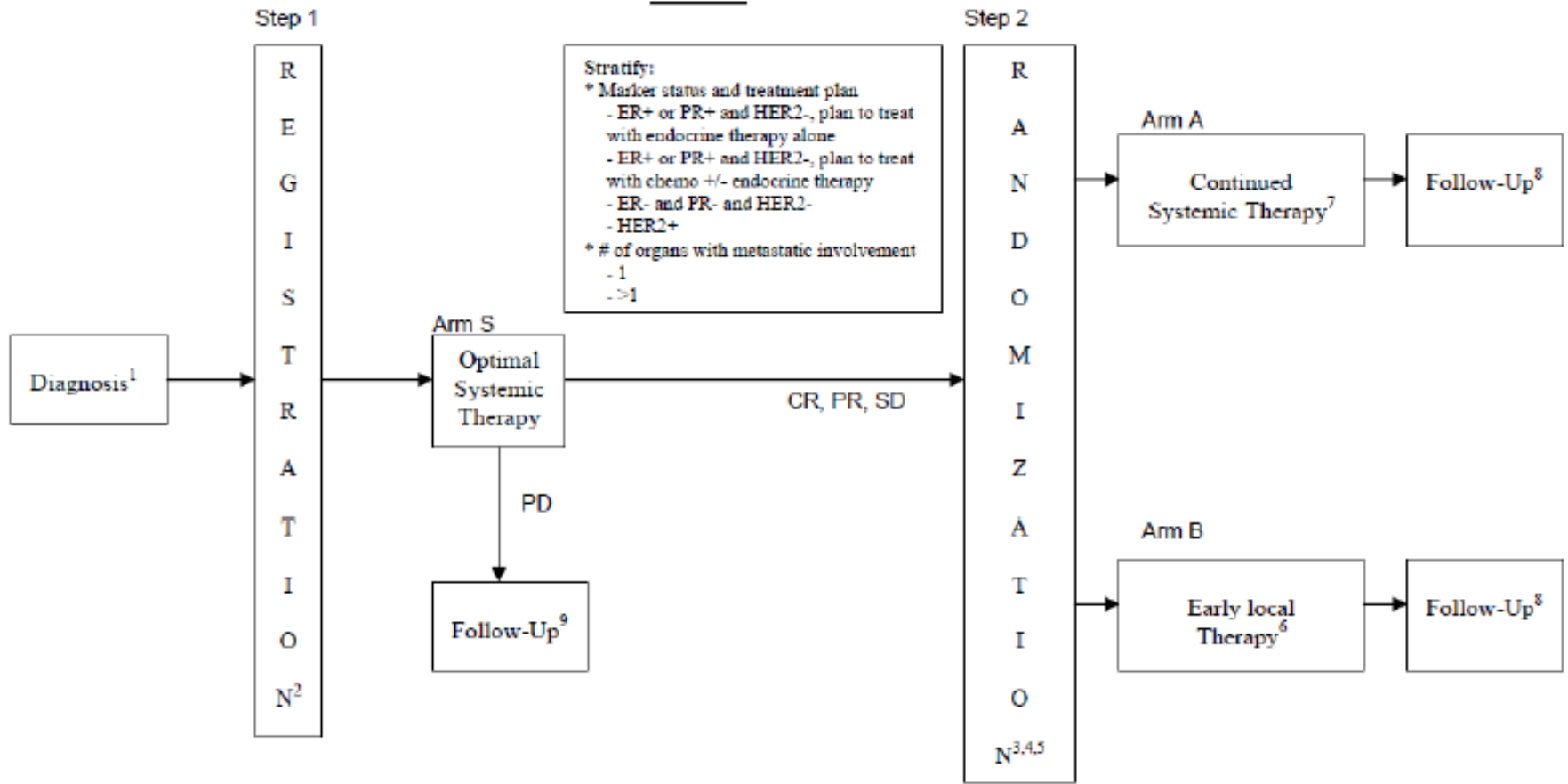


581 Breast Cancer  
patients  
Local RT 320 (55%)  
No RT 261 (45%)

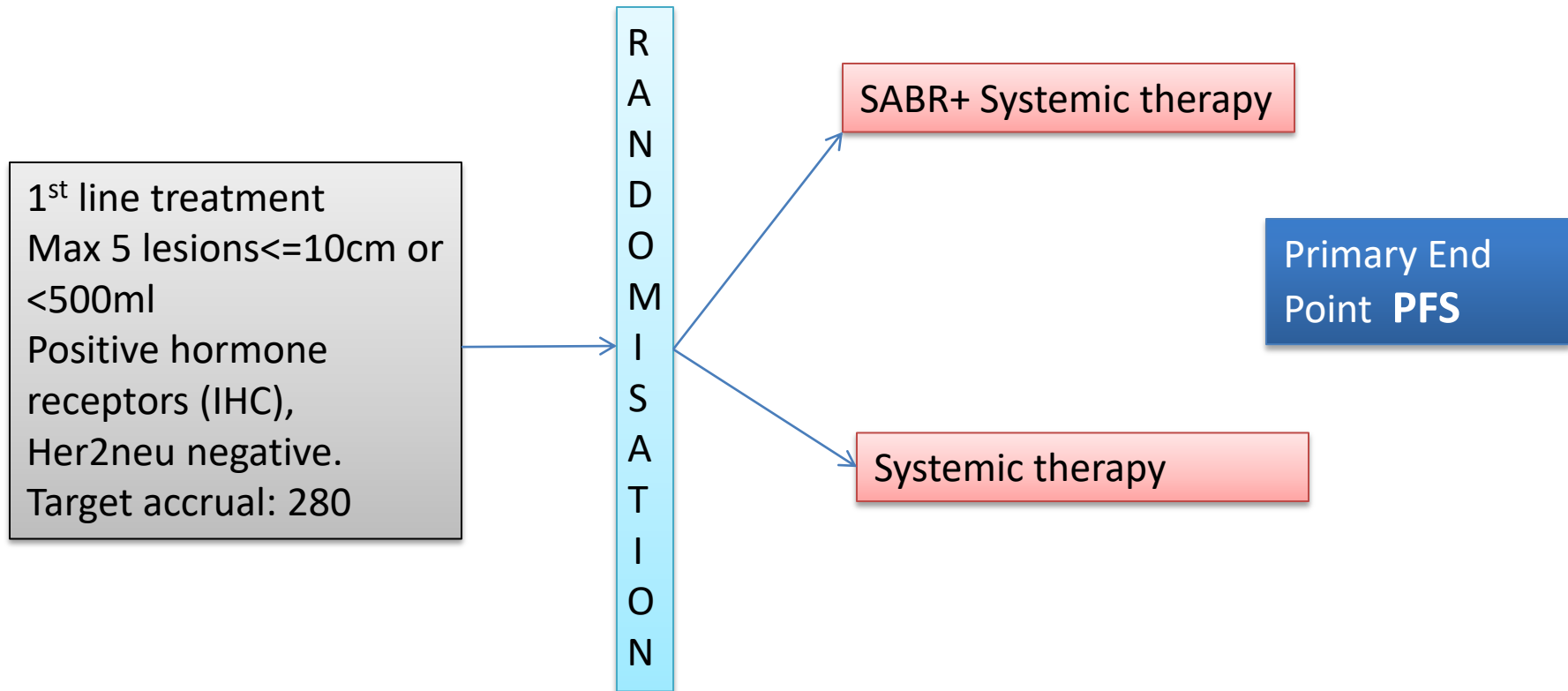


# E2108-ECOG

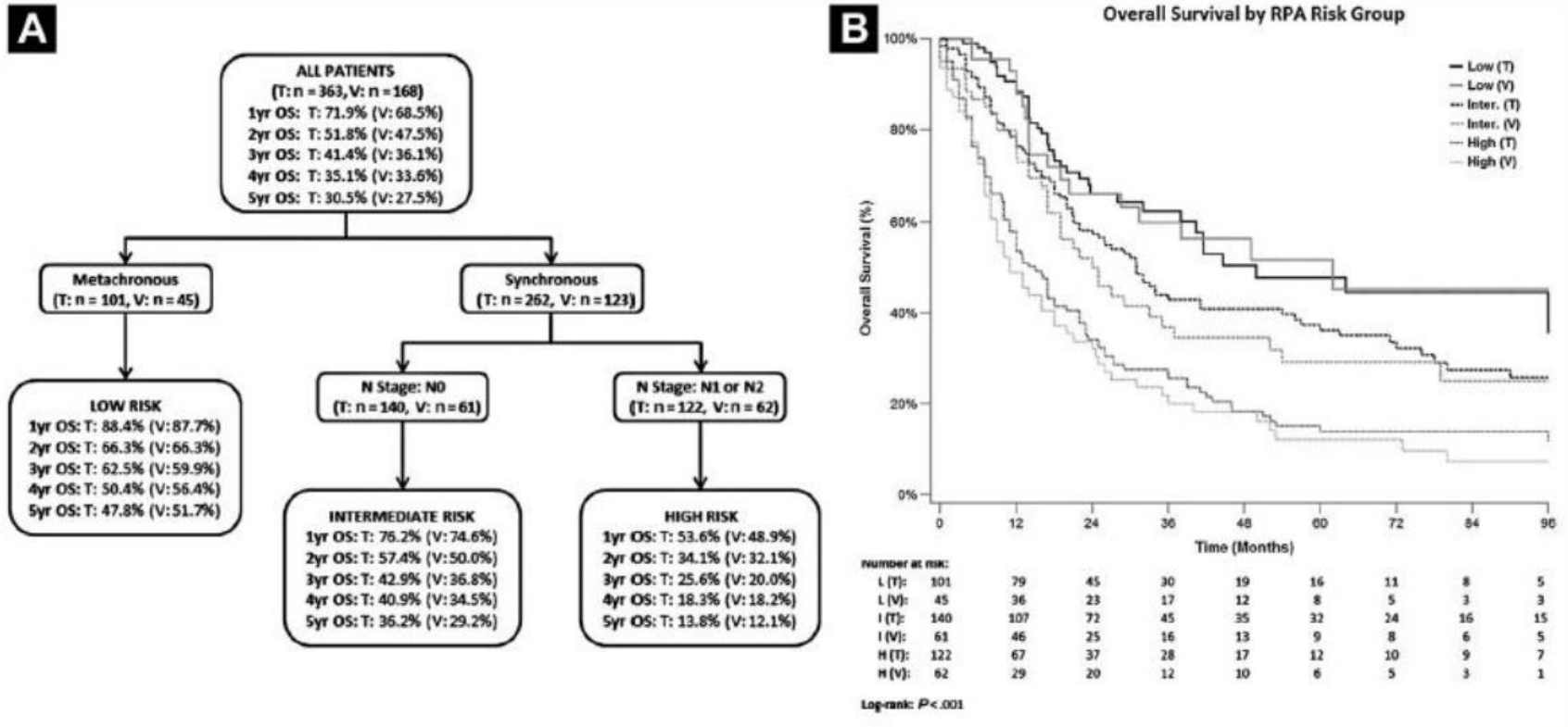
## SCHEMA



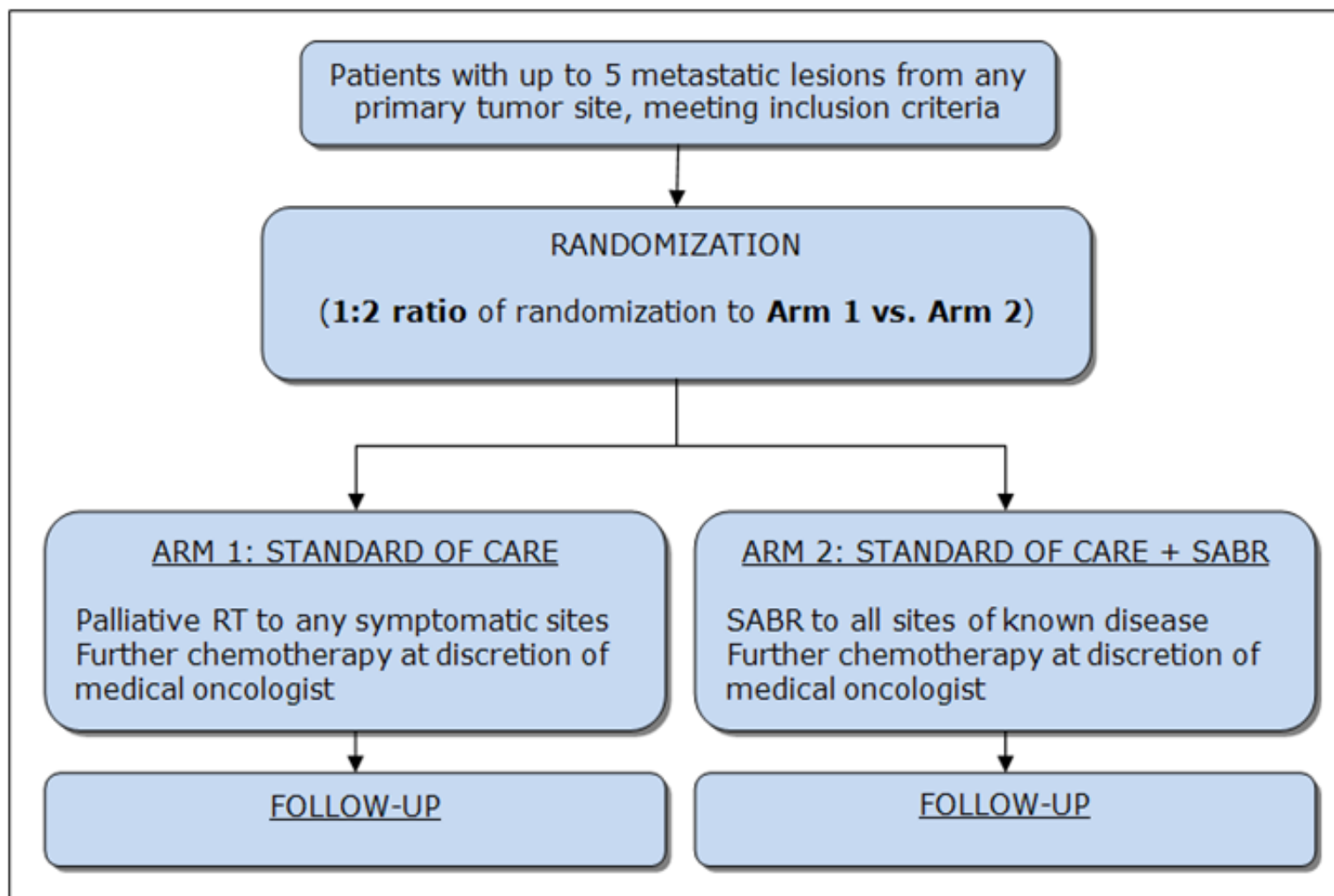
# Stereosein Trial: Impact of ablative RT on Mets (primary breast cancer)



# Experience from Lung



# SABR-COMET



# Endpoints

## **Primary Endpoint**

- Overall Survival

## **Secondary endpoints:**

- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate
- Number of cycles of further systemic therapy
  - Changed to binary variable “Receipt of systemic therapy” (Y/N)

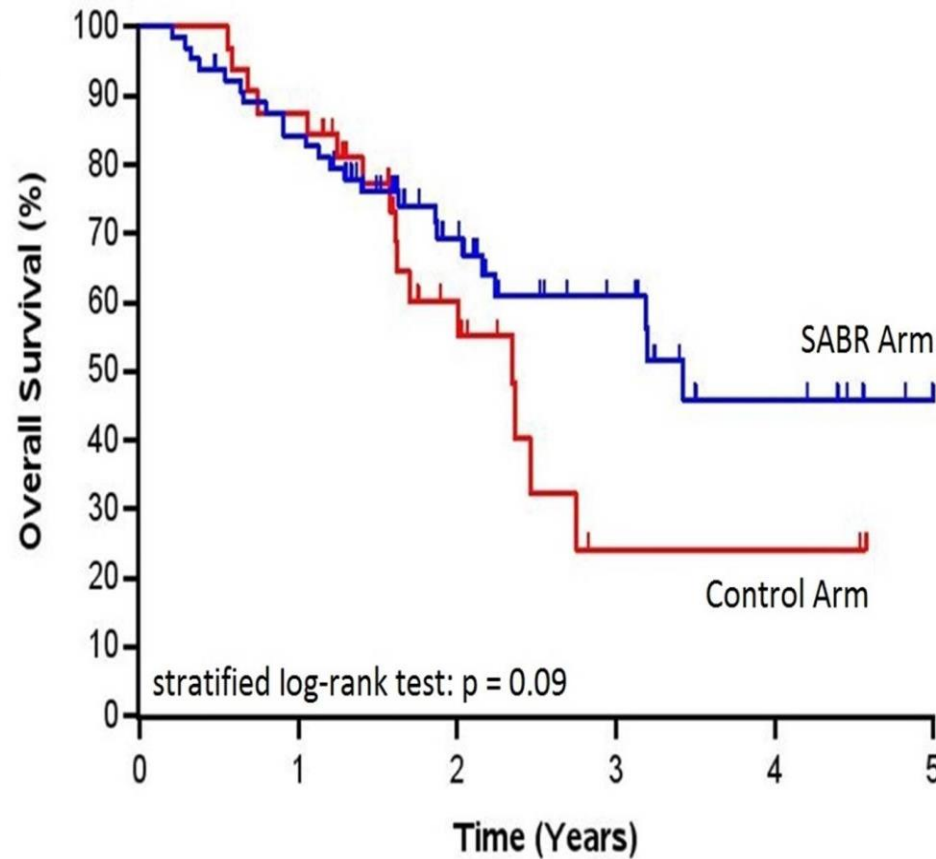
# Patient characteristics- SABR-COMET

<u>Characteristic</u>	<u>All Patients (n=99)</u>	<u>Control Arm (n=33)</u>	<u>SABR Arm (n=66)</u>	<u>p-value</u>
Age – median, (min, max)	68 (43, 89)	69 (44, 87)	67 (43, 89)	0.494
Sex – n(%)				0.772
Male	59 (59.6)	19 (57.6)	40 (60.6)	
Female	40 (40.4)	14 (42.4)	26 (39.4)	
Site of Original Primary				0.204
Tumor – n(%)	18 (18.2)	5 (15.2)	13 (19.7)	
Breast	18 (18.2)	9 (27.3)	9 (13.6)	
Colorectal	18 (18.2)	6 (18.2)	12 (18.2)	
Lung	16 (16.2)	2 (6.1)	14 (21.2)	
Prostate	29 (29.3)	11 (33.3)	18 (27.3)	
Other				

<u>Characteristic</u>	<u>All Patients</u> <u>(n=99)</u>	<u>Control</u> <u>Arm</u> <u>(n=33)</u>	<u>SABR Arm</u> <u>(n=66)</u>	<u>p-value</u>
<b>Number of Metastases –</b>				0.591
<b>n(%)</b>	42 (42.4)	12 (36.4)	30 (45.5)	
<b>1</b>	32 (32.3)	13 (39.4)	19 (28.8)	
<b>2</b>	18 (18.2)	6 (18.2)	12 (18.2)	
<b>3</b>	4 (4.0)	2 (6.1)	2 (3.0)	
<b>4</b>	3 (3.0)	0 (0.0)	3 (4.6)	
<b>5</b>				
<b>Location of Metastases –</b>				0.181
<b>n(%)</b>	9 (4.7)	2 (3.1)	7 (5.5)	
<b>Adrenal</b>	65 (34.0)	20 (31.3)	45 (35.4)	
<b>Bone</b>	19 (10.0)	3 (4.7)	16 (12.6)	
<b>Liver</b>	89 (46.6)	34 (53.1)	55 (43.3)	
<b>Lung</b>	9 (4.7)	5 (7.8)	4 (3.2)	
<b>Other</b>				

# Overall survival

A



## Median OS

Control Arm: 28 months  
(95% CI: 19-33 months)

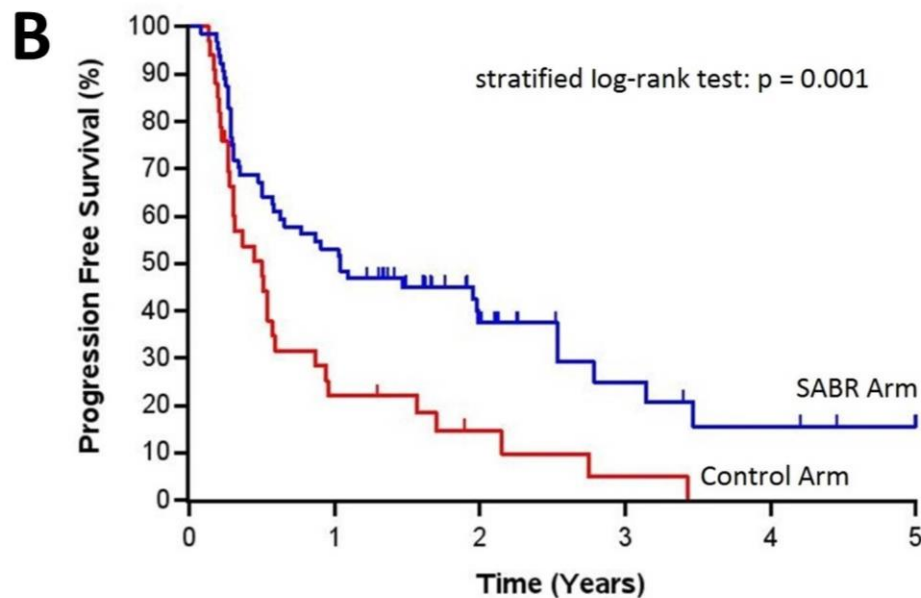
SABR Arm: 41 months  
(95% CI: 26 months to  
'not reached')

### Number at risk:

Control	33	28	12	2	2	
SABR	66	53	29	15	7	1



# Progression free survival



## Number at risk:

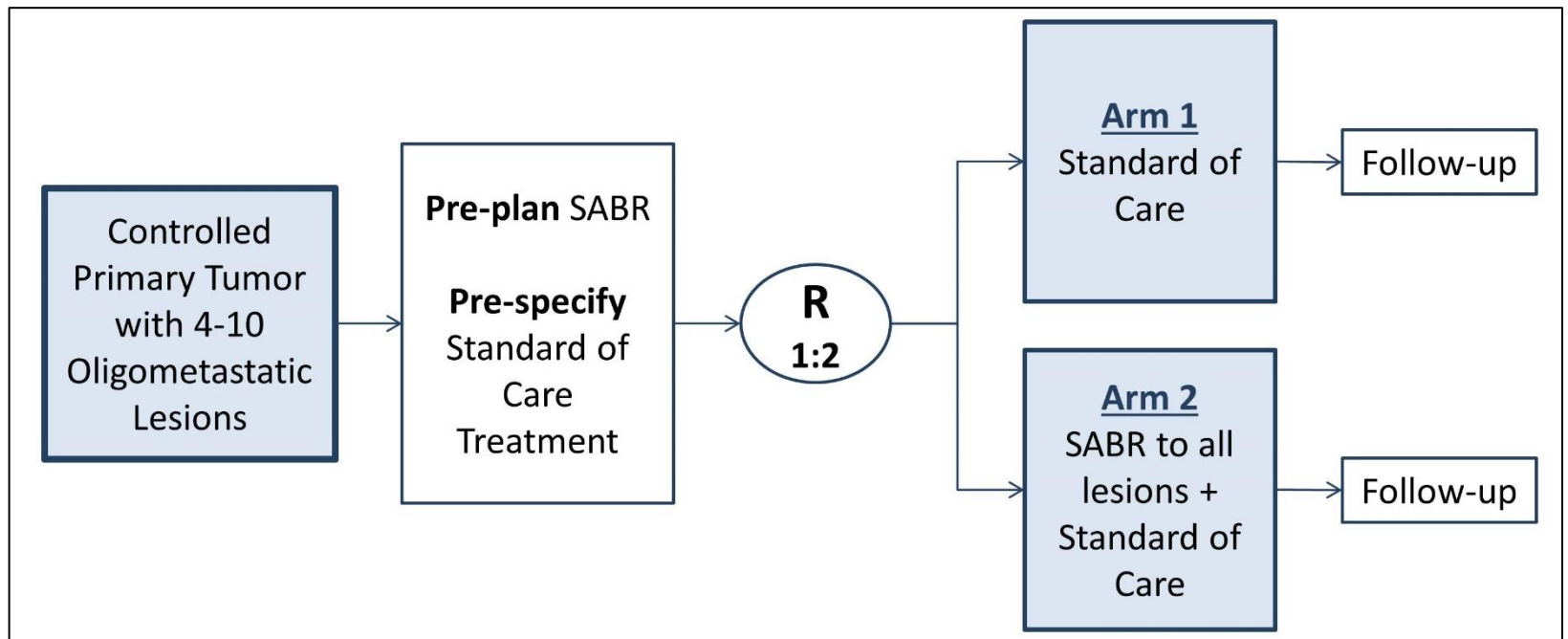
Control	33	7	3	1		
SABR	66	34	15	6	3	1

## Median PFS

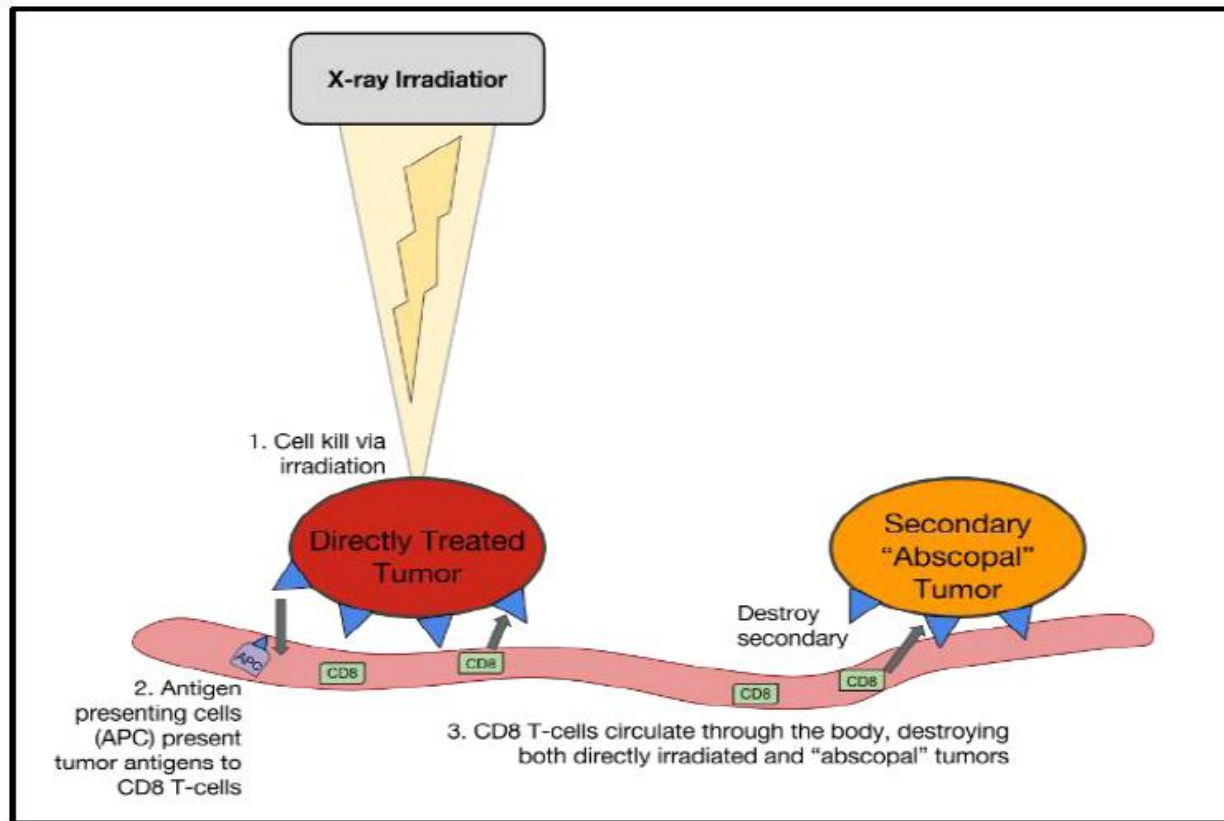
Control Arm: 6 months  
(95% CI: 3.4-7.1 months)

SABR Arm: 12 months  
(95% CI: 6.9-30 months)

# SABR-COMET 10



# Abscopal effect of radiation



# Ablative Radiotherapy + Immunomodulator

**A**

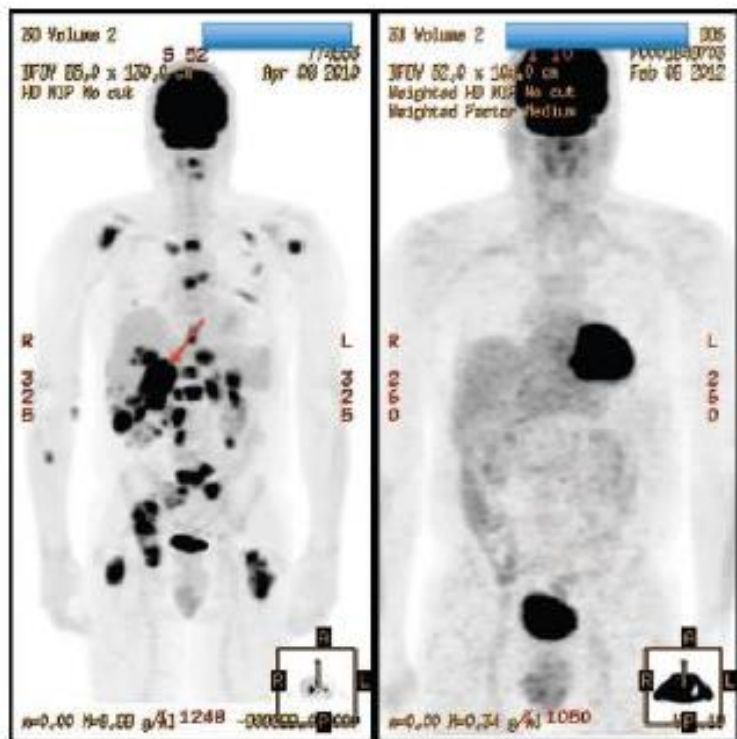
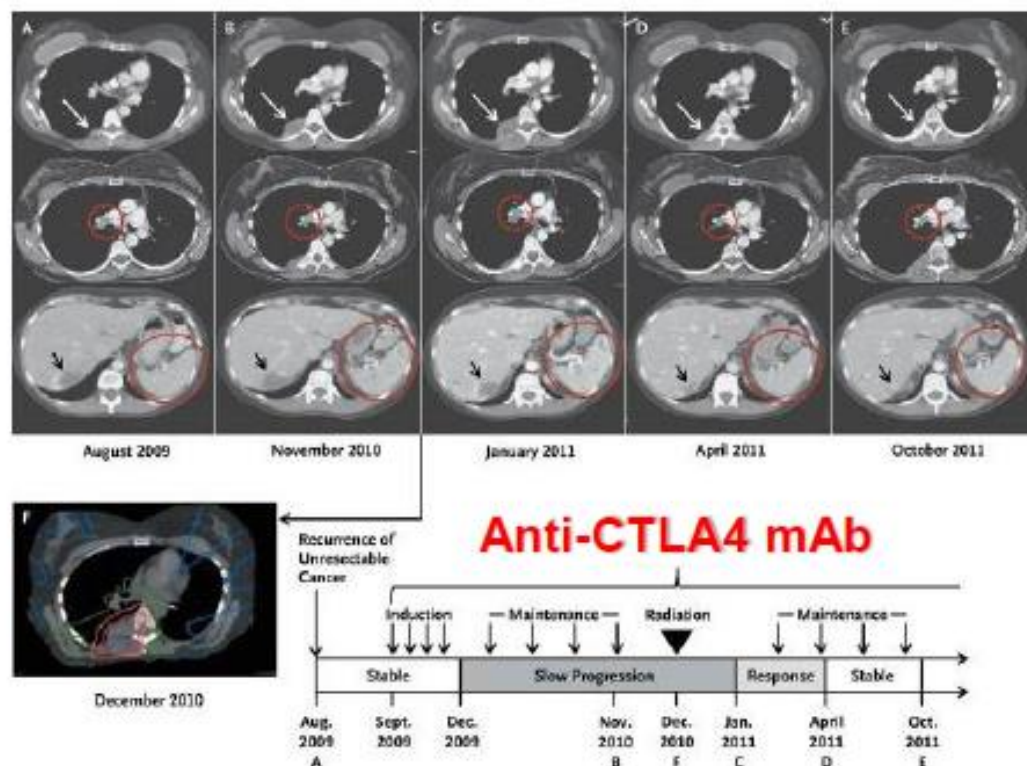


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

**B**



Postow, NEJM2012, Hinicker, NEJM2012

# Randomized evidence of ablative therapy

Study	Primary	Number	Protocol	Results
MDACC/ Colorado Trial: Phase 2 (Gomez, Lancet Oncology 2016)	NSCLC	49	Local consolidation Vs maintenance therapy or observation	PFS better in SABR + mChemo arm. (p=0.0054)
UT Southwestern Trial, Phase 2 (Iyenger et al JAMA Oncol 2018)	NSCLC	29	mChemo Vs SABR+ mChemo	PFS better in SABR+ mChemo (p=0.01)
STOMP Trial Phase 2 (Ost et al J Clin Oncology 2018)	Prostate	62	Surveillance vs metastatic directed therapy	PFS better in LCT arm (p=0.0054)
ORIOLE (Radwan et al BMC Cancer 2017)	Prostate	54	Observation Vs SABR	PFS better in SABR arm (p=0.03)

# Selection of favourable candidates

- Tumour Biology and growth kinetics.
- Clinical scenario.
  - I. Oligometastasis at presentation.
  - II. Residual oligometastasis after systemic therapy.
  - III. Relapsed oligometastases after curative locoregional therapy.

# Brain Metastasis

- Most common intracranial neoplasm.
- Most common intracranial metastatic site is brain parenchyma.
- Advances in systemic cancer management has lead to higher incidence of brain metastasis.
- Advanced imaging techniques and early suspicion has made it possible to detect oligo brain metastasis.

# Primaries

- Lung 39-56%
- **Breast 13-30%**
- Melanoma 6-11%
- Renal 2-6%
- Colorectal 3-4%



# Definitions

- Single Brain Metastasis
- Solitary Brain Metastasis
- Oligo Brain Metastasis.

# Conventional Management of Brain Metastases

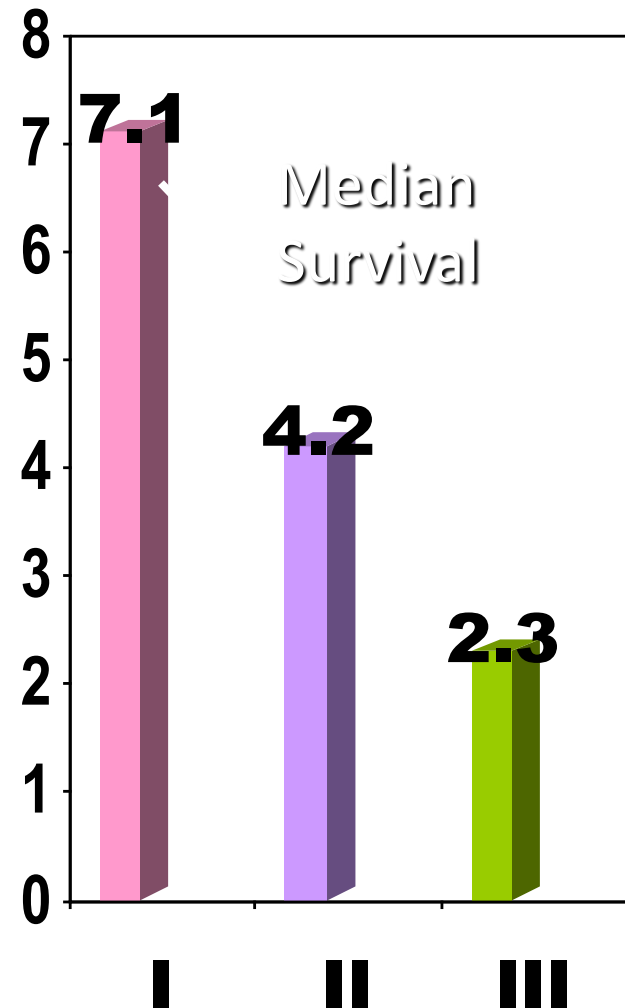
- Medical decompression → Steroids, Mannitol, Glycerol
- 1-3 lesions, resectable → Surgical resection + Whole Brain Radiotherapy
- Multiple/unresectable lesions → Whole Brain Radiotherapy

# Decision of Management

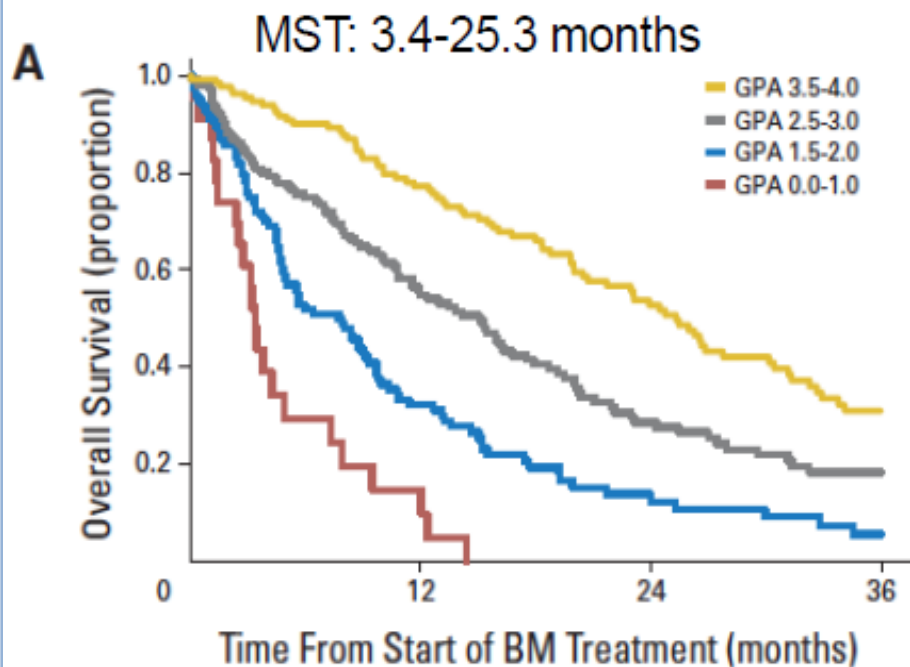
- Performance status
- Nature of metastasis
- Primary site
- Extracranial disease status
- Expected survival

# RTOG- Classes

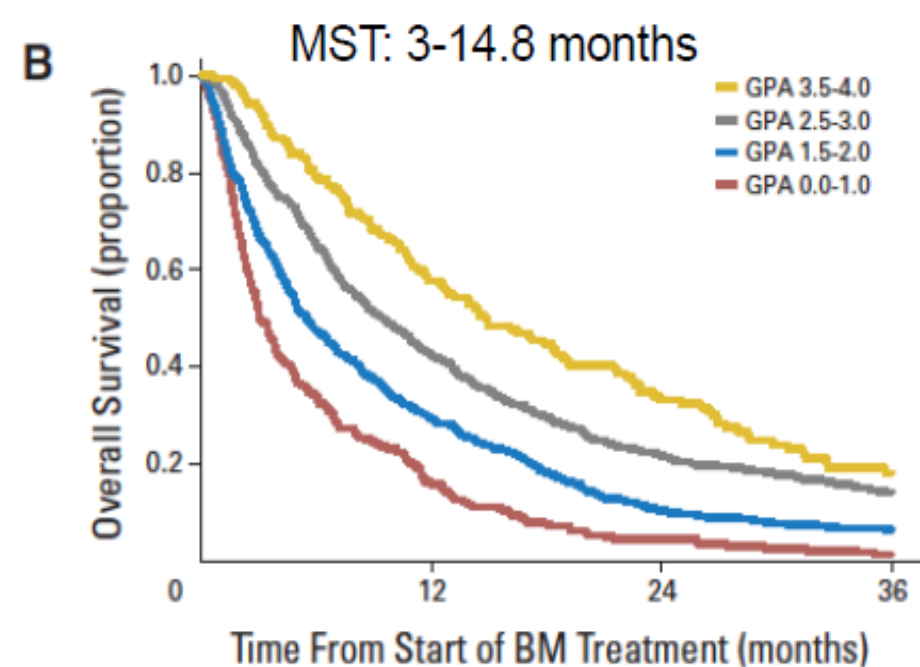
- Class I
  - < 65 years, KPS  $\geq$  70,
  - controlled primary
  - no extracranial mets
- Class II-Rest
- Class III-KPS <70



	KPS	Age	Number of mets	Extra-cranial mets	Tumour subtype
Lung	✓	✓	✓	✓	-
Breast	✓	✓	-	-	✓
Melanoma	✓	-	✓	-	-
Renal	✓	-	✓	-	-
GI	✓	-	-	-	-



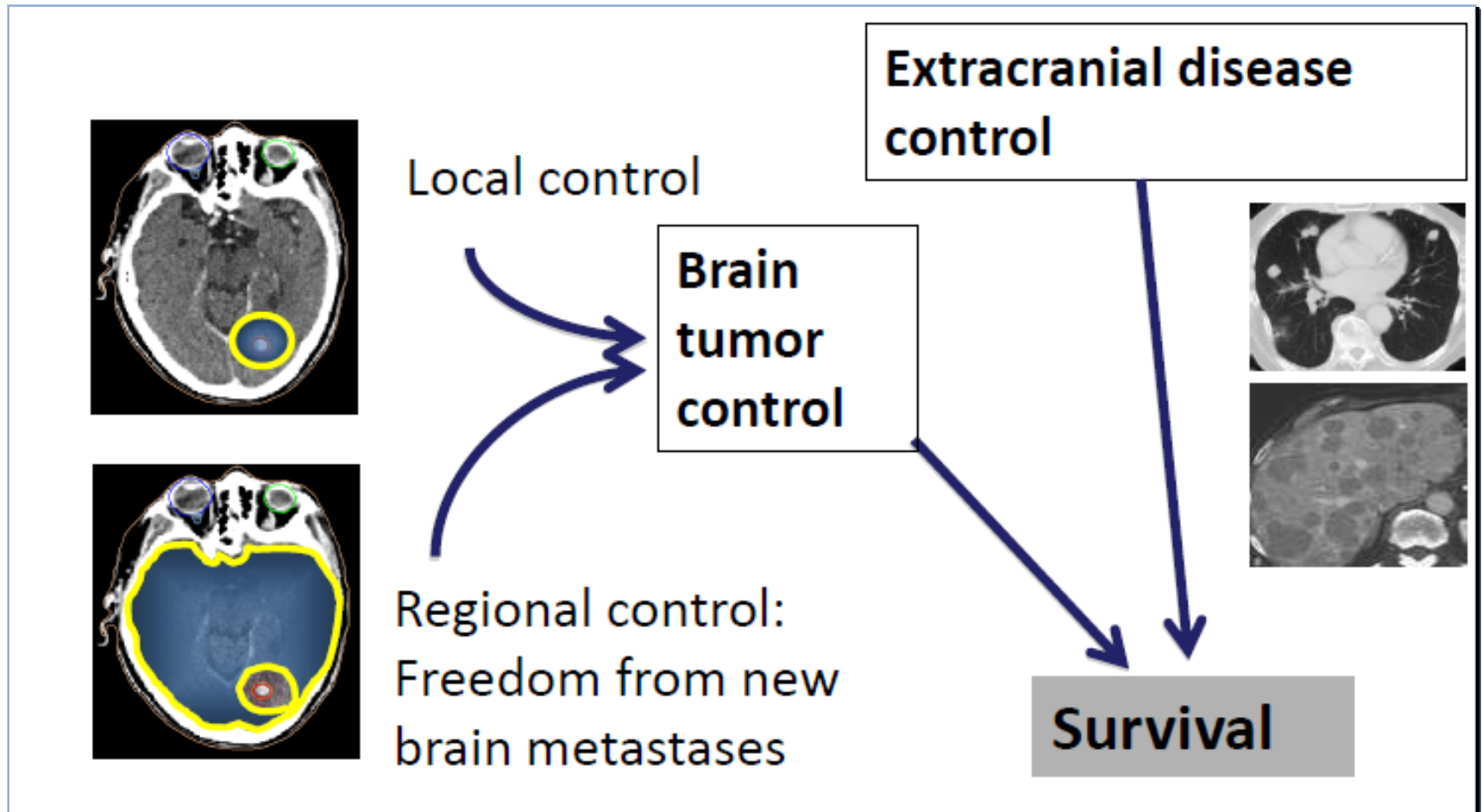
Breast cancer



NSCLC

Diagnosis-specific GPA

# Survival in Brain Metastasis



# What is New?

- Expanding definition of oligometastases [from 1-3 lesions with controlled primary to .....?]
- WBRT increasingly being replaced by focal RT (SRS/SRT)
- Surgical resection increasingly being replaced by focal RT (SRS/SRT)
- Emerging role of post-operative focal RT (SRS/SRT)
- Emergence of drugs which can cross the BBB
- Lack of efficacy of WBRT in patients with poor PS

# Evolving end points

- Survival
- Brain tumour control
- Quality of life
- Cognitive function



# WBRT

- Pros:
- Most chemotherapy drugs do not cross BBB
- Metastases to CNS can be multifocal
- Reduced steroid-dependence
- Cons:
- Cognitive decline
- Lack of survival benefit

- For single brain metastases, 2 out of 3 trials have shown surgical resection+ RT has OS & LC advantage over RT alone.

**S+RT vs  
RT**

Trial	N	Endpoint	Surgery +RT	RT	p value	Ref
Patchell et al (University of Kentucky)	48	OS*	40 weeks	15 weeks	<0.01	N Engl J Med 1990;322:494-500.
		Local failure	20%	52%	<0.02	
Noordjik et al (Dutch)	63	OS*	10 months	6 months	0.04	Int J Radiat Oncol Biol Phys 1994; 29:711-17.
		FIS*	7.5 months	3.5 months	0.06	
Mintz et al (Canadian)	84	OS*	5.6 months	6.3 months	NS	Cancer 1996;78:1470-76.
		FIS %	32%	32%	NS	

# Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

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

Lancet Oncol 2017

S+SRS vs  
S

- Phase III RCT
- N=132
- 1-3 metastases; resection cavity  $\leq 4$ cm
- Post-op SRS (N=64) vs observation (N=68)
- SRS done within 30 days of resection; dose=12-16Gy
- Median FU =11.1 months
- **Median 12-month freedom from local recurrence was significantly better for SRS (72%) vs observation (43%)**

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

*Lancet Oncol 2017*

**S + SRS vs  
S+WBRT**

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

- **Phase III RCT**
- N=194
- One resected brain metastases
- Resection cavity =<5cm diameter
- **SRS** (12-20Gy) [N=98]

vs

**WBRT**[N=96](30Gy/10#/2weeks  
OR 37.5Gy/15#/3 weeks)

- **Significantly longer cognitive –deterioration free survival with SRS** (median 3.7 vs 3 months)
- **Significantly poorer surgical bed control at 6 months with SRS (80.4%) vs WBRT (87.1%)**
- **Median OS similar :12.2 months (SRS) vs 11.6 months (WBRT)**

## S vs SRS

- No randomized trials
- Similar LC rates 80-90% (when either one is combined with WBRT)

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

## SRS + WBRT vs WBRT

- 3 randomised trials (2 small/non-standard).
- RTOG 9508 → N=333: **OS** benefit for **single** unresectable brain met (no breast cancer patients analysed in this subgroup), LC benefit for 2-3 brain mets, steroid-usage lowered with SRS.
- Subset analysis shows **OS** benefit for single brain met, NSCLC, RPA class I, tumor <2cm.
- For breast cancer patients with 1-3 brain metastases, presence of extracranial disease, TNBC & having >1 brain metastasis predicts for worse OS.

# Phase 3 Trials of Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis

Arjun Sahgal, MD,<sup>\*</sup> Hidefumi Aoyama, MD, PhD,<sup>†</sup> Martin Kocher, MD,<sup>‡</sup>  
Binod Neupane, PhD,<sup>§</sup> Sandra Collette, PhD,<sup>||</sup> Masao Tago, MD,<sup>¶</sup>  
Prakesh Shah, MD,<sup>#</sup> Joseph Beyene, PhD,<sup>§</sup> and Eric L. Chang, MD<sup>\*\*,††</sup>

- Meta-analysis of 3 randomised trials
- N=364
- SRS alone 51%;  
SRS+WBRT 49%

## SRS + WBRT vs SRS

- For patients <50 years age with 1-4 brain metastases, SRS has OS advantage over SRS+WBRT.
- Patients with single metastases had significantly better OS than with 2-4 metastases.
- Local control significantly better with WBRT in all age groups.

# Immediate vs delayed RT for asymptomatic oligo brain metastases

- Korean trial
- Metastatic NSCLC; 1-4 asymptomatic brain metastases
- N=105
- SRS (N=49) followed by chemotherapy vs upfront chemotherapy (N=49)
- No difference in OS / time to CNS progression

*Annals of Oncology* 26: 762–768, 2015  
doi:10.1093/annonc/mdu584  
Published online 23 December 2014

## **A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer**

S. H. Lim<sup>1</sup>, J. Y. Lee<sup>1</sup>, M.-Y. Lee<sup>1</sup>, H. S. Kim<sup>1</sup>, J. Lee<sup>1</sup>, J.-M. Sun<sup>1</sup>, J. S. Ahn<sup>1</sup>, S.-W. Um<sup>2</sup>, H. Kim<sup>2</sup>, B. S. Kim<sup>3</sup>, S. T. Kim<sup>4</sup>, D. L. Na<sup>5</sup>, J. Y. Sun<sup>6</sup>, S. H. Jung<sup>7,8</sup>, K. Park<sup>1</sup>, O. J. Kwon<sup>2</sup>, J.-I. Lee<sup>3</sup> &



# Neurocognitive decline

- Patients with brain metastases tend to have reduced neurocognition at the time of presentation, which is frequently not evaluated;
- Disease-progression, both intra- and extra-cranially, will negatively skew population distributions of neurocognitive scores;
- The effects of therapeutic interventions, such as chemotherapy, anticonvulsants, steroids, opiates, etc., remain inadequately documented.



Contents lists available at ScienceDirect

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journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)

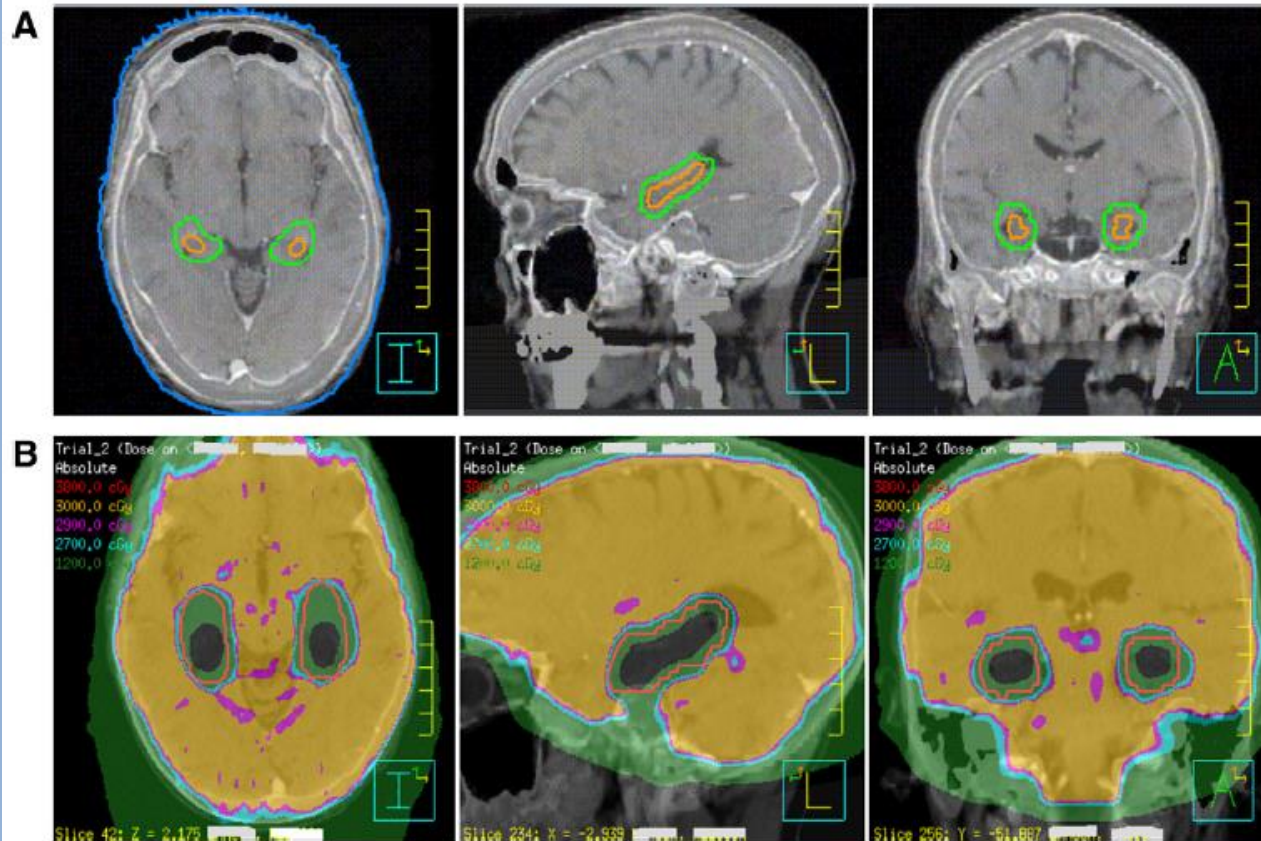


Review

## Why avoid the hippocampus? A comprehensive review

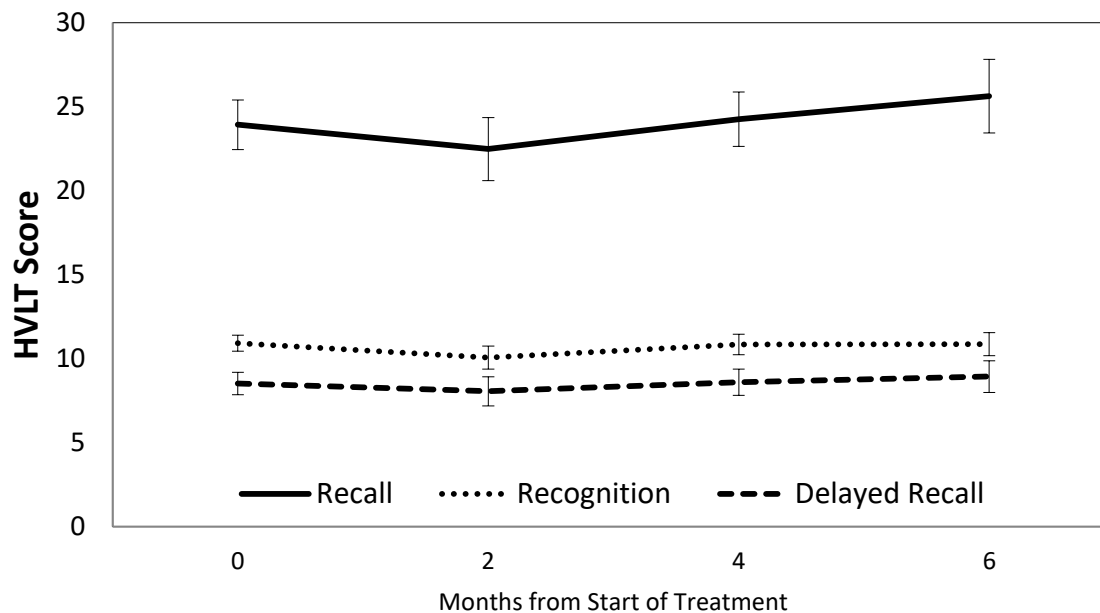
Vinai Gondi <sup>a,\*</sup>, Wolfgang A. Tomé <sup>a,b</sup>, Minesh P. Mehta <sup>a</sup>

<sup>a</sup>Department of Human Oncology; and <sup>b</sup>Department of Medical Physics, University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA



# RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions)
- Credentialing and central review of hippocampal contouring and IMRT planning

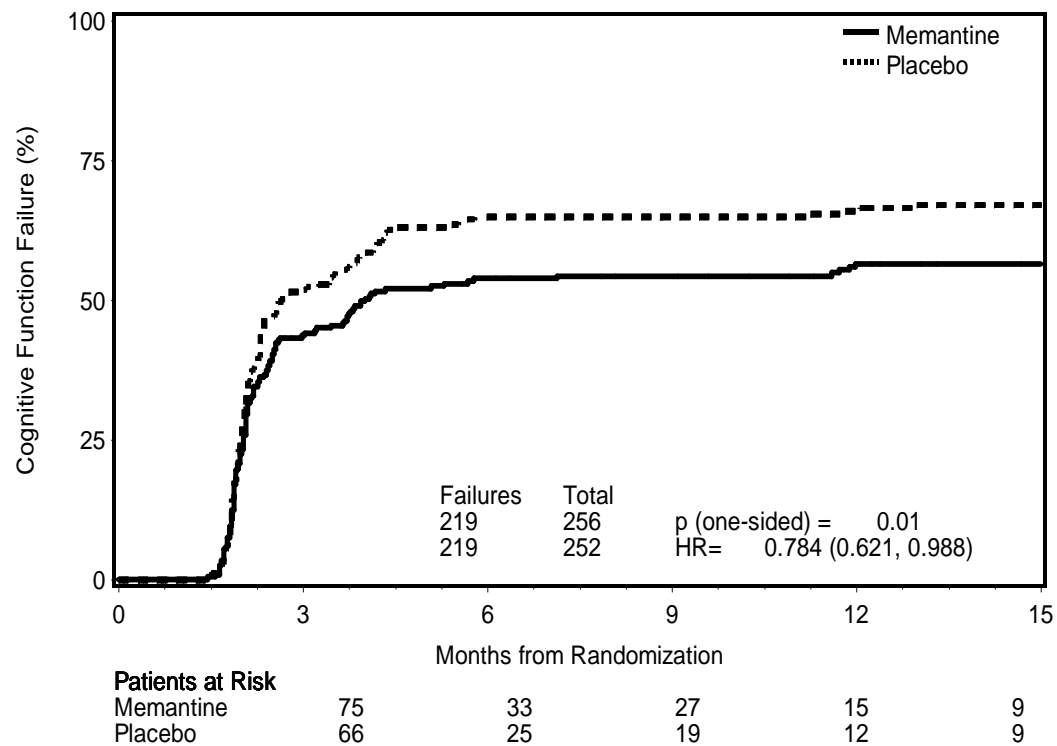


- **Mean decline in HVLt-Delayed Recall from baseline to 4 months: 7.0% (95% CI: -4.7-18.7%)**
- Significant compared to historical control: 30% ( $p=0.0003$ )

**Need phase III data for level I evidence**

# RTOG 0614

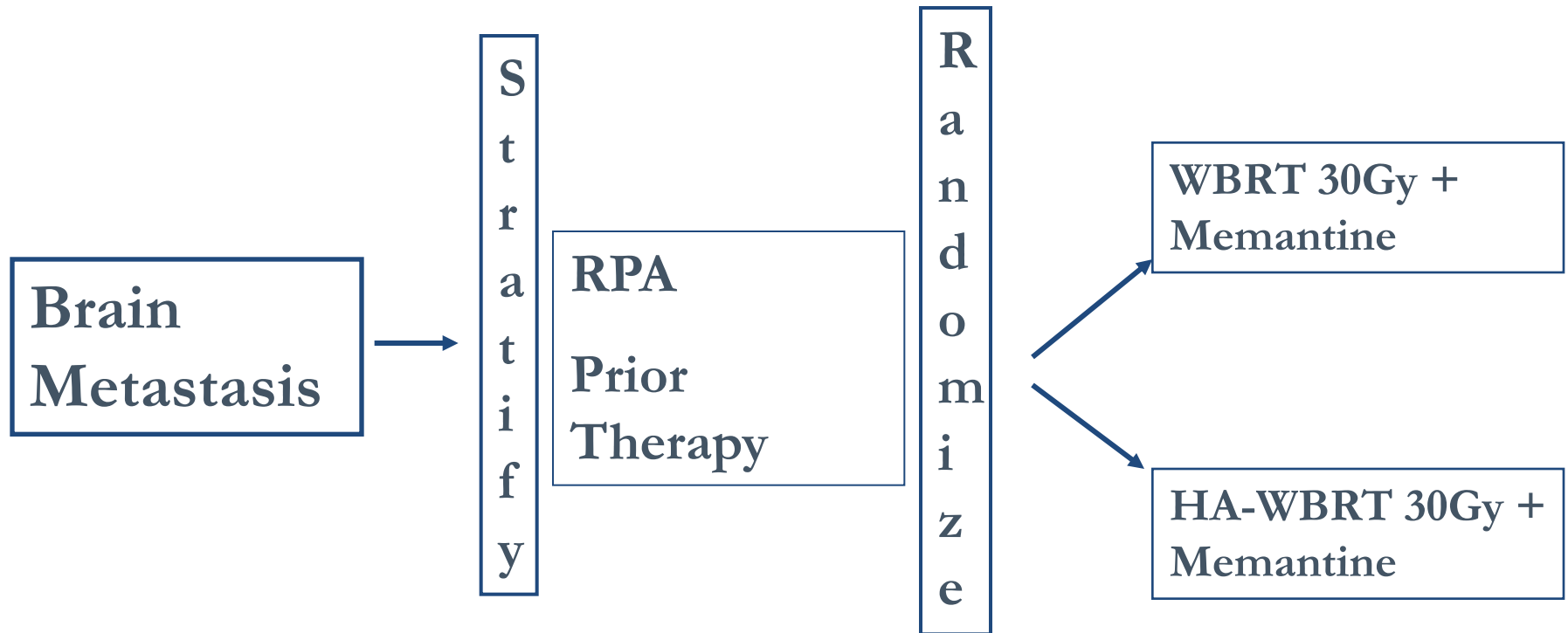
- Phase III trial of WBRT with or without memantine



**Memantine during WBRT became standard of care**

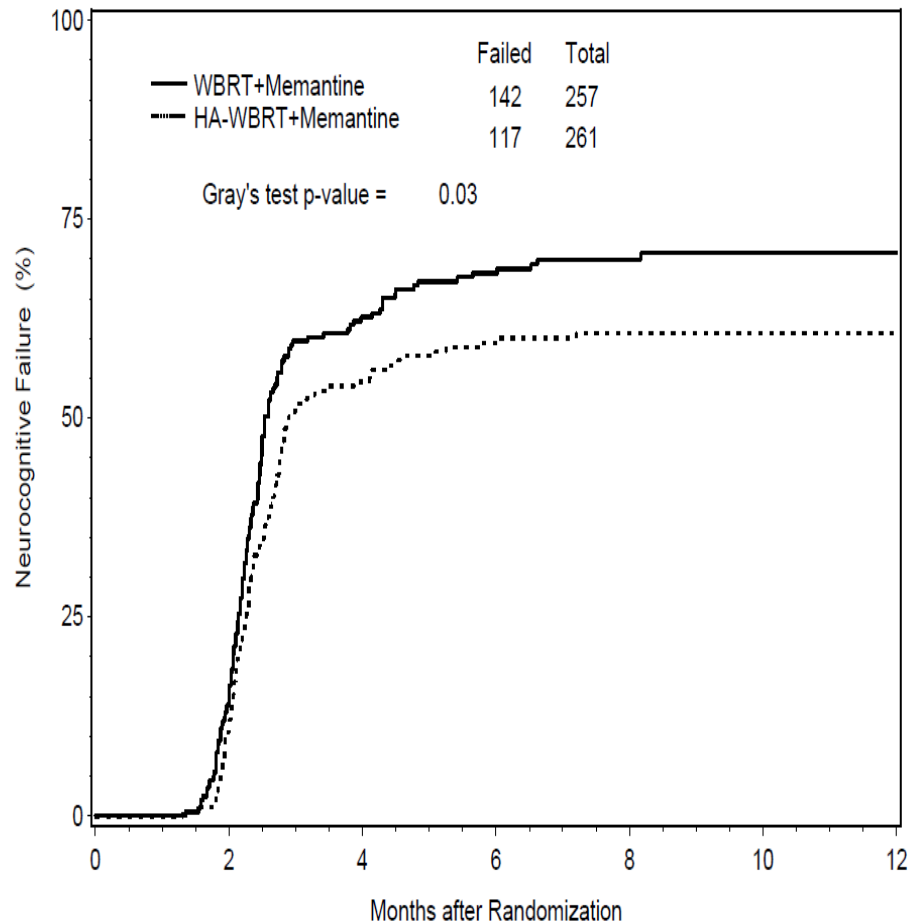
# NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS $\geq$ 70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing



# Primary Endpoint

- Hippocampal avoidance prolongs time to cognitive function failure
  - 6 months:
    - HA-WBRT+memantine 59.5%
    - WBRT+memantine: 68.2%
    - Hazard ratio = 0.76  $p=0.03$
  - Separation of the curves starting at 3 months and maintained through the follow-up period
  - Median follow-up for alive patients: 7.90 months



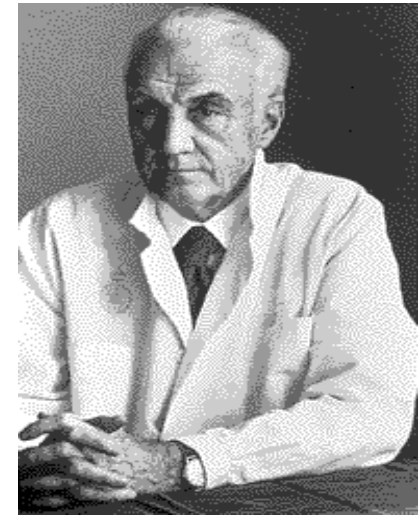
## Patients at Risk

WBRT+Memantine	257	133	34	18	8	6	4
HA-WBRT+Memantine	261	124	40	25	18	17	11

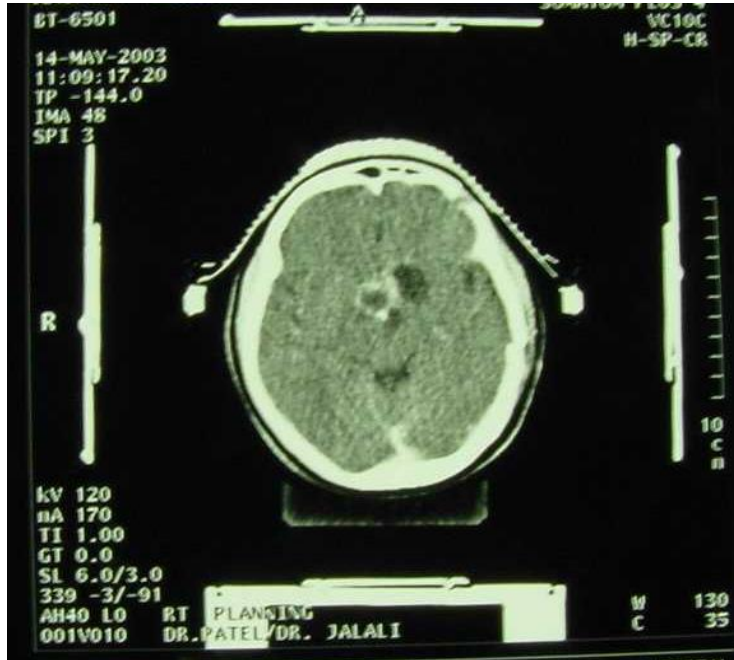
# Dose protocols-Brain Metastases

- SRS: (RTOG 90-05)
- FSRT:
- <2cm: 24Gy
- 2.1-3cm: 18Gy
- 3.1-4cm: 15 Gy
- 30Gy/5#
- 40Gy/10#
- Target=tumour+ small margin (1-2 mm)
- Unlike conventional RT, dose distribution is deliberately made inhomogeneous, by covering periphery of tumor by 50-80%, rather than 95%. This ensures high dose at the centre of the tumour as well as rapid fall off of dose beyond the periphery of the tumour.

# Frame based stereotaxy



*Stereos - solid*



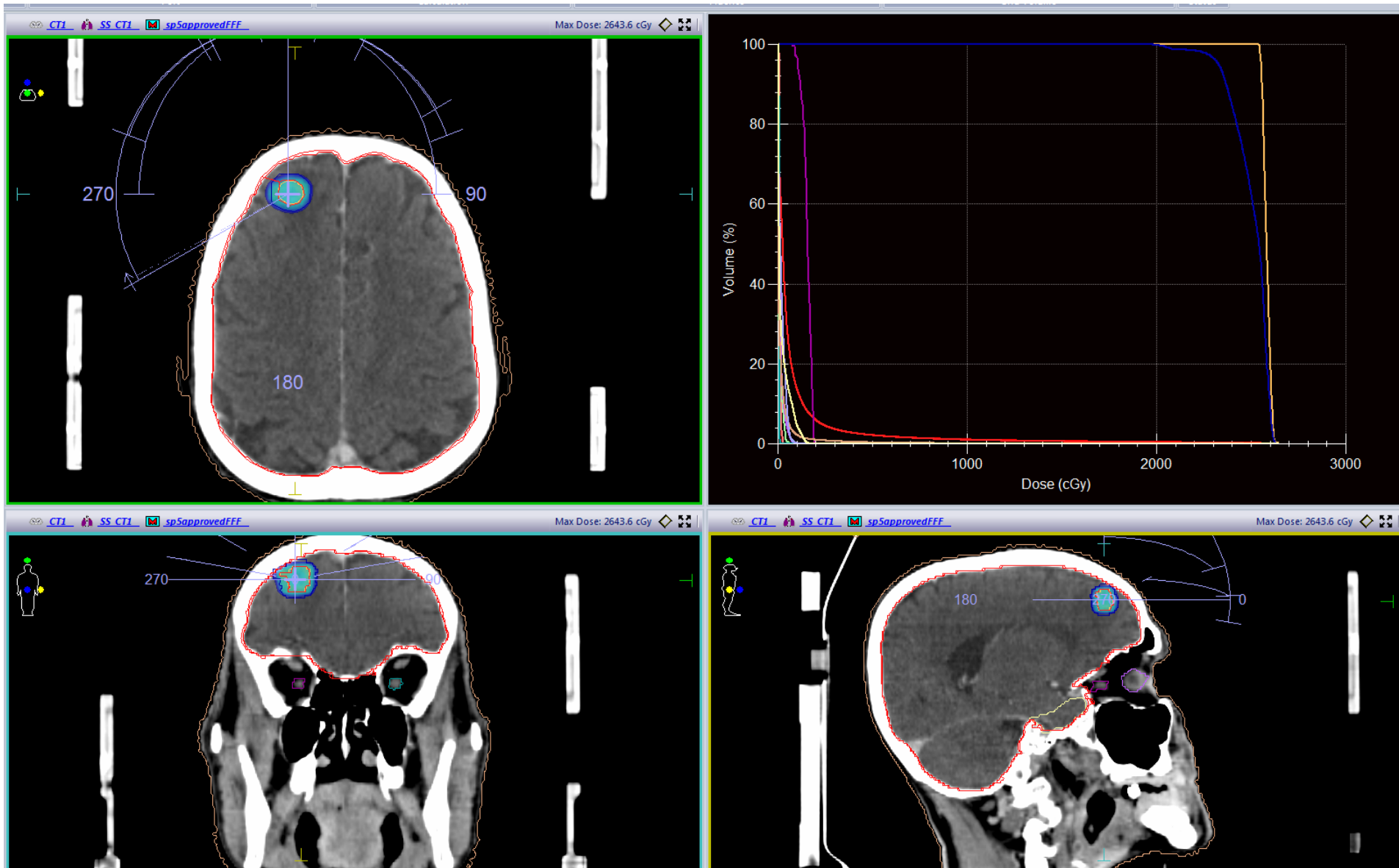
- Gamma knife
- **Modified Linacs**
- Proton beam



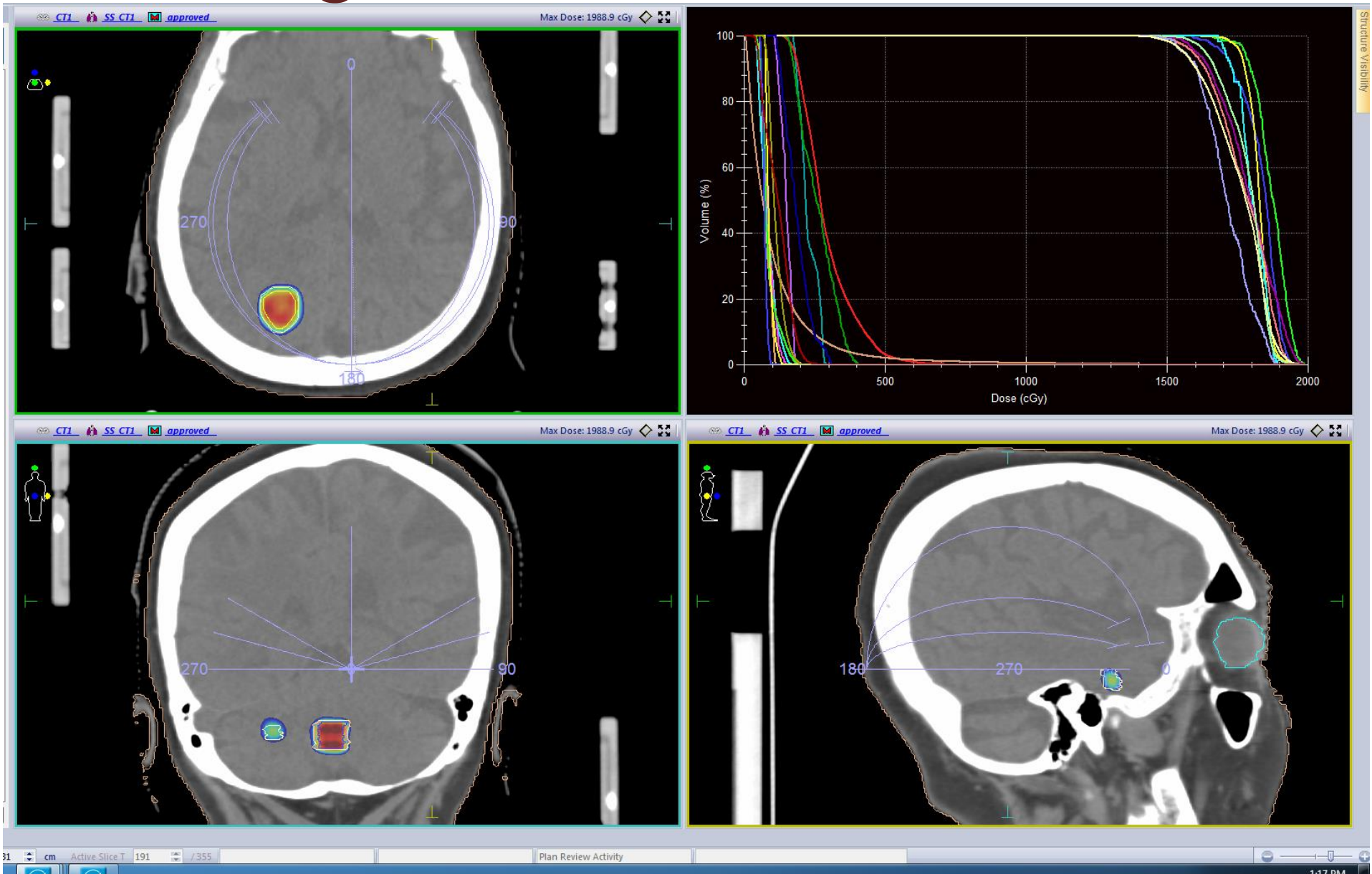
Firm immobilisation (stereotactic frames)  
Treatment planning (dedicated workstations)  
precise treatment delivery (high QA)



# Frameless stereotaxy in a solitary met



# Frameless stereotaxy in oligometastatic disease



**Is radiation dose escalation clinically relevant in patients with multiple BM?**

**Toxicity? Efficacy?**

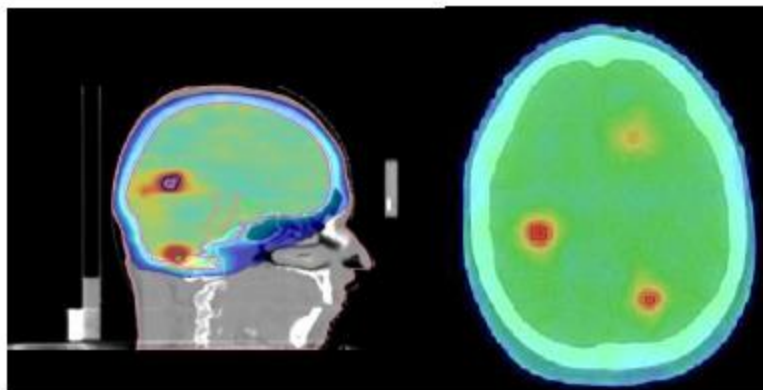


EORTC 22111-26111

Whole brain radiotherapy with or without synchronous integrated boost in patients with 2 to 5 brain metastases. A randomized Phase III Study of the EORTC ROG and BTG

PI: B. Baumert, S. Erridge, F. Lagerwaard

## Specific dosimetry for WBRT



Integrated WBRT + boost (VMAT)

New delivery techniques allow for more complex tailored planning, including **Simultaneous Integrated Boost (SIB)** on oligometes

20 Gy/5 fr WBRT; 40 Gy/5 fr SIB

- Dosimetric advantages (steeper dose gradients)
- Logistic advantages (no separate procedures)
- Patient tolerance advantages (outpatient, frameless, delivery ~5 minutes)



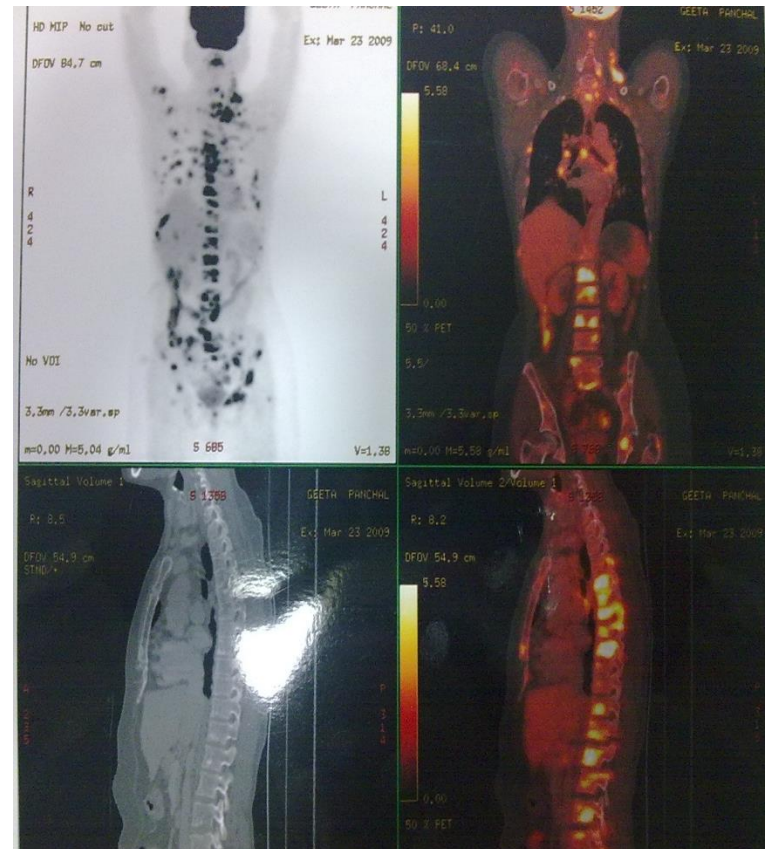


# Summary of trials

	Outcome	Level of evidence
SRS+WBRT Vs WBRT alone	Improve survival in single metastatic disease with KPS $\geq$ 70	Level I
	Improve local control	Level II
	Improve survival in multiple metastatic disease	Level III
SRS Vs WBRT+SRS	Equivalent survival	Level II
	improves cognitive function	Level II
	Higher out of field metastatic potential	Level II
Surgery+WBRT Vs SRS+/- WBRT	Equivalent survival in <3cm	Level II
SRS Vs WBRT	Better than WBRT up to 3 mets in survival	Level III
WBRT with hippocampal sparing +memantine	Delayed cognitive decline	Level II+

# Bone Metastasis

- **Most common** site of metastasis after lung & liver
- **Most common** malignancy affecting bone
- Prostate, Breast, Lung Most Common (50-70%)
- Thyroid, Bladder, Kidney (15-30%)
- 20% of **workload** in RT center
- 60-65% of all palliative cases



# Symptoms/Complications Related to Bone Metastases

- Pain
- Pathological fracture
- Spinal cord compression
- Hypercalcaemia

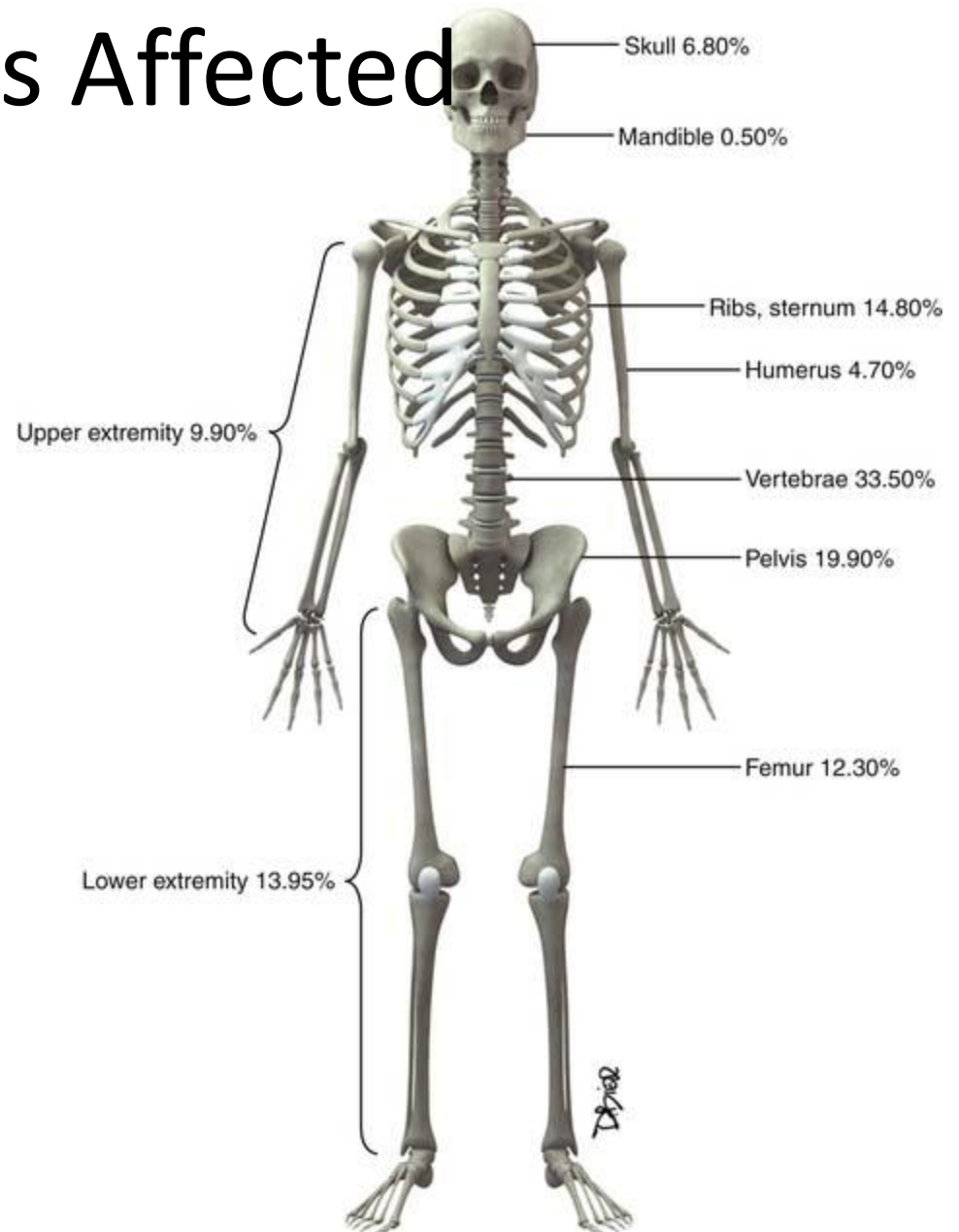


poor QOL



# Bones Affected

- Spine (**Dorsal > Lumbar > Cervical**)
- Pelvis
- Ribs
- Proximal Femur
- Humerus
- Skull



# Therapeutic Goals

- Improvement in the QOL
- Pain relief
- Maintenance and restoration of function
- Close surveillance for the development complications
- Treatment should be tailored to the patient's prognosis and life expectancy

# Treatment Modalities

- Radiotherapy
- Surgery
- Vertebroplasty/kyphoplasty
- Radiopharmaceuticals
- Radiofrequency ablation/Cryotherapy
- Bone modifying agent
- Systemic therapy

# Effects of RT on bone metastasis

- **Healing and ossification** – 65-85% of lesions show signs in about 6 mths
- Ionizing radiation diminishes **osteoclast activation and kill tumour cells.**
- Reduction in inflammatory cells and chemical pain mediators.

# Dose Fractionation (conventional rt)

- 8 Gy in a single fraction
- 20 Gy in 5 fractions
- 24 Gy in 6 fractions
- 30 Gy in 10 fractions

OPTIMAL DOSE FRACTIONATION SCHEDULE?

# Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy – A Systematic Review of Randomised Trials *Cochrane Unit* W.

M. Sze *Oncology* (2003) 15: 345–352

- 12 trials, 3621 sites
- Overall pain-response rates
  - SF- 60% (1080/1814) vs MF- 59% (1060/1807).
- Complete pain response rates
  - SF-34% (508/1476) vs MF- 32% (475/1473)
- Re-treatment rate
  - SF- 21.5% vs MF 7.4%

# Update on the Systematic Review of Palliative Radiotherapy Trials for Bone Metastases

E. Chow, L. Zeng , N. Salvo , K. Dennis , M. Tsao , S. Lutz y  
JCO:2012

25 RCTs, For intention-to-treat patients,

## Overall response (OR):

SF = **60%**(1,468 of 2,513 patients) Vs MF= **61%** (1,466 of 2,487 patients).

ODD's Ratio = 0.98(CI- 0.95-1.02)

**NO SIGNIFICANT  
DIFFERENCE**

## Complete response (CR) :

SF=**23%** 620 of 2641) Vs MF= **24%** (634 of 2622).

. ODD's Ratio = 0.97 (0.88-1.06)

## Increased risk in SF RT arm:

Pathological fractures **3.3%** in SF VS **3%** in MF . ODD's Ratio = 1.10 (0.65-1.86)

Spinal cord compressions, **2.8%** in SF Vs **1.9%** in MF . ODD's Ratio = 1.44 (0.90-2.30)

## Re-radiation Rates :

**20%** in SF Vs **8%** in MF (P .00001),--- “ this trend may have been influenced by the fact that physicians were more prepared to retreat those who received an initial single treatment”

# Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline

Stephen Lutz MD <sup>a,\*</sup>, Tracy Balboni MD MPH <sup>b</sup>, Joshua Jones MD <sup>c</sup>,  
Simon Lo MB ChB <sup>d</sup>, Joshua Petit MD <sup>e</sup>, Shayna E. Rich MD PhD <sup>f</sup>,  
Rebecca Wong MB ChB <sup>g</sup>, Carol Hahn MD <sup>h</sup>

Practical RadOnc.(2017)7,4-12

**Table 2** New prospective studies comparing SF vs MF RT regimens (KQs 1-3)

Investigator, y	Patients (n)	Fractionation	Complete or partial response (%)	Complete response (%)	Acute and late toxicity (%)	Repeat treatment rate (%)
Chow, 2012 <sup>8</sup>	5617 in 25 RCTs	SF	60	23	NR	20
		MF	61	24		8 <sup>a</sup>
Gutierrez Bayard, 2014 <sup>4</sup>	90	8 Gy in 1 fx	79	17	NR	13.3
		30 Gy in 10 fx	88	18		8.8 <sup>a</sup>
Howell, 2013 <sup>5</sup>	235		at 4 wk	at 4 wk		
		8 Gy in 1 fx	70	19	10	15
		30 Gy in 10 fx	62	17%	20 <sup>a</sup>	5 <sup>a</sup>
			at 3 mo	at 3 mo	(acute grade 2-4)	
Majumder, 2012 <sup>6</sup>	64	8 Gy in 1 fx	85	0	No statistically significant difference	NR
		30 Gy in 10 fx	77	0		
Meeuse, 2010 <sup>7</sup>	1157		at 1 month	at 1 month		
		8 Gy in 1 fx	53	NR	NR	7
		24 Gy in 6 fx	56			2
			(assessable patients)			

fx, fraction; MF, multiple fractions; NR, not reported; RCT, randomized controlled trial; SF, single fraction.

<sup>a</sup> Statistically significant comparison.



# Paradigm shift

- More utilization of single fraction RT in clinical practice
- SRS/SBRT (stereotactic radiosurgery/radiotherapy)- focusing more towards local control
- Newer radioisotopes

# Why Newer Paradigm Needed?

- Patients with metastatic disease represents a **heterogonous group**.
- Effective systemic and supportive therapies has **increased life expectancy** of metastatic patient- durable pain relief needed
- Oligometastatic patients and bone only metastasis patient have longer median survival- LC important
- What about metastasis from **radioresistant** tumour?
- Re-irradiation cases

# SRS/SBRT for spinal Mets

- Image guided **highly conformal** technique of EBRT that delivers large radiation dose in one or few fractions to target volume with **precision** (<1mm) and **steep dose gradients** .
- Provides higher **BED** to the tumour with relative **sparing** of the closely abutting sensitive critical normal tissue (spinal cord)
- Affects tumour vasculature and micro-environment and stimulates antitumour immunity- indirect action
- Increase in **local control** and more **durable pain response**.

# International Stereotactic Radiosurgery Society practice guidelines

TABLE 4. ISRS-recommended patient selection for consideration of spine SBRT outside a clinical trial\*

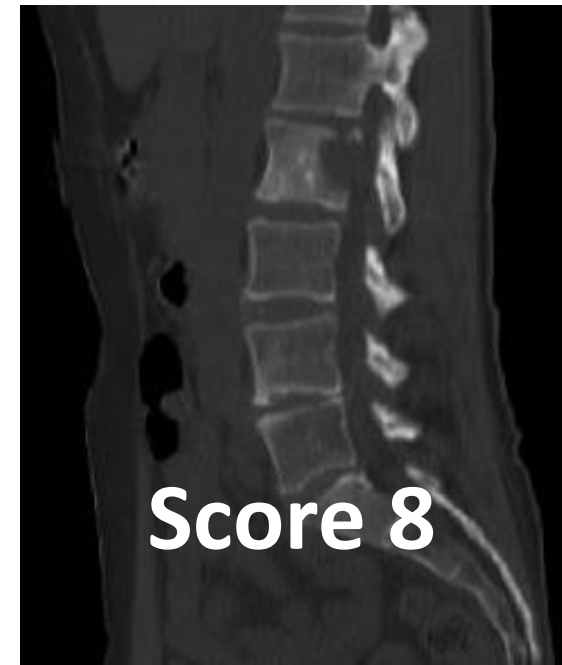
Criteria	Rationale
<b>Inclusion</b>	
Oligometastasis involving the spine	These pts generally have a long expected survival & thus are most likely to benefit from radiosurgery/SBRT
Pts w/ radioresistant histology (RCC, melanoma, sarcoma)	Higher doses of radiation might be associated w/ improved local tumor control
Patients with paraspinal extension contiguous to the spine	Pts w/ extraosseous extension might experience improved soft-tissue tumor control
<b>Exclusion</b>	
Pts w/ an expected survival time of <3 mos	Pts w/ a shorter expected survival time are less likely to benefit from SBRT
Mechanically unstable based on the SINS score	Pts w/ mechanical instability should be treated w/ surgical stabilization before radiotherapy
>3 sites to be treated in a single session	For logistical reasons, it is difficult to keep a pt adequately immobilized for long enough to accurately treat more than 3 lesions in a single session
Spinal cord compression or cauda equina syndrome	These pts should be preferentially treated w/ up-front decompressive surgery†

SINS = spinal instability neoplastic score.

## 2. Spinal Instability Neoplastic Score (SINS Score)

Fourney, JCO 2011

SINS Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal	0
Vertebral body height loss	
> 50%	3
< 50%	2
No collapse	1
None	0
Posterior element involvement	
Bilateral	3
Unilateral	2
None	0



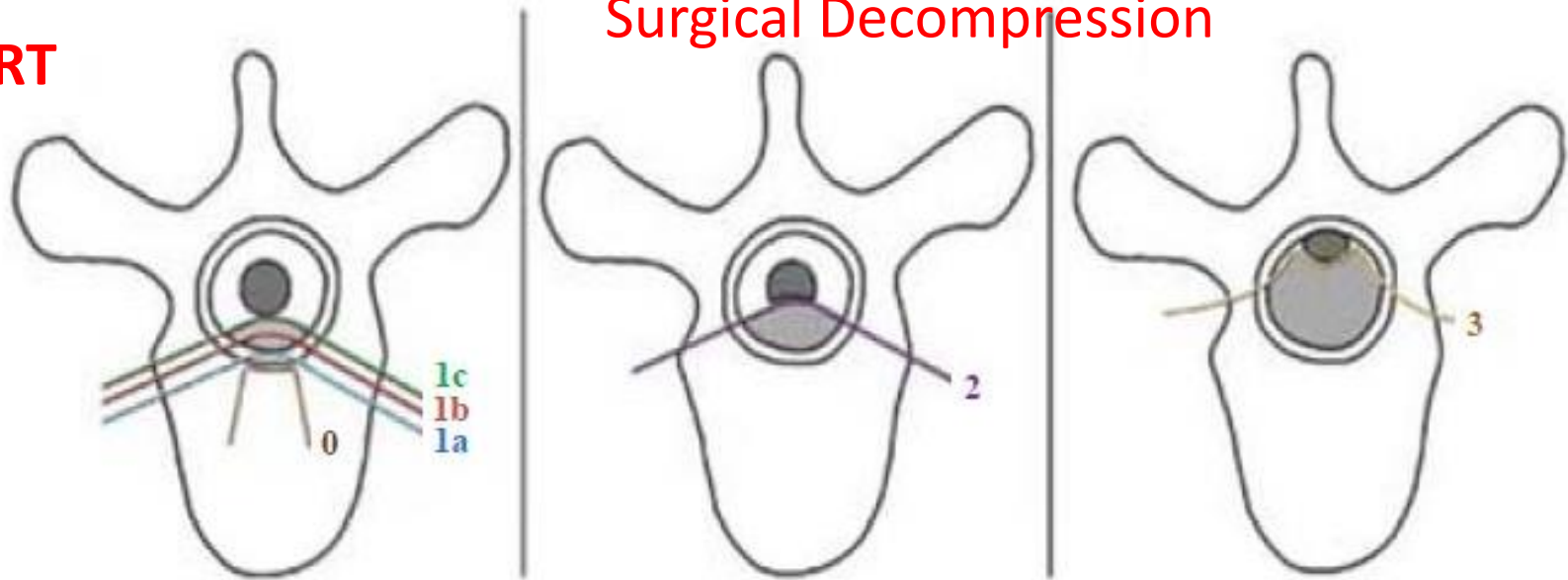
0 to 6 → stability  
 7 to 12 → indeterminate instability  
 13 to 18 → instability

**SINS 7-18 warrants surgical consultation before RT**

## 1. Epidural Spinal Cord Compression (ESCC) – the Bilsky Score

**SBRT**

**Surgical Decompression**



Schematic representation of the 6-point ESCC grading scale.

Grade 0	Bone-only disease
Grade 1a	Epidural impingement, without deformation of thecal sac
Grade 1b	Deformation of thecal sac, without spinal cord abutment
Grade 1c	Deformation of thecal sac, with spinal cord abutment, without cord compression
Grade 2	Spinal cord compression, with cerebral spinal fluid (CSF) visible around the cord
Grade 3	Spinal cord compression, no CSF visible around the cord

A six-point grading system was designed and validated by the Spine Oncology Study Group (SOSG) to describe the degree of ESCC

# Literature Review-Local Control

Authors & Year	Tumors/ Pts Treated (n/n)	Cancer Type	Follow-Up Duration Median (mos)	Local Control Rate (%)	Complete Pain Response (%)	Overall Survival	Tumor Dose (Gy)/ No. of Fx (range)	BED ( $\alpha/\beta = 10$ ) (Gy)
Chang et al., 2007	22/17	Mixed	NR	68.1 (7/22 failures)	NR	NR	27–30/3–5	48–51.3 (range)
Yamada et al., 2008	103/93	Mixed	15 (all pts)	93 (96/103, crude, 2 yrs)	NR	15 mos (all pts, median)	18–24/1	50.4–81.6 (range)
Sahgal et al., 2009	18/14	Mixed	9	77.8 (14/18, crude)	NR	NR	24/3 (median)	43.2 (median)
Chang et al., 2012	131/93	Mixed	23.7	89.2 (1-yr crude)	NR; 89.2 (at 1 yr, “pain control”)	19 mos	19.9/1 (mean equivalent)	59.5 (mean)
Gill et al., 2012	14/14	Mixed	34	85.7	NR	80% (1 yr), 57% (2 yr) (all)	30–35/5	48–59.5 (range)
Sohn et al., 2014	13/13	RCC	NR	85.7 (1 yr) 23.1	23.1	15 mos (median)	38/4 (mean)	74.1 (mean)
Guckenberge r et al., 2014	387/301	Mixed	11.8	90 (1 yr), 84 (2 yrs)	58	65% (1 yr), 44% (2 yrs) (median 19.5 mos)	24/3 (median) (10–60/1– 20)	43.2 (median) (range 20–78 )
Thibault et al., 2014	51/51	RCC	12.3	84.3 (crude)	NR	64.1% (1 yr)	24/2 (median)	52.8 (median)

# Pain Control

Study	No. of Patients	Fractionation	Complete /Partial Pain Response	Complete Pain Response	Duration
Prince 1986	288	1x8 Gy 10 x 3 Gy	73% 64%	45% 28%	59% @ 3 mo 50% @ 3 mo
Gaze 1997	280	1 x 10Gy 5 x 4.5 Gy	84% 89%	39% 48%	Median 3.5 mo Median 3.5 mo
Steenland 1999	1171	1 x 8 Gy 6 x 4 Gy	72% 69%	37% 33%	Median 5 mo Median 6 mo
Roos 2005	272	1 x 8 Gy 5 x 4 Gy	61% 53%	26% 27%	Median 3.5 mo Median 5.5 mo

**~70%**

**~25-40%**

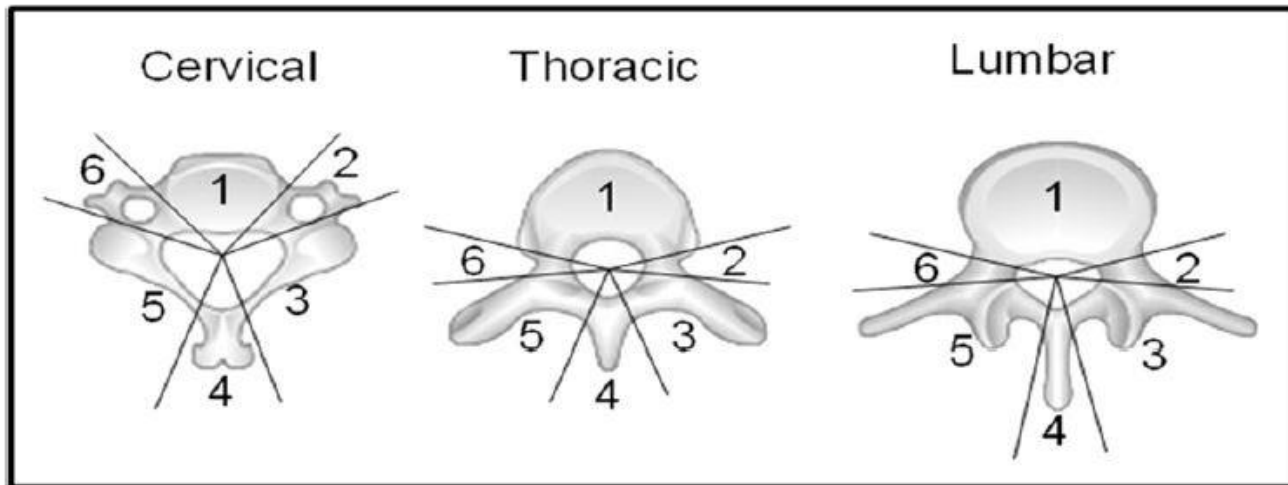
**~35% @ 3-6 mo**



# Target Volume Defination

- International Spine Radiosurgery Consortium Consensus Guidelines

Cox BW. IJROBP 2012;83(5):e597-605



**International Spine Radiosurgery Consortium anatomic classification system  
for consensus target volumes for spine radiosurgery**

**Table 4** Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

Target volume	Guidelines
GTV	<ul style="list-style-type: none"> <li>• Contour gross tumor using all available imaging</li> <li>• Include epidural and paraspinal components of tumor</li> </ul>
CTV	<ul style="list-style-type: none"> <li>• Include abnormal marrow signal suspicious for microscopic invasion</li> <li>• Include bony CTV expansion to account for subclinical spread</li> <li>• Should contain GTV</li> <li>• Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression</li> </ul>
PTV	<ul style="list-style-type: none"> <li>• Uniform expansion around CTV</li> <li>• CTV to PTV margin <math>\leq 3</math> mm</li> <li>• Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised</li> <li>• Never overlaps with cord</li> <li>• Should contain entire GTV and CTV</li> </ul>

*Abbreviations:* CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.

**Table 3** Guidelines for spinal SRS bony CTV delineation

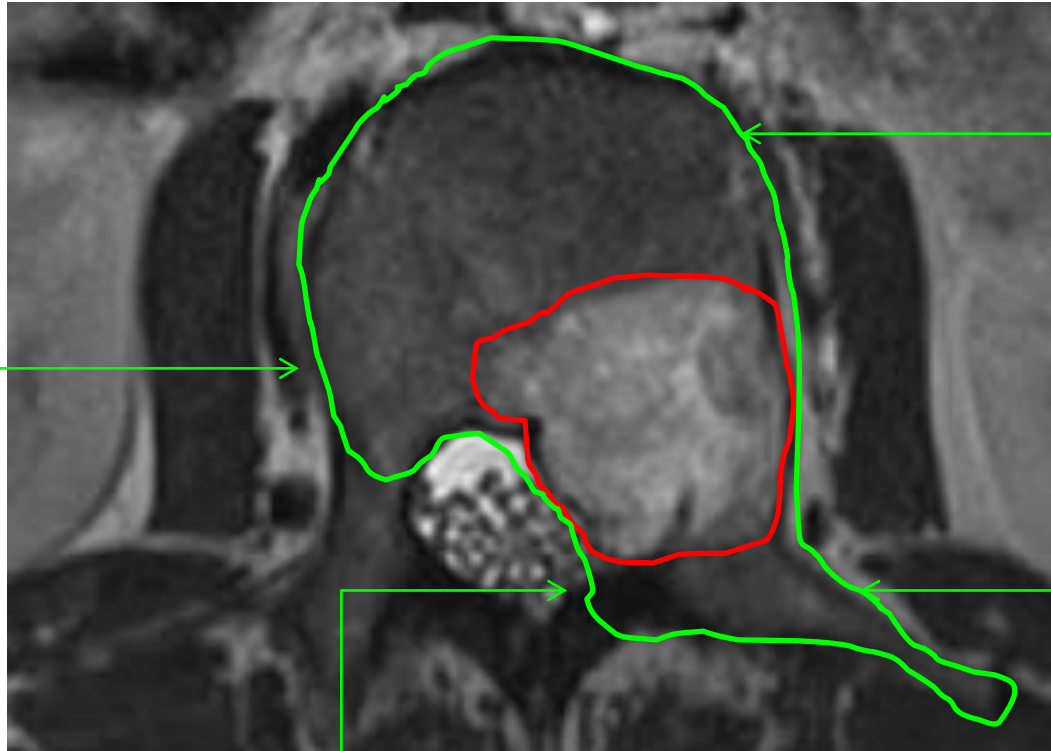
GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 $\pm$ 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, $\pm$ vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

*Abbreviations:* CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.

## CTV

Include Abnormal Marrow Signal

Include Bony  
CTV Extensions



Should contain  
GTV

Circumferential CTV encircling  
Cord should be avoided

# OAR Delineation

## Spinal Cord

( RTOG 0631 – Ryu S et al, 2015)

Two Spinal Cord Contour sets –

### 1. Conventional Spinal Cord

Fusion with T1 contrast & T2 MRI

At least 10cm above & Below the target volume

### 2. Partial Spinal Cord Volume

At least 6mm above & Below the target volume

Draw thecal sac separately

PRV – 2mm over Spinal Cord

•Other OARs- Within 10cm of target volume as per RTOG guideline

# Dose Fractionation

BED

• 16–24 Gy/1 fraction-	41.6-81.6
• 24 Gy/2 fractions	52.8
• 24–27 Gy/3 fractions	43.2-51.3
• 30–35 Gy/5 fractions	50.4-59.5

**GTV Dmin>14Gy (Single Fraction) or >21Gy (3 Fractions) – recommended**

BishopAJetal.IJROBP2015.92(5):1016-1026

# Late Complication

- **Nerve Damage**
- **Vertebral Compression Fracture-**
  - 1- and 2-year cumulative incidences 12.35% and 13.49%, respectively (24Gy/SF) and 8.5% and 13.8%. (24Gy/2#),  
(Tseng et al)
  - dose per fraction increases beyond 19 Gy, risk increases
  - significantly higher risk of VCF for the 24 Gy/fraction group and 20 to 23 Gy/fraction group.
  - baseline VCF, lytic tumor, and spinal misalignment (kyphosis/ scoliosis and subluxation/translation) were predictive

Sahgal et al, JCO, Sept 2013



# Response Assessment

Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Thibault et al

- Local Control

	RECIST version 1.1 <sup>35*</sup>	MDACC <sup>37†</sup>
Complete response	Disappearance of target lesions	Normalisation of signal intensity on MRI or bone density on CT, complete sclerotic fill for lytic lesions on CT, or both
Partial response	≥30% decrease in sum of target lesion diameters	≥50% decrease in measurable lesions (subjectively for ill-defined lesions), development of a sclerotic rim or partial sclerotic fill for lytic lesions on CT, or both
Progressive disease	≥20% increase in sum of target lesion diameters plus absolute increase of ≥5 mm, appearance of one or more new lesions, unequivocal progression of non-target lesions, or a combination	≥25% increase in measurable lesions (subjectively for ill-defined lesions)
Stable disease	Any response other than complete or partial response and progressive disease	Any response other than complete or partial response and progressive disease

RECIST=Response Evaluation Criteria in Solid Tumors. MDACC=MD Anderson Cancer Center. \*For bone metastases, osteolytic and mixed lesions are deemed measurable if identifiable soft tissue extension is >10 mm; osteoblastic metastases are non-measurable. †Measurements for bone metastases are based on the sum of a perpendicular bidimensional measurement of the greatest diameters of each individual lesion.

Table 2: Imaging-based tumour response classifications



# Pain Response

- BPI preferred, with assessment based on worst pain score
- ICPRE should be adopted as standard guidelines for pain response
- Pain response should be assessed at 3 months after SBRT

	ICPRE <sup>41*</sup>	MDACC <sup>43†</sup>
Complete response	Score of 0 at the treated site in patients with baseline pain, and no increase in analgesic requirements (converted to OMED)	Average pain score of 0 for two consecutive questionnaire assessments
Partial response	Pain reduction of $\geq 2$ at the treated site without increase in OMED, or analgesic reduction of $\geq 25\%$ from baseline without pain increase	Decrease of 2 points in the worst pain score for two consecutive questionnaire assessments
Pain progression	Pain score increase of $\geq 2$ above baseline with stable OMED, or analgesic increase of $\geq 25\%$ in OMED with a stable pain score or 1 point above baseline	Pain score $> 0$ that doesn't change within 8 weeks from start of treatment, or a 2-point pain score increase sustained at a higher level for 1 month after the start of treatment, or pain score decrease $\geq 2$ and subsequent sustained rise ( $\geq 2$ increase on two consecutive questionnaire assessments)
Indeterminate response	Any response other than complete or partial response and pain progression	NA

ICPRE=International Consensus Pain Response Endpoints. MDACC=MD Anderson Cancer Center. OMED=oral morphine equivalent dose. NA=not applicable. \*Only the worst pain score for the previous 3 days should be assessed and scored on a scale of 0–10. †Criteria taken directly from study protocol.

**Table 3: Pain response definitions**

# Optimal dose fractionation schedule?

- Ongoing randomized study from MSKCC (NCT01223248) is comparing two fractionation schedules- 27 Gy in three fractions (3 days) or 24 Gy in one fraction (1 day).

## COMPARISON WITH EBRT

### Sprave et al

- Phase II randomised trial comparing pain response b/w single-fraction SBRT (24 Gy) vs 3DCRT (30 Gy in 10 fractions).
- primary endpoint was pain relief of >2 points on the visual analog scale (VAS) measured within the irradiated region at 3 months
- At 3 months no differences in VAS score, 6 months following RT, significantly lower VAS values were reported in the SBRT group ( $p = 0.002$ ).

Ongoing study phase III- Canadian Clinical Trials Group (CCTG) Symptom Control (SC)-24 (SC-24) trial (NCT02512965), comparing 24 Gy in 2 SBRT fractions vs 20 Gy in 5 EBRT fraction

# Re-Irradiation

Study	# patients / cases	Follow-up (months)	Myelopathy	Local / pain control
Milker-Zabel 2003	18 / 19	12.3	0%	95%
Mahan 2005	8 / 8	15.2	0%	100%
Sahgal 2009	25 / 37	7	0%	70%
Choi 2010	42 / 51	7	n=1 G4	73%
Sterzing 2010	36 / 36	7.5	0%	63%
Damast 2010	94 / 97	12.1	0%	66%
Garg 2011	59 / 63	13	n=2 G3 peripheral nerve injury	76%
Mahadevan 2011	60 / 81	12	n=3 persistent radicular pain n=1 lower-extremity weakness	93%
Chang 2012	49 / 54	17.3	0%	79%

- Very low incidence of myelopathy
- Nerve damage a more frequent toxicity
- Promising local control 63 – 100%

Clinical Practice: **0% risk of myelopathy if**

- Initial course <50Gy (EQD2/2)
- SBRT course <25Gy (EQD2/2)
- Interval >5 months

*Sahgal IJROBP 2010*

# Post Operative SBRT

- Highly selected patients with single area of symptomatic MESCC decompressive surgery followed by RT can be considered.
- Consensus guidelines for postoperative stereotactic body radiation therapy for spinal metastases: results of an international survey [J](#)

## Consensus indications and contraindications for postoperative spine SBRT

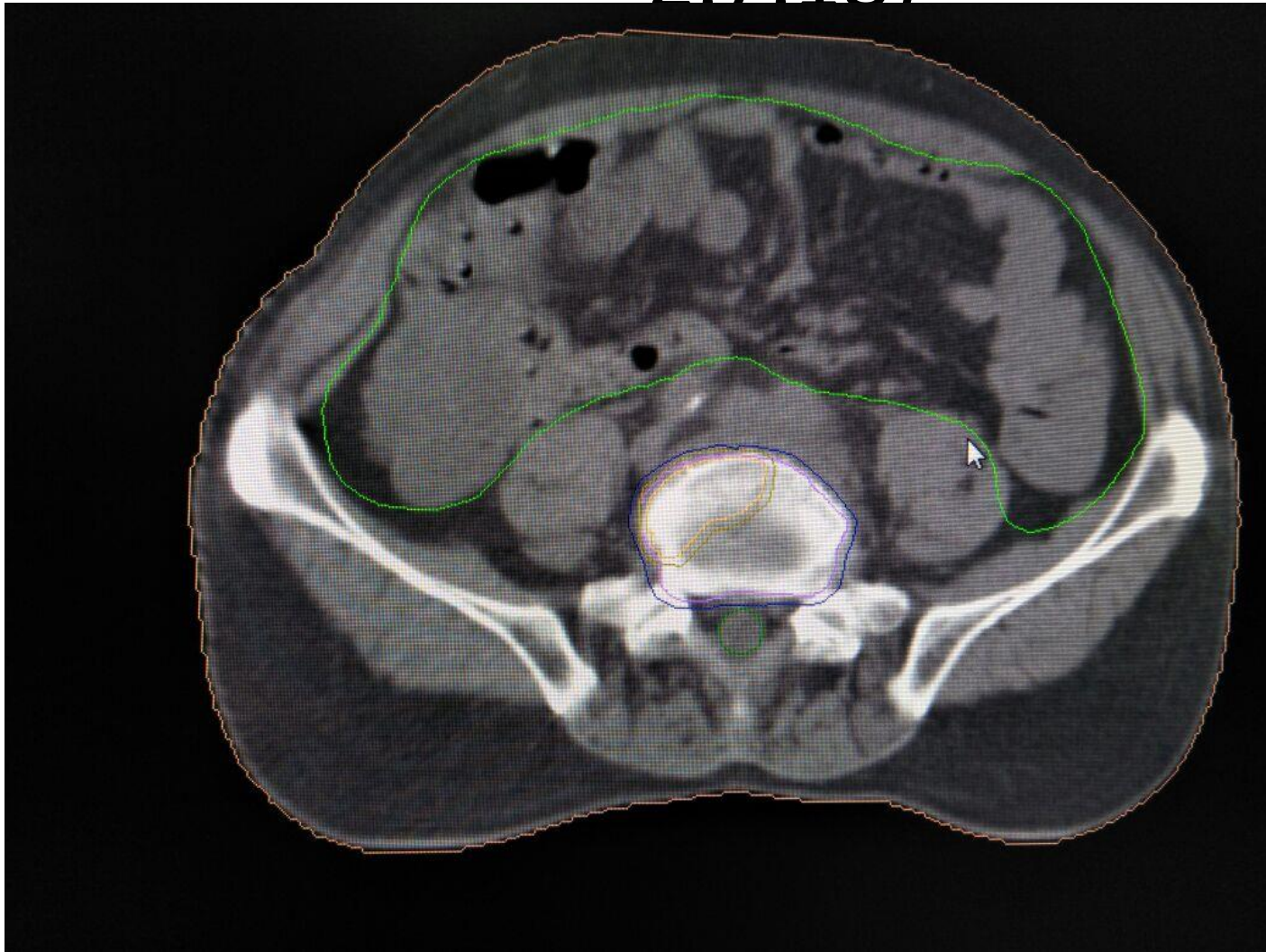
Indications	Contraindications
Radio-resistant primary 1–2 levels of adjacent disease	Involvement of more than 3 contiguous vertebral bodies
Prior overlapping radiation therapy	ASIA Grade A status (complete spinal cord injury without preservation of motor or sensory function)
	Postoperative Bilsky Grade 3 residual (spinal cord compression without any CSF around the spinal cord)

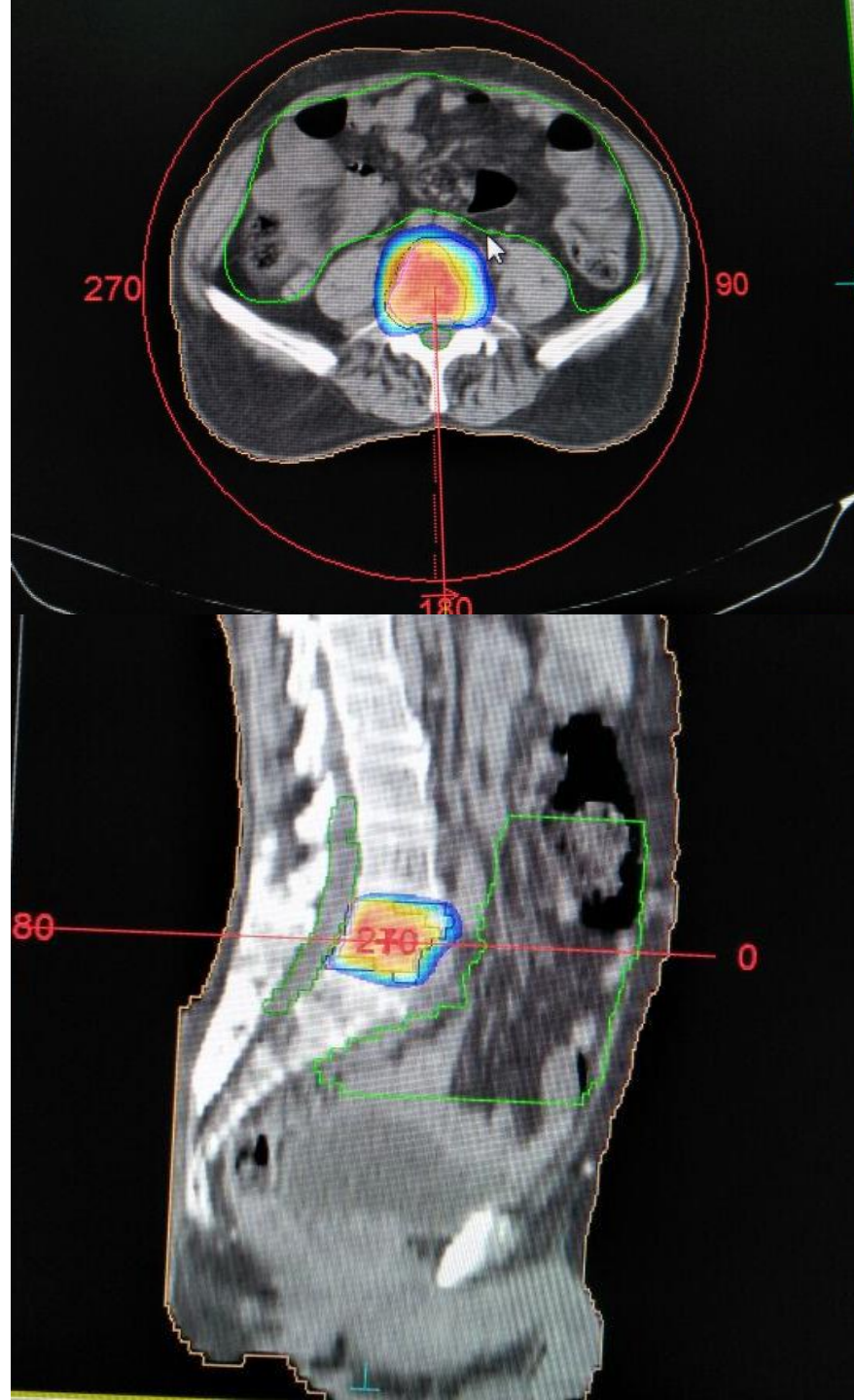
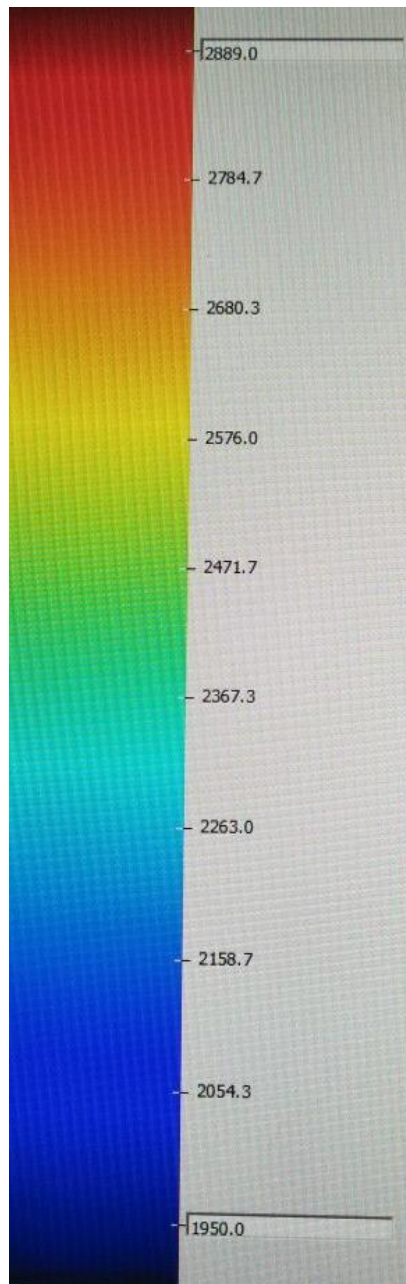
## Consensus and predominant practices for GTV, CTV, PTV, spinal cord, and spinal cord PRV delineation for postoperative spine SBRT

Volume	Include
Gross tumor volume (GTV)	Postoperative residual based on MRI
Clinical tumor volume (CTV)	Entire extent of preoperative tumor, anatomic compartment involved, & any postoperative residual Surgical instrumentation & incision not included unless involved Prophylactic circumferential treatment of epidural space controversial Additional expansion up to 5 mm for paraspinal extension controversial Consider an additional expansion of up to 5 mm cranio-caudally beyond known epidural disease extent based on pre- & postoperative imaging
Planning target volume (PTV)	0- to 2-mm expansion from CTV
Spinal cord	True spinal cord based on postoperative T2-weighted MRI or CT myelogram in cases of significant hardware artifact
Spinal cord planning risk volume (PRV)	0- to 2-mm expansion of spinal cord volume



SBRT with 27Gy/3# to GTV, 27Gy/3# to  
CTV (SIB) alternate day (27.6.18 to  
2.7.18)







# Newer Radiopharmaceutical- Radium 223

- For wide spread osteoblastic metastases → P32 / Sr89 / Sm153 \_ Beta emitters
- Radium 223 is an alpha emitting radionuclide, high LET, half-life of 11.4 days.
- FDA approved in 2013 for treatment of bone pain in patients with mCRPC with no other visceral metastases.
- ALSYMPCA trial, showed a significant improvement in overall survival, delay in symptomatic skeletal events, and quality of life.
- Given intravenously over 1 minute at 50 kBq/kg body weight every 4 weeks for a total of 6 injections.

# Questions unanswered

- “Better than expected” survival after ablative treatment.
- Effect on long term survival.
- Deffering initiation of systemivc therapy.
- Immunologic response?
- Lack of level I evidence.

# Summary

- Oligo-metastatic breast cancers are rare and may have curative potential.
- These patients can be identified through clinical features and maybe molecular parameters.
- The biology of oligo-metastatic breast cancer is not well understood.
- Adding curative therapy in this setting may have added value.