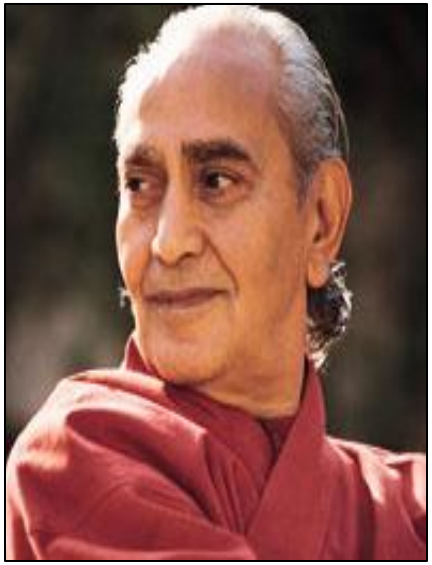


# Clinical Approach to Oligometastatic Breast Cancer

## Are We Treating Them with Radical Intent?


**Dr. Vipul Nautiyal**

**Professor and Head**

**Department of Radiation Oncology**

**Cancer Research Institute**

**Himalayan Institute of Medical Sciences**

**SRHU, Dehradun**

- **What is Oligometastasis?**
- **How this state happens??**

- **Definitions related to Oligomets**

- **Rationale for RT in Oligomets**

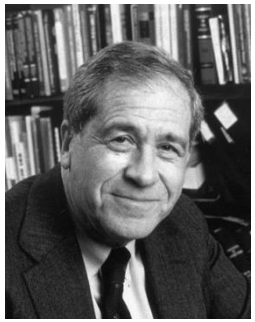
- **Sites where oligomets is being treated with RT**

- **Is treating Oligometastasis beneficial for patients??**

# Learning Objectives

- Define oligometastatic disease in breast cancer
- Discuss clinical approach and diagnostic workup
- Summarize treatment modalities (local + systemic)
- Review landmark clinical trials & evidence
- Debate: Radical vs Palliative intent

# Evolution of Breast Cancer Management



**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)**

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

# 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.

Peters LJ, Milas L, Fletcher GH Symp Fundum Cancer Res, 1983;36: 411-20

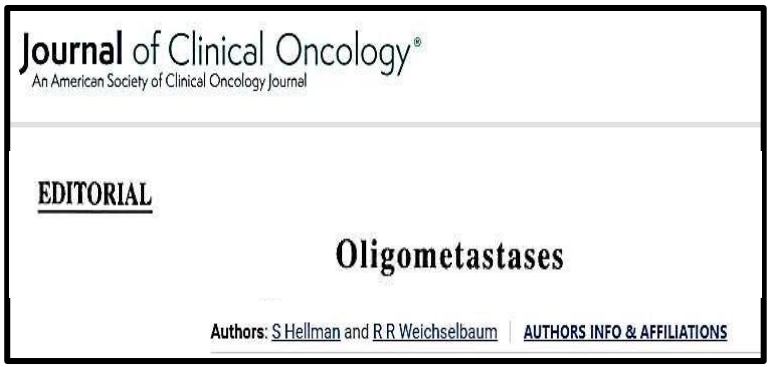
## SEED AND SOIL THEORY

STEPHEN PAGET, M.A., F.R.C.S.

:1889 AD

- Stephen Paget proposed his "seed and soil" theory of cancer.
- He analyzed over 1000 autopsy records of women who had breast cancer and found that the
- Thus, he proposed that tumor cells (the seeds) have a specific affinity for specific organs (the soil), and metastasis would only result if the seed and soil were compatible.

## SPECTRUM THEORY



Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

EDITORIAL

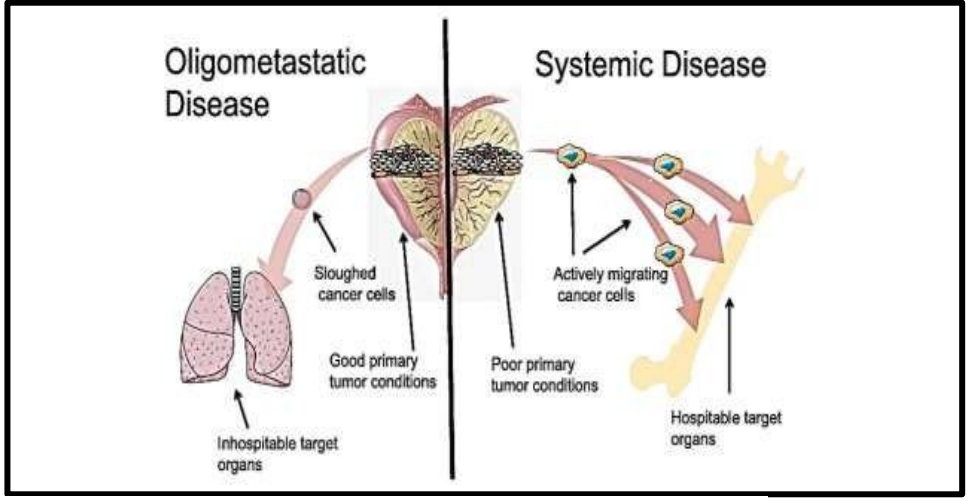
Oligometastases

Authors: S Hellman and R R Weichselbaum | AUTHORS INFO & AFFILIATIONS

1995

- Cancer spread is from the primary tumor through the lymphatics to the lymph nodes and then to distant sites.
- There are tumor states intermediate between purely localized lesions and those widely metastatic., existence of a clinical significant state of oligometastases.

**CLONAL THEROY** 2015




## Oligometastatic disease versus systemic disease

### Oligometastatic

Metastatic growth potential is limited, secondary to:
in the primary tumor
forestalling evolutionary clonal pressure,

- cancer cells that slough out of the that do not have the properties survive the circulation and invade organ sites
- Cancer cells land in inhospitable target organs.

### Systemic

Widespread metastatic growth unlimited, secondary to:

- due to environmental conditions in undifferentiated, aggressive clones
- cancer cells that actively migrate out primary tumor that have the to survive the circulation and invade organ sites

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 11

2015

# The biology and treatment of oligometastatic cancer

Diane K. Reyes[1], Kenneth J. Pienta[1,2]

- A disease state that exists in transitional zone between localized and widespread systemic disease, termed oligometastasis.
- Change in treatment paradigm, i.e. if primary cancer site (if still present) is controlled, or resected, and metastatic sites are ablated (surgically or with radiation), a prolonged DFS , and perhaps even cure, may be achieved

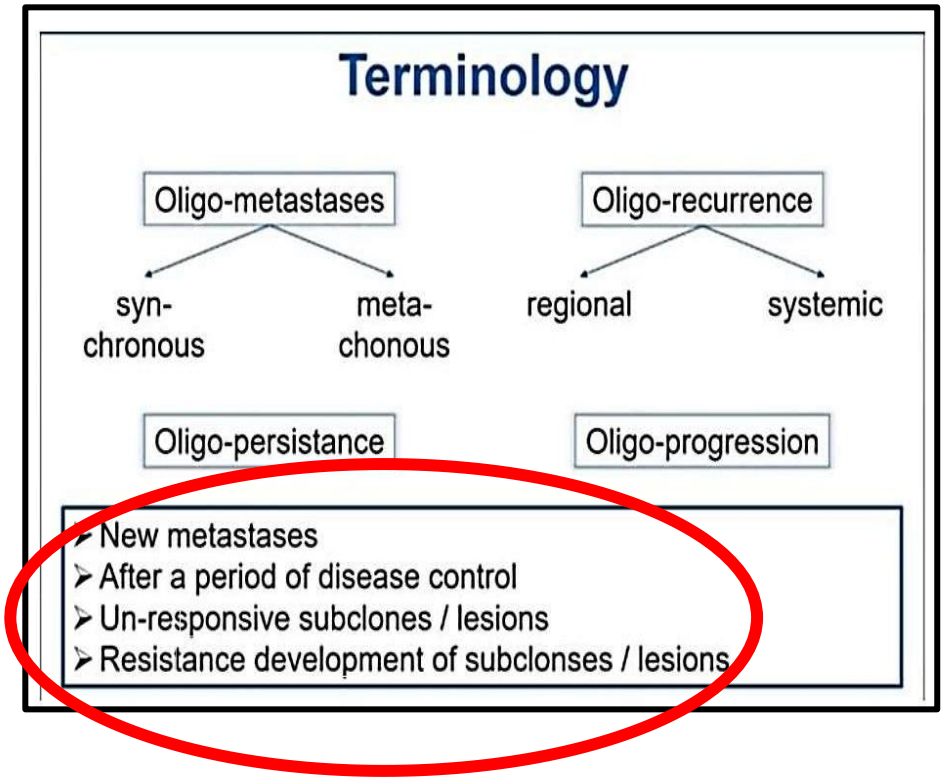
**Table 3: Definitions of Oligometastasis**

| Terms | Definition |
|---|---|
| Oligometastasis | "…metastases (from tumors early in the chain of progression) limited in number and location because the facility for metastatic growth has not been fully developed and the site for growth is restricted…" |
| Oligometastatic disease | Solitary or few detectable metastatic lesions that are usually confined to a single organ |
| Oligometastases | Due to limited metastatic competence and does not occur following otherwise successful systemic treatment. New metastases in this situation, albeit even limited, is likely to have more extensive malignant capabilities that were somehow spared from eradication by therapeutic means, or from the development of resistant clones |
| Induced oligometastases | Occurs when widespread micrometastatic disease is mostly eradicated by systemic chemotherapy but drug resistant clones are left behind, or tumor foci is located in a site not accessed by chemotherapy |
| Oligorecurrence | Limited metastases in the presence of a controlled primary lesion |
| Sync-oligometastases | ≤5 metastatic or recurrent lesions in the presence of active primary lesions |
| Synchronous oligometastasis | Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor |
| Metachronous oligometastasis | Development of oligometastatic disease after treatment of the primary tumor; interval for classification of metachronous versus synchronous is not standardized; between Controlled primary lesion except for concomitant primary and distant recurrence |
| Oligoprogression | Progression of a limited number of metastatic deposits, while remaining metastases are controlled with systemic therapy |
| Oligometastasis (specific to prostate cancer) | Rising PSA following primary therapy, with oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) is required to defer initiation of ADT |
| Oligometastasis (specific to prostate cancer) | Castrate resistant prostate cancer with a rising PSA and oligometastasis on imaging, in whom local treatment (surgical metastasectomy (usually LN dissection), or SBRT for bony mets or LN recurrence) may allow deferral of ADT |

Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation

Matthias Guckenberger, Yolande Lievens, Angelique B Bouma, Laurence Collette, Andre Dekker, Nandita M deSouza, Anne-Marie C Dingemans,

Lancet Oncol 2020




**Intermediate state between localised and systemically metastasised disease.**

- **Oligometastases is the state in which the patient shows distant relapse in only a limited number**
- **Oligo- primary site of the controll meaning call gross recurrent or sites could be treated using local therapy**

## Oligoprogressive disease :

a few ‘resistant’ clones progress

- Majority of metastatic disease controlled by systemic treatment,

## Induced Oligometastasis/Oligopersistance

widespread

- Induced oligometastasis occurs when micrometastatic disease is mostly eradicated by systemic chemotherapy but drug resistant clones are left behind, or tumor foci is located in a

## Metachronous oligometastasis

- After period initial disease-free interval, new presentation of oligo-metastases

## Synchronous oligometastatsis :

- De-novo presentation of oligo-metastases
- ≤5 metastatic or recurrent lesions in the presence of active primary lesions
- Oligometastatic disease is detected at the time of diagnosis of the primary tumor, therefore there is an active primary tumor

## Oligoprogressive disease :

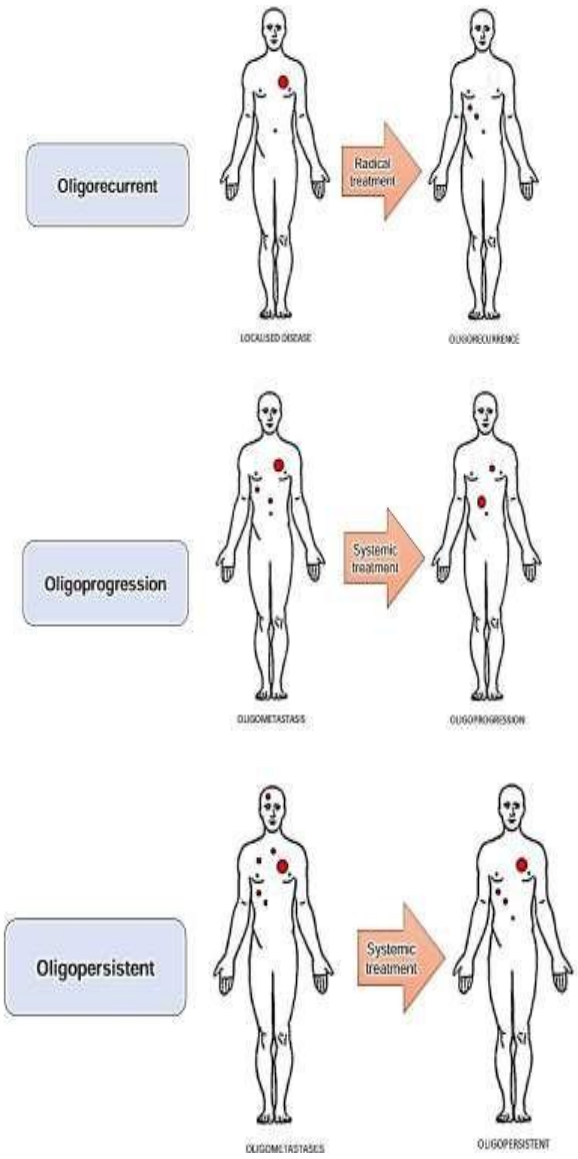
- Majority of metastatic disease controlled by systemic treatment, a few 'resistant' clones progress

## Induced Oligometastasis/Oligopersistance

- Induced oligometastasis occurs when micrometastatic disease is mostly eradicated by systemic chemotherapy but drug resistant clones are left behind, or tumor foci is located in a site not accessed by chemotherapy

## Metachronous oligometastasis

- After period initial disease-free interval, new presentation of oligo-metastases





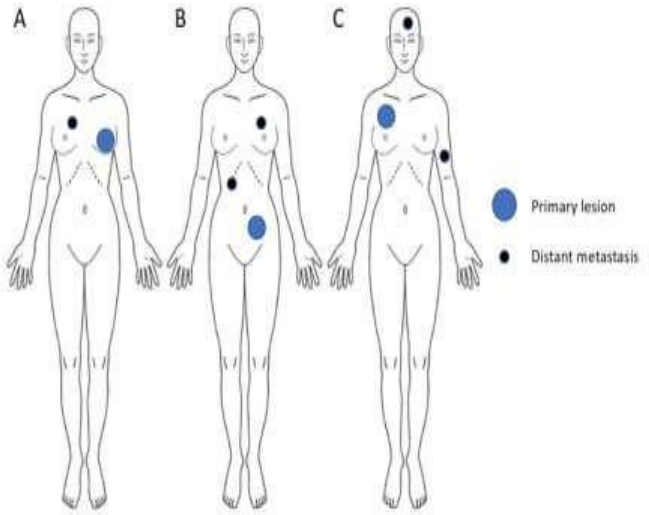




**Figure 1.** Schema of oligometastasis. Cases **A**, **B**, and **C** represent breast cancer with solitary pulmonary metastasis, colon cancer with liver and lung metastases, and non-small-cell lung cancer with brain and bone metastases, respectively. In oligometastatic disease, the number of metastatic lesions is limited, and both the primary and metastatic lesions should be treated with local treatment.

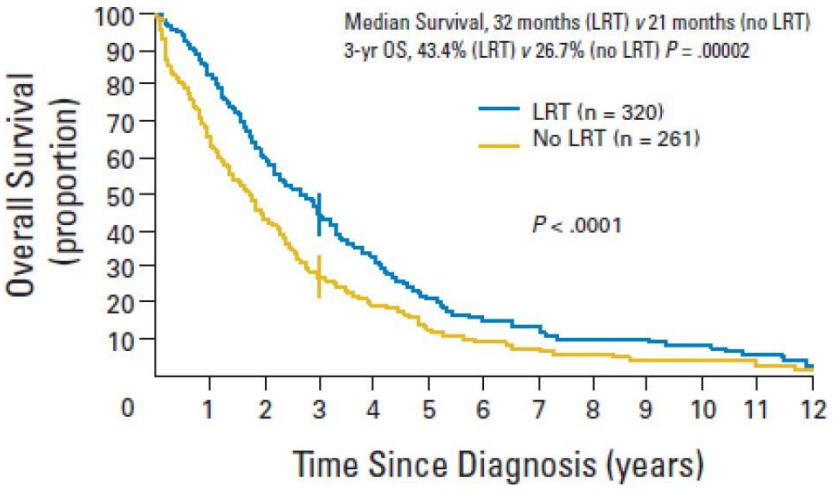
**Cancers 2019, 11, 133;**
**doi:10.3390/cancers11020133**

| PRIMARY | METASTATIC SITE |
|---|---|
| LUNG-NSCLC | ADRENAL, BRAIN |
| LUNG-SCLC | BRAIN |
| PROSTATE | BONE |
| COLORECTAL | LIVER |
| CERVIX | BONE |

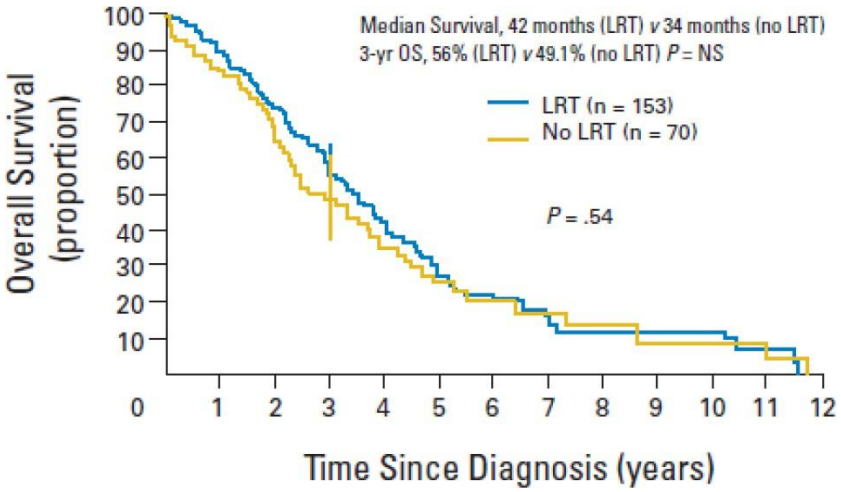
## FAVORABLE PRIMARY

- Hormone Receptor Positive Breast Ca
- ALK/EGFR/ ROS Positive Lung Ca
- Prostate Ca
- Thyroid Ca
- RCC

# Impact of local therapy in metastatic breast cancer

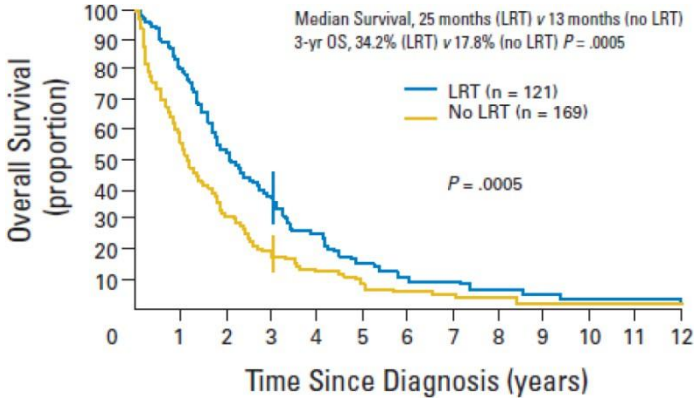



Distant Metastases




Bone Metastases

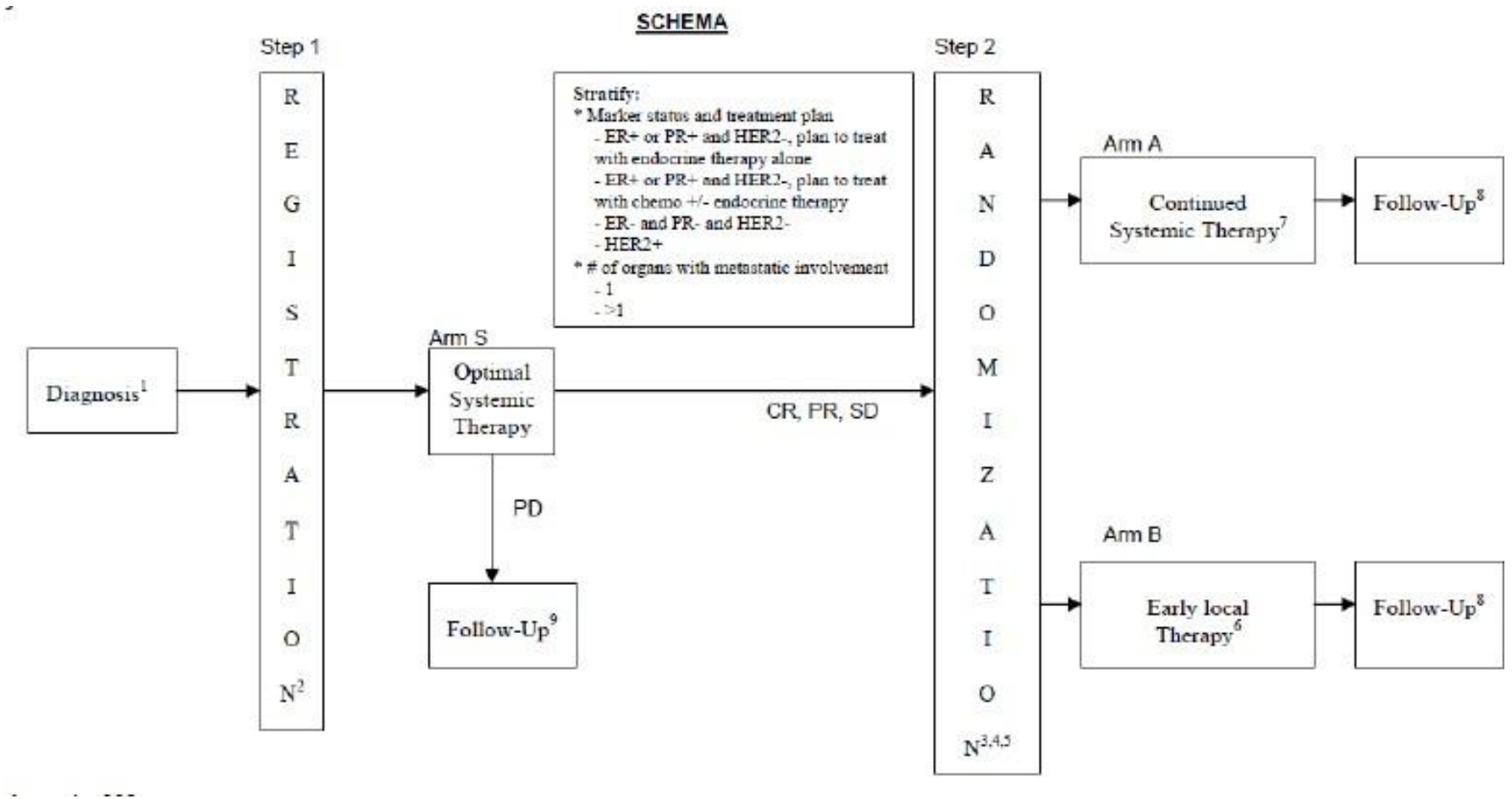
581 Breast Cancer patients
Local RT 320 (55%)
No RT 261 (45%)




Visceral Metastases

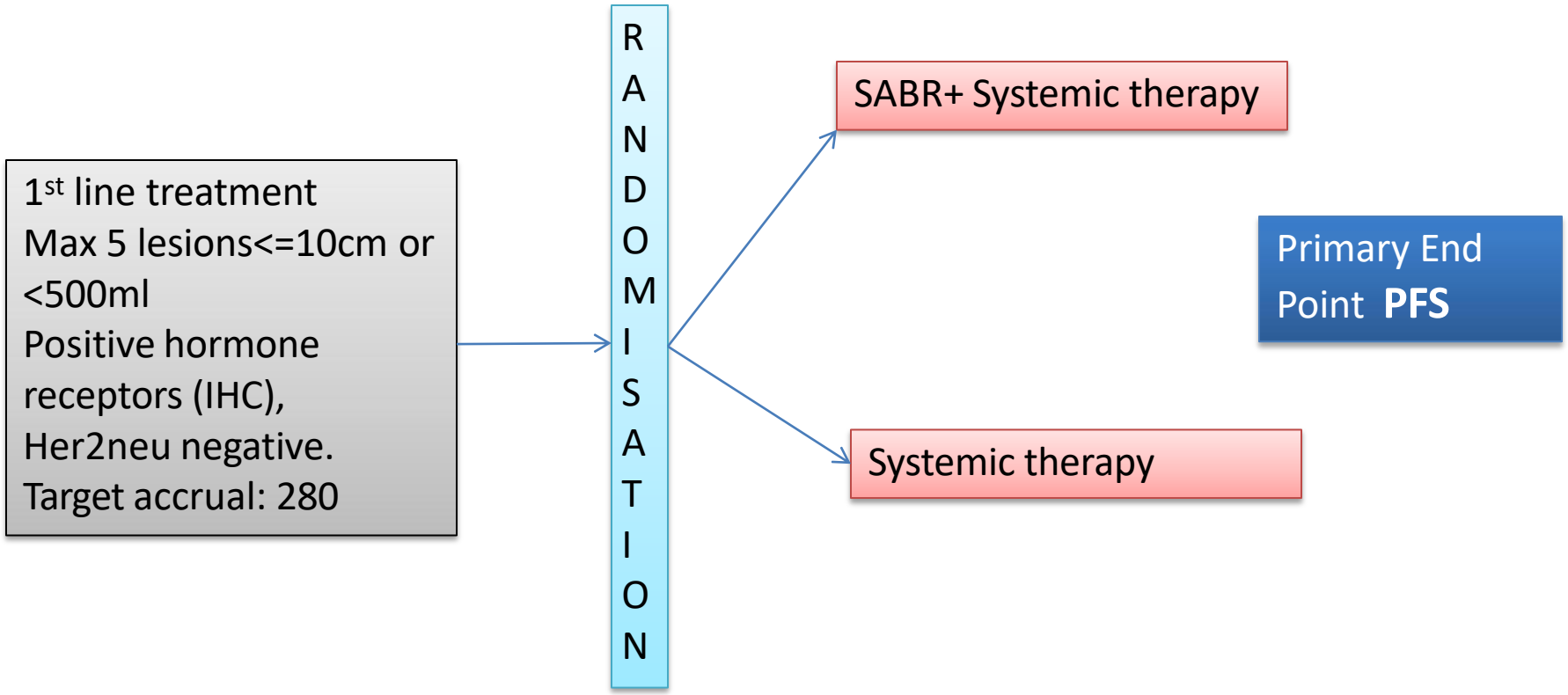
Lescodan, JCO 2009

# E2108-ECOG



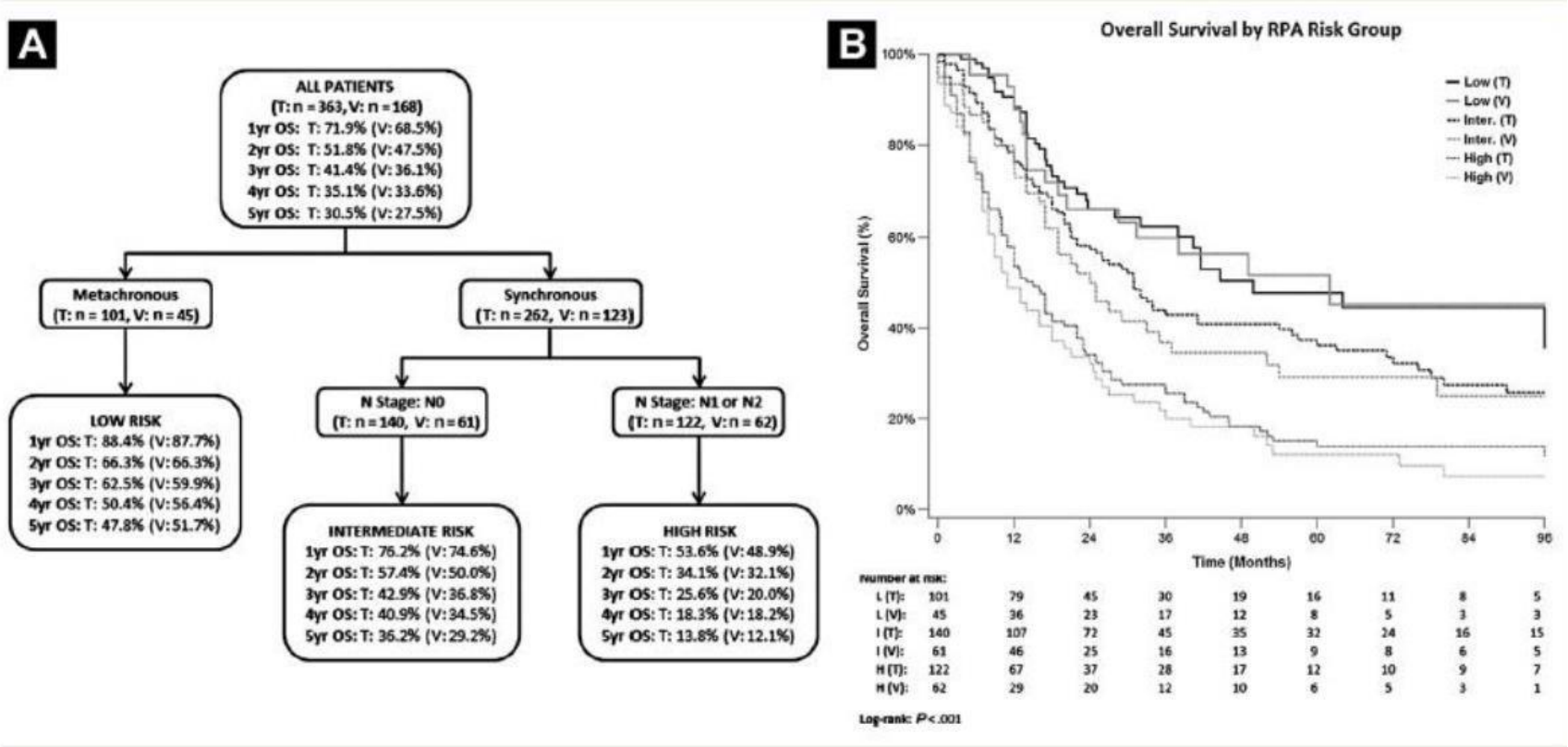

Seema A Khan et al, Clin trial.gov

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



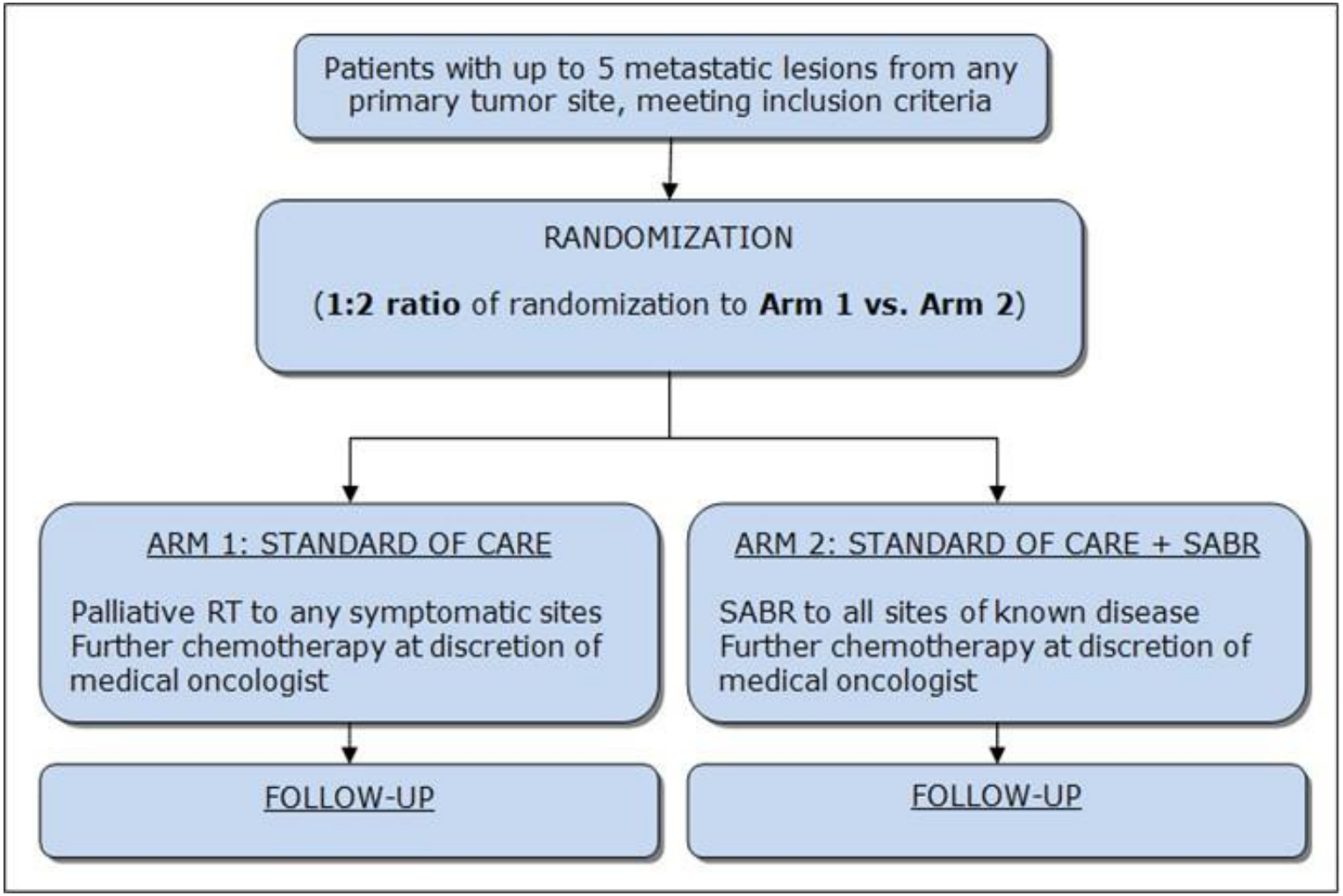

C Bougier, S Rivera

# Experience from Lung




Ashworth, Clin Lung Cancer 2014

# SABR-COMET


Patients with up to 5 metastatic lesions from any primary tumor site, meeting inclusion criteria
RANDOMIZATION
(1:2 ratio of randomization to Arm 1 vs. Arm 2)
ARM 1: STANDARD OF CARE
Palliative RT to any symptomatic sites
Further chemotherapy at discretion of medical oncologist
ARM 2: STANDARD OF CARE + SABR
SABR to all sites of known disease
Further chemotherapy at discretion of medical oncologist
FOLLOW-UP
FOLLOW-UP

# Endpoints

**Primary Endpoint**

- Overall Survival

**Secondary endpoints:**

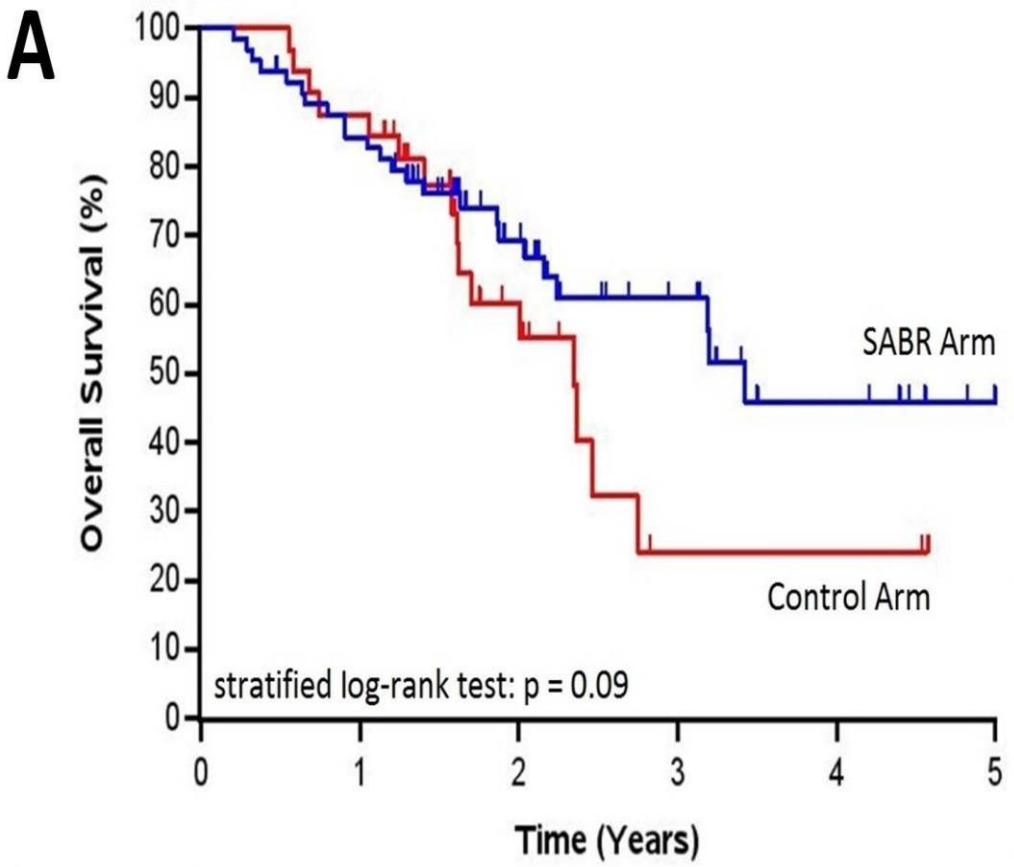
- Progression-free survival
- Toxicity (CTC-AE 4.0)
- Quality of life (FACT-G)
- Lesional control rate
- Number of cycles of further systemic therapy
  - Changed to binary variable “Receipt of systemic therapy” (Y/N)

# Patient characteristics- SABR-COMET

| Characteristic | All Patients (n=99) | Control Arm (n=33) | SABR Arm (n=66) | p-value |
|---|---|---|---|---|
| **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** | | | | |

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

# Overall survival




**Number at risk:**

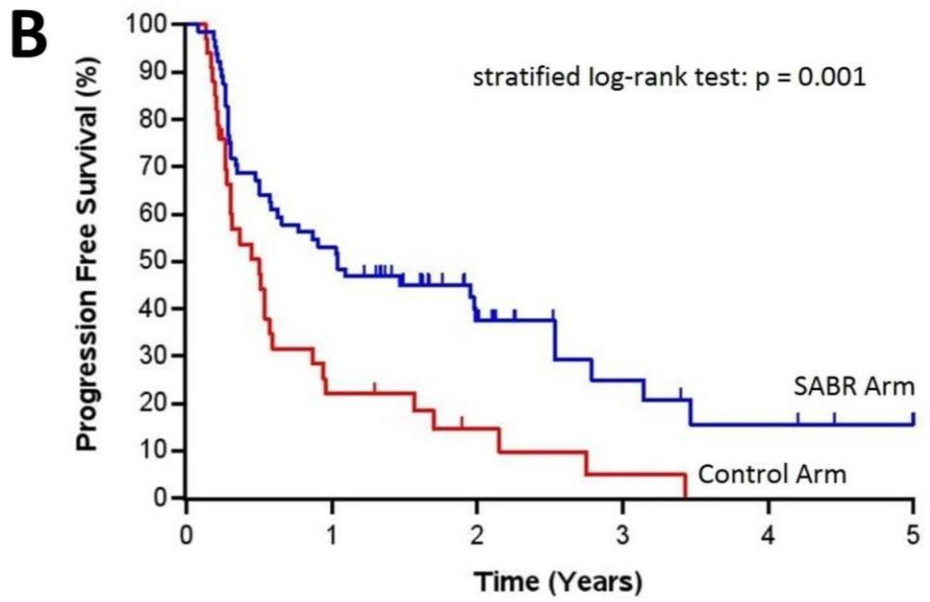
| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 33 | 28 | 12 | 2 | 2 | |
| SABR | 66 | 53 | 29 | 15 | 7 | 1 |

**Median OS**

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

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

# Progression free survival




**Number at risk:**

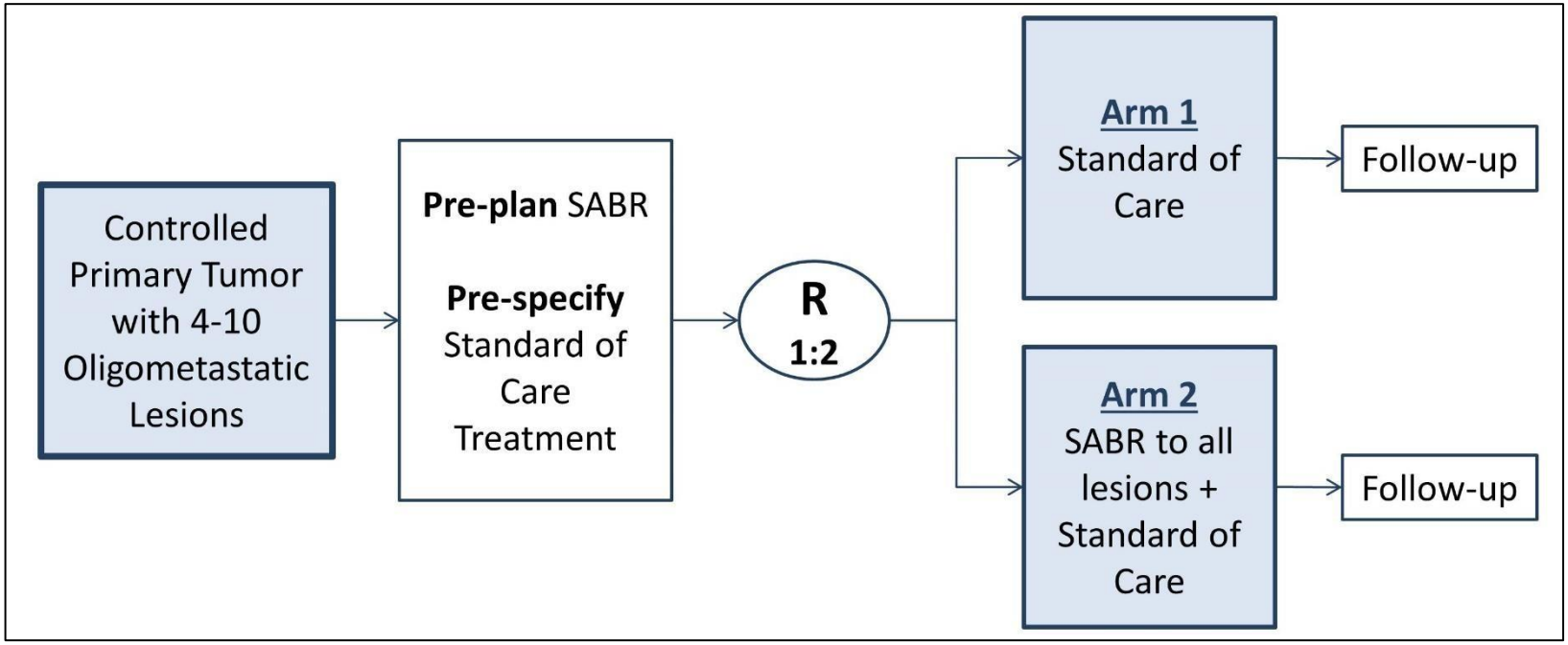
| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 33 | 7 | 3 | 1 | | |
| SABR | 66 | 34 | 15 | 6 | 3 | 1 |

**Median PFS**

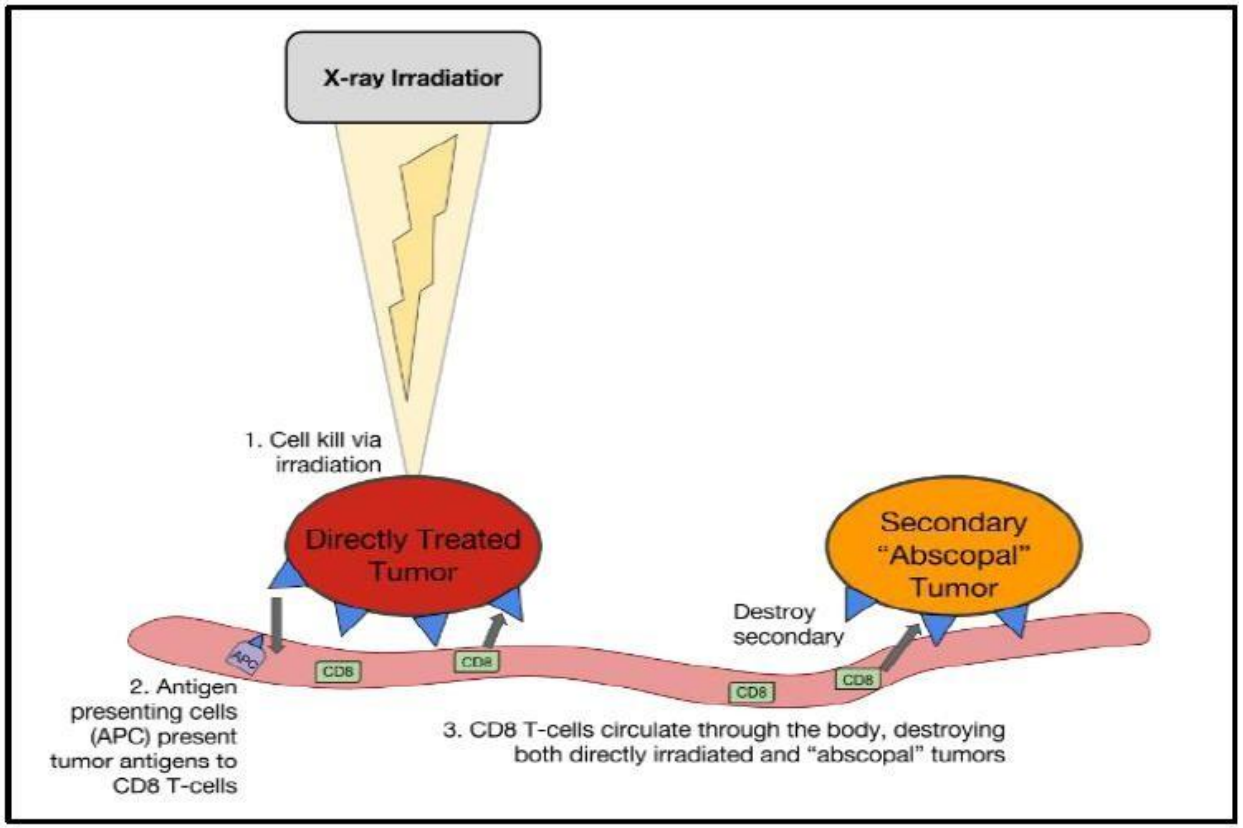
Control Arm: 6 months
(95% CI: 3.4-7.1 months)

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

# SABR-COMET 10



# Abscopal effect of radiation



# Ablative Radiotherapy + Immunomodulator

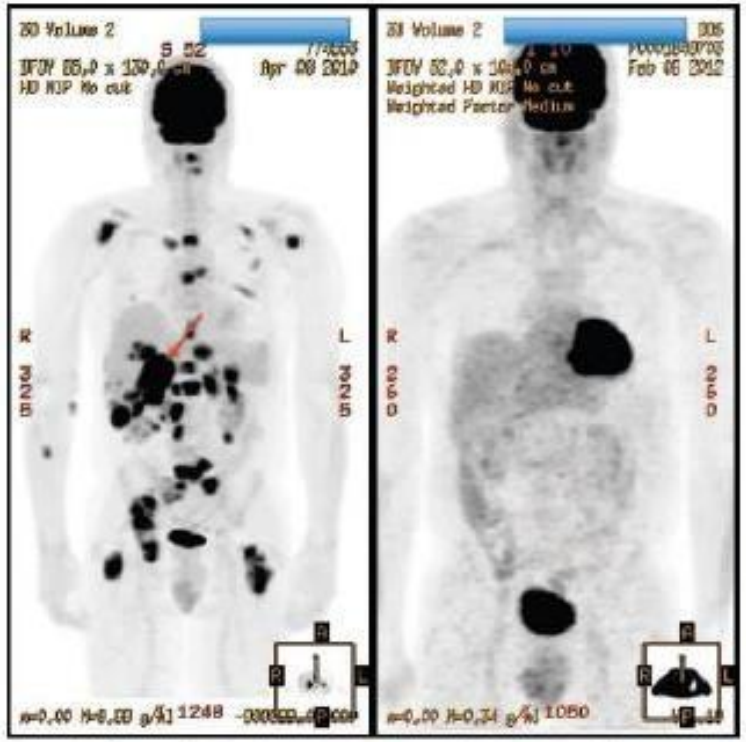



**Fig. 2.** Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

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%

# Controversies

- True cure vs long-term disease control?
- Risk of overtreatment & toxicity
- Cost-effectiveness
- Need predictive biomarkers (ctDNA, genomics)

# Definitions

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

# Conventional Management of Brain Metastases

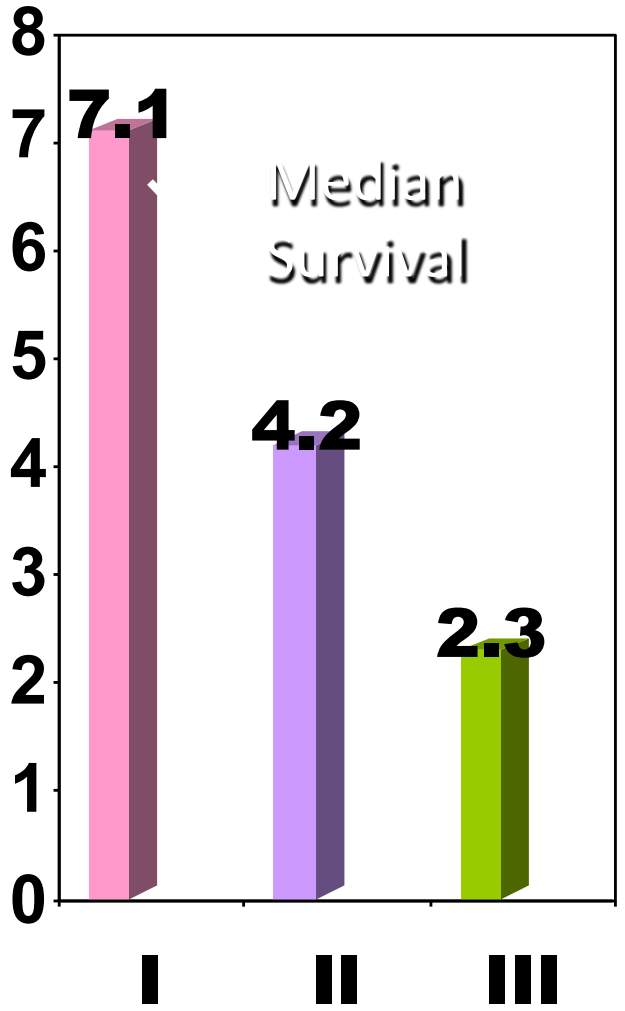
- Medical decompression → Steroids, Mannitol, Glycerol
- 1-3 lesions, resectable→ Surgical resection + Whole Brain Radiotherapy
- Multiple/unresectable lesions→ Whole Brain Radiotherapy

# Decision of Management

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

# RTOG- Classes

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



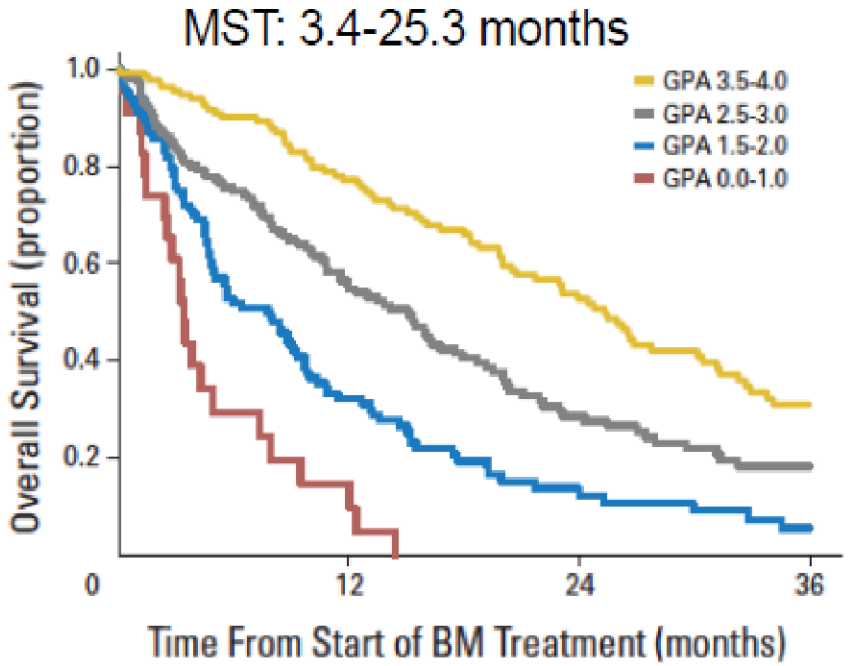

Gaspar, et al JNCI 1997

VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

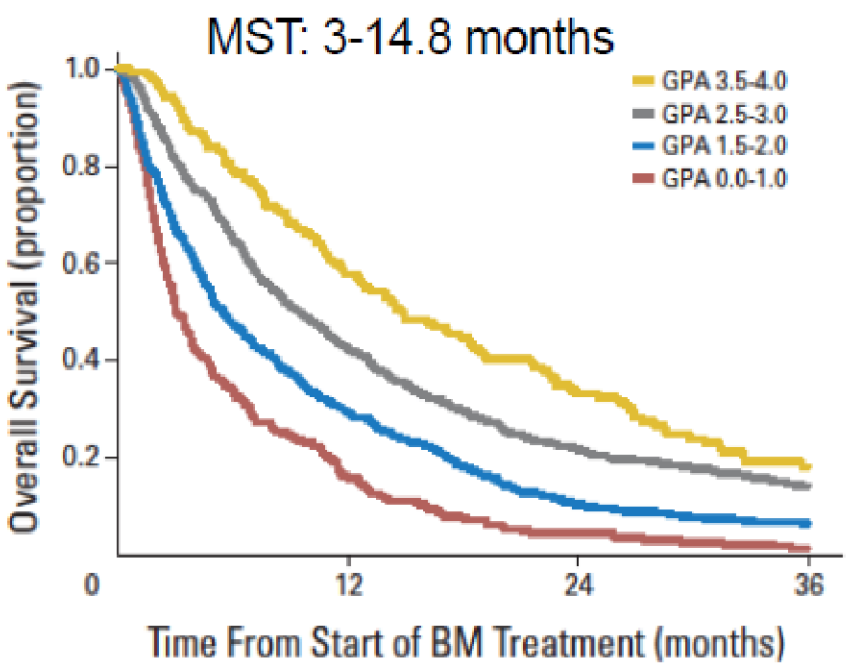
| | KPS | Age | Number of mets | Extra - cranial mets | Tumour subtype |
|---|---|---|---|---|---|
| Lung | ✔ | ✔ | ✔ | ✔ | - |
| Breast | ✔ | ✔ | - | - | ✔ |
| Melanoma | ✔ | - | ✔ | - | - |
| Renal | ✔ | - | ✔ | - | - |
| GI | ✔ | - | - | - | - |

A




Breast cancer

B

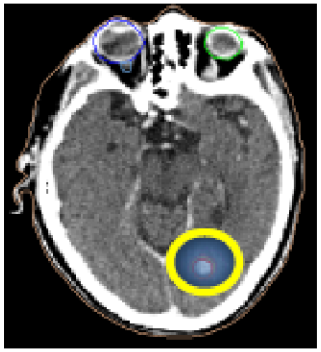


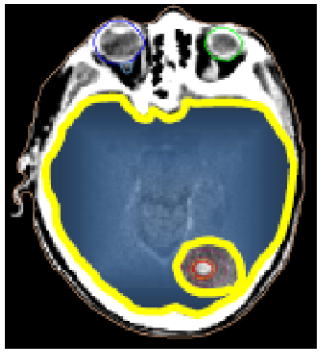

NSCLC

Diagnosis-specific GPA

Sperduto et al.

# Survival in Brain Metastasis



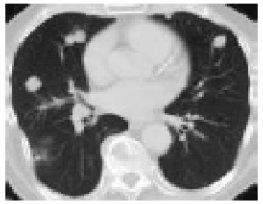


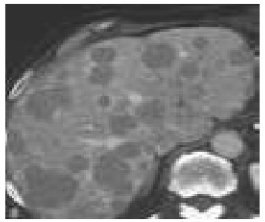
Local control

Regional control:
Freedom from new
brain metastases

**Brain tumor control**

**Extracranial disease control**





**Survival**

# 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*<br>Local failure | 40 weeks<br>20% | 15 weeks<br>52% | <0.01<br><0.02 | N Engl J Med 1990;322: 494-500. |
| Noordjik et al (Dutch) | 63 | OS*<br>FIS* | 10 months<br>7.5 months | 6 months<br>3.5 months | 0.04<br>0.06 | Int J Radiat Oncol Biol Phys 1994; 29:711-17. |
| Mintz et al (Canadian) | 84 | OS*<br>FIS % | 5.6 months<br>32% | 6.3 months<br>32% | NS<br>NS | Cancer 1996;78: 1470-76. |

# 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 =<4cm
- 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

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

S + SRS vs S+WBRT

- 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)

- 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)

# 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.

*Int J Radiation Oncol Biol Phys,* **2014**;90:*526-31*

Lancet 2004; **363:** 1665–72

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

- 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.

Int J Radiation Oncol Biol Phys, Vol. 91, No. 4, pp. 710–717, 2015

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

# 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.

Radiotherapy and Oncology 97 (2010) 370–376

Contents lists available at ScienceDirect

Radiotherapy and Oncology

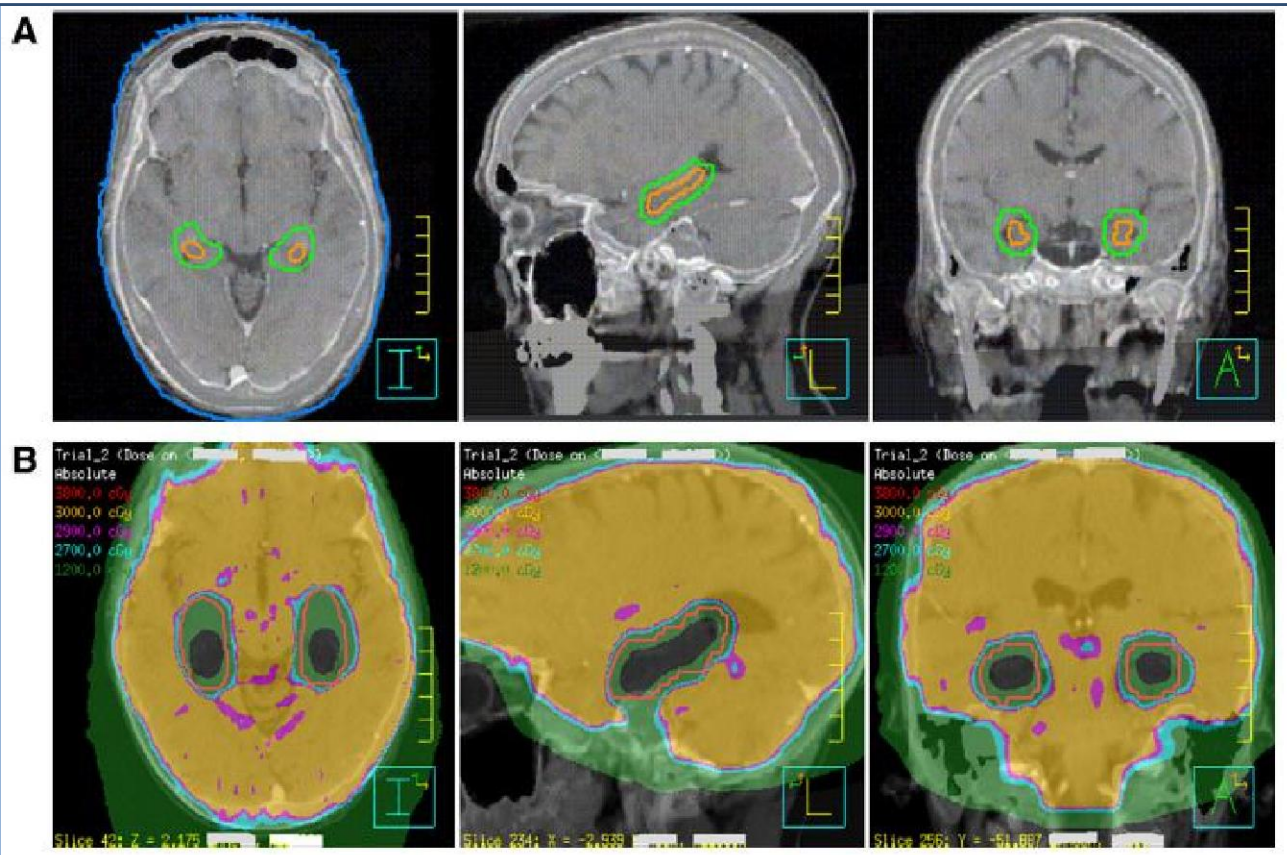
journal homepage: www.thegreenjournal.com

Review

# Why avoid the hippocampus? A comprehensive review

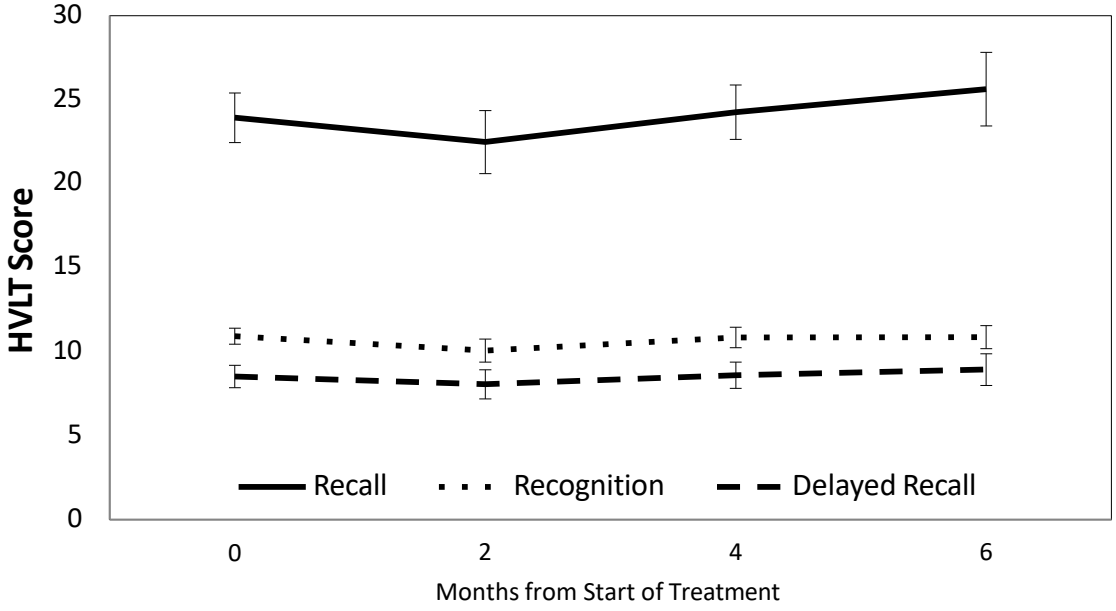
Vinai Gondi [a,*], Wolfgang A. Tomé [a,b], Minesh P. Mehta [a]

[a] Department of Human Oncology; and [b] 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



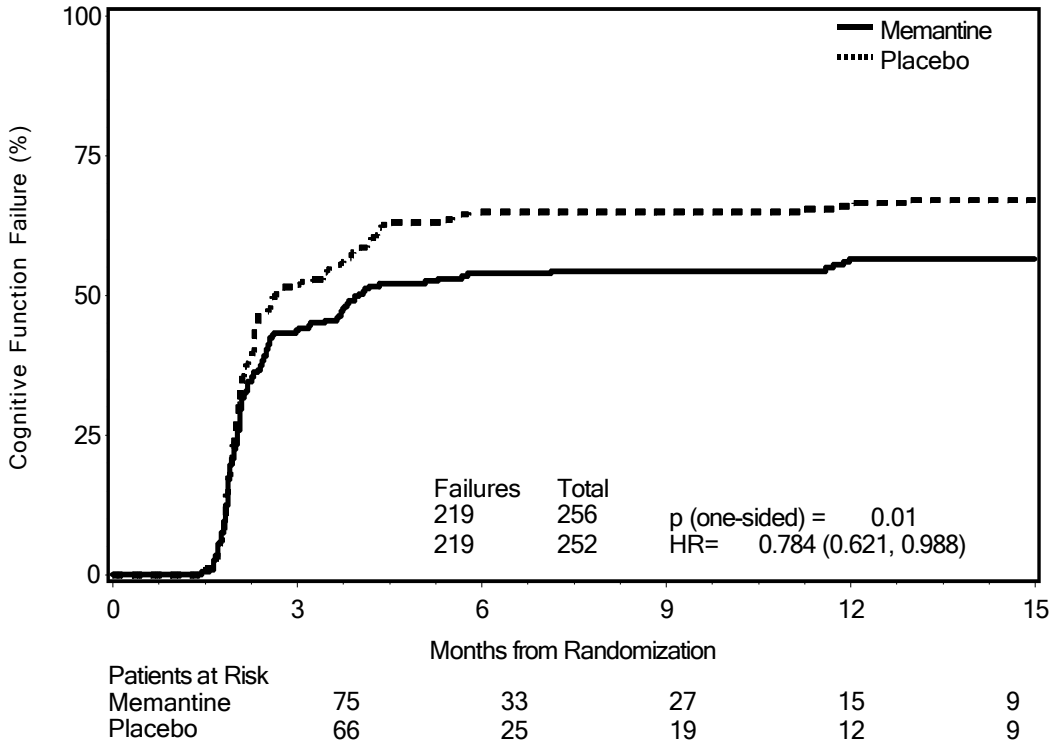

- **Mean decline in HVLT-Delayed Recall from baseline to 4 months:7.0% (95% CI: -4.7-18.7%)**
- Significant compared to historical control: 30% (*p*=0.0003)

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

Gondi et al. JCO 2014

# RTOG 0614

- Phase III trial of WBRT with or without memantine

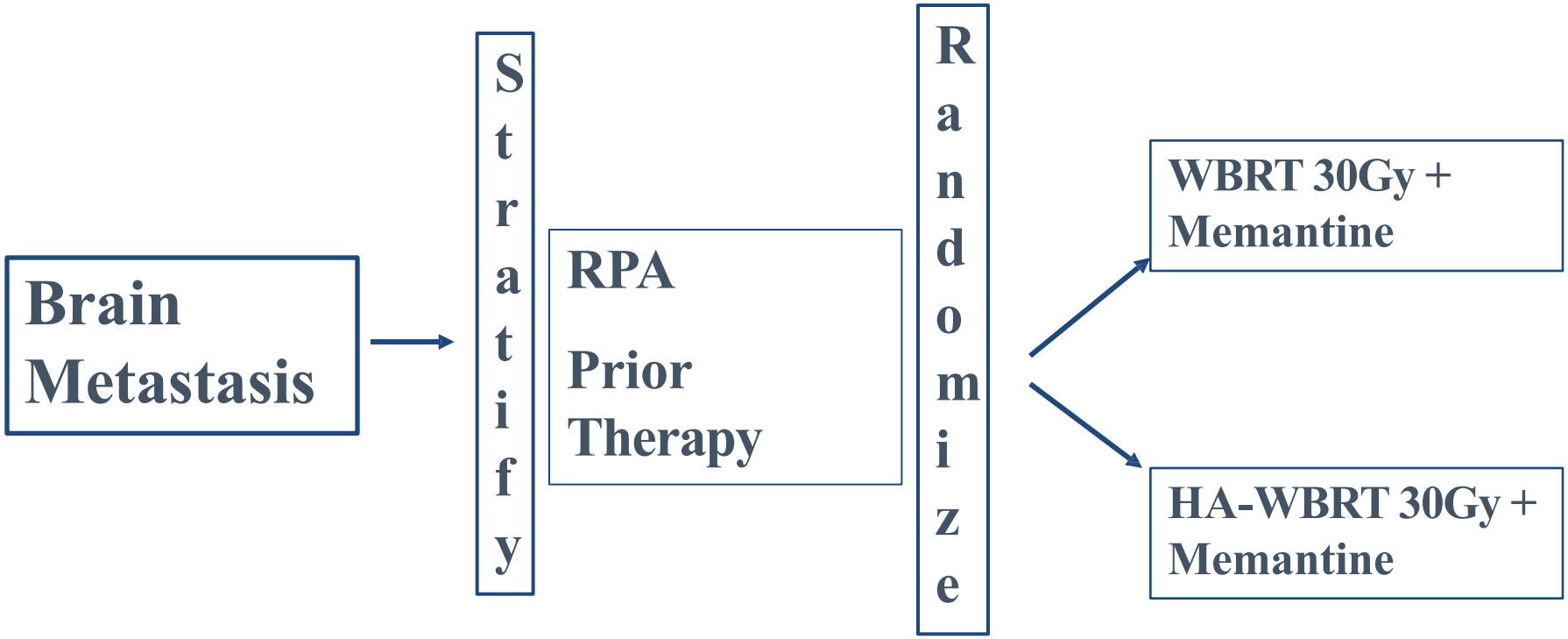



**Memantine during WBRT became standard of care**

Brown et al. Neuro-Oncol 2013

# 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≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing



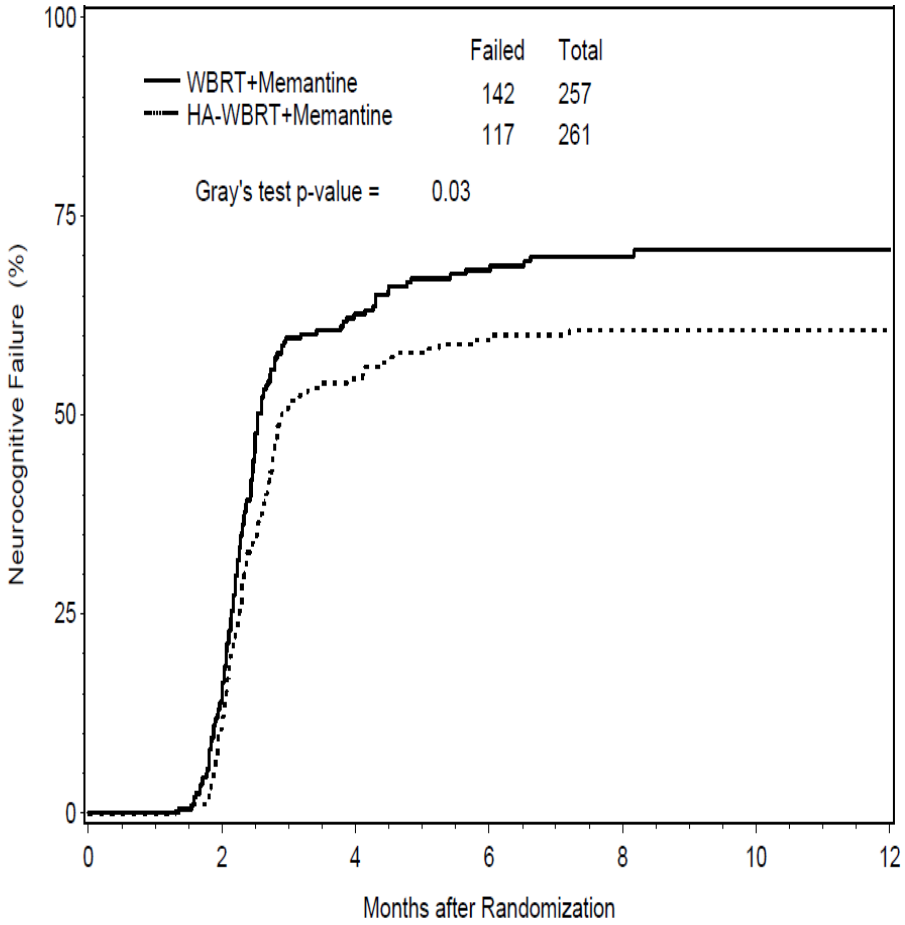
# Primary Endpoint

- 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



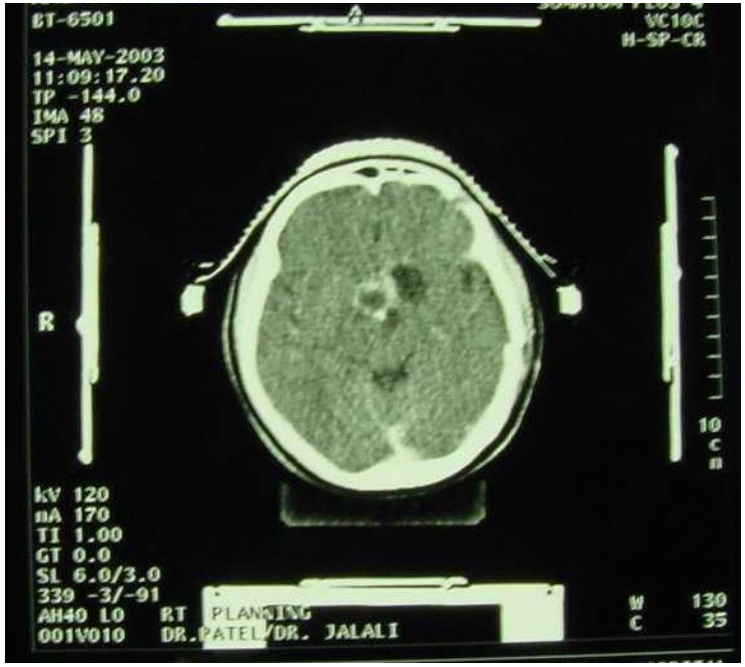

| Patients at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| WBRT+Memantine | 257 | 133 | 34 | 18 | 8 | 6 | 4 |
| HA-WBRT+Memantine | 261 | 124 | 40 | 25 | 18 | 17 | 11 |

# Dose protocols-Brain Metastases

- SRS: (RTOG 90-05)
  - <2cm: 24Gy
  - 2.1-3cm: 18Gy
  - 3.1-4cm: 15 Gy
- FSRT:
  - 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

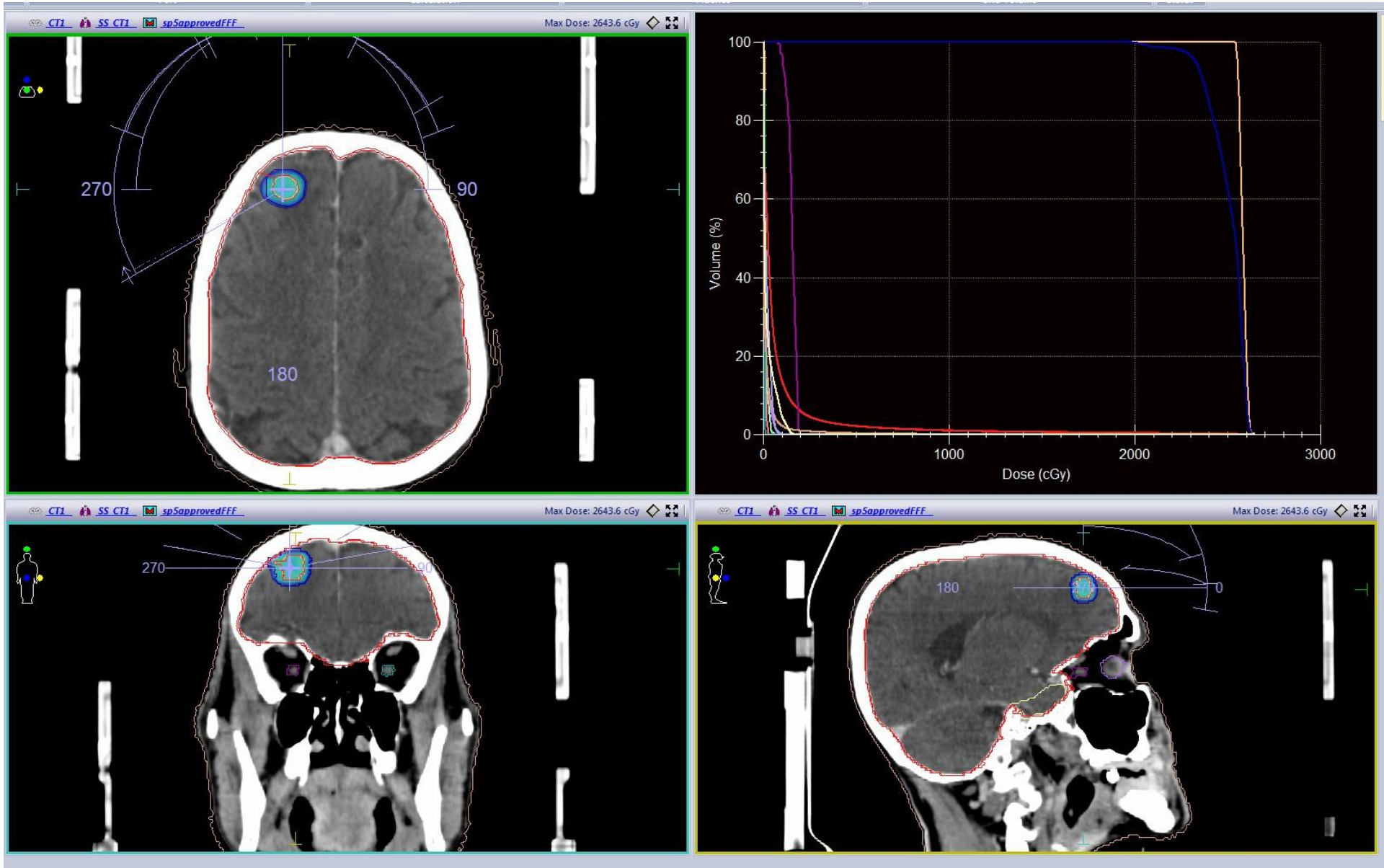



*Stereos* - solid

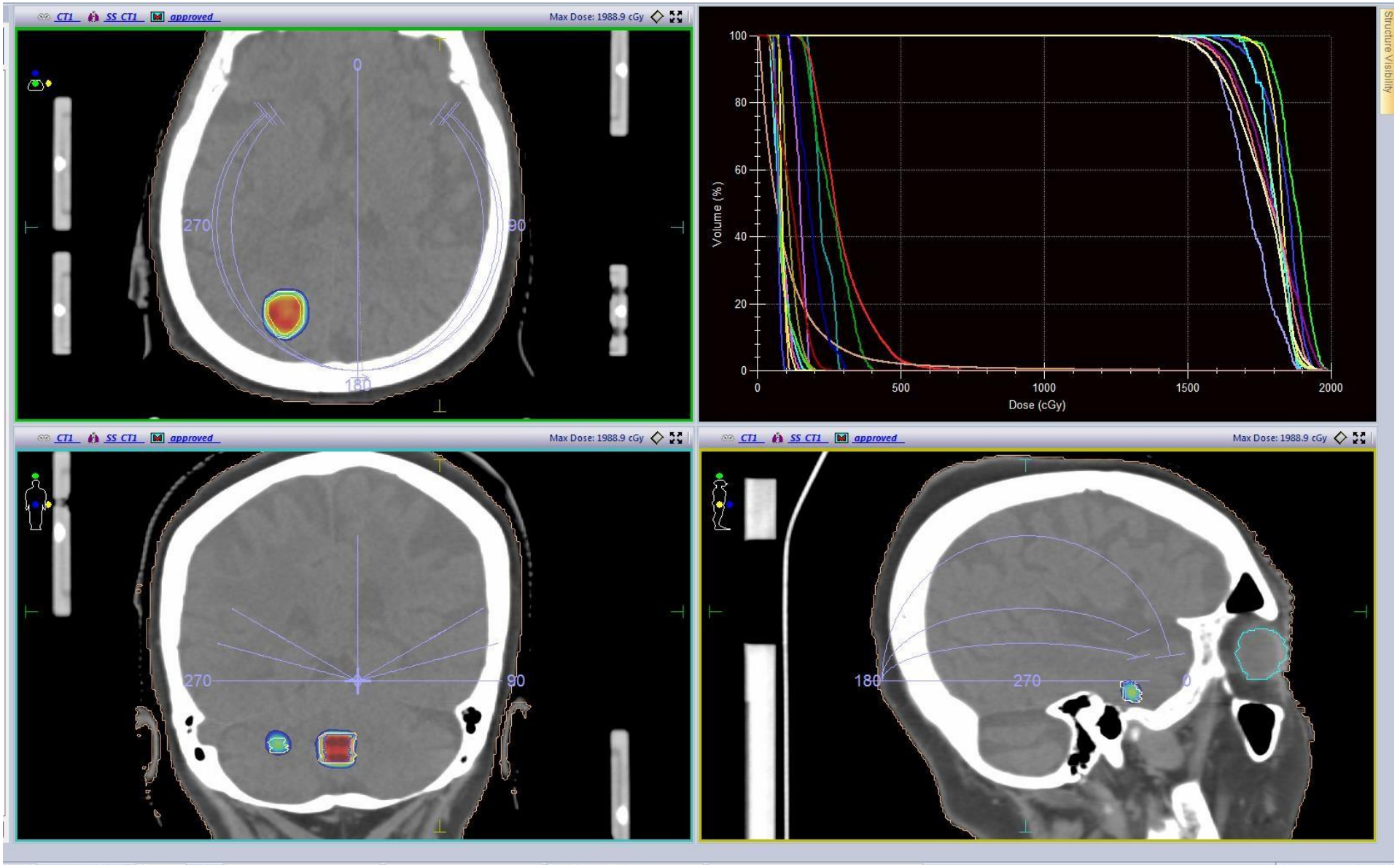
- Gamma knife
- **Modified Linacs**
- Proton beam

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

# Frameless stereotaxy in a solitary met



# Frameless stereotaxy in oligomestatic disease



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

**Toxicity? Efficacy?**

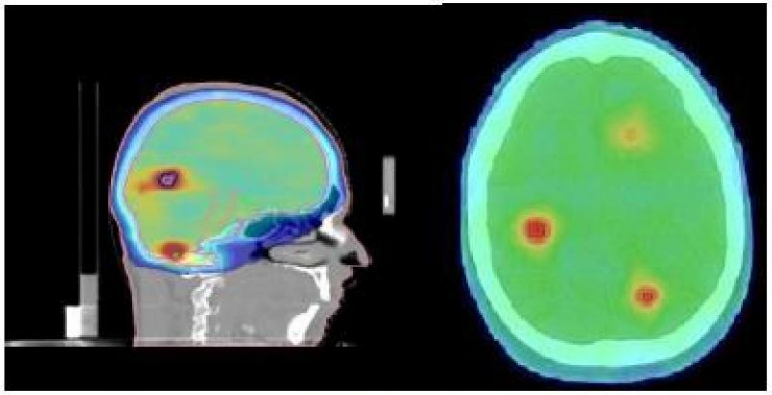
EORTC
*The future of cancer therapy*

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 oligomets**

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

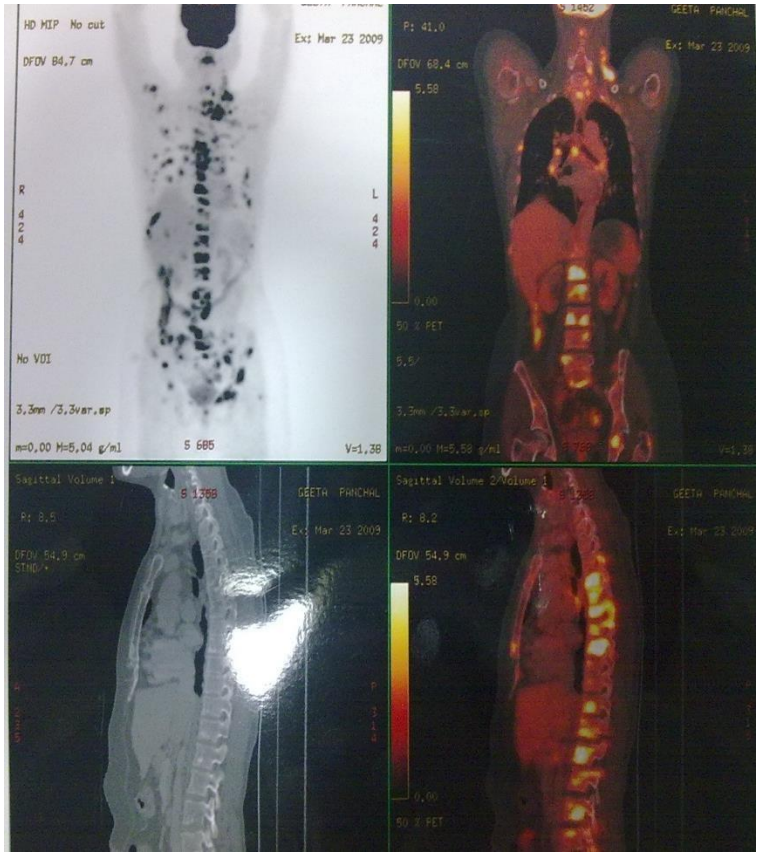
- Dosimetric advantages (steeper dose gradients)
- Logistic advantages (no separate procedures)
- Patient tolerance advantages (outpatient, frameless, delivery ~5 minutes)

# Summary of trials

| | Outcome | Level of evidence |
|---|---|---|
| SRS+WBRT Vs WBRT alone | Improve survival in single metastatic disease with KPS>=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



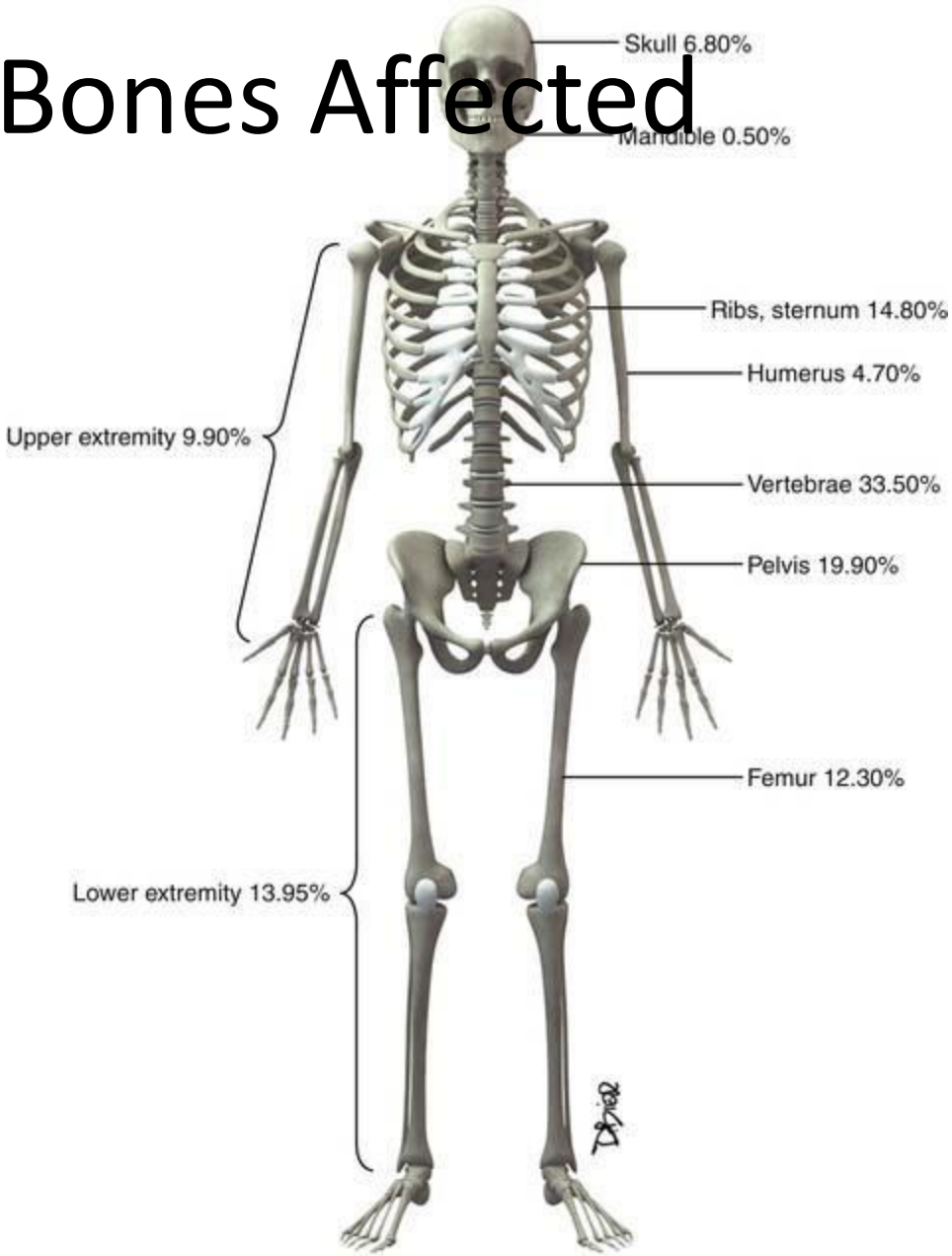
# Symptoms/Complications Related to Bone Metastases

- Pain
- Pathological fracture
- Spinal cord compression
- Hypercalcaemia

poor QOL

# Bones Affected

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




Clan A. et al. Br J ancer.1965;19:15-29

# 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
- Verteboplasty/kyphoplaty
- 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 [a,*], Tracy Balboni MD MPH [b], Joshua Jones MD [c], Simon Lo MB ChB [d], Joshua Petit MD [e], Shayna E. Rich MD PhD [f], Rebecca Wong MB ChB [g], Carol Hahn MD [h]

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[8] | 5617 in 25 RCTs | SF | 60 | 23 | NR | 20 |
| | | MF | 61 | 24 | | 8 [a] |
| Gutierrez Bayard, 2014[4] | 90 | 8 Gy in 1 fx | 79 | 17 | NR | 13.3 |
| | | 30 Gy in 10 fx | 88 | 18 | | 8.8 [a] |
| | | | at 4 wk | at 4 wk | | |
| Howell, 2013[5] | 235 | 8 Gy in 1 fx | 70 | 19 | 10 | 15 |
| | | 30 Gy in 10 fx | 62 | 17% | 20 [a] | 5 [a] |
| | | | at 3 mo | at 3 mo | (acute grade 2-4) | |
| Majumder, 2012[6] | 64 | 8 Gy in 1 fx | 85 | 0 | No statistically | NR |
| | | 30 Gy in 10 fx | 77 | 0 | significant difference | |
| | | | at 1 month | at 1 month | | |
| Meeuse, 2010[7] | 1157 | 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.

[a] 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 radoipharmaceuticals

# 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-enviroment 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***

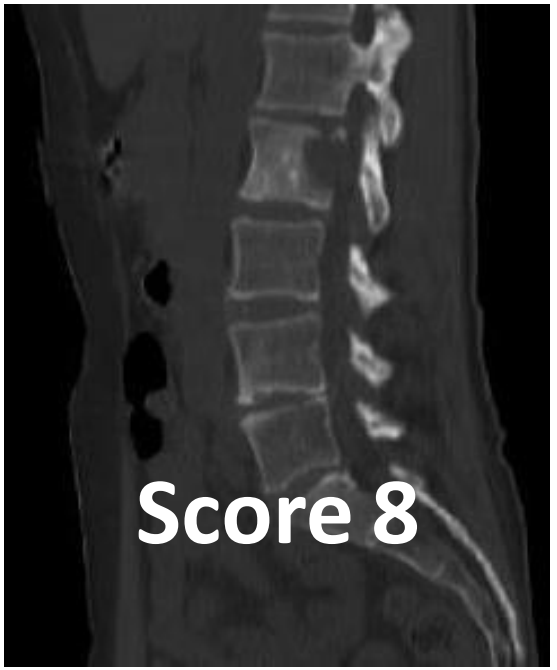
| Criteria | Rationale |
|---|---|
| Inclusion | |
| Oligometastasis involving the spine | These pts generally have a long expected survival & thus are most likely to benefit from radiosurgery/SBRT |
| Pts w/ radioresistant histology (RCC, melanoma, sarcoma) | Higher doses of radiation might be associated w/ improved local tumor control |
| Patients with paraspinal extension contiguous to the spine | Pts w/ extraosseous extension might experience improved soft-tissue tumor control |
| Exclusion | |
| 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 |
| Norma | |
| Vertebra | |
| > 50% | |
| < 50% | |
| No col | |
| None | |
| Posterol | |
| Bilater | |
| Unilate | |
| None | |




0 to 6 → stability

7 to 12 → indeterminate instability

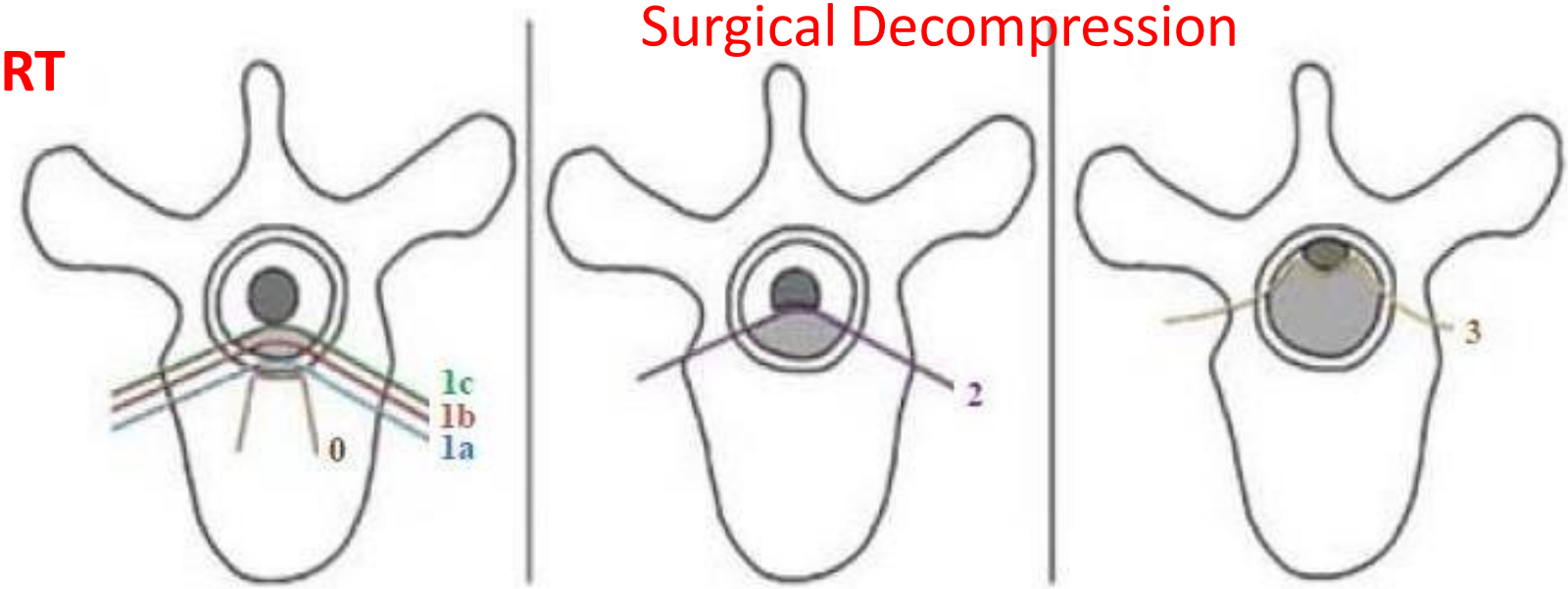
13 to 18 → instability

SINS 7-18 warrants surgical consultation before RT

## 1. Epidural Spinal Cord Compression Scale (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

Bilsky et al, 2010, J Neurosurg: Spine 13(3), 324-328

# 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) |
| Guckenberger 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) |

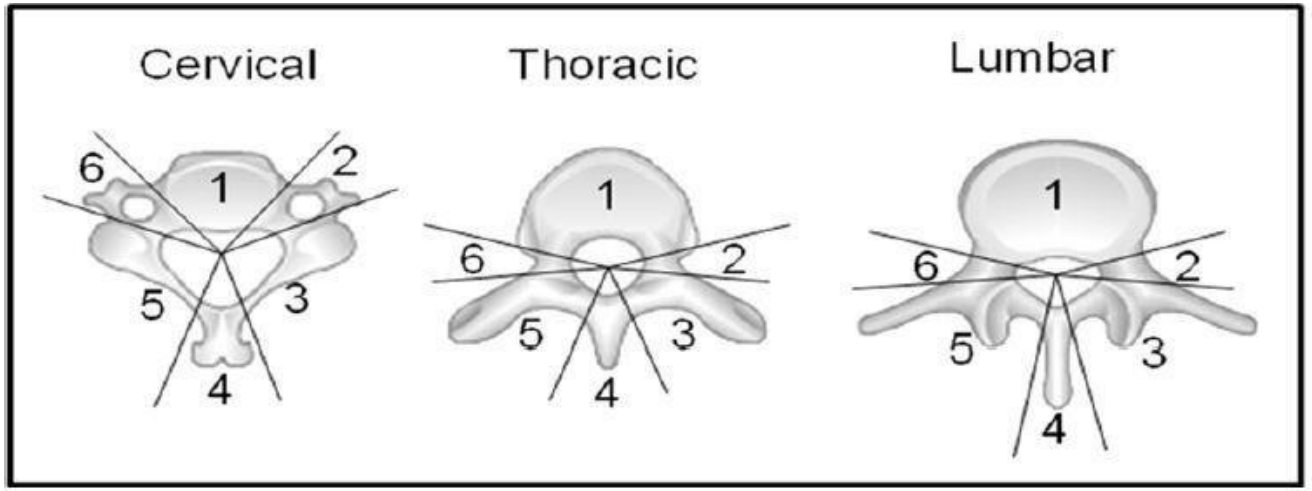
# Pain Control

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

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

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

| Target volume | Guidelines |
|---|---|
| GTV | • Contour gross tumor using all available imaging<br>• Include epidural and paraspinal components of tumor |
| CTV | • Include abnormal marrow signal suspicious for microscopic invasion<br>• Include bony CTV expansion to account for subclinical spread<br>• Should contain GTV<br>• 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 |
| PTV | • Uniform expansion around CTV<br>• CTV to PTV margin $\leq$3 mm<br>• Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised<br>• Never overlaps with cord<br>• Should contain entire GTV and CTV |

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

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

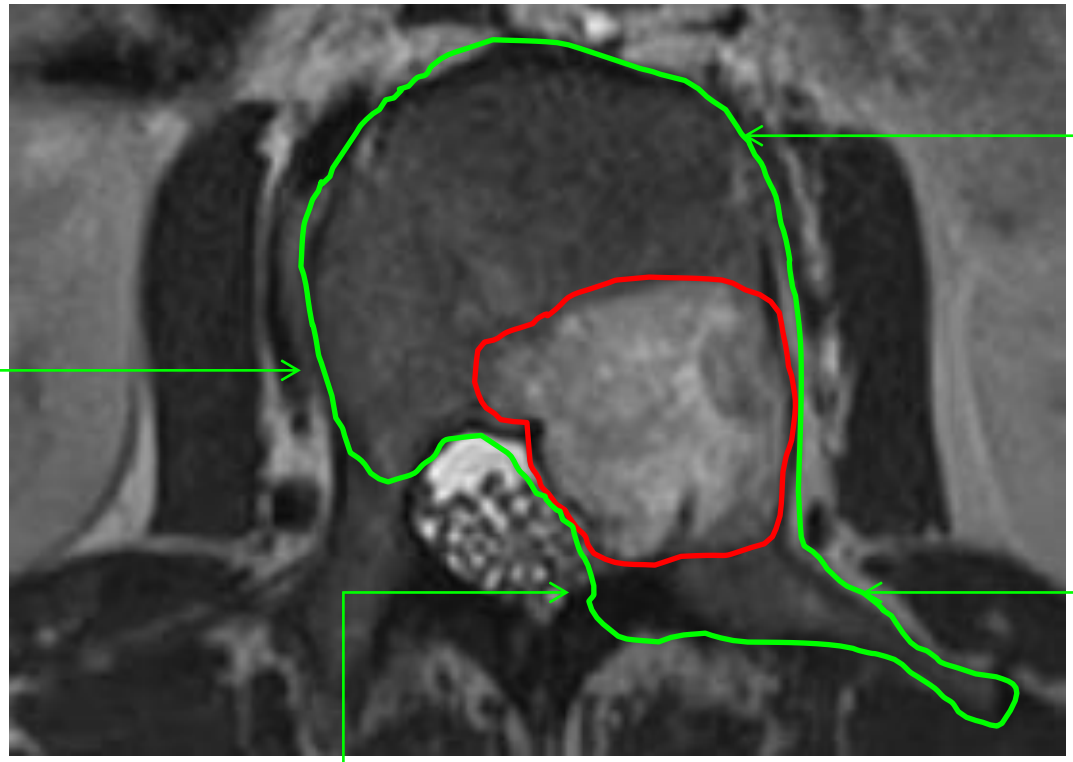
Cox BW. IJROBP 2012;83(5):e597-605

**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 ± 1 | Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± 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[35]* | MDACC[37]† |
|---|---|---|
| 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[41]* | MDACC[43]† |
|---|---|---|
| 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 ≥2 at the treated site without increase in OMED, or analgesic reduction of ≥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 ≥2 above baseline with stable OMED, or analgesic increase of ≥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 ≥2 and subsequent sustained rise (≥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 | Lcoal / 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<br>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

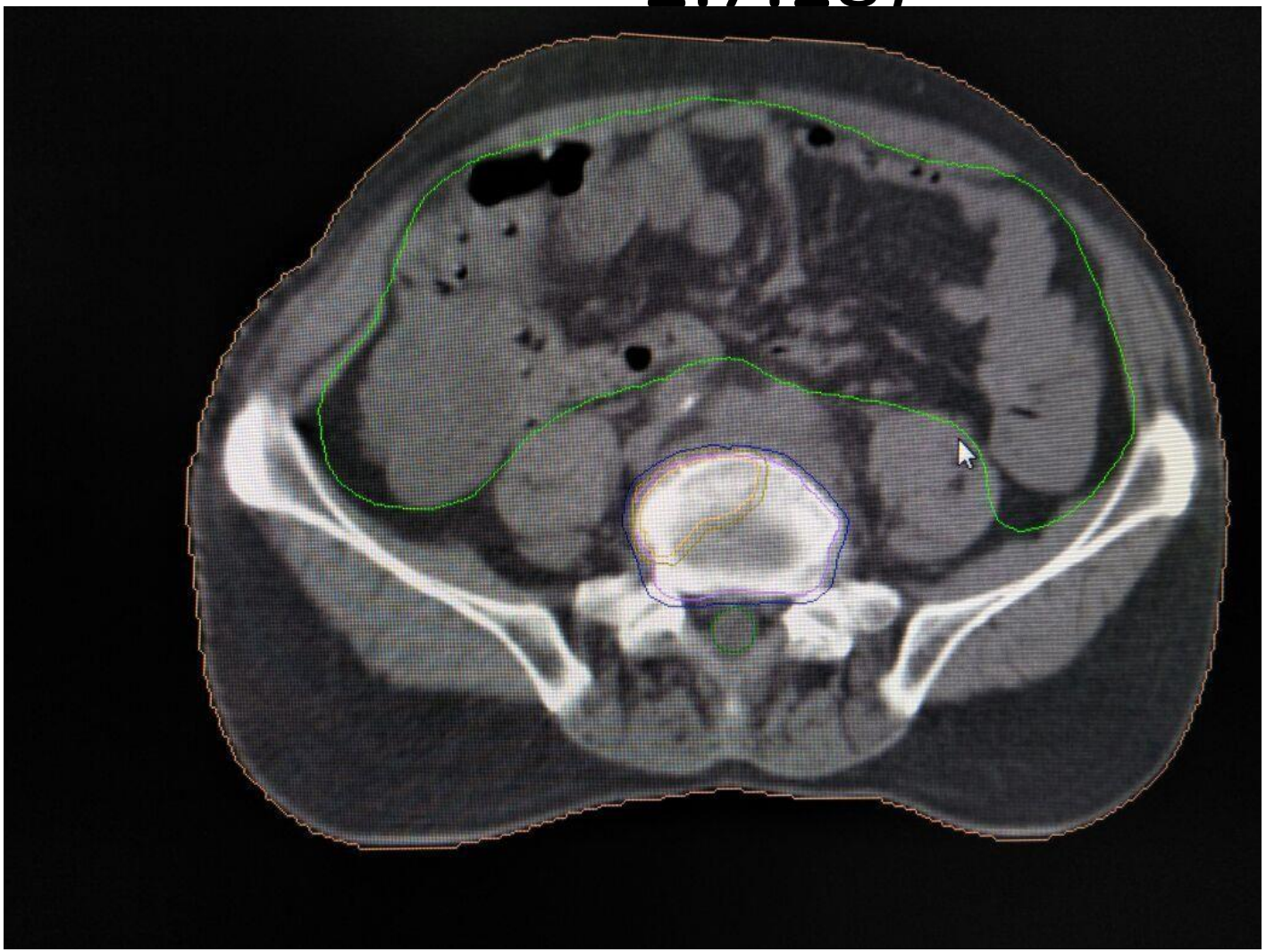
**Consensus indications and contraindications for postoperative spine SBRT**

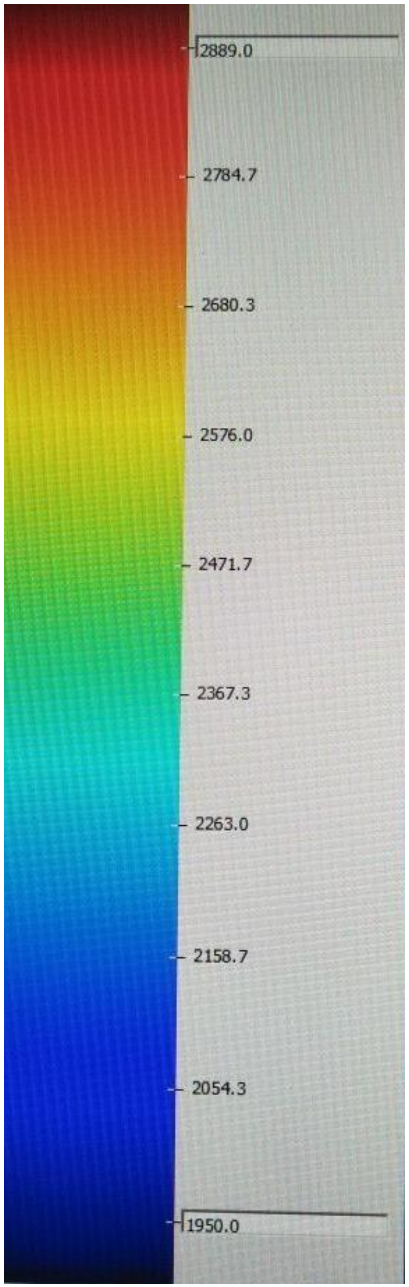
| Indications | Contraindications |
|---|---|
| Radio-resistant primary1–2 levels of adjacent disease<br>Prior overlapping radiation therapy | Involvement of more than 3 contiguous vertebral bodies<br>ASIA Grade A status (complete spinal cord injury without preservation of motor or sensory function)<br>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<br>Surgical instrumentation & incision not included unless involved<br>Prophylactic circumferential treatment of epidural space controversial<br>Additional expansion up to 5 mm for paraspinal extension controversial<br>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)

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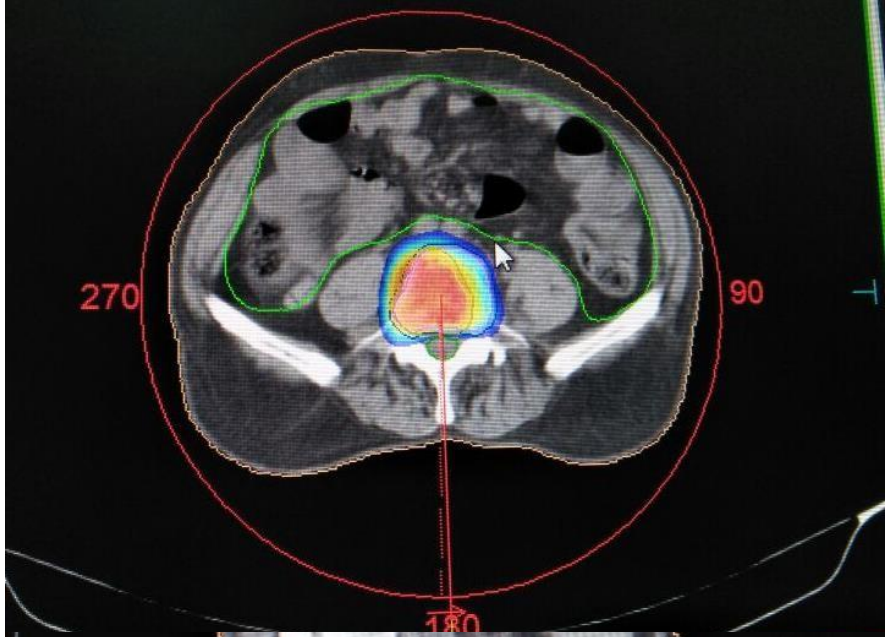
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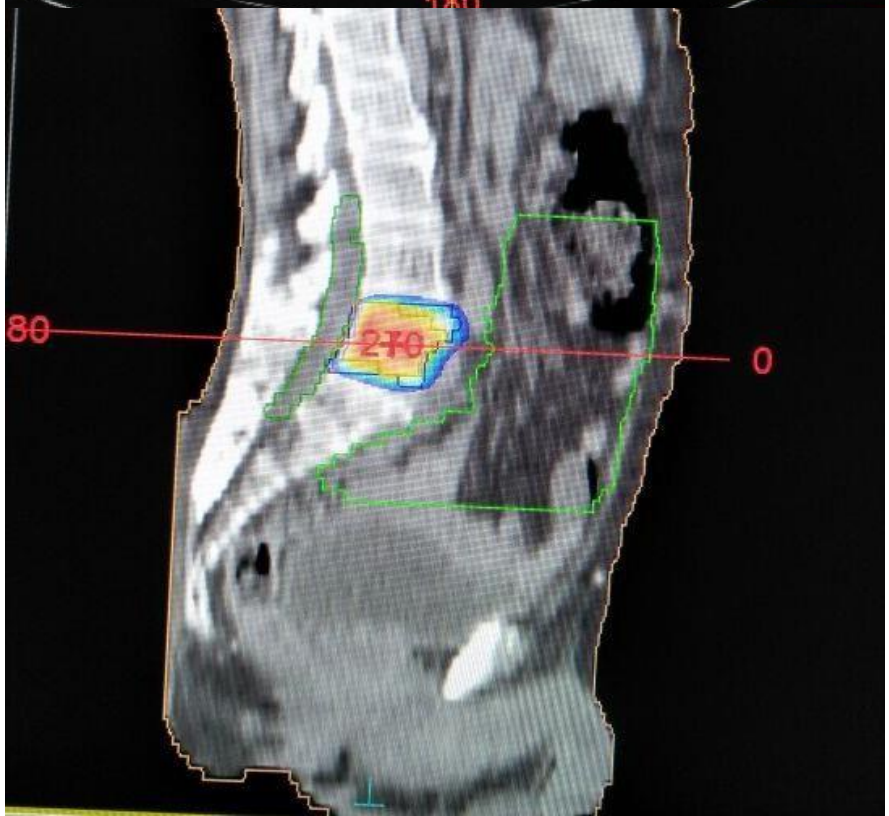
80
270
0

# Newer Radiopharmaceutical- Radium 223

- For wide spread osteoblastic metastases→ P32 / Sr89 / Sm153 _ Beta emitters
- Radium 223 in alpha emitting radionuclide, high LET, half-life of 11.4 days.
- FDA approved in 2013 for 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.


Any questions?