Radiotherapy for Oligometastatic NSCLCa

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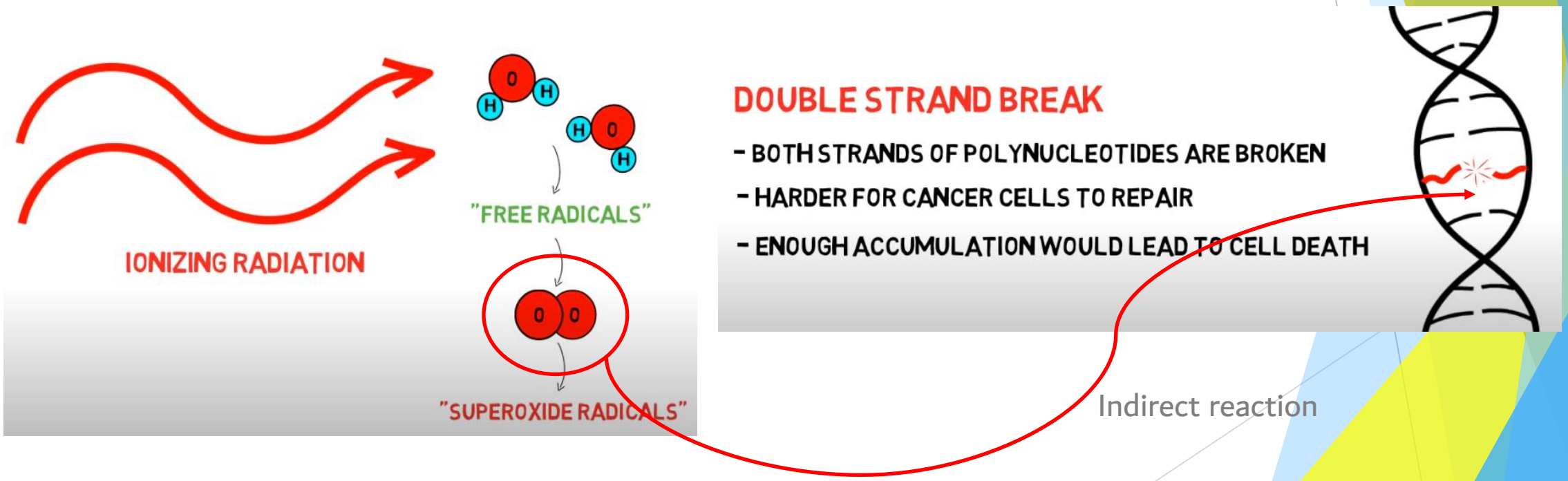
What is radiotherapy

- 전리방사선을 이용하여 tumor cell death 유발



Types of radiation therapy

- 이용하는 방사선의 종류에 따라 (X-ray, electron, proton, and heavy particle)
- 외부방사선치료 (external radiotherapy) or 근접치료 (brachytherapy)

- 방사선치료 scheme(fraction size, no. of fractions, duration 등)에 따라

Conventional

- ✓ 1.8~2Gy/fraction
- ✓ 20~35 fractions
- ✓ 5 fractions/week

Hypofractionated

- ✓ Bigger fractions size
- ✓ 10~20 fractions
- ✓ 3~5 fractions/week

SABR (Stereotactic ablative radiotherapy)

- ✓ > 5 Gy/fraction
- ✓ ≤ 5 fractions (usually)
- ✓ 2~3 fractions/week

방사선치료기의 발전 ; MLC

Types of radiation therapy machine

- TrueBeam, VersaHD, Infinity, RapidArc, VitalBeam, Halcyon, Tomotherapy…
- Cyberknife, Gammaknife
- Proton therapy, Heavy ion therapy

>> 전리방사선을 발생시켜 원하는 선량의 방사선을 원하는 모양으로 조사할 수 있는 장치

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- **Linear Accelerator (LINAC)** ; TrueBeam, VersaHD, Infinity, RapidArc, VitalBeam

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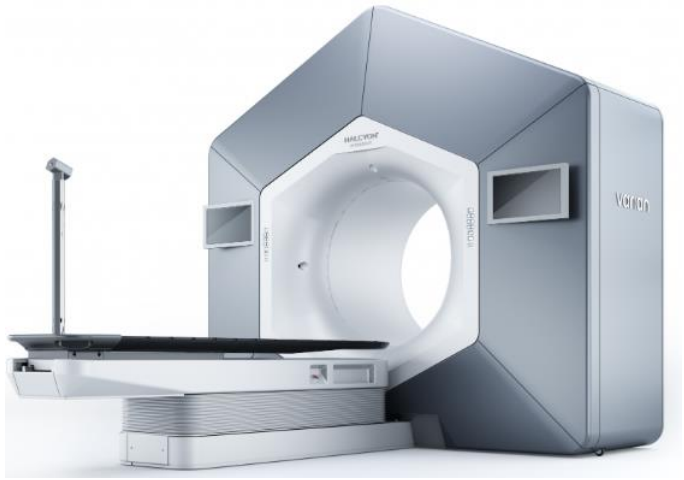
- **Helical therapy** ; Halcyon, Tomotherapy



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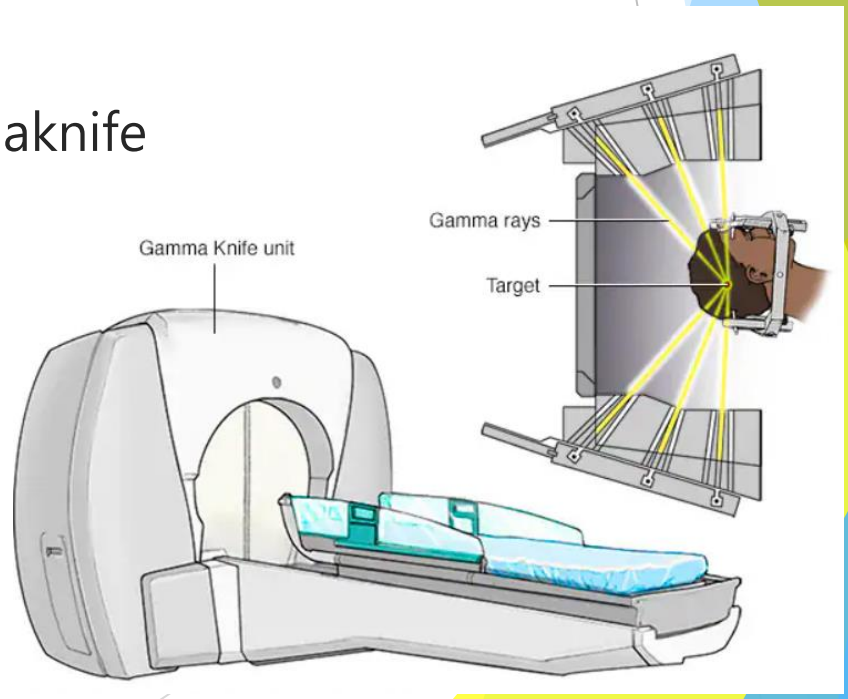
- Specialized **for radiosurgery** ; Cyberknife, Gammaknife



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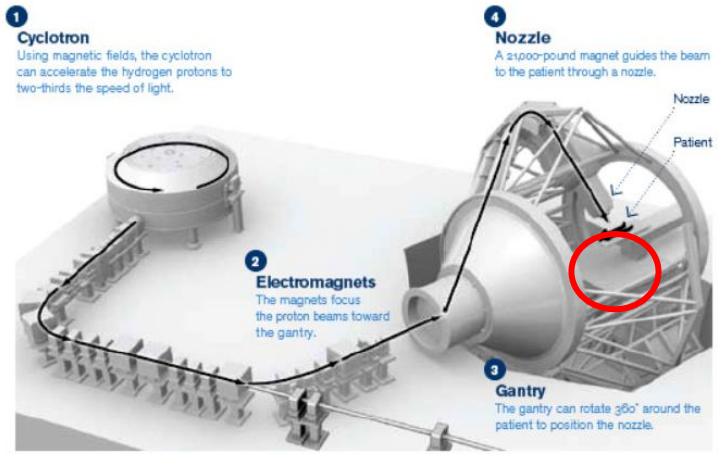
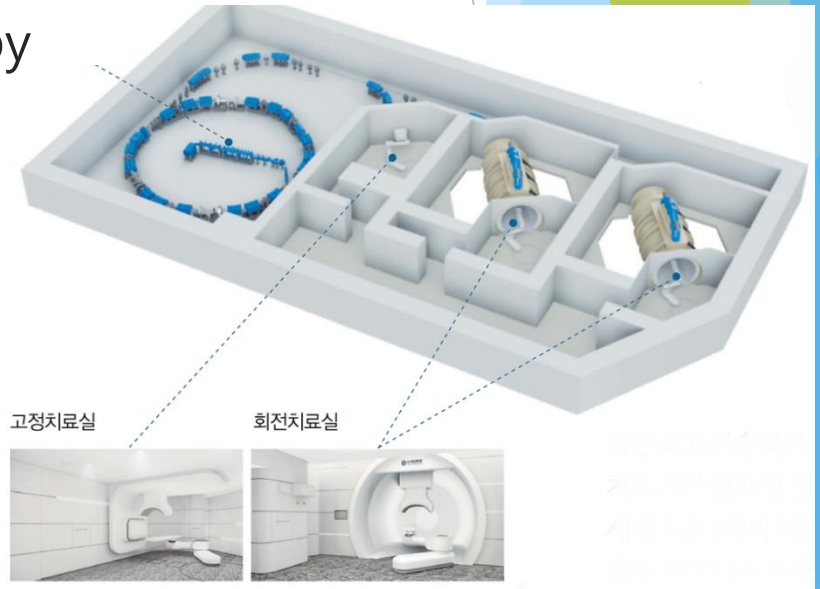
- **Particle beam therapy** ; Proton or Heavy particle therapy

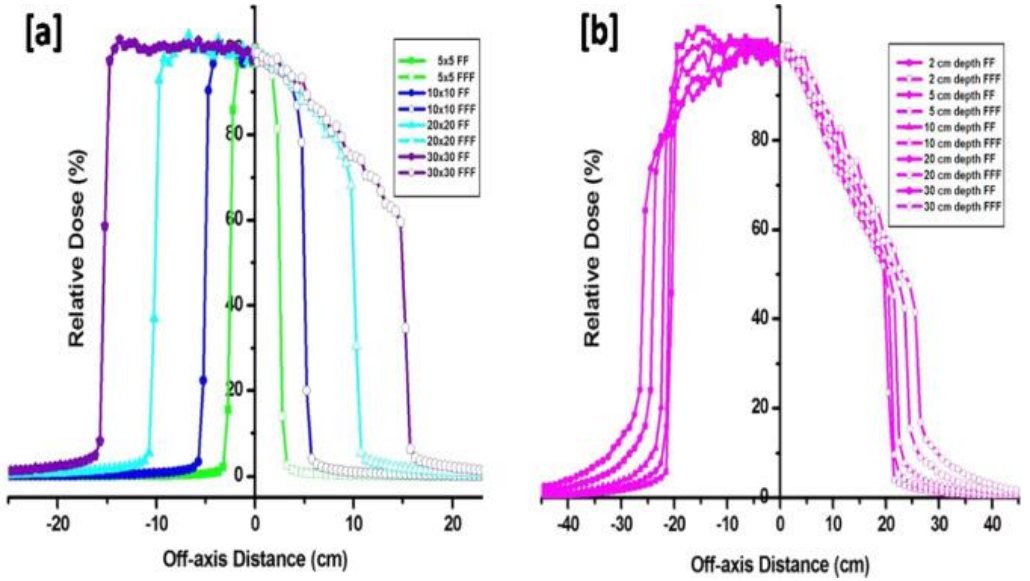




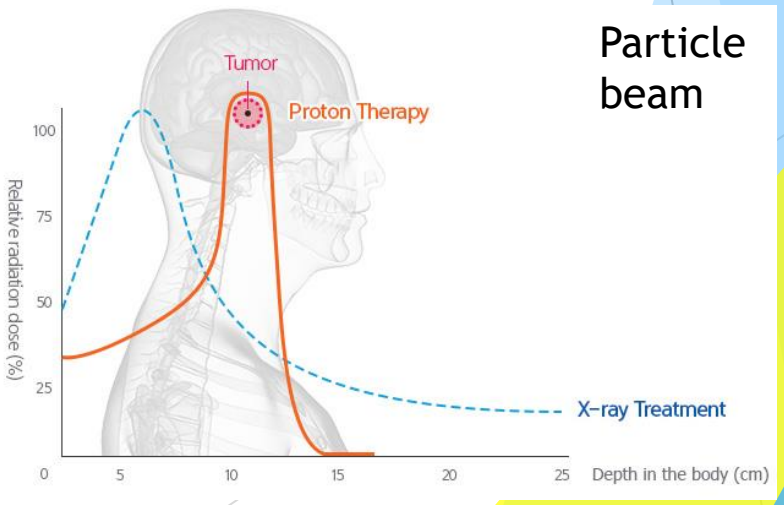
What is SABR (SBRT)

- **Very high precision** radiation therapy
- Usually small, localized extracranial lesions, not adjacent to vital organs
- Very high dose of radiation, 1~5 fractions, **Image-guided delivery**, immobilization
- Have advantages with **sharp dose gradient** (*vs.* dose homogeneity)

Radiosurgery



FFF beam



Particle beam

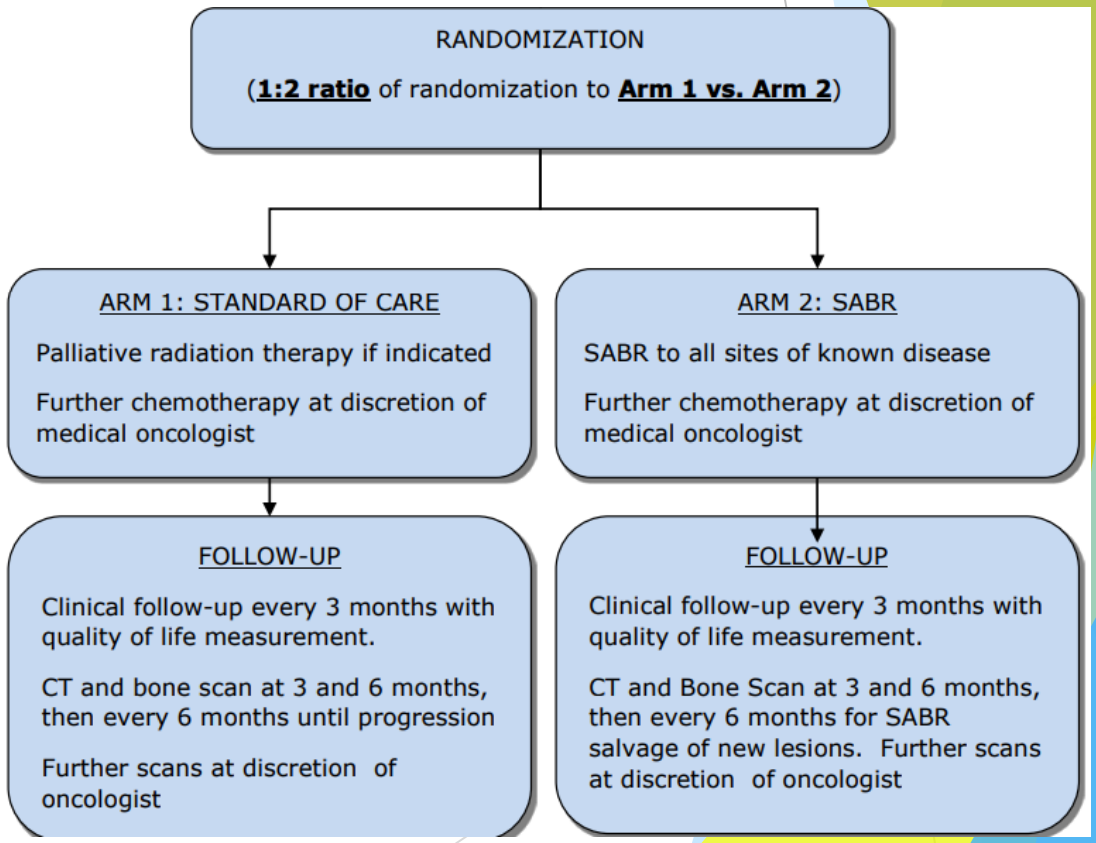
In case of oligometastatic disease,

SABR-COMET phase II Randomized trial 2020

- 99 pts c controlled primary & medically stable, from 10 centers
- 1~5, SABR-eligible metastases
- Primary endpoint : OS
- Secondary endpoints : QoL, PFS, Toxicity, lesional control rate, No. of further chemotherapy or systemic therapy

ECOG performance status 0-1
Controlled primary tumor
- defined as: at least 3 months since original tumor treated definitively, with no progression at primary site

All sites of disease can be safely treated based on criteria below
Maximum size of 3 cm for brain lesions
Maximum size of 5 cm for lesions outside the brain, except:
- Bone metastases up to 6 cm may be included, if in the opinion of the local PI it can be treated safely (e.g. rib, scapula, pelvis)



Arm 1 ; best palliative care

Brain: Whole brain radiotherapy
i.e. 20 Gy in 5 fractions, 30 Gy in 10 fractions

Lung: Palliative radiotherapy as per 2011 consensus guidelines.[15]
i.e. 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions

Bone: Palliative radiotherapy as per 2011 consensus guidelines.[16]
i.e. 8 Gy in 1 fraction (most common), 20 Gy in 5 fractions, 30 Gy in 10 fractions

Liver: 20 Gy in 5 fractions if standard institutional practice

	Optional whole brain to follow (see text)				
Liver	LRCP site: Dose is based on calculated normal tissue probability of <5%				Every second day
	Other sites	45-60	3-8	7.5-15	Every second day
Adrenal		60 Gy	8	7.5	Every second day

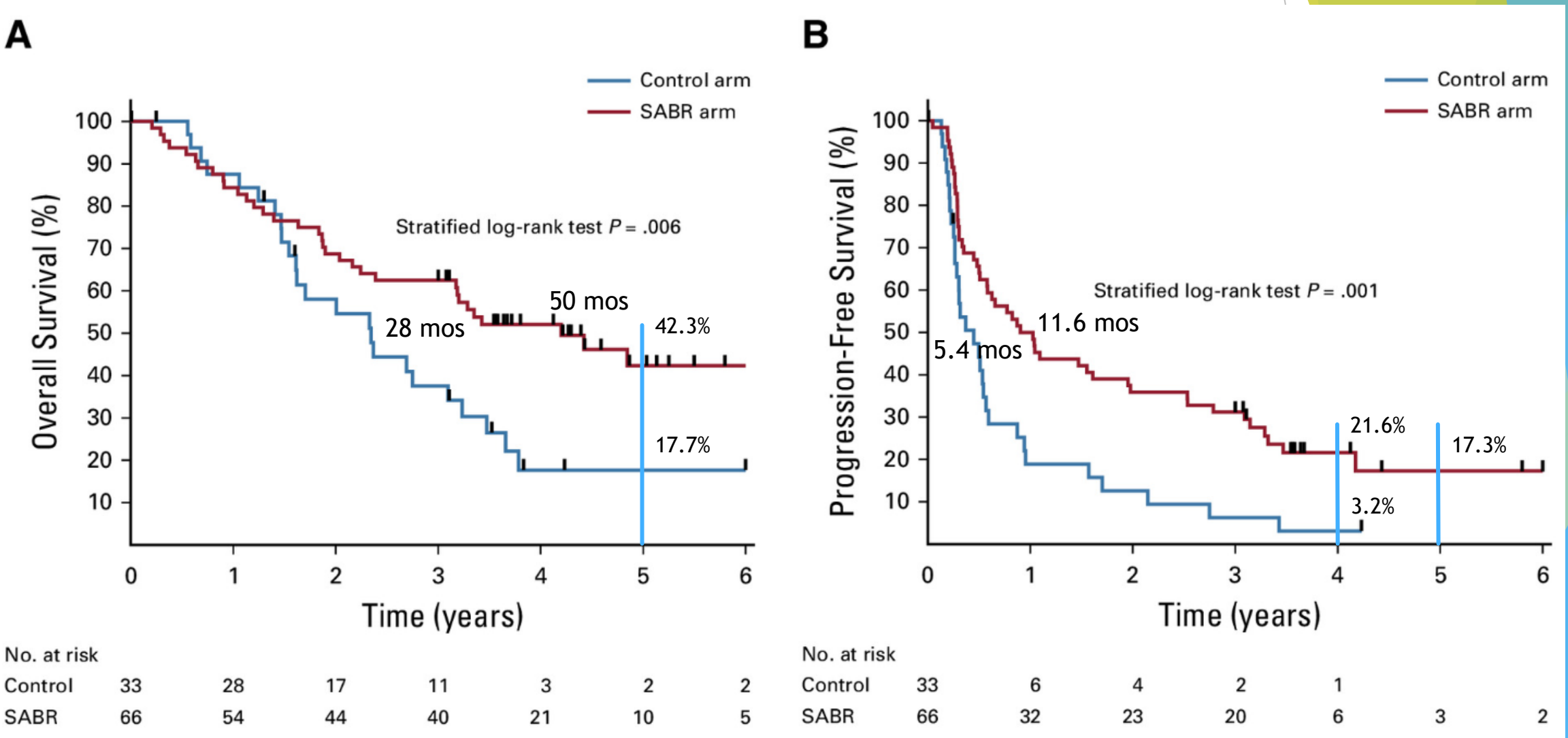
*If esophageal dose constraints cannot be met, 12 fractions should be used.

No CTV margin, 2~5mm of PTV margin

Arm 2 ; SABR

Tumor Location	**Description**	**Total Dose (Gy)**	**Number of fractions**	**Dose per fraction (Gy)**	**Frequency**
Lung	Tumors 3 cm or less surrounded by lung parenchyma	54	3	18	Every second day
	Abutting chest wall or >3 cm	55	5	11	Every second day
	Within 2 cm of mediastinum or brachial plexus	60	8*	7.5	Every second day
Bone	Any bone except femur	35 Gy	5	7	Daily
	Vertebral body: additional options	16-20 Gy *OR* 30 Gy	1 3	16-20 10	Single dose Every second day
Brain Metastases	Non-radiosurgical (If whole brain treated, then simultaneous boost to each lesion)	40 Gy to metastases 20 Gy whole brain (optional)	5 5	8 Gy to lesion 4 Gy WBRT	Daily Daily
	Radiosurgical **≤1 cm** **>1 and ≤2 cm** **>2 and ≤ 3 cm**	 22-24 Gy 20-22 Gy 18-20 Gy	 1 1 1	 22-24 Gy 20-22 Gy 18-20 Gy	 Single dose Single dose Single dose

Median FU ; 51 mos



Median FU ; 51 mos

- Overall long term local control (RECIST 1.1)

  46% (26/57) *vs.* 63% (65/104) (*p-value* 0.039)

  differences btw lesion site : adrenal(100%), bone(72%), lung(51%), liver(50%) (*p-value* 0.04)

- Overall rate of > gr 2 toxicities

  9% (3/33) *vs.* 29% (19/66) (*p-value* 0.03)

  3 deaths in SABR arm, probably related to the treatment

- No differences in total QoL score, or subscale scores
- No differences in cumulative incidences of new metastasis

- Upcoming COMET-3, COMET-10, and CORE trial

In case of oligometastatic NSCLCa,

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

JCO 2019

Authors: Daniel R. Gomez, MD, Chad Tang, MD, Jianjun Zhang, MD, PhD, George R. Blumenschein Jr, MD, Mike Hernandez, MS, J. Jack Lee, PhD, Rong Ye, MS, ... SHOW ALL ..., and John V. Heymach, MD, PhD | AUTHORS INFO & AFFILIATIONS

- 99 pts c ≤ 3 metastases, more than 3 months of controlled primary after frontline systemic therapy
- Randomly 1:1 assignment
- maintenance or observation (MT/O) vs local consolidative therapy to all active sites (LCT)
- Primary endpoint : PFS
- Secondary endpoints : OS, Toxicity, appearance of new lesion

Sites of Disease at Random Assignment	Treatment Regimen From Random Assignment to Off Study
(1) Lung/lymph nodes	(1) 66 Gy in 33 fractions RT + paclitaxel (99 mg) + carboplatin (190 mg) IV per week
(2) Spleen	(2) 50 Gy in four fractions
(1) Brain*	(1) Surgical resection
(2) Lung/lymph nodes	(2) 60 Gy in 15 fractions RT to GTV, 52.5 Gy in 15 fractions to PTV with SIB
(1) Lung/lymph nodes	(1) 67.5 Gy in 27 fractions RT
(2) Bone (humerus)	(2) 30 Gy in 10 fractions
(1) Lung/lymph nodes	(1) and (2) 70 Gy in 10 fractions (one field)
(2) Pleura	Continued maintenance therapy: erlotinib 150 mg PO per day
(1) Brain*	(1) Surgical resection
(2) Lung/lymph nodes	(2) Surgical resection
(1) Lung/lymph nodes	(1) 66 Gy in 30 fractions RT + paclitaxel (108 mg) + carboplatin (228 mg) IV per week
(2) Metastatic lung	(2) 50 Gy in four fractions RT
(1) Lung	(1) and (2) treated to 50 Gy in four fractions
(2) Metastatic lung lesions (n = 2)	
(1) Two brain lesions*	1) Gamma knife, 15 Gy and 20 Gy
(2) Lung/lymph nodes	2) Not treated (experienced progression before local therapy)
(1) Two bony sites (T9 and left humerus)*	(1) 30 Gy in 10 fractions each
(2) Lung/lymph nodes	(2) Surgical resection and PORT, 60 Gy in 30 fractions
(1) Lung	(1) 70 Gy in 10 fractions
(2) Metastatic lung (n = 2 nodules)	(2) 50 Gy in 4 fractions
(1) Lung/lymph nodes	(1) Surgical resection and PORT, 45 Gy in 15 fractions
(2) Metastatic lung	(2) Surgical resection
	Continued maintenance therapy: pemetrexed 500 mg/m^2

Conventional

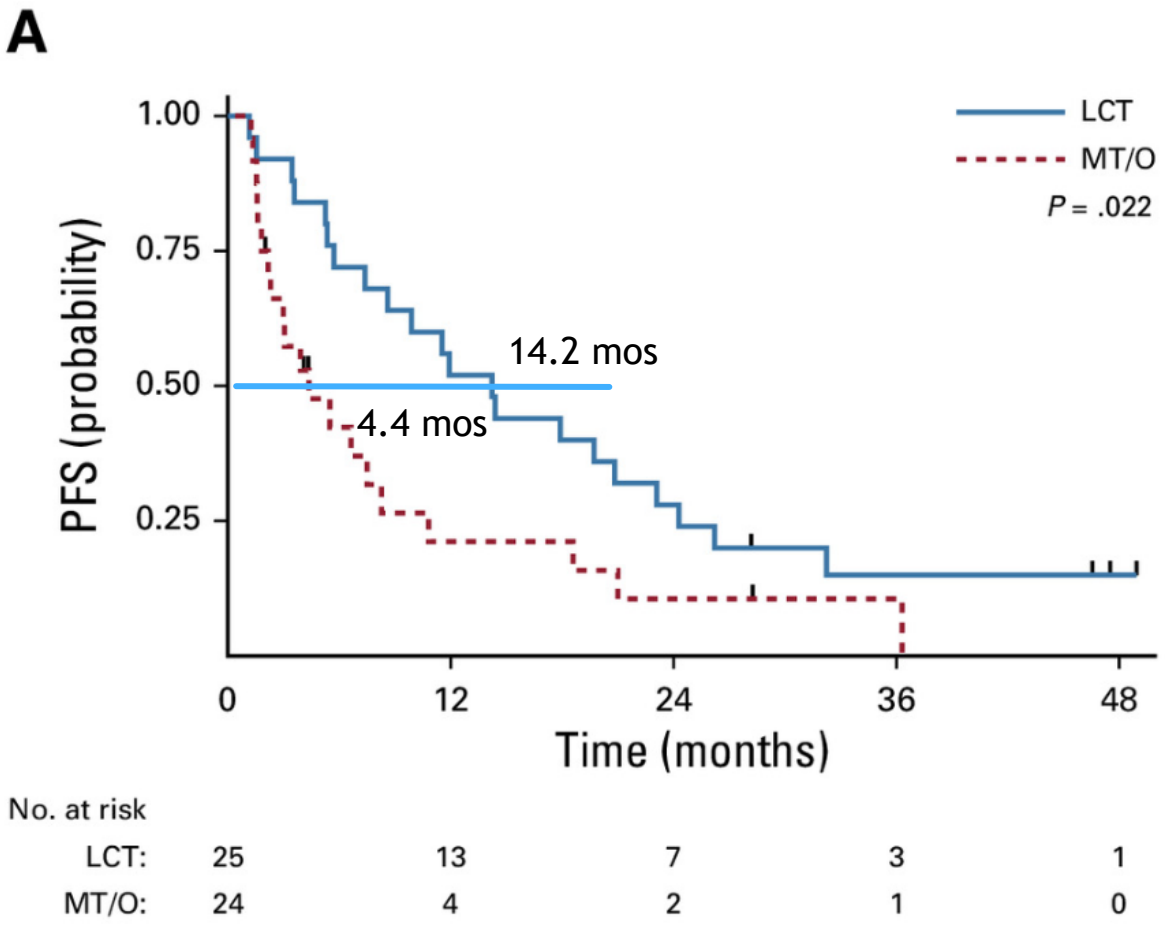
SABR

Hypofraction

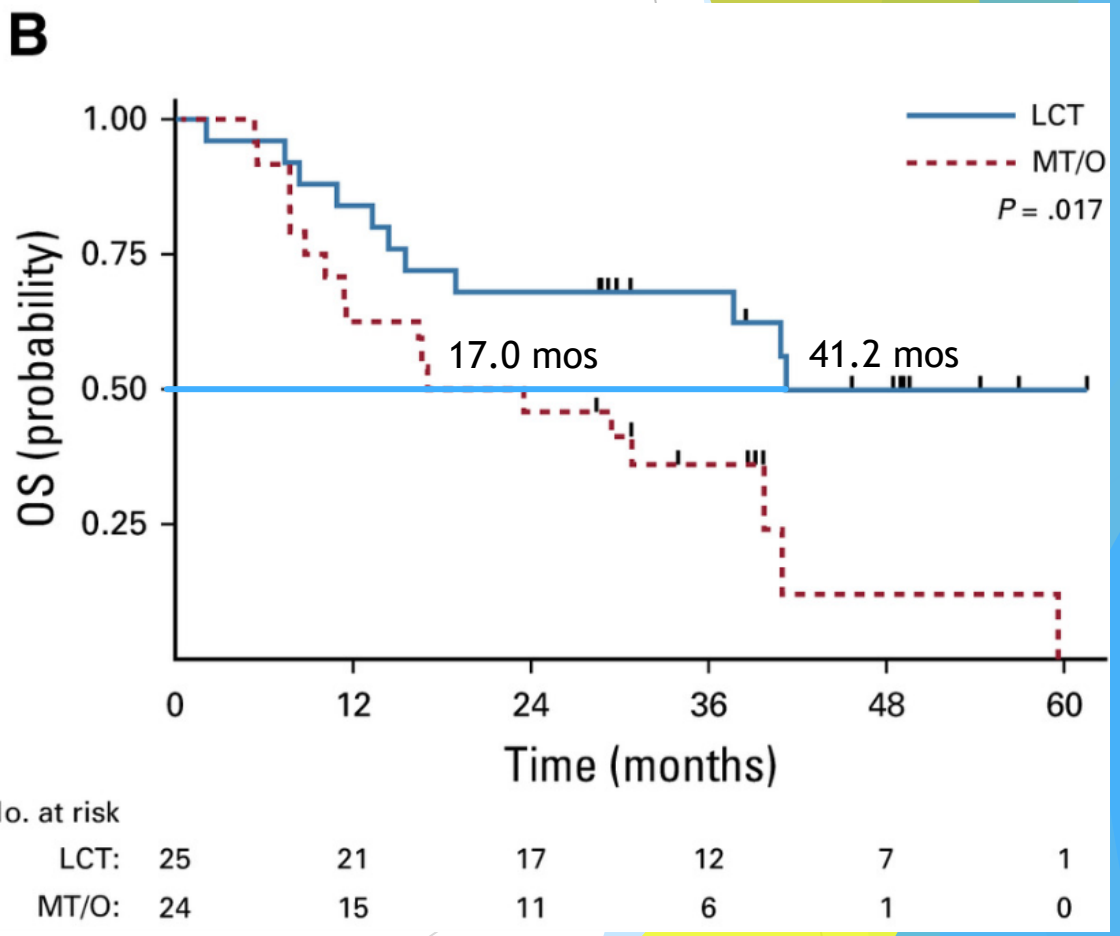
(1) Lung/lymph nodes	1) 52.5 Gy in 15 fractions to GTV, 45 Gy in 15 fractions to PTV with SIB
(2) Bone No. 1 (right rib)	2) 45 Gy in 15 fractions
3) Bone No. 2 (left iliac)	3) 40 Gy in 10 fractions
(1) Brain*	(1) Surgical resection + 15 Gy in one fraction to postoperative cavity
(2) Bone (left iliac)	(2) 40 Gy in 10 fractions
(1) Two brain lesions*	(1) 20 Gy to both sites
(2) Lung/lymph nodes	(2) 45 Gy in 15 fractions
(1) Lung/lymph nodes	(1) 52.5 Gy in 15 fractions to GTV, 45 Gy in 15 fractions to PTV with SIB
(2) Adrenal	(2) Resection
(3) Bone (L4)	(3) 18 Gy in one fraction
(1) Liver	(1) 50 Gy in 4 fractions
	Continued maintenance therapy: erlotinib 100 mg per day
(1) Bone (S1)	(1) 30 Gy in 10 fractions
(2) Lung/lymph nodes	(2) 66 Gy in 30 fractions RT + pemetrexed (1,270 mg) + carboplatin (828 mg) IV per week
1) Brain	(1) No local treatment (disease responded to chemotherapy)
2) Lung/Lymph Nodes	(2) 66 Gy in 30 fractions RT + paclitaxel (100 mg) + carboplatin (244 mg) IV per week
(1) Lung/lymph nodes	(1) 60 Gy in 30 fractions RT + pemetrexed (756 mg) + carboplatin (490 mg) IV per week
(2) Bone (R iliac)	(2) Not treated (not visible after completion of chemoradiation)
(1) Lung/lymph nodes	(1) 52.5 Gy in 15 fractions
(2) Liver	(2) 50 Gy in four fractions
(1) Lung/lymph nodes	(1) and (2) 45 Gy in 15 fractions
(2) Cervical lymph nodes	
(1) Lung (primary site)	(1) 60 Gy in eight fractions
(2) Adrenal	(2) 60 Gy in eight fractions
(1) Lung/lymph nodes	(1) and (2) 60 Gy in 30 fractions + cisplatin 25 mg/m^2 + etoposide 100 mg/m^2 IV every 21 days
(2) Cervical lymph nodes	
(1) Lung (primary Site, pleural metastases resolved)	(1) 48 Gy in four fractions
	Continued maintenance therapy: crizotinib 250 mg PO twice per day

Median FU ; 38.8 mos

median PFS for all pts 8.3 mos



median OS for all pts 37.7 mos



In case of bone metastases,

Review Article

Optimal timing for local ablative treatment of bone oligometastases in non-small cell lung cancer

Jayoung Lee [a], Jung A. Kim [b,c], Tai Joon An [b], Hyochun Lee [d], Eun Ji Han [e], Young Jo Sa [f], Hyo Rim Kim [g], Chan Kwon Park [b], Tae-Jung Kim [h], Jeong Uk Lim [b,*]

J BONE ONCOL 2023

1st line systemic treatment

	Pre-emptive	Consolidative
Advantages	• Early reduction of overall disease burden • Increase responsivity to systemic treatment • Early alleviation of symptoms in painful bone lesions	• Initial systemic chemotherapy may provide comprehensive disease control • Possibility of decreasing radiation fields after the initial systemic chemotherapy response • Can observe initial disease course
Disadvantages	• Radiation field may be large • Risk of unnecessary toxicities in patients with poor performance and multiple comorbidities	• Symptoms related to bone metastatic lesions can last longer • Cancer cells may earn time for treatment resi stance

Initial image assessment for synchronous bone metastatic lesions using PET/CT, MRI, etc

↓

Metastatic lesions equal or less than 5 sites

↓

*Initial assessment of the lesions
-disease burden
-weightbearing bones?
-risk for skeletal-related events
-symptomatic? (pain etc.)
-osteolytic vs osteogenic
-concurrent metastatic lesions of other organs

↓

*Undergo multi-disciplinary board discussion for assessment of
-possible treatment-related toxicity
-expected response of initial systemic treatment
-other non-bone lesions requiring upfront LAT
-patients' underlying diseases that may interfere with LAT (e.g. osteoporosis)

↓

*Undergo LAT to bone oligometastatic lesions if:
-expected clinical benefit outweighs potential treatment-related toxicity
-synergistic effect is expected from combination of LAT and systemic treatment
-rapid alleviation of symptoms associated with the lesions is necessary
-concurrent neurologic symptoms are present

High-risk bone metastasis

Prophylactic Radiation Therapy vs. Standard-of-Care for Patients with High-Risk, Asymptomatic Bone Metastases: A Multicenter, Randomized Phase II Trial

E.F. Gillespie [1], N.J. Mathis [2], C. Marine [2], Z. Zhang [3], C.A. Barker [2], D.M. Guttmann [2], R. Kotecha [4], A.F. McIntosh [5], M. Vaynrub [2], M. Bartelstein [2], A. Mitchell [2], D. Yerramilli [1], D.S. Higginson [2], Y. Yamada [1], C.J. Tsai [1], S.N. Powell [1], J.T. Yang [2]

IJROBP 2022

- High-risk bone lesions : bulky disease (≥2cm in longest diameter), junctional spine or posterior spinal element disease, disease involving hip or sacroiliac joint, or disease in long bone involving 1/3-2/3 cortical thickness
- Randomly 1:1 assignment >> RT arm *vs.* SOC (standard-of-care)
- 78 pts c 122 bone lesions
- Primary endpoint : Skeleton-related event (SRE, fracture, cord compression, or intervention with surgery or radiation)
- m/c primary site : lung (27%), followed by breast (24%), prostate (22%)

At 1 year,

- SRE occurred in 1/62 (1.6%, RT arm) *vs.* 14/49 (29%, SOC arm) (*p-value* <0.001)
  significant differences in time-to-SRE by type of high risk feature (*p-value* 0.016)
  most events occurred in **junctional spine, and bulky disease**
  fewer pts hospitalized for SRE in RT arm ; 0 *vs.* 4, (*p-value* 0.045)

Surgical intervention

Median FU ; 2.4 yrs

- OS : significantly longer in the RT arm (HR 0.50, *p-value* 0.02)
- Median OS among 11 pts c SRE was 1.1 yrs *vs.* 1.5 yrs among 67 pts s SRE
- Pain : reduced at 3 mos in the RT arm (*p-value* <0.05) compared to the SOC arm

Spinal instability neoplastic score, SINS

Component	Score
Location	
Junctional (O-C2; C7-T2; T11-L1; L5-S1)	3
Mobile spine (C3-6; L2-4)	2
Semirigid (T3-10)	1
Rigid (S2-S5)	0
Mechanical pain	
Yes	3
No	2
Pain free lesion	1
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
Deformity (kyphosis/scoliosis)	2
Normal	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement	
Bilateral	3
Unilateral	1
None of the above	0

	Score (Total = 0-18)		
	1-6	7-12	13-18
Clinical categories	Stable	Potentially unstable	Unstable
Binary scale	Stable	Current or potentially unstable = possible surgical intervention	

[a]Data adapted from Fischer et al.[9]