GBCC2019
Global Breast Cancer Conference 2019

Optimization of Radiotherapy for Bone Metastasis

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SAMSUNG MEDICAL CENTER

- ✓ **General aspects of radiotherapy (RT)**
- ✓ **Optimization of RT**
  - **Dose and fractionation (Fx)**
  - **Extent of RT**
  - **Techniques of RT**
  - **Combination with systemic Tx**

- ✓ **General aspects of radiotherapy (RT)**
- ✓ **Optimization of RT**
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  - **Combination with systemic Tx**

Role of RT

- ✓ **Relief of bone pain**
- ✓ **Local control of disease**
- ✓ **Prevent pathologic fracture**

Pain relief

✓ Pain relief by RT

- Overall response rate: ≈ 85%

  Partial relief (60-80%), complete relief (15-40%)

- Occurs rapidly

  ≥ 50% of responders showing benefit within 1-2 weeks

- Mechanism of pain relief is poorly understood

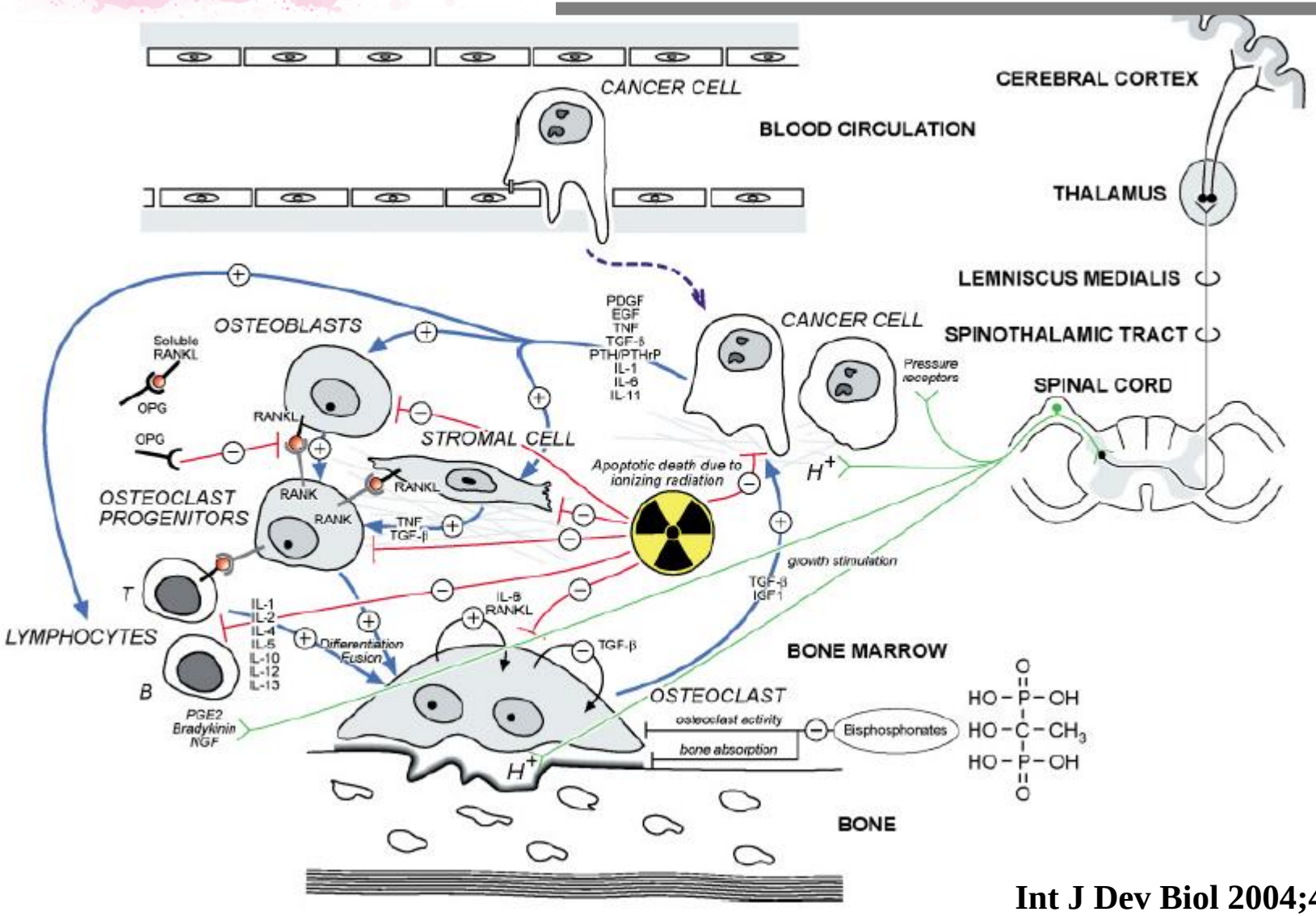
Pain relief

✓ Possible mechanism of bone pain

- Chemical mediators
- Pressure within the bone
- Microfractures
- Stretching of the periosteum
- Reactive muscle spasm
- Nerve root infiltration

Int J Dev Biol 2004;48:599-606

Pain relief



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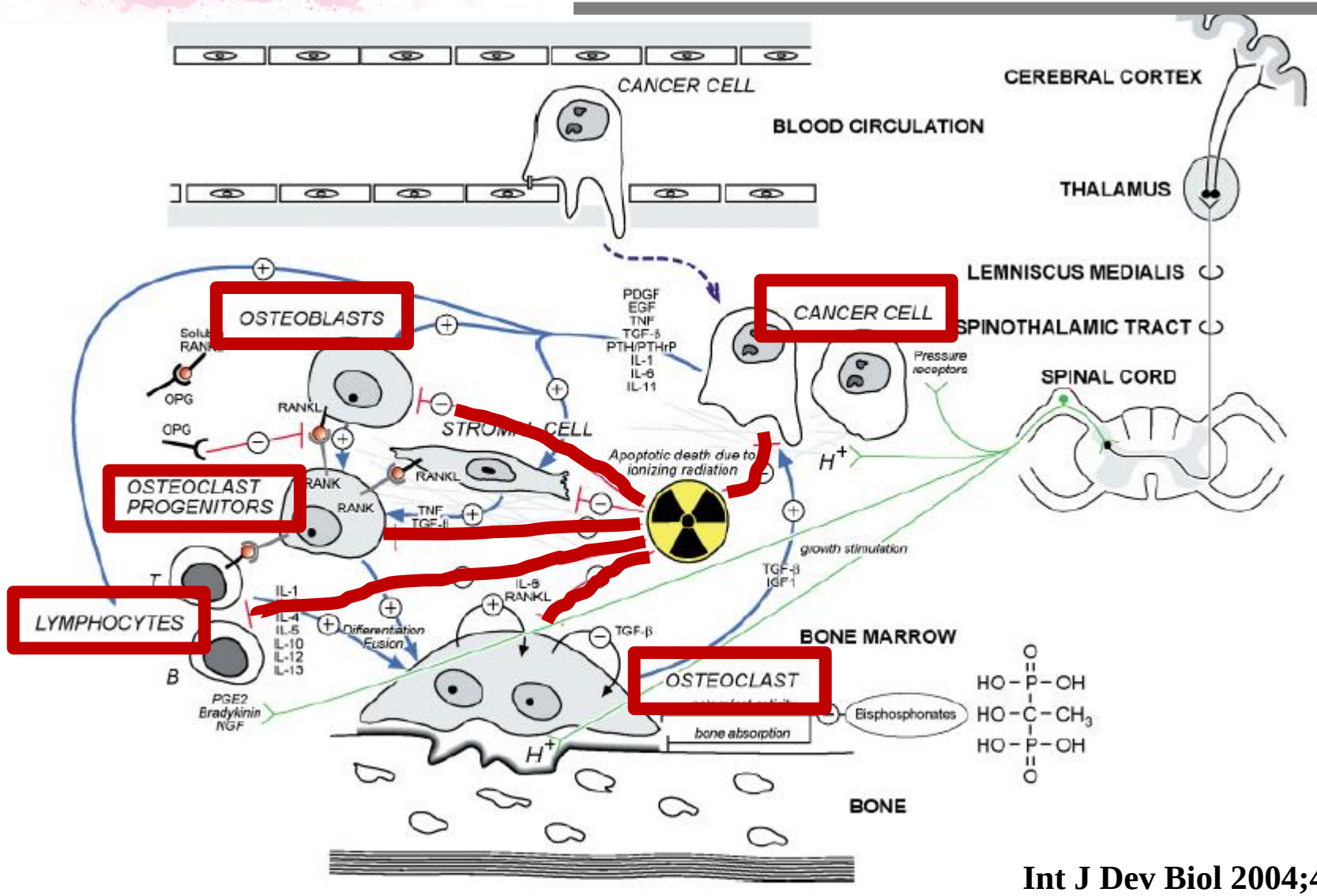
Pain relief



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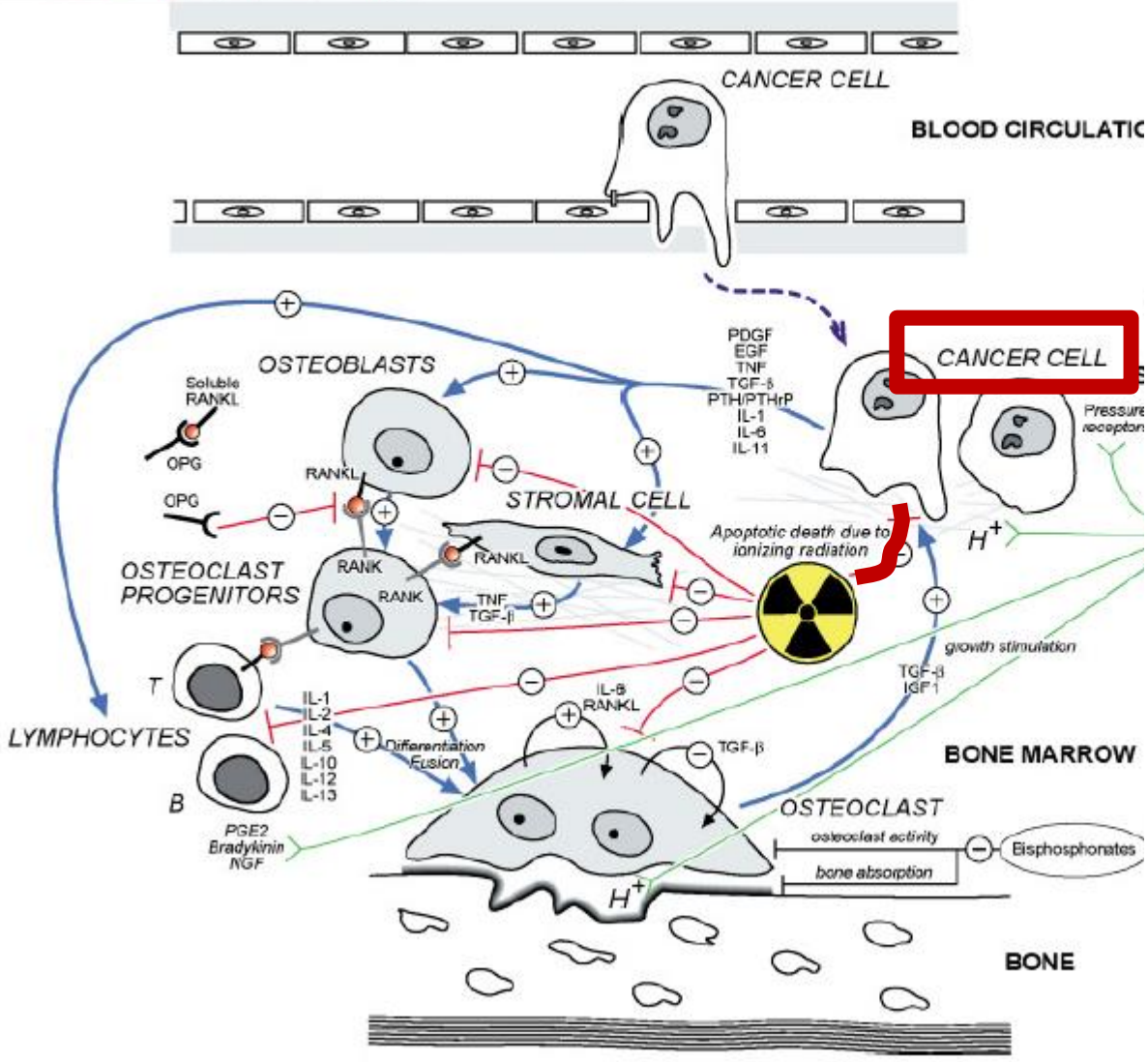


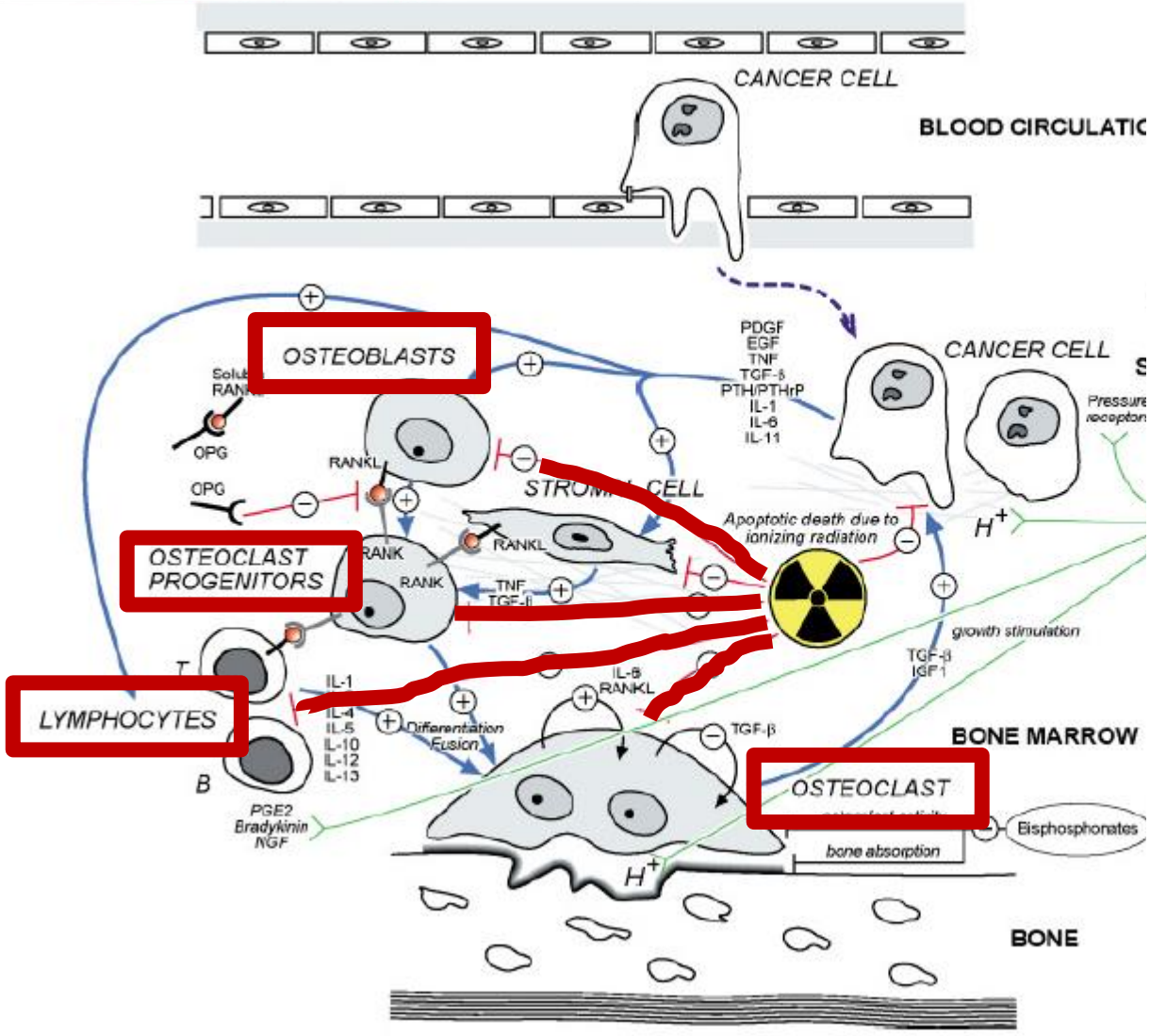
Mechanism of RT in reducing bone pain

✓ **Tumor shrinkage**

- **Pain diminish after a few sessions**
- **Unlikely to account for the early period of pain relief**

Int J Dev Biol 2004;48:599-606

Pain relief



Mechanism of RT in reducing bone pain

- ✓ **Reducing inflammatory cells**
- **Inhibits releasing chemical mediators**
- ✓ **Reducing osteoclast**

Int J Dev Biol 2004;48:599-606

Pain relief

RT

Time after RT

Within a few days

Affect on inflammatory cells/osteoclast

For several weeks to months

Affect on tumor cells

Pain relief

RT

Time after RT

Within a few days

Affect on inflammatory cells/osteoclast

For several weeks to months

Affect on tumor cells

Pain relief

RT

Time after RT

Within a few days

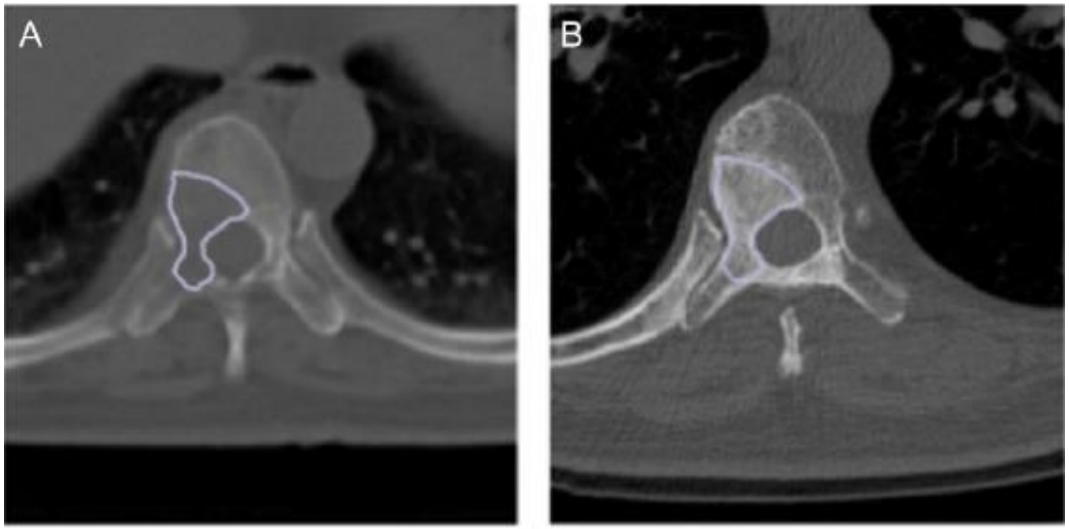
Affect on inflammatory cells/osteoclast

For several weeks to months

Affect on tumor cells

Bone density

- ✓ **Increase of bone density after RT**
  - **in metastatic lesion, not it unaffected bone**
  - **increasing density: multi-Fx > single Fx**



Pre-RT **Post-RT 3months**

J Radiat Res 2019; Feb, Epub

Influencing factors

✓ In deciding RT schemes

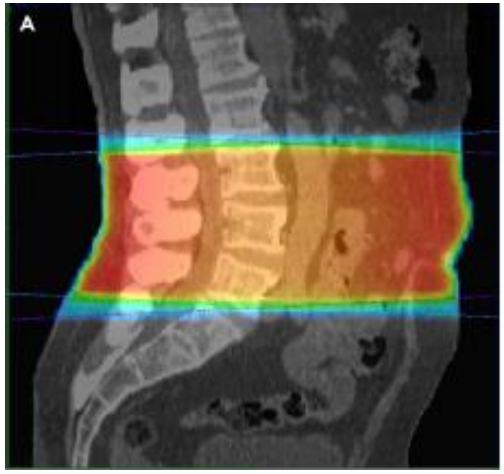
Patient-related factors	Tumor-related factors	Logistic issues
Performance status	Histology of primary tumor	Family member's assistance
Clinical circumstances	Time elapsed from primary diagnosis to bone mets	Location of hospital
painful uncomplicated bone mets	Time of developing pain	Distance from home to hospital
Spinal cord compression	Time of neurologic deficits before RT	Cost of RT
Reirradiation		Reimbursement issues
Life expectancy		
Socioeconomic status		

Cancers 2019; 11: 390

Techniques of RT

✓ External beam radiotherapy (EBRT)

Conventional radiotherapy (CRT)



- Radiation dose to normal organs (spinal cord, bowel, etc)
- Difficult to deliver high-dose RT

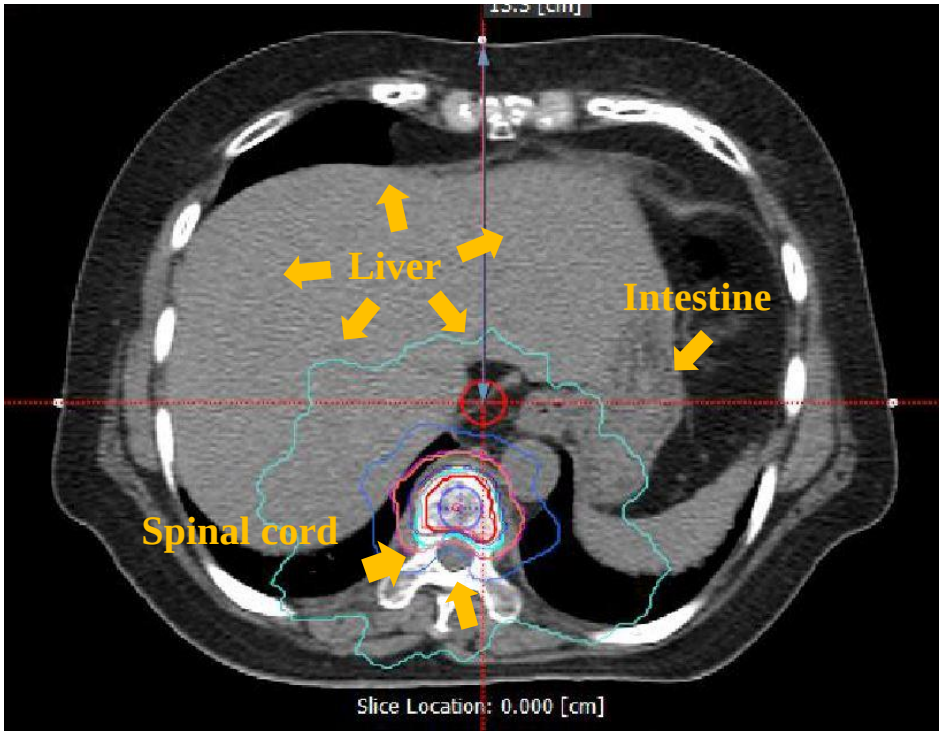
Stereotactic body radiotherapy (SBRT) or Stereotactic ablative radiotherapy (SABR)

- Highly conformal
- Can deliver high-dose RT

BMJ 2018;360:k821

Sites of RT

- ✓ **Spine vs. peripheral bones**



Life expectancy

✓ Estimating life expectancy

Model	No. of pts	Criteria for determining prognosis	Survival estimates
Chow et al.	840	Non-breast primary	Score 0-3 : 41% (12 Mo)
(2005, 2009)	395 (initial)	Metastases to other than bone only	
NRF model	445 (validation)	KPS of ≤ 50	Score 4: 10% (12 Mo)
		Fatigue score 4-10	
		Appetite score 8-10 on ESAS	Score 5-6: 3% (12 Mo)
		Shortness of breath score 1-10 on ESAS	
Krishnan et al.	862	Type of cancer (lung, others vs. Breast/prostate)	Score 0-1: median survival, 19.9 mo
(2013)		ECOG (2-4 vs. 0-1)	
TEACHH model		Chemotherapy (≥ 2 vs. 0-1 course)	Score 2-4: median survival, 5 mo
		Hospitalization within 3 mo of RT (0 vs. ≥ 1)	
		Hepatic mets (present vs. absent)	Score 5-6: median survival, 1.7 mo

CA Cancer J Clin 2014;64:295-310

✓ General aspects of radiotherapy (RT)

✓ **Optimization of RT**

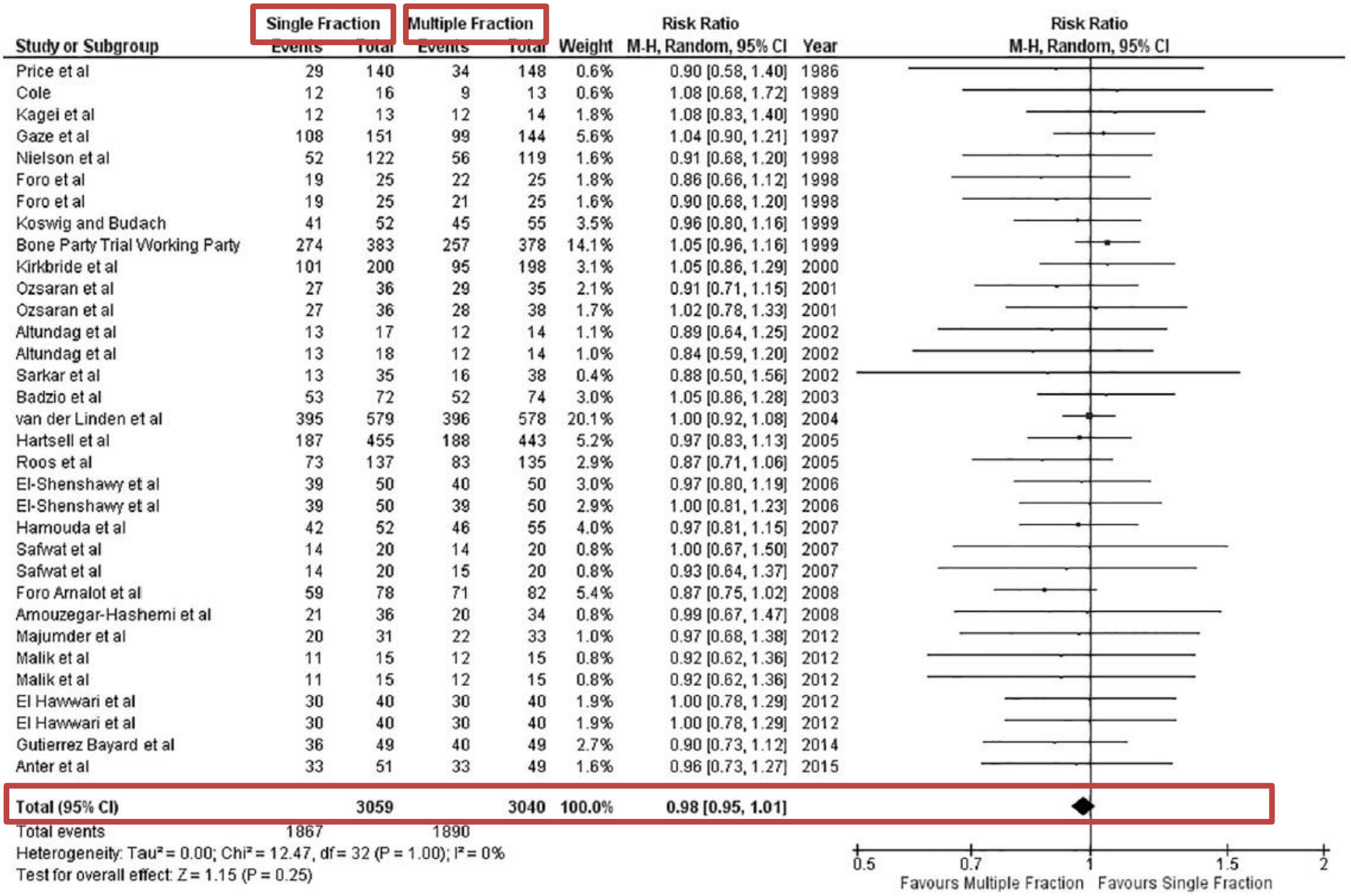
- **Dose and fractionation (Fx)**
- **Extent of RT**
- **Methods of RT**
- **Combination with systemic Tx**

Short vs. Long

✓ Single vs. multiple Fx (Pain relief)

- 26 randomized trials, **8 Gy/1 fx** vs. **20 Gy/5 fx or 30 Gy/10 fx**
- In patients with <u>uncomplicated painful bone mets</u>
- Comparison on;
  - response rate (overall or complete response)
  - pathologic fracture rate
  - re-treatment rate

Radiother Oncol 2018;126:547-557



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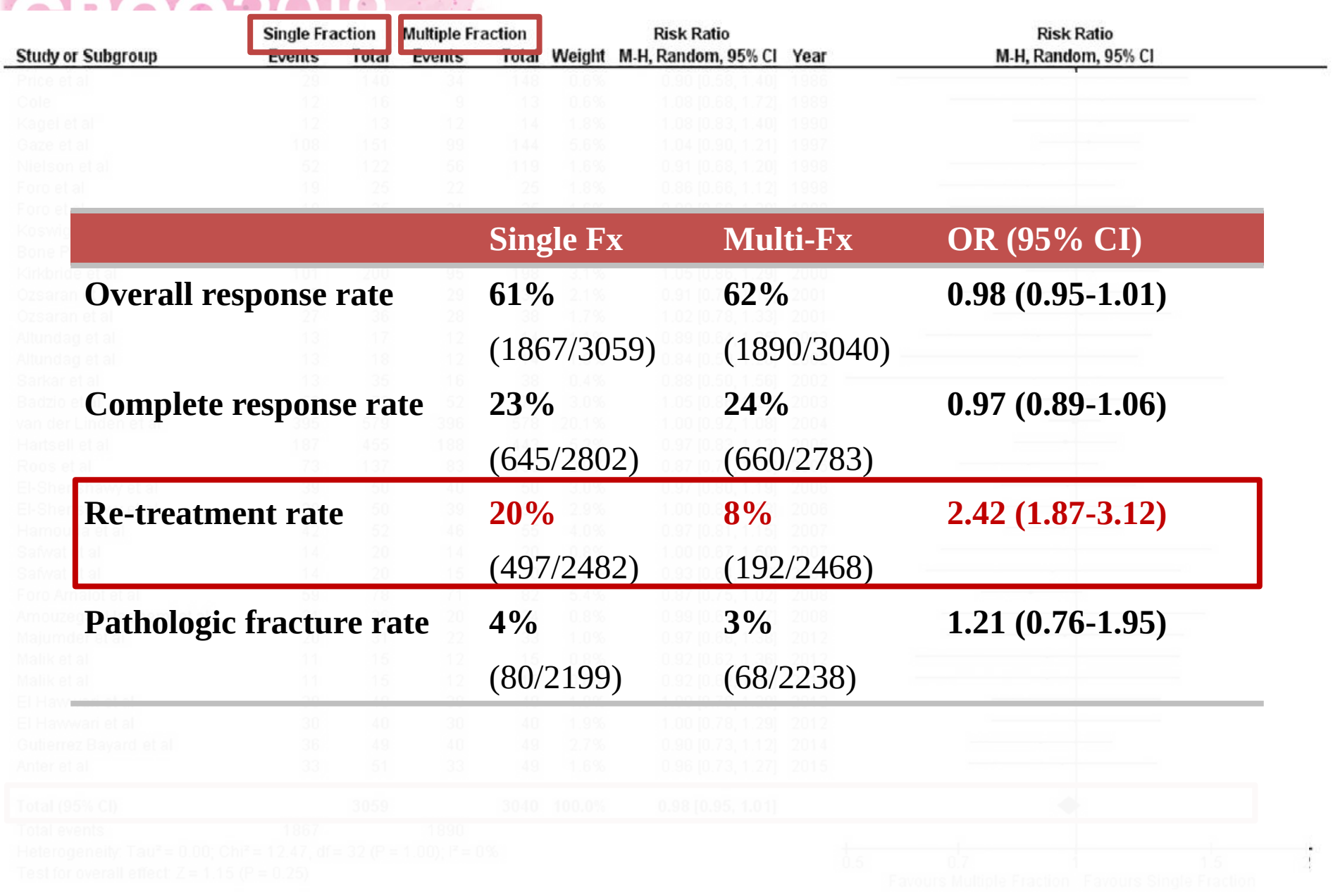
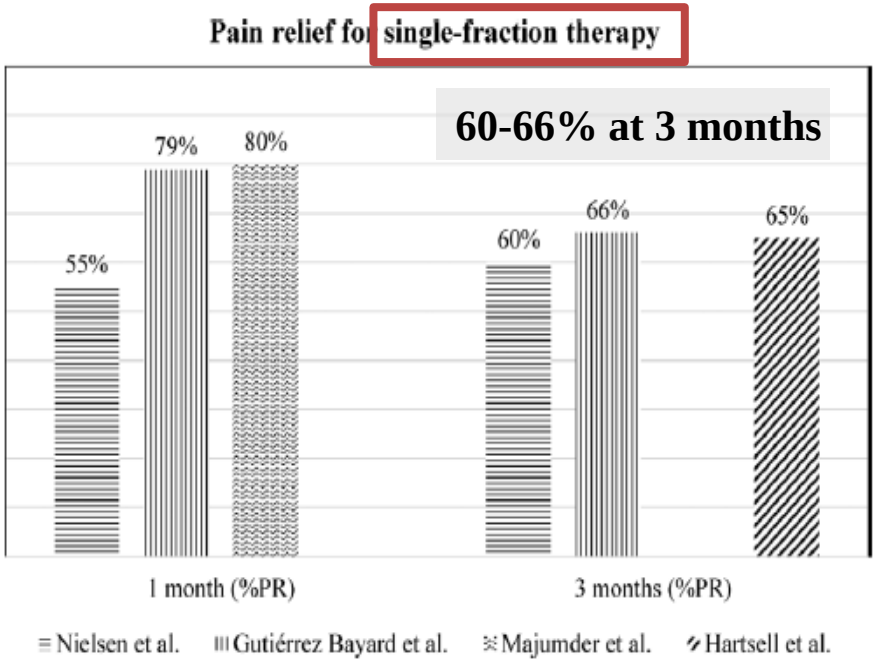


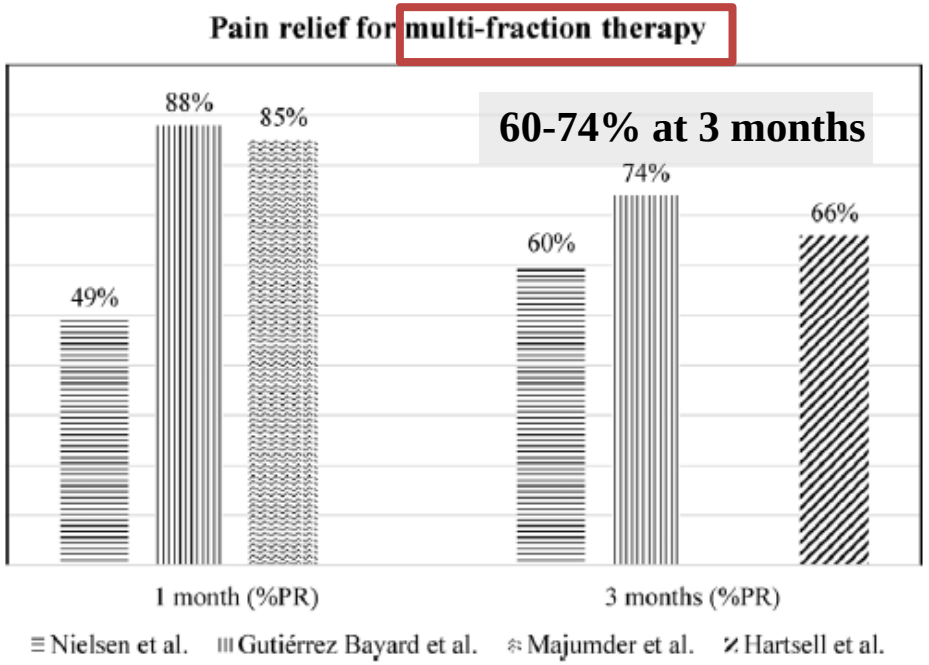
	Single Fx	Multi-Fx	OR (95% CI)
Overall response rate	**61%** (1867/3059)	**62%** (1890/3040)	**0.98 (0.95-1.01)**
Complete response rate	**23%** (645/2802)	**24%** (660/2783)	**0.97 (0.89-1.06)**
Re-treatment rate	**20%** (497/2482)	**8%** (192/2468)	**2.42 (1.87-3.12)**
Pathologic fracture rate	**4%** (80/2199)	**3%** (68/2238)	**1.21 (0.76-1.95)**

Radiother Oncol 2018;126:547-557

Short vs. Long

✓ Durability of pain relief





Critical Reviews in Oncology/Hematology 2018;123:132-137

Short vs. Long

✓ **In painful bone metastasis**

- **Single Fx is equally effective than multiple Fx**
- **Re-treatment rate: single Fx >> multiple Fx**
- **Guidelines recommend**
  - **: Single Fx for relieving pain**

Practical Radiation Oncology 2017;7:4-12

Ann of Oncology 2014;25 (supplement 3):iii 124-137

Short vs. Long

✓ Spinal cord compression

study		Fx schedules	Response
Rades et al.	Retrospective	5 fx schedules*	Improving motor function (26-31%) In-field recur at 2-year, higher in high-dose group
Rades et al.	Prospective	Short course (n=131) Long course (n=134)	1-year local control 61% (short) vs. 81% (long) (p<0.01) Improving motor function 37% (short) vs. 39% (long) (p=0.95)
Maranzano et al.	Phase III	8 Gy/1 fx (n=150) 16 Gy/2 fx (n=153)	No difference in response rate, duration of response, survival
Rades et al.	Retrospective	8 Gy/1 fx (n=121) 20 Gy/ 5x (n=121)	In-field Re-RT at 1-year 30% vs. 22% (p=0.11) Improving motor function 17% vs. 23%
Lee et al. (ICORG 0503)	Phase III	10 Gy/1 fx (n=38) 20 Gy/5 fx (n=38)	No difference in change in mobility at 5 weeks
Rades et al.	Phase III	20 Gy/5 fx (n=101) 30 Gy/10 fx (n=102)	Response rate (motor function) at 1 month: 87.2% vs. 89.6% Local progression free at 6 months: 75.2% vs. 81.8%

*5 schedules:8 Gy/1 fx, 20 Gy/5 fx, 30 Gy/10 fx, 37.5 Gy/15 fx, 40 Gy/20 fx

†Short course:8 Gy/1 fx, 20 Gy/5 fx, Long course: 30 Gy/10 fx, 37.5 Gy/15 fx, 40 Gy/20 fx

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- Improving motor function: 17-39%

- Local control: 75-81% (6 months), 61-81% (1-year)

- Multi-Fx is associated with better local control

*5 schedules:8 Gy/1 fx, 20 Gy/5 fx, 30 Gy/10 fx, 37.5 Gy/15 fx, 40 Gy/20 fx

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Short vs. Long

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- Outcomes were not affected by Fx schedules
- Short course RT is thought to be appropriate

*5 schedules:8 Gy/1 fx, 20 Gy/5 fx, 30 Gy/10 fx, 37.5 Gy/15 fx, 40 Gy/20 fx

†Short course:8 Gy/1 fx, 20 Gy/5 fx, Long course: 30 Gy/10 fx, 37.5 Gy/15 fx, 40 Gy/20 fx

Short vs. Long

✓ Reirradiation

Situations of reirradiation

- Persistent or recurrent pain
- More than 1 month following EBRT
- spinal cord compression (-) fracture (-)

Radiotherapy and oncology 2014;110:61-70

Short vs. Long

✓ Reirradiation

- **Efficacy (in meta-analysis of 15 studies)**

Response	Rate %
Complete response	20% (70/355)
Partial response	50% (177/355)
Overall response	68% (438/645)

- **Pain relieved, regardless of prior response**

Radiotherapy and oncology 2014;110:61-70

Short vs. Long

✓ **Reirradiation (Single vs. multi-Fx, phase III trial)**

- 8 Gy/1 fx vs. 20 Gy/5-8 fx
- 8 Gy/1 fx is non-inferior than 20 Gy/5-8 fx

Response	8 Gy/1 fx (n=258)	20 Gy/multi-fx (n=263)	P-value
Overall response	116 (45%)	134 (51%)	0.17
Complete response	35 (14%)	29 (11%)	
Partial response	81 (31%)	105 (40%)	

- No difference in pathologic fracture, cord compression
- More side effects with 20 Gy (anorexia, nausea, vomiting)

Lancet Oncol 2014;15:164-71

Short vs. Long

✓ **Single-Fx is equivalent to multi-Fx**

- **Painful uncomplicated bone mets**
  Spinal cord compression
  Reirradiation

- **Re-RT rate & local tumor control (?)**

Practical Radiation Oncology 2017;7:4-12

Short vs. Long

- ✓ **RT at the end of life**

  - **5-10% of cancer pts, 9-15% of pts with palliative RT**
  - **Bone accounts for 30-70%**
  - **Schedules: 30 Gy/10 fx (33-90%), Single Fx (0-59%)**
  - **Pain response: 70% at 1 month, 63% at 2 months**
  - **Median time to response: 2 wks**
  - **Single Fx may be beneficial**

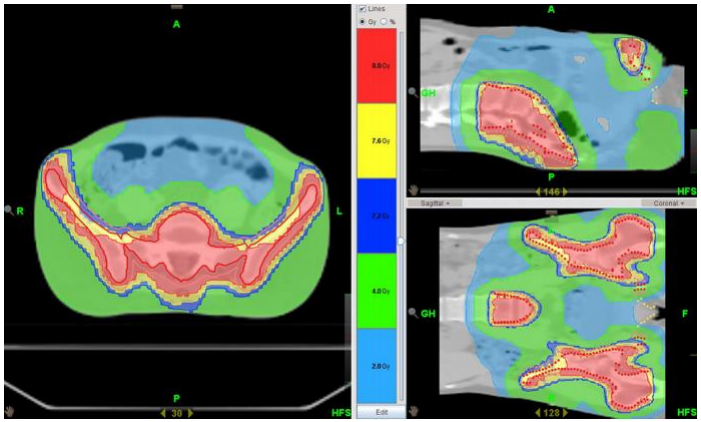
Radiother Oncol 2017;125: 193-199

Extent of RT

✓ Hemibody radiation

- For diffuse, widespread bone metastasis
- Lower hemibody (8 Gy/1 fx), lower hemibody (6 Gy/1 fx)
- Quick response; pain relief within 24-48 hrs, in 70-80%
- Pain relief persists ≥ 50% of remaining life

With CRT



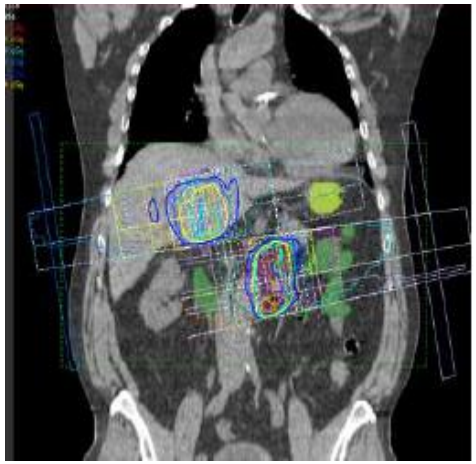
With tomotherapy

J Pain Symptom Manage 2014;47:174-80

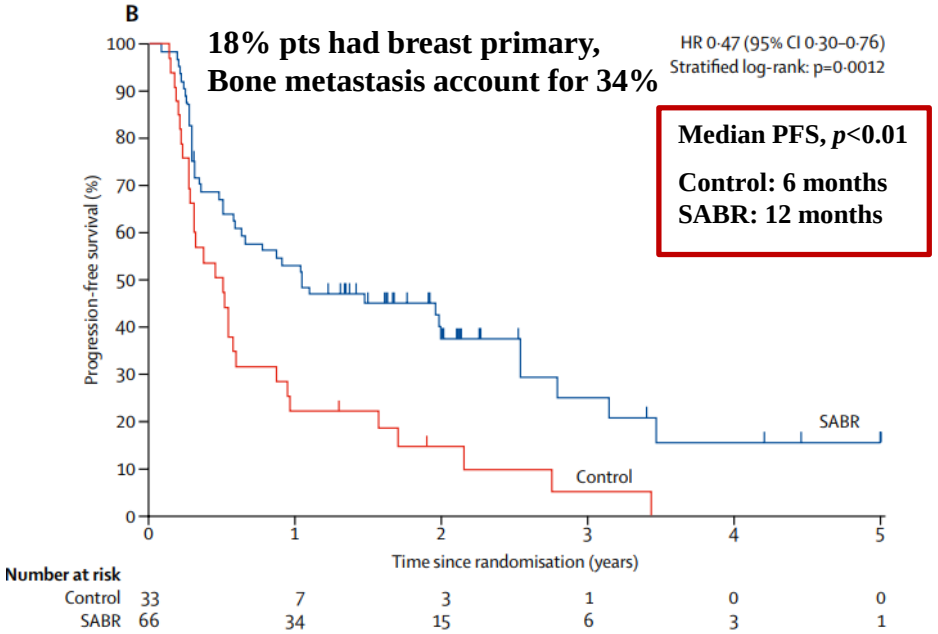
Extent of RT

✓ SBRT for oligometastatic disease

- Oligometastasis (≤1-5 visible mets), 1-10% of breast Ca.
- Bone: 30-45 Gy/3 fx or etc.



J clin oncol 2014;32:2902-2912



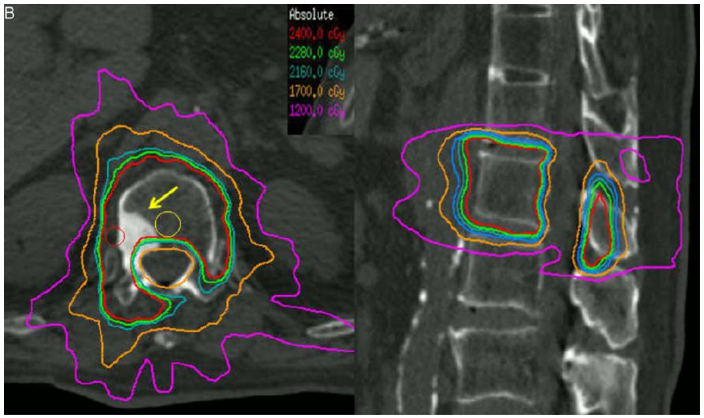
SBRT: stereotactic body radiotherapy, SABR: stereotactic ablative radiotherapy

Lancet 2019;April, E-pub

SBRT

✓ Ablative radiotherapy

- High biological dose to the target, sparing normal tissue
- 5-8 times of the dose of CRT
- Typically less than 5 fx (24 Gy/1-2 fx, 27-45 Gy/3-5 fx)
- Indications
  - Minimal epidural disease
  - No spinal instability
  - Reirraidation
  - Good performance status
  - Long life expectancy

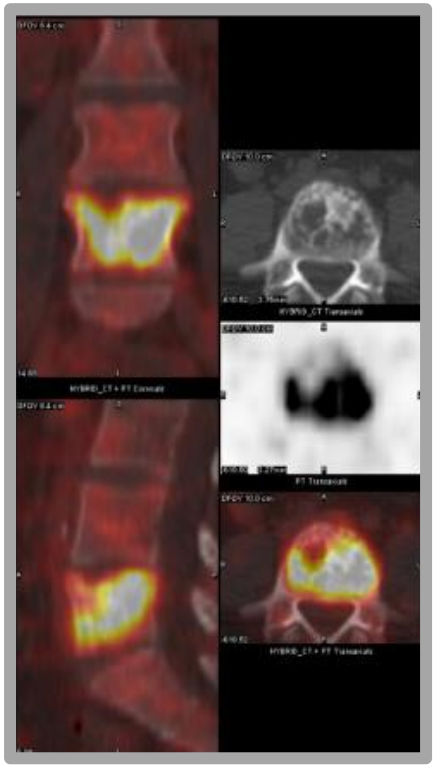


CRT; conventional radiotherapy, SBRT: stereotactic body radiotherapy

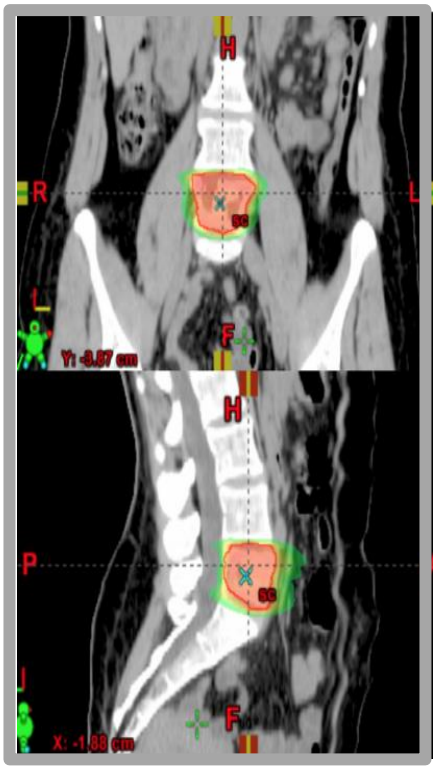
Neuro oncology practice 2016;3 (1):48-58

SBRT

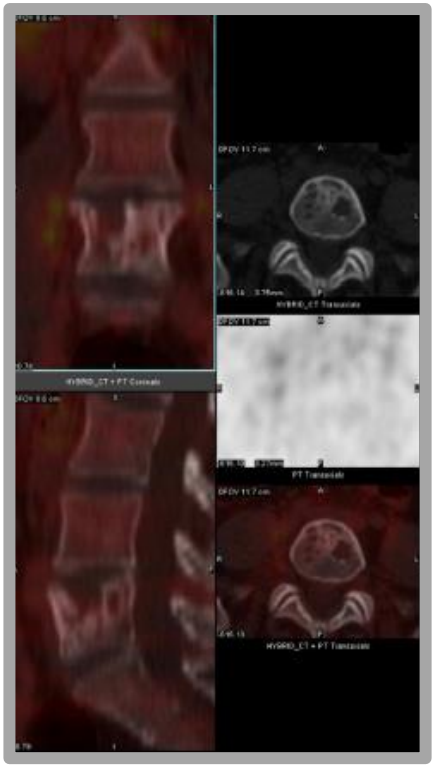
✓ Outcome of SBRT (local control)



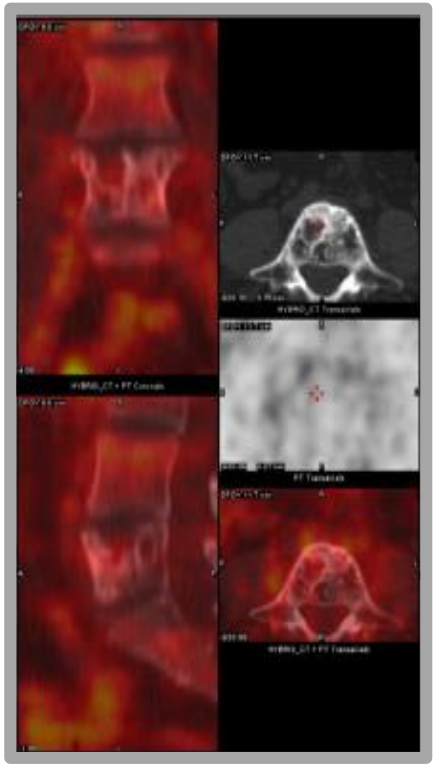
Isolated L5 metastasis



24 Gy/1 fx SBRT



Metabolic CR at 3 months



Disease-free at 36 months

SBRT: stereotactic body radiotherapy

The breast 2018;41:57-66

SBRT

✓ Outcome of SBRT (local control)

Setting	Dose/Fx	Local control rate
De novo	24 Gy/1 fx, 24 Gy/2 fx, 24-30 Gy/3 fx, 18-35 Gy/1-5 fx	81-95% at 1 year, 69-84% at 2 years
Postoperative	16-24 Gy/1 fx, 27 Gy/3 fx, 30 Gy/5 fx	80-92% at 1 year
Reirradiation	20-24 Gy/2 fx, 24-27 Gy/3 fx, 20-30 Gy/5 fx	66-93%

Complication

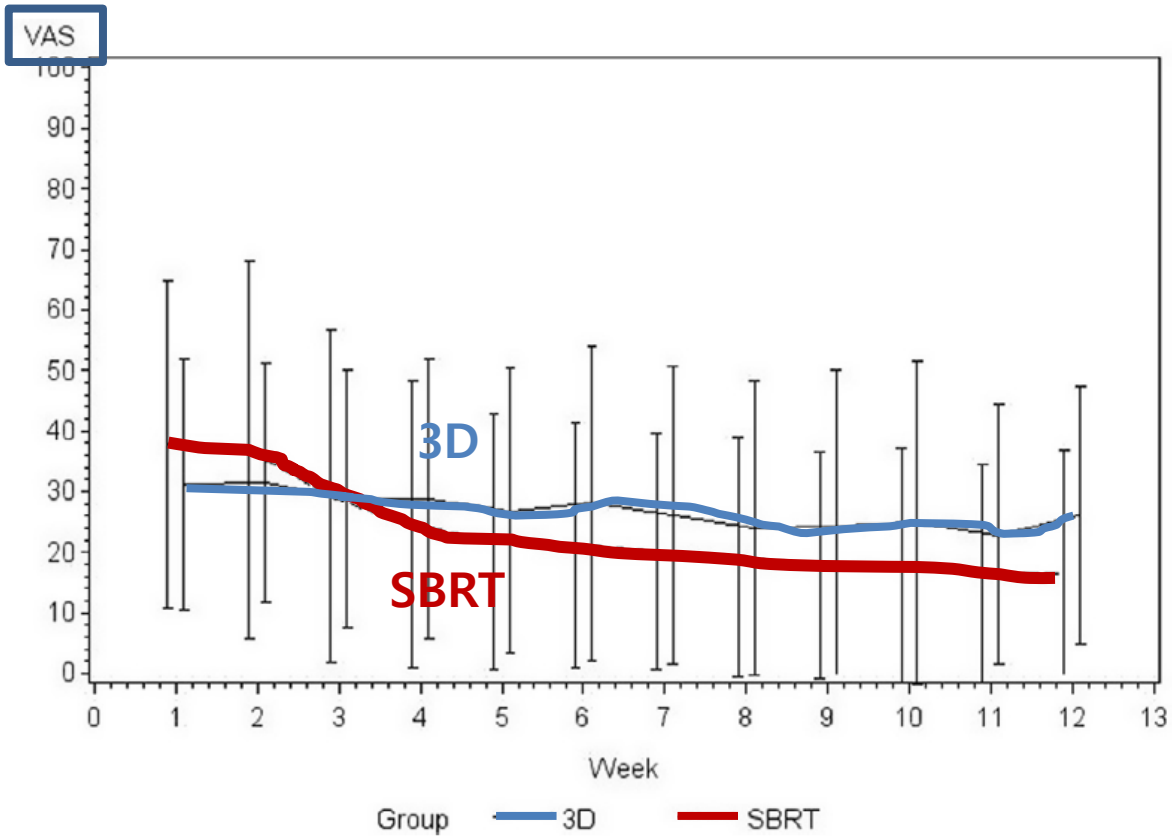
- Radiation myelopathy, rare (< 1-3%)
- Vertebral compression fracture (10-40%)
- Pain flare (20-68%); can be reduced by prophylactic dexamethasone

SBRT: stereotactic body radiotherapy

Neuro oncology practice 2016;3 (1):48-58

CRT vs. SBRT

✓ Outcome comparison (Pain relief, CRT vs. SBRT)



SBRT (24 Gy/1 fx)

- **Faster pain relief**
- **Longer duration of pain control**

In comparison to CRT (30 Gy/10 fx)

CRT; conventional radiotherapy, SBRT: stereotactic body radiotherapy

Radiother Oncol 2018;128:274-282

Combination Tx

✓ With bone-targeted agents

- Radiologic response, bone density: RT alone < RT + bisphosphonate

Study	Patients (*n*), histologic type	Bisphosphonate	EBRT	Pain relief	Mild acute toxicity (%)	Repeat treatment rate	Investigator	Year	Reference
Prospective trials that compared treatment regimens									
Zoledronic acid with high- or reduced dose RT	100, breast cancer	Zoledronic acid, 4 mg monthly	30 Gy/10 Fx	95%	ND	ND	Atahan	2009	105
			15 Gy/5 Fx	92%					
Zoledronic acid plus single-dose 6- or 8-Gy RT	139, various histologic types	Zolendronic acid, 4 mg every 4–5 wk	8 Gy/1 Fx	ND (all patients improved)	22	NR	Manas	2008	107
			6 Gy/1 Fx		14				
Dose escalation of pamidronate with concurrent RT	42, various histologic types	Pamidronate, 90–180 mg monthly	30 Gy/10 Fx	100%	23	None	Kouloulias	2003	106
		Pamidronate, 180 mg monthly			75	None			
		None			NR	NR			
Prospective studies									
RT with concurrent zoledronic acid	18, renal cell cancer	Zoledronic acid, 4 mg monthly	NR	100% (44% CR, 56% PR)	NR	NR	Vassiliou	2009	121
Combination ibandronate and RT	45, various histologic types	Ibandronate, 6 mg monthly	30–40 Gy	100% at 3 mo; 85% at 6 mo	13	None	Vassiliou	2007	108
RT plus disodium pamidronate	33, breast cancer	Pamidronate, 180 mg monthly	30 Gy/10 Fx	100% (88% CR, 12% PR)	39	NR	Kouloulias	2002	109
Image assessment of combined RT and bisphosphonates	18, breast cancer	Pamidronate, 180 mg monthly	30 Gy/10 Fx	100% (77% CR, 23% PR)	39	NR	Kouloulias	2002	110

Radiother Oncol 2016;119: 194-201

Summary

- ✓ **Single Fx is equivalent to multi-Fx RT**
- ✓ **SBRT can provide high local control**
- ✓ **Various factors should be taken into consideration**

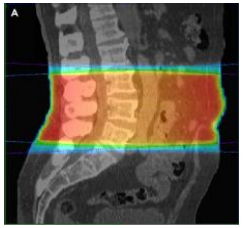
Summary

✓ One scheme doesn't fit all

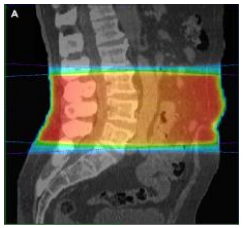
Palliative RT ≠ low-dose RT or simple technique RT

8 Gy/1 fx, Hemibody

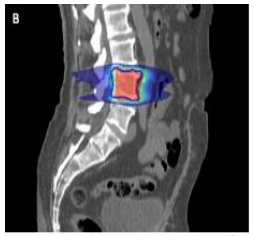
8 Gy/1 fx, using CRT



20 Gy/5 fx or 30 Gy/10 fx



24 Gy/1 fx, SBRT



More radical

Painful bone mets
Wide spread bone mets
Poor performance status
Impending cord compression
Residency distant from hospital

Require better local control
Residency close to hospital
Long life expectancy

Oligometastatic disease
Need more curative Tx
Long life expectancy
Good economic status

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Cases

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"Go Beyond Cure of Breast Cancer"

April 25 (Thu) - 27 (Sat), 2019
Songdo ConvensiA, Incheon, Korea

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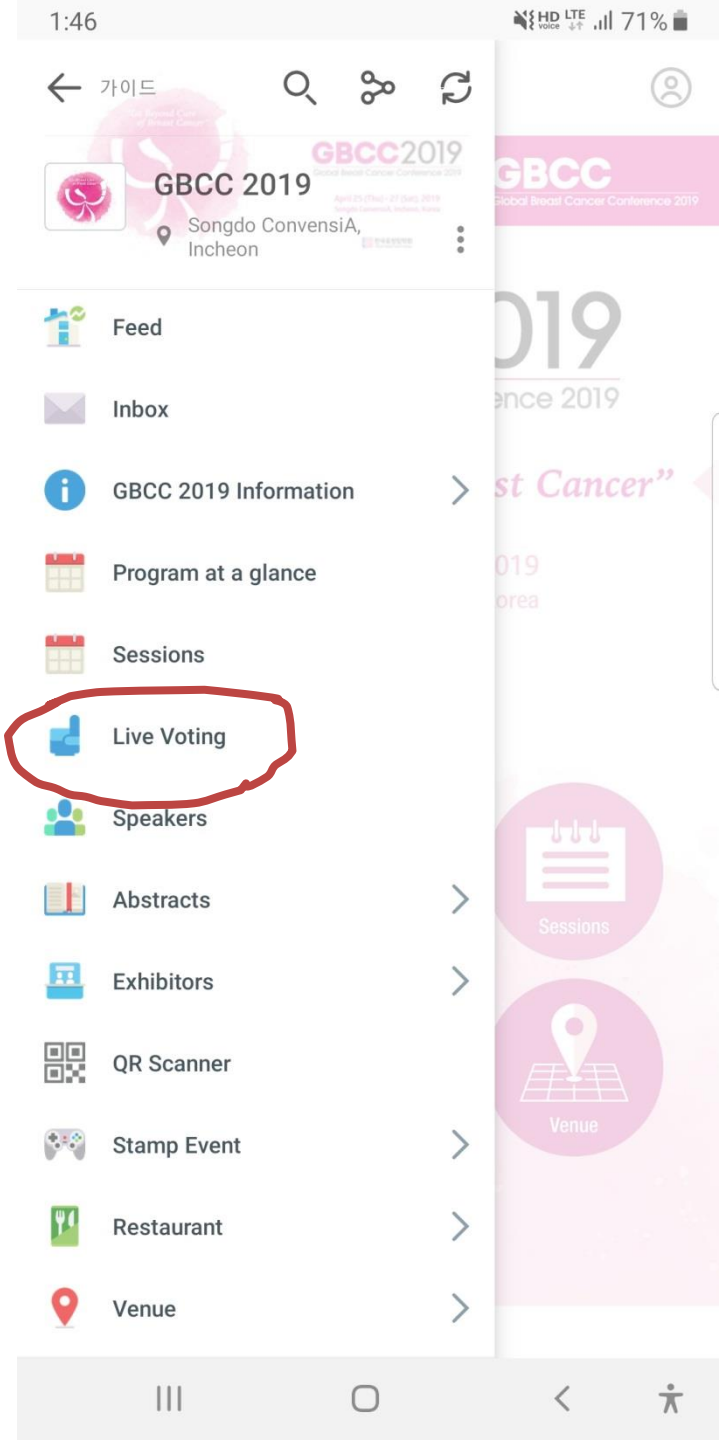
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Panel Discussion 1
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Panel Discussion 6
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Q2. Radiotherapeutic schedule ?

- 1. 8 Gy in 1 fraction with conventional planning
- 2. 30 Gy in 10 fractions with conventional planning
- 3. 20 Gy in 5 fractions with conventional planning
- 4. 30-45 Gy in 3-5 fractions with SBRT
- 5. Defer the decision to the radiation oncologist

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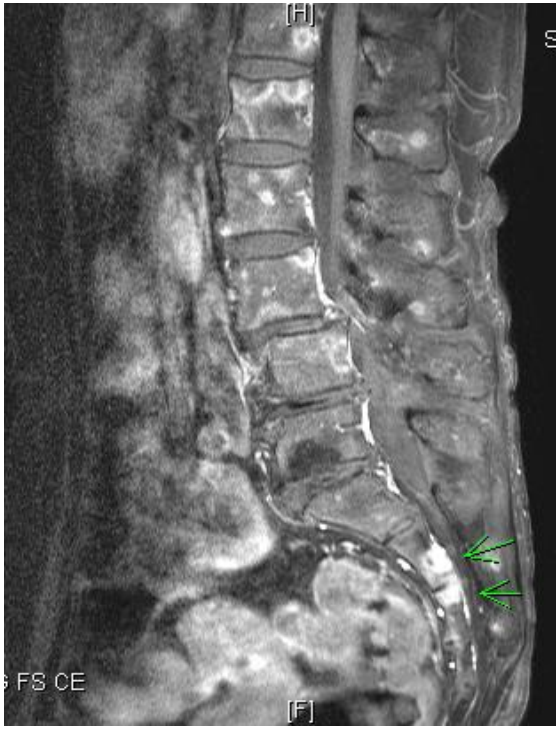
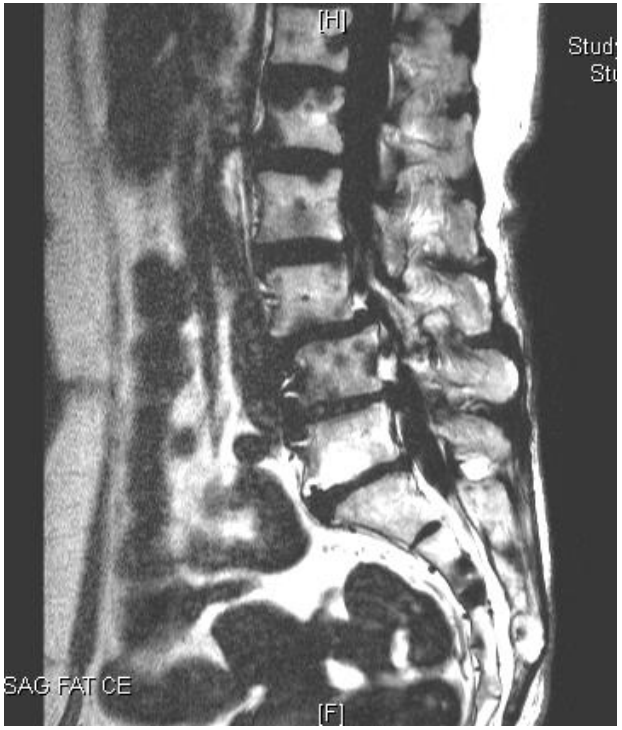
Case I

- ✓ **78 year-old pts with breast cancer, first diagnosed in 2008.**
- ✓ **Diagnosed with metastatic breast cancer (multiple bone, lung mets) in 2015**
- ✓ **Pain in her lower back, ECOG performance status 3**





Case I

✓ **Radiotherapeutic schedule ?**

1) 8 Gy in 1 fraction with conventional planning

2) 30 Gy in 10 fractions with conventional planning

3) 20 Gy in 5 fractions with conventional planning

4) 30-45 Gy in 3-5 fractions with SBRT

5) Defer the decision to the radiation oncologist

Case I

✓ **Single fraction is underutilized**

	(%) of single fraction RT
Canada, Ontario	44%
Canada, British Columbia	49%
US, NCDB	7.4%
US, Johns Hopkins university	7.6%

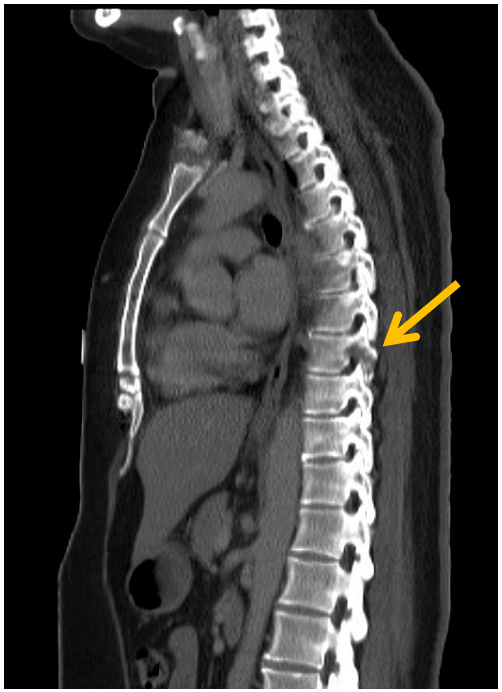
✓ **In Korea*,**

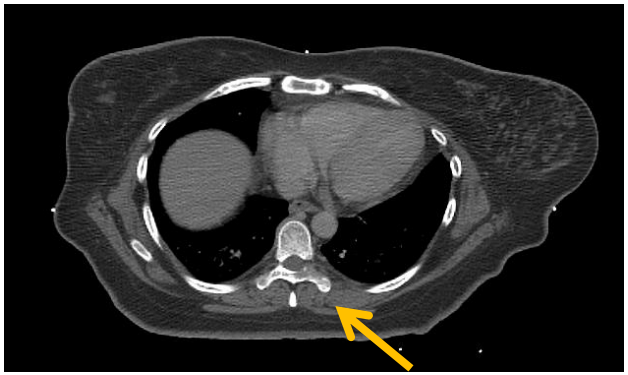
Less than 2% of radiation oncologist opted to prescribe single fraction RT According to a survey to 54 radiation oncologists in Korea.

*Cancer Res Treat 2017;48(3): 1102-1109

Case II

- ✓ **47 year-old pts with breast cancer, first diagnosed in 2012**
  - Rt. Breast Ca. (pT2N0, ER+/PR+/HER2-)
  OP, RT, CTx, Tamoxifen (~2018)
- ✓ **Diagnosed with metastatic breast cancer (bone only) in November, 2018**





Case II

- ✓ **Radiotherapeutic schedule ?**

1) 8 Gy in 1 fraction with conventional planning

2) 30 Gy in 10 fractions with conventional planning

3) 20 Gy in 5 fractions with conventional planning

4) 30-45 Gy in 3-5 fractions with SBRT

5) Defer the decision to the radiation oncologist

- ✓**Patients with favorable prognosis**
  - **More intensified treatment might be helpful**

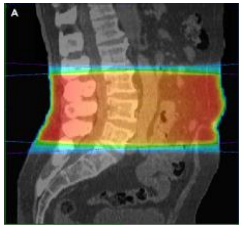
Summary

✓ Optimization of radiotherapy:

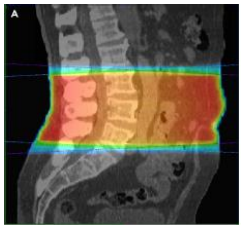
Stratification & modification !

8 Gy/1 fx, Hemibody

8 Gy/1 fx, using CRT



20 Gy/5 fx or 30 Gy/10 fx



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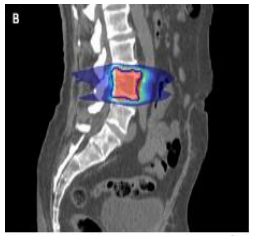

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