

# La radioterapia nel trattamento delle metastasi ossee

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# AGENDA

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- Management of uncomplicated bone metastases with radiotherapy
  - Dose and fractions
  - Conventional vs stereotactic radiotherapy
  - Re-irradiation
  
- Management of complicated bone metastases with radiotherapy
  - Surgery + radiotherapy or radiotherapy alone
  - Dose and fractions
  - Post-operative radiotherapy
  - Re-irradiation

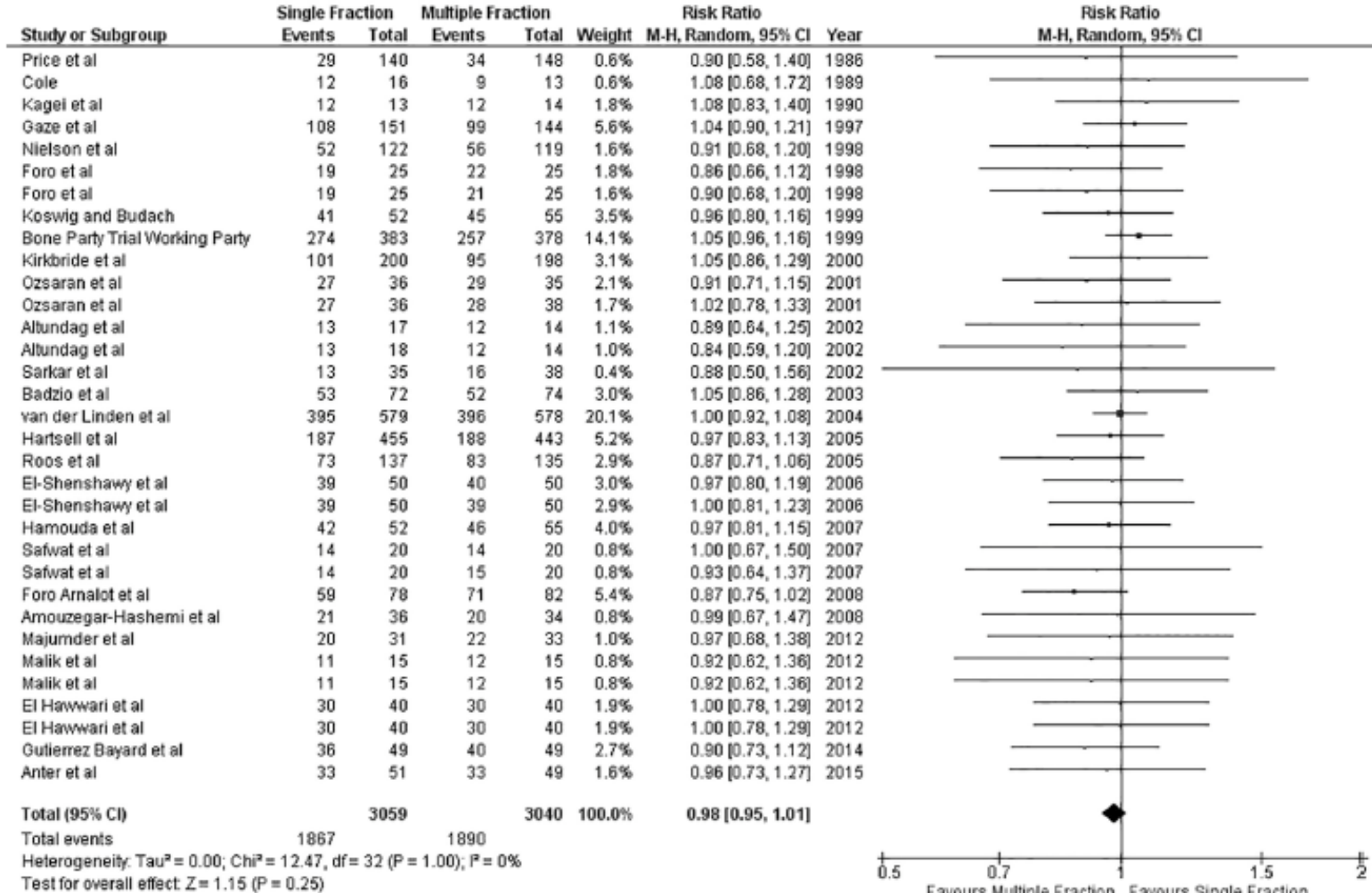
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# UNCOMPLICATED BONE METASTASES

## Dose and fractions



Overall response

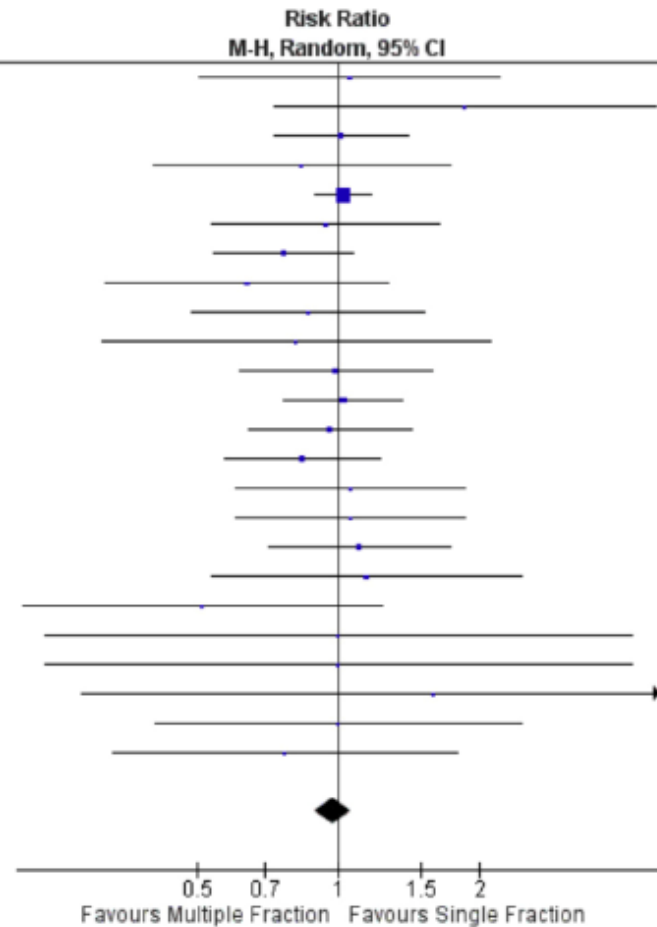
Single vs. multiple  
Fractions  
61% vs. 62%

\* 8 Gy in 1 fraction vs 20 Gy in 5 fractions or 30 Gy in 10 fractions

# UNCOMPLICATED BONE METASTASES

## Dose and fractions

Study or Subgroup	Single Fraction		Multiple Fraction		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
Price et al	13	140	13	148	1.4%	1.06 [0.51, 2.20]	1986
Kagei et al	8	14	4	13	0.9%	1.86 [0.73, 4.72]	1990
Gaze et al	50	151	47	144	7.1%	1.01 [0.73, 1.41]	1997
Nielson et al	12	122	14	119	1.4%	0.84 [0.40, 1.73]	1998
Bone Pain Trial Working Party	199	383	192	378	39.5%	1.02 [0.89, 1.17]	1999
Koswig and Budach	16	52	18	55	2.4%	0.94 [0.54, 1.64]	1999
Kirkbride et al	44	200	57	198	6.5%	0.76 [0.54, 1.07]	2000
Altundag et al	7	17	9	14	1.6%	0.64 [0.32, 1.28]	2002
Altundag et al	10	18	9	14	2.3%	0.86 [0.49, 1.53]	2002
Sarkar et al	6	35	8	38	0.8%	0.81 [0.31, 2.11]	2002
Badzio et al	23	72	24	74	3.4%	0.98 [0.61, 1.58]	2003
van der Linden et al	78	579	76	578	8.7%	1.02 [0.76, 1.37]	2004
Roos et al	35	137	36	135	4.7%	0.96 [0.64, 1.43]	2005
Hartsell et al	44	455	51	443	5.2%	0.84 [0.57, 1.23]	2005
El-Shenshawy et al	17	50	16	50	2.4%	1.06 [0.61, 1.86]	2006
El-Shenshawy et al	17	50	16	50	2.4%	1.06 [0.61, 1.86]	2006
Hamouda et al	23	52	22	55	3.8%	1.11 [0.71, 1.73]	2007
Foro Amalot et al	12	78	11	82	1.3%	1.15 [0.54, 2.45]	2008
Amouzegar-Hashemi et al	6	36	11	34	1.0%	0.52 [0.21, 1.24]	2008
Malik et al	3	15	3	15	0.4%	1.00 [0.24, 4.18]	2012
Malik et al	3	15	3	15	0.4%	1.00 [0.24, 4.18]	2012
Majumder et al	3	31	2	33	0.3%	1.60 [0.29, 8.92]	2012
Gutierrez Bayard et al	8	49	8	49	0.9%	1.00 [0.41, 2.45]	2014
Anter et al	8	51	10	49	1.1%	0.77 [0.33, 1.79]	2015
<b>Total (95% CI)</b>		<b>2802</b>		<b>2783</b>	<b>100.0%</b>	<b>0.97 [0.89, 1.06]</b>	
Total events	645		660				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 10.35, df = 23 (P = 0.99); I <sup>2</sup> = 0%							
Test for overall effect: Z = 0.60 (P = 0.55)							



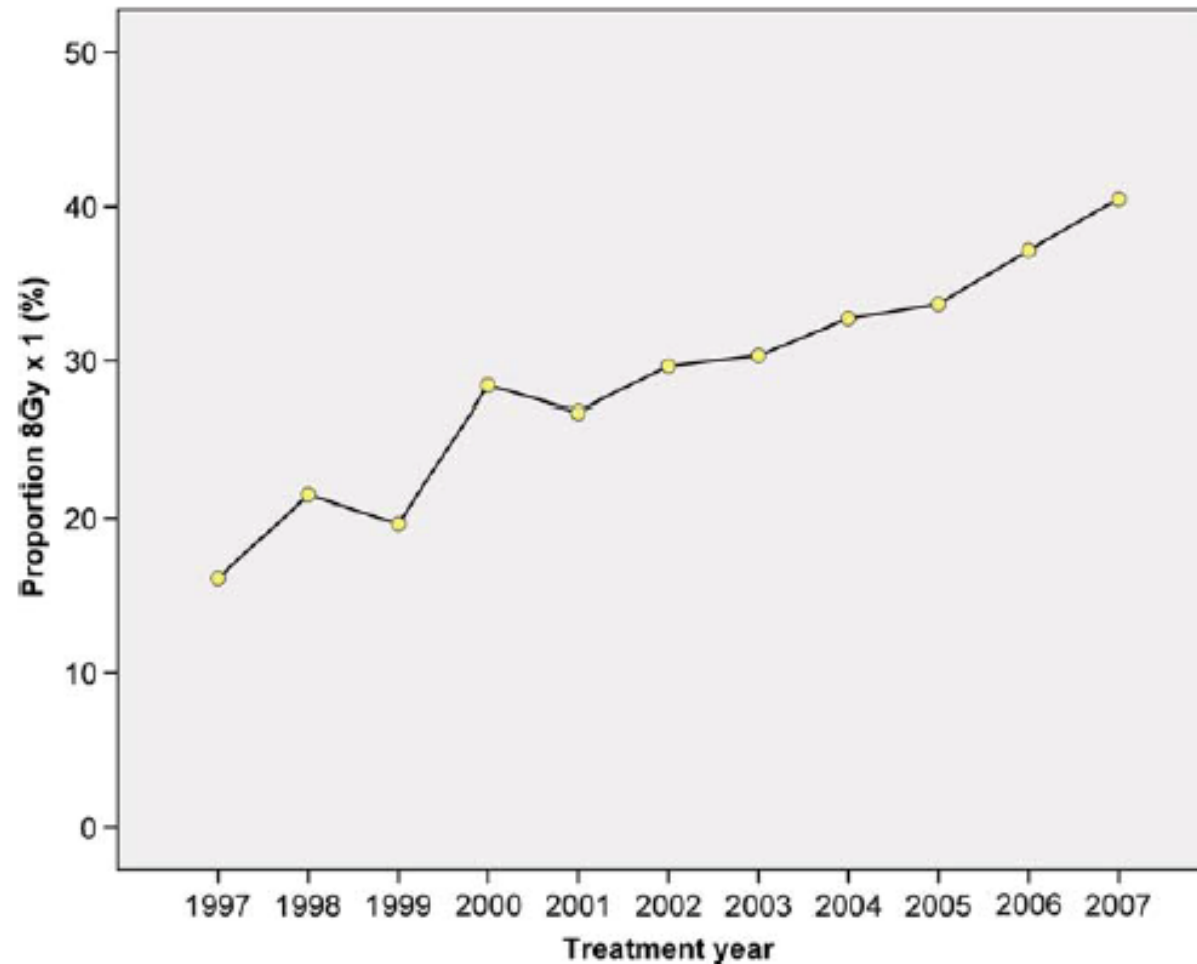
Complete response

Single vs. multiple  
Fractions\*

\* 8 Gy in 1 fraction vs 20 Gy in 5 fractions or 30 Gy in 10 fractions

# UNCOMPLICATED BONE METASTASES

## *Dose and fractions*



# UNCOMPLICATED BONE METASTASES

## *Disseminated bone metastases – HALF IRRADIATION BODY (HIB)*

Weeks after treatment	Patients (n)	Partial <sup>1</sup> or complete pain relief n (%)	Complete pain relief n (%)	Patients (n)	Reduced dose of analgesics <sup>2</sup> n (%)
2	36	22 (61)	3 (8.3)	36	10 (28)
4	34	26 (76)	3 (8.8)	37	13 (35)
8	27	19 (70)	5 (19)	29	10 (34)
16	21	14 (67)	5 (24)	19	5 (26)
24	13	9 (69)	1 (7.7)	11	5 (45)

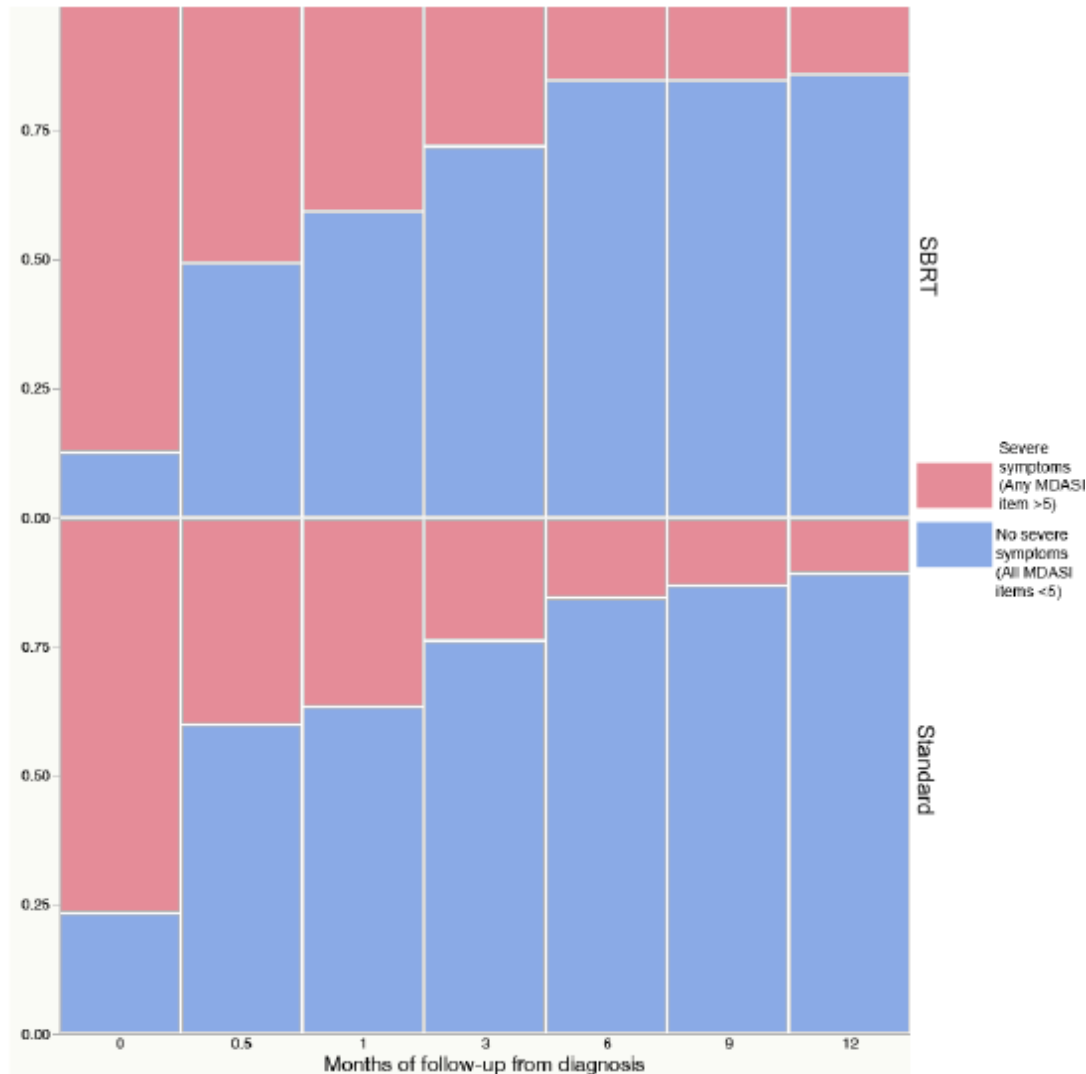
- Phase II trial – 44 patients
- 93% patients with prostate cancer
- Upper body 6-7 Gy, Lower 8 Gy

Weeks after treatment	Patients (n)	Vomiting <sup>1</sup> (%)	Patients (n)	Diarrhoea <sup>2</sup> (%)	Patients (n)	Fatigue <sup>3</sup> (%)
0	43	42	42	14	43	40
2	42	50	41	49*	40	63
4	39	31	38	21	37	46
8	32	25	31	19	31	39
16	23	22	23	7.0	23	57
24	15	33	15	13	15	60

- Primary outcome: pain and QoL
- Secondary outcome: side effects

# UNCOMPLICATED BONE METASTASES

## *Stereotactic radiotherapy vs. conventional fractionation*



- Phase II trial – 160 patients
- Majority lung cancer
- 12-16 Gy/1# vs 30 Gy/10#
- Limited spinal metastases
- Primary outcome: pain relief



# UNCOMPLICATED BONE METASTASES

## Stereotactic radiotherapy vs. conventional fractionation

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)	p value
<b>1-month assessment</b>			
Complete response	20 (17%)	30 (26%)	0.10*
Partial response	33 (29%)	34 (30%)	..
Stable pain	38 (33%)	26 (23%)	..
Progressive pain	14 (12%)	9 (8%)	..
Indeterminant	10 (9%)	15 (13%)	..
Mean daily OME consumption, mg	44 (122)	27 (95)	0.26
<b>3-month assessment</b>			
Complete response	16 (14%)	40 (35%)	0.0002*
Partial response	29 (25%)	20 (18%)	..
Stable pain	34 (30%)	27 (24%)	..
Progressive pain	14 (12%)	7 (6%)	..
Indeterminant	22 (19%)	20 (18%)	..
Mean daily OME consumption, mg	43 (106)	37 (97)	0.70
Mean change in SINS from baseline	-0.49 (1.61)	-0.94 (1.69)	0.034
<b>6-month assessment</b>			
Complete response	18 (16%)	37 (32%)	0.0036*
Partial response	18 (16%)	10 (9%)	..
Stable pain	32 (28%)	26 (23%)	..
Progressive pain	8 (7%)	5 (4%)	..
Indeterminant	39 (34%)	36 (32%)	..
Mean daily OME consumption, mg	36 (126)	36 (84)	1.00
Mean change in SINS from baseline	-0.74 (1.99)	-0.73 (1.86)	0.88

	Conventional external beam radiotherapy group (n=115)			Stereotactic body radiotherapy group (n=110)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Dysphagia	0	0	0	1 (1%)	1 (1%)	0
Oesophagitis*	2 (2%)	0	0	2 (2%)	0	0
Nausea	2 (2%)	1 (1%)	0	1 (1%)	0	0
Pain†	4 (3%)	5 (4%)	0	2 (2%)	5 (5%)	0
Fatigue	0	1 (1%)	0	0	0	0
Vertebral compression fracture	0	0	1 (1%)	0	1 (1%)	0

Data are n (%). Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. No grade 5 adverse events were reported. \*Oesophagitis events are presented as an aggregate of oesophageal pain, oesophagitis, and pharyngeal mucositis. †Pain events are presented as an aggregate of general disorders pain, neoplasm-related tumour pain, and musculoskeletal and connective tissue disorders.

- Primary outcome: pain relief

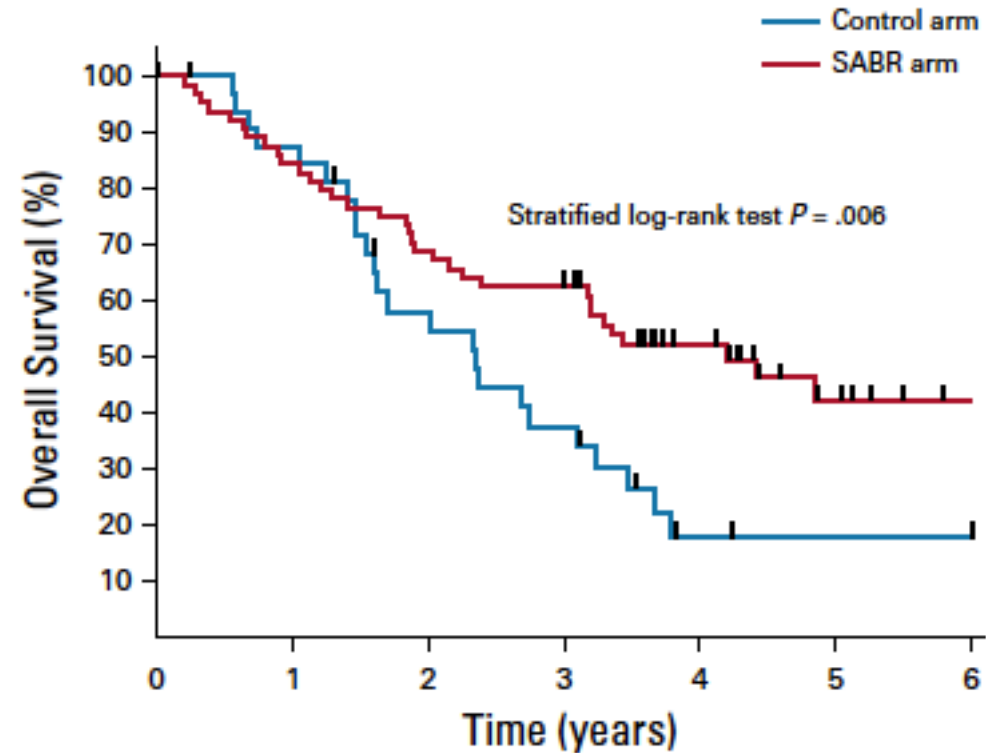
# UNCOMPLICATED BONE METASTASES

## Stereotactic radiotherapy in oligometastatic

Characteristic	Arm, No. (%)	
	Control (n = 33)	SABR (n = 66)
Median age, years (IQR)	69 (64-75)	67 (59-74)
Sex		
Male	19 (58)	40 (61)
Female	14 (42)	26 (39)
Site of original primary tumor		
Breast	5 (15)	13 (20)
Colorectal	9 (27)	9 (14)
Lung	6 (18)	12 (18)
Prostate	2 (6)	14 (21)
Other	11 (33)	18 (27)
Median time from diagnosis of primary tumor to random assignment, years (IQR)	2.3 (1.3-4.5)	2.4 (1.6-5.3)
No. of metastases		
1	12 (36)	30 (46)
2	13 (40)	19 (29)
3	6 (18)	12 (18)
4	2 (6)	2 (3)
5	0 (0)	3 (5)
Location of metastases (n = 191 lesions)		
Adrenal	2 (3)	7 (6)
Bone	20 (31)	45 (35)
Liver	3 (5)	16 (13)
Lung	34 (53)	55 (43)
Other <sup>a</sup>	5 (8)	4 (3)

Median follow-up: 51 months

Primary endpoint OS!!



Median overall survival

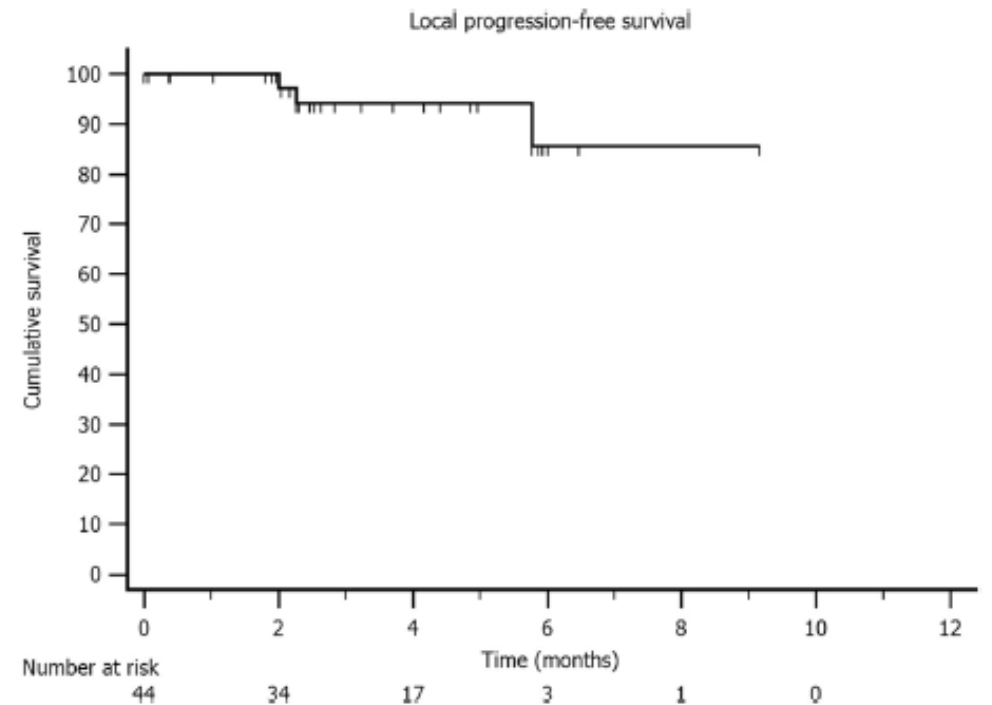
28 months (95% CI 18–39) in the control group vs 50 months (95% CI 29–83) in the SABR

# UNCOMPLICATED BONE METASTASES

## *Stereotactic radiotherapy in oligometastatic*



**24 Gy in 3 fractions**



# UNCOMPLICATED BONE METASTASES

## *Side effects in bone metastases radiation treatment – pain flare*

**Purpose:** Pain flare is a temporary increase in pain and is a potential side effect of radiotherapy treatment. However, its incidence has been reported only in recent studies, and with great variability. A few studies have reported on the use of dexamethasone as a prophylactic agent in the prevention of pain flare. The objective of this study is to present a review of the available literature regarding the incidence of pain flare and use of dexamethasone as a preventative measure.

**Methods:** A literature search was conducted in PubMed using subject keywords including: “radiation therapy”, “stereotactic radiation therapy”, “bone metastases”, “pain flare”, and “dexamethasone”. The search was limited to English only but not restricted to any time period. Additionally, a search was also conducted in the American Society for Therapeutic Radiology and Oncology (ASTRO) 2014 book of published abstracts. Inclusion criteria were primary studies published with full text and/or abstracts only. Letters to the editor were excluded.

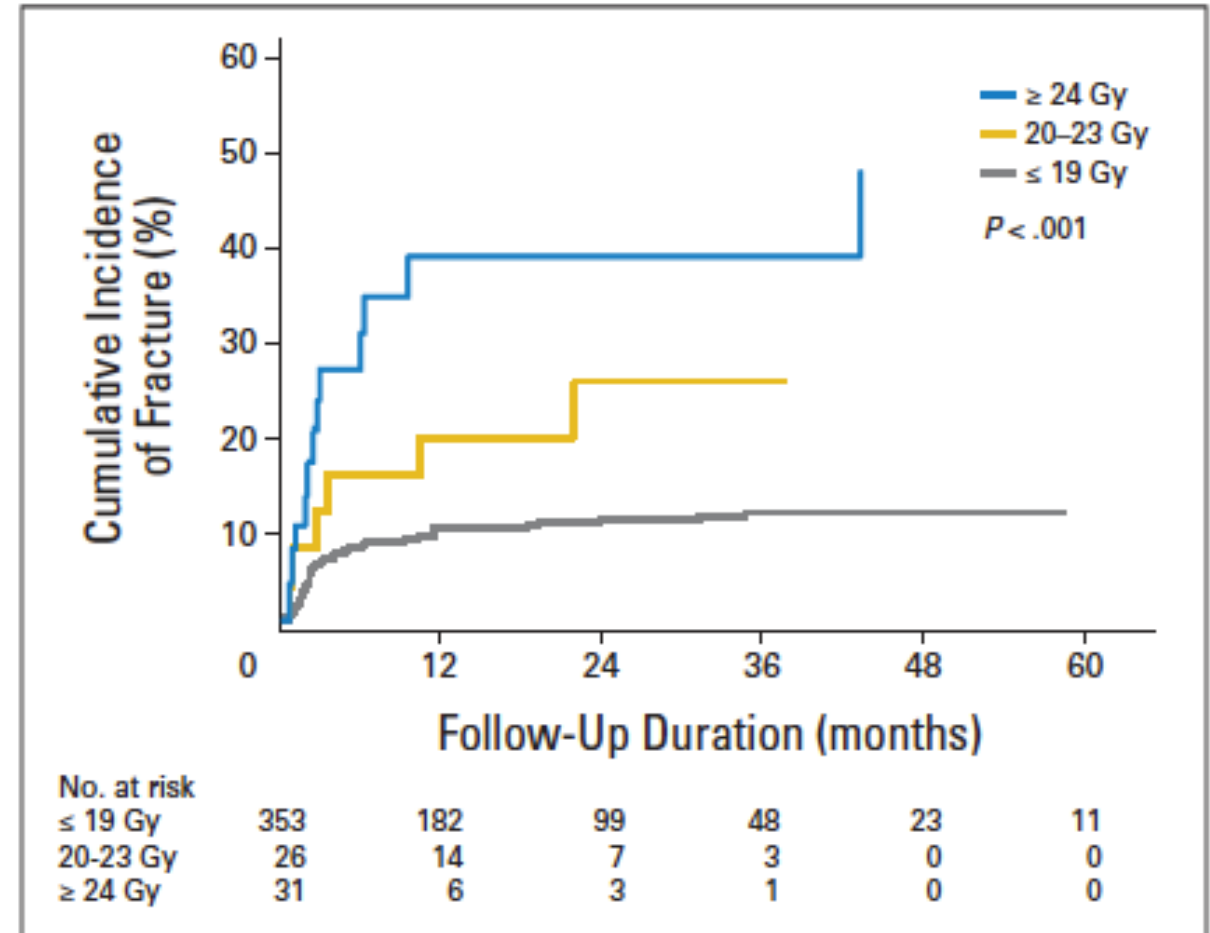
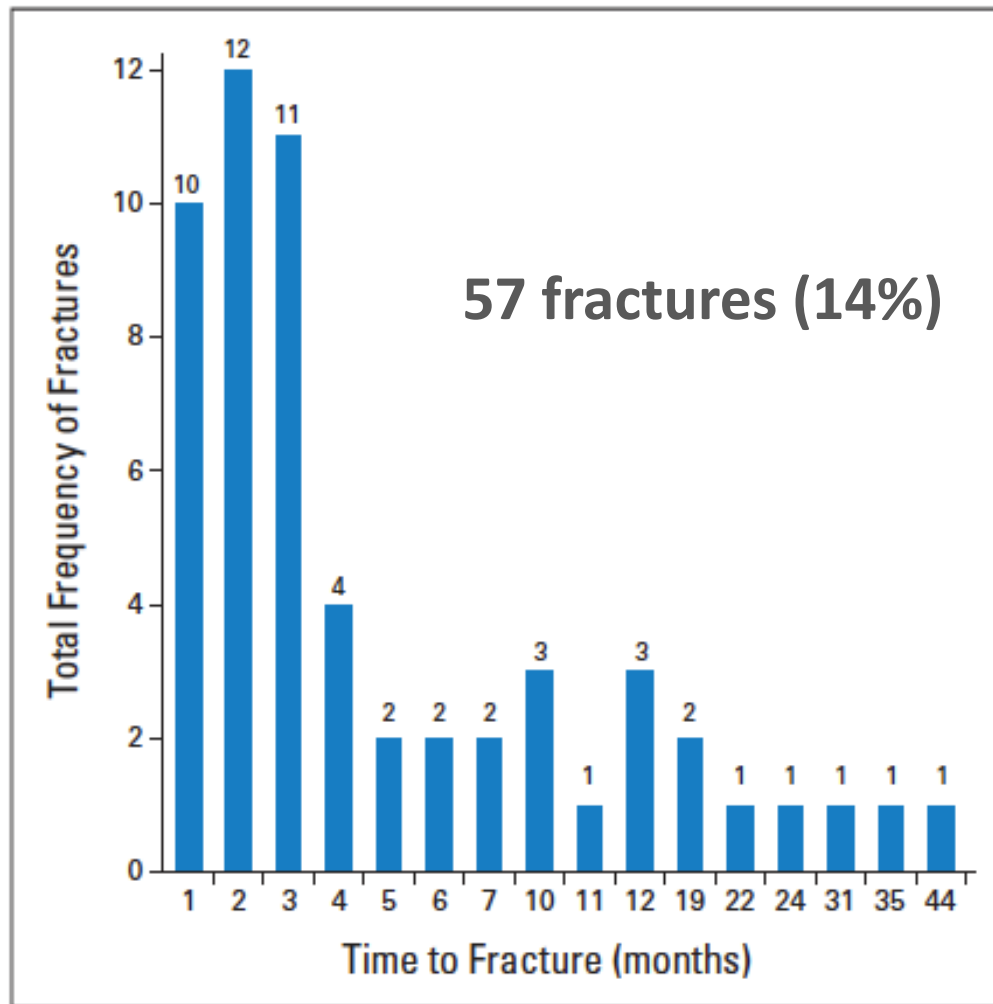
**Results:** A total of 11 studies were selected, two of which were abstracts published by ASTRO in 2014. Seven articles investigated pain flare and/or dexamethasone use for conventional external beam radiation therapy (EBRT) while the remaining four investigated stereotactic body radiation therapy (SBRT). Pain flare incidence ranged from 2 to 44% for EBRT and 10 to 68% in SBRT. The use of dexamethasone also showed to be effective in both the prophylaxis and treatment of pain flare.

**Conclusions:** Pain flare has been established as an acute toxicity of both EBRT and SBRT, although its incidence is widely variable due to differences in data collection. The use of dexamethasone in the prophylaxis of pain flare is efficacious. Future studies are required in order to both optimize the reporting of pain and the dexamethasone regimens in the prevention of pain flare.



# UNCOMPLICATED BONE METASTASES

## Side effects in bone metastases radiation treatment – Fractures



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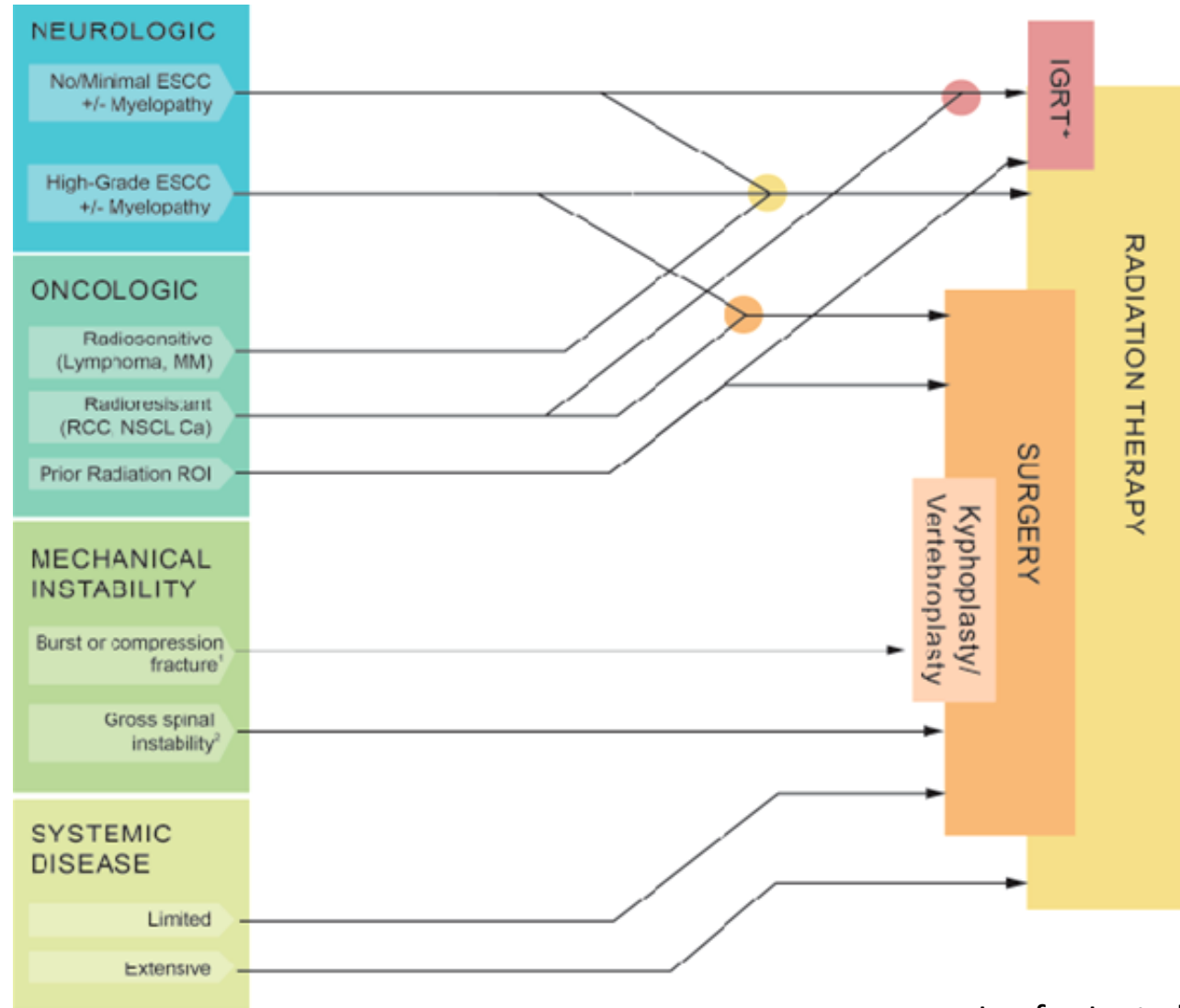
# COMPLICATED BONE METASTASES

## *Incidence of metastatic spinal cord compression*

Tumour Primary Site	Number (%) n = 2656
Breast	605 (22.8)
Lung	416 (15.7)
Prostate	340 (12.8)
Myeloma/Lymphoma	269 (10.1)
Renal/GU	225 (8.5)
GI	110 (4.1)
Melanoma	74 (2.8)
Sarcoma	55 (2)
Unknown	160 (6)
Other	402 (15.1)

# COMPLICATED BONE METASTASES

## NOMS Algorithm

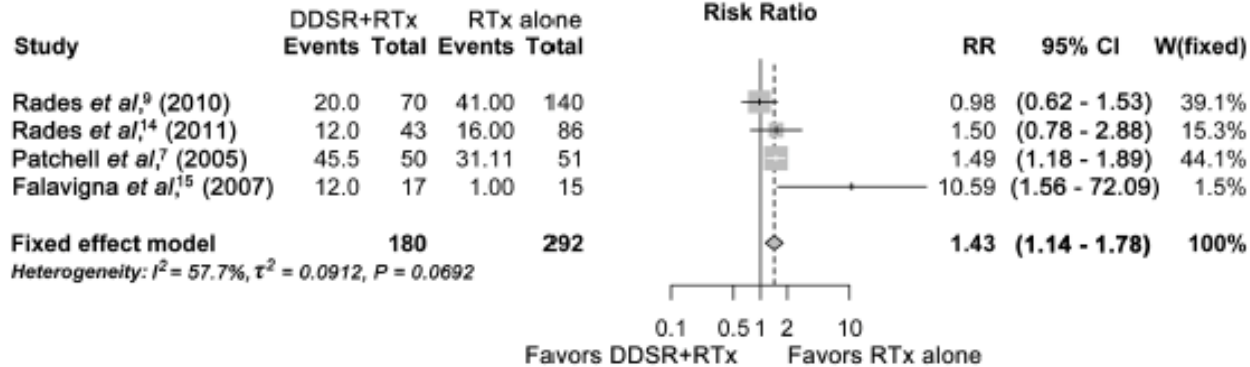




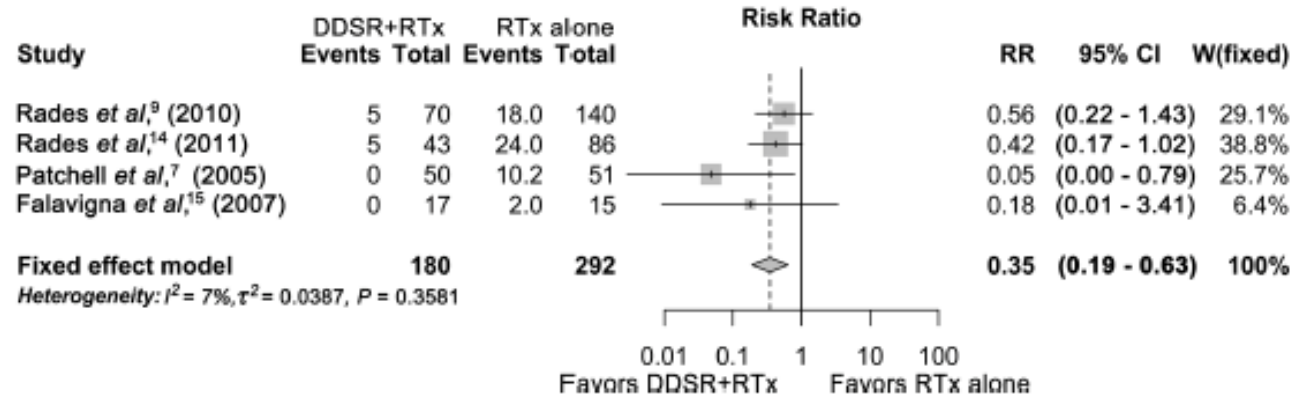
# COMPLICATED BONE METASTASES

## Surgery and radiotherapy vs. radiotherapy alone

### Improvement of ambulatory status



### Deterioration of ambulatory status

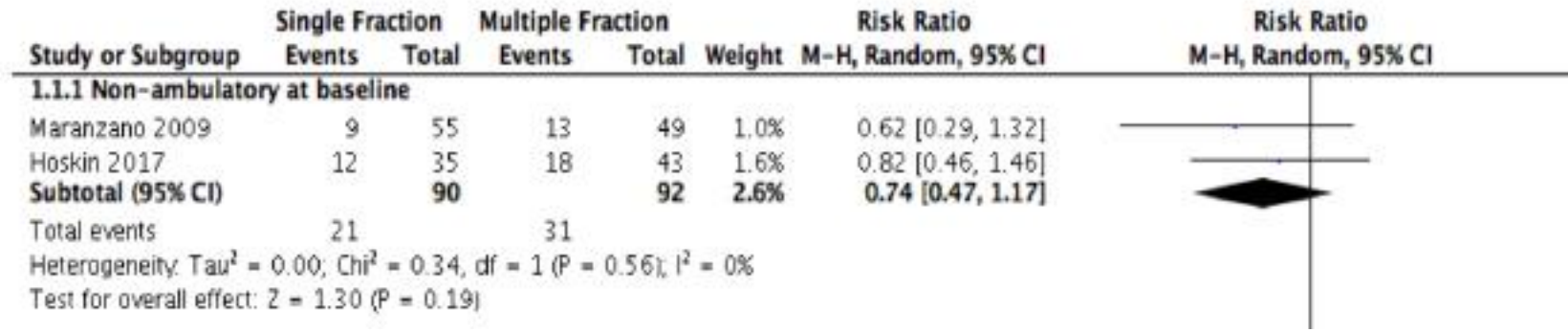


# COMPLICATED BONE METASTASES

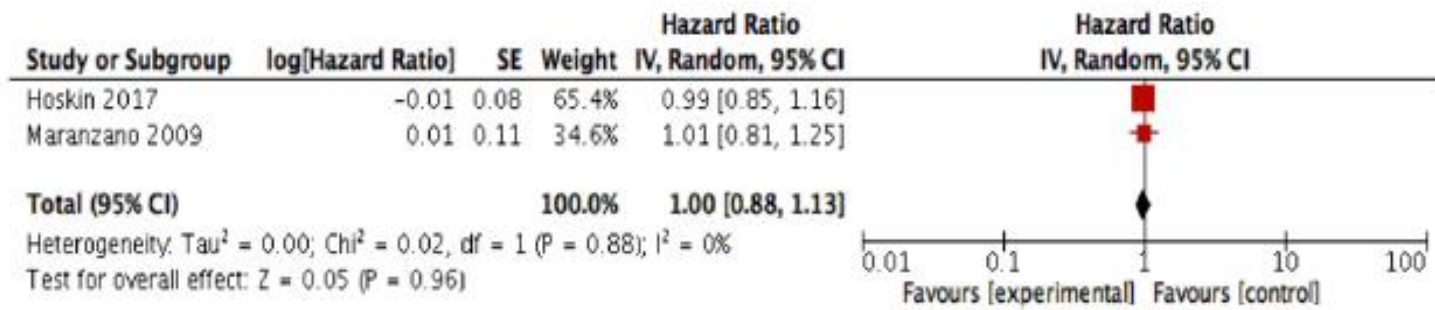
## *Dose and fractions – single fraction vs. multiple fractions*



**Motor response**



**Ambulatory status**



**Overall survival**

# COMPLICATED BONE METASTASES

## Post-operative radiotherapy after decompression

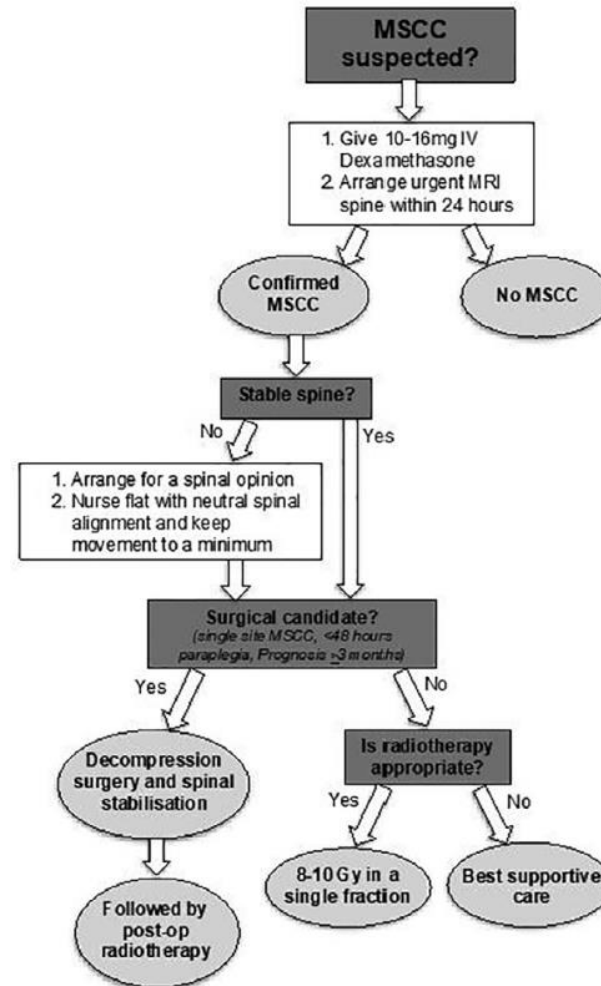
	Radiation group (n=51) median	Surgery group (n=50) median	Relative risk*	95% CI*	P*	Significant predictors**
Maintenance of continence	17 days	156 days	0.47	0.25-0.87	0.016	Surgery RR=0.51 (0.29-0.90) Baseline Frankel Score RR=0.56 (0.3-0.73)
Maintenance of ASIA score	72 days	566 days	0.28	0.13-0.61	0.001	Surgery RR=0.30 (0.14-0.62) Stable Spine RR=0.43 (0.22-0.83) Cervical Spinal Level RR=0.49 (0.26-0.90) Baseline Frankel Score RR=0.65 (0.46-0.91)
Maintenance of Frankel score	72 days	566 days	0.24	0.11-0.54	0.0006	Surgery RR=0.26 (0.12-0.54) Stable Spine RR=0.39 (0.20-0.75) Cervical Spinal Level RR=0.53 (0.74-0.98) Baseline Frankel Score RR=0.62 (0.44-0.88)
Survival time	100 days	126 days	0.60	0.38-0.96	0.033	Surgery RR=0.60 (0.40-0.92) Breast Primary Tumour RR=0.29 (0.13-0.62) Lower Thoracic Spinal Level RR=0.65 (0.43-0.99)

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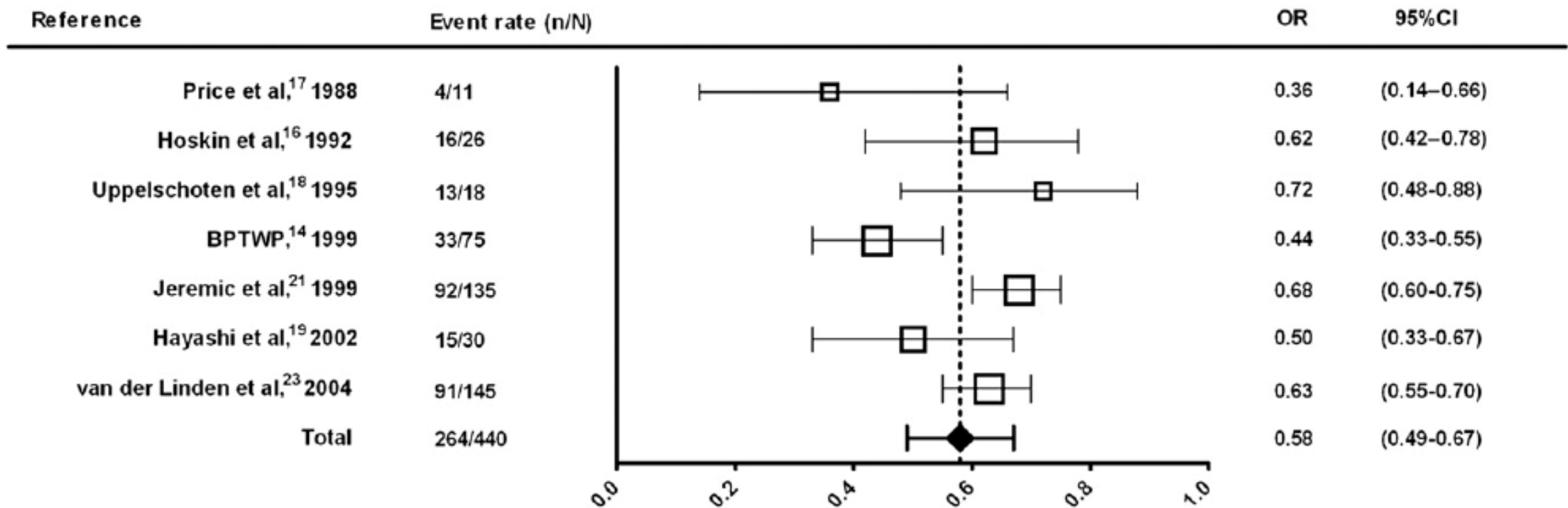
walk

# COMPLICATED BONE METASTASES

## Management of complicated bone metastases



## Re-irradiation



Random effects model  
 $I^2 = 63.3\%$ ,  $p = 0.01$

Overall response rate ( OR ) for reirradiation

**Re-irradiation response rate probability 60%**

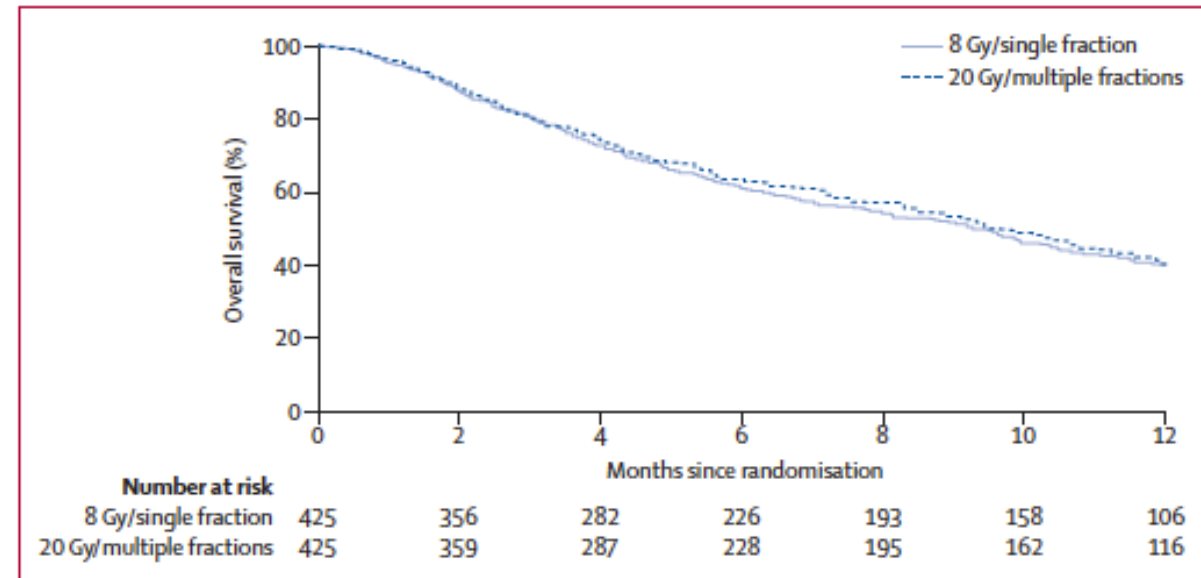
# UN & COMPLICATED BONE METASTASES

## Re-irradiation

	Intention-to-treat analysis		Per-protocol analysis	
	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N=425)	8 Gy/single fraction (N=258)	20 Gy/multiple fractions (N=263)
Overall response	118 (28%)	135 (32%)	116 (45%)	134 (51%)
Complete response	36 (8%)	30 (7%)	35 (14%)	29 (11%)
Partial response	82 (19%)	105 (25%)	81 (31%)	105 (40%)
Not assessable	162 (38%)	160 (38%)	0	0
Not defined*	92 (22%)	91 (21%)	91 (35%)	91 (35%)
No change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain progression	46 (11%)	32 (8%)	44 (17%)	31 (12%)

Data are number (%). \*Response assessments that could not be classified as complete response, partial response, no change, or pain progression.

**Table 2: Response to treatment according to Brief Pain Inventory score and daily oral morphine equivalent at 2 months in the intention-to-treat and per-protocol populations**



Single dose comparable to multiple fractions in terms of response to treatment and OS



## UNCOMPLICATED BONE MESTASTASES

- 8 Gy in single fraction should be preferred to multiple fractions in patients with uncomplicated bone metastases [**Grade A, Level 1**]
- Stereotactic radiotherapy did not improve pain relief when compared to single fraction in bone metastases [**Grade A, Level 1**]
- Pain flare, occurring in around one third of patients, could be managed by symptomatic measures such as paracetamol or dexamethasone. [**Grade D, Level 5**]
- Patients with insufficient pain relief, no pain relief or pain relapse after initial radiotherapy, should be considered for reirradiation. [**Grade A, Level 1**]

## COMPLICATED BONE MESTASTASES

- Single site MSCC, < 48h paraplegia and life expectancy of 3 months should be referred for urgent surgical decompression, stabilisation and followed by post-operative radiotherapy **[Grade A, Level 1B]**
- A single dose of 8–10 Gy should be delivered in patients not fit or ineligible for surgery. **[Grade A, Level 1A]**
- 30 Gy in 10 fractions should be used post-operatively. **[Grade B, Level 1]**
- Patients with insufficient pain relief, no pain relief or pain relapse after initial radiotherapy, should be considered for reirradiation. **[Grade A, Level 1]**