La radioterapia nel trattamento delle metastasi ossee

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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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Dose and fractions

	Single Fra	oction	Multiple Fra	ction		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Price et al	29	140	34	148	0.6%	0.90 (0.58, 1.40)	1986	
Cole	12	16	9	13	0.6%	1.08 [0.68, 1.72]	1989	
Kagei et al	12	13	12	14	1.8%	1.08 [0.83, 1.40]	1990	
Gaze et al	108	151	99	144	5.6%	1.04 [0.90, 1.21]	1997	
Nielson et al	52	122	56	119	1.6%	0.91 [0.68, 1.20]	1998	
Foro et al	19	25	22	25	1.8%	0.86 [0.66, 1.12]	1998	
Foro et al	19	25	21	25	1.6%	0.90 [0.68, 1.20]	1998	
Koswig and Budach	41	52	45	55	3.5%	0.96 (0.80, 1.16)	1999	
Bone Party Trial Working Party	274	383	257	378	14.1%	1.05 (0.96, 1.16)	1999	+•
Kirkbride et al	101	200	95	198	3.1%	1.05 (0.86, 1.29)	2000	
Ozsaran et al	27	36	29	35	2.1%	0.91 (0.71, 1.15)	2001	
Ozsaran et al	27	36	28	38	1.7%	1.02 (0.78, 1.33)	2001	
Altundag et al	13	17	12	14	1.1%	0.89 [0.64, 1.25]	2002	
Altundag et al	13	18	12	14	1.0%	0.84 (0.59, 1.20)	2002	
Sarkar et al	13	35	16	38	0.4%	0.88 (0.50, 1.56)	2002	
Badzio et al	53	72	52	74	3.0%	1.05 [0.86, 1.28]	2003	
van der Linden et al	395	579	396	578	20.1%	1.00 [0.92, 1.08]	2004	-
Hartsell et al	187	455	188	443	5.2%	0.97 [0.83, 1.13]	2005	
Roos et al	73	137	83	135	2.9%	0.87 [0.71, 1.06]	2005	
El-Shenshawy et al	39	50	40	50	3.0%	0.97 [0.80, 1.19]	2006	
El-Shenshawy et al	39	50	39	50	2.9%	1.00 [0.81, 1.23]	2006	
Hamouda et al	42	52	46	55	4.0%	0.97 [0.81, 1.15]	2007	
Safwat et al	14	20	14	20	0.8%	1.00 [0.67, 1.50]	2007	
Safwat et al	14	20	15	20	0.8%	0.93 [0.64, 1.37]	2007	
Foro Arnalot et al	59	78	71	82	5.4%	0.87 (0.75, 1.02)	2008	
Amouzegar-Hashemi et al	21	36	20	34	0.8%	0.99 (0.67, 1.47)	2008	
Majumder et al	20	31	22	33	1.0%	0.97 (0.68, 1.38)	2012	
Malik et al	11	15	12	15	0.8%	0.92 [0.62, 1.36]	2012	
Malik et al	11	15	12	15	0.8%	0.92 [0.62, 1.36]	2012	
El Hawwari et al	30	40	30	40	1.9%	1.00 [0.78, 1.29]	2012	
El Hawwari et al	30	40	30	40	1.9%	1.00 [0.78, 1.29]	2012	
Gutierrez Bayard et al	36	49	40	49	2.7%	0.90 [0.73, 1.12]	2014	
Anter et al	33	51	33	49	1.6%	0.96 [0.73, 1.27]	2015	
Total (95% CI)		3059		3040	100.0%	0.98 [0.95, 1.01]		•
Total events	1867		1890					
Heterogeneity: Tau ^a = 0.00; Chi ^a	= 12.47, df:	= 32 (P =	: 1.00); P = 0	%				0.5 0.7 1 1.5 2
Test for overall effect: Z = 1.15 (F								0.5 0.7 1 1.5 2 Favours Multiple Fraction Favours Single Fraction

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

Rich SE et al. Radiother Oncol. 2018;126:547-557



Dose and fractions

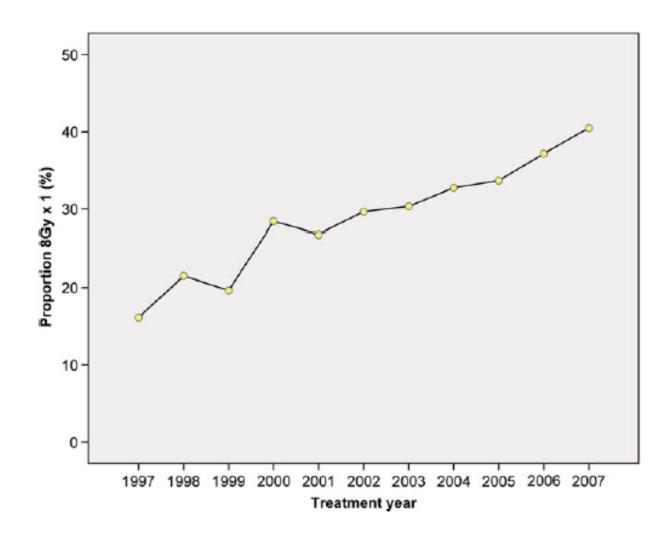
	Single Fra	action	Multiple Fr	action		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Yea	ar M-H, Random, 95% Cl	
Price et al	13	140	13	148	1.4%	1.06 [0.51, 2.20] 198	36	
Kagei et al	8	14	4	13	0.9%	1.86 [0.73, 4.72] 199	90	
Gaze et al	50	151	47	144	7.1%	1.01 [0.73, 1.41] 199	97	
Nielson et al	12	122	14	119	1.4%	0.84 [0.40, 1.73] 199	98	
Bone Party Trial Working Party	199	383	192	378	39.5%	1.02 [0.89, 1.17] 199	99 —	
Koswig and Budach	16	52	18	55	2.4%	0.94 [0.54, 1.64] 199	99	
Kirkbride et al	44	200	57	198	6.5%	0.76 [0.54, 1.07] 200		
Altundag et al	7	17	9	14	1.6%	0.64 [0.32, 1.28] 200		
Altundag et al	10	18	9	14	2.3%	0.86 [0.49, 1.53] 200		
Sarkar et al	6	35	8	38	0.8%	0.81 [0.31, 2.11] 200		Complete receence
Badzio et al	23	72	24	74	3.4%	0.98 [0.61, 1.58] 200	13	Complete response
van der Linden et al	78	579	76	578	8.7%	1.02 [0.76, 1.37] 200	04	
Roos et al	35	137	36	135	4.7%	0.96 [0.64, 1.43] 200		
Hartsell et al	44	455	51	443	5.2%	0.84 [0.57, 1.23] 200		
El-Shenshawy et al	17	50	16	50		1.06 [0.61, 1.86] 200	06	
El-Shenshawy et al	17	50	16	50	2.4%	1.06 [0.61, 1.86] 200	06	
Hamouda et al	23	52	22	55	3.8%	1.11 [0.71, 1.73] 200	07	Single vs. multiple
Foro Arnalot et al	12	78	11	82	1.3%	1.15 [0.54, 2.45] 200		
Amouzegar-Hashemi et al	6	36	11	34	1.0%	0.52 [0.21, 1.24] 200		
Malik et al	3	15	3	15	0.4%	1.00 [0.24, 4.18] 201	2	Fractions*
Malik et al	3	15	3	15	0.4%	1.00 [0.24, 4.18] 201	2	Tractions
Majumder et al	3	31	2	33		1.60 [0.29, 8.92] 201	12	
Gutierrez Bayard et al	8	49	8	49	0.9%	1.00 [0.41, 2.45] 201	4	
Anter et al	8	51	10	49	1.1%	0.77 [0.33, 1.79] 201	5	
Total (95% CI)		2802		2783	100.0 %	0.97 [0.89, 1.06]		
Total events	645		660					
Heterogeneity: Tau ² = 0.00; Chi ²	= 10.35, df	= 23 (P =	: 0.99); I ² = 0)%			0.5 0.7 1 1.5 2	
Test for overall effect Z = 0.60 (P	9 = 0.55)						0.5 0.7 1 1.5 2 Favours Multiple Fraction Favours Single Fraction	

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

Rich SE et al. Radiother Oncol. 2018;126:547-557



Dose and fractions



Laugsand TS, et al. ActaOncol 2013;52:1129–36.



Disseminated bone metastases – HALF IRRADIATION BODY (HIB)

Weeks after treatment	Patients (n)	Partial ¹ or complete pain relief n (%)	Complete pain relief n (%)	Patients (n)	Reduced dose of analgesics ² 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

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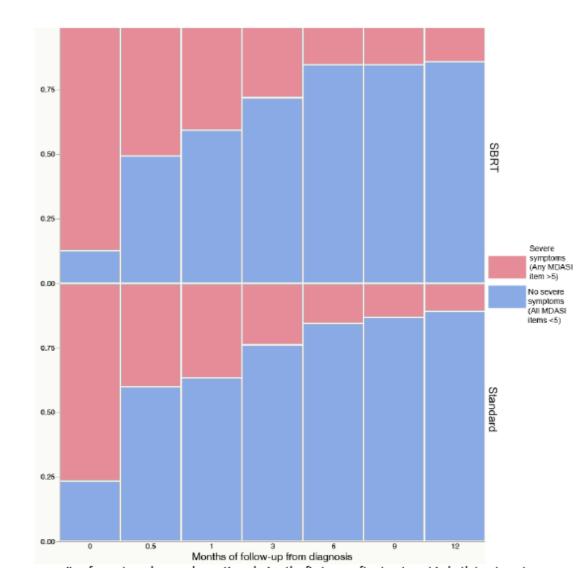
Secondary outcome: side effects

Weeks after treatment	Patients (n)	Vomiting ¹ (%)	Patients (n)	Diarrhoea ² (%)	Patients (n)	Fatigue ³ (%)
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

Berg RS, et al Acta Oncol. 2009;48:556-561.



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

Nguyen QN, et al. JAMA Oncol. 2019;5:872-878.



Stereotactic radiotherapy vs. conventional fractionation

	Conventional external beam radiotherapy group (n=115)	Stereotactic body radiotherapy group (n=114)	p value
1-month assessment			
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
3-month assessment			
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
6-month assessment			
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

		onal externa apy group (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.

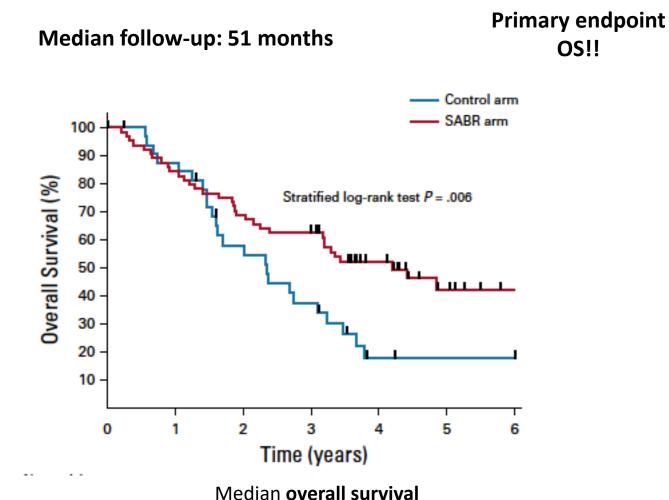
• Primary outcome: pain relief

Sahgal A, et al. Lancet Oncol. 2021;22:1023-1033.



Stereotactic radiotherapy in oligometastatic

	Arm, No. (%)					
Characteristic	Control (n = 33)	$\frac{\text{SABR}}{(n = 66)}$				
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"	5 (8)	4 (3)				

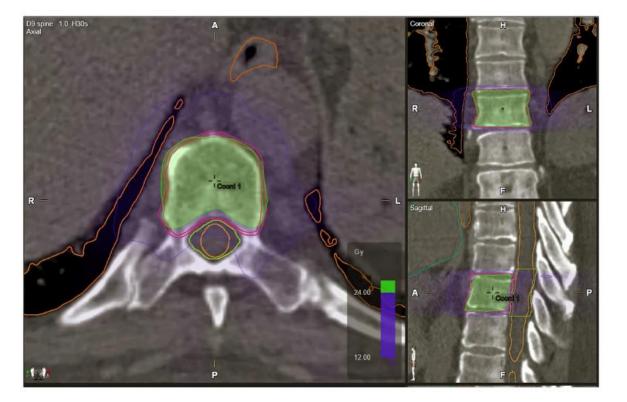


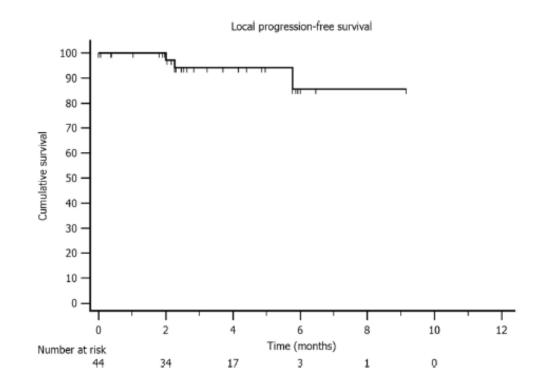
28 months (95% CI 18–39) in the control group vs 50 months (95% CI 29–83) in the SABR

Palma D et al., J Clin Oncol 2020



Stereotactic radiotherapy in oligometastatic





24 Gy in 3 fractions



Side effects in bone metastases radiation treatment – pain flare

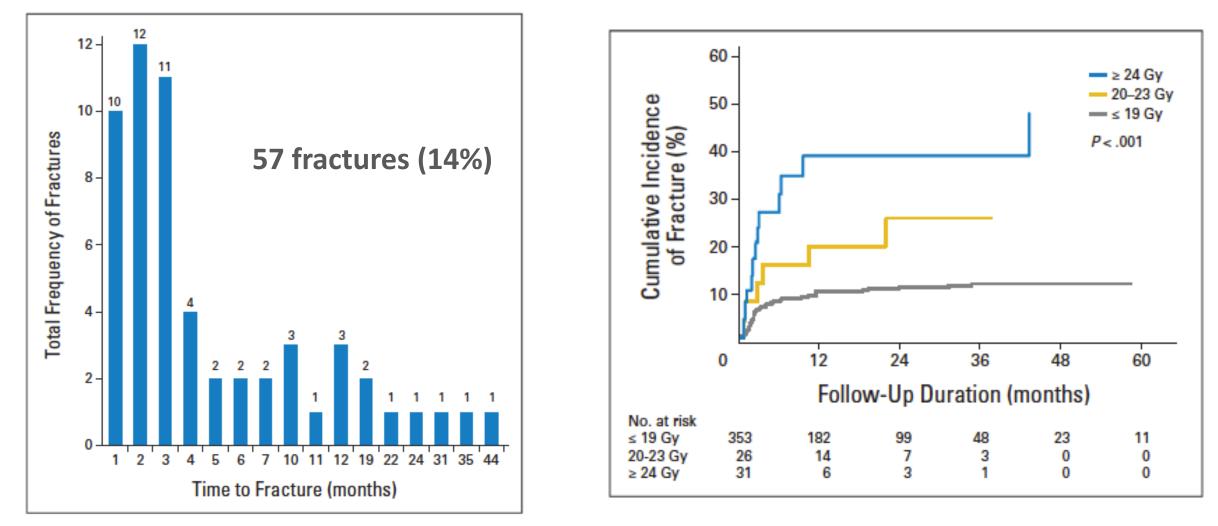
Purpose: Pain flare is a temporary increase in pain and is a potential side effect of radiotherapy treatment. However, its incidence has been reported only in recent studies, and with great variability. A few studies have reported on the use of dexamethasone as a prophylactic agent in the prevention 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.



Side effects in bone metastases radiation treatment – Fractures



Sahgal A, et al. J Clin Oncol. 2013;31:3426-3431.



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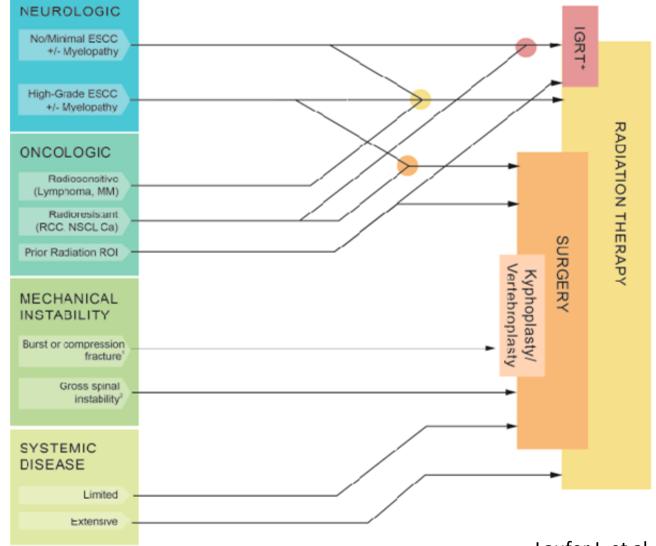


Incidence of metastatic spinal cord compression

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)



NOMS Algorithm



Laufer I, et al. Oncologist. 2013;18:744-751



Surgery and radiotherapy vs. radiotherapy alone

Improvement of ambulatory status

	DDSR	+RTx	RTx	alone	Risk Ratio			
Study	Events	Total	Events	Total		RR	95% CI	W(fixed)
Rades et al,9 (2010)	20.0	70	41.00	140		0.98	(0.62 - 1.53)	39.1%
Rades et al,14 (2011)	12.0	43	16.00	86		1.50	(0.78 - 2.88)	15.3%
Patchell et al,7 (2005)	45.5	50	31.11	51		1.49	(1.18 - 1.89)	44.1%
Falavigna et al,15 (2007)	12.0	17	1.00	15		- 10.59	(1.56 - 72.09)) 1.5%
Fixed effect model		180		292	\$	1.43	(1.14 - 1.78)	100%
Heterogeneity: $I^2 = 57.7\%$, τ^2	= 0.0912	, P = 0.	0692		r			

0.1 0.51 2 10 Favors DDSR+RTx Favors RTx alone

Deterioration of ambulatory status

Study	DDSR- Events		RTx : Events	alone Total	Risk Ratio	RR	95% CI	W(fixed)	
								. ,	
Rades et al,9 (2010)	5	70	18.0	140		0.56	(0.22 - 1.43)	29.1%	
Rades et al,14 (2011)	5	43	24.0	86		0.42	(0.17 - 1.02)	38.8%	
Patchell et al,7 (2005)	0	50	10.2	51 ·		0.05	(0.00 - 0.79)	25.7%	
Falavigna et al,15 (2007)	0	17	2.0	15		0.18	(0.01 - 3.41)	6.4%	
Fixed effect model Heterogeneity: $I^2 = 7\%$, $\tau^2 = 0$	0.0387, P =	180 0.3581		292	÷	0.35	(0.19 - 0.63)) 100%	
				Favor	0.01 0.1 1 10 100 s DDSR+RTx Favors RTx	alone			

Kim JM et al. Spine. 2012;37:78-84



Hoskin 2017

Maranzano 2009

Total (95% CI)

-0.01 0.08

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); l² = 0%

Test for overall effect: Z = 0.05 (P = 0.96)

0.01 0.11 34.6%

65.4%

100.0%

0.99 [0.85, 1.16]

1.01 [0.81, 1.25]

1.00 [0.88, 1.13]

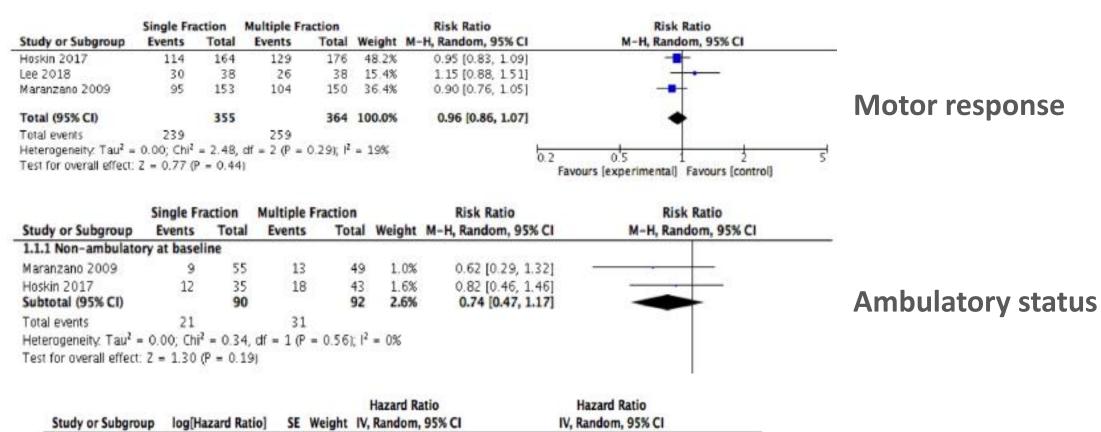
0.01

0''

Favours [experimental] Favours [control]

COMPLICATED BONE METASTASES

Dose and fractions – single fraction vs. multiple fractions



Donovan EK et al. Radiother Oncol. 2019;134:55-66

Overall survival

100

10

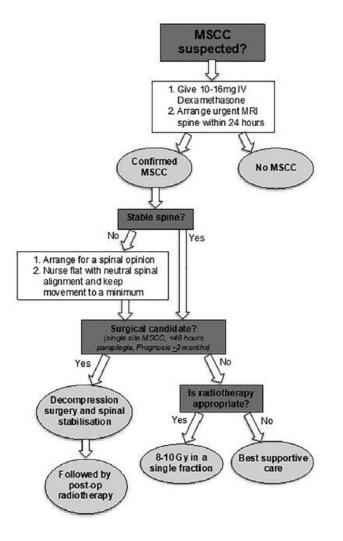


Post-operative radiotherapy after decompression

100-					_	
	Radiation group (n=51) median	Surgery group (n=50) median	Relative risk*	95% Cl*	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)



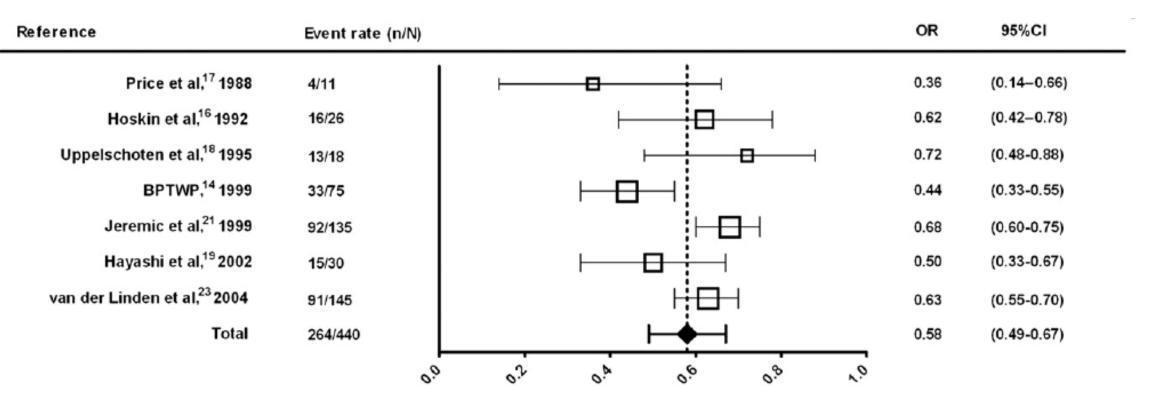
Management of complicated bone metastases



Oldenburger E et al. Radiother Oncol. 2022;173:240-253



Re-irradiation



Overall response rate (OR) for reirradiation

Re-irradiation response rate probability 60%

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

Huisman M et al. Int J Radiat Oncol Biol Phys. 2012 ;84:8-14

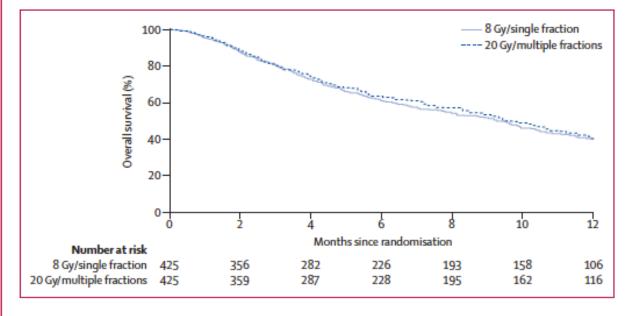


Re-irradiation

	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



CONCLUSIONS (1)

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]



CONCLUSIONS (2)

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]