

LES METASTASES OSSEUSES



Dr A. ZOUHAIR, PD & MER
Radio-Oncologie, CHUV-Lausanne

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LES METASTASES OSSEUSES

- Généralités
- Les complications squelettiques
- Physiopathologie
- Action de la Radiothérapie externe
- Essais randomisés
- Compression médullaire
- Conclusions

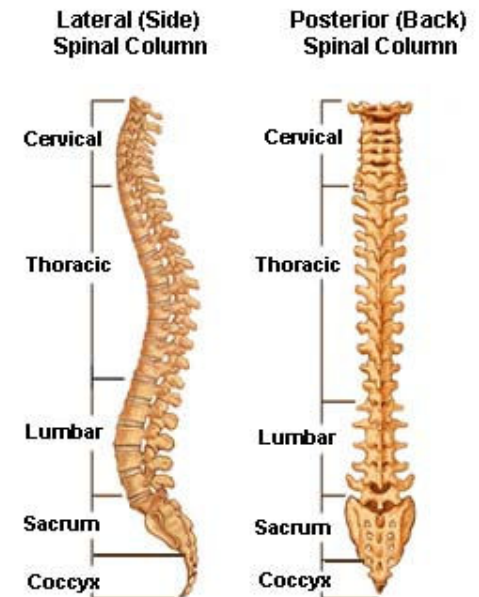
GENERALITES I

- 50% des patients avec un diagnostic de cancer nécessitent une RTH palliative
- 50% des patients développeront des métastases durant l'évolution naturelle de leurs cancers
- 85% des patients qui décèdent d'un cancer de **la prostate** ont des métastases osseuses

GENERALITES II



- Les métastases osseuses sont dans 50% des cas secondaires: **sein**, prostate et poumons
- Survie médiane de **3 ans** depuis le Dg des métastases osseuses d'origine prostatique



Clinical Importance and Prognosis of Bone Metastases

	US Prevalence (in thousands)	Bone Mets Incidence* (%)	Median Survival (mo)
Prostate	1,448	65-75	36
Bladder	582	40	6-9
Renal	198	20-25	12
Breast	1993	65-75	24
Myeloma	75-100	70-95	24
Lung	386	30-40	7
Melanoma	467	14-45	6
Thyroid	207	60	48

*In advanced disease cases.

National Cancer Institute, 1999.

International Myeloma Foundation, 2001.

GENERALITES II



- **Siège préférentiel des métastases: Colonne, pelvis et les côtes**
- **La tumeur métastase à travers le plexus veineux**
- **Environnement fertile riche en facteur de croissance (Os)**

The frequency and site of bone metastases varies with the site of the primary tumour

LES COMPLICATIONS SQUELETTIQUES

- Douleur locale ou générale dans 78% des cas
- Altération de la mobilité
- Fractures pathologiques 8%
- Compression radiculaire ou médullaire
- Hypercalcémie

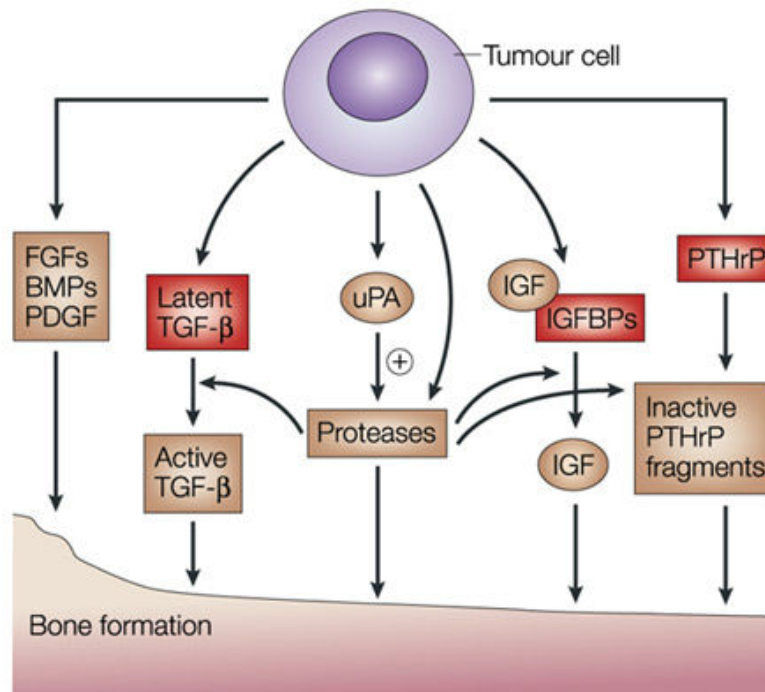
LES MODALITES THERAPEUTIQUES

- La radiothérapie externe
- L'hormonothérapie
- La chimiothérapie
- La vertébroplastie
- La chirurgie palliative de décompression
- Les analgésiques (OMS)
- Les biphosphonates

LES MODALITES THERAPEUTIQUES

La prise en charge
est multidisciplinaire

PHYSIOPATHOLOGIE I



Nature Reviews | Cancer

1-métast. produit des substances (prostaglandines, cytokines....FGFs,PDGF, BMPs) qui stimulent l'activité ostéoblastique

2- Protéases stimulées par urokinase (uPA) active TGF and inactivate the osteolytic factor parathyroid hormone related peptid (PTHrP)

3- La tumeur croit et continue à produire ces substances et perturbe le cycle de résorption oss

ETIOLOGIE DE LA DOULEUR: MECANIQUE ET CHIMIQUE

- Lyse osseuse et sécrétion de prostaglandines, cytokines qui stimulent les terminaisons nerveuses
- Destruction du périoste
- Fractures
- Infiltration nerveuse des tissus avoisinants par la tumeur

MODE D'ACTION DE LA RTH

- *Anti-tumoral*
- *Antalgique*
- *Anti-inflammatoire*
- *Recalcification*

MODE D'ACTION DE LA RTH

- Anti-tumoral?
- Détruit les cellules hôtes radio-sensibles: macrophages et libération de prostaglandines E2
- A faible dose: activation et induction des cytokines (TGF, BMP...)
- Recalcification des lésions lytiques plus précoce après RT / CT ou HT.

LES SCHEMAS HYPOFRACTIONNES EN RTH

- 30 Gy en 10 fractions de 3 Gy
- 20 Gy en 5 fractions de 4 Gy
- 8 Gy en dose unique (Flash)

LE FRACTIONNEMENT

- Le rapport α/β représente la capacité des tissus à réparer les lésions radio-induites
- Les rapports α/β sont différents selon les tissus à réponse rapide ou lente
- $\alpha/\beta = 10$: tissus précoces et tumeurs?
- $\alpha/\beta = 3$: tissus tardifs

LE FRACTIONNEMENT

n: nombre de fractions

d: dose par fraction

D: dose totale (=nd)

BED

$$D_1 \left(\frac{\alpha}{\beta} + d_1 \right) = D_2 \left(\frac{\alpha}{\beta} + d_2 \right)$$

$$\Rightarrow \frac{D_2}{D_1} = \frac{d_1 + \alpha/\beta}{d_2 + \alpha/\beta}$$

LES DOSES EQUIVALENTES

$$\alpha/\beta=10$$

- 10x3Gy correspond à un BED 2Gy= 32.5 Gy
- 5x4Gy correspond à un BED 2Gy= 23.3 Gy
- 1x8Gy correspond à un BED 2Gy= 12 Gy

$$\alpha/\beta=3$$

- 10x3Gy correspond à un BED 2Gy= 36 Gy
- 5x4Gy correspond à un BED 2Gy= 28 Gy
- 1x8Gy correspond à un BED 2Gy= 17 Gy

RESULTATS DE LA RTH

- Efficacité prouvée dans plusieurs essais
- Le taux de réponse globale est de **70-100%**
- La réponse complète **20-59%**



Vertèbre en ivoire

The effect of single fraction compared to multiple fractions: Dutch Bone Metastasis Study

- Essai randomisé incluant 1171 patients
- 1x8 Gy (585 pat) vs 6x4 Gy (586 pat)
- La tumeur primaire: Sein (38%), Prostate (24 %), Poumons (25%), autres (13%)
- La réponse est basée sur l'échelle de la douleur (diminution de 2 points)
- Questionnaire et évaluation du coût

The effect of single fraction compared to multiple fractions: Dutch Bone Metastasis Study

- La survie médiane est de 30 semaines (W)
(sein: 69 W, prostate: 40 W, 13 W: poumon)
- La R. globale méta prost 78% (flash) vs 77%
- La R. globale méta pulm 62% (flash) vs 58%
- La réponse complète 38% vs 44% (prostate)
- L'intervalle libre jusqu'à la progression:
sein > **prostate** > poumon

The effect of single fraction compared to multiple fractions: Dutch Bone Metastasis Study

- Le nombre de retraitements: **22 %** ttt par flash vs **11 %** ttt fractionné ($p < 0.0001$)
- Durée de réponse est plus courte (flash)
- Les fractures pathologiques plus fréquentes dans le ttt par flash **5 %** vs **2 %**
- Les 2 schémas sont identiques

Radiother and Oncol 52, (1999): 101-109

8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up

- Essai randomisé incluant 761 patients
- 1x8 Gy (383) vs 5x4 Gy/10x3 Gy (378)
- La tumeur primaire: **Sein (36%)**, Prostate (33 %), Poumons (13%), autres (18%)
- Réponse basée sur l'échelle de la douleur, prise d'antalgique, questionnaire aux patients

8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up

- La survie globale à 1 an est de 44%
- La réponse globale 78% (flash) vs 78%
- La réponse complète 57% vs 58% +++
- Pas de différence des effets secondaires aigus

8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. UK study

- Le nombre de retraitements est de **23 %** flash *vs* **10 %** ttt fractionné
- Pas de différence significative dans le nombre de fractures pathologiques (7 cas *vs* 2)
- Les 2 schémas sont identiques

Radiother and Oncol 52, (1999): 111-121

Randomized trial of dose versus fractionated palliative radiotherapy of bone metastases .

- Essai randomisé incluant 241 patients
- 1x8 Gy (122 pat) vs 5x4 Gy (119 pat)
- La tumeur primaire: **Sein (39%)**, Prostate (34%) , Poumons (13%), autres (14%)
- Réponse basée sur l'échelle de la douleur , prise d'antalgique, questionnaire aux patients, qualité de vie

Randomized trial of dose versus fractionated palliative radiotherapy of bone metastases .

- La survie globale à 1 an est de 36%
- La réponse complète à 4W 62% vs 74%
- Pas de différence dans la durée de réponse
- Le retraitement est 2 x plus fréquent dans les doses uniques (25 pat vs 14)
- Les 2 schémas sont efficaces

Radiother and Oncol 47, (1998): 233-240

Radiation therapy in the management of symptomatic bone metastases: The effect of total dose and histology on pain relief and response duration

- Essai prospectif incluant 205 patients
- 40-46 Gy *vs* 30-36 Gy *vs* 8-28 Gy
- La tumeur primaire: **Sein (56%)**, Prostate (11%), Poumons (14%), autres (19%)
- La réponse est basée sur l'échelle de la douleur, prise d'antalgique, questionnaire

Radiation therapy in the management of symptomatic bone metastases: The effect of total dose and histology on pain relief and response duration

- La réponse globale (CR+PR) est de 76%
- La réponse complète est de 62%
- La réponse dépend de la tumeur primaire
Sein (83%), prostate (65%) et poumon (46%)
- Possible relation avec le type histologique

Radiation therapy in the management of symptomatic bone metastases: The effect of total dose and histology on pain relief and response duration

- La durée de réponse est plus longue sein > prostate > poumon
- La réponse dépend de la dose administrée:
40-46 Gy(**81%**), 30-36Gy(**65%**) et 8-28Gy(**46%**)
- La survie médiane dépend de la dose

Int J Radiat Oncol Biol Phys 42, (1998): 1119-1126

Phase III Randomized Trial of 8 Gy in 1 fraction vs. 30 Gy in 10 fractions for painful bone metastases: preliminary results of RTOG 97-14

- Métastases osseuses prostate et sein
- 949 patients inclus entre 1998-2002
- Réponse globale à 66 % (RC 17% + RP 49%)
 - 8 Gy (RC 15% + RP 50%)
 - 30 Gy (RC 18% + RP 48%)
- Pas de différence entre les 2 groupes à 3 mois

Int J Radiat Oncol Biol Phys 57, (2003): S124

CONTINUING EVIDENCE FOR POORER TREATMENT OUTCOMES FOR SINGLE MALE PATIENTS: RETREATMENT DATA FROM RTOG 97-14

ANDRE KONSKI, M.D., M.B.A., M.A.,* MICHELLE DESILVIO, PH.D.,[†] WILLIAM HARTSELL, M.D.,[‡]
DEBORAH WATKINS-BRUNER, PH.D.,[§] JAMES COYNE, PH.D.,[¶] CHARLES SCARANTINO, M.D., PH.D.,^{||}
AND NORA JANJAN, M.D.[#]

Departments of *Radiation Oncology and [§]Population Science, Fox Chase Cancer Center, Philadelphia, PA;

[†]Statistical Headquarters, Radiation Therapy Oncology Group, Philadelphia, PA; [‡]Department of Radiation Oncology, Advocate Good Samaritan Hospital, Downers Grove, IL; [¶]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA;

^{||}Rex Healthcare, Raleigh, NC; [#]Department of Radiation Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX

Purpose: The specific aim of this study was to evaluate outcome differences by gender and partner status for patients treated on Radiation Therapy Oncology Group (RTOG) protocol 97-14.

Methods and Materials: RTOG 97-14 randomized patients with metastatic breast or prostate cancer to bone to receive 8 Gy in 1 fraction or 30 Gy in 10 fractions. Retreatment rates and overall survival were made based upon gender, marital status, and Karnofsky Performance Status (KPS). The cumulative incidence method was used to estimate retreatment time at 36 months from enrollment, and Gray's test was used to test for treatment differences within the same groupings. Marital status, gender, KPS, and treatment were variables tested in a univariate Cox model evaluating the time to retreatment.

Results: Married men and women and single women receiving 30 Gy had significantly longer time to retreatment, $p = 0.0067$, $p = 0.0052$, and $p = 0.0009$ respectively. We failed to show a difference in retreatment rates over time in single men receiving either 30 Gy or 8 Gy. Univariate analysis of the entire group determined patients receiving 30 Gy in 10 fractions significantly less likely to receive retreatment, $p < 0.0001$, with a trend toward single patients less likely to be re-treated, $p = 0.07$.

Conclusion: Non-disease-related variables, such as social support, might influence the results of clinical trials with subjective endpoints such as retreatment rates. The statistically nonsignificant difference in the 36-month retreatment rates observed in single male patients receiving 8 Gy may be a result of inadequate social support systems in place to facilitate additional care. Patients receiving 8 Gy in a single fraction had significantly higher retreatment rates compared with patients receiving 30 Gy in 10 fractions. © 2006 Elsevier Inc.

Table 1. Pretreatment characteristics

	8 Gy		30 Gy	
	Male (n = 222)	Female (n = 233)	Male (n = 223)	Female (n = 220)
Age				
Mean	71	60	71	59
Median	72	59	71	58
Range	38–92	33–92	35–90	31–91
Marital status				
Married or other live-in	154 (69%)	112 (48%)	147 (66%)	106 (48%)
Single, divorced, separated	54 (24%)	99 (42%)	61 (27%)	98 (45%)
Unknown/No answer	14 (6%)	22 (9%)	15 (7%)	16 (7%)
Race				
White	161 (73%)	182 (78%)	168 (75%)	176 (80%)
Hispanic	6 (3%)	12 (5%)	12 (5%)	12 (5%)
Black	49 (22%)	34 (15%)	39 (17%)	28 (13%)
Asian	4 (2%)	4 (2%)	3 (1%)	2 (1%)
Native American	1 (<1%)	1 (<1%)	0	0
Other	1 (<1%)	0	1 (<1%)	0
Prefers not to answer	0	0	0	0
Karnofsky Performance Status				
40–60	45 (20%)	59 (25%)	51 (23%)	53 (24%)
70–80	123 (55%)	132 (57%)	128 (57%)	101 (46%)
90–100	54 (24%)	42 (18%)	42 (19%)	64 (29%)
Unknown	0	0	2 (1%)	2 (1%)
Painful sites				
Solitary	121 (55%)	150 (64%)	114 (51%)	122 (55%)
Multiple	101 (46%)	83 (36%)	109 (49%)	98 (45%)
Treatment site				
Weight-bearing	119 (54%)	137 (59%)	126 (57%)	120 (55%)
Non-weight-bearing	103 (46%)	96 (41%)	97 (44%)	100 (45%)
Worst pain score				
<5	9 (4%)	3 (1%)	10 (4%)	1 (<1%)
5–6	61 (27%)	52 (22%)	54 (24%)	59 (27%)
7–10	152 (68%)	178 (76%)	159 (71%)	160 (73%)
Receiving pamidronate/bisphosphonates				
No	202 (91%)	128 (55%)	207 (93%)	118 (54%)
Yes	20 (9%)	105 (45%)	16 (7%)	102 (46%)

Table 3. Brief Pain Inventory (BPI) worst pain score and overall response to treatment at 3 months after treatment

Parameter	No. of patients (%)		P*
	8-Gy arm (n = 288)	30-Gy arm (n = 285)	
BPI worst pain score			
0	44 (15)	51 (18)	.854
1-4	99 (34)	98 (34)	
5-6	56 (19)	53 (19)	
7-10	89 (31)	83 (29)	
No answers/2 answers	2	5	
Overall response type			
Complete	44 (15)	51 (18)	.6
Partial	143 (50)	137 (48)	
Stable	74 (26)	69 (24)	
Progressive	27 (9)	28 (10)	

*The chi-square test was used for comparison of treatments. All statistical tests were two-sided. There were only 845 patients with a baseline BPI to use to compare with those with the month 3 BPI. Only 573 of those patients had a month 3 BPI, 128 patients died before submitting a month 3 BPI, seven patients completed the BPI incorrectly, and 137 patients did not submit a month 3 BPI.

Table 4. Overall rates of analgesic and narcotic use at 3 months

Drug	No. of patients (%)		P*
	8-Gy arm (n = 318)	30-Gy arm (n = 310)	
None	65 (20)	69 (22)	.483
Nonnarcotic analgesic	40 (13)	30 (10)	
Narcotic	213 (67)	211 (68)	

*The chi-square test was used for comparison of treatments. All statistical tests were two-sided. Seventy patients died before the month 3 time point. An additional 82 patients did not have any information at 3 months, and 126 patients did not respond to the narcotic question on the 3-month follow-up form.

C/C: Plus de retraitement dans le bras single dose

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy- A Systematic Review of Randomised Trials

SINGLE VERSUS MULTIFRACTION RADIOTHERAPY FOR BONE METASTASES

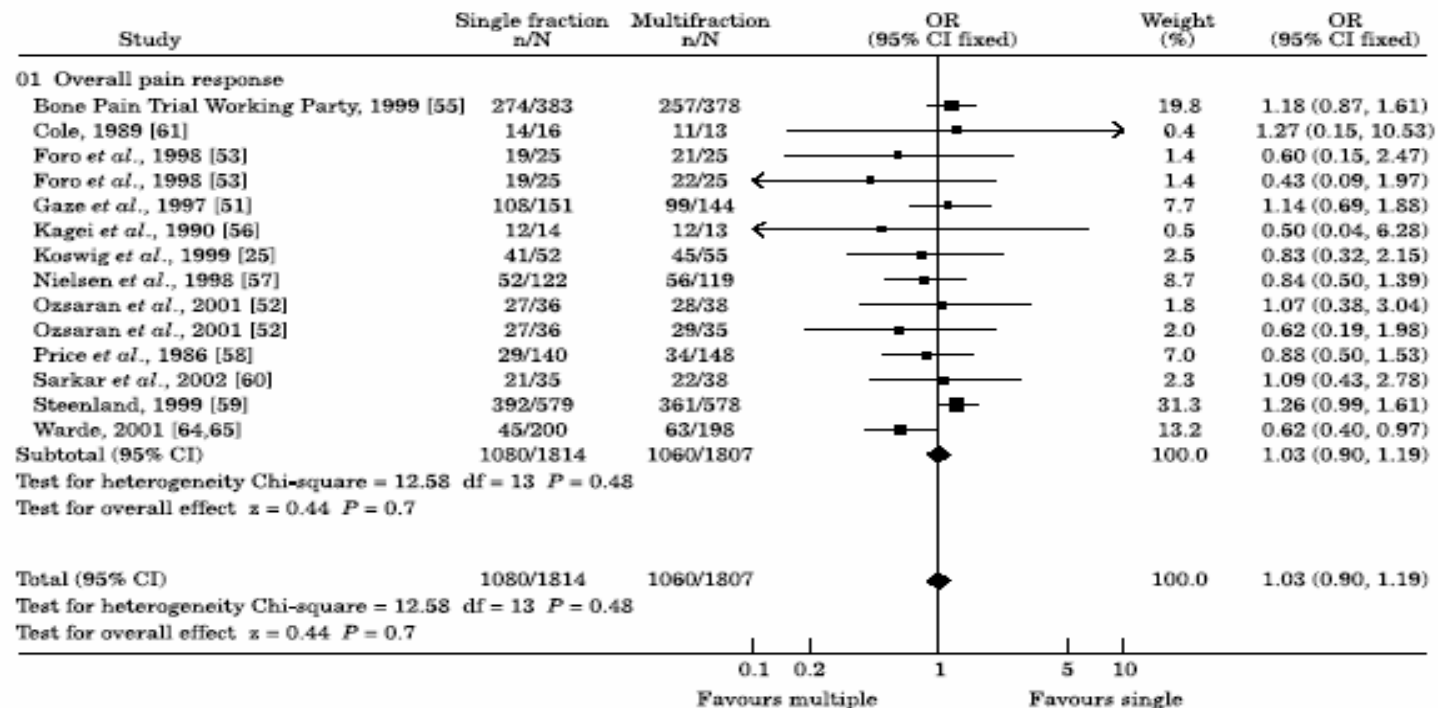


Fig. 1 – Overall pain response; single=single fraction radiotherapy; multiple=multifraction radiotherapy; BPTWP=Bone Pain Trial Working Party. Foro and Ozsaran studies were three arm studies. The control arm was counted twice in the analysis.

OR=SF:60% et MF:59%

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy- A Systematic Review of Randomised Trials

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CLINICAL ONCOLOGY

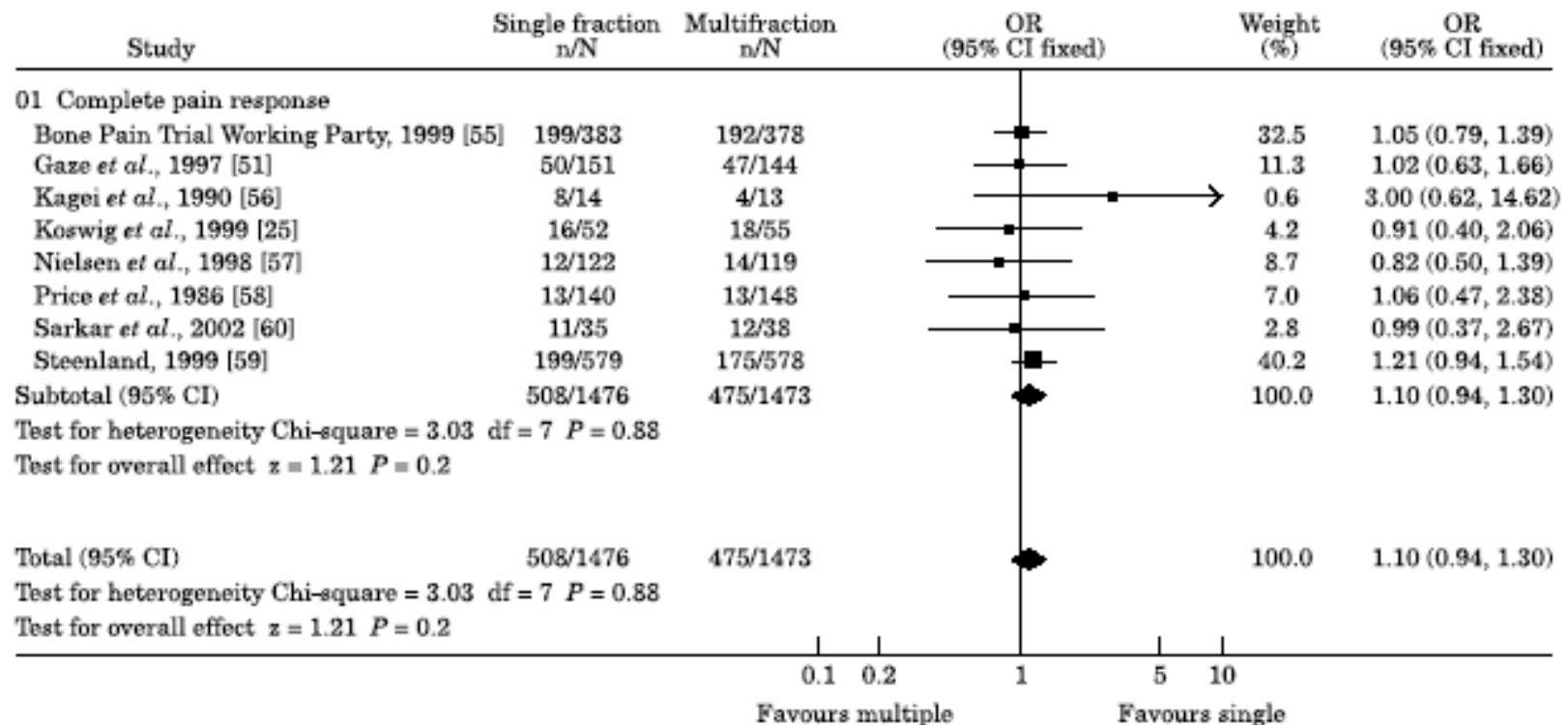


Fig. 2 – Complete pain response; single=single fraction radiotherapy; multiple=multifraction radiotherapy; BPTWP=Bone Pain Trial Working Party.

CR=SF:34% et MF:32%

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy- A Systematic Review of Randomised Trials

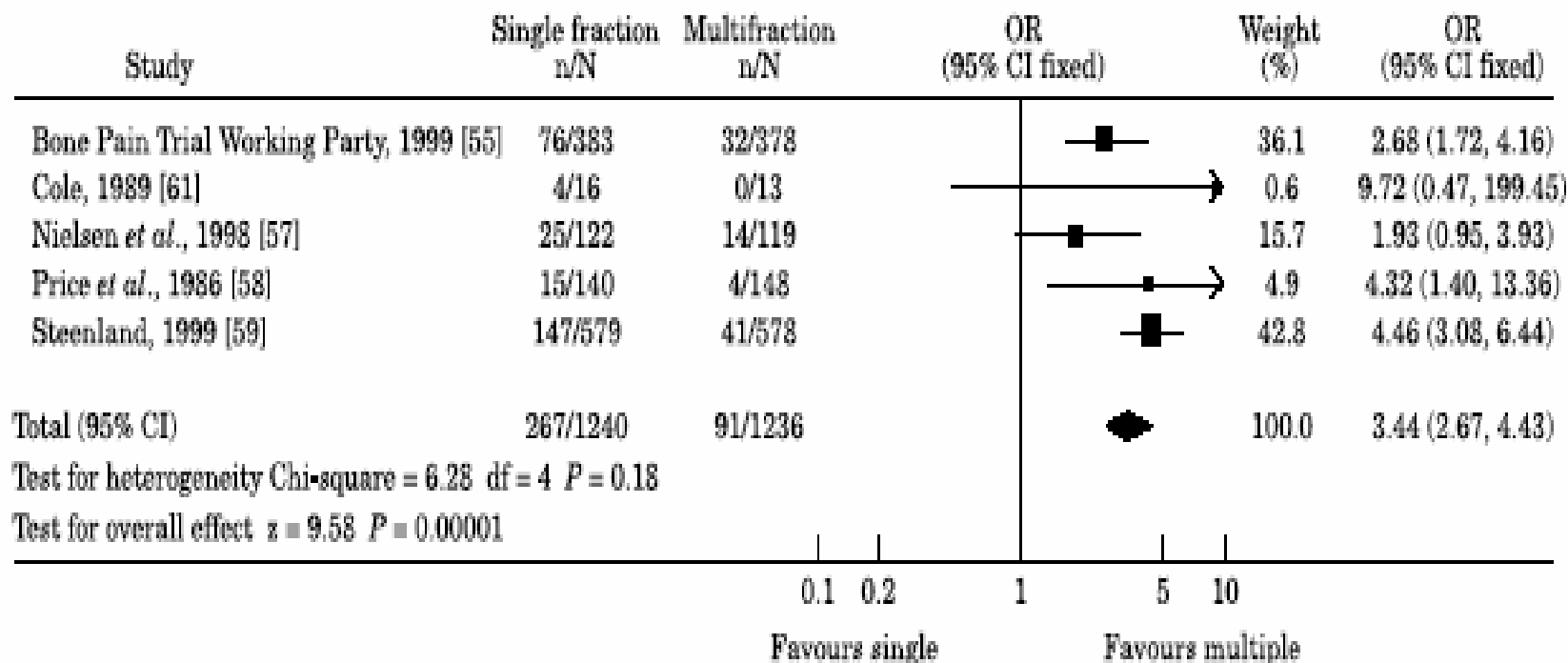


Fig. 3 - Re-treatment rate; single=single fraction radiotherapy; multiple=multifraction radiotherapy; BPTWP=Bone Pain Trial Working Party.

RT=SF:21.5% et MF:7.4%

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy- A Systematic Review of Randomised Trials

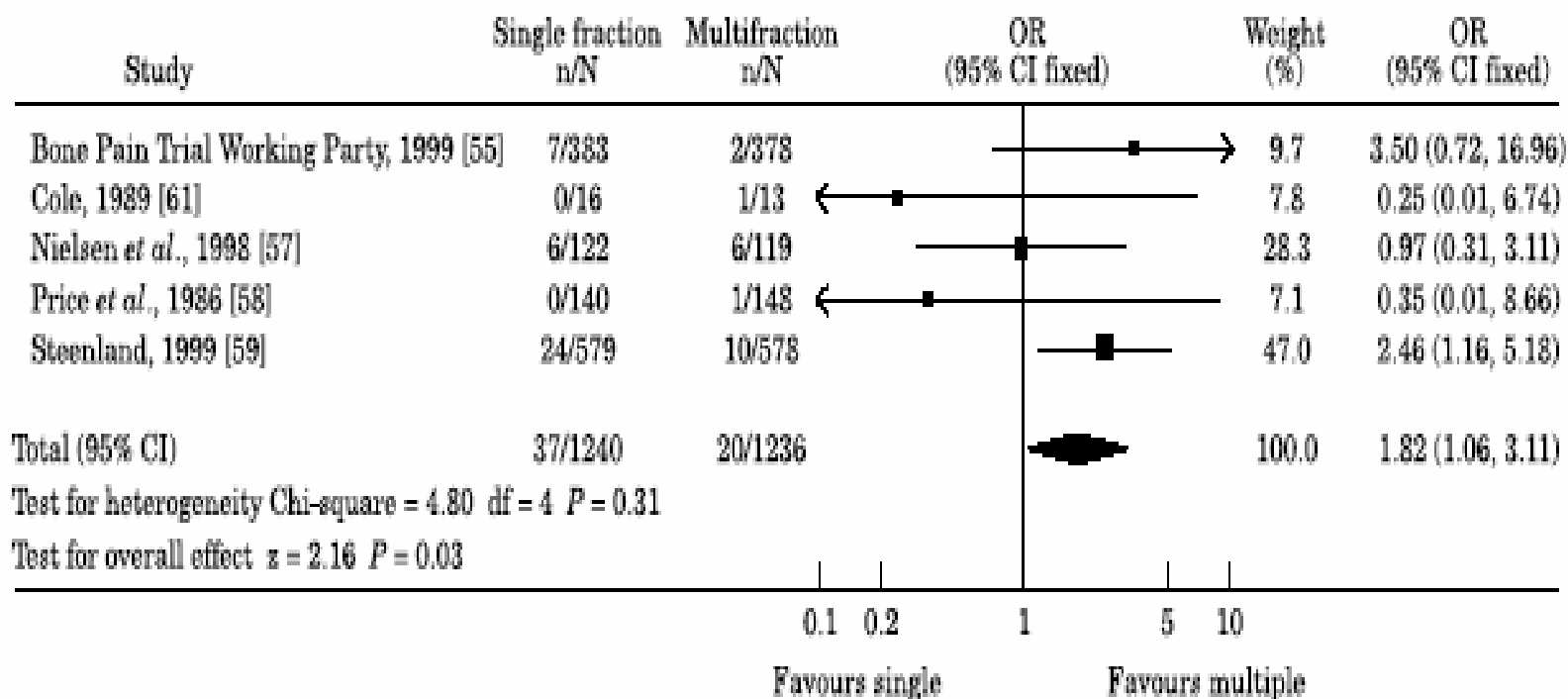


Fig. 4 – Pathological fracture rate; single=single fraction radiotherapy; multiple=multifraction radiotherapy; BPTWP=Bone Pain Trial Working Party.

PFR=SF:3% et MF:1.6%

Palliation of Metastatic Bone Pain: Single Fraction versus Multifraction Radiotherapy- A Systematic Review of Randomised Trials

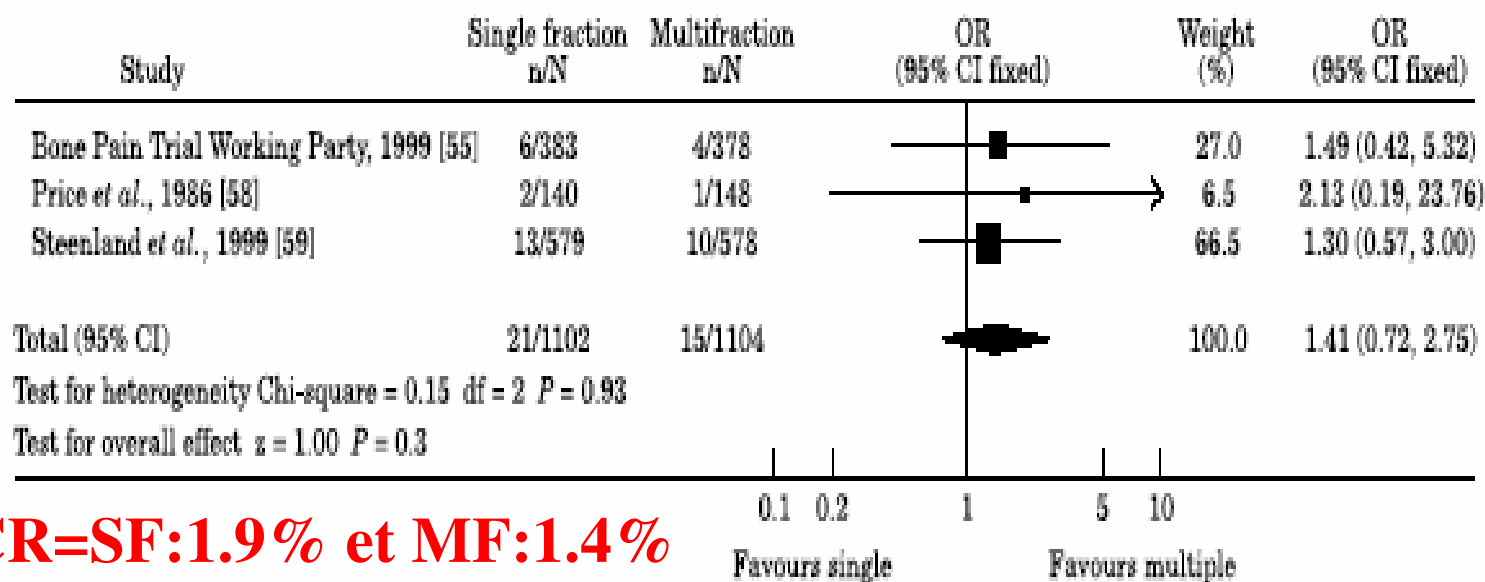


Fig. 5 - Spinal cord compression rate - all randomised patients included; single=single fraction radiotherapy; multiple=multifraction radiotherapy; BPTWP=Bone Pain Trial Working Party.

Clin Oncol 15, (2003): 345-352

SPINAL REIRRADIATION AFTER SHORT-COURSE RT FOR METASTATIC SPINAL CORD COMPRESSION

DIRK RADES, M.D.,* LUKAS J. A. STALPERS, M.D.,[†] THEO VENINGA, M.D.,[‡]
AND PETER J. HOSKIN, M.D.[§]

*Department of Radiation Oncology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [†]Department of Radiotherapy, Academic Medical Center, Amsterdam, The Netherlands; [‡]Department of Radiotherapy, Dr. Bernard Verbeeten Institute, Tilburg, The Netherlands; [§]Mount Vernon Centre for Cancer Treatment, Northwood, Middlesex, United Kingdom

Purpose: To investigate the feasibility and effectiveness of reirradiation (re-RT) for in-field recurrence of metastatic spinal cord compression after primary RT with 1×8 Gy or 5×4 Gy.

Methods and Materials: A total of 62 patients, treated with 1×8 Gy ($n = 34$) or 5×4 Gy ($n = 28$) between January 1995 and August 2003, received re-RT for in-field recurrence of metastatic spinal cord compression. The median time to recurrence was 6 months (range, 2–40 months). Re-RT was performed with 1×8 Gy (after 1×8 Gy or 5×4 Gy, $n = 34$), 5×3 Gy (after 1×8 Gy or 5×4 Gy, $n = 15$), or 5×4 Gy (after 1×8 Gy, $n = 13$). The cumulative biologically effective dose (primary RT plus re-RT) was 80–100 Gy₂. The median follow-up after re-RT was 8 months (range, 2–42 months). Motor function was evaluated up to 6 months after re-RT.

Results: After re-RT, 25 patients (40%) showed improvement of motor function, 28 (45%) had no change, and 9 (15%) had deterioration. Of the 16 previously nonambulatory patients, 6 (38%) regained the ability to walk. No second in-field recurrence in the same spinal region was observed after re-RT. The outcome was not significantly influenced by the radiation schedule. Radiation myelopathy was not observed.

Conclusions: Spinal re-RT with 1×8 Gy, 5×3 Gy, or 5×4 Gy for in-field recurrence of metastatic spinal cord compression appears safe and effective. Myelopathy seems unlikely, if the cumulative biologically effective dose is ≤ 100 Gy₂. © 2005 Elsevier Inc.

Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial

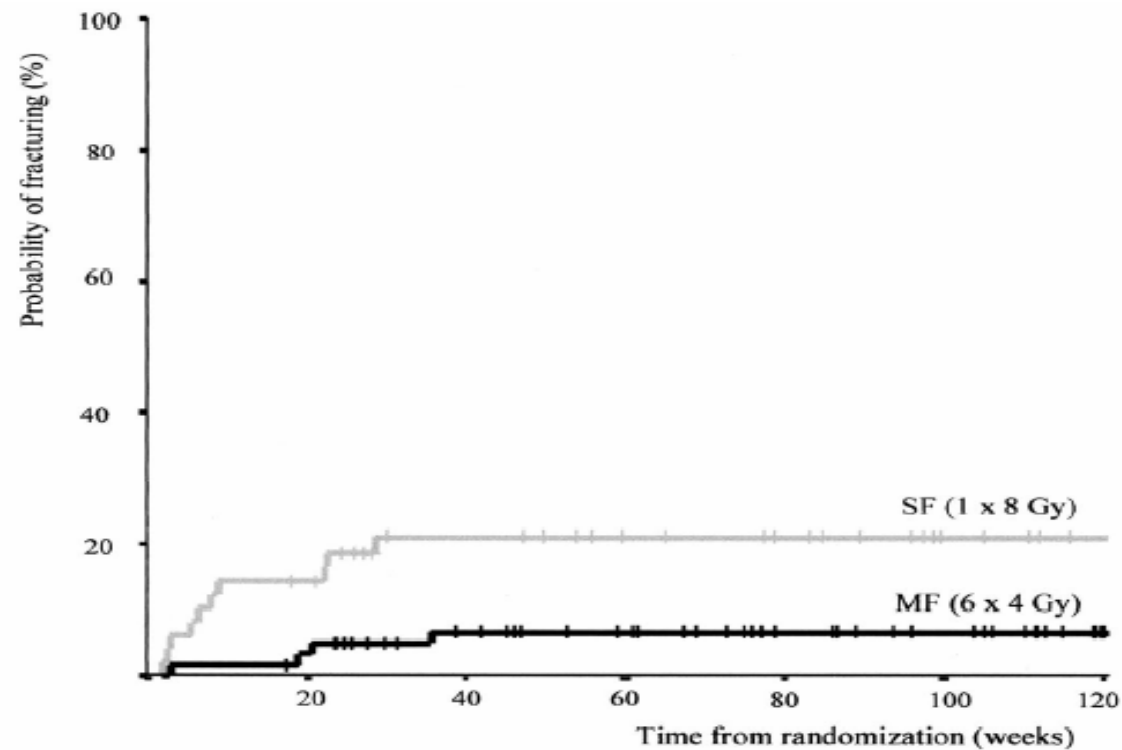


Fig. 3. Probability of fracturing in 110 femoral metastases for the treatment schedule single fraction of 8 Gy (SF) versus six fractions of 4 Gy (MF) in patients treated with in the Dutch Bone Metastasis Study.

Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial

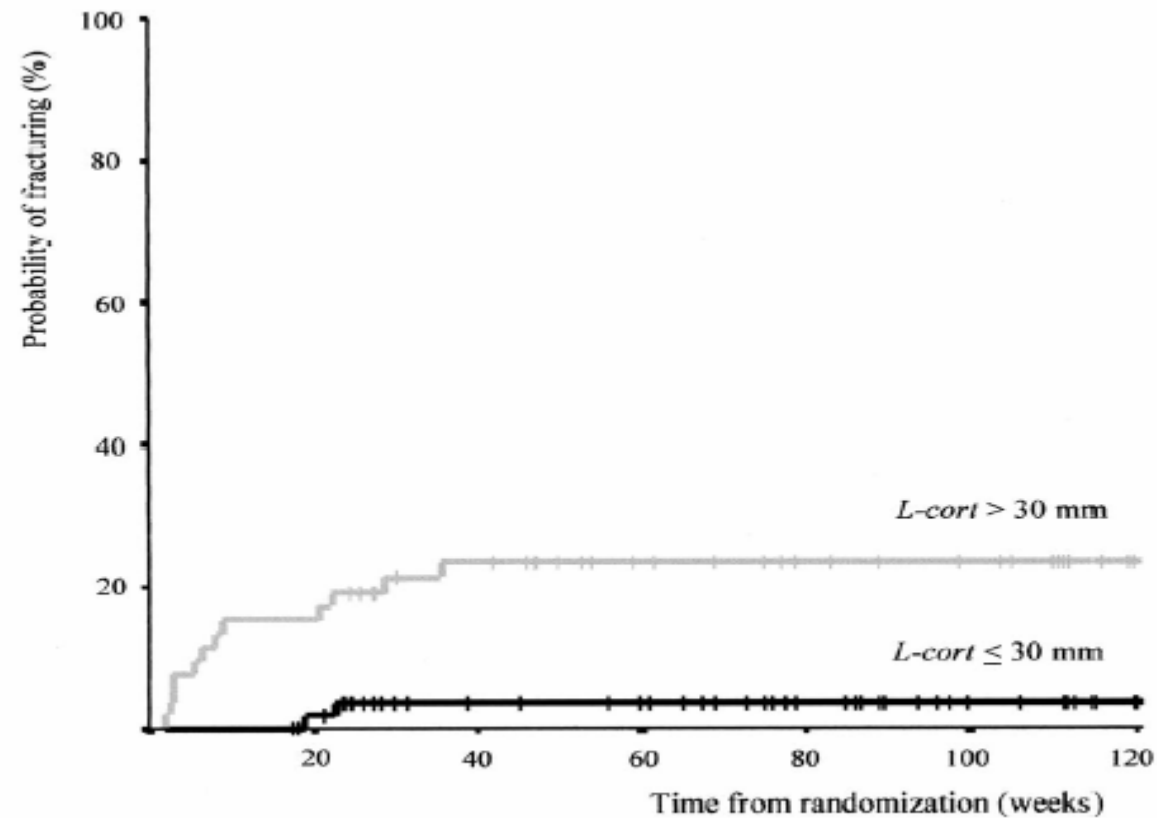


Fig. 4. Probability of fracturing in 110 femoral metastases for an axial cortical involvement $L\text{-cort} < 30\text{ mm}$ versus $L\text{-cort} > 30\text{ mm}$ in patients treated within the Dutch Bone Metastasis Study.

International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases

- Conduire d'autres essais
- Définir des critères de réponse, effets secondaires aigus, doses RT, techniques....
- Le nombre de ré-irradiations
- Un long suivi avec des paramètres bien définis
- La qualité de vie

Radiother Oncol 64, (2002): 275-280



CONCLUSIONS

- Efficace avec différents fractionnements
- Opter pour un schéma moins toxique
- Tenir compte de l'état général des patients
- Siège des métastases
- Préserver la qualité de vie
- La réponse ne dépend pas de l'histologie

COMPRESSION MEDULLAIRE

- Urgence Oncologique +++
- Complication neurologique dans les cancers de stades avancés (5-10%)
- Poumons > Prostate chez l'homme
- 1-12 % des patients avec Ca prostate
- 12-19% : symptôme inaugural

European Urology 44, (2003): 527-532.

COMPRESSION MEDULLAIRE

- Status neurologique initial +++
- Douleur souvent premier signe
- Délai souvent hélas long ???
- IRM +++
- Décompression chirurgicale + RT vs RT seule
- Approche multidisciplinaire +++++



J Neurooncol 23, (1995): 135-147.

Metastatic Spinal Cord Compression: A Randomised Trial of Direct Decompressive Surgical Resection plus Radiotherapy vs. Radiotherapy Alone

- 50 pat (S+RT) vs. 51 pat RT seule
- Différents types de tumeurs
- IRM
- 30 Gy (10 Fr x 3 Gy)
- Meilleure mobilité, moins corticoïdes et opiacées, ambulatoires (S+RT)



IJROBP 57,(2003): S125

Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial



Lancet 2005

Roy A Patchell, Phillip A Tibbs, William F Regine, Richard Payne, Stephen Saris, Richard J Kryszak, Mohammed Mohiuddin, Byron Young

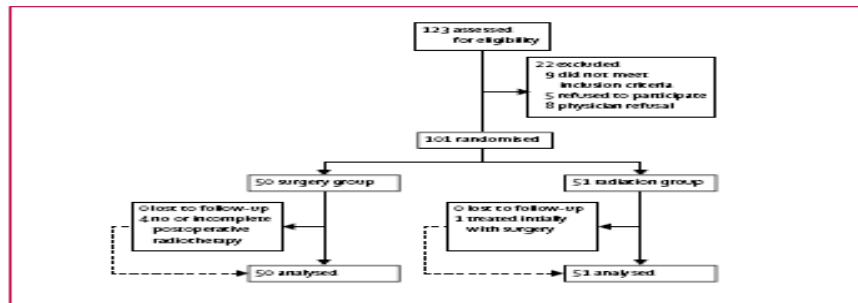


Figure 1: Trial profile

Between Sept 1, 1992, and Dec 31, 2002, 123 patients were assessed for eligibility and, of these, 101 were entered into the trial before it closed (figure 1). Protocol violations occurred with five patients. In the surgery group, three patients did not receive postoperative

	Radiation group (n=51)	Surgery group (n=50)
Men/Women	37/14	33/17
Median age, years	60	60
Primary tumours		
Lung	13	13
Breast	4	7
Prostate	10	9
Other genitourinary	6	5
Gastrointestinal	4	2
Melanoma	3	3
Head and neck	2	1
Unknown	3	5
Other	4	4
Walking at entry	25	34
Conscious at entry	32	30
Median Frankel score at entry	0	0
Median ASIA score at entry	90	85
Spinal level of compression		
Cervical	5	8
T1-T6	18	20
T7-T12	28	22
Position of spinal tumour		
Anterior	33	28
Lateral	11	9
Posterior	7	12
Unstable spine	18	20
Median time between diagnosis of primary tumour and development of MESCC	7 months	3 months
Median time between development of motor symptoms and treatment of MESCC	12 days	10 days
D=ambulatory but with neurological symptoms.		

Table 1: Baseline characteristics of study patients

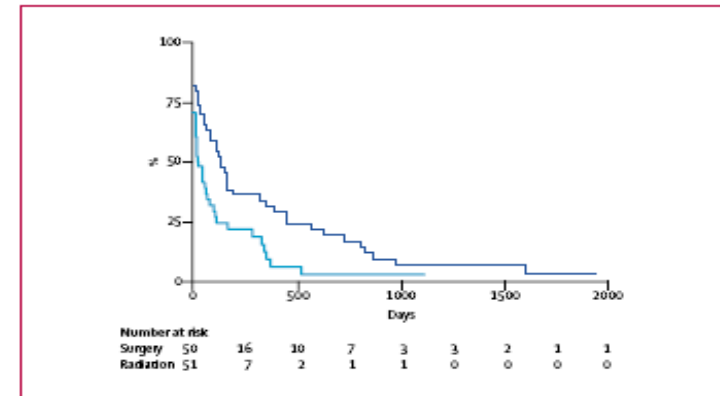


Figure 2: Kaplan-Meier estimates of length of time all study patients remained ambulatory after treatment

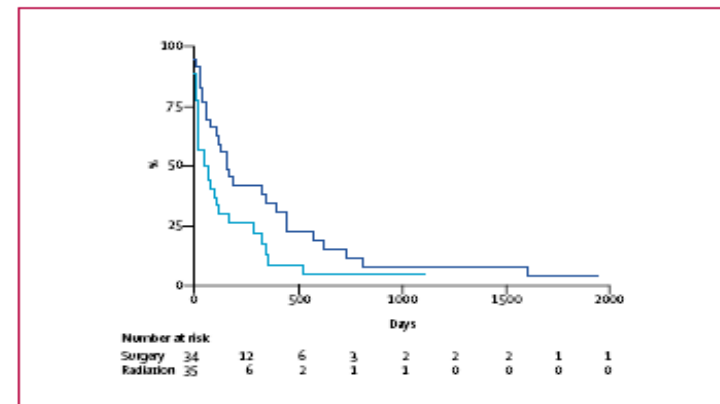


Figure 3: Kaplan-Meier estimates of length of time patients who were ambulatory at study entry remained ambulatory after treatment