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SEDE: "Centro Formazione e Solidarietà"

IRCCS Sacro Cuore - Don Calabria
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GESTIONE DELL'URGENZA/EMERGENZA IN ONCOLOGIA: Ruolo della radioterapia nella Compressione midollare

Rosario Mazzola

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review

Radiotherapy in palliative treatment of painful bone metastases

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Bone metastases are associated with considerable skeletal morbidity, including:

Severe bone pain

Spinal cord or nerve root compression

Pathological fractures Hypercalcaemia

* In **bold** the clinical scenarios in which the role of Radiotherapy is well-known

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Metastatic Spinal Cord Compression (MSCC): ROLE of Radiotherapy

Indication for surgery of MSCC is usually limited to:

- > Patients with a good performance status
- Survival prognosis of more than 3 months
- > Involvement of only one spinal segment

These clinical scenarios are represented for only about 10% of all MSCC patients

Radiotherapy alone remains still an important treatment option for MSCC

Metastatic Spinal Cord Compression (MSCC): ROLE of Radiotherapy

There are three goals of treatment with radiotherapy:
Prevention of neurological deterioration
☐ Improvement of neurological function
☐ Pain relief

☐ Prevention of neurological deterioration

- Early detection before neurological deterioration and treatment improve outcome in patients with MSCC
- ☐ The distribution of symptoms are associated to anatomical site of lesions (differences in the diameter of the spinal canal that differs from the thoracic to lumbar spine)
- ☐ To reduce delays in MSCC several steps have to be considered: 1) initiation of steroids; urgent MRI, Consultation with both surgeons and radiation oncologists
- Prolonged loss of motor function cannot be restored by either surgery or radiotherapy

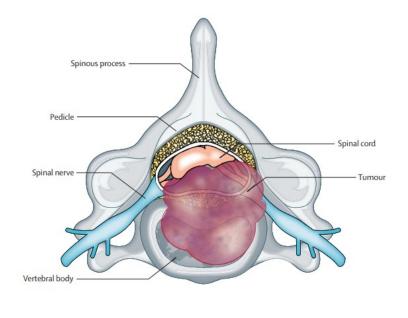


Figure 1: Tumour in the vertebral body

The tumour is anterior to the spinal cord and grows posteriorly to compress the spinal cord.

Cole et al. Lancet Neurol. 2008 May;7(5):459-66

□ Prevention of neurological deterioration

Taylor & Francis



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Always on a Friday? Time Pattern of Referral for Spinal Cord Compression

Philip Poortmans, Ans Vulto, Esther Raaijmakers

Clinical Oncology (2002) 14: 135–138 doi:10.1053/clon.2001.0036, available online at http://www.idealibrary.com on IDEAL®

Spinal Cord Compression: Personal View

Spinal Cord Compression – a Personal and Palliative Care Perspective

M. J. BAINES

St. Christopher's, London and the Ellenor Foundation, Dartford, Kent

- ☐ Gli schemi più impiegati sono 20 Gy in 5 frazioni e 30 Gy in 10 frazioni
- ☐ Il trattamento richiede che le prime due frazioni siano date in giorni consecutivi, quindi se necessario anche di sabato e domenica, cosa che può comportare difficoltà organizzative

GESTIONE DELL'URGENZA/EMERGENZA IN ONCOLOGIA. Negrar di Valpolicella, 15 Maggio 2019



☐ Improvement of neurological function

Table 4 Comparisons of patients undergoing surgery within 48 h versus after 48 h

	Surgery within 48 h (Groups 1 and 2)	Surgery after 48 h (Group 3)	p value
No.	68	53	
Mean age	62	61	0.68
Gender (M:F)	44:24	31:22	0.31
Mean Tokuhashi score	8.7	8.9	0.71
Frankel grade pre-op (a	nd post-op)		0.048
A	6 (3)	0 (1)	
В	3 (4)	1 (0)	
C	19 (11)	7 (11)	
D	30 (30)	45 (27)	
E	0 (18)	0 (14)	
Mean length of stay in days (range)	21 (2–75)	20 (2–66)	0.4
Complications % (no./total)	41 % (28/68)	42 % (22/53)	0.97
Infection % (no./total)	13 % (9/68)	17 % (9/53)	0.37
Mean survival (days)	657	643	0.79

*The Frankel Grade classification provides an assessment of spinal cord function and is used as a tool in spinal cord injury

Table 5 Primary tumour type, levels of spinal involvement, revised Tokuhashi score and number of metastases versus outcome variables

	Length of stay	Change in Frankel grade	Survival	Complications
Histology of prin	nary tumou	ır		
Pearson correlation	-0.05	0.11	-0.09	0.14
p value	0.54	0.14	0.22	0.07
Levels of spinal	metastases			
Pearson correlation	-0.06	-0.02	0.06	-0.03
p value	0.40	0.73	0.40	0.68
Revised Tokuhas	shi score			
Pearson correlation	-0.07	-0.06	0.33	0.09
p value	0.37	0.39	0.01**	0.26
Number of meta	stases in th	e spine		
Pearson correlation	-0.05	0.01	0.004	-0.16
p value	0.53	0.84	0.96	0.05**

Eur Spine J (2013) 22:1383-1388



1	Pain	Re	lief
		110	

 ".. In up to 70% to 80% of patients, significant pain relief can be achieved. This pain relief results in both an improved quality of life and a significant reduction of pain medication."

Complete Response in 30-50% of cases (oppioids interruption)

Clinical Management & Therapeutic Strategies

- ☐ Combining Surgery and RT?
- ☐ What is the role of Steroids?
- ☐ RT-schedules?

☐ Metastatic Spinal Cord Compression (MSCC): Combining Surgery and RT

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



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

Summary

Background The standard treatment for spinal cord compression caused by metastatic cancer is corticosteroids and radiotherapy. The role of surgery has not been established. We assessed the efficacy of direct decompressive surgery.

Methods In this randomised, multi-institutional, non-blinded trial, we randomly assigned patients with spinal cord compression caused by metastatic cancer to either surgery followed by radiotherapy (n=50) or radiotherapy alone (n=51). Radiotherapy for both treatment groups was given in ten 3 Gy fractions. The primary endpoint was the ability to walk. Secondary endpoints were urinary continence, muscle strength and functional status, the need for corticosteroids and opioid analgesics, and survival time. All analyses were by intention to treat.

Findings After an interim analysis the study was stopped because the criterion of a predetermined early stopping rule was met. Thus, 123 patients were assessed for eligibility before the study closed and 101 were randomised. Significantly more patients in the surgery group (42/50, 84%) than in the radiotherapy group (29/51, 57%) were able to walk after treatment (odds ratio $6 \cdot 2$ [95% CI $2 \cdot 0$ –19 ·8] p=0 ·001). Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days ν s 13 days, p=0 ·003). 32 patients entered the study unable to walk; significantly more patients in the surgery group regained the ability to walk than patients in the radiation group $(10/16 [62\%] \nu$ s 3/16 [19%], p=0 ·01). The need for corticosteroids and opioid analgesics was significantly reduced in the surgical group.

Interpretation Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.

Lancet 2005; 366: 643-48



Metastatic Spinal Cord Compression (MSCC): Surgery Followed by Radiotherapy

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



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

	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)
Based on a Cox model with all co		sed on a Cox model w	vith only significant p	predictors include	d (stepwise s	

Lancet 2005; 366: 643-48



What is the role of steroids?

Table 1 - Administration of dexamethasone

Reference	Patients (n)	Study design	Dexamethasone dose	Results	Serious adverse effects
[22]	57	Randomised	96 mg/4 days vs no steroids	Ambulatory 81% vs 63% (P = 0.046)	11% vs 0% (psychoses, ulcers)
[23]	37	Randomised	100 mg + 16 mg/day vs 10 mg + 16 mg/day	Improvement 25% vs 8% (P = 0.22)	Not stated
[24]	66	Case—control study	96 mg/4 days vs 10 mg + 16 mg/day	Not stated	14% vs 0% (ulcers, bleeding, perforation)

- ➤ Radiotherapy must be supplemented by the administration of dexamethasone, which should be started as soon as possible, usually before the first radiation fraction can be delivered
- ➤ High-dose dexamethasone (96-100 mg/day) seems more effective than low-dose dexamethasone (10-16 mg/day), but has been associated with significantly more serious adverse effects
- ➤ Moderate-dose dexamethasone (16-32 mg/day) is proven to be effective and safe

Agarawal et al Clin Oncol 2006

RT-SCHEDULES?

Practical Radiation Oncology (2017) 7, 4-12



Special Article

Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline



Stephen Lutz MD a,* , Tracy Balboni MD MPH b , Joshua Jones MD c , Simon Lo MB ChB d , Joshua Petit MD e , Shayna E. Rich MD PhD f , Rebecca Wong MB ChB g , Carol Hahn MD h

		Duration of	
Dosage	Prognosis and Indications	Therapy	Response Rate
1 x 8 Gy	Prognosis: life expectancy <3 mo —painful uncomplicated bone metastases	1 d	60%–90%
2 x 7.5 Gy	Prognosis: life expectancy only a few weeks —bronchogenic carcinoma with bronchial occlusion/compression	I WK	30%–90%
16×051Cy	Inhibition of inflammation	1 wk	70% 00%
5 x 3–4 Gy	Prognosis: life expectancy <3–6 mo —bone metastases affecting soft tissue	1 wk	60%–90%
	imminent bronchial occlusion / bleeding, —ulcerated or painful metastases in soft tissue —multiple brain metastases, poor general condition and uncontrolled extracranial tumor		
10 x 3 Gy	Prognosis: life expectancy <1 year —bone metastases with the aim of recalcification	2 wks	60%–90%
13–15 x 3 Gy	 advanced bronchogenic carcinoma multiple brain metastases, Karnofsky index >70 % Prognosis: life expectancy not very much longer than 1 year bone metastases without any further tumor manifestations advanced bronchogenic carcinoma, reasonable 	3 wks	60%–90%
20–30 x 2 Gy	general condition, comorbidities Prognosis: life expectancy >1 year —advanced bronchogenic carcinoma stage III and good general condition (possibly also in the form of palliative radiochemotherpy)	4–6 wks	60%–90%
20–30 x 2–3 Gy IMRT	Patients in sufficient general condition with advanced tumors, re-irradiation, Patients in good general condition with, eg, isolated paraspinal metastases, isolated vertebral metastases affecting intraspinal areas	5–6 wks	65%–90%
1–3 x 12–26 Gy stereotaxy	Patients in good general condition with individual/ few solitary or singular brain metastases Individual/few solitary lung or liver metastases	max. 1 wk	70%–90%





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How to predict Life-Expectancy in Bone mts?

Table 4. Significant prognostic factors and score for each factor.

Prognostic factor		Regression coefficient	Score
Primary site			
Slow growth	Hormone-dependent breast and prostate cancer, thyroid cancer, multiple myeloma, and malignant lymphoma		0
Moderategrowth	Lung cancer treated with molecularly targeted drugs, hormone-independent breast and prostate cancer, renal cell carcinoma, endometrial and ovarian cancer, sarcoma, and others	0.99	2
Rapid growth	Lung cancer without molecularly targeted drugs, colorectal cancer, gastric cancer, pancreatic cancer, head and neck cancer, esophageal cancer, other urological cancers, melanoma, hepatocellular carcinoma, gall bladder cancer, cervical cancer, and cancers of unknown origin	1.70	3
Visceral metastasis	Nodular visceral or cerebral metastasis	0.65	1
	Disseminated metastasis ¹	1.11	2
Laboratory data	Abnormal ²	0.64	1
	Critical ³	1.04	2
ECOG PS	3 or 4	0.73	1
Previous chemotherapy		0.32	1
Multiple skeletal metastases Total		0.43	1 10

¹Disseminated metastasis: Pleural, peritoneal, or leptomeningeal dissemination.

Katagiri et al. Cancer Med. 2014;3:1359-67



²Abnormal: CRP \geq 0.4 mg/dL, LDH \geq 250 IU/L, or serum albumin <3.7 g/dL.

 $^{^{3}}$ Critical: platelet <100,000/ μ L, serum calcium ≥10.3 mg/dL, or total bilirubin ≥1.4.

How to predict Life-Expectancy in Bone mts?

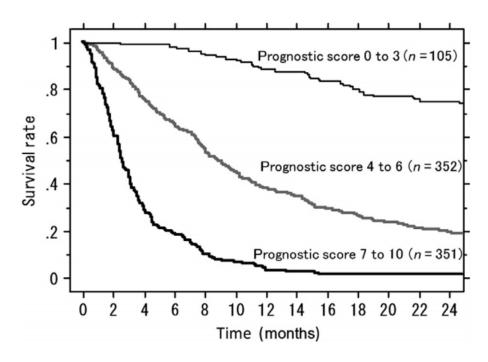


Figure 3. Kaplan–Meier survival curves for patients with prognostic scores of 0–3 (low-risk group), 4–6 (intermediate-risk group), and 7–10 (high-risk group). The rates of survival for these three groups are significantly different.

Katagiri et al. Cancer Med. 2014;3:1359-67



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Systematic Review

Single versus multifraction radiotherapy for spinal cord compression: A systematic review and meta-analysis



Elysia K Donovan ^{a,*}, Julianna Sienna ^b, Gunita Mitera ^c, Nidhi Kumar-Tyagi ^b, Sameer Parpia ^d, Anand Swaminath ^b

 Table 3

 Summary of findings for SFRT compared to MFRT in patients with metastatic epidural spinal cord compression (MESCC).

	Relative			Certainty	What happens	
	effect 95% CI)			Difference		
Bladder Dysfunction Assessed: Patient or clinician reported, or requirement of catheterization & of participants: 696(3 RCTs)	RR 0.97 (0.85- 1.11)	79.6%	77.2% (67.7–88.4)	2.4% fewer (11.9 fewer to 8.8 more)	⊕⊕○○ LOW ^{a,b}	
Overall Survival Assessed: time in days from treatment follow up: median 4 months Me of participants: 643 (2 RCTs)	RR 1.00 (0.88– 1.13)	100.0%	100.0% (88- 100)	0.0% fewer (12 fewer to 13 more)	⊕⊕⊕⊕ HIGH	Median Survival: Maranzano 4 months in SFRT and MFRT, ICORG 0503 4 months in SFRT and MFRT, SCORAD 12.4 weeks SFRT vs 13.7 weeks MFRT (ranges not provided)
Motor Response Assessed: Tomita (modified) Scale (Ambulatory without aid, ambulatory with aid, non- ambulatory, paralyzed) follow up: range 1 days to 3 months % of participants: 719 (3 RCTs)	RR 0.96 (0.86 to 1.07)	71.2%	68.3% (61.2 to 76.1)	2.8% fewer (10 fewer to 5 more)	⊕⊕⊕○ MODERATE ^a	

There was no evidence of an observed difference with respect to motor response, bladder dysfunction and OS between SFRT and MFRT for MESCC in patients with a limited prognosis

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Original article

Update of the systematic review of palliative radiation therapy fractionation for bone metastases

Shayna E. Rich^a, Ronald Chow^b, Srinivas Raman^b, K. Liang Zeng^b, Stephen Lutz^c, Henry Lam^b, Maurício F. Silva^d, Edward Chow^{b,*}

³ Haven Hospice, Gainesville, OH, USA; ^b Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Canada; ^c Blanchard Valley Regional Cancer Center, Findlay, USA; ^d Radiation Oncology Unit at Santa Maria Federal University, Santa Maria, Brazil

- 1. OVERALL RESPONSE RATE: similar in patients for single fraction treatments (61%) and those for multiple fraction treatments (62%)
- COMPLETE RESPONSE RATE: nearly identical in both groups (23% vs 24%, respectively)
- **3. RE-TREATMENT:** significantly more frequent in the single fraction treatment arm, with 20% receiving additional treatment to the same site versus 8% in the multiple fraction treatment arm (p < 0.01)
- 4. No significant difference was seen in the risk of pathological fracture at the treatment site, rate of spinal cord compression at the index site, or in the rate of acute toxicity



12.7.2 E' possibile procedere con una reirradiazione in pazienti con recidiva di compressione midollare?

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nel caso di compressione midollare metastatica recidivante dopo radioterapia è possibile la re-irradiazione in pazienti adeguatamente selezionati. Se è presente un'istologia associata a prognosi favorevole si preferisce un trattamento radiante di 2 Gy frazione fino alla dose totale di 20-24 Gy. Se l'istologia è a prognosi sfavorevole possono essere utilizzati regimi di radioterapia quali 8 Gy frazione in dose unica.	Positiva Debole



Short-course vs Long-course RT: Metastatic Spinal Cord Compression (MSCC)

Table 3 - Functional outcome at 1 month after radiotherapy related to different primary tumours [34-38]

	Improvement (n (%))	No change (n (%))	Deterioration (n (%))	P
Breast cancer (n = 335)				
Short-course radiotherapy	44 (34)	74 (57)	12 (9)	
Long-course radiotherapy	61 (30)	118 (58)	26 (12)	0.81
Prostate cancer (n = 281)				
Short-course radiotherapy	52 (34)	78 (50)	25 (16)	
Long-course radiotherapy	40 (32)	72 (57)	14 (11)	0.83
Non-small cell lung cancer $(n = 252)$				
Short-course radiotherapy	16 (15)	58 (55)	31 (30)	
Long-course radiotherapy	19 (13)	78 (53)	50 (34)	0.87
Myeloma (n = 172)				
Short-course radiotherapy	24 (39)	35 (58)	2 (3)	
Long-course radiotherapy	66 (59)	43 (39)	2 (2)	0.10
Renal cell carcinoma $(n = 87)$				
Short-course radiotherapy	10 (27)	24 (65)	3 (8)	
Long-course radiotherapy	15 (30)	28 (56)	7 (14)	0.91

□ Short- (1 x 8Gy) and long-course radiotherapy (5 x 4Gy) resulted in comparable functional outcome in breast cancer, prostate cancer, lung cancer and renal cell carcinoma patients

☐ In Myeloma Patients, long-course radiotherapy seems to be associated with a better functional outcome than short-course radiotherapy at 6 months (67% vs 43% improvement of motor function, P 0.043) and at 12 months (76% vs 40%, P 0.003)



Metastatic Spinal Cord Compression (MSCC)

RT-SUMMARY

	Direct decompressive surgery followed by RT is superior to RT-alone
•	RT may be preferable for breast cancer and prostate cancer patients with a good cause it is associated with fewer MSCC recurrences in patients with such tumors
☐ In myel	ma patients, the functional outcome may also be better after long-course RT