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Defining the appropriate radiotherapy regimen for metastatic spinal cord compression in non-small cell lung cancer patients

Dirk Rades[a,*], *Lukas J.A. Stalpers*[b], *Rainer Schulte*[c], *Theo Veninga*[d], *Hiba Basic*[e], *Rita Engenhart-Cabilic*[f], *Steven E. Schild*[g], *Peter J. Hoskin*[h]

[a]*Department of Radiation Oncology, University Medical Center Hamburg Eppendorf, University Hospital Hamburg, Martinistr. 52, D-20246 Hamburg, Germany*
[b]*Department of Radiotherapy, Academic, Medical Center, Amsterdam, The Netherlands*
[c]*Department of Radiation Oncology, University Hospital, Lubeck, Germany*
[d]*Department of Radiation Oncology, Dr. Bernard Verbeeten Institute, Tilburg, The Netherlands*
[e]*Department of Radiotherapy, University Hospital, Sarajevo, Bosnia and Herzegovina*
[f]*Department of Radiation Oncology, Philipps-University, Marburg, Germany*
[g]*Department of Radiation Oncology, Mayo Clinic Scottsdale, Arizona, USA*
[h]*Department of Clinical Oncology, Mount Vernon Centre for Cancer Treatment, Northwood, United Kingdom*

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ABSTRACT

Many different schedules are used world wide for radiotherapy (RT) of metastatic spinal cord compression (MSCC). Non-small cell lung cancer (NSCLC) patients have an extraordinarily poor survival prognosis and would benefit from a short overall treatment time. This retrospective study compares short-course RT (1 × 8 Gy/1 day, 5 × 4 Gy/1 week) and long-course RT (10 × 3 Gy/2 weeks, 15 × 2.5 Gy/3 weeks, 20 × 2 Gy/4 weeks) for functional outcome in 252 NSCLC patients developing MSCC. Improvement of motor function occurred in 14% of patients, no change in 54%, and deterioration in 32%. Functional outcome was affected by the time of developing motor deficits before RT (>14 days better than 1–7 days and 8–14 days, $P < 0.001$), not by the radiation regimen ($P = 0.87$). In the short-course RT group, functional outcome was similar for 1 × 8 Gy and 5 × 4 Gy ($P = 0.94$). Short-course and long-course RT appear similarly effective for MSCC in NSCLC patients. As 1 × 8 Gy and 5 × 4 Gy showed comparable results, 1 × 8 Gy can be considered appropriate.

1. Introduction

About 5–10% of all cancer patients develop metastatic spinal cord compression (MSCC) during the course of their disease. In most cases, an urgent start in treatment is required to avoid progression of motor deficits leading to paraplegia.[1] Radiotherapy (RT) is the most frequently applied treatment modality.[2] The indication for surgery is usually restricted to the involvement of only one spinal segment.[2] Life expectancy of most MSCC patients is limited to a few months, depending on the type of primary tumour.[3–5] Lung cancer patients with vertebral metastases are reported to have an extraordinarily poor survival, even if there is no spinal cord compression.[6–9] Regarding the patient's transport to the department of

* *Corresponding author*: Tel.: +49 40 42803 6139; fax: +49 40 42803 2846.
E-mail address: Rades.Dirk@gmx.net (D. Rades).
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radiation oncology and the positioning on the treatment couch, every treatment session may be associated with major discomfort for the often debilitated patients. Thus, a radiation schedule with a short overall treatment time (short-course RT) appears preferable, especially for MSCC patients with a markedly reduced life expectancy such as lung cancer patients. However, short-course RT with 1×8 Gy (overall treatment time 1 day) or 5×4 Gy (1 week) can only be recommended, if it provides similar outcome as more protracted schedules (long-course RT such as 10×3 Gy in 2 weeks, 15×2.5 Gy in 3 weeks, or 20x2 Gy in 4 weeks).

This international multi-center study is the first study that focuses on the treatment of MSCC in patients with non-small cell lung cancer (NSCLC). It investigates a possible reduction of the overall treatment time in the largest series of these patients facing a very short survival time ever presented.

2. Patients and methods

In this retrospective analysis, 252 NSCLC patients irradiated for MSCC between 1/1991 and 6/2005 were included. Data were obtained from the patients' files and their general practitioners. Inclusion criteria were NSCLC, confirmation of MSCC by computed tomography (CT) or magnetic resonance imaging (MRI), motor deficits of the lower extremities, no previous surgery or RT of the spinal region concerned, no concurrent chemotherapy or chemotherapy within 2 months before and after RT, and dexamethasone (16–32 mg/day for at least 1 week). Small cell lung cancer (SCLC) patients were excluded from the analysis, as SCLC is more sensitive to RT than NSCLC.[9]

Before RT was started, patients were usually presented to a neurosurgeon to discuss the option of decompressive surgery. Patients were irradiated in supine position. Radiation doses were prescribed to the spinal cord using CT-scans and MRI. Due to the palliative situation, irradiation was performed with a simple technique using a single posterior field. Depending on the depth to the spinal cord, RT was either performed with 6 MV photons and cobalt 60 (depth to spinal cord ⩽6 cm) or with 10–16 MV photons (>6 cm). The treatment volume encompassed one normal vertebra above and below the metastatic lesions.

Of the entire cohort, 57 patients (23%) were female and 195 were male (77%). Median age was 61 years (range 26–87 years). 125 patients (50%) were ambulatory before RT. The time of developing motor deficits before RT was 1–7 days in 97 patients (38%), 8–14 days in 69 patients (27%), and >14 days in 86 patients (34%). Performance status according to the Eastern Cooperative Oncology Group (ECOG) was 1–2 in 88 patients (35%), and 3–4 in 164 patients (65%). In 104 patients (41%), only 1–2 vertebra were involved. Patients (105) received short-course RT consisting of 1×8 Gy given in 1 day ($n = 47$) or 5×4 Gy given in 1 week ($n = 58$). Patients (147) received long-course RT consisting of 10×3 Gy given in 2 weeks ($n = 60$), 15×2.5 Gy given in 3 weeks ($n = 51$) or 20×2 Gy given in 4 weeks ($n = 36$). Patient characteristics related to the RT schedules are summarized in Table 1.

Motor function and ambulatory status were evaluated prior to RT, as well as at 1 month and at 3 months following RT. Motor function was graded with a 5-point scale according to Tomita and colleagues [10]: 0 normal strength; 1 ambulatory without aid; 2 ambulatory with aid; 3 not ambulatory; 4 paraplegia. Improvement or deterioration of motor function was defined as a change of at least one point.

The following potential prognostic factors were evaluated for functional outcome: age (⩽60 versus >60 years), ECOG performance status (1–2 versus 3–4), number of involved vertebra (1–2 versus ⩾3), ambulatory status before RT (ambulatory versus non-ambulatory), time of developing motor deficits before RT (1–7 versus 8–14 and >14 days), and RT regimen (short-course RT versus long-course RT). The potential prognostic factors were included in an univariate analysis that was performed with the ordered-logit-model, as the data for functional outcome are ordinal (-1 = deterioration, 0 = no change, 1 = improvement). Results were considered significant if $P < 0.05$.

Table 1 – Patient characteristics related to the radiation schedules

	Short-course RT *N* patients (%)	Long-course RT *N* patients (%)	*P*
Age			
⩽60 years	49 (47)	72 (49)	0.86
>60 years	56 (53)	75 (51)	
ECOG performance status			
1–2	39 (37)	49 (33)	0.77
3–4	66 (63)	98 (67)	
Involved vertebra (n)			
1–2	42 (40)	62 (42)	0.89
⩾3	63 (60)	85 (58)	
Ambulatory status before RT			
Ambulatory	54 (51)	73 (50)	0.92
Non-ambulatory	51 (49)	74 (50)	
Time of developing motor deficits before RT			
1–7 days	43 (41)	54 (37)	0.85
8–14 days	26 (25)	43 (29)	
>14 days	36 (34)	50 (34)	

3. Results

Thirty-five patients (14%) had improvement of motor function, 136 (54%) no change, and 81 (32%) deterioration. Of the 127 non-ambulatory patients, 19 (15%) regained the ability to walk, 8 of 54 patients (15%) after short-course RT, and 11 of 73 patients (15%) after long-course RT ($P = 0.99$).

The impact of the potential prognostic factors on functional outcome is shown in Table 2. The effect of RT on motor function was significantly influenced only by the time of developing motor deficits before RT (>14 days better than 8–14 and 1–7 days). The number of involved vertebra (1–2 better than ⩾3) was of borderline significance. The RT schedule had no significant impact. Results at 1 month after RT ($n = 252$, Fig. 1) were similar to those observed at 3 months after RT ($n = 183$, Fig. 2).

The fact that short-course RT and long-course RT had a similar effect on functional outcome means a reduction in overall treatment time from 2–4 weeks to 1 week. In the

Table 2 – Impact of potential prognostic factors on motor function (univariate analysis)

	Improvement of motor function N patients (%)	No change of motor function N patients (%)	Deterioration of motor function N patients (%)	P
Age				
⩽60 years (n = 121)	16 (13)	70 (58)	35 (29)	0.70
>60 years (n = 131)	19 (15)	66 (50)	46 (35)	
ECOG performance status				
1–2 (n = 88)	17 (19)	47 (54)	24 (27)	0.51
3–4 (n = 164)	18 (11)	89 (54)	57 (35)	
Involved vertebra (n)				
1–2 (n = 104)	21 (20)	62 (60)	21 (20)	0.06
⩾3 (n = 148)	14 (9)	74 (50)	60 (41)	
Ambulatory status before RT				
Ambulatory (n = 127)	15 (12)	72 (57)	40 (31)	0.74
Non-ambulatory (n = 125)	20 (16)	64 (51)	41 (33)	
Time of developing motor deficits before RT				
1–7 days (n = 97)	4 (4)	35 (36)	58 (60)	<0.001
8–14 days (n = 69)	2 (3)	51 (74)	16 (23)	
>14 days (n = 86)	29 (34)	50 (58)	7 (8)	
Radiation schedule				
Short-course RT (n = 105)	16 (15)	58 (55)	31 (30)	0.87
Long-course RT (n = 147)	19 (13)	78 (53)	50 (34)	

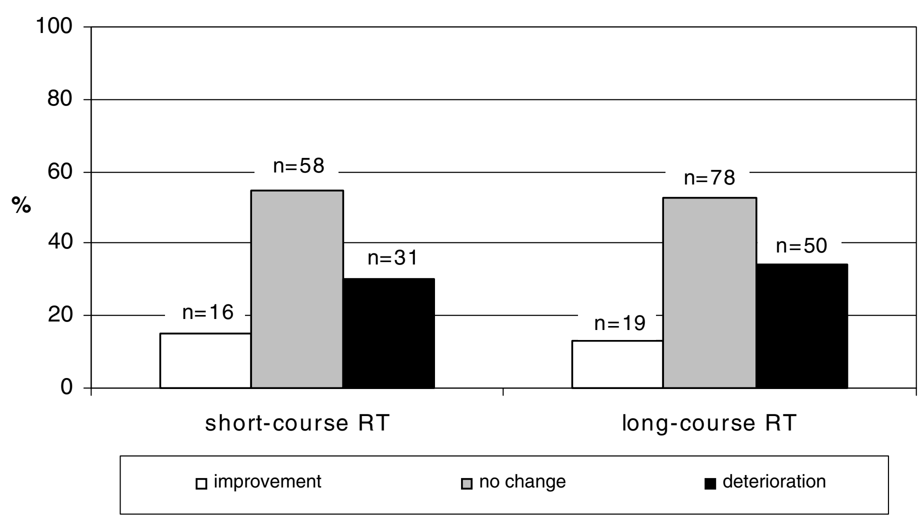

Fig. 1 – Short-course RT versus long-course RT: functional outcome (improvement, no change or deterioration of motor function) at 1 month following RT (P = 0.87).

short-course RT group, 1 × 8 Gy was compared to 5 × 4 Gy to investigate a further reduction from 1 week (5 × 4 Gy) to 1 day (1 × 8 Gy). A significant difference between the two short-course schedules was not observed (Table 3).

Median survival in the entire cohort was 4 months (range 2–27 months). Eighty percentage of the patients (n = 201) died within 6 months after RT. A local recurrence of MSCC within the irradiated volume occurred in 9 patients (4%) after median 7 months (range 2–18 months). The overall recurrence rates were 8% after short-course RT and 1% after long-course RT (P = 0.013), respectively. Treatment for recurrence of MSCC after short-course RT was re-irradiation (re-RT), 1 × 8 Gy in 4 patients, 5 × 3 Gy in 2 patients, and 5 × 4 Gy in 2 patients. The patient initially treated with long-course RT (15 × 2.5 Gy) received 30.6 Gy (17 × 1.8 Gy). Re-RT led to an improvement of motor function in 2 patients (22%), no change in 3 patients (33%), and deterioration in 4 patients (44%).

After both initial RT and re-RT, acute radiation toxicity was absent or mild in all patients. Late radiation toxicity such as myelopathy or vertebral body fractures did not occur.

4. Discussion

The life expectancy of most MSCC patients is markedly reduced. Because MSCC in lung cancer patients is associated with an extraordinarily poor survival prognosis of about 3

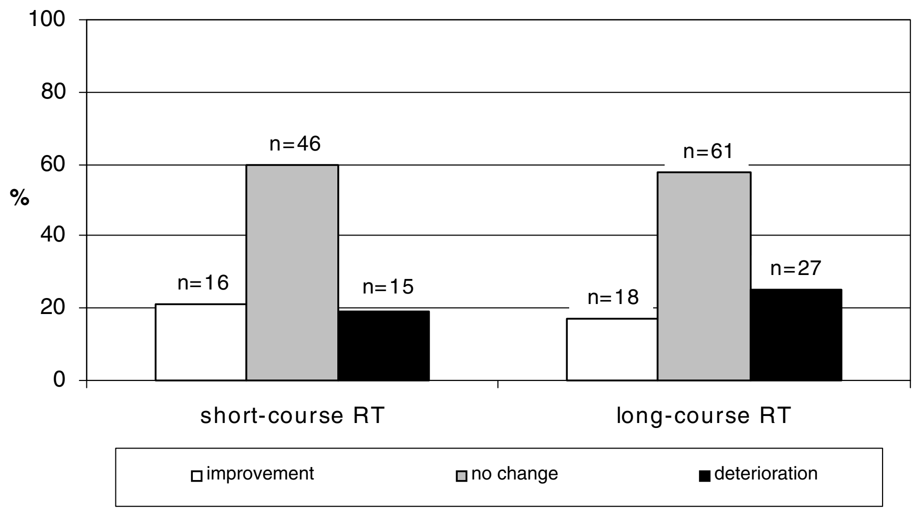

Fig. 2 – Short-course RT versus long-course RT: functional outcome (improvement, no change or deterioration of motor function) at 3 months following RT (*P* = 0.79).

Table 3 – Short-course RT: comparison of 1 × 8 Gy and 5 × 4 Gy with respect to functional outcome

	Improvement of motor function *N* patients (%)	No change of motor function *N* patients (%)	Deterioration of motor function *N* patients (%)	*P*
1 × 8 Gy (*n* = 47)	7 (15)	25 (53)	15 (32)	0.94
5 × 4 Gy (*n* = 58)	9 (15)	33 (57)	16 (28)	

months, these patients would benefit in particular from a radiation schedule with a short overall treatment time.[6–9]

Only very few reports compared short-course RT and long-course RT for MSCC.[5,11–13] Hoskin and colleagues presented a retrospective series of 102 patients treated with various short-course and long-course regimens.[5] No significant difference was observed between the schedules regarding functional outcome. Maranzano and colleagues presented a retrospective analysis with 44 patients and a randomized study with 276 patients that both compared short-course RT (2 × 8 Gy) and an unusual split-course regimen (3 × 5 Gy followed by 4 days rest and 5 × 3 Gy).[11,12] Both schedules had a similar effect on motor function. In our previous analysis, short-course RT and long-course RT appeared comparable for functional outcome.[13] That series was not homogeneous regarding the distribution of primary tumours like the prospective study by Maranzano and colleagues [12].

This international multi-center study compares short-course RT and long-course RT in patients with NSCLC. Both RT regimens proved to be similarly effective with respect to improving or maintaining motor function. Short-course RT may be performed with several-fraction RT such as 5 × 4 Gy, or with single-fraction RT such as 1 × 8 Gy. The most desirable treatment for NSCLC patients with MSCC would be a radiation schedule applied in 1 day. In the present study, 1 × 8 Gy and 5 × 4 Gy were similar effective for functional outcome. Thus, 1 × 8 Gy appears the most appropriate schedule for NSCLC patients. Furthermore, a short program substantially reduces the cost of therapy.

Functional outcome was significantly influenced by the length of time of developing motor deficits prior to RT, which has been suggested a relevant prognostic factor before.[14] The comparably bad prognosis after rapid development of motor dysfunction can be explained by disruption of the arterial blood flow, which may lead to spinal cord infarction. A slower development of motor deficits is considered as a result of venous congestion, which is more likely to be reversible.[15] It may be questioned whether the functional results of one of the two compared RT schedules are confounded by a high rate of local recurrences of MSCC. The overall local recurrence rate was significantly higher after short-course RT than after long-course RT. However, it was less than 10% in both groups. Furthermore, it has to be taken into account that only 20% of the patients in the entire cohort survived longer than 6 months and that only 4% survived longer than 12 months. A bias may have been introduced due to the fact, that more patients may have had recurrences, but were not referred for re-RT due to poor prognosis or the wrong impression that re-RT is not effective. Due to the fact that only very few patients are at risk to develop a recurrence of MSCC, local control is of minor importance in NSCLC patients. If a local recurrence of MSCC occurs after short-course RT, re-RT can be safely performed taking into account the tolerance dose for radiation myelopathy.[16]

This study included the largest cohort of NSCLC patients with MSCC to date. The treatment groups were well balanced with respect to the potential prognostic factors, survival and follow-up, which considerably reduces the risk of a selection bias. However, the retrospective nature of this study has to be taken into account. Furthermore, one should be cautious regarding the routine use of short-course RT for MSCC treatment in other than NSCLC patients, especially in patients with a better survival prognosis such as breast cancer or myeloma patients, since local control becomes more important in long-term survivors.

Conflict of interest statement

All authors hereby confirm that there is no conflict of interest related to this study. The study was not funded.

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