Re-irradiation of Spinal Cord Compression Due to Metastasis in Elderly Patients

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Abstract. *Background/Aim: The present study investigated efficacy and toxicity of re-irradiation for an in-field recurrence of spinal cord compression due to metastasis (SCCM) in elderly patients. Patients and Methods: Data of 60 patients aged ≥65 years who were irradiated for an in-field recurrence of SCCM were retrospectively analyzed. The fractionation regimen of re-irradiation and eight additional potential prognostic factors were evaluated for motor function. Results: Median time to in-field recurrence was 6 (2-45) months. After re-irradiation, 25 patients (42%) showed improvement of motor function, 28 (47%) no change, and 7 (12%) deterioration. No second in-field recurrences were observed. Post-treatment motor function was not associated with the fractionation regimen. Radiation myelopathy was not observed. The cumulative biologically-effective dose for myelopathy was 80-137 Gy_2. Conclusion: Re-irradiation for in-field recurrences of SCCM in elderly patients appears safe and effective. Myelopathy appears unlikely, if the cumulative biologically effective dose is 137 Gy_2 or less. The fractionation regimen had no significant impact on motor function.*

Radiotherapy alone is the most commonly administered treatment for spinal cord compression due metastatic cancer (SCCM). A prospective study found that approximately 20% of patients receiving longer-course radiotherapy programs (such as 10×3 Gy in two weeks or 20×2 Gy in four weeks) and about 40% of patients receiving single-fraction or short-course or multi-fraction radiotherapy (such as 5×4 Gy in one week) develop a recurrence of SCCM in the irradiated portion of the spine (in-field recurrence) (1). Since decompressive surgery is not possible or indicated in many of these patients, re-irradiation may be required. This is particularly true for elderly patients who often have severe comorbidities and may not be able to withstand an invasive treatment such as spinal surgery (2). However, one may question whether a second course of radiotherapy in the same portion of the spine is effective in elderly patients in terms of improving motor deficits and preventing further progression. A second important question is whether re-irradiation is safe and does not lead to radiation-induced myelopathy. It is also helpful to define the most appropriate fractionation regimen. In particular for elderly patients, a fractionation regimen with a short overall treatment time, which is less burdensome than longer-course radiotherapy programs, is preferable if it were as effective as longer-course irradiation. The present study aims to address these issues. A cohort of 60 elderly patients, defined as 65 years or older, was evaluated for the effects of re-irradiation on motor function and the risk of radiation myelopathy. Four different fractionation regimens were compared in order to identify the most appropriate treatment.

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Patients and Methods

Data of 60 elderly (≥65 years) patients who had received spinal re-irradiation alone for motor deficits due to an in-field recurrence of SCCM between 1995 and 2011 were retrospectively analyzed. Prior to re-irradiation, the patients were reviewed by a surgeon for possible decompressive surgery. The patients had no previous surgery of the involved spinal region. The diagnosis of an in-field recurrence was based on magnetic resonance imaging (MRI) scans. Dexamethasone treatment was given at the time of re-irradiation. Both primary irradiation and re-irradiation were performed with 6-10 MV photon beams. The treatment volume encompassed one normal vertebra above and below the metastatic lesions. In cases

Table I. *Patients' characteristics at the time of re-irradiation.*

	N (%)
Age	
≤73 years	32 (53)
≥74 years	28 (47)
Gender	
Female	14 (23)
Male	46 (77)
Type of primary tumor	
Breast cancer	6 (10)
Prostate cancer	25 (42)
Lung cancer	12 (20)
Myeloma	4 (7)
Other	13 (22)
ECOG performance status	
1-2	33 (55)
3-4	27 (45)
Interval between primary and re-irradiation	
≤6 months	32 (53)
>6 months	28 (47)
Number of involved vertebrae	
1-2	27 (45)
≥3	33 (55)
Ambulatory status	
Ambulatory	42 (70)
Not ambulatory	18 (30)
Fractionation regimen of re-irradiation	
1×8 Gy	22 (37)
5×4 Gy	16 (27)
5-7×3 Gy	14 (23)
10-12×2 Gy	8 (13)
Cumulative BED (α/β=10 Gy)	
≤45 Gy_{10}	32 (53)
>45 Gy_{10}	28 (47)

Table II. *Improvement of motor function at one month following re-iradiation.*

	Improvement of motor function (%)	*p*-Value
Age		
≤73 years	38	
≥74 years	46	0.75
Gender		
Female	36	
Male	43	0.92
Type of primary tumor		
Breast cancer	50	
Prostate cancer	52	
Lung cancer	17	
Myeloma	75	
Other	31	0.42
ECOG performance status		
1-2	52	
3-4	30	0.26
Interval between primary and re-irradiation		
≤6 months	41	
>6 months	43	0.97
Number of involved vertebrae		
1-2	41	
≥3	42	0.98
Ambulatory status		
Ambulatory	52	
Not ambulatory	17	0.08
Fractionation regimen of re-irradiation		
1×8 Gy	36	
5×4 Gy	50	
5-7×3 Gy	43	
10-12×2 Gy	38	0.93
Cumulative BED (α/β=10 Gy)		
≤45 Gy_{10}	34	
>45 Gy_{10}	50	0.47

where lesions affecting the thoracic spine also affected the cervical spine, two normal vertebrae above the metastatic lesions were irradiated.

Motor function was evaluated prior to re-irradiation and at one, three and six months following re-irradiation with the Tomita scale (3) grade 0: normal strength; grade 1: ambulatory without aid, grade 2: ambulatory with aid, grade 3: not ambulatory, grade 4: paraplegia. Improvement or deterioration of motor function was defined as a change of at least one point. The following nine potential prognostic factors at the time of re-irradiation were evaluated with respect to improvement of motor function: age (≤73 *vs.* ≥74 years, median age=73 years), gender, primary tumor type (breast cancer *vs.* prostate cancer *vs.* lung cancer *vs.* myeloma *vs.* other type), Eastern Cooperative Oncology Group (ECOG) performance score (1-2 *vs.* 3-4), interval between primary irradiation and re-irradiation (≤6 *vs.* >6 months, median interval=6 months), number of involved vertebrae (1-2 *vs.* ≥3), ambulatory status (ambulatory *vs.* not ambulatory), the fractionation regimen of re-irradiation (1×8 Gy *vs.* 5×4 Gy *vs.* 5-7×3 Gy *vs.* 10-12×2 Gy), and the cumulative (primary irradiation plus re-irradiation) biologically effective dose (BED) (α/β ratio=10 Gy; BED ≤45 Gy_{10} *vs.* BED >45 Gy_{10}). Univariate analyses were performed with the Chi-square test. Data were obtained from patient files and from interviews with the patients and their treating physicians. Patient characteristics are shown in Table I.

The BED was calculated with the equation $BED=D\times[1+(d/\alpha/\beta)]$, as derived from the linear-quadratic model where D=total dose, d=dose per fraction, α=linear (first-order dose-dependent) component of cell killing, β=quadratic (second-order dose dependent) component of cell killing, α/β=dose at which both components of cell killing are equal (4). An α/β ratio of 10 Gy was chosen for the treatment effect (improvement of motor function). With respect to radiation myelopathy, we calculated the BED with an α/β ratio of 2 Gy and no allowance for recovery of tolerance from the primary irradiation (worst case scenario).

Re-irradiation was performed either with 1×8 Gy (N=22), 5×4 Gy (N=16), 5-7×3 Gy (N=14), or 10-12×2 Gy (N=8). These four dose groups were compared for the effect of motor function (improvement, no change and deterioration of motor deficits) with the Chi-square test.

Table III. *Effect of re-irradiation on motor function at one, three and six months, according to the four fractionation regimens of re-irradiation.*

Time point	Entire cohort N (%)	Regimen N (%)				
		1×8 Gy	5×4 Gy	5-7×3 Gy	10-12×2 Gy	*p*-Value
1 Month						
Improvement	25 (42)	8 (36)	8 (50)	6 (43)	3 (38)	0.93
No change	28 (47)	11 (50)	7 (44)	6 (43)	4 (50)	0.99
Deterioration	7 (12)	3 (14)	1 (6)	2 (14)	1 (13)	0.90
3 Months						
Improvement	24 (45)	8 (40)	7 (50)	6 (50)	3 (43)	0.96
No change	22 (42)	9 (45)	6 (43)	4 (33)	3 (43)	0.97
Deterioration	7 (13)	3 (15)	1 (7)	2 (17)	1 (14)	0.90
6 Months						
Improvement	22 (69)	8 (57)	6 (75)	5 (100)	3 (60)	0.77
No change	10 (31)	6 (43)	2 (25)	0 (0)	2 (40)	0.48
Deterioration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.00

Results

The median interval between primary irradiation of SCCM and irradiation of an in-field recurrence of SCCM was 6 months (range 2-45 months). On univariate analyses, none of the nine investigated potential prognostic factors was significantly associated with improvement of motor function at one month following re-irradiation (Table II). Therefore, a multivariate analysis was not performed.

In order to analyze the potential impact of the fractionation regimen of re-irradiation on post-treatment motor function, the four-dose groups of re-irradiation,1×8 Gy, 5×4 Gy, 5-7×3 Gy and 10-12×2 Gy were compared for improvement, no change and deterioration of motor deficits at one, three and six months following re-irradiation. No significant difference was observed between the four dose groups (Table III). The post-treatment ambulatory rates were 67% (40/60) in the entire cohort, and 73% (16/22) after 1×8 Gy, 69% (11/16) after 5×4 Gy, 57% (8/14) after 5-7×3 Gy, and 63% (5/8) after 10-12×2 Gy, respectively (p=0.96).

The patients were followed-up until death or for a median of seven months (range=2-46 months) for survivors. At the last contact after re-irradiation, 27/60 patients (45%) were alive. The median follow-up periods were nine months after 1×8 Gy, eight months after 5×4 Gy, seven months after 5-7×3 Gy, and seven months after 10-12×2 Gy. During the follow-up period after re-irradiation, no second in-field recurrence in the same spinal region was observed. Acute toxicity (nausea, diarrhea, skin reactions) did not exceed grade 1 according to CTCAE.

The cumulative BED calculated with an α/β-ratio of 2 Gy for myelopathy ranged between 80 Gy_2 and 137 Gy_2 (median=100 Gy_2). It was ≤120 Gy_2 in 52 patients (87%). Late toxicity such as radiation myelopathy was not observed after primary irradiation or after re-irradiation.

Discussion

An in-field recurrence of SCCM occurs in up to 40% of patients at one year following radiotherapy (1). The risk of radiation myelopathy is likely to increase with the BED delivered to the spinal cord. Since re-irradiation of the same spinal region increases the cumulative BED, myelopathy appears more likely after re-irradiation than after primary irradiation. Therefore, many radiation oncologists are reluctant to administer a second course of radiotherapy to the same portion of the spine. In case of an in-field recurrence following radiotherapy, decompressive surgery appears a reasonable option. However, surgery may not be possible or indicated in the majority of patients developing an in-field recurrence of SCCM. Patients suitable for spinal surgery should have a relatively favorable performance status (ECOG 0-2), few comorbidities, and a survival prognosis of at least three months (2). The complication rates of decompressive surgery in a randomized trial of 101 patients were 12% for primary surgery and 40% for salvage surgery (2). Surgery- and anesthesia-related complications are more likely in elderly patients. Therefore, one should be more cautious in performing decompressive surgery in this group of patients. Furthermore, in a matched-pair analysis of 126 elderly patients aged ≥65 years, who received either radiotherapy-alone or radiotherapy-plus- upfront decompressive surgery for primary treatment of SCCM, the addition of surgery did not provide benefit with respect to functional outcome, local control of SCCM, or survival (5).

It is still not clear whether re-irradiation of SCCM is safe and effective in elderly patients. The current study aimed to contribute to addressing these issues. According to the results of this study, the response rate (improvement or prevention from further progression of motor deficits) was 88% (53 out

of 60 patients), which is similar to the response rates of 89% and 83% achieved with radiotherapy-alone or radiotherapy-plus-upfront surgery, respectively, for primary treatment of SCCM (5). Improvement of motor function was observed in 42% of patients after re-irradiation in the present study and in 24% and 21% after primary treatment in the previous matched-pair analysis (5). The finding that the results seem to be better after re-irradiation may be explained by the fact that all patients included in the present study had responded to primary irradiation. These data revealed that re-irradiation of SCCM in elderly patients is effective. The effect of re-irradiation on motor function was not significantly associated with the fractionation regimen used. One may speculate whether 5×4 Gy is superior to the other three regimens with rates of 50% for improvement of motor function and 94% for overall response (improvement plus prevention of further progression of motor deficits). It is possible that a significant difference was not achieved because of the relatively small number of patients included in this study. Ideally, a much larger series of patients may be required in order to have the statistical power to detect these types of clinical differences. However, a larger series of elderly patients receiving re-irradiation for an in-field recurrence of SCCM is unlikely to be collected in the near future, since more patients including elderly patients, undergo decompressive surgery for primary treatment or re-treatment.

Taking into account the results of the present study, one may tend to recommend 5×4 Gy for re-irradiation of SCCM if the cumulative BED does not exceed 137 Gy_2. The present study was too small to be able to clearly discern which regimen was best. However, this regimen is effective and short, leading to less patient inconvenience.

In the present study, the cumulative BED ranged between 80 Gy_2 and 137 Gy_2. No radiation myelopathy was observed following re-irradiation. In the review of Nieder *et al*. including 78 re-irradiated patients with SCCM, and in our own previous study of 124 patients of any age, no radiation myelopathy occurred if the cumulative BED was ≤120 Gy_2 (6, 7). According to that review, the BED of each of the two courses of radiotherapy should not exceed 98 Gy_2, and the interval between courses should be at least six months. For patients, in whom the cumulative BED would exceed 137 Gy_2 and who are not candidates for decompressive surgery, stereotactic body radiation therapy may be utilized taking into account the tolerance doses of the spinal cord and the vertebral bone (8).

In conclusion, re-irradiation for an in-field recurrence of SCCM appears to be both safe and effective and should not be withheld from elderly patients. Radiation myelopathy appears quite unlikely if the cumulative BED does not exceed 137 Gy_2. The fractionation regimen had no significant impact on post-treatment motor function. Additional studies are required to better define the optimal fractionation regimen of re-irradiation of SCCM in elderly patients.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interests related to this study.

References

1 Rades D, Lange M, Veninga T, Stalpers LJ, Bajrovic A, Adamietz IA, Rudat V and Schild SE: Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys *79*: 524-530, 2011.

2 Patchell R, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M and Young B: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet *366*: 643-648, 2005.

3 Tomita T, Galicich JH and Sundaresan N: Radiation therapy for spinal epidural metastases with complete block. Acta Radiol Oncol *22*: 135-143, 1983.

4 Barendsen GW: Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys *8*: 1981-1997, 1982.

5 Rades D, Huttenlocher S, Evers JN, Bajrovic A, Karstens JH, Rudat V and Schild SE: Do elderly patients benefit from surgery in addition to radiotherapy for treatment of metastatic spinal cord compression? Strahlenther Onkol *188*: 424-430, 2012.

6 Nieder C, Grosu AL, Andtratschke NH and Molls M: Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys *66*: 1446-1449, 2006.

7 Rades D, Rudat V, Veninga T, Stalpers LJ, Hoskin PJ and Schild SE: Prognostic factors for functional outcome and survival after re-irradiation for in-field recurrences of metastatic spinal cord compression. Cancer *113*: 1090-1096, 2008.

8 Kirkpatrick JP, van der Kogel AJ and Schultheiss TE: Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys *76(3 Suppl)*: S42-49, 2010.

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