Local Control of Metastatic Spinal Cord Compression Following Radiotherapy

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Abstract

Radiotherapy (RT) alone is the most frequently applied treatment modality for metastatic spinal cord compression (MSCC). Short-course RT (overall treatment time one week or less) provides a similar functional outcome to longer programmes. Therefore, short-course RT should be seriously considered for many MSCC patients, especially for those with a poor survival prognosis. By contrast, a considerable proportion of MSCC patients live long enough to experience a local recurrence of MSCC in the previously irradiated area of the spinal cord. Long-course RT (30–40Gy in two to four weeks) results in significantly better local control than short-course RT and should therefore be administered to patients with a more favourable survival prognosis. Survival can be estimated with a newly developed scoring system. If re-irradiation is required, a second course of RT can be safely administered in most cases after primary short-course RT. After primary long-course RT, re-irradiation should optimally be performed with high-precision techniques in order to reduce the risk of radiation-related myelopathy.

Keywords

Metastatic spinal cord compression, radiotherapy, local control, fractionation, re-irradiation

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Up to 10% of all cancer patients will develop metastatic spinal cord compression (MSCC) during the course of their disease.[1] Radiotherapy (RT) is the most frequently applied treatment modality, either alone or following decompressive surgery. The indication for surgery of MSCC is usually limited to patients with solid tumours, involvement of only one spinal segment, a good performance status and a relatively favourable survival prognosis.[2] Thus, RT alone is the most commonly used modality in the treatment of MSCC. The optimal radiation fractionation regimen is still a matter of debate. As many MSCC patients are debilitated, a shorter overall treatment time would be preferable if it provided similar results to more protracted regimens.

Several retrospective and prospective studies have demonstrated that short-course RT with lower total doses (overall treatment time one week or less) achieved similar results to long-course RT with higher total doses (overall treatment time two to four weeks) in terms of post-treatment motor function and pain relief.[3–8] Thus, short-course RT may be considered for the treatment of MSCC. This particularly applies to patients with a poor expected survival of only a few months. By using a short-course RT regimen, the need for these patients to spend a considerable proportion of their limited lifespan receiving treatment may be decreased.

By contrast, a considerable proportion of MSCC patients live much longer than a few months.[9] Some patients live for years. As the vast majority of recurrences of MSCC in the previously irradiated area of the spinal cord develop at only six months or later following irradiation, patients with a more favourable survival prognosis are at a higher risk of developing a local recurrence. Due to the rather limited indications for surgery, re-irradiation is the primary treatment option for many of these recurrences.[2] However, re-irradiation may carry an increased risk of radiation-related myelopathy that may be associated with severe neurological deficits. Therefore, both post-treatment neurological function and local control are important end-points following irradiation of MSCC. This article focuses on local control of MSCC following irradiation. The impact of fractionation, potential prognostic factors and the option of spinal re-irradiation of a local recurrence are reviewed.

Impact of the Fractionation Regimen

Many different fractionation regimens are used worldwide for the RT of MSCC. These include single-fraction regimens such as 1x8Gy, multifraction short-course regimens such as 4x4Gy over four days, 5x4Gy over one week or 5x5Gy over one week, and multifraction long-course regimens such as 10x3Gy over two weeks, 15x2.5Gy over three weeks or 20x2Gy over four weeks. Most studies that compared different fractionation regimens investigated the effect of RT on pain relief or on neurological deficits such as motor dysfunction. Limited data are available in terms of local control of MSCC. A large retrospective study of 1,304 patients suggested that local control of MSCC was significantly better after long-course RT with 10x3Gy, 15x2.5Gy or 20x2Gy than after single-fraction RT with 1x8Gy or multifraction short-course RT with 5x4Gy.[7] These results were

confirmed in a subsequent retrospective study of 1,852 MSCC patients that focused on local control of MSCC.[9] The one-year local control rates in the latter study were 93% after long-course RT and 82% after single-fraction/short-course RT (p<0.001). The two-year local control rates were 90 and 74%, respectively. These findings remained significant in the multivariate analysis performed with the Cox proportional hazards model (relative risk [RR] 0.54, 95% confidence interval [CI] 0.45–0.65; p<0.001). However, retrospective studies are at an increased risk of including uncontrolled biases. Furthermore, the rate of recurrences may be underestimated due to the fact that many patients may not have been referred back to the radiation oncologist for re-irradiation. Many physicians are concerned about a potentially increased risk of radiation myelopathy if a second RT series is administered to the same portion of the spine.

In 2006, the prospective Spinal Cord cOmpression Recurrence Evaluation 1 (SCORE-1) study was started.[10] The primary goal of the SCORE-1 study was to evaluate whether short-course RT with 1x8Gy over one day or 5x4Gy over one week results over similar local control of MSCC to long-course RT with 10x3Gy over two weeks, 15x2.5Gy over three weeks or 20x2Gy over four weeks. As the radiation schedule considered the standard treatment varied between the countries of the contributing centres, randomisation was not possible. Short-course RT is the standard regimen in The Netherlands, whereas long-course RT is the standard regimen in Germany; therefore, patients treated in The Netherlands received short-course RT and the patients treated in Germany received long-course RT. The series of each contributing centre represented an unselected series of patients. The final results of this study (n=265) have recently been presented in abstract form.[10] The local control rate at 12 months was 81% after long-course RT and 61% after short-course RT (p=0.005). These results were confirmed in a multivariate analysis (p=0.018). Studies from other authors did not often focus on local control. In a randomised study of 276 patients, the median duration of improvement in motor function was 3.5 months following both 1x8Gy and a split-course regimen (3x5Gy followed by one-week rest and 5x3Gy).[6] In another randomised study of 327 patients by the same authors, the median duration of improvement in motor function was 4.5 months after 1x8Gy compared with five months after 2x8Gy in eight days (p=0.4).[8] However, these authors did not differentiate between recurrences within (in-field recurrence) or outside (out-field recurrence) the previously irradiated area of the spinal cord. Therefore, while these studies are helpful in terms of functional outcomes, they are not particularly helpful if one aims to define the optimal fractionation regime in terms of local control.

The reported studies that focused on local control (freedom from in-field recurrence) of MSCC suggested that long-course RT is superior to short-course or single-fraction regimens.[7,9,10] The fact that significantly more MSCC recurrences were observed after short-course RT than after long-course RT can be explained by the higher total radiation doses given in the long-course protocols (30–40Gy versus 8–20Gy). However, the biological effectiveness of a radiation schedule depends on both the total dose and the dose per fraction. A comparison of radiation schedules that include different total doses and doses per fraction can be performed with the equivalent dose in 2 gray fractions (EQD2). The EQD2 is calculated with the equation $EQD2 = Dx[(d+\alpha/\beta)/2Gy+\alpha/\beta)]$, as derived from the linear-quadratic model: 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 ratio = the dose at which both components of cell killing are equal.[11] Assuming an α/β ratio of 10Gy for tumour cell kill, the EQD2 of some of the investigated radiation schedules are as follows: 12Gy for 1x8Gy, 23.3Gy for 5x4Gy, 32.5Gy for 10x3Gy, 39.1Gy for 15x2.5Gy and 40Gy for 20x2Gy. Therefore, even if the different doses per fraction are considered, the effective total doses of the long-course protocols are higher than those of the short-course protocols, which may serve as an explanation for the finding that better local control of MSCC can be achieved with long-course RT than with short-course RT.

Table 1: Prognostic Score Predicting Survival of Metastatic Spinal Cord Compression Patients[12]

	Score
Type of Primary Tumour	
Breast cancer	8
Prostate cancer	7
Myeloma/lymphoma	9
Lung cancer	3
Other tumours	4
Other Bone Metastases at the Time of Radiotherapy	
Yes	5
No	7
Visceral Metastases at the Time of Radiotherapy	
Yes	2
No	8
Interval Between Tumour Diagnosis and MSCC	
≤15 months	4
>15 months	7
Ambulatory Status Before Radiotherapy	
Ambulatory	7
Non-ambulatory	3
Time of Development of Motor Deficits Before Radiotherapy	
1–7 days	3
8–14 days	6
>14 days	8

MSCC = metastatic spinal cord compression.
The scores relate to the six significant prognostic factors on multivariate analysis.

Table 2: Prognostic Score Predicting Survival of Metastatic Spinal Cord Compression Patients[12]

	Survival Rate at 6 Months (%)	Survival Rate at 12 Months (%)
Group A (20–25 points)	4	0
Group B (26–30 points)	11	6
Group C (31–35 points)	48	23
Group D (36–40 points)	87	70
Group E (41–45 points)	99	89

Survival rates of the five groups (p<0.0001).

Other Potential Prognostic Factors

The above-mentioned study of 1,852 patients further aimed to identify potential prognostic factors in terms of local control of MSCC.[9] In the univariate analysis, the type of primary tumour and visceral metastases at the time of RT were associated with local control of MSCC. The one-year local control rates were 94% for myeloma patients, 92% for breast cancer patients, 84% for prostate cancer patients, 79% for lung cancer patients and 83% for patients with other tumours (p<0.001). In patients without visceral

metastases the one-year local control rate was 91% compared with 71% in those patients with visceral metastases (p<0.001). In the multivariate analysis (Cox proportional hazards model), visceral metastases remained significant (RR 2.64, 95% CI 1.76–3.90; p<0.001), whereas the type of primary tumour did not (RR 1.09, 95% CI 0.97–1.21; p=0.14).

Predicting the Survival Prognosis of Patients Irradiated for Metastatic Spinal Cord Compression

Long-course RT appears the better option for MSCC patients with a favourable survival prognosis, as these patients may live long enough to develop a recurrence of MSCC in the previously irradiated area of the spinal cord. A scoring system helping to predict the survival prognosis of MSCC patients could be helpful to select the most appropriate radiation regimen for the individual patient. Based on the multivariate analysis of the retrospective study of 1,852 MSCC patients treated with RT alone, just such a scoring system was developed.[12] In the multivariate analysis, six factors were significantly associated with survival. These factors were type of primary tumour (better survival in myeloma and breast cancer patients than in patients with other tumours), other bone metastases at the time of RT (better survival in the case of no other bone metastases), visceral metastases at the time of RT (better survival in the case of no visceral metastases), interval from first diagnosis of cancer to onset of MSCC (better survival after a longer interval, >15 versus ≤15 months), pre-RT ambulatory status (better survival if patients were ambulatory) and time of developing motor deficits before RT (better survival in the case of a longer time period, >14 versus one to 14 days). The score for each prognostic factor was determined by dividing the six-month survival rate (given in %) by 10 (see *Table 1*). Total scores represented the sum of the six scores obtained for each of the six prognostic factors, and ranged from 20 to 45 points. Five groups were defined: 20–25, 26–30, 31–35, 36–40 and 41–45 points. The six-month survival rates were 4% for patients with 20–25 points, 11% for those with 26–30 points, 48% for those with 31–35 points, 87% for those with 36–40 points and 99% for those with 41–45 points (p<0.0001) (see *Table 2*). Subgroup analyses were performed for each group comparing short-course RT with longer-course RT. Patients with 36 points had significantly longer survival with long-course than with short-course RT. Those with scores <36 points had similar survival with either short- or longer-course RT. Thus, patients with 36 points should receive longer-course RT and those with <36 points should receive short-course RT. Patients with >41 points may be considered candidates for lower doses per fraction or for high-precision RT techniques such as intensity-modulated RT (IMRT), radiosurgery, fractionated stereotactic body RT (FSBRT) or proton beams in order to maximise local control and reduce the risk of potential radiation-related late morbidity.[13–15]

In a retrospective series of 18 patients receiving re-irradiation with IMRT and/or FSBRT, improvement of neurological deficits was observed in 42%.[14] In another retrospective series, neurological deficits improved in 84% (27/32) of the patients after Cyberknife® radiosurgery as primary treatment.[15]

Re-irradiation of a Local Recurrence of Metastatic Spinal Cord Compression

A second episode of MSCC occurs in <14% of the previously irradiated patients.[9,16,17] Decompressive surgery is a very reasonable option. However, in many patients who develop a recurrence in the previously irradiated area of the spinal cord (in-field recurrence), surgery may not be possible or indicated. Re-irradiation may be the only reasonable treatment option. However, many physicians are concerned about delivering a second course of RT to the same spinal area. The relatively high cumulative EQD2 (EQD2 of the primary RT plus EQD2 of the re-irradiation) may result in an increased risk of radiation myelopathy that may be associated with severe neurological deficits.[11] According to the available literature, re-irradiation appears safe if the cumulative EQD2 does not exceed $60Gy_2$, if the interval between primary RT and re-irradiation is at least six months, and if the EQD2 of each course of RT does not exceed $49Gy_2$.[18–20] Thus, a second course of RT after primary short-course RT can be considered safe in most cases. Re-irradiation with 1x8Gy, 5x3Gy or 5x4Gy has been suggested to be effective. Improvement of motor function occurred in 40% of the patients, and further progression of motor dysfunction could be prevented in another 45% of the patients.[18] However, if an in-field recurrence develops after primary long-course RT with a higher EQD2, a second course of RT to the same area of the spinal cord may not be considered safe in many cases. These patients should be considered for treatment with high-precision RT techniques.[13–15]

Summary

Most MSCC patients are not candidates for decompressive surgery and receive RT alone. Those patients with a comparably good survival prognosis live long enough to be at greater risk of developing recurrence of MSCC. As long-course RT results in better local control rates than short-course RT, patients with an expected survival of more than six months should be treated with long-course RT. The survival prognosis of MSCC patients can be estimated using a newly developed scoring system.

If a recurrence in the previously irradiated area of the spinal cord occurs, decompressive surgery should be seriously considered. However, in many cases surgery is neither possible nor indicated and re-irradiation is the only reasonable option. Re-irradiation following primary short-course RT with lower total doses is effective and safe. A second course of irradiation following primary long-course RT with higher doses cannot always considered safe. In such a situation, high-precision RT techniques should be seriously considered. ■

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