Supportive Oncology

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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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.¹ These results were...
confirmed in a subsequent retrospective study of 1,852 MSCC patients that focused on local control of MSCC. 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. 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. 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 subsequent retrospective study of 1,852 patients. 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. 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 subsequent retrospective study of 1,852 patients.

<table>
<thead>
<tr>
<th>Type of Primary Tumour</th>
<th>Score</th>
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<tbody>
<tr>
<td>Breast cancer</td>
<td>8</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>7</td>
</tr>
<tr>
<td>Myeloma/lymphoma</td>
<td>9</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3</td>
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<tr>
<td>Other tumours</td>
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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.17 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 interval, >15 versus ≤15 months). The score for each prognostic factor was determined by dividing the six-month survival rate (given in %) by 10 (see ambulatory). The score range was 0 to 45 points. 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 5% for patients with 20–25 points, 11% for those with 26–30 points, 33% for those with 31–35 points, 71% for those with 36–40 points and 91% for those with 41–45 points (p=0.0001) (see Table 1). 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 compared to short-course RT. Those with scores <36 points had similar survival with either short- or long-course RT. Thus, patients with 36 points should receive long-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.17–19

In a retrospective series of 18 patients receiving re-irradiation with IMRT and/or FSBRT, improvement of neurological deficits was observed in 94%.20 In another retrospective series, neurological deficits improved in 84% (27/32) of the patients after Cyberknife® radiosurgery as primary treatment.21

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

A second episode of MSCC occurs in <14% of the previously irradiated patients.19,21 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 neurologic deficits.21 According to the available literature, re-irradiation appears safe if the cumulative EQD2 does not exceed 60Gy23 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 49Gy24,25 Thus, a second course of RT after primary short-course RT can be considered safe in most cases. Re-irradiation with 1x8Gy, 3x3Gy or 3x4Gy 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.26 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.21,26

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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