Spinal cord compression

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Background

Spinal cord compression (SCC) in cancer patients is predominately due to bone metastases within the vertebral column. Lymphoma, leukaemia, or myeloma may arise in the vertebrae and thus may not be metastatic when causing SCC. However, these patients account for only a minority of patients with SCC [1]. Therefore, for the purposes of this manuscript, metastatic spinal cord compression (MSCC) is used synonymously with SCC.

MSCC was first described by Spiller in 1925 [2] and can be defined as 'comprehensive indentation, displacement, or encasement of the thecal sac that surrounds spinal cord or cauda equina by spinal epidural metastases'. In 50–70% of all cancer patients, metastatic disease is evident at the time of death, and most patients have bone metastases [3]. The spinal column is the most frequently affected site, involved in up to 40% of cancer patients [4,5]. Patients without neurological deficits but with epidural tumour touching the spinal cord have an 'impending' MSCC. MSCC occurs with a fairly even distribution throughout the spine. The cervical spine is involved in <10% of patients, the thoracic spine in 60–80%, and the lumbar spine in 15–30%. More than one spinal segment is involved in half of patients [6–9].

Despite improved treatment approaches regarding surgical intervention and modern radiation techniques, the treatment of MSCC remains challenging and the prognosis generally poor.

Epidemiology

Overall, MSCC occurs in 5–10% of all cancer patients during the course of their disease [10,11]. The incidence of MSCC depends on the type of primary tumour and ranges between 0.2% (pancreatic cancer) and 7.9% (myeloma). The incidence decreases with age, and ranges between 4.4% in patients aged 40–50 years and 0.5% in patients aged 70–80 years [10]. The most common tumours are breast cancer, prostate cancer, and lung cancer, which each account for about 20%, followed by myeloma, which accounts for a little more than 10% [12].

Pathophysiology

The compression of the spinal cord is most frequently caused by posterior extension of a vertebral body mass or by anterior extension of a mass arising from the dorsal elements of the spine [1]. Direct arterial embolisation of tumour cells, in particular of clonogenic cells with affinity to spinal marrow, has been suggested the most relevant mechanism of metastatic spread to the spine [13]. A vertebral body mass can impinge on the thecal sac, spinal cord, and epidural venous plexus. In addition, pathological vertebral body fractures may also occur with dislocation of bony fragments into the epidural space. Rarely, MSCC may be caused by growth of a mass that invades through the vertebral foramen from the paraspinal region or by metastases of the epidural space.

Animal studies have demonstrated that MSCC is associated with white-matter oedema and axonal swelling which may result in necrosis and gliosis of the white matter [14–16]. Disrupted blood flow was observed for both venous and arterial circulation. The white-matter changes vary with the speed at which MSCC develops. A slower development leads to venous congestion and vasogenic oedema of the white matter resulting in mainly reversible neurological deficits. A faster development may lead to a disruption of the arterial blood flow followed by ischaemia, spinal cord infarction, and irreversible neurological deficits. The impact of the time of developing MSCC was demonstrated in dogs more than 50 years ago [17, 18]. Tarlov and colleagues suggested that the rapid development of MSCC required decompression within 8–10 h to reverse neurological dysfunction. After slower development of MSCC, decompression could reverse the neurological dysfunction when performed within 7 days. A prospective study demonstrated that significantly more patients irradiated for MSCC improved motor function after a slower development

of motor deficits before radiotherapy (>14 days) compared to patients who had a faster development of motor dysfunction (86% versus 19.5%, $P < 0.001$) [19].

Diagnostic imaging

The diagnostic procedures for detection of MSCC include plain radiographs, myelography, computed tomography (CT), magnetic resonance imaging (MRI), bone scan, and positron emission tomography (PET). Spinal MRI is the diagnostic test of choice [20–22]. The rates of sensitivity, specificity, and diagnostic accuracy regarding the detection of MSCC are 93%, 97%, and 95%, respectively [20]. The rates of sensitivity, specificity, and diagnostic accuracy regarding the differentiation between benign spinal cord compression such as spondylodiscitis and MSCC are 98%, 100%, and 98%, respectively [20]. Spondylodiscitis is not very uncommon in patients initially presented as patients with MSCC. In a series of 170 patients referred for irradiation of MSCC with only plain radiographs and spinal CT, a spinal MRI led to a change of the diagnosis from MSCC to spondylodiscitis in 6% of patients [22].

Thus, a spinal MRI should be performed, when available, prior to treatment for MSCC. Additionally, MRI is an excellent method to determine whether multiple sites of MSCC are present.

Clinical symptoms

The most common symptoms are vertebral pain (70–96%), motor deficits (61–91%), sensory deficits (46–90%), and autonomic dysfunction (40–57%) [11, 23–25]. Pain is the initial symptom in most patients. If pain is the only symptom, the situation is more appropriately described as 'impending' MSCC. If motor deficits occur, pain has usually been present for several weeks or even months. The vertebral pain becomes more intense with time, and it may change from localised to radicular.

Motor deficits are considered the hallmark finding of MSCC. The major goal of treatment is to regain and maintain the ambulatory function. In the 1990s, more than 50% of the patients were not ambulatory at presentation [26,27]. Because of greater awareness of physicians of MSCC, the proportion of patients who are ambulatory at presentation was much higher during the last decade [12]. Sensory deficits are little less frequent than motor deficits [11,28]. However, they are much less noticeable to patients than motor weakness. The sensory levels are generally one to five segments below the level of MSCC. The level of MSCC may be localised clinically based on a careful neurological history and physical examination. Percussion tenderness at the site of MSCC is quite common and helps clinically localise the involved site. Autonomic dysfunction (dysfunction of bladder and bowel control) occurs relatively late compared to the other symptoms [1]. However, its presence is associated with a poor functional outcome following treatment. Patients with autonomic dysfunction should be considered for immediate surgical intervention if possible because immediate decompression may be needed to salvage any vestige of neurological function.

Grading of motor function

Several grading systems of motor function are available. Motor function may be evaluated with a 5-point scale [29]: 0 normal strength; 1 ambulatory without aid, 2 ambulatory with aid, 3 not ambulatory, 4 paraplegia. Alternatively, the American Spinal Injury Association (ASIA) and the International Medical Society of Paraplegia (IMSOP) [30] use an 8-point scale: 0 complete paraplegia, 1 palpable or visible muscle contractions, 2 active movement of the leg without gravity, 3 active movement of the leg against gravity, 4 active movement of the leg against mild resistance, 5 active movement of the leg against moderate resistance, 6 active movement of the leg against severe resistance, 7 normal strength.

Treatment

Radiotherapy (RT) is the most common treatment for MSCC, and is administered either alone or following surgical intervention. MSCC patients should be evaluated by both the neurosurgeon and the radiation oncologist to decide whether the patient is a better candidate for decompressive surgery followed by RT or for RT alone. The indications for surgery are usually limited to patients with a favourable performance status, expected survival of $\geqslant$3 months, involvement of only one spinal area, and those without very radiosensitive tumours (such as lymphoma, germ cell tumours, and myeloma) [31]. Many patients are not surgical candidates and, therefore, RT alone remains the primary treatment for most cases of MSCC.

Radiotherapy alone

The most appropriate RT regimen for the individual MSCC patient is still controversial. Most patients with MSCC have a markedly reduced life expectancy [1]. For these patients, a RT regimen with a short

overall treatment time (short-course RT, treatment time: 1–5 days) is preferable to standard RT with 10×3 Gy (treatment time: 2 weeks), as these often-debilitated patients would spend less of their limited lifespan receiving treatment. However, short-course RT can only be recommended if it provides similar functional outcome as more protracted regimens such as 10×3 Gy. The first radiation fraction should be delivered as soon as possible, but no later than 24 h from the detection of MSCC. The immediate use of high doses of corticosteroids is also critical.

Prognostic factors for functional outcome

In a series of 1,304 MSCC patients, motor function following RT was significantly associated with age, performance status, type of primary tumour, number of involved vertebrae, ambulatory status before RT, interval from first diagnosis of the tumour to onset of MSCC, and the time of developing motor deficits before RT [32]. In the multivariate analysis, improved post-treatment motor function was associated with younger age (⩽63 versus ⩾64 years, $P = 0.026$), better performance status (Eastern Cooperative Oncology Group performance status 1–2 versus 3–4, $P < 0.001$), involvement of only 1–2 vertebrae (versus ⩾3 vertebrae, $P = 0.001$), ambulatory status (versus non-ambulatory, $P < 0.001$), an interval from tumour diagnosis to MSCC >24 months (versus ⩽24 months, $P < 0.001$), and a slower development of motor deficits before RT (>14 days versus 8–14 days and 1–7 days, $P < 0.001$). In contrast, gender and the radiation schedules (1×8 Gy versus 5×4 Gy versus 10×3 Gy versus 15×2.5 Gy versus 20×2 Gy) had no significant impact on functional outcome. The prognostic value of primary tumour type, pre-RT ambulatory status, and time of developing motor deficits has been previously described [19,25,26,33]. Because pre-RT ambulatory (functional) status is an important prognostic factor and because motor function may rapidly deteriorate, RT should be started as soon as possible.

Radiation techniques

Irradiation is performed most often with 6–10 MV linear accelerators or cobalt-60 units. The radiation dose is delivered either through a single posterior field or through parallel opposed fields depending on the depth of the spinal cord. If the distance between the patient's skin and the spinal cord exceeds 5.5 cm, the maximum dose may exceed 115% of the dose prescribed at depth (Fig. 1). This is not optimal because it may result in fibrosis of the subcutaneous tissue. The dose-distribution is generally more favourable for parallel-opposed fields than for a single posterior field. Thus, parallel-opposed fields are preferable. If the distance between the patient's skin and the spinal cord exceeds 11.5 cm, the energy of both parallel-opposed fields should be 15–18 MV (Fig. 1).

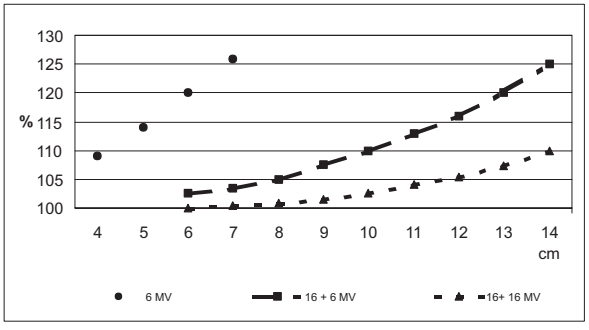

Fig. 1. Fraction of maximum dose over prescribed dose for different photon beam techniques and various prescription depths. Examples shown below are single posterior field with 6 MV photons, opposed fields with 6 MV (posterior field) and 16 MV (anterior fields) photons, and opposed fields with 16 MV photons (posterior and anterior fields).

The RT dose is usually prescribed to the mid-plane when using parallel opposed fields or the posterior part of the vertebral body when using a single posterior field. Treatment volumes usually encompass 1–2 normal vertebrae above and below the metastatic lesions.

Radiation schedules

Many different radiation schedules are used worldwide. These schedules include single-fraction programs given in 1 day such as 1×8 Gy and 1×10 Gy, multi-fraction short-course programs given in about 1 week such as 4×4 Gy, 5×4 Gy, 5×5 Gy, and 6×4 Gy, long-course programs given in 2–4 weeks such as 10×3 Gy, 15×2.5 Gy, and 20×2 Gy, and split-course regimens.

Only two prospective studies compared different RT dose-fractionation schedules with regard to the resulting functional outcome. The first and non-randomised prospective study compared two long-course programs (10×3 Gy in 2 weeks versus 20×2 Gy in 4 weeks) but found no significant difference regarding improvement of motor function and ambulatory status [34]. A randomised trial that compared 2×8 Gy (treatment time: 8 days) and a split-course regimen (3×5 Gy followed by 4-day-rest and 5×3 Gy) also found both schedules to be similarly effective regarding functional outcome [35].

Regarding the patient's transport to the radiotherapy department and the positioning on the treatment couch,

every RT session may cause discomfort to these often-debilitated patients. A schedule with a short overall treatment time (short-course RT) appears preferable, especially for patients with a markedly reduced life expectancy, if it provides similar functional outcome as long-course programs.

Long-course RT with 10×3 Gy has been demonstrated to result in better re-calcification of the osteolytic bone/vertebra compared to short-course RT with 1×8 Gy [36]. In a randomised trial that included patients with painful bone metastases (not patients with MSCC), a higher rate of pathological fractures was observed after 1×8 Gy than after 6×4 Gy [37]. However, relevant re-calcification can only be expected several months following RT and is therefore not important for the patients with a markedly reduced life expectancy. The majority of patients with MSCC will not benefit from long-course RT in terms of better re-calcification, because median survival of MSCC patients usually ranging between 2.3 and 6 months is too short [26,33,35,38–42].

Functional outcome

Pain relief can be achieved in 60–80% of the patients by RT alone [37,43–45], and improvement of sphincter dysfunction can be expected in >40% of patients [26]. Following pain, motor dysfunction is the second most common symptom from MSCC.

The effect of RT depends on the endpoint investigated. Klimo and colleagues defined success as the ability to walk after treatment (gait function maintained, improved, or regained). Success rates after RT alone ranged between 34% and 73% (mean 47%, median 47%) and were comparable to those after posterior decompressive laminectomy followed by RT (43–57%, mean 47%, median 46%), and higher than after decompressive laminectomy alone (14–58%, mean 30%, median 30%) [46]. In more recent series, the ambulatory rates after RT alone ranged between 63% and 74% [32,35,42].

Only a few reports have compared different radiation schedules for MSCC [32,34,35,42,47–49]. The first studies of our group did not reveal a difference in functional outcome between 10×3 Gy, 15×2.5 Gy, and 40 Gy, nor between 1×8 Gy and 10×3 Gy [34, 48,49]. In a more recently published retrospective series of 1,304 patients comparing five RT schedules, improvement of motor function occurred in 28% of patients, no further progression of motor dysfunction in another 57% [32]. The radiation schedule had no significant impact on post-treatment motor function. Improvement occurred in 26% after 1×8 Gy, 28% after 5×4 Gy, 27% after 10×3 Gy, 31% after 15×2.5 Gy, and 28% after 20×2 Gy. No further progression was noted in 58%, 57%, 58%, 52%, and 56%, respectively. The post-treatment ambulatory rates were 69%, 68%, 63%, 66%, and 74%, respectively ($P = 0.58$). Hoskin and colleagues presented a retrospective series of 102 patients treated with various short-course and long-course regimens [42]. No significant difference was observed between the schedules regarding functional outcome. Maranzano and colleagues presented a retrospective analysis and a randomised study that both compared short-course RT (2×8 Gy) and a split-course regimen (3×5 Gy, 4 days rest, 5×3 Gy) [35,47]. Both schedules were associated with similar functional outcome. The available studies suggested that short-course RT and long-course RT result in similar functional results.

Tumours have a great variety of radiosensitivity [1]. Thus, it appears reasonable to consider each tumour entity separately. The comparisons between long-course and short-course RT regarding improvement of motor function, halting further progression of motor dysfunction, and deterioration of motor function, related to seven common primary tumours in MSCC patients are summarised in Table 1 [50–56]. For six tumour types, short-course RT provided similar functional outcome as long-course RT such as 10×3 Gy. Therefore, short-course RT can be recommended for a large proportion of MSCC patients especially those with a poor survival prognosis. However, in myeloma patients, there was significantly better motor function at 6 months ($P = 0.043$) and 12 months ($P = 0.003$) following long-course RT [53]. Therefore, short-course RT was not recommended for myeloma patients.

Local control of MSCC

In the largest series of MSCC patients ($n = 1{,}852$), a recurrence of MSCC in the irradiated site was observed in 144 patients (8%) after median 7 months (range 2–62 months) [12]. The 1-year and 2-year local control rates were 89% and 83%, respectively. In a multivariate analysis, two significant prognostic factors for local control of MSCC were identified. The absence of visceral metastases and the administration of long-course RT (10×3 Gy, 15×2.5 Gy, or 20×2 Gy) instead of short-course RT (1×8 Gy or 5×4 Gy) were associated with better local control. The 1 and 2 year local control rates were 93% and 90% after long-course RT and 82% and 74% after short-course RT ($P < 0.001$). The comparisons of long-course RT and short-course RT related to the six most common primary tumours revealed that long-course RT was associated with significantly better 1-year local control of MSCC than short-course RT in breast cancer

Table 1
The comparison of short-course RT and long-course RT with respect to post-RT functional outcome, related to seven different primary tumour types

Type of Primary Tumour	Improvement of motor deficits		No change of motor deficits		Deterioration of motor deficits		*P*
	N	(%)	N	(%)	N	(%)	
Breast Cancer (N = 335) [50]							
Short-course RT	44	(34%)	74	(57%)	12	(9%)	
Long-course RT	61	(30%)	118	(58%)	26	(12%)	0.81
Prostate Cancer (N = 281) [51]							
Short-course RT	52	(34%)	78	(50%)	25	(16%)	
Long-course RT	40	(32%)	72	(57%)	14	(11%)	0.83
NSC-Lung Cancer (N = 252) [52]							
Short-course RT	16	(15%)	58	(55%)	31	(30%)	
Long-course RT	19	(13%)	78	(53%)	50	(34%)	0.87
Myeloma (N = 172) [53]							
Short-course RT	34	(39%)	35	(58%)	2	(3%)	
Long-course RT	66	(59%)	43	(39%)	2	(2%)	0.10
Unknown Primary (N = 143) [54]							
Short-course RT	5	(7%)	49	(72%)	14	(21%)	
Long-course RT	10	(13%)	32	(43%)	33	(44%)	0.74
Renal cell carcinoma (N = 87) [55]							
Short-course RT	10	(27%)	24	(65%)	3	(8%)	
Long-course RT	15	(30%)	28	(56%)	7	(14%)	0.91
Colorectal cancer (N = 81) [56]							
Short-course RT	5	(16%)	21	(68%)	5	(16%)	
Long-course RT	6	(12%)	34	(68%)	10	(20%)	0.50

patients (96% versus 84%, $P = 0.008$) and in prostate cancer patients (94% versus 77%, $P = 0.001$), but not in patients with NSCLC, renal cell carcinoma, nor an unknown primary [50–55]. A trend was observed for myeloma patients ($P = 0.08$) [53]. Thus, long-course RT appears the better option for MSCC patients with a comparably favourable survival prognosis, in particular for breast cancer, prostate cancer, and myeloma patients, as these patients may live long enough to develop a recurrence of MSCC. Patients with a comparably poor expected survival may be treated with short-course RT, which is more convenient for patients. A score that allows predict the survival prognosis of patients with MSCC would be helpful to select the appropriate RT regimen for the individual patient (see the *Survival* section below).

Spinal re-irradiation

A second episode of MSCC occurs in 7–14% of the patients [12,39,57]. In many patients who develop a recurrence of MSCC in the previously irradiated spinal region (in-field recurrence), surgery may not be possible nor indicated. Re-irradiation (re-RT) may be the only available treatment option. Many radiation oncologists are concerned about delivering a second series of RT to the same spinal area due to the higher biologically effective dose (BED), which is associated with an increased risk of radiation myelopathy. The BED can be calculated with the equation $BED = D \times [1 + (d/\alpha/\beta)]$, 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 [58]. The α/β-ratio suggested for radiation myelopathy is 2 Gy. Re-RT appears safe if the cumulative BED (primary RT plus re-RT) is 100 Gy_2 or less [59]. If two series of short-course RT are delivered, radiation myelopathy appears unlikely. The cumulative BED is 80 Gy_2 for 1×8 Gy

plus 1×8 Gy, 97.5 Gy_2 for 5×4 Gy plus 5×3 Gy, and 100 Gy_2 for 5×4 Gy plus 1×8 Gy, respectively. If long-course RT with a higher BED (BED = 75 Gy_2 for 10×3 and BED = 80 Gy_2 for 20×2 Gy) was the primary treatment, the risk of radiation myelopathy appears small for a cumulative BED of 135.5 Gy_2 or less, if the interval between primary RT and re-RT is ⩾6 months and the BED of each RT course is ⩽98 Gy_2 [60].

Re-RT with 1×8 Gy, 5×3 Gy, or 5×4 Gy is effective. Improvement of motor function occurred in 40% of the re-irradiated patients with no further progression of motor dysfunction in another 45% [59]. After primary long-course RT, new radiation techniques such as IMRT, stereotactic radiosurgery, tomotherapy, and proton therapy can be used to reduce the cumulative BED delivered to the spinal cord, in particular if the cumulative BED exceeds 135.5 Gy_2 [61,62].

Survival

In the above mentioned series of 1,852 patients, the 1-year and 2-year survival rates were 43% and 32%, respectively [12]. In the multivariate analysis, improved survival was associated with favourable primary tumour type (myeloma/lymphoma, breast cancer, prostate cancer) ($P < 0.001$), absence of other bone metastases ($P = 0.018$) and visceral metastases ($P < 0.001$) at the time of RT, a longer interval from tumour diagnosis to MSCC ($P < 0.001$), pre-RT ambulatory status ($P < 0.001$), and slower development of motor deficits before RT (>14 days) ($P < 0.001$). The impact of visceral metastases or other bone metastases and of the pre-RT ambulatory status on survival has been previously described [1,25,26,40,42,63].

Based on the multivariate analysis described above [12], a scoring system was developed to predict the survival of MSCC patients in order to select the appropriate RT regimen (short-course RT or long-course RT). This scoring system included the six significant prognostic factors. The score for each prognostic factor was determined by dividing the 6-month survival rate (given in %) by 10. The total score represented the sum of the six scores obtained for each prognostic factor. The total scores ranged between 20 and 45 points. Five groups were defined according to the total scores: 20–25, 26–30, 31–35, 36–40, and 41–45 points. The 6-month survival rates were 4% for patients with a score of 20–25 points,11% for those with a score of 26–30 points, 48% for those with a score of 31–35 points, 87% for those with a score of 36–40 points, and 99% for those with a score of 41–45 points ($P < 0.001$). The survival rates at 12 months were 0%, 6%, 23%, 70%, and 89%, respectively. Subgroup analyses were performed for each of the five groups comparing short-course RT with 1×8 Gy or 5×4 Gy to long-course RT with 10×3 Gy, 15×2.5 Gy, or 20×2 Gy with respect to survival. Patients with scores of ⩾36 had significantly longer survival with long-course RT compared to short-course RT, and those with scores of <36 points had similar survival with either short or long course RT. Thus, patients with scores of ⩾36 points should receive long-course RT, whereas those with scores of <36 points may be treated with short-course RT [64].

Decompressive surgery followed by radiotherapy

The major advantages of spinal surgery when compared to irradiation are immediate decompression of the spinal cord and direct mechanic stabilisation of the spine. The indications for spinal surgery include intraspinal bony fragment, spinal instability, impending or present sphincter dysfunction, no response to RT, and a recurrence of MSCC after long-course RT with a high total dose (and BED) [1,12].

Laminectomy is indicated in case of MSCC due to anterior extension of a mass arising from the dorsal elements, but not in the more common situation of compression due to posterior extension of a vertebral body mass [65,66]. In the latter situation, laminae and spinosus processes represent the last pillar responsible for the stability of the involved vertebral segment. Thus, laminectomy may lead to greater instability. Surgery should be performed as anterior decompression. Anterior decompression includes a resection of the entire vertebral body and the tumour mass followed by replacement by cement and fixation of the involved vertebral segment [6,67].

The benefit of surgical intervention plus RT when compared to RT alone is still controversial. Klimo and colleagues defined success of treatment as the ability to walk after treatment (gait function was maintained, improved, or regained) [46]. In their review article, mean success rates were 47% after RT alone (11 reports, $n = 841$), 47% after surgery followed by RT (nine reports, $n = 866$), and 30% after surgery alone (13 reports, $n = 1003$) in patients treated for MSCC between 1957 and 1990. However, surgery was performed as posterior decompressive laminectomy and not as anterior decompression plus stabilisation. A more recent meta-analysis by the same group also included patients treated with an anterior approach followed by reconstruction and intermediate stabilisation considered the ‘modern’ surgical technique for MSCC. In this meta-analysis, 24 reports with 999 patients who received surgical intervention (mainly in conjunction with RT) were

compared to 543 patients from four reports who received RT alone [68]. The post-treatment ambulatory rates were 85% for the operated patients and 64% having RT alone. In the surgical group, 228 of 384 (59%) non-ambulatory patients regained the ability to walk versus 79 of 265 (30%) patients in the RT alone group. However, the results may have been confounded due to selection biases. Patients in the surgery group had more favourable prognostic factors known to affect functional outcome such as higher proportion of ambulatory patients, better performance status, younger age, and involvement of fewer vertebrae. The distribution of other relevant prognostic factors such as time of developing motor deficits and the interval from tumour diagnosis to MSCC was not even stated. Thus, the results of the meta-analysis by Klimo and colleagues suggesting an advantage for surgical intervention must be regarded with caution [68].

A randomised study reported by Patchell and colleagues used appropriate surgical techniques and found a benefit for surgery plus RT versus RT alone [31]. The study was stopped after an interim analysis of 101 patients. Significantly more patients in the surgery plus RT group were able to walk after treatment (84% versus 57%, $P = 0.001$). Patients who received surgery maintained the ability to walk longer (122 days versus 13 days, $P = 0.003$). 10/16 and 3/16 patients regained the walking ability after treatment ($P = 0.01$). The use of both opioid analgesics and steroids was significantly less in the surgery plus RT group. Additionally, the surgical patients survived longer (126 days versus 100 days, $P = 0.033$). However, concerns were addressed regarding that study suggesting that the results may have been confounded due to methodological problems [69,70]. Because it took 10 years to accrue the comparably small number of 101 patients, it was questioned if really all eligible patients have been included. One institution included about 70% of the patients. This means that the average inclusion rate of each other institution was only about one patient every 2 years. It was also criticised that the functional results after RT alone appeared very poor when compared to the literature. Regarding the small number of patients ($n = 101$), in particular of those not ambulatory before treatment ($n = 32$), the study appeared statistically underpowered. Only patients with an expected survival of $\geqslant$3 months, a Karnofsky performance score of $\geqslant$70, and involvement of only a single spinal area were considered eligible for the Patchell study. Patients with very radiosensitive tumours such as germ cell tumours, myeloma, or lymphomas were excluded. Furthermore, the patients could not have brain metastases, complete paraplegia for >48 h, cauda equina compression, or previous RT to the area of MSCC. Thus, the Patchell criteria regarding suitability for surgery are only applicable to a minority of patients with MSCC. Surgery related complications occurred in 12% of patients.

In addition to the Patchell trial, two other studies compared RT alone versus surgery plus RT. A very small randomised study ($n = 23$) did not detect a difference regarding the post-treatment ambulatory rates (38% versus 38%) [71]. A retrospective study of 345 patients compared RT alone ($n = 149$), surgery alone ($n = 105$), and surgery plus RT ($n = 91$) [72]. The post-treatment ambulatory rates were 38%, 34%, and 53%, respectively ($P = 0.001$). Patients treated with laminectomy followed by radiotherapy seemed to respond better than patients treated with radiotherapy or laminectomy alone, but when the patients' pre-treatment motor function was taken into account no significant difference was found between the three treatments. Regarding the available studies that compared RT alone and RT with preceding surgical intervention, decompressive surgery appears beneficial for select patients with MSCC. However, there is an urgent need for large prospective studies with an adequate statistical power evaluating the role of surgical intervention for the majority of patients with MSCC.

Corticosteroids

Corticosteroids support cellular energy metabolism. Additionally they reduce vasogenic oedema, lipid peroxidation, lipid hydrolysis, ischaemia, and intracellular calcium accumulation [73]. The most commonly administered corticosteroid in MSCC treatment is dexamethasone. There is a consensus regarding the efficacy of corticosteroids in MSCC treatment, in particular regarding improvement or maintaining of the functional status. However, the optimal corticosteroid schedule is controversial [74]. Loading doses ranging from 10 mg to 100 mg are followed by single doses of 4 mg to 24 mg given up to four times per day.

There was one randomised trial comparing high-dose dexamethasone (96 mg daily) to no corticosteroids during RT. Ambulation was maintained after RT in 81% of the patients who had received high-dose dexamethasone in comparison to 63% of those without steroids [75]. Another prospective study compared initial high-dose (100 mg) followed by low-dose (16 mg daily) dexamethasone versus initial low-dose (10 mg) followed by low-dose (16 mg daily) dexamethasone. Improvement of motor function occurred in 25% and

8% of patients, respectively ($P = 0.22$). In a historical case-control series comparing high-dose (96 mg i.v. loading dose, decreasing doses to zero in 14 days) to moderate-dose (16 mg daily, reduced to zero in 14 days) dexamethasone, a significantly higher rate of serious side effects such as ulcers, bleeding, and perforation occurred after the high-dose regimen (14% versus 0%) [76]. Regarding both effect on motor function and acute toxicity, beginning with dexamethasone at an intermediate dose level (24–40 mg daily) appears reasonable, tapering down over several weeks.

Bisphosphonates

In cancer patients with bone metastases, several prospective studies have demonstrated a significant effect for bisphosphonates such as ibandronate, pamidronate, and zoledronate regarding the prevention from skeletal related events such as pathologic fractures and MSCC [77–79]. Thus, patients with MSCC who have an expected survival of at least 6 months should be considered for bisphosphonates.

Oral bisphosphonates should not be used in patients with serious oesophageal disease or patients at bed rest who can't stay upright for an hour. Bisphosphonates should be used with caution in patients with abnormal white blood cells, with high PTH, and in children (no long-term safety data). Potential side effects include hypocalcaemia, increased PTH, skin rash, and jaw osteonecrosis. Oesophageal ulceration has been reported after oral administration. Fever, transient leucopenia, bone pain, eye inflammation, and nephrotic syndrome have been reported after intravenous administration.

Chemotherapy

Chemotherapy has a very limited role in the treatment of MSCC. It may be applied in addition to radiotherapy in case of chemo-sensitive tumours such as haematological or germ cell malignancies [79–82]. Aviles and colleagues presented 48 lymphoma patients with SCC who received either RT alone, chemotherapy alone, or both [80]. Although neurological recovery was similar in the three groups, the 10-year local control rates were non-significantly different (50%, 46%, and 76%, respectively). Wallington and colleagues reported on 48 lymphoma and myeloma patients who received RT alone or RT plus chemotherapy. No further progression of symptoms was observed in 58% and 75% of patients, respectively [81]. Although the results did not achieve statistical significance because of the small cohort size, there may be a rationale based on these outcomes.

Oligometastatic disease

Oligometastatic disease can be defined as involvement of $\leqslant 3$ vertebrae and lack of other bone or visceral metastases. In a series of 521 MSCC patients with oligometastatic disease treated with RT alone, motor function improved in 40%, remained stable in 54%, and deteriorated in 7% [83]. After RT, 54% of the non-ambulatory patients became ambulatory, and 94% of the initially ambulatory patients remained ambulatory. Local control at 1 and 2 years was 92% and 88%, respectively, and overall survival at 1 and 2 years was 71% and 58%, respectively. The most significant prognostic factors associated with a better treatment outcome were a favourable primary tumour (myeloma/lymphoma, breast cancer) and a slow development of motor deficits before RT (>14 days). The patients with such a slow development of motor deficits were further analysed. In this subgroup, the best results were observed for myeloma/lymphoma and breast cancer patients. None of these patients had a progression of motor deficits after RT (99–100% of patients were ambulatory). The 1-year-local control was 98–100%, and 1-year-survival was 89–94%.

Regarding the comparably favourable outcome of oligometastatic MSCC patients treated with RT alone, it is possible that surgical intervention may not be needed, in particular for those patients with favourable tumours and a slow development of motor deficits before RT. However, these results were obtained from a retrospective analysis and do not carry the same level of evidence as phase III-trials. Despite the large number of patients, retrospective analyses are always associated with a risk of a hidden bias. Randomised trials with large patient cohorts are needed to further define subgroups of patients who may not require surgical intervention.

Summary

Radiotherapy alone is the most frequently applied treatment in patients with MSCC. Decompressive surgery followed by RT is beneficial in terms of functional outcome and survival in selected patients (expected survival of $\geqslant 3$ months, performance status adequate for surgical intervention, involvement of only one spinal segment. There is no proven role of surgical intervention in radiosensitive tumours such as germ cell or haematological malignancies. MSCC patients should immediately receive dexamethasone at an intermediate dose level in addition to RT, if there

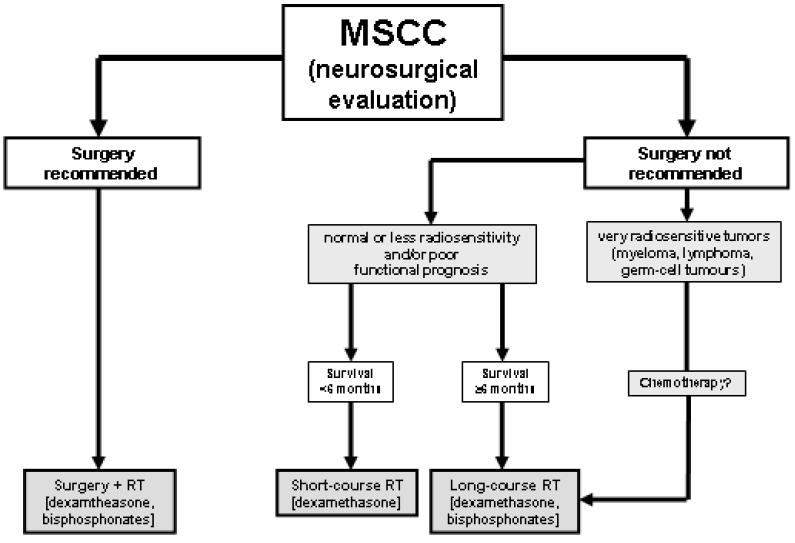

Fig. 2. Algorithm for the treatment of MSCC. Patients with oligo-metastatic disease and a favourable functional prognosis (see the *Oligometastatic disease* section) may possibly be treated with RT alone.

are no contraindications. Bisphosphonates have been demonstrated to reduce the rate of skeletal related events and should be considered for MSCC patients with a comparably good survival prognosis and no contraindications. Chemotherapy has an unclear role for MSCC treatment and may be considered for selected patients haematological or germ cell malignancies (Fig. 2).

If RT alone is applied, it is important to select the appropriate regimen, short-course RT with lower total doses or long-course RT with higher total doses. Long-course RT is associated with significantly better local control than short course RT in breast cancer and prostate cancer patients. Thus, patients with an expected survival of $\geqslant$6 months following RT, in particular breast cancer and prostate cancer patients, should receive long-course RT. These patients may live long enough to develop a recurrence of MSCC. Survival can be predicted by using a scoring system (see the *Survival* section above). Myeloma patients should be treated with long-course RT, as in these patients long-course RT is associated with better functional outcome than short-course RT. Patients with primary tumours other than myeloma and an expected survival of <6 months should be treated with short-course (Fig. 2).

A recurrence of MSCC in the previously irradiated spinal region after short-course RT may be treated with another short-course of RT, which appears both safe and effective. If the primary treatment included long-course RT with higher total doses and higher BED, surgical intervention should be considered. Alternatively, one of the new radiation techniques (IMRT, stereotactic radiosurgery, fractionated stereotactic radiotherapy, tomotherapy, or proton beam therapy) may be used to reduce the cumulative BED received by the spinal cord.

Despite several recent reports contributing to the improvement of MSCC treatment, larger prospective trials are required to refine the therapy of patients with MSCC in the various situations that occur.

Conflict of interest statement

None declared.

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