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Review Article

Malignant cord compression: A critical appraisal of prognostic factors predicting functional outcome after surgical treatment

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Abstract

Objectives: Advanced tumor disease and metastatic spinal cord compression (MSCC) are two entities with a high impact on patients' quality of life. However, prognostic factors on the outcome after primary decompressive surgery are less well-defined and not yet standardized. The aim of this review was to identify prognostic variables that predict functional or ambulatory outcomes in surgically treated patients with symptomatic MSCC. **Materials and Methods:** We conducted MEDLINE database searches using relevant keywords in order to identify abstracts referring to prognostic factors on ambulatory outcomes in surgically treated MSCC patients. Details of all selected articles were assembled and the rates of ambulation were stratified. **Results:** Evidence from five retrospective comparative trials and one observational prospective study summarizes different prognostic factors with a positive or negative influence on postoperative ambulatory status. Ambulatory patients maintaining ambulation status after decompression of the spinal cord constituted 62.1%. The overall rate of MSCC patients losing the ability to ambulate was 7.5% compared to 23.5 % who regained ambulation. Preoperative ambulation status, time to surgery, compression fracture and individual health status seem to be the most relevant prognostic factors for ambulatory outcome. **Conclusions:** There is a lack of standardized prognostic tools which allow predicting outcome in surgically treated patients. A quantitative score consisting of reliable prognostic tools is essential to predict loss and/or regain of ambulation and requires validation in future prospective clinical trials.

Key words: Functional outcome, metastatic spinal cord compression, prognostic factors

INTRODUCTION

Advanced tumor disease and metastatic spinal cord compression (MSCC) are two entities with a high impact on patients' quality of life. As the life expectancy of patients with treatable malignancy and treatment options have improved considerably in the last decade,[1-4] orthopedic and spinal surgeons are nowadays frequently confronted with MSCC. Cord compression occurs in approximately 5% of all cancer patients[5] and requires emergent decompressive surgery which is considered to be the "gold standard" in tumors which are not specifically radiosensitive.[6,7] This is also supported by the evidence of regained ambulation after primary radiation therapy which ranged from 18[8] to 51%[9] and primary surgical treatment of MSCC (50[10]–100%).[11] Carefully selected patients in acceptable health conditions with a single site of cord compression, who have not been paraplegic for more

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than 48 hours, are considered to receive decompressive surgery before radiotherapy.[6]

Ambulation constitutes a primary outcome measure in evaluating different treatment outcomes in MSCC. Postoperative ambulation is a functional parameter contributing to quality of life and to a decline of spinal cord injury related complications[12] in MSCC patients, with a positive prognostic influence on survival outcome.[13,14] Improvement of functional outcome is of clinical relevance in MSCC patients as it contributes directly to quality of life, health care, nursing costs and long-term consequences such as pressure sores, neurogenic bowel and bladder dysfunction. In many instances, oncologic spine surgery intends to prolong survival, preventing neurological decline and improving functional outcomes. Preoperative neurological status and motor function are suggested to have a positive impact on postoperative ambulation.[12] Considering ambulatory rates, the proportion of patients *maintaining* ambulation and the proportion of patients *regaining* ambulation need to be distinguished.[6]

Ambulatory recovery in patients with metastatic spinal cancer treated by ventral and dorsal stabilization has been reported to range between 40 and 100%.[15,16] Furthermore, laminectomy alone has been considered to improve ambulatory function only in 23–47%.[17,18] The range of functional improvement gives reason to question the role of possible predictive factors in patients with MSCC.

As most studies include patients with vertebral metastases as well as symptomatic MSCC, essential factors with a positive or negative influence on postoperative functional outcome can be easily missed.[19,20] Proper patient selection is a prerequisite to construct reasonable guidelines for managing MSCC and to analyze the influence of preoperative prognostic tools on outcome measures. The primary aim of this review was to identify the prognostic variables that predict the ambulatory outcome in surgically treated patients with symptomatic MSCC.

MATERIALS AND METHODS

To identify relevant studies referring to prognostic tools before surgery with a possible impact on ambulatory outcome as primary endpoint in patients with MSCC, an electronic search of the MEDLINE (PubMed) database, EMBASE and Cochrane Collaboration Library was conducted. The search strategy used both key words and the following medical subject heading (MeSH) terms: metastatic compression of the spinal cord, metastatic spinal cord compression (MSCC), malignant cord compression (MCC) outcome, operation, laminectomy, anterior approach, posterolateral approach, vertebrectomy, prognosis, functional recovery and ambulation. Abstracts and references of all identified articles were also examined for importance, relevance, and overlap.

We limited our search to clinical studies in adults published from 1966 to March 2010 in English language and excluded all experimental, animal studies, expert opinion, case reports and case series. Clinical studies including a surgical approach were regarded as eligible for this review and graded for their level of evidence (I–III). All clinical trials including surgery in combination to other treatment options (e.g., radiotherapy, chemotherapy or corticosteroids) were excluded. Combined therapies were regarded as confounders influencing primary surgical outcome. Studies were also excluded if surgical treatment was repeated because of a relapse.

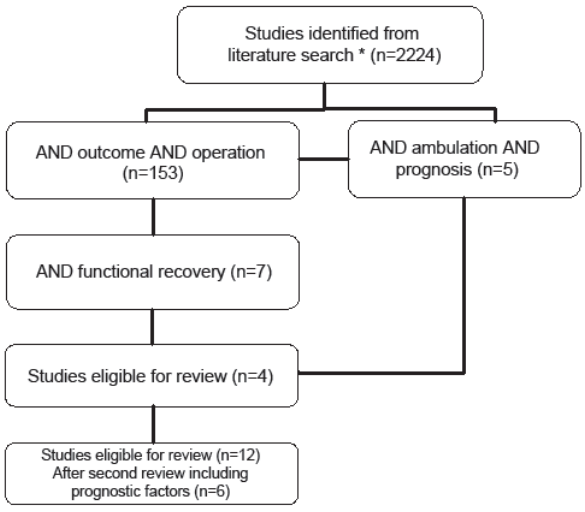
Two independently working reviewers (C.P. and C.H.F.) reviewed the abstracts of all articles including ambulation outcome and determined their relevance for the current study. Details of all selected articles including only patients with MSCC were assembled and the rates of ambulation were stratified.

RESULTS

The search strategy for metastatic spinal cord compression resulted in 2224 potentially relevant articles from MEDLINE considering the study question, but only 12 surgical clinical articles[12,18,21-30] were eligible for further text review. Six articles[18,21,24,26,27,29] which did not include any statement on prognostic factors influencing ambulation outcome were excluded after a second review [Figure 1]. Finally, six articles[12,22,23,25,28,30] and their references were analyzed for relevant prognostic tools influencing ambulatory function. The search in other relevant literature databases yielded no additional articles.

Prognostic factors were found to be related to mechanical factors, biological factors, patients' general status and the duration of neurological symptoms [Table 1].

The number of different primary tumors causing symptomatic



*metastatic compression of the spinal cord OR metastatic spinal cord compression OR malignant cord compression (" 1966"[Publication Date]: "2010/03/31"[Publication Date])

Figure 1: Outline of the literature search on metastatic spinal cord compression

MSCC evaluated in the included studies ranged from 4 to 11.[12,22,23,25,28,30]

Mechanical factor

Preoperative vertebral compression fracture resulting in spinal instability was associated with decreased postoperative ambulatory status. Therefore, patients with MSCC and a pathological vertebral compression fracture should be identified as soon as possible due to a diminished possibility of walking postoperatively and/or maintaining of the ability to walk.[12,23] Further, compression fractures were assumed to be a negative predictor of functional outcome in five studies[12,23,23,25,30] (statistically significant within two studies).[12,23]

Chaichana *et al.*[23] pointed out that an initial compression fracture due to spinal instability has a poor functional outcome compared to progressive spinal stenosis. The authors analyzed only those patients who maintained ambulation. Controversially, the authors noted a much higher functional recovery rate in non-ambulatory patients due to compression fractures compared to those with epidural metastatic compression of the spinal cord. Neither the extent of myelopathy in the fracture group and the comparison group nor the location of MSCC was discussed. Further, the degree of metastatic infiltration of vertebrae as well as the timing between onset of neurological deficit and decompression of the spinal cord was not taken into account.

Patient related factors

All six studies[12,22,23,25,28,30] confirmed that the preoperative ambulation status constitutes a prognostic variable that predicts ambulatory outcome. However, only two[12,23] studies reported that this correlation was statistically significant.

After surgical intervention, incomplete MSCC patients with an average Tokuhashi score[31] of 10 showed not only neurological improvement in the ASIA Impairment Scale (AIS), but also the best prognosis to regain ambulatory function. Thirty-one patients with a high Tokuhashi Score and a survival prognosis of more than 12 months benefited from an early surgical treatment with moderate improvement in sensorimotor function.[30]

Table 2 shows an overview of prognostic variables discussed in all six studies that predict ambulation outcome in MSCC patients. As the type of tumor and the presence of visceral metastases are included in the Tokuhashi Score, these parameters were regarded as equivalent and related to patients' health conditions. One study[30] found that the Tokuhashi Score was significantly related to ambulatory outcome. Further, visceral metastases included as sub-items in the Tokuhashi Score were assessed by two studies.[25,30]

Biological factors

The type of primary tumor is not associated with ambulatory outcome.[22] The type of primary cancer was mentioned in five studies,[12,22,23,25,30] but statistical analysis assessing the influence on ambulation outcome after surgery [Table 2] was applied in one study.[22] The prognosis to regain ambulation depending on the type of cancer was analyzed in a retrospective clinical trial limited to six types of primary cancer (lung, prostate, mamma, kidney, gastrointestinal tumors and melanoma), but without statistical significance.

Marquardt *et al.*[28] found a significant positive correlation between preoperative values of protein S-100b and initial degree of paresis.

Duration of neurological symptoms

Prompt surgical intervention within 48 hours after the appearance of sensorimotor dysfunction results in an increased likelihood of recovering ambulation.[12,25] The factor time as a prognostic factor was cited by five studies,[12,22,23,25,30] but only two studies[12,25] confirmed this hypothesis.

Clinical data and ambulation outcome

Overall, a pooled number of 423 patients from five retrospective comparative trials and one observational prospective study were included in this review and screened for prognostic factors having an impact on functional outcome after decompression of the spinal cord.

Table 3 presents the reported clinical data of MSCC before surgical intervention. Five studies[12,22,23,25,30] differentiated between tetra- and paraplegia, but only two studies[25,30] used the ASIA classification and included patients with incomplete MSCC. As the neurological and functional recovery potential is higher in incomplete compared to complete spinal cord injury (SCI),[32] possible confounding factors within the four remaining studies[12,22,23,28] have to be considered. As mentioned above, one study[28] failed to indicate any clinical or neurological information for MSCC.

Table 1: An overview of prognostic factors in the included surgical prospective and retrospective studies

Author	Year	Study/level of evidence	Prognostic factors	Functional outcome measure
Chaichana[22]	2009	Retrospective clinical study/3	Type of primary tumor	Ambulation (with)out assistive device
Chaichana[23]	2009	Retrospective clinical study/3	Vertebral compression fracture	Ambulation (with)out assistive device
Fürstenberg[25]	2009	Retrospective clinical study/3	Early decompression (<48 hours)	Mobility sub-item (SCIM)
Putz[30]	2008	Retrospective clinical study/3	Tokuhashi Score	Mobility sub-item (SCIM)
Chaichana[12]	2008	Retrospective clinical study/3	Early decompression (<48 hours) Ambulation before treatment Glucose level	Ambulation (with)out assistive device
Marquardt[28]	2004	Prospective clinical study/3	Protein S-100b	Motor grades (0-4)

SCIM = Spinal cord independence measure

Table 2: Overview of prognostic variables that predict ambulatory outcome in metastatic spinal cord compression patients

Author	Tokuhashi Score	Primary tumor	Visceral metastases	Duration of symptoms	Presence of pathological fracture	Ambulation preoperatively	Protein S-100b
Chaichana[22]	-	x[b]	-	x[a]	x[a]	x[b]	-
Chaichana [23]	-	x[a]	-	x[a]	x[c]	x[c]	-
Fürstenberg[25]	x[a]	x[a]	x[a]	x[c]	x[a]	x[a]	-
Putz[30]	x[c]	x[a]	x[a]	x[a]	x[a]	x[a]	-
Chaichana [12]	-	x[a]	-	x[c]	x[c]	x[c]	-
Marquardt [28]	-	-	-	-	-	x[a]	x[c]

x, Data available; -, not applicable, [a]Factors discussed, but not statistically analyzed, [b]Factors discussed, but not statistically significant, [c]Factors discussed and statistically significant

Ambulation was assessed using different outcome measures including ambulation with and without assistive devices,[12,22,23] evaluation of motor grades 0–IV[28] and the sub-item *mobility* of the SCIM[25,30] as a more precise method to assess functional outcome. We stratified in all six studies parameters reflecting ambulation before and after surgery [Table 4]. The mean recovery of ambulation in preoperatively non-ambulatory patients was 23.5%, ranging from 2.7 to 88%, whereas 7.5% (range 2–9%) lost the ability to ambulate. In 62.1% (range 23–95%) of all cases, ambulatory patients maintained ambulation after decompression of the spinal cord. Overall, 80.2% of the patients across all studies were able to walk postoperatively, compared to 65.7% preoperatively.

Table 3: Reported descriptive clinical data of MSCC before surgical intervention

MSCC Author	Complete/ incomplete MSCC	Tetra/ paraplegia	AIS	Presence of MSCC (nos)
Chaichana[22]	-	x	-	x**
Chaichana[23]	-	x	-	x**
Fürstenberg[25]	x (ic)	x	x	-
Putz[30]	x (ic)	x	x	-
Chaichana[12]	-	x	-	x**
Marquardt[28]	-	-	-	x*

nos = not otherwise specified; MSCC = Metastatic spinal cord compression; AIS = ASIA Impairment Scale; ic = incomplete, x, data available; -, not applicable, *Patients were examined by a classification using motor grades 0–IV, **Patients were categorized based on whether they presented motor, sensory deficit, bladder and/or bowel incontinence

DISCUSSION

As stated by the National Cancer Institute (www.cancer.gov), a prognostic factor is a condition or a characteristic of a patient that can be used to estimate the chance of recovery from disease. The current literature in spine oncology is mainly based on retrospective studies defining important prognostic factors affecting local recurrence and survival.[33] These indices were developed from historical data and included not all prognostic factors or relevant information. The principle purpose of a prognostic factor is to guide treatment decision-making in individual patients.

The biological, patient related, mechanical and time-dependent aspects influencing the prognosis of functional outcome have been discussed in this review. Evidence from five retrospective comparative trials and one observational prospective study summarizes four different prognostic factors with a significantly positive or negative impact on postoperative ambulatory status: (1) vertebral compression fracture,[23] (2) early decompression (<48 hours),[12,25] (3) Tokuhashi Score[30] and (4) ambulation before treatment.[12] On the other side, the discrepancies in the analysis of the factors, primary tumor[22] and protein S-100b,[28] might have resulted from limited patient-related confounding factors and different assessment tools.

With regard to the influence of the type of primary tumor on ambulatory outcome,[12,22] it is suggested to use the Tokuhashi Score.[31] The parameter "primary site of the cancer" is one of the six parameters of the Tokuhashi Score and is rated from 0 to 5 to differentiate the tumor biology and aggressiveness. The true prognostic value of histopathologic findings remains unclear as different types of tumors were grouped in the same study population. Of note, the location of MSCC at cervical, thoracic or lumbar level results in different deficits of sensorimotor function. The thoracic spine is the most common site for vertebral metastases, with an occurrence of 70% of all metastases to the spine.[34] This consequence has already been highlighted by previous studies, including traumatic injury and degenerative disease of the thoracic spine.[20,35]

Until standardized outcome measures have been introduced, results of studies included in the current review should be evaluated critically. In our own studies,[25,30] we stated that patient related factors are important and need to be considered in prognosis. For this purpose, the Tokuhashi Score is an excellent tool which represents not only the general health status but also tumor related indices, and takes the severity of the neurological deficit into account.

We found a mean of 62.1% (range 23–95%) of patients maintaining ambulation after surgical treatment. This confirms the hypothesis that ambulatory status before surgical treatment is a strong prognostic factor for postoperative ambulation.[12] Delay in diagnosis and treatment can lead to functional decline. In contrast to our study, Chaichana *et al.* reported on

Table 4: Ambulation outcome pre- and postoperatively

Author	Ambulation preoperatively	Ambulation postoperatively	Maintenance of ambulation	Regain of ambulation in non-ambulatory patients	Loss of ambulation
Chaichana[5]	88 (77)	91 (80)	81 (71)	7 (2.7)	7 (8)
Chaichana[6]	42 (70) fracture 85 (83) no fracture	46 (77) 87 (85)	37 (88) 81 (95)	9 (15) 6 (6)	4 (6) 2 (2)
Fürstenberg[12]	26 (74)	29 (83)	n.a.	2 (9) surgery ≤ 48 h 1 (8) surgery > 48 h	n.a.
Putz[38]	26 (74)	29 (83)	21 (60)		3 (9)
Chaichana[4]	55 (70)	49 (63)	49 (63)	6 (8)	6 (8)
Marquardt[32]	8 (23)	31 (91)	8 (23)	23 (88)	3 (9)
Mean	65.7%	80.2%	62.1%	23.5 %	7.5%

n/a = not applicable, Values which indicated in parenthesis are in percentage

a lower postoperative ambulation status (63%) compared to ambulatory function preoperatively (70%). It remains unclear if these patients who lost ambulation had disease progression leading to pain and incapacity to walk. In this review, the loss of ambulation rate was 7.5% (range 2–9%), whereas the recovery rate of ambulation was 23.5% (range 2.7–88%). The wide range of recovery of ambulation is due to the results of Marquardt *et al.*[28] (88%), whereas the other included studies[12,22,23,25,30] showed recovery rates of ambulation between 2.7 and 15%. The timing of surgery is an important prognostic factor influencing the therapeutic effect of the operation and should be performed within 48 hours if the patient is a candidate for surgery.[12,25] The influence of early surgical decompression (<48 hours) was supported by two studies,[12,25] with similar distribution of patients regaining ambulation (8–9%).

The definition of ambulation differs in the literature and has not yet been standardized.[21,12,22-30,36] Patchell *et al.*[37] defined ambulation as the ability to take at least two steps with each foot either unassisted or using an assistive device after radiotherapy. Maranzano *et al.*[38] considered a patient ambulatory when walking with or without support at 1 month was possible. In addition, several studies measured ambulation at different time points.[39,11,40] For this reason, we suggest to use the mobility sub-item of the Spinal Cord Independence Measure[41] preoperatively, postoperatively and at properly defined time points in order to standardize ambulation or functional outcome more properly.

Progress in spine surgery provides an opportunity for direct decompression of the spinal cord and stabilization. In fact, early decompressive surgery has become the standard treatment in metastatic lesions that are not radiosensitive. Patchell *et al.*[37] justified the use of surgery as the first line of therapy in ambulant patients because 20% of the patients randomized to the radiotherapy arm crossed over to surgery due to the occurrence of neurological deterioration and the loss of the ability to walk. Only 30% of them regained the ability to walk. This could be due to a primary unstable spine which constitutes a predictor for poor outcome.[23] In this randomized prospective controlled trial, overall, 63% of non-ambulant patients regained the ability to walk with surgery and radiotherapy as compared with only 19% in those receiving radiotherapy alone.

The assessment of spinal instability in MSCC is described by different scores.[33,42-44] The direct relation between the resulting pathological fractures and the neurological deficit remains unclear. Actually, there are two types of MSCC causing sudden or slow compression of the spinal cord. Sudden compression can be explained by disruption of arterial blood flow to the spinal cord with fast-growing tumors or pathologic fracture leading to spinal cord infarction, whereas slowly growing tumors with a low proliferation rate cause slow compression through venous congestion and edema.[45]

In this review, we selected only studies that included MSCC patients who received primary surgical treatment and in whom the parameter ambulation was analyzed pre- and postoperatively. By applying this strict approach, we were able to include only six studies (five retrospective trials and one observational prospective study) with a level of evidence graded 3–4. However, as there is no consensus on a common set of prognostic factors, which allow predicting outcome in surgically treated patients in the current MSCC literature, we consider this approach to be justified. To this point, no classification system has been established and validated in the framework of prospective clinical trials. Our intention was to use the best available literature to develop the basis for a quantitative score based on a ranking scheme of prognostic factors to predict quality of life, loss and/or regain of ambulation in the MSCC patient population.

To optimize MSCC care, we must face the challenging search for factors contributing to neurologic and functional outcome by using appropriate classification systems, e.g., standards of American Spinal Injury Association Impairment Scale[46] or mobility sub-item of the Spinal Cord Independence Measure.[41] Since there are several known predictive factors influencing functional outcomes after surgical decompression in MSSC patients, it is unlikely that a single prognostic factor or marker will predict functional outcomes. The introduction of a valid and reliable spinal oncology specific measure including prognostic

factors may provide a more robust and standardized measure in future studies. A well-designed prospective trial taking into account most relevant prognostic factors may provide an answer to this problem and should be supported by collaboration of centers specialized in oncologic spine surgery and spinal cord medicine.

CONCLUSION

Due to a lack of standardized prognostic tools, prediction of ambulatory outcome after primary surgery in MSCC patients is currently limited. Preoperative ambulation status, time to surgery, compression fracture and individual health status seem to be the most relevant and statistically significant prognostic factors for ambulatory outcome. The evaluation and integration of identified prognostic factors in preoperative assessment protocols of future prospective clinical trials is important to evaluate the quality of life and factors predicting loss and/or regain of ambulation.

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