

# Prediction of Spinal Epidural Metastases

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**Context:** Early diagnosis and treatment of spinal epidural metastases (SEM) is of the utmost importance to prevent neurological deficit due to spinal cord compression. Magnetic resonance imaging (MRI) has become the final tool in that diagnostic process. However, access to MRI is still limited in the Netherlands, requiring cost-effective use. It is generally acknowledged that patients with systemic cancer who present with a radiculopathy or myelopathy should undergo an MRI. However, the diagnostic policy in patients with systemic cancer who present with recently developed back pain is still a matter of debate.

**Objective:** To identify the patients with back pain in whom MRI can safely be omitted because of a low risk of SEM.

**Methods:** In a prospective series of 170 consecutive patients with cancer with recently developed back pain, prediction of spinal metastatic disease (SMD) and especially SEM was studied by means of a multivariate risk analysis of the parameters of the standard neurological evaluation (medical history, neurological examination, and plain films of the whole spine). Magnetic resonance imaging was used as the criterion standard. We calculated the risk implications of omitting MRI in patients with an estimated risk below different cutoff points.

**Results:** Spinal metastatic disease was diagnosed in 80 patients (47%); of these, 31 had SEM. A metastatic abnormality on plain films was the strongest independent predictor for SMD. Other important predictors were night pain, progressive pain, and Karnofsky score. Advanced age, exacerbation of pain during recumbency, and osteoporotic fracture imply a low risk of SMD. Night pain and the Karnofsky score proved to be the main predictors for SEM. A plain film showing an osteoporotic fracture strongly decreased the risk of SEM. The discriminating value of the multivariate analysis was too low, and too few patients can be excluded from undergoing MRI on the basis of the standard neurological checkup. To identify all the patients with SMD ( $P < .01$ ), MRI would be excluded in only 7 patients. Identification of all patients with SEM ( $P < .001$ ) reduced the number of MRIs by 21 at the expense of plain films of the whole spine for any patient.

**Conclusions:** Selection of patients with cancer with back pain at risk of SEM was not possible with the standard neurological checkup. After intake by the neurologist, the next step should be MRI of the whole spine.

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**E**PIDURAL SPINAL cord compression due to metastatic tumor is a dreadful complication of systemic cancer. Spinal epidural metastases (SEM) are diagnosed during life in 1% to 5% of patients with systemic cancer.<sup>1,2</sup> In almost half the patients breast or lung cancer is the primary tumor. Approximately 70% are localized in the thoracic spine, 20% in the lumbosacral part of the spine, and 10% in the cervical part of the spine.<sup>3-5</sup> Spinal epidural metastases are reported to be multiple in 17% to 30% of patients.<sup>6</sup> The prognosis of patients with SEM is poor. The 1-year survival rate is as low as 35%.<sup>3,5</sup> The neurological status at the time of diagnosis is the most important prognostic factor in patients with SEM.<sup>3,4,7</sup> After treatment, 67% to 100% of the patients with SEM who are ambulant at presentation can still walk; 30% to 40% of patients with

paraparesis may regain ambulation with adequate treatment compared with only 10% or fewer patients with paraplegia.<sup>3,4,7</sup> Unfortunately, even in more recent studies,<sup>8-16</sup> more than 20% of the patients are unable to walk at the time of diagnosis.

When we consider the still unsatisfactory results with respect to the diagnosis and treatment of SEM, new strategies warrant a systematic study. It is generally acknowledged that new strategies should be developed to diagnose and treat SEM or its precursor, vertebral metastases, before the onset of an often irreversible neurological deficit. We think that this is only possible if an extensive diagnostic workup is performed at the time of the first symptom, back pain. This diagnostic evaluation should include obtaining the medical history, performing a neurological examination, and taking plain films of the spine;

## PATIENTS AND METHODS

### PATIENT SELECTION

We prospectively evaluated 170 consecutive patients with cancer presenting with recently developed back pain, radiating pain, or both. The patients were recruited from St Elisabeth Hospital and Maria Hospital, Tilburg, the Netherlands. Inclusion criteria for the study were a history of systemic cancer and recently developed back pain or radiating pain or radiating pain without local back pain. Also, patients who had synchronous back pain and primary tumor were included. During the study period, the general practitioners in the area and the medical staff of the 2 hospitals and the Dr Bernard Verbeeten Institute for Radiotherapy, Tilburg, immediately referred eligible patients to the Department of Neurology at St Elisabeth Hospital and Maria Hospital. Exclusion criteria were age younger than 20 years, location of the primary tumor in the central nervous system, history of SEM or vertebral metastases, spinal metastases in the results of bone scintigraphy, symptoms and signs of myelopathy without local back pain, contraindication for MRI, and refusal of the patient to undergo MRI. We informed the patients who met the criteria about the background and procedures of the study and obtained informed consent.

### DIAGNOSTIC EVALUATION AND COLLECTION OF DATA

Patients were evaluated immediately (in emergent cases) or within 3 days after referral by a neurologist participating in the study (G.E.M.K., C.B.T., and L.R.C.). Using a standardized interview, we collected demographic data, general information about diagnosis and treatment of the primary tumor, and symptoms indicative of compression of the spinal cord, cauda equina, and spinal roots. We obtained information about pain characteristics, ambulatory status, weakness, sensory loss, and autonomic dysfunction. Thereafter, we searched for signs of the compression based on the results of a structured neurological examination. In particular, we recorded information about vertebral tenderness on percussion, axial compression pain, radicular compression tests, ambulatory status, weakness, sensory loss, reflexes, presence of an extensor plantar response, and urinary retention.

Radiography of the whole spine was performed in anteroposterior and lateral projections. Radiologists scored the main abnormality for the whole spine. We distinguished the following diagnostic categories according to severity: metastatic fracture, other metastatic abnormalities, osteoporotic fracture, degenerative abnormality, or no abnormality.

Magnetic resonance imaging of the whole spine was performed within 2 days or, if indicated, within 12 hours. In both hospitals, the spinal column was imaged by a sagittal T1-weighted spin echo technique. In the St Elisabeth Hospital, images were obtained with a Gyroscan T5 (Philips Medical Systems, Shelton, Conn), with a superconductive magnet and a field strength of 0.5 T. In the Maria Hospital, images were obtained using a Magnetom P8 (Siemens, Munich, Germany), with a permanent magnet and a field strength of 0.2 T. Radiologists scored the main abnormality

for the whole spine. We distinguished the following diagnostic categories according to severity: SEM, vertebral metastases, and nonmetastatic disease. *Spinal metastatic disease* was defined as SEM or vertebral metastases. In the category nonmetastatic disease, we distinguished osteoporotic compression fracture, degenerative abnormality, other abnormalities, or no abnormality. A diagnosis of SEM was made from the results of MRI in case of vertebral metastases with soft tissue extension into the epidural space with or without spinal cord compression. A pure epidural metastasis, that is, an epidural metastatic mass without metastatic involvement of the adjacent vertebra(e) or a paravertebral tumor growing into the epidural space through intervertebral foramina, was also classified as SEM. Leptomeningeal carcinomatosis was categorized as SEM, and bulging of a metastatic vertebra into the epidural space, vertebral metastases. The diagnosis of vertebral metastases was based on focal or diffuse areas of decreased signal intensity on T1-weighted images. The diagnosis of osteoporotic compression fracture was made in case of a fracture of the anterior column with preservation of the signal intensity of normal bone in the intact midposterior column. Fractures of the middle column or fractures with complete replacement of the signal intensity of normal bone were considered malignant.

### RISK FUNCTIONS

To evaluate the risk of SMD and SEM, a logistic multivariate regression analysis was performed. To construct prediction models for SMD and SEM, stepwise logistic regression analysis was performed by following the order in which variables became available. Therefore, we started with the variables of the standardized neurological history, added the variables of the neurological examination, and finally included the variables of the plain films. Independent variables were used. The interpretation depended on the data-coding strategy.

In this article, only the final results of this procedure are presented. We constructed prediction models for SMD and SEM according to an inclusion criterion of  $P = .10$ , which enabled an optimal selection of patients at risk of SMD and SEM. For this purpose, the stepwise logistic regression procedure SPSS (SPSS Inc, Chicago, Ill) was used. The Karnofsky score was handled as a continuous variable. Missing values of the variables exacerbation of pain at night, mentioned night pain, and exacerbation of pain by a Valsalva maneuver were considered as separate parameters.

The information content of the models was compared using the  $-2 \log$  likelihood. To evaluate the discriminative ability of the risk functions for SMD and SEM, we also used receiver operating characteristic (ROC) curves. These ROC curves were corrected for overestimation by the jackknife dispersion test. This method shows the changes in the regression coefficient when the patient in question is excluded from the model. With this method, the probability for SMD and SEM was calculated for each patient on the basis of a model (risk function) that was built on all but the patient in question ( $n-1$  observations).

We calculated a table with the number of missed cases of SEM and excluded MRIs for different increasing cutoff points. The cutoff points were derived from the ROC curves for SMD and SEM calculated with our risk function.

however, magnetic resonance imaging (MRI) has increasingly become the final diagnostic tool in the diagnostic process. Nowadays, MRI is generally accepted as the best imaging technique (criterion standard) in patients with suspected spinal metastatic disease (SMD)<sup>17-26</sup> because of excellent tissue contrast and direct visualization of the relationship between the spine, epidural space, and spinal cord. With a profound knowledge of the MRI characteristics, the detection of vertebral metastases,<sup>27</sup> the distinction between a benign and a malignant vertebral collapse, and the detection of metastatic compression of the spinal cord are highly accurate.<sup>28</sup> Finally, MRI is cheaper than myelography as demonstrated in a retrospective comparative study<sup>29</sup> of the capacity in a hospital in London, England. In another study<sup>30</sup> on this topic, the authors suggested that the diagnostic workup of metastatic spinal cord compression is at least 65% more costly without MRI. In the Netherlands, MRI capacity is still limited and thus requires cost-effective use.

It is generally acknowledged that patients with systemic cancer who present with a radiculopathy or myelopathy should undergo definite evaluation with MRI. However, the diagnostic policy in patients with systemic cancer who present with recently developed back pain and seem to have a low risk for the presence of SEM is still a matter of debate. The aim of this study was to identify a subpopulation of patients in whom MRI can safely be omitted because of a low risk of SEM. Our hypothesis is that adequate selection of the patients at risk of SEM on the basis of the standard neurological checkup is not possible in the early stage of the disease. We think that missing SEM in patients is unwanted. Therefore, MRI may only be omitted if the chance of SEM is very low. We used multivariate analysis to estimate the probability of SEM in patients.

## RESULTS

### BASELINE CHARACTERISTICS

One hundred seventy patients were eligible for the study (97 women and 73 men). The range of ages was 36 to 90 years (median, 66 years). Breast cancer was the primary tumor in 63 patients (37%), lung cancer in 35 (21%), and prostate carcinoma in 16 (9%). Eight patients had more than 1 primary tumor, and 4 patients had metastases of an unknown primary tumor. The median Karnofsky performance score was 80 for patients younger than 65 years and 70 for patients older than 65 years. The first column of **Table 1** shows the baseline characteristics of the patients. In half the patients, the pain worsened at night. A gait disturbance was noted in 27 patients (16%) who walked with assistance or could not walk at all. A bladder dysfunction was noted in 18 patients (11%); 7 of these had serious autonomic dysfunction. A gait disturbance was observed during the neurological examination in 18 patients (11%); of these, 14 (8%) could walk with assistance and 4 (2%) were unable to walk, 1 because of severe pain. The results of the neurological examination were normal in 77 patients (45%); radiculopathy was diagnosed in 76 patients (44%) and spinal cord compression in 13 patients (8%). Of the 13 patients, 8 (5%) had myelopathy; 3 (2%), lesion of the conus medullaris; and 2 (1%), cauda equina

syndrome. Of 155 patients who had plain films (plain films were not obtained in 15 patients), the plain films of 51 patients (33%) showed metastatic abnormalities, and 22 (14%) showed a metastatic fracture. The MRI results showed SMD in 80 patients (47%) and SEM in 31 (18%). One patient with a lymphoma and SEM had a pure epidural metastasis. A paravertebral tumor growing into the epidural space through the foramina was observed in 1 patient with lung cancer, and another patient had leptomeningeal carcinomatosis of small cell lung cancer. Both patients were categorized as having SEM. Vertebral metastases were diagnosed in 49 patients (29%). Nonmetastatic disease was diagnosed in 90 patients (53%): osteoporotic fractures, 20 patients (12%); degenerative abnormalities, 31 (18%); and serious other abnormalities, 4 (2%) (syrinx [2], spondylodiscitis [1], and possible meningioma [1]). Thirty-five patients (21%) had no abnormalities.

### RISK FUNCTIONS

Table 1 shows the univariate odds ratios (ORs) for SMD and SEM of the investigated parameters of medical history, neurological examination, and plain films. The main risk factors for SMD in the univariate analysis were metastatic abnormalities and metastatic fractures on plain films, prostate cancer, and the Karnofsky score. Patients with metastatic abnormalities on plain films had a 50-fold increased risk of SMD. The OR of the Karnofsky score was 0.95, which means that if the score increases 1 point the associate risk is multiplied by a factor 0.95. (A decrease of 10 points increases the OR to 1.65.) For SEM, the main risk factors were night pain; pain score of 7 to 10; pain exacerbated by Valsalva maneuver; and specific neurological complaints, such as bladder dysfunction, numbness, gait disturbance (defined as walking with support), and paresthesias.

The following tabulation shows the multivariate prediction model for SMD in 151 patients (model 1).

Characteristic	OR (95% Confidence Interval)
Medical history	
Age >75 y	0.29 (0.09-0.97)
Karnofsky score	0.94 (0.92-0.99)
Night pain present	5.01 (1.61-15.60)
Night pain absent	3.99 (0.53-29.90)
Pain during recumbency	0.16 (0.04-0.62)
Progressive pain	4.15 (1.43-12.00)
Neurological examination	
Percussion pain	3.02 (1.07-8.53)
Plain films of whole spine	
Metastatic fracture	3.91 (0.71-21.40)
Metastatic abnormality	125.00 (8.93-1738.00)
Osteoporotic fracture	0.10 (0.01-0.69)
Degenerative abnormality	0.59 (0.15-2.26)
- 2 Log likelihood	105.90 (not applicable)
Area under the curve	0.91 (not applicable)

Night pain and progressive pain in particular increased the risk of SMD, whereas advanced age and exacerbation of pain during recumbency decreased the risk of SMD. Among the variables of neurological examination, only vertebral pain on percussion proved to be an asset for the prediction of SMD. With the outcome of plain films, the prediction of SMD improved substantially. A metastatic abnormality on plain film was the strongest indepen-

**Table 1. Odds Ratios of Baseline Characteristics for Spinal Metastatic Disease and Spinal Epidural Metastases\***

Risk Factor	Reference	No. (%) of Patients	Odds Ratio (95% Confidence Interval)	
			Spinal Metastatic Disease	Spinal Epidural Metastases
<b>Medical History</b>				
Men	Women	73/170 (43)	1.73 (0.94-3.19)	1.80 (0.82-3.94)
<b>Age, y</b>				
55-65	<55	44/170 (26)	1.16 (0.48-1.34)	0.99 (0.34-2.86)
66-75	<55	51/170 (30)	0.87 (0.37-2.06)	0.54 (0.17-1.65)
>75	<55	40/170 (24)	0.78 (0.31-1.95)	0.60 (0.18-1.92)
Prostate cancer	Other	16/170 (9)	5.63 (1.54-20.60)†	2.24 (0.72-6.98)
Karnofsky score	...	...	0.95 (0.93-0.98)†	0.94 (0.92-0.97)†
Radicular pain	No	94/170 (55)	1.92 (1.04-3.56)†	1.60 (0.71-3.58)
Acute pain	No	39/164 (24)	1.13 (0.55-2.33)	1.67 (0.68-4.08)
Progressive pain	No	47/169 (28)	2.24 (1.13-4.47)†	1.86 (0.82-4.21)
Pain score 7-10	No	108/170 (64)	1.93 (1.01-3.69)†	3.31 (1.20-9.18)†
Night pain	No	85/154 (55)	2.62 (1.41-4.87)†	4.38 (1.77-10.90)†
<b>Pain exacerbated by</b>				
Recumbency	No	44/166 (27)	0.65 (0.32-1.31)	0.41 (0.13-1.25)
Movement	No	95/166 (57)	1.21 (0.65-2.25)	1.19 (0.52-2.73)
Valsalva maneuver	No	49/148 (33)	1.57 (0.81-3.07)	2.90 (1.30-6.47)†
Walking with support	No support	27/170 (6)	2.61 (1.10-6.21)†	2.75 (1.10-6.90)†
Paresthesia	No	46/170 (27)	1.18 (0.60-2.31)	2.75 (1.22-6.19)†
Numbness	No	34/170 (20)	1.81 (0.84-3.88)	4.06 (1.73-9.51)†
Bladder dysfunction	No	18/163 (11)	2.46 (0.88-6.92)	6.63 (2.34-18.80)
<b>Neurological Examination</b>				
Percussion pain	...	92/170 (54)	2.84 (1.52-5.32)†	2.92 (1.22-6.97)†
Axial compression pain	...	33/165 (19)	2.15 (0.99-4.70)	1.51 (0.58-3.94)
Positive radicular compression test	...	31/170 (18)	1.27 (0.58-2.77)	2.16 (0.88-5.30)
Radicular sensory loss	...	29/169 (17)	1.24 (0.55-2.75)	1.94 (0.77-4.91)
Sensory level	...	5/169 (3)	0.74 (0.12-4.52)	3.10 (0.50-19.40)
Extensor plantar response	...	4/170 (2)	1.13 (0.16-8.20)	...
Urinary retention	...	2/165 (2)	1.03 (0.99-1.06)	4.82 (0.29-79.40)
<b>Plain Films of the Whole Spine</b>				
Metastatic fracture	...	22/156 (14)	4.74 (1.37-16.40)†	2.77 (0.76-10.10)
Metastatic abnormality	...	29/156 (19)	49.80 (5.77-429.00)†	2.11 (0.61-7.30)
Osteoporotic fracture	...	21/156 (13)	0.42 (0.11-1.63)	0.00 (0.00-∞)
Degenerative abnormality	...	59/156 (38)	0.61 (0.22-1.66)	0.14 (0.03-0.78)

\*Ellipses indicate not applicable.

†The level of significance was P<.05.

dent predictor of SMD. On the contrary, osteoporotic fracture decreased the risk of SMD considerably. The ROC curve of model 1 for SMD with a correction for overestimation is presented in **Figure 1**.

The multivariate prediction model for SEM in 151 patients is shown below (model 2).

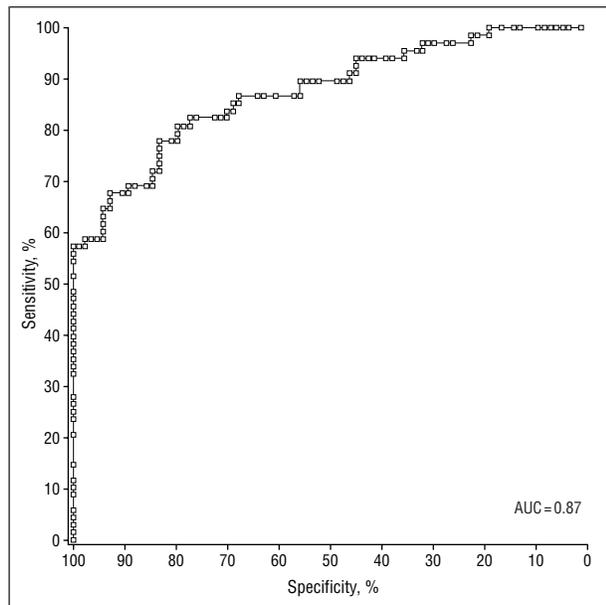
Characteristic	OR (95% Confidence Interval)
<b>Medical history</b>	
Karnofsky score	0.93 (0.88-0.98)
Night pain present	11.80 (2.55-54.60)
Night pain absent	3.58 (0.24-52.80)
Pain during recumbency	0.07 (0.01-0.43)
<b>Plain films of whole spine</b>	
Metastatic fracture	0.72 (0.10-5.38)
Metastatic abnormality	1.32 (0.23-7.49)
Osteoporotic fracture	0.00 (0.00-∞)
Degenerative abnormality	0.06 (0.01-0.62)
- 2 Log likelihood	62.6 (not applicable)
Area under the curve	0.93 (not applicable)

Model 2 shows 2 significant predictors of the medical history for SEM: night pain and Karnofsky score. This model also shows that exacerbation of pain during recum-

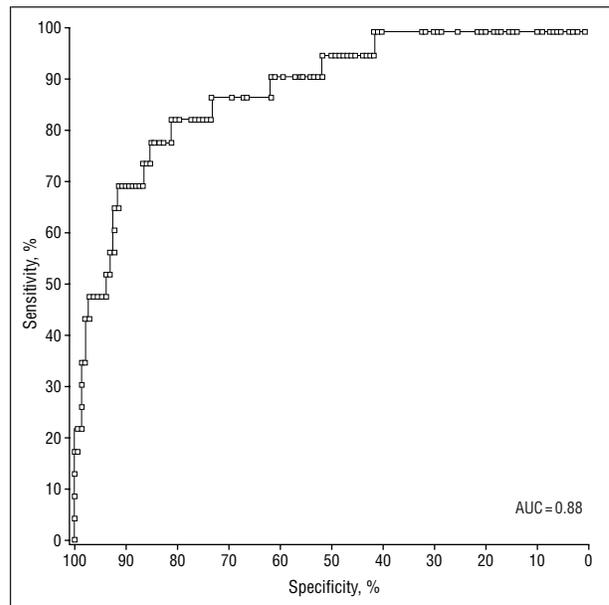
bency was a strong indication against SEM. None of the parameters of the neurological examination were predictors for SEM in the presented model. When we added the outcome of plain film to the regression analysis, the value of the prediction models increased significantly. Both osteoporotic fractures and degenerative abnormalities were strong indicators against SEM. Among the included variables of the model, night pain and the Karnofsky score proved to be the main predictors for SEM. **Figure 2** shows the ROC curve of model 2 for SEM corrected for overestimation.

### RISK IMPLICATIONS

**Table 2** shows the number of MRIs excluded and missed cases of SMD. At a cutoff point of P<.01, all 80 patients with SMD would be identified, whereas 7 patients would be excluded from MRI. With a less strict cutoff point of P<.06, 75 (94%) of the 80 patients with SMD would be identified among 135 (79%) of 170 patients. This finding means that 35 patients would be excluded from MRI at the expense of 5 patients whose MRIs showed SMD



**Figure 1.** Receiver operating characteristic curve of model 1 for the prediction of spinal metastatic disease. AUC indicates area under the curve.



**Figure 2.** Receiver operating characteristic curve of model 2 for the prediction of spinal epidural metastases. AUC indicates area under the curve.

(missed cases). Table 2 also shows the number of MRIs excluded and missed cases at several cutoff points for SEM. At a cutoff point of  $P < .01$ , MRI would be excluded in 62 patients at the expense of 1 false-negative case. At a less strict cutoff point of  $P < .06$ , 27 (87%) of the 31 patients with SEM would be identified in 81 patients. At that cutoff point, MRI would be excluded in 89 patients; of these, 4 actually had SEM according to MRIs (false-negative results).

#### COMMENT

We present the results of a multivariate analysis of risk factors for SMD and SEM derived from the medical history, neurological examination, and plain films. In multivariate analysis, metastatic abnormalities on plain films (32% of our patients) was, as expected, the main predictor for SMD. Other important predictors were night pain, progressive pain, and Karnofsky score. Advanced age, exacerbation of pain during recumbency, and osteoporotic fracture implied a low risk of SMD. The main predictors of SEM were night pain and Karnofsky score. Plain films without metastatic abnormalities strongly decreased the risk of SEM. Signs of spinal cord compression had no predictive value for the diagnosis of SEM because spinal cord compression was rare in our patients. Contrary to what we expected, exacerbation of pain during recumbency decreased the risk of SMD. We have no clear explanation for this finding; however, a possible explanation may be a misinterpretation of the question by the patients themselves (moving into a recumbent position instead of being in a recumbent position).

Our results showed that the discriminating value of the standard neurological evaluation (medical history, neurological examination, and plain films of the spine) was low; MRI would be excluded in too few patients on the basis of the standard neurological checkup. To identify the 80 patients with SMD, only 7 patients would be

**Table 2. Risk Implications of Prediction Models in 170 Patients With Cancer and Back Pain\***

Cutoff Point	SMD		SEM	
	Missed Cases	Excluded MRI	Missed Cases	Excluded MRI
$P < .001$	0	0	0	21
$P < .01$	0	7	1	62
$P < .03$	2	17	3	76
$P < .06$	5	35	4	89
$P < .10$	8	44	6	100
$P < .15$	10	52	6	106
$P < .25$	12	66	7	116

\*The cutoff points are derived from the receiver operating characteristic curves for spinal metastatic disease (SMD; Figure 1) and spinal epidural metastases (SEM; Figure 2). The number of patients with an estimated risk for SMD or SEM below the cutoff point can be excluded from magnetic resonance imaging (MRI). Patients whose results of MRI indicate SMD or SEM are the missed cases.

excluded from MRI. Identification of all the patients with SEM reduces the number of MRIs by only 21 (12%).

Plain films of the whole spine were not useful in identifying SEM and therefore should not be performed. This would potentially represent a substantial overall saving in cost and time.

In the literature, only Bernat et al<sup>31</sup> reported a risk function predicting SEM, but their study was carried out in a population with possible epidural compression of the spinal cord or cauda equina (late diagnosis). The authors concluded that this risk function distinguished patients with and without SEM (compression on myelogram) fairly well. Most of the patients who actually had compression had a high probability of compression and vice versa. They identified a model with 8 variables: being male; advanced age; abnormal plain films; sensory loss noted during the examination (radicular loss or sensory level); history of local pain, weakness, and radicu-

lar pain; and paraparesis or radicular weakness on neurological examination. As expected, signs of spinal cord compression and radicular compression were important predictors of SEM in the results of Bernat et al because in more advanced stages of spinal disease nearly every case of SEM will cause signs of radicular or spinal cord compression. Unlike the results in our study, advanced age was a predictor for SEM in the results of Bernat et al. A possible explanation could be the negative correlation with the Karnofsky score ( $r=-0.24$ ) in our study. This correlation had a negative correlation with the risk of SMD ( $r=-0.33$ ) and changed a positive correlation between age and SMD into a negative one. Another explanation could be that younger patients harbor more aggressive tumors with a higher propensity to metastasize. In contrast to our study, being male proved to be a predictor for SEM in the study by Bernat et al. In our opinion, this finding can be ascribed to the relatively high frequency of lung cancer and prostate cancer in their study. Overall, we think that the risk profile of Bernat et al supports our assumption that their patients were evaluated in a more advanced stage of spinal disease, providing another risk profile with more parameters of neurological deficit.

In conclusion, our study indicated that identification of patients at risk for SEM was not possible with the standard neurological checkup. Therefore, after intake by a neurologist, the next step should be to perform an MRI of the whole spine. Plain films of the spine can be left out.

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