

## Number of Extraplural Organs with Metastases: A Prognostic Factor of Survival in Patients with Metastatic Spinal Cord Compression (MSCC) from Non-small Cell Lung Cancer (NSCLC)

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**Abstract.** *Background/Aim:* In patients irradiated for MSCC from NSCLC, the number of extrapural organs involved by metastases was investigated for associations with survival. *Patients and Methods:* The data of 131 patients irradiated with 10×3 Gy in two weeks for MSCC were evaluated. The number of involved extrapural organs plus eight other factors were retrospectively analyzed. *Results:* The 6-month survival rates were 72%, 57%, 20%, and 11% for the involvement of 0, 1, 2, and ≥3 extrapural organs, respectively ( $p < 0.001$ ). On multivariate analysis, the number of involved extrapural organs remained significant (risk ratio 1.60; 95% CI 1.28-2.00;  $p < 0.001$ ). Gender ( $p = 0.028$ ), ECOG performance score ( $p = 0.001$ ), histology ( $p = 0.014$ ), ambulatory status ( $p = 0.002$ ), and time to developing motor deficits ( $p = 0.041$ ) were also independent prognostic factors for survival. *Conclusion:* The number of extrapural organs with metastases is an independent prognostic factor for the survival of NSCLC patients presenting with MSCC and should be considered in future studies.

Although a randomized trial has suggested that the addition of upfront decompressive surgery to radiotherapy can improve treatment outcomes in carefully selected patients with metastatic spinal cord compression (MSCC), radiotherapy-alone is the most commonly administered palliative treatment (1, 2). Many different fractionation

regimens of radiotherapy are used worldwide for MSCC including 1×8 Gy in 1 day, 5×4 Gy in 1 week, 10×3 Gy in 2 weeks, and 20×2 Gy in 4 weeks. Several studies have shown that single-fraction radiotherapy such as 1×8 Gy or short-course multi-fraction radiotherapy such as 5×4 Gy in one week are similarly effective as longer-course regimens such as 10×3 Gy in two weeks or 20×2 Gy in four weeks with respect to pain relief and improvement of motor deficits (3-6). Therefore, it appears reasonable to use single-fraction or short-course multi-fraction radiotherapy for MSCC in order to keep the overall treatment time short for these patients who are often debilitated and have a survival prognosis of only very few months. Longer-course regimens have been shown to result in better re-calcification of the osteolytic bone and better local control of MSCC in the irradiated parts of the spinal cord (7, 8). However, re-calcification usually takes several months and the risk of developing a local recurrence of MSCC increases with longer survival. Therefore, patients with an expected survival of six months or longer should receive a longer-course radiotherapy regimen. Furthermore, a matched-pair study from 2011 has suggested that patients with a 6-month survival probability of greater than 85% likely benefit from an escalation of the radiation dose beyond 10×3 Gy in terms of better local control, progression-free survival, and overall survival (9). In addition, selected patients with a favorable survival prognosis may also be candidates for high-precision radiotherapy techniques such as single-fraction radiosurgery or fractionated stereotactic body radiotherapy (10).

Thus, in order to be able to provide the most appropriate treatment for each patient with MSCC, a precise estimate of the patient's survival time is required. This goal can only be achieved with a clear understanding of independent prognostic factors having a significant impact on survival. Such prognostic factors for survival have already been

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identified for patients with MSCC and included in survival scores (11, 12). In those studies, the presence of extraspinal metastasis was one of the most important prognostic factors for survival of patients with MSCC. However, only the presence of or absence of such extraspinal metastasis were investigated but not the number of extraspinal organs involved by metastases. This study investigated the prognostic impact of the number of extraspinal organs involved by metastases on survival of patients with MSCC due to NSCLC. Only patients with MSCC from NSCLC, who were treated with 10x3 Gy of radiotherapy-alone were included in this study. This was done to reduce the risk of selection biases based on the primary tumor type and the treatment approach.

**Patients and Methods**

A total of 131 patients treated with 10x3 Gy in two weeks of radiotherapy-alone for metastatic spinal cord compression from NSCLC were included on this retrospective study. The number of extraspinal organs involved by metastatic disease (0 vs. 1 vs. 2 vs. ≥3) plus eight additional potential prognostic factors were investigated for associations with survival. The other investigated prognostic factors included age (≤65 vs. ≥66 years, median age: 66 years), gender, Eastern Cooperative Oncology Group (ECOG) performance score (1-2 vs. 3-4), histology (adeno carcinoma vs. squamous cell carcinoma vs. anaplastic carcinoma), number of involved vertebrae (1-2 vs. ≥3), interval between the first diagnosis of NSCLC and radiotherapy (≤15 vs. >15 months), ambulatory status prior to radiotherapy (not ambulatory vs. ambulatory), and the time-to-developing motor deficits before start of radiotherapy (1-7 vs. 8-14 vs. >14 days). Patients' characteristics are presented in Table I.

The univariate analyses of survival were performed with the Kaplan-Meier method and the log-rank test (13). The additional multivariate analysis was performed by the Cox hazards proportional model. Since the ECOG performance score and the pre-radiotherapy ambulatory status may have been confounding variables, two separate multivariate analyses were run, one including the ECOG performance score and the other including the ambulatory status.

In addition to the analysis of the entire cohort, separate univariate and multivariate analyses of the 113 patients who had an involvement of one or more extraspinal organs were performed to assure that a significant result regarding the number of involved extraspinal organs was not solely due to the difference between patients with *versus* those without metastatic involvement of extraspinal organs.

**Results**

On univariate analysis, improved survival was significantly associated with age ≤65 years ( $p=0.014$ ), female gender ( $p=0.004$ ), ECOG performance score 1-2 ( $p<0.001$ ), adenocarcinoma ( $p=0.004$ ), interval between the first diagnosis of NSCLC and radiotherapy >15 months ( $p=0.025$ ), being ambulatory prior to radiotherapy ( $p<0.001$ ), and a slower development (>14 days) of motor

Table I. *Patients' characteristics.*

	Patients N (%)
Age	
≤65 years	63 (48)
≥66 years	68 (52)
Gender	
Female	41 (31)
Male	90 (69)
ECOG Performance Score	
1-2	40 (31)
3-4	91 (69)
Histology	
Adenocarcinoma	66 (50)
Squamous cell carcinoma	32 (24)
Anaplastic carcinoma	33 (25)
Number of involved vertebrae	
1-2	59 (45)
≥3	72 (55)
Interval from NSCLC diagnosis-to-RT	
≤15 months	116 (89)
>15 months	15 (11)
Ambulatory status prior to RT	
Not ambulatory	54 (41)
Ambulatory	77 (59)
Time to developing motor deficits	
1-7 days	53 (40)
8-14 days	33 (25)
>14 days	45 (34)
Number of involved extraspinal organs	
0	18 (14)
1	37 (28)
2	30 (23)
≥3	46 (35)

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy.

deficits prior to radiotherapy ( $p<0.001$ ), and metastatic involvement of only 0-1 extraspinal organs ( $p<0.001$ ) (Figure 1). Involvement of only 1-2 vertebrae showed a strong trend towards better survival ( $p=0.058$ ). Results of the univariate analysis are shown in Table II.

In the multivariate analyses of the entire cohort, female gender ( $p=0.028$ ), better ECOG performance score ( $p=0.001$ ), adenocarcinoma ( $p=0.014$ ), ambulatory status prior to radiotherapy ( $p=0.002$ ), a slower development of motor deficits before the start of radiotherapy ( $p=0.041$ ), and metastatic involvement of only 0-1 extraspinal organs ( $p<0.001$ ) maintained significance. The interval between first diagnosis of NSCLC and radiotherapy ( $p=0.09$ ) and the number of involved vertebrae ( $p=0.45$ ) were not significant in multivariate analysis. The results of the multivariate analyses are summarized in Table III.

In the additional analyses of the 113 patients who had an involvement of one or more extraspinal organs, the number of involved extraspinal organs was significantly associated

Table II. Univariate analysis of survival.

	Survival at 6 months (%)	Survival at 12 months (%)	p-Value
Age			
≤65 years	27	15	
≥66 years	41	31	0.014
Gender			
Female	46	40	
Male	29	13	0.004
ECOG Performance Score			
1-2	73	51	
3-4	17	6	<0.001
Histology			
Adenocarcinoma	44	27	
Squamous cell carcinoma	34	20	
Anaplastic carcinoma	15	12	0.004
Number of involved vertebrae			
1-2	42	30	
≥3	28	10	0.058
Interval from NSCLC diagnosis-to-RT			
≤15 months	31	19	
>15 months	60	44	0.025
Ambulatory status prior to RT			
Not ambulatory	13	5	
Ambulatory	49	34	<0.001
Time to developing motor deficits			
1-7 days	17	6	
8-14 days	33	17	
>14 days	56	41	<0.001
Number of involved extraspinal organs			
0	72	56	
1	57	37	
2	20	8	
≥3	11	5	<0.001

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy.

to survival in both the univariate ( $p<0.001$ ) and the multivariate analyses (risk ratio 1.49; 95% Confidence Interval 1.15-1.95;  $p=0.003$ ).

### Discussion

Due to the different clinical and biological behavior of primary tumors associated with MSCC, each tumor entity should be examined separately in order to provide the best individual treatment approach for patients suffering from MSCC. Patients with MSCC from NSCLC have a worse prognosis than those with MSCC from other tumors such as breast cancer, prostate cancer and myeloma (1). Furthermore, NSCLC is quite common and accounts for approximately 20% of all patients presenting with MSCC. The present

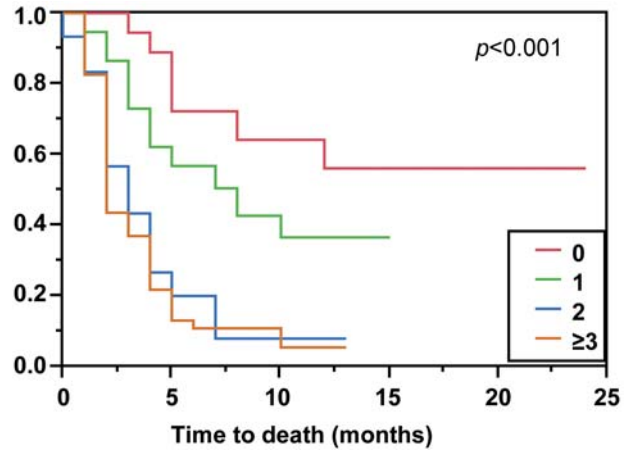


Figure 1. Impact of the number of extraspinal organs involved by metastases (0 vs. 1 vs. 2 vs. ≥3 organs) on survival.

Table III. Multivariate analysis of survival.

	Risk Ratio	95% Confidence Interval	p-Value
Age	1.22	0.80-1.87	0.35
Gender	1.67	1.06-2.73	0.028
ECOG Performance Score	2.36	1.39-4.11	0.001
Histology	1.37	1.07-1.76	0.014
Number of involved vertebrae	1.09	0.87-1.36	0.45
Interval from NSCLC diagnosis-to-RT	1.36	0.96-2.06	0.09
Ambulatory status prior to RT	2.07	1.32-3.26	0.002
Time to developing motor deficits	1.31	1.01-1.72	0.041
Number of involved extraspinal organs	1.60	1.28-2.00	<0.001

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy.

study particularly examined patients with MSCC from NSCLC. The major goal of the study was to identify a new independent prognostic factor for the survival of this patient group. In recent years, several prognostic factors could already be identified for patients with MSCC from NSCLC. In the multivariate analysis of a retrospective study including 356 patients, improved survival was significantly associated with female gender (risk ratio (RR) 1.32,  $p=0.043$ ), ECOG performance score 1-2 (RR 1.45,  $p=0.034$ ), ambulatory status prior to radiotherapy (RR 1.72,  $p<0.001$ ), absence of other bone metastases (RR 1.38,  $p=0.010$ ), absence of visceral metastases (RR 2.87,  $p<0.001$ ), an interval from NSCLC diagnosis-to-radiotherapy of >15 months (RR 1.19,  $p=0.035$ ), and a slower development of motor deficits prior to radiotherapy (RR 1.28,  $p<0.001$ ) (14).

In an additional study of that group, the entire cohort of patients was divided in a test group (N=178) and a validation group (N=178) in order to create a validated survival score for patients with MSCC from NSCLC (15). In the test group of that study, improved survival was significantly associated with better ECOG performance score (RR 1.98,  $p<0.001$ ), pre-radiotherapy ambulatory status (RR 1.65,  $p=0.029$ ), absence of visceral metastases (RR 2.44,  $p<0.001$ ), and a slower development of motor deficits prior to radiotherapy (RR 1.33,  $p=0.001$ ). Based on these four independent prognostic factors, a survival score for patients with MSCC from NSCLC was designed (15). A separate score for each of the four prognostic factors was determined by dividing the 6-month survival rate (%) by 10. The risk scores represented the sum of the separate scores for each prognostic factor and ranged between 6 and 19 points. According to the risk scores, the patients were divided into three prognostic groups. The 6-month survival rates were 6% for 6-10 points, 29% for 11-15 points, and 78% for 16-19 points ( $p<0.001$ ). The corresponding survival rates of the validation group were 4%, 24% and 76%, respectively ( $p<0.001$ ). Since the survival rates of both the test group and the validation group were quite similar, the specific survival score can be considered valid and reproducible.

However, in that survival score, the rating of visceral metastases was allowed either as present (“yes”) or as absent (“no”) of such metastases, whereas the number of organs involved by metastatic disease was not regarded. Since it appears likely that the number of extraspinal organs involved by metastases (*i.e.* visceral metastases and other bone metastases outside the spine) matters, the present study was initiated. This study included a cohort of patients with MSCC from only one primary tumor type treated as homogeneously as possible to reduce the risk of introducing selection biases. Therefore, only patients who received 10×3 Gy in two weeks of radiotherapy-alone for MSCC from NSCLC were included.

According to the results of the present study, the number of extraspinal organs involved by metastases is an independent prognostic factor of survival. Patients with involvement of 0-1 extraspinal organs had a significantly better survival than patients with involvement of two or more organs. To assure that these findings were not solely caused by the difference between the patients who had an involvement of one or more extraspinal organs and the patients without extraspinal metastatic involvement, separate analyses were performed in the 113 patients with involvement of at least one extraspinal organ. The results of these sub-group analyses confirmed the results of the entire cohort. This finding further supports the result that the number of extraspinal organs involved by metastases is an independent predictor of survival. However, the retrospective design of the present study should be taken into account when interpreting these findings. Although we have included only patients with MSCC from NSCLC who

were treated homogeneously, the risk of a hidden selection bias may not have been entirely excluded.

In the multivariate analysis of the present study, improved survival was also significantly associated with female gender, a better performance status, histology, ambulatory status prior to radiotherapy, and a slower development of motor deficits prior to radiotherapy. These findings agree well with previous studies identifying independent prognostic factors for survival of patients with MSCC (14, 15). Female gender has also been reported to be positively associated with the survival of NSCLC patients without MSCC (16). The results of the present study should optimally be confirmed in prospective trials. However, such data will likely not be available in the near future.

In conclusion, according to the findings of the present study, the number of extraspinal organs involved by metastases is an additional independent prognostic factor for the survival of patients with MSCC from NSCLC. This prognostic factor can contribute to better personalization of the treatment for these patients. It should also be considered in future clinical trials for this group of patients.

### Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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