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Prognostic factors in patients with skeletal-related events at non-small-cell lung cancer diagnosis

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Abstract. The aim of the present study was to detect prognostic factors in patients with skeletal-related events (SREs) and bone metastasis at the time of non-small-cell lung cancer (NSCLC) diagnosis. A total of 85 NSCLC patients were retrospectively enrolled, 47 (55.2%) of whom presented with SREs at the time of NSCLC diagnosis. Multivariate logistic regression analysis identified squamous cell carcinoma as a risk factor for SRE. Kaplan-Meier analysis demonstrated that there was no difference in the overall survival between the SRE and no SRE groups. Cox hazard model revealed that a higher Eastern Cooperative Oncology Group (ECOG) performance status (PS) score was a risk factor for poor prognosis, while surgery for bone metastasis and molecular-targeted therapy were factors for better prognosis in patients with SREs at the time of NSCLC diagnosis. Multivariate analysis revealed that a higher ECOG PS score and metastasis to the adrenal gland were risk factors for poor prognosis, while surgery for bone metastasis and molecular-targeted therapy were factors for better prognosis. Thus, while surgical treatment and molecular-targeted therapy appear to improve the prognosis of patients with bone metastasis at the time of NSCLC diagnosis, those with a higher ECOG PS score and adrenal metastasis may benefit more from radiotherapy or supportive care.

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Abbreviations: NSCLC, non-small-cell lung cancer; SREs, skeletal-related events; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

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Key words: bone metastases, molecular-targeted treatment, non-small-cell lung cancer, prognostic factors, skeletal-related events

Introduction

Lung cancer is the leading cause of cancer-related mortality in Japan as well as worldwide (1). Non-small-cell lung cancer NSCLC is the third most common cause of bone metastases following breast and prostate cancer (2). It has been reported that 84.8% of patients exhibit multiple skeletal metastases at the time of NSCLC diagnosis, which cause complications including bone pain, pathological fractures, spinal cord compression and dysmotility (3). There are differences in the prognosis of NSCLC patients with and without bone metastases (4,5). In addition, 54.3% of patients experience skeletal-related events (SREs) at the time of NSCLC diagnosis (3). SREs include radiotherapy, pathological fractures, spinal cord compression, orthopedic surgery and hypercalcemia. SREs affect not only the prognosis but also the activities of daily living (6). However, to the best of our knowledge, there are currently no reports evaluating the risk factors for SREs at NSCLC diagnosis. The aim of the present study was to examine the risk factors for SREs and overall survival in patients with SREs or bone metastases at the time of NSCLC diagnosis.

Patients and methods

Patients. A total of 1,072 NSCLC patients who were treated at Kagoshima University Hospital between 2006 and 2013 were retrospectively identified, and 85 patients with bone metastases at the time of NSCLC diagnosis, whose histopathological diagnosis of NSCLC was available, were enrolled in the present study. All deaths were due to NSCLC or cancer-related complications. The presence of bone metastasis was diagnosed by physicians, radiologists and orthopedic surgeons. Bone metastases were detected by X-ray, computed tomography (CT) scans, magnetic resonance imaging (MRI) of the skeleton, or positron emission tomography (PET)-CT. In all the cases, diagnosis was confirmed by pathological examination. All the patients who received molecular-targeted therapy had epidermal growth factor receptor (EGFR) mutations. Pathological fractures, spinal cord compression and hypercalcemia were defined as SREs, as were radiotherapy and orthopedic surgery that were performed for bone metastases at the time of NSCLC diagnosis.

Improvements in the primary tumor were defined as partial or complete response according to the Response Evaluation Criteria In Solid Tumors guidelines (7). Improvements in bone metastases were defined as reduced tumor size on CT scan. When the Mirel's score was >8 points, surgical treatment for long bone metastases was undertaken (8). In one case with a Tokuhashi score of 1, surgery for spinal metastasis was undertaken according to the patient's request.

The local Ethics Committee of Kagoshima University reviewed and approved the present study, and access to the database was approved by the Research Ethics Committee at the Kagoshima University (trial registration no. 438; name of registry: 'Evaluation of utility of imaging analysis of metastatic bone tumor'; URL of registry: http://www.orthop-kagoshima-u.com/; date of registration: 02/05/2014). All the patients provided written informed consent for their records to be used in this study.

Statistical analysis. Kaplan-Meier analysis was used to evaluate prognosis. Multiple logistic regression analysis was used to evaluate the risk factors for SREs. The Cox proportional hazards model was used to examine the risk factors for survival. All statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd. Tokyo, Japan). P-values of <0.05 were considered to indicate statistically significant differences.

Results

Squamous cell carcinoma is a risk factor for SREs. The median patient age was 66.0 years (range, 55.0-72.0 years), and 52 of the 85 patients were male (61.2%). The median follow-up period from NSCLC diagnosis was 7 months (range, 4.9-9.1 months). The histopathological diagnosis of NSCLC was adenocarcinoma (n=55), squamous cell carcinoma (n=16), and other types of NSCLC (n=14). A total of 73 patients (85.9%) were affected by multiple bone metastases at the time of NSCLC diagnosis. The most common site of bone metastases was the spine (n=70), followed by the pelvis (n=46), sacrum (n=31) and extremities (n=26) (Table I). A total of 47 patients (55.2%) were affected by SREs at the time of NSCLC diagnosis. The most frequent SREs were radiotherapy (87.2%) followed by spinal cord compression (31.9%), pathological fracture (21.3%), surgery (14.9%), and hypercalcemia (8.5%) (Table II). Univariate analysis revealed that a higher ECOG PS score (9) and squamous cell carcinoma were risk factors for SREs at the time of NSCLC diagnosis. Multivariate logistic regression analysis revealed that squamous cell carcinoma was a risk factor for SREs at the time of NSCLC diagnosis (Table III). The incidence rate of SREs in squamous cell carcinoma and adenocarcinoma was 87.5% (14/16) and 47.3% (26/55), respectively. The Fisher's exact test also revealed that the incidence rate of SREs was significantly higher in squamous cell carcinoma compared with that in adenocarcinoma patients at the time of NSCLC diagnosis (Table IV).

Survival rates of patients with bone metastasis at the time of NSCLC diagnosis. The median survival after diagnosis of NSCLC and bone metastasis was 7.0 months. The 1-, 2-, 3- and 5-year survival rates of patients with bone metastasis at the time of NSCLC diagnosis were 38.8, 23.5, 12.9 and 3.5%, respectively (Fig. 1).

Table I. Non-small-cell lung cancer patients with bone metastases (n=85).

Characteristics	Values
Male sex, no. (%)	52 (61.2)
Age (years), median (range)	66.0 (55.0-72.0)
ECOG PS, median (range)	2 (1-2)
BMI (kg/m^2), median (range)	20.3 (18.2-22.8)
Days on treatment after diagnosis, median (range)	15.0 (6.0-24.0)
Brinkmann index, median (range)	200 (0-840)
Adenocarcinoma, no. (%)	55 (64.7)
Squamous cell carcinoma, no. (%)	16 (18.8)
Spine metastasis, no. (%)	70 (82.4)
Cervical metastasis, no. (%)	25 (29.4)
Thoracic metastasis, no. (%)	50 (58.8)
Lumbar metastasis, no. (%)	43 (50.6)
Sacral metastasis, no. (%)	31 (36.5)
Pelvic metastasis, no. (%)	46 (54.1)
Bone of extremities metastasis, no. (%)	26 (30.6)
Multiple bone metastasis, no. (%)	73 (85.9)
Single bone metastasis, no. (%)	12 (14.1)
Brain metastasis, no. (%)	32 (37.6)
Adrenal gland metastasis, no. (%)	18 (21.2)
Liver metastasis, no. (%)	18 (21.2)
Lymph node metastasis, no. (%)	72 (84.7)
SREs, no. (%)	47 (55.3)
Spinal complaint, no (%)	15 (17.6)
Hypercalcemia, no. (%)	4 (4.7)
Fracture, no. (%)	10 (11.8)
Operation for bone metastasis, no. (%)	7 (8.2)
Radiotherapy, no. (%)	41 (48.2)
Molecular-targeted therapy, no. (%)	18 (21.2)
Chemotherapy, no. (%)	43 (50.6)
Bisphosphonates, no. (%)	22 (25.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; SREs, skeletal-related events.

Table II. SREs at the time of NSCLC diagnosis.

SREs	No. (%)
Total	47 (55.2)
Radiotherapy	41 (87.2)
Spinal cord compression	15 (31.9)
Pathological fracture	10 (21.3)
Hypercalcemia	4 (8.5)
Surgery	7 (14.9)

SREs, skeletal-related events; NSCLC, non-small-cell lung cancer.

Table III. Risk factors for SREs at the time of NSCLC diagnosis.

		Univariate analysis		Multivariate analysis	
Factors	Median (range)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	66 (55-73)	1.00 (0.97-1.04)	0.93	(-)	
Male sex	28	0.85 (0.36-2.07)	0.74	(-)	
BMI	20.3 (18.2-21.6)	0.94 (0.83-1.06)	0.29	(-)	
Smoking	28	1.07 (0.45-2.55)	0.88	(-)	
Number of bone metastases	4 (2-7)	1.02 (0.92-1.13)	0.72	(-)	
Spine metastasis	41	2.12 (0.68-6.61)	0.20	3.11 (0.74-13.09)	0.12
Cervical metastasis	14	1.04 (0.41-2.66)	0.93	(-)	
Thoracic metastasis	27	0.88 (0.34-2.10)	0.77	(-)	
Lumbar metastasis	23	0.86 (0.37-2.03)	0.73	(-)	
Sacral metastasis	17	0.47 (0.40-2.36)	0.95	(-)	
Pelvic metastasis	28	1.64 (0.69-3.88)	0.26	(-)	
Thigh metastasis	14	1.59 (0.59-4.32)	0.36	1.46 (0.52-4.16)	0.47
Rib metastasis	20	0.54 (0.23-1.28)	0.16	(-)	
Humerus metastasis	7	2.04 (0.49-8.50)	0.33	(-)	
Brain metastasis	14	0.92 (0.36-2.32)	0.86	(-)	
Liver metastasis	6	0.65 (0.20-2.12)	0.47	(-)	
Adrenal gland metastasis	16	1.049 (0.35-3.14)	0.932	(-)	
Lymph node metastasis	40	0.32 (0.06-1.63)	0.17	(-)	
PS score	2 (1-3)	**1.67 (1.08-2.60)**	**0.021**	1.40 (0.88-2.24)	0.16
Squamous cell carcinoma	14	**7.64 (1.61-36.16)**	**0.01**	**9.41 (1.65-53.81)**	**0.012**
Adenocarcinoma	26	**0.38 (0.15-0.99)**	**0.04**	(-)	
Molecular-targeted therapy	18	1.35 (0.47-3.92)	0.58	(-)	

Bold print indicates statistical significance. HR, hazard ratio; CI, confidence interval; SREs, skeletal-related events; NSCLC, non-small-cell lung cancer; BMI, body mass index; PS, performance status.

Table IV. Association between SREs and pathological diagnosis of NSCLC.

Type of NSCLC	SREs at the time of NSCLC diagnosis	No SREs at the time of NSCLC diagnosis
Squamous cell carcinoma	14	2
Adenocarcinoma	26	29

Fisher's exact test (P<0.01). SREs, skeletal-related events; NSCLC, non-small-cell lung cancer.

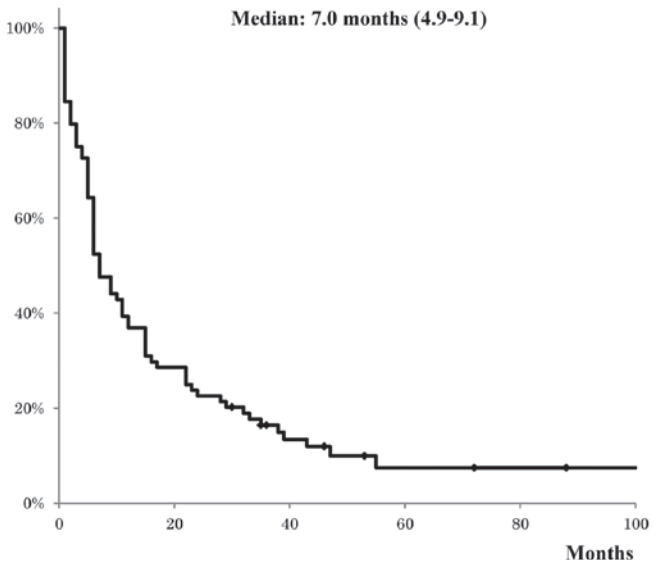

Figure 1. Kaplan-Meier curve analysis showing the overall survival from the time of diagnosis of non-small-cell lung cancer with bone metastases.

Prognostic factors for patients with bone metastasis at the time of NSCLC diagnosis. The Cox proportional hazards model was used to evaluate the prognostic factors for patients with bone metastasis at the time of NSCLC diagnosis. Univariate analysis revealed that older age, male sex, higher ECOG PS score, and presence of adrenal gland and liver metastasis, were risk factors for poor prognosis, whereas molecular-targeted therapy, chemotherapy and improvement of bone metastasis on CT were factors for better prognosis (Table V). Multivariate analysis revealed that higher ECOG PS score and metastasis to the adrenal gland were risk factors for poor prognosis, while surgery for bone metastasis and molecular-targeted therapy were factors for better prognosis (Table V). In addition,

Table V. Risk factors of poor prognosis for patients with bone metastasis at the time of NSCLC diagnosis: Cox proportional hazards model for survival.

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	**1.03 (1.01-1.06)**	**0.006**	(-)	
Male sex	**2.00 (1.24-3.24)**	**0.005**	(-)	
ECOG PS	**1.34 (1.07-1.68)**	**0.01**	**1.46 (1.16-1.84)**	**0.002**
BMI	1.02 (0.96-1.09)	0.51	(-)	
Smoking	1.41 (0.89-2.25)	0.14	(-)	
Adenocarcinoma	0.71 (0.45-1.14)	0.16	(-)	
Squamous cell carcinoma	1.13 (0.64-2.00)	0.67	(-)	
Number of bone metastasis	1.04 (0.99-1.09)	0.12	(-)	
Only bone metastasis	0.68 (0.31-1.49)	0.33	(-)	
Brain metastasis	0.68 (0.45-1.13)	0.13	(-)	
Adrenal gland metastasis	**3.02 (1.66-5.48)**	**<0.001**	**2.34 (1.27-4.31)**	**<0.001**
Liver metastasis	**2.80 (1.49-5.24)**	**0.001**	(-)	
Lymph node metastasis	1.43 (0.68-2.99)	0.34	(-)	
SREs	0.84 (0.53-1.33)	0.46	(-)	
Spinal complaint	1.09 (0.63-1.96)	0.76	(-)	
Hypercalcemia	0.56 (0.17-1.79)	0.32	(-)	
Fracture	1.10 (0.55-2.21)	0.79	(-)	
Radiotherapy	0.81 (0.52-1.28)	0.37	(-)	
Operation for bone metastasis	0.40 (0.16-1.02)	0.05	**0.35 (0.13-0.97)**	**0.04**
Molecular-targeted therapy	**0.38 (0.21-0.69)**	**0.002**	**0.37 (0.20-0.70)**	**0.002**
Bisphosphonates	0.77 (0.45-1.31)	0.34	(-)	
Chemotherapy	**0.40 (0.25-0.64)**	**<0.001**	0.66 (0.39-1.01)	0.11
Improvement of bone metastasis	**0.29 (0.09-0.92)**	**0.036**	(-)	
Improvement of primary lesion	0.56 (0.30-1.04)	0.065	(-)	

Bold print indicates statistical significance. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; SREs, skeletal-related events.

Kaplan-Meier analysis revealed that adenocarcinoma with molecular-targeted therapy had a better prognosis compared with squamous cell carcinoma and adenocarcinoma without molecular-targeted therapy (Fig. 2).

Prognostic factors for patients with SREs at the time of NSCLC diagnosis. Kaplan-Meier analysis revealed that there was no difference in the overall survival between the SRE and no SRE groups (Fig. 3). Cox hazard model analysis was performed using four factors that were found to be significant for the prognosis of patients with bone metastasis at the time of NSCLC diagnosis. The Cox hazard model demonstrated that a higher ECOG PS score was a risk factor for poor prognosis, while surgery for bone metastasis and molecular-targeted therapy were factors for better prognosis (Table VI).

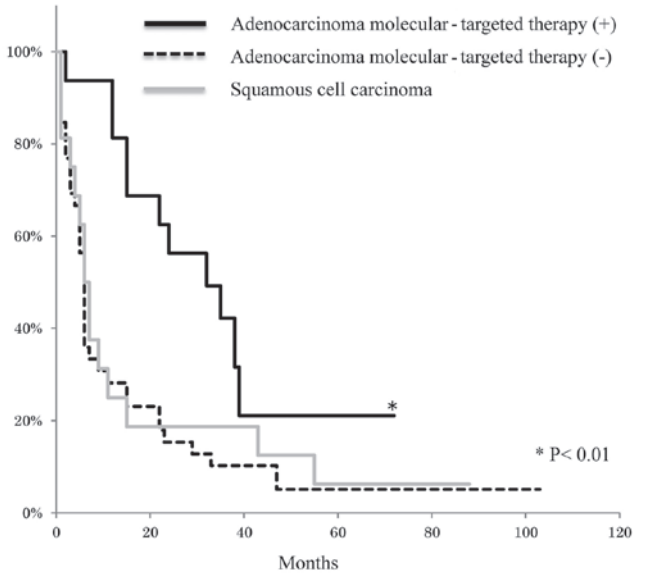

Figure 2. Kaplan-Meier analysis showing the overall survival of adenocarcinoma with and without molecular-targeted therapy and squamous carcinoma in patients with bone metastasis at the time of non-small-cell lung cancer diagnosis.

Discussion

The overall prognosis of NSCLC for a substantial portion of patients remains poor, as the majority of patients have metastasis at the time of NSCLC diagnosis. Although several risk factors affect overall survival in NSCLC (10-15), it remains

Table VI. Risk factors of poor prognosis with SREs at the time of NSCLC (n=47) Cox proportional hazards model for survival.

	Univariate analysis		Multivariate analysis	
Factors	HR (95% CI)	P-value	HR (95% CI)	P-value
ECOG PS	**1.49 (1.10-2.00)**	**0.01**	**1.77 (1.30-2.42)**	**<0.001**
Adrenal gland metastasis	**3.11 (1.39-6.97)**	**<0.01**	2.01 (0.87-4.62)	0.10
Surgery for bone metastasis	0.39 (0.15-1.03)	0.06	**0.23 (0.08-0.69)**	**0.01**
Molecular-targeted therapy	**0.47 (0.22-0.99)**	**0.04**	**0.32 (0.14-0.72)**	**0.01**

Bold print indicates statistical significance. SREs, skeletal-related events; NSCLC, non-small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

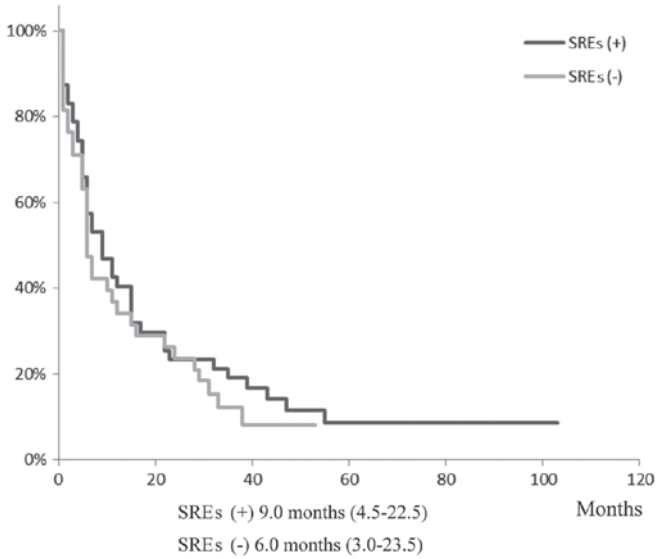

Figure 3. Kaplan-Meier analysis showed the overall survival of the patients with or without skeletal-related events (SREs) at the time of non-small-cell lung cancer diagnosis.

unclear which risk factors crucially affect SREs. It was hypothesized that examination of the risk factors for patients with SREs and bone metastasis at the time of NSCLC diagnosis would provide a more accurate prediction of prognosis and more suitable therapeutic strategies for these patient groups. Squamous cell carcinoma was found to be an independent risk factor for SREs at the time of NSCLC diagnosis. It has been reported that the frequency of distant metastases is higher in adenocarcinoma (3,16,17); there are discrepancies between those findings and the findings of the present study. It was also observed that the incidence rate of SREs was significantly higher in squamous cell carcinoma compared with that in adenocarcinoma patients at the time of NSCLC diagnosis. These findings suggest that bone metastasis of squamous cell carcinoma causes the development of SREs earlier compared with adenocarcinoma. The development of bone metastasis is a multistage process involving penetration of cancer cells from the surrounding tissue, invasion into the lymphatic or vascular circulation, transportation to the bone, proliferation in the bone tissue and bone destruction (18,19). Our findings suggest that bone metastasis from squamous cell carcinoma may destroy bone tissue more quickly compared with that from adenocarcinoma. Osteoclast cells in close proximity to bone metastases by squamous cell carcinoma were strongly activated for bone resorption (20), which supports this hypothesis.

Although SREs are reported to reduce quality of life, physical function, emotional happiness and overall survival (21-23), the present results revealed no difference in overall survival between the SRE and no SRE groups. Multivariate analysis revealed that a higher ECOG PS score was a risk factor for poor prognosis in patients with SREs at the time of NSCLC diagnosis, while surgery for bone metastasis and molecular-targeted therapy were factors for better prognosis. These findings indicated that radical cure may be considered for patients with SREs at the time of NSCLC diagnosis.

Multivariate analysis revealed that a higher ECOG PS score was a risk factor for poor prognosis, while molecular-targeted therapy was a factor for better prognosis in patients with bone metastasis at the time of NSCLC diagnosis. These findings are consistent with previous reports (4,24). Kaplan-Meier analysis revealed that adenocarcinoma with molecular-targeted therapy had a better prognosis compared with squamous carcinoma and adenocarcinoma without molecular-targeted therapy. All the cases treated with molecular-targeted therapy had adenocarcinoma with EGFR mutations. Adenocarcinoma with and without mutations may be categorized into different subgroups of NSCLC for prognosis research.

In addition, surgery for bone metastasis was found to be a factor for better prognosis. In accordance with our findings, several reports demonstrated that a surgical approach to metastatic NSCLC may improve prognosis (25-27). There is a possibility that surgery was performed only on patients who were expected to have better prognosis. Nonetheless, our multivariate analysis included several critical explanatory variables for prognosis, including ECOG PS, number of bone metastases, visceral metastasis, SREs, chemotherapy, and molecular-targeted therapy. The inclusion of these critical prognostic factors in the multivariate analysis excludes a significant deviation in the indication for surgery by prediction of overall survival.

The multivariate analysis revealed that metastasis to the adrenal gland was a risk factor for poor prognosis. The adrenal gland is a major site of NSCLC metastases (15%) (28). Adrenal metastases of NSCLC usually exhibit hematogenous spread to other sites. In accordance with our findings, it has been

reported that NSCLC metastasizing to the adrenal glands is incurable (29,30).

There were several limitations to the present study: Data collection was retrospective. Furthermore, although the majority of cases with bone metastasis should be referred to the Department of Orthopaedic Surgery of Kagoshima University Hospital, as this is the only university hospital that undertakes orthopedic surgery and therapeutic radiology, several cases were referred to other hospitals in the area.

Several prognostic factors for SREs and bone metastasis patients at the time of NSCLC diagnosis were identified. While surgical treatment and molecular-targeted therapy improve the prognosis of patients with SREs or bone metastasis at the time of NSCLC diagnosis, patients with higher ECOG PS score and adrenal metastasis may benefit more from radiotherapy or best supportive care.

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