Original Article

Prognostic Factors in Lung Adenocarcinoma with Brain Metastasis

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Abstract

Introduction: Brain metastasis (BM) is significantly seen in lung adenocarcinoma and adversely affects survival. We aimed to evaluate the factors affecting the prognosis in patients with BM diagnosed with lung adenocarcinoma. **Materials and Methods:** Patients with BM between 2012 and 2022 were reviewed retrospectively. Demographic characteristics of the patients, primary tumor characteristics, presence of mutation, BM number, localization, size, development time, and treatment characteristics were evaluated. Inflammatory indices at the time of BM were examined. The overall survival time was calculated. **Results:** About 92.9% of 113 patients were male, the median age was 62 years (54.5–68.5), and follow-up was 8 months (3–18). BM was detected at the time of diagnosis in 62 (54.9%) of the patients, whereas BM developed later in 51 (45.1%) patients. Systemic treatment was applied to 72.5% of the patients. Survival was lower in patients with BM at diagnosis (4 vs. 14 months, $P < 0.001$). Primary tumor maximum standardized uptake value level was higher on fluorodeoxyglucose-positron emission tomography-computed tomography at diagnosis in patients with late BM ($P = 0.004$). The development time of BM was 9 months (4–16), and the median survival was 8 months (6.2–9.8). There was no difference between tumor localization or inflammatory indices and the development of BM and prognosis. The presence of BM at diagnosis and lack of systemic treatment were found to be factors that independently reduced survival ($P < 0.001$, $P = 0.007$). **Conclusion:** The presence of BM at diagnosis significantly reduces survival. It has been observed that systemic treatments applied in addition to local treatments have a positive effect on the prognosis.

Keywords: Brain metastases, inflammatory indices, lung adenocarcinoma, survival, systemic therapy

Introduction

Lung cancer is the most important cause of cancer-related death in men and women. Lung adenocarcinomas constitute a significant portion of nonsmall cell lung cancers (NSCLCs). It differs from other lung cancers in histology, mutational status, and behavior. Brain metastasis (BM) is more common than other histological subtypes.[1,2] The brain is an area where metastases are more common than primary tumors. It has been shown that BM develops at the time of diagnosis in 10%–20% of NSCLCs, whereas BM develops later in 25%–30%.[3,4] Knowing the prognostic factors in patients with BM is important in terms of patient follow-up, treatment, and survival. It is important to control the BM with surgical and radiotherapy treatments and with systemic treatments. Especially in patients with targeting mutations, survival improves significantly with systemic treatments.[4,5]

The prognostic role of inflammation indices in both early and advanced stages of lung cancer has been investigated. Studies have heterogeneous results, and the prognostic role of inflammatory and nutritional indices in patients with BM has not been evaluated.[6,7]

The aim of our study is to evaluate the factors affecting the prognosis in patients with BM diagnosed with lung adenocarcinoma. Knowing the prognostic factors in these patients and drawing attention to this issue will enable better

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management of patients with BM, which is difficult and difficult to control in the clinic.

Materials and Methods

Study design

This study was a retrospective cohort study.

Study setting

Lung adenocarcinoma patients who applied to the radiation oncology outpatient clinic between 2012 and 2022 were evaluated.

Sample size

Brain metastases were detected in 162 of 1253 lung adenocarcinoma patients. One hundred and thirteen patients who met the study criteria were evaluated.

All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2000.

IRB approval

The study was carried out with the relevant center's work permit numbered E-642471-79-799 and dated April 28, 2022.

Criteria for inclusion

1. Patients aged ≥18 years with a diagnosis of lung adenocarcinoma
2. Presence of BM
3. No synchronous cancer
4. No active infection at the time BM was detected
5. At least a 2-month follow-up in our center.

Criteria for exclusion

1. Patients who did not receive oncological treatment
2. Patients with immunosuppressive disease
3. Patients who underwent surgery for BM and primary tumor.

Demographic characteristics of patients such as age and gender, primary tumor location and size in the lung, tumor fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) maximum standardized uptake value (SUV_{Max}) levels in the lung at the time of diagnosis, extracranial metastases (ECMs) locations and number, BM location and number, largest tumor diameter of BM, date of BM, whether or not radiotherapy was administered to the patient, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene-1 (ROS-1) mutation status, and the types of systemic treatments (chemotherapy/tyrosine kinase inhibitor/immunotherapy) administered to the patient were noted.

Survival assessment

The patients have been followed until January 2022. Overall survival (OS) was calculated as the time of diagnosis to death or last follow-up.

From the laboratory parameters at the time the patients were diagnosed with BM, neutrophil count/lymphocyte count, platelet count/lymphocyte count, monocyte count/lymphocyte count, hemoglobin albumin lymphocyte and platelet score (HALP=hemoglobin (g/L) × albumin (g)' /L) × lymphocyte count/platelet count) and systemic immune-inflammation index = platelet count × neutrophil count/lymphocyte count were calculated.[6-8]

Statistics

SPSS 22.0 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY) statistical package program was used in the analysis of the data. Descriptive statistics of evaluation results; numbers and percentages for categorical variables, mean, standard deviation, median, and minimum and maximum for numerical variables were given. Receiver operating characteristic (ROC) analysis was performed to determine the threshold value to evaluate the laboratory parameters. Chi-square test was used to compare qualitative data. Kaplan–Meier test was used for survival analysis. Factors affecting survival were evaluated with Cox regression analysis. The statistical alpha significance level was accepted as $P < 0.05$.

Results

Of the 113 patients, 105 (92.9%) were male and 8 (7.1%) were female. Data on the clinical features of the patients are shown in Table 1. The median age was calculated as 61.51 ± 10.49 (32–86). Tumor localization of 110 patients was evaluated. The tumor of 58 patients (52.7%) was located in the right lung, and the tumor of 52 (47.2%) patients was located in the left lung.

BM was detected at the time of diagnosis in 62 patients (54.9%), whereas BM developed in 51 patients (45.1%) without BM at the time of diagnosis, within a median of 9 months (4–16). The mean size of their BM was 2.36 ± 1.46 cm (0.34–10). About 61.1% of BMs were multiple and 62.1% were supratentorial localized. Seventy patients (61.9%) had ECMs, of which 74.3% had multiple metastases. The targetable mutation was detected in 9 (7.9%) patients. Systemic treatment was applied to 82 patients (72.5%), and whole-brain radiotherapy (WBRT) was applied to 91 patients (84.3%).

The characteristics of patients with BM at diagnosis and patients with late BM were compared in Table 2. There was no difference between the two groups in terms of age, gender, tumor diameter, tumor localization, number of BM, BM location, BM size, presence of ECMs, presence of mutation, and inflammatory indices. Primary tumor SUV_{max} level was high in FDG-PET/CT in patients who developed late BM ($P = 0.004$). Survival time was significantly reduced in those with BM at diagnosis (4 vs. 14 months, $P < 0.001$).

During a median follow-up of 8 months (3–18), 110 patients (97.3%) died. Median OS was 8 months (6.2–9.8). While OS was 4 months (2.5–5.5) in patients with BM at diagnosis, 14 months (7.9–20.1) in those with late BM, which was statistically significant [$P < 0.001$, Figure 1].

Table 1: Demographic and clinical characteristics of patients

	n (%)
Gender	
Male	105 (92.9)
Female	8 (7.1)
Age Mean±SD (minimum-maximum)	61.51±10.49 (32–86)
Tumor size Mean±SD (minimum-maximum)	4.8±2.2 (1.1–10.8)
Tumor size (cm)	
≥3	78 (76.5)
<3	24 (23.5)
Tumor localization	
Right upper	36 (32.7)
Right middle	9 (8.2)
Right lower	13 (11.8)
Left upper	39 (34.5)
Left lower	13 (11.8)
Tumor SUV_{max} mean±SD (minimum-maximum)	14.38±10.81 (3.7-84.0)
Median (IQR)	12.50 (8.55-17.08)
Brain metastasis time	
Initial metastasis	62 (54.9)
Late metastasis	51 (45.1)
The time between first diagnosis and the first appearance of brain metastasis (month), median (range)	
Whole group	0 (0–7.5)
Late metastases	9 (4–16)
Maximum size of brain metastasis (cm) median (range)	2.1 (1.3–3.1)
Location of brain metastasis	
Supratentorial	64 (62.1)
Infratentorial	14 (13.6)
Bilateral	25 (24.3)
Number of brain metastases	
1	44 (38.9)
≥2	69 (61.1)
Whole-brain radiotherapy	
Yes	91 (84.3)
No	17 (15.7)
Presence of ECM	
Yes	70 (61.9)
No	43 (38.1)
Location of metastasis	
Multiple	52 (46.1)
Liver	1 (0.9)
Bone	8 (7.1)
Brain	33 (29.2)
None	10 (8.8)
Others	9 (7.9)
Mutation status	
EGFR	8 (88.9)
ALK/ROS-1	1 (11.1)
Treatment modalities	
Chemotherapy	70 (85.4)
Chemotherapy after TKI	9 (11.0)
Chemotherapy + immunotherapy	1 (1.2)
TKI	2 (2.4)
Death	
Yes	110 (97.3)
No	3 (2.7)
OS (month), median (range)	8 (6.2-9.8)

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS-1: ROS proto-oncogene-1, TKI: Tyrosine kinase inhibitors, SD: Standard deviation, IQR: Interquartile range, OS: Overall survival, SUV_{max}: Maximum standardized uptake value, ECM: Extracranial metastasis

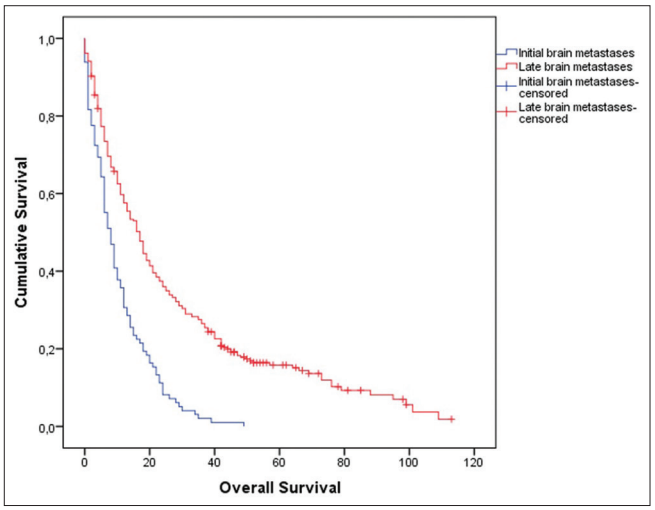

Figure 1: OS between those with brain metastases at diagnosis and those with subsequent brain metastases. OS: Overall survival

In univariate analysis in Table 3, it was observed that advanced age, BM at diagnosis, and lack of systemic treatment decreased survival ($P = 0.009$, $P < 0.001$, and $P < 0.001$). The presence of BM at diagnosis and the absence of systemic treatment were found to be factors that independently reduced survival in the multivariate analysis ($P < 0.001$, $P = 0.007$).

Discussion

The presence of BM is an important problem in lung adenocarcinomas. Having a BM at diagnosis adversely affected the prognosis and significantly reduced survival (4 vs. 14 months, $P < 0.001$). The time to develop BM after diagnosis was 9 months (4–16), and those with late BM had a higher level of primary tumor FDG-PET/CT SUV_{max} at diagnosis. High SUV_{max} levels may predict BM development. There was no correlation between the presence of BM and inflammatory/nutritional indices. Systemic treatment had a positive effect on survival ($P = 0.007$).

Due to the blood–brain barrier, the brain is a very difficult and complex region to metastasize.[3] Lung cancer, breast cancer, and malignant melanoma are the tumors that metastasize to the brain most frequently.[9] The incidence of BM in NSCLC is 20%–60% and approximately 15% of patients have BM at diagnosis.[3] The risk of developing BM in lung

Table 2: Relationship between demographic, clinical, and laboratuvar parameters in patients

	Total (*n*=113; 100.0%), *n* (%)	Initial metastases (*n*=62; 54.4%), *n* (%)	Late metastases (*n*=51; 44.7%), *n* (%)	*P*
Age (mean)	61.51±10.49	61.84±10.56	61.12±10.49	0.718**
Gender (male/female)	105 (92.9)/8 (7.1)	57 (91.9)/5 (8.1)	48 (94.1)/3 (5.9)	0.728††
Tumor size (cm), mean	4.8±2.2	4.8±2.1	4.8±2.4	0.892**
Tumor localization (right/left)	58 (52.7)/52 (47.3)	34 (55.7)/27 (44.3)	24 (49.0)/25 (51.0)	0.480**
Tumor SUV_{max}				
Mean±SD (minimum-maximum)	14.38±10.81 (3.7-84.0)	12.8±11.2 (3.7-84.0)	17.0±9.8 (5.7-52.8)	0.004‡‡
Median (IQR)	12.50 (8.55-17.08)	11.8 (7.8-13.6)	15.1 (10.3-18.4)	
Number of brain metastasis (one/multiple)	44 (38.9)/69 (61.1)	26 (41.9)/36 (58.1)	18 (35.3)/33 (64.7)	0.598††
Location of brain metastasis				
Supratentorial	64 (62.1)	38 (67.9)	26 (55.3)	0.406††
Infratentorial	14 (13.6)	6 (10.7)	8 (17.0)	
Bilateral	25 (24.3)	12 (21.4)	13 (27.7)	
Presence of ECM (yes/no)	70 (61.9)/43 (38.9)	38 (61.3)/24 (38.7)	32 (62.7)/19 (37.3)	1.000††
Mutation status				
EGFR	9 (90.0)	3 (75.0)	6 (100.0)	0.400††
ALK/ROS-1	1 (10.0)	1 (25.0)	-	
Laboratuvar parameters				
NLR	3.53 (2.39-5.90)	3.82 (2.51-6.18)	3.28 (1.97-5.58)	0.304‡‡
PLR	169.23 (105.11-237.65)	176.30 (101.32-251.03)	155.55 (104.76-227.64)	0.586‡‡
MLR	0.38 (0.25-0.54)	0.42 (0.26-0.55)	0.36 (0.25-0.51)	0.497‡‡
HALP	30.05 (18.45-47.50)	30.23 (17.51-49.78)	30.05 (19.26-47.40)	0.968‡‡
SII	981.55 (551.29-1583.53)	1011.57 (576.14-1643.20)	904.80 (505.67-1562.63)	0.338‡‡
OS (month)	8 (6.2-9.8)	4 (2.5-5.5)	14 (7.9-20.1)	<0.001***

**Student's *t*-test, ***Kaplan-Meier test, ††Chi-square test, ‡‡Mann-Whitney *U*-test. ECM: Extracranial metastasis, EGFR: Epidermal growth factor receptor, ALK: *Anaplastic lymphoma kinase,* ROS-1: ROS proto-oncogene-1, HALP: Hemoglobin albumin lymphocyte and platelet score, SII: Systemic immune-inflammation index, SD: Standard deviation, IQR: Interquartile range, OS: Overall survival, SUV_{max}: Maximum standardized uptake value, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MLR: Monocyte lymphocyte ratio, OS: Overall survival

adenocarcinomas is higher than in other NSCLCs. BMs mostly develop hematogenously. They are seen in parietal and frontal gray-white junctions fed by the middle cerebral artery, followed by 15% in the cerebellum and 5% in the brain stem.[3,9] In our study, 78% of the patients had cerebrum metastases.

In studies, age, gender, performance status, tumor histology, stage, presence of nodal involvement, presence and number of ECMs, high carcinoembryonic antigen (CEA), EGFR, and ALK status were shown as risk factors for the development of BM.[3,9-11] In the study of Waqar *et al*., age <70 years, adenocarcinoma/large cell histological subtype, tumor > 3 cm, Grade ≥2, or node positivity were reported as a high-risk group.[12] However, in the study of Maldonado *et al*., adenocarcinoma histology, the presence of EGFR/ALK mutation or CEA >20 was determined a high risk.[13] In our study, most of the patients were male, under 65 years of age, with multiple ECMs. In the literature, it has been shown in some studies that tumors in the lower lobes have a more aggressive course due to the difficulty of applying local treatments, but this could not be demonstrated in some.[14,15] In our study, patients with BM had a normal distribution in primary tumor localization. No difference was found between primary tumor localizations at diagnosis and in tumors with late BM.

BMs usually occur in the last stage of the disease and there are concomitant widespread systemic metastases. The most common bone and least lymph node metastases are accompanied by distant organ metastases.[3] In our study, 61.9% of the patients had ECM, excluding BM, and 74.2% of them were multiple. The most common isolated site of distant metastasis other than BM was bone in line with the literature.

Lung adenocarcinomas are the histological subtype in which targeting mutations are common. The incidence of EGFR mutation is 40%–60%, especially in nonsmoker, female gender, and Asian race.[16] This rate decreases to 10% in the Western population, as in our study.[17] Although it is known that EGFR mutations increase tumor invasion and metastasis, it has not yet been clarified why the risk of BM is increased in those with EGFR mutations. A quarter of patients with mutations are at risk of having BM at diagnosis. BMs of these patients tend to be small, multiple, and disseminated.[18] In some studies, it has been reported that EGFR mutation status may differ in primary tumor and BM, although it is rare (0.28%).[19] Despite the presence of BM, survival can be improved in these patients with systemic treatments and targeted drugs (osimertinib, afatinib, and erlotinib). Today, other targetable mutations are ALK, ROS-1 rearrangement, MET Exon 14 skip mutation, RET rearrangement, BRAF V600E, HER-2, KRAS G12C, and NTRK1/2/3 gene fusion are less common targeting mutations.[9] Since our study examined patients with BM from 2012 to the present, our

Table 3: Factors affecting overall survival in univariate and multivariate analysis

	P	OR	95.0% CI
Univariate Cox regression analyses			
Age (reference: <65 years) ≥65 years	0.009	1.685	1.137-2.496
Gender (reference: Male) Female	0.725	0.877	0.421-1.826
Tumor size <3 cm ≥3 cm	0.606	1.132	0.706-1.815
Inıtial brain metastasis Late metastasis	<0.001	2.481	1.669-3.688
Number of brain metastasis (reference: 1)	0.217	1.277	0.866-1.883
Location of brain metastasis (reference: supratentorial)			
Infratentorial	0.707	0.894	0.499-1.602
Bilateral	0.830	0.949	0.590-1.527
Size of brain metastasis	0.079	0.889	0.779-1.014
Presence of extracranial metastasis	0.713	0.930	0.631-1.370
Presence of multiple metastases	0.294	1.225	0.838-1.791
Presence of EGFR/ALK/ROS-1 mutation	0.235	0.659	0.332-1.311
Receiving systemic therapy (reference: available) none	<0.001	2.764	1.746-4.377
Receiving TKI therapy	0.331	1.385	0.718-2.670
NLR	0.997	1.000	0.977-1.023
PLR	0.265	1.001	0.999-1.003
MLR	0.985	0.995	0.572-1.729
Hemoglobin albumin lymphocyte and platelet score	0.755	1.001	0.995-1.007
Systemic immune-inflammation index	0.413	1.000	1.000-1.000
Tumor PET CT SUV_{max}	0.677	0.996	0.976-1.016
Multivariate cox-regression analyses			
Age (reference: <65 years) ≥65 years	0.069	1.473	0.970-2.237
Inıtial brain metastasis Late metastasis	<0.001	2.168	1.419-3.13
Receiving systemic therapy (reference: Available) none	0.007	1.977	1.207-3.239

EGFR: Epidermal growth factor receptor, ALK: *Anaplastic lymphoma kinase,* ROS-1: ROS proto-oncogene-1, OR: Odds ratio, CI: Confidence interval, TKI: Tyrosine kinase inhibitors, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MLR: Monocyte lymphocyte ratio, SUV_{max}: Maximum standardized uptake value, PET: Positron emission tomography, CT: Computerized tomography

targeting mutation rates were found to be lower than the literature.

Inflammation is a hallmark of cancer. It has been associated with tumor growth, invasion, and metastasis. Cancer patients are mostly immunosuppressive and chemotherapy treatments also deepen immunosuppression.[20] Inflammatory and nutritional indices reflect the tumor microenvironment and their prognostic role has been investigated in many tumors.[6-8] In our study, no difference was found between nutritional and inflammatory indices and survival. This situation can be explained by other factors affecting the prognosis of this patient group.

It is known that a high FDG-PET/CT SUV_{max} level of the primary tumor in lung cancer is a poor prognostic factor.[21] In imaging performed to evaluate the response to oncological treatments, changes in tumor metabolism can predict prognosis. In our study, it was observed that a high rate of BM developed in patients with high FDG-PET/CT SUV_{max} levels in the primary tumor at diagnosis. This supports the prognostic role of FDG-PET/CT.

The main treatment in BMs consists of surgery, radiotherapy (WBRT, stereotactic radiosurgery), and systemic treatments (targeted therapies, chemotherapy).[22] The location, number, localization of BM, mutation status, and control of the primary disease are factors that affect treatment selection. Rodrigus *et al*. showed that survival in patients with isolated single BM was better than those with multiple ECMs.[23] Sakamoto *et al*. also showed that the prognosis of patients with relapse with BM alone is better than those with combined ECMs.[24] In our study, only 29.2% of the patients had isolated BM. It is thought that this situation is not reflected in statistical significance due to the limited number of patients. Xue *et al*. compared the patients with BM at diagnosis and those who subsequently developed BM and showed that the presence of BM at diagnosis negatively affects survival.[25] This situation was also supported in our study. Studies have shown that adding systemic treatments to local treatments improves survival.[9,26] In our study, it was shown that survival was better in those who added systemic treatment to local treatments. The 2-year survival in NSCLC is <10% in the presence of the BM. Patchell *et al*. reported that the median survival was 6 months in patients with BM at diagnosis.[27] Sugimura *et al*. found the median OS of patients with BM for the first relapse to be 8 months.[28] Although we were not included in our study due to the scarcity of patients who underwent brain surgery, our survival rates were similar to those in the literature. In our study, it was observed that the primary factor determining the prognosis was the application of local and systemic treatments in patients with BM.

Our study is based on real-life data in which retrospective, single-center data were analyzed. Our limitations are the limited number of our patients and the fact that they were not included in the study due to the small number of patients who underwent surgery. In this regard, it is important to conduct comprehensive studies involving larger numbers of patients.

Conclusion

The presence of BM is still one of the most important problems for lung adenocarcinomas and detection of BM at diagnosis has been shown to significantly reduce survival. Systemic treatment was found to have a positive effect on prognosis. These patients should be approached multidisciplinary and it is beneficial to add systemic therapy to the treatment according to the presence of targeting mutation and local control.

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Conflicts of interest

There are no conflicts of interest.

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