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Original Article

Overall survival and prognostic factors in lung cancer patients with brain metastases

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Abstract

Aim: The aim of this study was to investigate overall survival in patients with lung cancer with brain metastasis. Our other aim was to investigate prognostic value of the maximum standardized uptake value (SUVmax) of primary tumor on ^{18}Fluorine-fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET / CT) FDG PET / CT and other clinicopathological parameters.
Material and Methods: Fifty-eight patients with lung cancer who underwent for oncologic purpose and had metastatic lesions in the brain were included in the study. The location of the primary lung mass and whether other organ metastases presence was evaluated on the ^{18}F-FDG PET / CT. In axial images, the volume of interest (VOI) was plotted semi-automatically to include lung tumor tissue and SUVmax of the primary lung tumor was measured. Survival analyzes were performed with Kaplan-Meier survival analysis. The prognostic value of the parameters was evaluated using Cox regression analysis.
Results: Of the 58 patients included in the study, 6 (10%) were female and 52 (90%) were male. The mean age was 64.8 ± 9.5 years. The mean SUVmax of primary tumor was 10.4 ± 4.5. Median survival was 7 months. Patient age and localization of the primary tumor were prognostic factors for survival in univariate analysis, whereas sex, SUVmax of primary tumor, presence of distant metastasis outside the brain, histologic subtype, surgical status of the metastatic brain mass and treatment type were not. Overall survival was lower in patients with primary tumor located in the left lung than in the right lung.
Conclusion: In conclusion, age and localization of primary tumor are prognostic factors, whereas SUVmax of primary tumor does not appear to be a prognostic factor in lung cancer patients with brain metastases.

Keywords: Lung cancer; brain metastasis; FDG PET / CT

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in men (1). Distant metastasis often coexists with the primary tumor at diagnosis. Metastasis may occur more rapidly through the hematogenous pathway than the lymphatic pathway. Lung cancer is the most common type of cancer that metastasizes to the brain. Intracranial metastasis can be seen in 30% of patients with lung cancer. In addition, bone and adrenal glands are the most common sites of metastasis (2,3). Staging in lung cancer plays a very important role in the choice of treatment. ^{18}F-FDG PET / CT is a recommended imaging method for lung cancer staging in guidelines (4), its use is increasing over time. Although surgery is recommended as the first-line treatment option in patients without distant metastasis, systemic therapies are preferred in case of distant metastasis. Surgery in lung cancer with brain metastasis is preferred in limited conditions (single lesion in the brain and no extracranial metastasis), whereas chemotherapy, immunotherapy and whole brain radiotherapy (WBRT) are frequently preferred treatment methods (5). In patients with brain metastasis; tumor subtype, chemotherapy and surgery for brain metastasis were associated with prognosis (6). The aim of this study was to evaluate overall survival in patients with lung cancer diagnosed with brain metastasis and to investigate the SUVmax value of primary tumor in ^{18}F-FDG PET / CT, and prognostic value of other clinical, pathological and demographic parameters.

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MATERIAL and METHODS

Patients

In our study; 58 patients with lung cancer who underwent ^{18}F-FDG PET / CT in our department between 2014 and 2018 and who had metastatic mass lesion in the brain detected by surgery, biopsy or radiology were enrolled. 51 patients were diagnosed histopathological (from brain mass or primary malignancy) and 7 were diagnosed by final clinical decision. Clinical, laboratory and imaging (chest radiography, chest CT, PET / CT) findings were considered in the final clinical decision. The time from diagnosis to death was calculated. The follow-up period ranged from 1 to 50 months.

F-18 FDG PET / CT

The images of the patients were obtained with PHILIPS GEMINI TF 16 Slice PET / CT device. In patients who had fasting for at least 6 hours; FDG (0.1 mCi / kg) injection was administered intravenously if the blood glucose level was below 200 mg/dl. Images were obtained 1 hour after the injection. Firstly, non-diagnostic CT and thereafter PET images were obtained. PET emission images were taken at 9-10 bed positions with 1.5 minutes per bed. CT and PET images were loaded on the workstations and CT data was used for attenuation correction. Patients were evaluated for primary lung mass and brain and other organ metastasis. On axial images, VOI was plotted semi-automatically to include lung tumor tissue and SUVmax of the primary lung tumor was measured.

Statistical Analysis

All statistical analyzes were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL). Univariate Cox regression analysis was used to analyze the prognostic value of age, sex, histopathological parameters and ^{18}F-FDG PET / CT findings in terms of overall survival. Survival analyzes were performed with Kaplan-Meier survival analysis with log rank test. P <0.05 was considered statistically significant.

RESULTS

Fifty-eight patients included in the study; 6 (10%) were female and 52 (90%) were male. The mean age was 64.8 ± 9.5 years. The diagnosis of the 24 (41%) patients was made by surgery for brain mass, 8 (14%) by biopsy for brain mass, 19 (33%) by lung biopsy, 7 (12%) by clinical and imaging methods. During 50 months follow-up period; fifty-five (95%) patients had died and 3 (5%) were alive. While 13 (22%) patients had no metastasis other than lung and brain, 19 (33%) had mediastinal lymph node metastasis and 26 (45%) had other metastases.

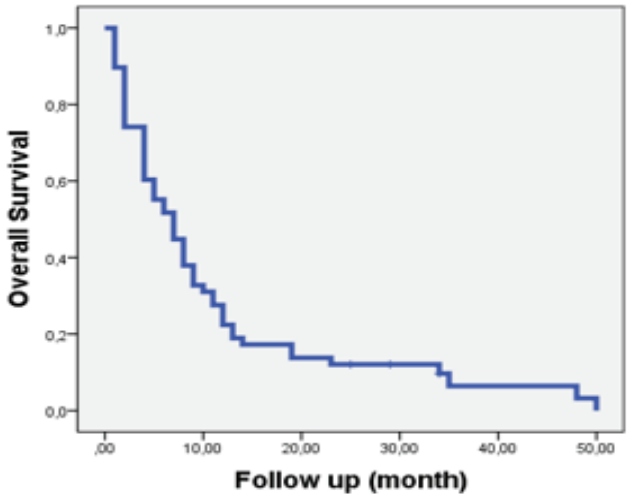

Figure 1. Kaplan-Meier estimate of overall survival

Table 1. Univariate analysis of death

Variables	Univariate			
	Wald	HR	95 % CI	P
Sex (F/M)	0.039	1.090	0.464-2.560	0.843
Age	4.429	1.032	1.002-1.063	0.035*
SUVmax of primary tumor	0.737	1.026	0.969-1.087	0.391
Is there extracranial metastasis? (yes/no)	0.029	0.945	0.496-1.803	0.864
Histological type (SCLC/NSCLC)	1.671	0.610	0.288-1.291	0.196
Location of primary tumor (right lung/left lung)	4.853	0.536	0.308-0.934	0.028*
Has a metastatic mass in the brain been operated? (yes/no)	0.283	NA	NA	0.868
Treatment type (chemotherapy / radiotherapy /operation)	6.890	NA	NA	0.333

SUVmax: maximum standardized uptake value; SCLC: Small cell lung cancer, NSCLC: Nonsmall cell lung cancer; NA: not applicable *=p<0.05

The most common site of metastasis outside the brain is in bones (17 patients), adrenal glands (9 patients), and contralateral lungs (6 patients). The mean SUVmax of the primary tumor was 10.4 ± 4.5. Median survival was 7 months (range, 1 to 50 months) (Figure 1). The methods used for treatment; five (8.6%) patients had chemotherapy only, 17 (29%) radiotherapy, 19 (33%) chemotherapy and radiotherapy, 2 (3%) brain surgery, 4 (7%) brain surgery + radiotherapy, 1 (2%) brain surgery + chemotherapy, and 10 (17%) patients had not received any treatment.

All the 3 surviving patients were male. Two patients had mediastinal lymph node metastasis and one patient had no other metastasis. Three of them were located in the right lung and 3 of them were NSCLC patients. The metastatic mass in the brain was operated in 3 patients.

In univariate analysis; patient age and localization of the primary tumor had prognostic value in terms of survival. Sex, SUVmax value of primary tumor, presence of distant metastasis outside the brain, histological subtype, whether metastatic brain mass was operated, and treatment type did not have significant prognostic value (Table 1).

The Kaplan-Meier analysis, for the overall survival according to location of primary tumor, is shown in Figure 2. There was a significant difference in overall survival for localization of the primary tumor in the right or left lung (p =0.018). Median survival was 5 months in patients with primary tumor at left lung and 9 months in patients with primary tumor at right lung.

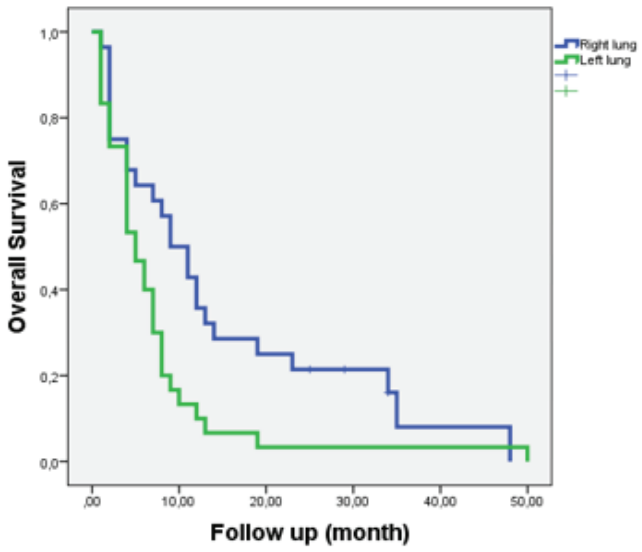

Figure 2. Kaplan–Meier curve depicting the overall survival according to Location of primary tumor (p<0.018)

The Kaplan – Meier analysis, for the overall survival according to age, is shown in Figure 3. There was a significant difference between patients 65 years and under, and those older than 65 years in terms of overall survival (p = 0.039). Median survival was 7 months in patients with ≤65 years and 6 months in patients with > 65 years.

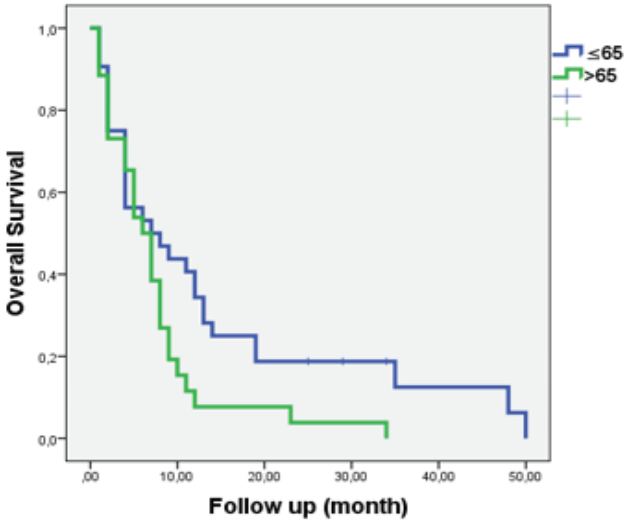

Figure 3. Kaplan–Meier curve depicting the overall survival according to age (p<0.039)

DISCUSSION

In our study, overall median survival was 7 months in patients with lung cancer with brain metastasis. In univariate analysis; age of patient and tumor location (right or left lung) was prognostic factors.

Brain metastasis is a common site of metastasis in lung cancer and its prognosis is poor. In studies conducted to investigate prognostic parameters in lung cancer patients with brain metastasis; radiotherapy, systemic chemotherapy, surgical removal of metastatic brain mass and histological subtypes are defined as prognostic factors in the literature (6-9). In the study conducted by Kanau et al. (7) reported that patients with brain metastasis in non-small cell lung cancer (NSCLC) had low survival, but surgical resection, normal carcinoembryonic antigen (CEA) level, small tumor size, and lymph node negativity could be beneficial. Bernhardt et al. (8) reported that surgical treatment after WBRT is a prognostic factor in patients with small cell lung cancer (SCLC) with single brain metastasis. Bae et al. (6) reported that adenocarcinoma histologic type, long disease-free period, systemic chemotherapy, local surgery for brain metastasis are independent positive prognostic factors for survival in NSCLC patients with brain metastasis without extracranial metastasis. In the study of Lin et al. (9) detected that gamma knife combined with systemic chemotherapy contribute significantly to survival in patients with NSCLC with brain metastases. In our study, histologic type (NSCLC or SCLC), extracranial metastasis or treatment combinations did not have a significant effect on overall survival.

^{18}F-FDG PET / CT is a recommended and frequently used test for staging and restaging in lung cancers. It has been shown to have 70% sensitivity and high specificity in detecting brain metastases (10). It is known that SUVmax

value on ^{18}F-FDG PET / CT has prognostic value in patients with stage I-III lung cancer. Studies have shown that overall survival is lower in patients with high SUVmax, and that the risk of recurrence and risk of distant metastases are increased (11,12). In the study conducted by Yoo et al., MTV was a prognostic factor in patients with stage IV lung cancer, whereas SUVmax was not a prognostic factor (13139). Lee et al. showed that the body's metabolic tumor burden in ^{18}F-FDG PET / CT is an independent prognostic factor in patients with stage IV lung cancer (13). In our study, SUVmax value of primary tumor had no significant effect on prognosis in lung cancer patients with brain metastasis. In the light of these studies; SUVmax value of primary tumor loses its prognostic value in patients with distant metastasis of lung cancer, while metabolic tumor volume of primary tumor continues to be related with prognosis.

Age is one of the well-known prognostic factors in lung cancer (14). It was also found to be a prognostic factor in NSCLC patients with brain metastasis (15). In our study, age had a significant prognostic value in terms of overall survival in univariate analysis. Median survival was 7 months in patients aged ≤65 years and 6 months in patients aged > 65 years.

Studies showing that central or peripheral localization is a prognostic factor in lung cancer are available in the literature (16-19). In a study by Sun et al. (16), reported that centrally located tumors had negative prognostic value because they increased lymph node metastasis. In the study of Shaverdian et al. (17) emphasized that lower lobe localization is associated with poor prognosis in patients with stage 1 NSCLC undergoing stereotactic body radiation therapy (SBRT), and that the radiation therapy (RT) dose should be selected well. In the study of Ito et al. (18) indicated that tumor placement in the upper or lower lobes had a prognostic value, whereas it was not a significant prognostic factor in the right or left lung. In the study of Puri et al. (19), tumor site (right-left or upper-lower) did not have a significant relationship with prognosis in early stage NSCLC patients. In the study of Ye et al. (20) showed that tumors in the left lower lobe were a negative prognostic factor compared to tumors located in all other regions in patients with resectable, non-small cell lung cancer. In this study, LLL tumors were positively correlated with large tumor size and high degree of histology. It was thought that this relationship might be related to the difficulty of diagnosis due to left heart shadow. The results of our study were parallel to the results of the study by Ye et al. Tumors located in the left lung may be associated with lower survival, perhaps due to delay in diagnosis. However, since all patients had brain metastasis in our study, it seems controversial whether it may still be a factor in delayed diagnosis. In addition, there may be various limitations in RT planning of tumors located in the left lung. We think that more comprehensive studies are needed on this subject.

CONCLUSION

In conclusion, age and tumor localization were found to be prognostic factor for overall survival in in lung cancer patients with brain metastasis. The overall median survival of patients with primary tumor in the left lung was significantly lower to the right. SUVmax of primary tumor does not appear to be a prognostic factor.

Competing interests: The authors declare that they have no competing interest.
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