EJMI

DOI: 10.14744/ejmi.2024.70227
EJMI 2024;8(3):157–163

Research Article

Baseline Demographic and Clinicopathologic Characteristics Affecting Treatment Efficacy in Metastatic NSCLC

Nadiye Sever,[1] Emil Yunusov,[2] Abdussamet Çelebi,[1] Nargiz Majidova,[1] Erkam Kocaaslan,[1] Pınar Erel,[1] Yeşim Ağyol,[1] Ali Kaan Güren,[1] Selver Işık,[1] Rukiye Arıkan,[1] Osman Köstek,[1] Murat Sarı,[1] İbrahim Vedat Bayoğlu[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Marmara University Hospital, İstanbul, Türkiye
[2]Department of Internal Medicine, Marmara University Hospital, İstanbul, Türkiye

Abstract

Objectives: We investigated the effects of demographic characteristics and clinicopathologic factors on survival in patients with metastatic non-small cell lung cancer (mNSCLC).

Methods: We enrolled 320 patients treated for mNSCLC between January 2012 and December 2023. Progression free survival (PFS) and overall survival (OS) were evaluated. Univariate and multivariate analysis were performed for all parameters for prognostic evaluation.

Results: Among 320 patients; median age was 63 years. Either presence of bone metastasis (p=0.005), brain metastasis (p=0.024), liver metastasis (p=0.08) and the number of metastasis is 3 or more (p=0.02) were associated with better PFS in univariate analysis. ECOG performance status 0-1 (p=0.001), de novo metastatic disease (p=0.05), bone metastasis (p=0.001), brain metastasis (p=0.016), liver metastasis (p=0.00), also the number of metastasis 3 or more (p=0.001) and use of immunotherapy (p=0.00) were related with longer OS. In multivariate analysis, either presence of brain metastasis (HR:1.50, 95% CI:1.13-1.99, p=0.004), liver metastasis (HR: 1.53, 95% CI: 1.06-2.21, p=0.02), number of metastatic site (HR:0.72, 95% CI: 0.54-0.97, p=0.03) and use of immunotherapy (HR:0.37, 95 % CI: 0.26-0.52, p=0.00) remained significant predictors of OS.

Conclusion: Our results showed that liver and brain metastasis, number of metastatic site and use of immunotherapy were assosiated with survival and these can be used as stratification factors when designing randomized clinical trials.

Keywords: Survival, metastatic NSCLC, chemotherapy, immunotherapy

Cite This Article: *Sever N, Yunusov E, Çelebi A, Majidova N, Kocaaslan E, Erel P, et al. Baseline Demographic and Clinicopathologic Characteristics Affecting Treatment Efficacy in Metastatic NSCLC. EJMI 2024;8(3):157–163.*

Lung cancer is the most common cause of cancer deaths worldwide with an estimated 1.6 million deaths each year.[1] It is the most common type of cancer and one of the most common causes of cancer deaths in our country as in the whole world. The most important etiological factor in the formation of lung cancer is tobacco and tobacco products with a rate of 90%. It is more common in men than in women and the differences in smoking habits between men and women reflect the epidemiological changes in the incidence of lung cancer.[2] Non-small cell lung cancer (NSCLC), including the histological subtypes adenocarcinoma, squamous cell carcinoma and large cell carcinoma, represents approximately 85% of all new cases of lung cancer. Adenocarcinoma is the most common subtype of lung cancer in the United States and is also the most common histology in never-smokers.[3,4] Precisely defining the histo-

Address for correspondence: Nadiye Sever, MD. Division of Medical Oncology, Department of Internal Medicine, Marmara University Hospital, İstanbul, Türkiye
Phone: +90 546 660 66 21 **E-mail:** dr.nadya@hotmail.com

Submitted Date: August 14, 2024 **Revision Date:** October 07, 2024 **Accepted Date:** October 11, 2024 **Available Online Date:** October 22, 2024

logical subtype of lung cancer has become more important in the last few years due to the increasing number of therapeutic agents directed at specific subtypes.

Metastatic NSCLC (mNSCLC) treatment options include cytotoxic chemotherapy, targeted therapy and immunotherapy. The availability of targeted therapy and immunotherapy has changed the treatment paradigm and improved survival rates. New treatment options have led to an additional 11% reduction in mortality between 2018 and 2023. Platinum-based chemotherapy is the first-line treatment option in cancer patients without targetable driver mutations and without access to immunotherapy. In patients with disease progression under first-line treatment, second-line treatment options are limited and the expected overall survival is below 12 months despite treatment.[5] In addition to treatment options, there are many factors affecting survival, including the site of metastasis, performance status of the patient, tumour histology and the treatment used. In this study, we aimed to evaluate the 1st and 2nd line treatment responses, the effect of immunotherapy on survival and clinicopathological features affecting survival in patients with NSCLC.

Methods

Patients who were seen in the medical oncology outpatient clinic of our hospital between 2012 and 2023 and were diagnosed with non-small cell lung cancer (adenocancer or squamous cell cancer) and developed metastases at diagnosis or during follow-up were examined. 320 patients had no targetable driver mutation or translocation, who received at least one series of cytotoxic chemotherapy and were followed up for at least 3 months from diagnosis were retrospectively examined. The study was approved by our hospital's local ethics committee, approval number (22.04.2024.494). Demographic and clinical characteristics of the patients were accessed from patient files and electronic database. Age, gender, smoking history, Eastern cooperative oncology group (ECOG) performance status, comorbidities, medications used and tumor histology characteristics were recorded. In this study, clinicopathological features and treatment options affecting overall survival (OS) and progression-free survival (PFS) were examined.

Statistical Analysis

The data analysis was performed using SPSS 26.0 statistical software, with continuous data summarized as median and interquartile range. Categorical variables were analyzed using a Chi-square or Fisher's exact test. Survival curves were generated using the Kaplan-Meier method for each subgroup, with 95% confidence intervals (CIs). The log-rank test was used to compare the differences in survival between the groups. Prognostic factors were examined using univariate analysis, with subsequent examination of factors with a p-value of less than 0.5 in the multivariate analysis. Hazard ratios (HRs) for these comparisons were calculated using a Cox proportional hazards model. Statistical significance was established at $p<0.05$.

Results

The Study Population's Demographic and Clinical Characteristics

The study population consisted of 320 patients with a median age of 63 years (interquartile range: 57-69). The majority of patients were male (89.4%). The male/female ratio was 8.43. ECOG performance status showed that 90.6% of patients had a score of 0-1. Histopathological analysis revealed that the majority of patients had adenocarcinoma (58.1%) and the remainder had squamous cell carcinoma (41.9%). 73.5% of female and 56.3% of male patients had adenocarcinoma. 91.9% of patients have cigarette exposure. At diagnosis, the majority of patients (80.3%) presented with de novo metastasis and visceral metastasis being the most common (87.2%), followed by bone (44.7%), brain (27.5%) and liver (13.4%) metastases. A significant proportion of patients (34.7%) had metastasis in 3 or more organs. 91.9% of patients were exposed to smoking. 22.2% of patients used immunotherapy at any stage of treatment and 59.2% of patients used immunotherapy as first or second line treatment (Table 1).

Survival Analysis

The median PFS was 3.63 months (95% CI: 3.15-7.78). In addition, the median OS time was 12.9 months (95% CI: 7.12-21.8).

ECOG performance status 0-1 ($p=0.09$), Either presence of bone metastasis ($p=0.005$), brain metastasis ($p=0.024$), liver metastasis ($p=0.08$) and the number of metastasis is 3 or more ($p=0.02$) were associated with better PFS in univariate analysis. Multivariate analysis indicated that brain metastasis was a significant predictor of PFS (HR: 1.40, 95% CI: 1.07-1.83, $p=0.01$). Age, presence or absence of visceral metastasis at diagnosis were not significantly associated with PFS (Table 2).

Univariate analysis revealed that, ECOG performance status 0-1 ($p=0.001$), de novo metastasis ($p = 0.05$), either bone metastasis ($p=0.001$), brain metastasis ($p=0.016$) (figure 1a), liver metastasis ($p<0.001$) (figure 1b), the number of metastasis is 3 or more ($p=0.001$) (figure 1c) and use of immunotherapy ($p=0<0.001$) (figure 1d) were significantly related with longer OS. In multivariate analysis, presence of brain metastasis (HR:1.50, 95% CI:1.13-1.99, $p=0.004$), presence of liver metastasis (HR: 1.53, 95% CI: 1.06-2.21,

Table 1. Demographic and clinical characteristics of the study patients

	n	%		n	%
Age, (year) median (IQR)	63 (57-69)		De novo metastasis at diagnosis	257	80.3
Gender			Visceral metastasis	279	87.2
Female	34	10.6	Bone metastasis	143	44.7
Male	286	89.4	Brain metastasis	88	27.5
ECOG-performance score			Liver metastasis	43	13.4
0-1	290	90.6	Metastatic organ site		
2 and above	30	9.4	1-2	209	65.3
Charlson comorbidity index			3 and above	111	34.7
1-4	29	9.1	Immunotherapy	71	22.2
5-8	172	53.8	Smoking status		
8 and above	119	37.2	Ex- smoker	150	46.9
Histopathology			Smoker	144	45
Adenocarcinoma	186	58.1	None	26	8.1
Squamous cell carcinoma	134	41.9			

IQR: Interquartile range; ECOG: Eastern cooperative oncology group.

Table 2. Univariable and multivariable factors associated with PFS

	Univariate		Multivariate	
	Median PFS (95% CI)	**p**	**HR (95%CI)**	**p**
Age				
<65 years	4.6 (4.0-5.1)	0.55		
≥65 years	4.8 (3.7-5.9)			
Gender				
Female	3.3 (2.2-4.3)	**0.43**	Ref	0.18
Male	4.8 (4.3-5.3)		0.75 (0.50-1.13)	
ECOG-PS				
2 and above	3.6 (2.6-4.7)	**0.09**	Ref	0.39
0-1	5.2 (4.6-5.9)		0.83 (0.55-1.25)	
De novo metastasis (+)	4.6 (4.0-5.1)	0.51		
Metastasis at follow-up	5.7 (4.7-6.7)			
Visceral metastasis (-)	3.9 (2.5-5.3)	**0.21**	Ref	0.25
Visceral metastasis (+)	4.8 (4.1-5.5)		0.79 (0.52-1.18)	
Bone metastasis (-)	5.2 (4.4-6.0)	**0.005**	Ref	0.09
Bone metastasis (+)	3.8(3.3-4.4)		1.26 (0.96-1.65)	
Brain metastasis (-)	5.0 (4.2-5.7)	**0.024**	Ref	**0.01**
Brain metastasis (+)	4.2 (3.3-5.1)		1.40 (1.07-1.83)	
Liver metastasis (-)	4.8 (4.3-5.4)	**0.08**	Ref	0.4
Liver metastasis (+)	3.5 (2.6-4.4)		1.17 (0.80-1.70)	
Metastases number, ≥3	3.7 (3.0-4.3)	**0.02**	Ref	0.37
Metastases number, <3	5.1 (4.4-5.8)		0.87 (0.64-1.17)	
Immunotherapy				
No	4.4 (3.9-4.9)	**0.41**	Ref	0.75
Yes	5.3 (4.4-6.2)		0.95 (0.72-1.26)	
Histoloji				
SCC	4.3 (3.4-5.2)	**0.38**	Ref	0.31
Adenocancer	4.7 (4.1-5.3)		0.88 (0.70-1.12)	

PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern cooperative oncology group performance status; SCC: squamous cell cancer.

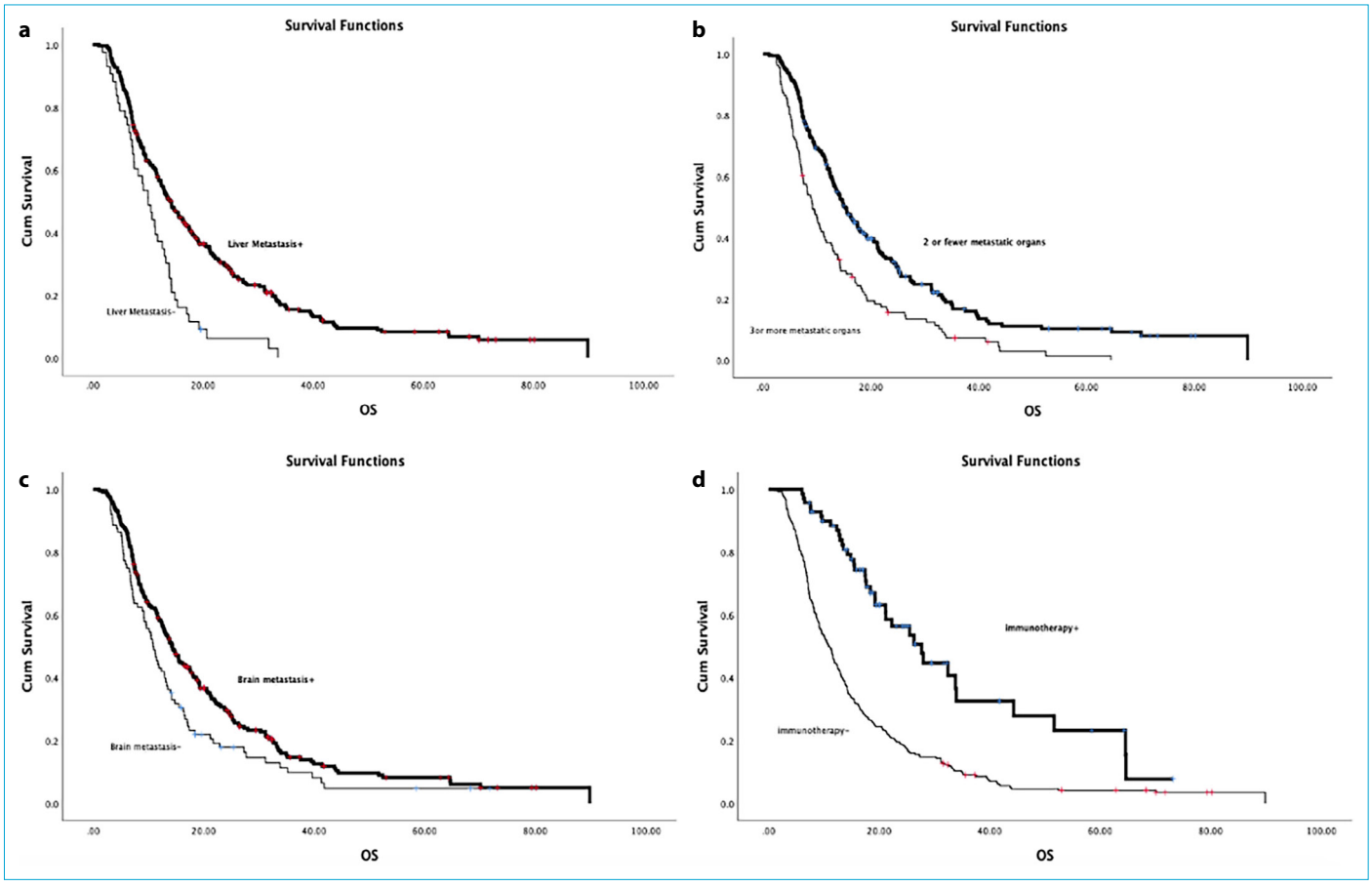

Figure 1. (a) Association of LV metastasis and survival. (b) Association of metastatic organ number and survival. (c) Association of brain metastasis and survival. (d) Association of use of immunotherapy and survival.

OS: Overall survival.

p=0.02), number of metastasis (HR:0.72, 95% CI: 0.54-0.97, p=0.03) and use of immunotherapy (HR:0.37, 95 % CI: 0.26-0.52, p=0.00) remained significant predictors of OS (Table 3).No difference was found in patients under 65 years of age compared to patients over 65 years of age when immunotherapy was used (p=0.53). In patients receiving immunotherapy, PDL-1 positivity and smoking history were not associated with overall survival (Table 4).

Discussion

When we investigated demographic characteristics and factors affecting survival in patients with mNSCLC, we found that brain metastasis, liver metastasis, number of metastatic organs (3 or more) at diagnosis and use of immunotherapy were associated with better OS in both univariate and multivariate analysis. In a multivariate analysis, brain metastasis was the only factor associated with better PFS. Histologic subtype, performance status, age, gender and bone metastasis were not associated with PFS and OS in multivariate analysis.

The landscape of lung cancer treatment has changed dramatically in the past decade. As more therapies both cytotoxic and biologic are approved, patients are living longer. Despite new treatment options, survival is poor in cases of with a high number of metastatic sites, liver and brain metastases. The brain is a common metastatic site for NSCLC, with 40–50% of patients developing brain metastases during the course of their disease.[6,7] Patients with NSCLC and brain metastases have a poor prognosis, with a median overall survival (OS) of 4 to 9 months with chemotherapy.[8] In our study, survival of patients without brain metastases was better than those with brain metastases. Median overall survival of patients with brain metastases was 10.8 months. Previous studies suggested that median survival increases to 10.9-16.4 months with surgery in a single brain metastasis.[9] Stereotactic radiosurgery is also an option in patients with brain metastases. Patients' age, performance status, neurological status, number, localization and diameter of tumors, and extent of primary disease were shown to be factors that influence the choice of the optimal treatment modality.[9] Due to the relatively small number of pa-

Table 3. Univariable and multivariable factors associated with OS

	Univariate		Multivariate	
	Median OS (95% CI)	**p**	**HR (95%CI)**	**p**
Age				
<65 years	13.3 (11.2-15.4)	0.62		
≥65 years	12.8 (10.5 -15.07)			
Gender				
Male	13.0 (11.5-14.5)	**0.21**	Ref	0.61
Female	13.4 (9-17.8)		1.11(0.72-1.72)	
ECOG-PS				
2 and above	7.6 (5.2-10)	**0.001**	Ref	0.18
0-1	13.5(12.1-15.0)		0.75 (0.50-1.14)	
De novo metastasis (+)	12.3 (11.2-13.6)	**0.05**	Ref	0.20
Metastasis at follow-up	19.3 (15.2-23.4)		0.80 (0.57-1.12)	
Visceral metastasis (-)	13.5 (12.1-15)	**0.2**	Ref	0.14
Visceral metastasis (+)	11.1(6-16.3)		0.72 (0.47-1.11)	
Bone metastasis (-)	14.8 (12.6-16.9)	**0.001**	Ref	0.07
Bone metastasis (+)	10.4 (7.8-13)		1.27 (0.97-1.67)	
Brain metastasis (-)	14.3 (12.4-16.1)	**0.016**	Ref	**0.004**
Brain metastasis (+)	10.8 (9-12.8)		1.50 (1.13-1.99)	
Liver metastasis (-)	14.2 (12.4-16.0)	**<0.001**	Ref	**0.02**
Liver metastasis (+)	10 (7.8 -12.3)		1.53 (1.06-2.21)	
Metastases number, ≥3	9.1 (7.5-10.8)	**<0.001**	Ref	**0.03**
Metastases number, <3	15.4 (12.9-17.9)		0.72 (0.54-0.97)	
Immunotherapy				
No	10.9 (9.4-12.3)	**<0.001**	Ref	**0.00**
Yes	27.6 (20.6-34.7)		0.37 (0.26-0.52)	

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern cooperative oncology group performance status;

tients in our study, we did not perform subgroup analysis as whole brain radiotherapy, patients who underwent surgery and received adjuvant radiotherapy or patients who underwent sterotactic radiosurgery. This is one of the limitations of our study. Despite all these treatment options, median overall survival remains low. Brain metastases in NSCLC remain a significant burden on patients and society due to poor outcomes and high treatment costs, underscoring the need to develop more effective therapies.

Despite its relatively low incidence, liver metastases (LM) are one of the prognostic factors affecting survival in NSCLC patients. In our study, the median OS of patients with liver metastases was 10 months. Unlike bone or brain metastasis, limited data exist to look at LM of NSCLC. Marina C et al.[10] found that first-line chemotherapy in patients with non-squamous NSCLC with liver metastases alone had an objective response rate of 14.3%, which was lower than in patients without liver metastases. In a paper by Maeda and his colleague, in 261 patient with mNSCLC who had been enrolled in clinical trials conducted by the Okayama Lung Cancer Study Group between 1978 and 1992, the presence of liver metastases was associated with poor survival.[11] When we reviewed the literature, there are conflicting data regarding the survival outcomes of immunotherapy in patients with LM. In a study examining the survival con-

Table 4. Subgroup analysis of immunotherapy patients

Immunotherapy	**Median OS**	**p**
Smoker	18.4 (16.4-20.4)	0.33
Never smoked	16.5 (1.3-31.8)	
≥65 years	17.4 (16.4-18.5)	0.53
<65 years	19.4 (16.4-22.3)	
PDL1+	18.43 (15.2-20.1)	0.88
PDL1-	17 (13-21.1)	
Adenocancer	21.1 (14.6-27.7)	0.47
SCC	17.5 (14.8-20.1)	

PDL: Programmed death ligand 1; SCC: squamous cell cancer.

tribution of immunotherapy in patients with LM, it was shown that the use of immunotherapy did not contribute to survival.[12] A recent meta-analysis showed no difference in outcomes due to liver metastasis in patients receiving both immunotherapy and conventional chemotherapy.[13] In another meta-analysis including five clinical trials, immunotherapy significantly improved OS in patients with LM.[14] In our study, the relationship between the presence of LM and survival in patients receiving immunotherapy was not analyzed due to the small number of patients.

Several reports have noted that the outcome varies between different metastatic sites. Yang et al.[15] pointed out that NSCLC patients with multiorgan metastases had a significantly more unfavorable prognosis than those with single organ metastases. All evidence strongly supports metastatic heterogeneity in NSCLC. Results from many studies other than lung cancer have also shown that survival decreases as the number of metastatic sites increases. In our study, consistent with the literature, a metastatic organ count of 3 or more was associated with worse survival.

The treatment of lung cancer has changed with the incorporation of immunotherapy options into the current treatment algorithm. Although immunotherapy in NSCLC is currently included in the standard first-line treatment, historically the first approval was in the second line after multiple randomized trials showed that immune checkpoint inhibitors were superior to docetaxel in the second line.[16,17] Immunotherapy options with proven efficacy both in the first line treatment and in the second line and subsequent lines are now available to our patients in our country. Most of the patients evaluated in our study were treated with nivolumab in 2nd line. Both PFS and OS were significantly longer in patients using immunotherapy, regardless of the treatment line in our analysis. 2nd line immunotherapy options include nivolumab, pembrolizumab and atezolizumab. In 2nd-line treatment, the use of nivolumab and atezolizumab covers all patients regardless of programmed cell death ligand (PD-L1) expression, while pembrolizumab is approved for use in patients with PD-L1 ≥1% based on the design of their respective clinical trials.[18,19] Consistent with the literature results, our study patients showed a survival benefit independent of PDL1 level.

Multivarite analysis showed that, poor performance status, bone metastasis and female gender were not significant related to OS. In contrast to our study, performance status was found to be an independent prognostic factor in many studies.[20,21] This result may be explained by the low number of patients with poor performance status who could receive chemotherapy. Although there are studies in the literature showing that female gender has a better prognosis than male gender,[22,23] this relationship has not been clearly confirmed. It is still unclear why female gender has a longer survival than male gender in some tumors Considering the relationship between bone metastasis and survival, a study conducted with 29720 patients in the literature showed that the presence of bone metastasis was associated with worse survival.[24] In our study, a significant association between bone metastasis and survival was observed in univariate analysis, but this association could not be confirmed in multivariate analysis (p=0.07). However, there was a worse trend in terms of survival in patients with bone metastases. This unverifiable association may be explained by the small number of patients.

In clinical studies examining the factors affecting immunotherapy response, it was found that patients with cigarette exposure were more likely to respond to immunotherapy than patients without exposure.[25] It has been hypothesized that this may be related to the higher mutation burden resulting from smoking.[26] Gender and patient age (<65 or ≥65) were not significantly associated with immunotherapy response.[27] In the subgroup analysis of our patients who received immunotherapy, no significant correlation was observed between age, gender and smoking and survival. This can be explained by the small number of patients who received immunotherapy in our study and the duration of smoking exposure is not clearly known due to the retrospective study.

Some limitations of this single-center study include the fact that it reflected the sociodemographic characteristics of the patients in a specific region, the retrospective nature of the study and the small number of patients.The fact that radiotherapy information was not included is another limitation of our study.

In conclusion, when we examined the factors affecting survival in NSCLC; the absence of liver and brain metastasis, the number of metastatic organs and the use of immunotherapy were associated with better survival. These data suggest that these can be used as stratification factors when designing randomized clinical trials.

Disclosures

Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Ethics Committee (date: 22.04.2024, no: 494).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.S., N.M.; Design – N.S., O.K., M.S.; Supervision – N.S., E.K., Y.A.; Materials – E.Y., N.S., P.E.; Data collection &/or processing – N.S., A.K.G.; Analysis and/or interpretation – İ.V.B., S.I., N.S.; Literature search – R.A., N.S., E.Y.; Writing – N.S.,A.Ç., M.S.; Critical review – N.S., E.Y., O.K.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87-108.
2. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013;368(4):351-64.
3. Tsao MS, Nicholson AG, Maleszewski JJ, Marx A, Travis WD. Introduction to 2021 WHO Classification of Thoracic Tumors. J Thorac Oncol 2022;17(1):e1-e4.
4. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization classification of lung tumors: Impact of genetic, Clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10(9):1243-60.
5. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103.
6. Sorensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: Frequency, risk groups, and prognosis. J Clin Oncol 1988;6(9):1474-80.
7. Patchell RA. The management of brain metastases. Cancer Treat Rev 2003;29(6):533-40.
8. Owonikoko TK, Arbiser J, Zelnak A, Shu HK, Shim H, Robin AM, et al. Current approaches to the treatment of metastatic brain tumours. Nat Rev Clin Oncol 2014;11(4):203-22.
9. Ferrara M, Bizzozzero L, Talamonti G, D'Angelo VA. Surgical treatment of 100 single brain metastases. Analysis of the results. J Neurosurg Sci 1990;34(3-4):303-8.
10. Rodriguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: Protocol-specified final analysis from KEYNOTE-189. Ann Oncol 2021;32(7):881-95.
11. Maeda T, Ueoka H, Tabata M, Kiura K, Shibayama T, Gemba K, et al. Prognostic factors in advanced non-small cell lung cancer: Elevated serum levels of neuron specific enolase indicate poor prognosis. Jpn J Clin Oncol 2000;30(12):534-41.
12. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. JAMA Oncol 2019;5(10):1411-20.
13. Qin BD, Jiao XD, Liu J, Liu K, He X, Wu Y, et al. The effect of liver metastasis on efficacy of immunotherapy plus chemotherapy in advanced lung cancer. Crit Rev Oncol Hematol 2020;147:102893.
14. Yang F, Wang Y, Tang L, Mansfield AS, Adjei AA, Leventakos K, et al. Efficacy of immune checkpoint inhibitors in non-small cell lung cancer: A systematic review and meta-analysis. Front Oncol 2022;12:955440.
15. Yang J, Zhang Y, Sun X, Gusdon AM, Song N, Chen L, et al. The prognostic value of multiorgan metastases in patients with non-small cell lung cancer and its variants: A SEER-based study. J Cancer Res Clin Oncol 2018;144(9):1835-42.
16. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373(17):1627-39.
17. Borghaei H, Gettinger S, Vokes EE, Chow LQM, Burgio MA, de Castro Carpeno J, et al. Five-Year outcomes from the randomized, Phase III trials checkmate 017 and 057: Nivolumab versus docetaxel in previously treated non-small-cell lung cancer. J Clin Oncol 2021;39(7):723-33.
18. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL, et al. Five-year survival update from KEYNOTE-010: Pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1-positive advanced NSCLC. J Thorac Oncol 2021;16(10):1718-32.
19. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389(10066):255-65.
20. Capewell S, Sudlow MF. Performance and prognosis in patients with lung cancer. The Edinburgh Lung Cancer Group. Thorax 1990;45(12):951-6.
21. Martins SJ, Pereira JR. Clinical factors and prognosis in non-small cell lung cancer. Am J Clin Oncol 1999;22(5):453-7.
22. Cerfolio RJ, Bryant AS, Scott E, Sharma M, Robert F, Spencer SA, et al. Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. Chest 2006;130(6):1796-802.
23. Palomares MR, Sayre JW, Shekar KC, Lillington LM, Chlebowski RT. Gender influence on weight-loss pattern and survival of nonsmall cell lung carcinoma patients. Cancer 1996;78(10):2119-26.
24. Cetin K, Christiansen CF, Jacobsen JB, Norgaard M, Sorensen HT. Bone metastasis, skeletal-related events, and mortality in lung cancer patients: A Danish population-based cohort study. Lung Cancer 2014;86(2):247-54.
25. Li JJN, Karim K, Sung M, Le LW, Lau SCM, Sacher A, et al. Tobacco exposure and immunotherapy response in PD-L1 positive lung cancer patients. Lung Cancer 2020;150:159-63.
26. Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn MJ, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: The MYSTIC Phase 3 randomized clinical trial. JAMA Oncol 2020;6(5):661-74.
27. Kasherman L, Siu DHW, Lee KWC, Lord S, Marschner I, Lewis CR, et al. Efficacy of immune checkpoint inhibitors in older adults with advanced stage cancers: A meta-analysis. J Geriatr Oncol 2020;11(3):508-14.