Original Article

Prognostic factors of patients who received chemotherapy after cranial irradiation for non-small cell lung cancer with brain metastases: A retrospective analysis of multicenter study (Anatolian Society of Medical Oncology)

Ali İnal, Hilmi Kodaz[1], Hatice Odabas[2], Ayse Ocak Duran[3], Mehmet Metin Seker[4], Mevlide İnanc[5], Emin Tamer Elkıran[6], Yusuf Gunaydın[7], Serkan Menekse[8], Turkan Ozturk Topcu[9], Zuhat Urakcı[10], Didem Tastekin[11], Mehmet Bilici[12], Sener Cihan[13], Caglayan Geredeli[14], Emel Sezer[15], Dogan Uncu[16], Erkan Arpacı[17], Banu Ozturk[18], Oznur Bal[19], Mukremin Uysal[20], Ozgur Tanrıverdi[21], Mahmut Gumus[22], Bala Basak Oven Ustaalioglu[23], Ali Suner[24], Suna Cokmert[25], İlhan Hacıbekiroglu[1], Kubra Aydın[2], Abdurrahman Isıkdogan[10]

Department of Medical Oncology, Mersin Hospital, Mersin, [15]Department of Medical Oncology, Mersin University, Mersin, [1]Department of Medical Oncology, Trakya University, Edirne, [2]Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, [11]Department of Medical Oncology, İstanbul University, [13]Department of Medical Oncology, Okmeydanı Education and Research Hospital, İstanbul University, [22]Department of Medical Oncology, Bezmialem Vakif

ABSTRACT

Purpose: Almost half of all patients diagnosed with non-small cell lung cancer (NSCLC) have distant metastases at presentation. One-third of patients with NSCLC will have brain metastases. Without effective treatment, the median survival is only 1 month. However, it is difficult to treat brain metastases with systemic chemotherapy since the agents have difficulty crossing the blood-brain barrier. Therefore, it is important to estimate the patient's survival prognosis. The aim of this study was to analyze prognostic factors for survival in Turkish patients who received chemotherapy after cranial irradiation for NSCLC with brain metastases.

Methods: We retrospectively reviewed 698 patients with brain metastases resulting from NSCLC. Ten potential prognostic variables were chosen for analysis. Univariate and multivariate analyses were conducted to identify prognostic factors associated with overall survival (OS).

Results: Among the 10 variables for univariate analysis, six were identified to have prognostic significance; these included sex, smoking history, histology, number of brain metastases, extracranial metastases, and neurosurgical resection. Multivariate analysis by the Cox proportional hazard model showed that a smoking history, extracranial metastases, and neurosurgical resection were independent negative prognostic factors for OS.

Conclusion: Smoking history, extracranial metastases, and neurosurgical resection were considered independent negative prognostic factors for OS. These findings may facilitate pretreatment prediction of survival and can be used for selecting patients for more appropriate treatment options.

KEY WORDS: Brain metastases, non-small cell lung cancer, prognostic factors

INTRODUCTION

Lung cancer is the most common cause of cancer deaths in both men and women worldwide. Non-small cell lung cancer (NSCLC) represents 80–85% of all diagnosed lung cancer cases.[1] Almost half of all patients diagnosed with NSCLC have distant metastases at presentation.[2] One-third of NSCLC patients will have brain metastases.[3] Without effective treatment, the median survival time is only 1 month in NSCLC patients with brain metastasis.[4]

Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.176417

Quick Response Code:

Cite this article as: İnal A, Kodaz H, Odabas H, Duran AO, Seker MM, İnanc M, *et al*. Prognostic factors of patients who received chemotherapy after cranial irradiation for non-small cell lung cancer with brain metastases: A retrospective analysis of multicenter study (Anatolian Society of Medical Oncology). J Can Res Ther 2018;14:578-82.

University, [23]Department of Medical Oncology, Haydarpasa Numune Education and Research Hospital, [25]Department of Medical Oncology, Kent Hospital, İstanbul, [3]Department of Medical Oncology, Erciyes University, [5]Department of Medical Oncology, Kayseri Numune Education and Research Hospital, Kayseri, [4]Department of Medical Oncology, Cumhuriyet University, Sivas, [6]Department of Medical Oncology, Inonu University, Malatya, [7]Department of Medical Oncology, Gazi University, Ankara, [16]Department of Medical Oncology, Ankara Numune Education and Research Hospital, [19]Department of Medical Oncology, Ankara Onkoloji Education and Research Hospital, [8]Department of Medical Oncology, Celal Bayar University, Manisa, [9]Department of Medical Oncology, Karadeniz Teknik University, Trabzon, [10]Department of Medical Oncology, Dicle University, Diyarbakir, [12]Department of Medical Oncology, Atatürk University, Erzurum, [14]Department of Medical Oncology, Konya Numune Hospital, Konya, [17]Department of Medical Oncology, Sakarya University, Sakarya, [18]Department of Medical Oncology, Gaziosmanpasa University, Yozgat, [20]Department of Medical Oncology, Afyon Kocatepe University, Afyon, [21]Department of Medical Oncology, Mugla Sıtkı Kocman University, Mugla, [24]Department of Medical Oncology, Gaziantep University, Gaziantep, Turkey

For correspondence: Dr. Ali İnal, Department of Medical Oncology, Mersin State Hospital, Mersin, Turkey. E-mail: dr.ainal@gmail.com

Current treatment options include whole brain radiotherapy (WBRT), surgical resection, stereotactic radiosurgery, and combined treatment approaches. WBRT is currently recommended as the standard treatment approach for multiple brain metastases. However, the median survival time following WBRT alone is only 2.4–4.8 months.[5-7] Systemic chemotherapy, which is commonly accepted as a treatment option for advanced NSCLC, has improved survival. However, it is difficult to treat brain metastases with these agents because of the blood-brain barrier. The selection of the optimal treatment regimen is likely to be influenced by the patient's prognosis.[8-12] Therefore, it is important to be able to estimate the patient's survival prognosis, which can be facilitated by using prognostic factors.

We performed a retrospective analysis of prognostic factors in patients who received chemotherapy after WBRT for NSCLC with brain metastases.

METHODS

Patient population

We retrospectively reviewed 698 patients with histologically or cytologically proven NSCLC from February 2001 to April 2014. All patients had complete clinical and follow-up records. All of the patients met the following inclusion criteria: (1) histologic or cytologic diagnosis of metastatic NSCLC; (2) 18 years of age or older; (3) had received chemotherapy after WBRT; and (4) had a measurable disease, as defined by the Response Evaluation Criteria in Solid Tumors.

Factors analyzed

Ten potential prognostic variables were chosen based on previously published clinical trials. Each variable was divided into two categories: Gender (male or female), performance status (PS) (0-1-2-3), age (<65 or ≥65), histology (squamous cell carcinoma or nonsquamous cell carcinoma), smoking history (present or absent), number of brain metastases (1–3 or ≥4), extracranial metastases (present or absent), neurosurgical resection (present or absent), synchronous brain metastases (present or absent), and neurological symptoms (present or absent).

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL, USA). The differences in the clinical characteristics between the two groups were analyzed by Chi-square tests, and overall survival (OS) was calculated from the date of diagnosis of brain metastases to the date of death from any cause or the date of the last follow-up. OS was estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine statistically significant variables related to survival. Differences were considered significant when $P < 0.05$.

RESULTS

Between February 2001 and April 2014, 698 patients with advanced NSCLC were enrolled in this study.

The median patient age was 58 years (range: 20–95) with 603 (86.4%) males and 95 (13.6%) females.

The number of patients with a PS score 0-1 was 544 (77.9%). Adenocarcinoma was the most common histologic type (56.7%). The estimated median OS was 7.0 months. The patients' baseline characteristics are listed in Table 1.

Among the ten variables for univariate analysis, six variables were identified as having prognostic significance: sex ($P = 0.006$), smoking history ($P = 0.001$), histology ($P = 0.007$), number of brain metastases ($P = 0.03$), extracranial metastases ($P = 0.002$), and neurosurgical resection ($P = 0.001$). The results of the univariate analysis for OS are summarized in Table 2.

The results of the multivariate analysis are shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that smoking history, extracranial metastases, and neurosurgical resection were considered independent negative prognostic factors for OS ($P = 0.006$, $P = 0.01$, and $P = 0.004$, respectively) [Figures 1-3].

DISCUSSION

Patients with brain metastases from NSCLC usually have a poor prognosis. The median survival time without any treatment is only 1 month, 2–3 months with glucocorticoid therapy, and 2.4–4.8 months with WBRT.[5-7]

Table 1: The general characteristics of the patients

Characteristic	No. of patients (%)
Sex	
Male	603 (86.4)
Female	95 (13.6)
Age (years)	
<65	560 (80.2)
≥65	138 (19.8)
Performance status	
0-1	544 (77.9)
2-3	137 (19.6)
Unknown	17 (2.5)
Smoking history	
Current or former	510 (73.1)
Never	122 (17.5)
Unknown	66 (9.4)
Histology	
Adenocarcinoma	396 (56.7)
Squamous cell carcinoma	116 (16.6)
Other	14 (2.0)
NSCLC NOS	172 (24.7)
Number of brain metastases	
1	290 (41.5)
2-3	155 (22.2)
≥4	230 (33.0)
Unknown	23 (3.3)
Neurosurgical resection	
Yes	175 (25.1)
No	513 (73.5)
Unknown	10 (1.4)
Extracranial metastasis	
Yes	349 (50.0)
No	347 (49.7)
Unknown	2 (0.3)

Table 2: Univariate analysis of OS by categorical variable

Variable	Log-rank test value	Degrees of freedom	*P* value
Sex	7.47	1	0.006
Age	0.10	1	0.74
Performance status	1.75	1	0.18
Smoking history	11.6	1	0.001
Histology	7.21	1	0.007
Number of brain metastases	6.48	2	0.03
Extracranial metastases	10.0	1	0.002
Neurosurgical resection	10.1	1	0.001
Synchronous brain metastases	0.003	1	0.95
Neurologically symptom	0.22	1	0.63

Table 3: Multivariate analysis of prognostic factors

Parameter	OR	%95 CI	*P* value
Smoking history	1.53	1.13-2.07	0.006
Extracranial metastases	1.35	1.07-1.71	0.01
Neurosurgical resection	0.0.66	0.50-0.884	0.004

Systemic chemotherapy, which is commonly accepted as a treatment option for advanced NSCLC, has been shown to improve survival. However, it is difficult to treat brain metastases with these agents because of the blood-brain barrier. Patients eligible for chemotherapy should be selected carefully. Very different prognostic factors for survival have been identified in patients with brain metastases.[13-16]

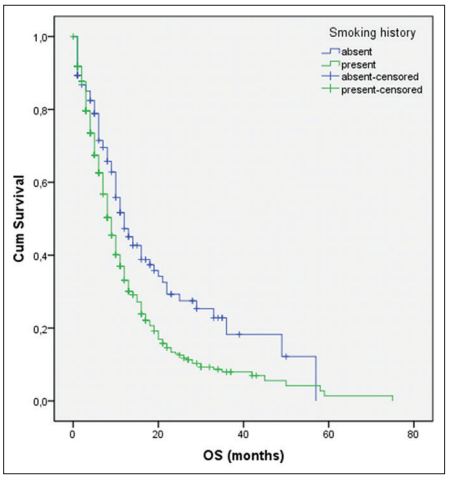

Figure 1: Survival of patients according to smoking history

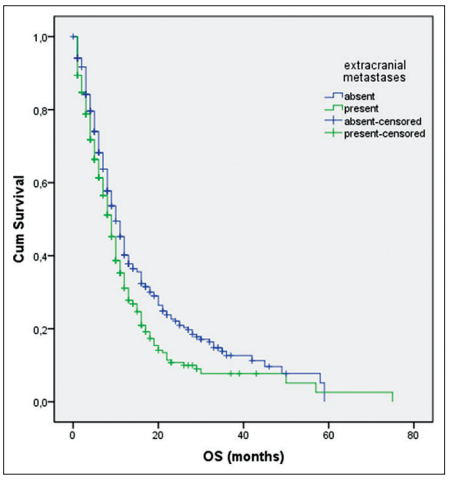

Figure 2: Survival of patients according to extracranial metastases

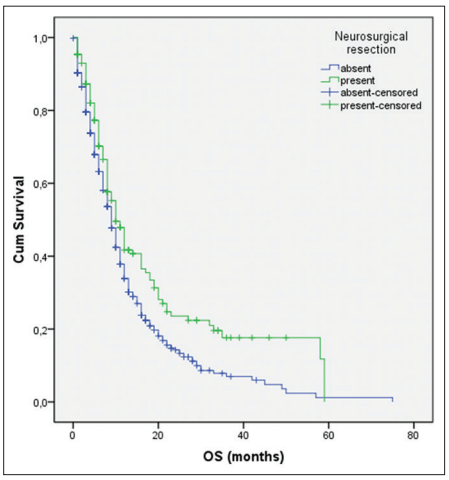

Figure 3: Survival of patients according to neurosurgical resection

Previously, many authors have shown that the presence of extracranial metastasis at the initial discovery of the brain metastases was a significantly negative prognostic factor for the treatment of brain metastases in NSCLC patients.[17-19]

Similarly, our results demonstrated that the lack of extracranial metastasis was a significantly favorable finding that improved the OS. For this reason, these findings suggest that control of the extracranial region is also very important in cases with brain metastases.

According to the current ESMO guidelines, resection of cranial metastases is a treatment option for selected patients with a solitary metastasis.[20] Nevertheless, level 1 evidence promising improved OS after aggressive treatment is lacking, apart from the resection of a single brain metastasis.[21,22] Patients with symptomatic brain metastases owing to a mass effect may be considered for metastasectomy. Consistent with the published literature,[21-23] we found that surgical resection could prolong survival. Therefore, surgical resection should be considered in patients with controlled systemic disease, and symptomatic brain metastases.

Smoking is a well-known causative factor in the development of lung cancer.[24] Several previous studies have demonstrated that smokers show a significantly poor prognosis when compared with nonsmokers with regard to NSCLC.[24-26] There is little information available about the prognostic significance of smoking in patients who have received chemotherapy after cranial irradiation for NSCLC with brain metastases. Griffioen *et al*. did not observe a prognostic value of smoking status in patients with brain metastases.[21] The current study demonstrated that smoking status was an independent negative prognostic factor of survival.

CONCLUSION

Smoking history, extracranial metastases, and neurosurgical resection were considered independent negative prognostic factors for OS. These findings may facilitate pretreatment prediction of survival and can be used for the selecting patients for more correct choice of treatment. Therefore, a prospective trial and larger clinical trials are needed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16:481-8.
2. Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, *et al.* Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: A population-based study, 2004-2007. Thorax 2013;68:551-64.
3. Kvale PA, Simoff M, Prakash UB; American College of Chest Physicians. Lung cancer. Palliative care. Chest 2003;123 1 Suppl:284S-311S.
4. Pesce GA, Klingbiel D, Ribi K, Zouhair A, von Moos R, Schlaeppi M, *et al.* Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss group for clinical cancer research (SAKK 70/03). Eur J Cancer 2012;48:377-84.
5. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005;23:6207-19.
6. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 2006;24:1295-304.
7. Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. Oncologist 2007;12:884-98.
8. Fan Y, Huang Z, Fang L, Miu L, Lin N, Gong L, *et al.* Chemotherapy and EGFR tyrosine kinase inhibitors for treatment of brain metastases from non-small-cell lung cancer: Survival analysis in 210 patients. Onco Targets Ther 2013;6:1789-803.
9. Bearz A, Garassino I, Tiseo M, Caffo O, Soto-Parra H, Boccalon M, *et al.* Activity of pemetrexed on brain metastases from non-small cell lung cancer. Lung Cancer 2010;68:264-8.
10. Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, *et al.* Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer 2009;65:351-4.
11. Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, *et al.* Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: A phase II study (CTONG-0803). Ann Oncol 2013;24:993-9.
12. Wu C, Li YL, Wang ZM, Li Z, Zhang TX, Wei Z. Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain. Lung Cancer 2007;57:359-64.
13. Sánchez de Cos J, Sojo González MA, Montero MV, Pérez Calvo MC, Vicente MJ, Valle MH. Non-small cell lung cancer and silent brain metastasis. Survival and prognostic factors. Lung Cancer 2009;63:140-5.
14. Jacot W, Quantin X, Boher JM, Andre F, Moreau L, Gainet M, *et al.* Brain metastases at the time of presentation of non-small cell lung cancer: A multi-centric AERIO analysis of prognostic factors. Br J Cancer 2001;84:903-9.
15. Penel N, Brichet A, Prevost B, Duhamel A, Assaker R, Dubois F, *et al.* Pronostic factors of synchronous brain metastases from lung cancer. Lung Cancer 2001;33:143-54.
16. Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, *et al.* A new survival score for patients with brain metastases from non-small cell lung cancer. Strahlenther Onkol 2013;189:777-81.
17. Sakamoto J, Sonobe M, Kobayashi M, Ishikawa M, Kikuchi R, Nakajima D, *et al.* Prognostic factors for patients in postoperative brain metastases from surgically resected non-small cell lung cancer. Int J Clin Oncol 2014;19:50-6.
18. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, *et al.* Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA 2006;295:2483-91.
19. Serizawa T, Saeki N, Higuchi Y, Ono J, Iuchi T, Nagano O, *et al.* Gamma knife surgery for brain metastases: Indications for and limitations of a local treatment protocol. Acta Neurochir (Wien) 2005;147:721-6.
20. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii56-64.
21. Griffioen GH, Toguri D, Dahele M, Warner A, de Haan PF, Rodrigues GB, *et al.* Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors. Lung Cancer 2013;82:95-102.
22. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, *et al.* Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: Long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 2012;7:1547-55.

23. Li Z, Zhang X, Jiang X, Guo C, Sai K, Yang Q, *et al*. Outcome of surgical resection for brain metastases and radical treatment of the primary tumor in Chinese non-small-cell lung cancer patients. Onco Targets Ther 2015;8:855-60.
24. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p 53 mutations in smoking associated cancers. Oncogene 2002;21:7435-51.
25. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. Chest 2004;126:347-51.
26. Chen RJ, Chang LW, Lin P, Wang YJ. Epigenetic effects and molecular mechanisms of tumorigenesis induced by cigarette smoke: An overview. J Oncol 2011;2011:654931.