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## ORIGINAL ARTICLE

# Clinical Features and Prognostic Factors in Non–Small-Cell Lung Cancer Patients Receiving Whole Brain Radiotherapy

**CY Wong, WWY Tin, WH Mui, SF Nyaw, FCS Wong**

*Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong SAR, China*

## ABSTRACT

***Objective:*** *Brain metastases are common in non–small-cell lung cancer (NSCLC) and significantly impact quality of life and survival. Despite advances in systemic treatment and stereotactic radiotherapy, whole brain radiotherapy (WBRT) remains frequently used during the disease course. However, prognostic tools to guide WBRT decisions are lacking. This study aimed to identify prognostic factors in NSCLC patients with brain metastases receiving WBRT.*

***Methods:*** *We conducted a retrospective study of NSCLC patients with brain metastases treated with WBRT at our hospital between January 2020 and April 2023. Overall survival (OS) was estimated using the Kaplan–Meier method. Prognostic factors for OS were identified using a multivariable Cox regression model.*

***Results:*** *A total of 135 patients were included. The median OS was 138 days (95% confidence interval = 102.3-173.7). The 30-day mortality rate was 16.3% and the 1-year OS rate was 19.3%. Multivariable analysis identified a Karnofsky Performance Scale score of 70 or above, neutrophil-to-lymphocyte ratio of smaller than 4, and systemic treatment after WBRT as independent favourable prognostic factors for OS.*

***Conclusion:*** *WBRT remains an effective treatment for selected NSCLC patients with brain metastases. Karnofsky Performance Scale score of 70 or above, neutrophil-to-lymphocyte ratio of smaller than 4, and receipt of systemic treatment after WBRT were significant predictors of improved survival. Prospective studies are needed to further evaluate the role and timing of WBRT and to develop an accurate prognostic index to guide treatment decisions between WBRT and supportive care.*

***Key Words:*** *Brain; Brain neoplasms; Carcinoma, non–small-cell lung; Prognosis*

***Correspondence:*** *Dr CY Wong, Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong SAR, China*
*Email: federicawong@ha.org.hk*

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# 中文摘要

## 接受全腦放療的非小細胞肺癌患者的臨床特徵和預後因素

黃仲昕、佃穎恩、梅永豪、饒仕鋒、黃志成

**目的：**非小細胞肺癌患者常見腦轉移，對生活質素及存活率有重大影響。雖然全身治療及立體定位放療已大有進展，但全腦放療在病程中仍經常被採用。然而，目前缺乏針對全腦放療治療決策的預後工具。本研究旨在找出接受全腦放療的非小細胞肺癌腦轉移患者的預後因素。

**方法：**我們對2020年1月至2023年4月期間在本院接受全腦放療治療的非小細胞肺癌腦轉移患者的臨床資料進行回顧性分析。整體存活期以Kaplan–Meier方法估算，並以多變項Cox回歸模型分析預測整體存活期的相關預後因素。

**結果：**本研究共納入135名患者。整體中位存活期為138天（95%置信區間：102.3-173.7 天）。30天內死亡率為16.3%，一年整體存活率為19.3%。多變項分析顯示，Karnofsky表現評分（KPS）70或以上、嗜中性白血球與淋巴球比率（NLR）少於4，以及接受全腦放療後的全身治療均為獨立的有利預後因素。

**結論：**對於部分合適的非小細胞肺癌腦轉移患者而言，全腦放療仍是有效的治療選擇。KPS 70或以上、NLR少於4，以及全腦放療後接受全身治療與較佳存活結果顯著相關。未來應進行前瞻性研究，進一步探討全腦放療的角色與時機，並研發準確的預後評估工具，以協助臨床上在全腦放療與支持治療之間作出合適選擇。

## INTRODUCTION

Brain metastases adversely affect the quality of life and survival of cancer patients. Non–small-cell lung cancer (NSCLC) has a brain metastasis incidence of up to 40% during its clinical course, and it is increasing due to advances in systemic treatment and imaging.[1-5]

Life expectancy with steroids alone is typically 1 to 2 months; whole brain radiotherapy (WBRT) increases this to approximately 5 months and improves symptoms in 40% to 60% of patients.[6-12] However, the treatment landscape for brain metastasis in NSCLC is evolving, with WBRT now mainly reserved for patients unsuitable for stereotactic radiosurgery/radiotherapy (SRS/SRT). Despite concerns about the neurocognitive toxicity of WBRT and controversy of additional survival and quality-of-life benefits, it is still widely used and reported as the primary treatment for brain metastases in 23.6% to 25.2% of patients in recent studies.[13-15]

The QUARTZ (Quality of Life after Treatment for Brain Metastases) study[16] found that routine WBRT in NSCLC patients did not improve survival or quality of life compared with best supportive care, supporting its omission to avoid unnecessary treatment burden and toxicity. However, details on systemic treatment were not reported, limiting its application in the modern era, where molecular characteristics markedly influence NSCLC treatment.

Patient selection is critical and decisions regarding WBRT should be personalised. Evidence remains limited in the context of evolving systemic treatments and other local therapies, and prognostic factors are not consistently defined. This study aimed to review survival outcomes and clinical characteristics in NSCLC patients who received WBRT in our hospital.

## METHODS

The study included NSCLC patients who received WBRT at Tuen Mun Hospital, Hong Kong from 1 January 2020 to 30 April 2023. WBRT was considered for patients not eligible for neurosurgery or SRS/SRT. Demographic data, disease characteristics, and treatment outcomes were retrieved from electronic medical records.

Performance status was assessed using the Karnofsky Performance Scale (KPS) at the radiotherapy planning clinic. Overall survival (OS) was defined as the time from the first day of WBRT to death or when censored

(data cut-off: 12 May 2024). Statistical analysis was performed using SPSS version 26.0 (IBM Corp, Armonk [NY], United States).

Categorical variables were summarised as frequencies and percentages; continuous variables as medians with interquartile ranges (IQRs). OS was estimated using the Kaplan–Meier method and compared using the log-rank test. A multivariable Cox regression model identified prognostic factors for OS.

In addition to clinical features included in the Disease-Specific Graded Prognostic Assessment (DS-GPA), recursive partitioning analysis, and lung-molecular GPA score, liver metastases, neutrophil-to-lymphocyte ratio (NLR) of 4 or above, lymphocyte percentage, low albumin level, and elevated albumin-to-globulin ratio have been reported as prognostic indicators in NSCLC.[16-21] We investigated their prognostic value in our cohort.

# RESULTS

## Patient Characteristics

A total of 135 NSCLC patients received WBRT (median age: 64 years; 65.2% male). Among them, 11.9% had disease recurrence post-treatment, including one who received chemoradiotherapy (CRT) while others underwent surgery. The median time from surgery/CRT to recurrence was 419 days.

Overall, 55.6% were diagnosed with brain metastases within 3 months since the diagnosis of advanced lung cancer. 87 patients (64.4%) and 109 patients (80.7%) received systemic treatment before and after WBRT, respectively (Figure 1). As shown in Table 1, 34.1% of patients had received at least two lines of systemic anticancer treatment. Systemic treatment post-WBRT was given to 55.6% of patients.

Among patients, 61.5% had a smoking history, and 91.1% had adenocarcinoma. Half (50.4%) had treatable mutations (epidermal growth factor receptor [*EGFR*], *ALK* [anaplastic lymphoma kinase], *ROS1* [ROS proto-oncogene 1], and *HER2* [human epidermal growth factor receptor 2]). A total of 43.0% received targeted therapy before or after WBRT; 3% received antibody-drug conjugates.

76.3% received WBRT for newly diagnosed brain metastasis; the rest received it upon intracranial progression. Local treatments (surgery or SRS/SRT) were given in 16.3%. Leptomeningeal metastasis was present in 21.5%. All received short-course radiotherapy: four patients receiving 30 Gy in 10 fractions and others receiving 20 Gy in five fractions. Further details are shown in Table 1.

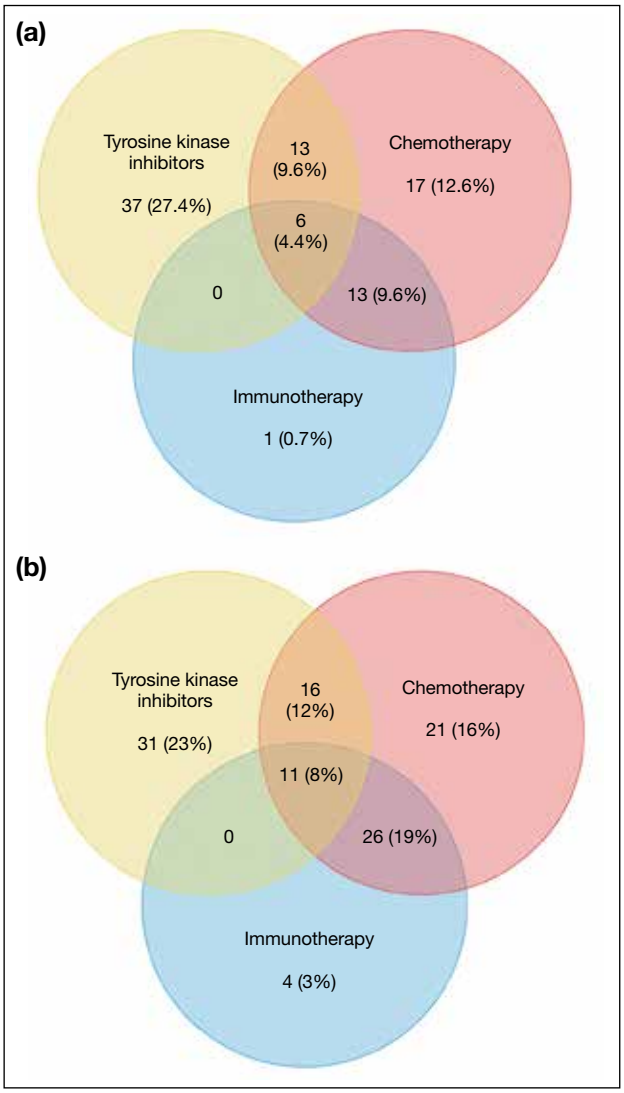


**Figure 1.** Treatment received (a) before and (b) after whole brain radiotherapy (n = 135).*
* Data are shown as No. (%).

## Prognostic Factors for Survival

On univariate Cox regression, the following were significant prognostic factors: KPS score of less than 70, uncontrolled extracranial disease, lymphocytes less than 20%, NLR of 4 or above, local treatment to brain metastasis, disease recurrence, at least two lines of systemic treatment before WBRT, no systemic treatment after WBRT, and presence of neurological symptoms.

**Table 1.** Patient characteristics (n = 135).*

| | |
|---|---|
| Age, y | 64 (57-68) |
| ≤60 | 42 (31.1%) |
| 61-70 | 67 (49.6%) |
| >70 | 26 (19.3%) |
| Gender | |
| Male | 88 (65.2%) |
| Female | 47 (34.8%) |
| Smoking status | |
| Smoker | 83 (61.5%) |
| Never-smoker | 52 (38.5%) |
| KPS score | |
| 40 | 1 (0.7%) |
| 50 | 6 (4.4%) |
| 60 | 39 (28.9%) |
| 70 | 39 (28.9%) |
| 80 | 37 (27.4%) |
| 90 | 13 (9.6%) |
| RPA class | |
| I | 2 (1.5%) |
| II | 88 (65.2%) |
| III | 45 (33.3%) |
| DS-GPA score | |
| 0 | 18 (13.3%) |
| 0.5 | 42 (31.1%) |
| 1 | 38 (28.1%) |
| >1 | 37 (27.4%) |
| Lymphocytes, % | 12.4 (6.0-18.6) |
| <20 | 106 (78.5%) |
| ≥20 | 29 (21.5%) |
| NLR | 6.0 (3.75-14) |
| <4 | 42 (31.1%) |
| ≥4 | 93 (68.9%) |
| Albumin, g/L | 37 (33-40) |
| ≤35 | 52 (38.5%) |
| >35 | 83 (61.5%) |
| AGR | 1.11 (0.97-1.29) |
| <1.12 | 69 (51.1%) |
| ≥1.12 | 66 (48.9%) |
| Adenocarcinoma | |
| Yes | 123 (91.1%) |
| No | 12 (8.9%) |
| Mutations | |
| *EGFR* sensitising mutation | 53 (39.3%) |
| *ALK* | 1 (0.7%) |
| *ROS1* | 2 (1.5%) |
| *EGFR* exon 20 insertion | 6 (4.4%) |
| *HER2* mutation | 6 (4.4%) |
| PD-L1 TPS, % | |
| <1 | 35 (25.9%) |
| 1-49 | 32 (23.7%) |
| ≥50 | 23 (17.0%) |
| Not available | 45 (33.3%) |

Abbreviations: AGR = albumin-to-globulin ratio; *ALK* = anaplastic lymphoma kinase; BM = brain metastasis ; CNS = central nervous system; DS-GPA = Disease-Specific Graded Prognostic Assessment; *EGFR* = epidermal growth factor receptor; *HER2* = human epidermal growth factor receptor 2; KPS = Karnofsky Performance Scale; NLR = neutrophil-to-lymphocyte ratio; PD-L1 = programmed death ligand 1; RPA = recursive partitioning analysis; *ROS1* = *ROS* proto-oncogene 1; SACT = systemic anticancer treatment; TPS = Tumor Progression Score; WBRT = whole brain radiotherapy.
* Data are shown as No. (%) or median (interquartile range).

**Table 1.** (cont'd)

| | |
|---|---|
| No. of SACT courses before WBRT | |
| 0 | 48 (35.6%) |
| 1 | 41 (30.4%) |
| 2 | 31 (23.0%) |
| 3 | 11 (8.1%) |
| 4 | 4 (3.0%) |
| SACT after WBRT | |
| Yes | 75 (55.6%) |
| No | 60 (44.4%) |
| Lung cancer recurrence | |
| Yes | 16 (11.9%) |
| No | 119 (88.1%) |
| Extracranial metastasis | |
| Yes | 130 (96.3%) |
| No | 5 (3.7%) |
| Uncontrolled extracranial disease | |
| Yes | 108 (80.0%) |
| No | 27 (20.0%) |
| Liver metastasis | |
| Yes | 30 (22.2%) |
| No | 105 (77.8%) |
| Brain metastasis status | |
| Newly diagnosed | 103 (76.3%) |
| Progressive disease | 32 (23.7%) |
| Interval from cancer to BM | |
| Within 3 months | 75 (55.6%) |
| Over 3 months | 60 (44.4%) |
| Local treatment for BM | |
| Yes | 22 (16.3%) |
| No | 113 (83.7%) |
| No. of brain metastases | |
| ≤2 | 38 (28.1%) |
| 3-4 | 29 (21.5%) |
| 5-10 | 50 (37.0%) |
| >10 | 18 (13.3%) |
| Leptomeningeal metastasis | |
| Yes | 29 (21.5%) |
| No | 87 (64.4%) |
| Not available | 19 (14.1%) |
| CNS symptoms | |
| Yes | 111 (82.2%) |
| No | 24 (17.8%) |

Multivariable analysis identified KPS score of lower than 70, no systemic treatment after WBRT, and NLR of 4 or above as independent poor prognostic factors (Table 2).

## Survival Outcomes

The median OS was 138 days (95% confidence interval [95% CI] = 102.3-173.7). Four patients (3.0%) did not complete WBRT due to a change in clinical condition, all had KPS score of lower than 70. The 30-day mortality rate was 16.3% and the 1-year OS rate was 19.3%.

Patients with KPS score of 70 or above had significantly better median survival than those with KPS score of

**Table 2.** Simple and multivariable analyses of the prognostic factors of overall survival.

| Factor | Simple analysis | Multivariable analysis | | |
|---|---|---|---|---|
| | p Value | HR | 95% CI | p Value |
| Stage IVB | 0.818 | | | |
| Extracranial metastasis | 0.169 | | | |
| Liver metastasis | 0.267 | | | |
| Uncontrolled extracranial disease | 0.034 | | | |
| Lymphocytes <20% | 0.006 | | | |
| NLR ≥4 | 0.001 | 1.896 | 1.277-2.815 | 0.002 |
| Albumin level ≤35 g/L | 0.001 | | | |
| AGR ≥1.12 | 0.595 | | | |
| No. of brain metastases >4 | 0.184 | | | |
| Leptomeningeal metastasis | 0.255 | | | |
| Smoking history | 0.078 | | | |
| Gender | 0.131 | | | |
| Age ≥60 y | 0.411 | | | |
| KPS score <70 | <0.001 | 1.748 | 1.196-2.554 | 0.004 |
| Brain metastasis progression | 0.999 | | | |
| Interval from cancer diagnosis to BM ≥3 months | 0.137 | | | |
| No local treatment to brain metastasis | 0.041 | | | |
| Recurrence | 0.014 | | | |
| Mutation (*EGFR*, *ROS1*, *ALK*) | 0.526 | | | |
| Adenocarcinoma | 0.393 | | | |
| PDL1 positive | 0.085 | | | |
| Neurological symptoms | 0.005 | | | |
| ≥2 lines of treatment before WBRT | 0.044 | | | |
| No systemic treatment after WBRT | <0.001 | 3.408 | 2.321-5.004 | <0.001 |

Abbreviations: 95% CI = 95% confidence interval; AGR = albumin-to-globulin ratio; *ALK* = anaplastic lymphoma kinase; BM = brain metastasis; *EGFR* = epidermal growth factor receptor; HR = hazard ratio; KPS = Karnofsky Performance Scale; NLR = neutrophil-to-lymphocyte ratio; PDL1 = programmed death ligand 1; *ROS1* = *ROS* proto-oncogene 1; WBRT = whole brain radiotherapy.

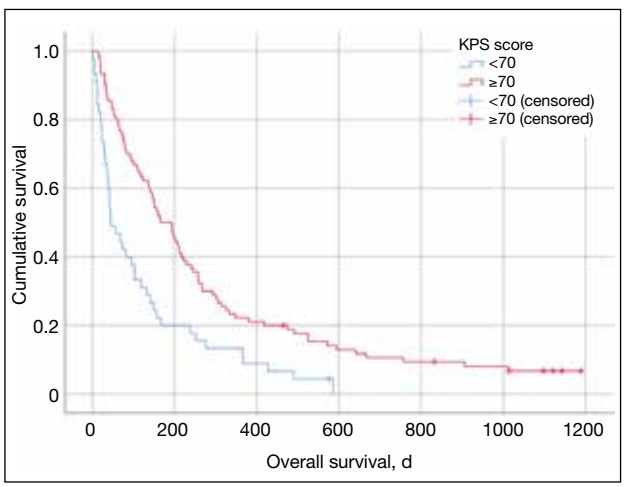


**Figure 2.** Kaplan–Meier curves for overall survival stratified by Karnofsky Performance Scale (KPS) scores.

lower than 70: 165 days (95% CI = 102.3-173.7) versus 45 days (95% CI = 15.4-75.8; p < 0.001) [Figure 2]. Their 30-day mortality rates were 9.0% and 30.4%, respectively (p < 0.002). Among patients with KPS score of 70 or above, the 1-year OS was 23.6%.

Six patients survived at data cut-off, with a median follow-up of 1110.5 days. Three received osimertinib, two received pembrolizumab-pemetrexed-carboplatin, and one was under surveillance after WBRT as there was no extracranial disease progression after thoracic chemoradiation; adjuvant durvalumab was stopped after neurosurgery and WBRT.

Among patients with KPS score of 70 or above, those receiving systemic treatment post-WBRT (n = 56) had a median survival of 257 days (95% CI = 208.8-305.2), compared to 65 days (95% CI = 40.2-89.8) in those without (n = 33; p < 0.001) [Figure 3].

Among patients with KPS score of lower than 70, those receiving systemic therapy post-WBRT (n = 19) had a median survival of 149 days (95% CI = 62.3-235.7), compared to 41 days (95% CI = 25.7-56.3) in those without (n = 27; p < 0.001) [Figure 4]. Of these 19 patients, five had not received any prior systemic treatment. Ten patients had sensitising *EGFR* mutations and were treated with erlotinib or osimertinib. Two other patients received tyrosine kinase inhibitors, three

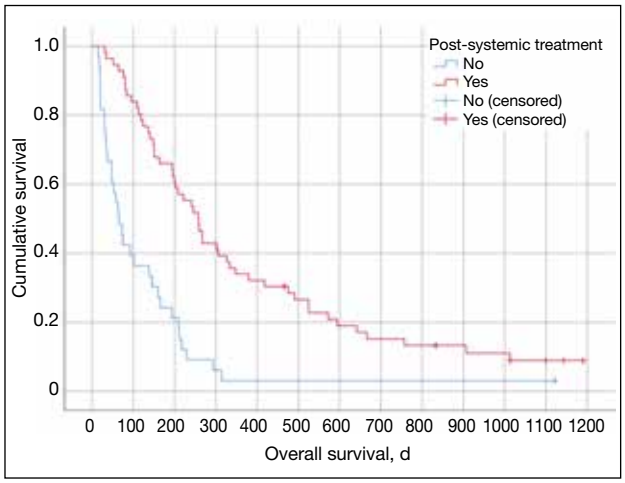


**Figure 3.** Kaplan–Meier curves for overall survival in patients with Karnofsky Performance Scale score of 70 or above, with and without systemic treatment after whole brain radiotherapy.

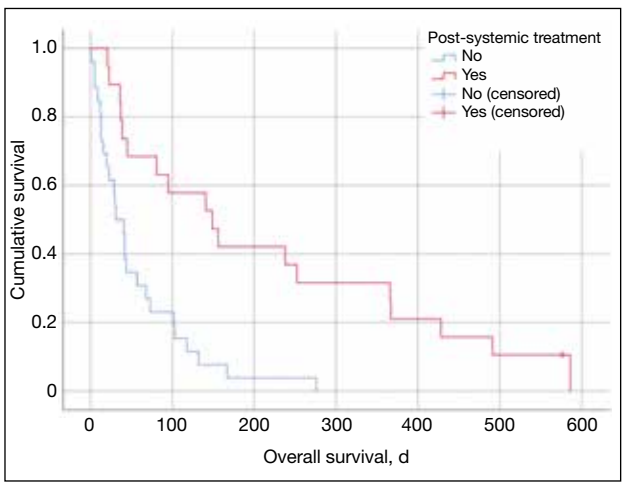


**Figure 4.** Kaplan–Meier curves for overall survival in patients with Karnofsky Performance Scale score lower than 70, with and without systemic treatment after whole brain radiotherapy.

received chemoimmunotherapy, and two patients each received immunotherapy alone or chemotherapy alone.

## DISCUSSION

Sensitising *EGFR* mutations are common in NSCLC, present in up to 47.5% of patients according to the 2021 Hong Kong Cancer Registry data.[22] While these mutations are linked to better survival, they are not significantly prognostic after WBRT in our study.[23] This may be due to the heavily pretreated nature of these patients: among 56 with *EGFG*, *ALK*, or *ROS1* mutations, 94.7% had prior systemic treatment, 47.4% had received at least two lines of treatment, and 33.9% had not received systemic therapy after WBRT. The median OS from the start of WBRT was 144 days (IQR, 9-1190), and from the time of brain metastases diagnosis was 375 days (IQR, 25-1588).

Most prognostic tools (e.g., DS-GPA) estimate survival from initial brain metastases diagnosis. However, these are less applicable to patients with intracranial progression considering WBRT (23.7% in this study), for whom the additional prognostic factors (NLR, systemic treatment after WBRT) identified, may be more relevant.

Although extracranial disease is a known prognostic factor, it was not significant in this study, likely due to the small number of patients (3.7%) without such disease. Age, another common factor, was also not significant for unclear reasons.

There are no consistent guidelines for WBRT in this population. Our findings support that good performance status, systemic treatment after WBRT, and NLR of smaller than 4 are associated with better survival, aligning with recursive partitioning analysis and DS-GPA recommendations.

Given the inconsistency in estimating post-WBRT treatment eligibility, our analysis focused on whether systemic treatment was administered. The median OS was 138 days (19.7 weeks), but among patients with poor performance status receiving only supportive care, it was just 41 days, suggesting WBRT may be omitted in such cases.

NLR of 4 or above was an independent prognostic factor, reflecting increased neutrophil count and/or relative lymphopenia, a pro-inflammatory tumour microenvironment.[19]

Prospective trials are needed to evaluate the role and timing of WBRT in the era of evolving systemic treatment and local therapies to develop an accurate prognostic index to aid treatment decisions. We recommend cautious use of WBRT, particularly in patients with KPS score of lower than 70, no post-WBRT systemic treatment, and NLR of 4 or above.

### Limitations

The major limitation of our study is its retrospective design, which may be related to selection bias. Patients who did not receive WBRT were excluded. Lung cancer

is molecularly heterogeneous, yet programmed death ligand 1 status was unavailable in one-third of our patients. WBRT-related toxicities and quality of life were not assessed.

## CONCLUSION

WBRT remains a potentially effective treatment for selected NSCLC patients. KPS score of 70 of above, systemic treatment after WBRT, and NLR of smaller than 4 were significant prognostic factors. Further trials are needed to evaluate the role and timing of WBRT alongside systemic treatment and local therapies. A prospective study is essential to develop an accurate prognostic index to guide WBRT versus supportive care decisions.

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