



The risk factors for brain metastases in patients with non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) with brain metastasis is the most common central nervous system malignancy, accounting for as much as 20% of every brain metastasis case (1). The incidence of brain metastasis has been increasing due to improvements in the control of systemic extra-cranial disease and the widespread availability of imaging modalities such as magnetic resonance imaging (MRI), which has increased the detection of subclinical disease (2-4). NSCLC with brain metastasis often has a poor prognosis, with the median survival ranging between 4 and 6 months (5). Although brain MRIs are performed more often than ever before for the diagnosis of brain metastasis, this imaging procedure is still not performed in all patients with NSCLC. In recent guidelines, including both the National Comprehensive Cancer Network and American College of Chest Physicians, brain MRI was not recommended for asymptomatic stage I patients (6,7). However, recent studies have revealed that brain metastasis can occur even in patients with early stage disease or in those without any symptoms (8,9). There have been many studies about the risk factors of brain metastasis to predict the development of brain metastasis in patients with NSCLC. In addition, there have been several studies that have shown that clinical factors such as age, stage, and histology are associated with brain metastasis in NSCLC patients (10-14).

Waqar *et al.* published a study using the population-based Surveillance, Epidemiology, and End Results (SEER) database on clinical risk factors to predict the development of brain metastasis (15). They searched the SEER-17

registry data for patients with NSCLC diagnosed over a 10-year period between January 1, 1988, and December 31, 1997. There was no record of brain metastasis in the SEER database, but patients who were referred to as “brain radiotherapy indicated” were considered to have brain metastases. Of the total 142,023 patients, 10,567 whose brain radiotherapy status was unknown were excluded. Among the remaining 131,456 patients, 10,963 (8.3%) were “brain radiotherapy indicated”. A multivariable analysis revealed that the following were significantly associated with brain radiotherapy use: younger age [odds ratio (OR), 0.65], adenocarcinoma histology (OR, 1.67), large cell or other histology (OR, 1.67), tumor size >3 cm (OR, 1.22 in tumor >3.1 to 5 cm and 1.25 in tumor >5 cm), tumor grade III or IV (OR, 1.82 and 1.91), and N1, N2 or N3 nodal involvement (OR, 1.33, 2.24 and 2.39). The authors analyzed the clinical factors associated with the development of brain metastasis in NSCLC using a large-scale database and they also reported that the incidence of brain metastasis was 8.3% in patients with NSCLC, which has been infrequently mentioned in previous studies. However, there are limitations to this study. First, the data used in this study were collected 20 to 30 years ago and may not reflect the current situation. In addition, the incidence of brain metastasis may have been underestimated, since brain MRI was not commonly performed at that time. Second, there were no data on patients with brain metastases in the SEER database, and the authors used “brain radiotherapy indicated” as the surrogate maker for brain metastasis.

Recently, another study from the same authors was

published to investigate a similar subject in patients with NSCLC based on the National Cancer Data Base registry between 2010 and 2012 (16). This more recent study improved upon the limitations of the previous study. In the later study, the authors used information about patients with brain metastases from a more recent database. In addition, a larger number of patients were included in the analysis. In the recent study, multivariable analysis revealed that a younger age, non-squamous histology, tumor size, tumor grade, and node-positive disease were clinical factors associated with brain metastasis. The incidence of brain metastasis was 10.4%, which was higher than the previous study. Brain metastasis is common at initial presentation of primary lung cancer, and 91% of patients are diagnosed with brain metastasis within 1 year of initial diagnosis (17). Therefore, in patients with clinical factors that are thought to be associated with the development of brain metastasis (younger age, high tumor grade, non-squamous histology), brain MRI should be considered more actively at the time of diagnosis.

In addition to the clinical factors, various biomarkers have been reported to be associated with brain metastases (18-22). In patients with lung adenocarcinomas, the frequency of EGFR mutation was statistically higher for patients with brain metastases compared with epidermal growth factor receptor (EGFR) wild type (21). Brain metastases were more common in patients with echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK)-positive compared with EGFR mutant patients (22). However, there were no statistically significant differences in the incidence of brain metastases based on *ROS1*, *ALK*, *EGFR*, *KRAS*, or *BRAF* mutation status in another study (23). Further studies are required to elucidate the biomarkers associated with brain metastases in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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