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Original article

Epidermal growth factor receptor mutation predicts favorable outcomes in non-small cell lung cancer patients with brain metastases treated with stereotactic radiosurgery

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ABSTRACT

Purpose: The impact of epidermal growth factor receptor (EGFR) mutations on radiotherapy for brain metastases (BM) is undetermined. We evaluated the effects of EGFR mutation status on responses and outcomes in non-small cell lung cancer (NSCLC) patients with BM, treated with upfront or salvage stereotactic radiosurgery (SRS).

Methods and materials: From 2008 to 2015, 147 eligible NSCLC patients with 300 lesions were retrospectively analyzed. Patterns of tyrosine kinase inhibitor (TKI) therapy were recorded. Radiographic response was assessed. Brain progression-free survival (BPFS) and overall survival were calculated and outcome prognostic factors were evaluated.

Results: Median follow-up time was 13.5 months. Of the EGFR-genotyped patients, 79 (65%) were EGFR mutants, and 42 (35%) were wild type. Presence of EGFR mutations was associated with higher radiographic complete response rates (CRR). Median time to develop new BM after SRS was significantly longer for mutant-EGFR patients (17 versus 10.5 months, $p = 0.02$), predominantly for those with adjuvant TKI therapy (26.3 versus 15 months, $p = 0.01$). EGFR mutations independently predicted better BPFS (HR = 0.55, $p = 0.048$) in multivariate analysis.

Conclusions: In patients with NSCLC treated with SRS for BM, the presence of EGFR mutations is associated with a higher CRR, longer time for distant brain control, and better BPFS. The combination of SRS and TKI in selective patient group can be an effective treatment choice for BM with favorable brain control and little neurotoxicity.

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death, with a high risk of brain metastases (BM) prevalent in around 20–40% of cases [1,2]. Without treatment, overall survival (OS) is only a few months. Progress in systemic therapies, together with the strategic use of surgical resection, stereotactic radiosurgery (SRS), and whole brain radiotherapy (WBRT), has improved the number of long-term survivors, as well as median survival [3]. Upfront WBRT is the standard treatment for the majority of patients with BM, but this method has been criticized for its risk of long-term neurotoxicity, while effective alternative treatments such as radiosurgery alone are available [4,5]. However, the negative impact of intracranial progression on neurologic and cognitive function when WBRT is omitted, as well as the uncertainty surrounding the efficacy of salvage treatments in reversing neurological deficits, are arguments in favor of WBRT [6]. Randomized trials have demonstrated that adjuvant WBRT does not improve OS, though intracranial relapse occurs considerably more frequently in SRS alone for patients with 1 to 4 BM [7–9]. Adding to this, some studies have reported that SRS alone is an effective treatment for patients with multiple BM [10–12], and for those with recurrent BM after prior WBRT [13,14]. Though distant brain progression rate was significantly higher for patients treated by SRS alone, only the minority of relapsed patients needed salvage whole brain radiotherapy [12]. Therefore, SRS with close monitoring has become the preferred treatment strategy for patients with limited BM, and constitutes an alternative option in the case of multiple BM.

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Advances in molecular diagnostics have allowed researchers to identify a subgroup of NSCLC patients, especially prevalent in East Asia, characterized by mutations in exons 18–21 of the epidermal growth factor receptor (EGFR) gene [15]. Patients in advanced stages of the disease who harbor a mutant form of EGFR show dramatically enhanced clinical responses and improved outcomes following administration of tyrosine kinase inhibitors (TKIs) of the EGFR [16]. Clinical studies have also demonstrated the efficacy of TKIs in treating BM in NSCLC patients with EGFR mutations [17,18], whether used alone or in combination with WBRT. In addition, recent studies have shown that EGFR mutations are associated with increases in radiosensitivity. Das et al. discovered that kinase-domain-mutant EGFR cancer cells were more sensitive to ionizing radiation compared with wild-type EGFR cancer cell lines [19]. In our previous work, both the presence of EGFR mutations and the concurrent use of EGFR TKIs independently predicted clinical response to WBRT in BM of NSCLC [20]. Other retrospective studies have also evaluated the effects of genetic alteration in EGFRs on clinical outcomes [21–26]. However, the results have been inconsistent, possibly due to heterogeneity in patient characteristics, differences in radiotherapy techniques, small sample sizes, and short follow-up times.

The purpose of the present study is to investigate the role of EGFR mutation status with respect to radiographic responses, patterns of failure, and clinical outcomes in NSCLC patients with BM treated with upfront or salvage SRS, in order to help customize treatment strategies in this era of precision medicine.

Materials and methods

Patients

This retrospective research was approved by the Institutional Research Ethics Committee. From May 2008 to January 2015, 234 patients with NSCLC received SRS for BM. After excluding ineligible patients (Supplementary Fig. S1), 147 patients with 300 lesions who met the inclusion criteria were enrolled for further analysis. Age, gender, Karnofsky performance score (KPS), status of primary tumor control, presence of extracranial metastasis (ECM), initial treatment for BM, recursive partitioning analysis (RPA) class, diagnosis-specific graded prognostic assessment (GPA) score, details of SRS, and patterns of TKI therapy were recorded.

Patients who showed disease progression under TKI use and had received any intervening systemic treatment were defined as having TKI failure at SRS.

Genotyping

The results of EGFR mutation testing—the genotyping method of which has been previously reported [27]—were available for 121 patients (Supplementary materials and methods). EGFR mutation testing was carried out mainly on intra-thoracic lesions or metastatic lymphadenopathies.

Stereotactic radiosurgery

All patients were treated with the CyberKnife® G4 radiosurgical system (Accuray Inc., Sunnyvale, CA) (See Supplementary materials and methods for detail treatment settings). Most patients (98%) underwent single-fraction SRS, with only 3 patients (2%) receiving fractionated (2 or 3 fractions) treatments. For analytical purposes, their prescription doses were converted to a single-fraction equivalent dose using the linear-quadratic model with an alpha–beta ratio of 10 Gy. The median prescribed marginal dose was 20 Gy (range 12–26 Gy) at the median isodose line of 78%. A 1-mm 3-dimensional margin surrounded the gross tumor was allowed according to physicians' preference and was used in 42.6% of measurable lesions.

Response and outcome assessment

After SRS, patients received follow-up brain imaging every 2–3 months, or when clinically indicated. Treatment response was assessed according to the revised Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, version 1.1. For patients with multiple lesions, the sum of the largest two lesions was used for response assessment. Objective response rate (ORR) was defined as either CR or PR. Measurable lesions, defined as lesions with a maximum diameter of at least 10 mm, were recorded and analyzed separately. Of 300 treated lesions, 204 (68%) were measurable. Local failure was defined as either pathologically proven recurrence or serial increases in size of enhancing lesions observed in imaging. Radionecrosis (RN, also known as pseudo-progression) was determined either pathologically at the time of resection or clinically by a multi-disciplinary team consisting of a neuroradiologist, neurosurgeon, and radiation oncologist. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Brain progression was defined as either local failure or development of new intracranial lesions. Time to event was calculated from the first SRS treatment date. Treatment responses and clinical outcomes were retrospectively collected while blinded to genotyping information.

Statistical analysis

Chi-square or Fisher's exact tests were used for categorical data analysis. Independent *t*-tests were used for continuous variable comparisons, while Mann–Whitney *U*-tests were applied to ordinal, nonparametric data. Survival curves were estimated using the Kaplan–Meier method, and differences between patient or treatment characteristics were assessed by log-rank tests. Cox proportional hazards models were performed for univariate and multivariate analyses. All statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). A two-sided *p*-value less than 0.05 was considered statistically significant.

Results

Median age was 60 years old (range: 32–90 years old), and median follow-up time was 13.5 months (range: 2.2–67.1 months). Among patients with EGFR genotyping information, 79 patients had mutant EGFR (muEGFR) tumors, and 42 had wild-type EGFR (wtEGFR) tumors. Patient characteristics are summarized in Table 1. The muEGFR cohort included a greater proportion of female patients (68% versus 43%, $p = 0.007$). There were no significant differences in extracranial disease status, distribution of RPA classes, or GPA score between the muEGFR and wtEGFR cohorts. The percentage of patients treated with any TKI therapy was significantly higher in the muEGFR cohort (90% versus 21%, $p < 0.001$).

Treatment characteristics, responses, and outcomes are summarized in Table 2. There were no significant differences in the median prescribed dose or mean treatment volume between the muEGFR and wtEGFR cohorts. No differences in objective response rate (ORR) or complete response rate (CRR) were found between the mutation subtypes of exon 19 deletion and exon 21 L858R (Supplementary Table E1).

When assessing responses for measurable lesions, ORR and CRR were also significantly higher in the muEGFR group than in the wtEGFR group (ORR: 72% versus 50%, $p < 0.01$; CRR: 38% versus 16%, $p < 0.01$). Measurable muEGFR lesions tended to have a longer median time to local progression than their wtEGFR counterparts

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