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Impacts of EGFR-mutation status and EGFR-TKI on the efficacy of stereotactic radiosurgery for brain metastases from non-small cell lung adenocarcinoma: A retrospective analysis of 133 consecutive patients

Shoji Yomo*, Kyota Oda

Division of Radiation Oncology, Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto-city, Nagano-prefecture, Japan

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ABSTRACT

Objectives: Recent advances in target therapies have prolonged overall survival (OS) for patients with epidermal growth factor receptor (EGFR)-mutant lung cancer. The impact of EGFR mutations on stereotactic radiosurgery (SRS) for brain metastases (BM) has yet to be determined. The present study sought to evaluate the efficacy and limitations of SRS, administered with EGFR-tyrosine kinase inhibitors (TKI), for BM from EGFR-mutant lung adenocarcinoma.

Materials and methods: This retrospective observational study analyzed data from patients with BM arising from EGFR-mutant lung adenocarcinoma who received upfront Gamma Knife SRS between December 2010 and April 2016. OS and distant and local intracranial disease control rates were calculated. The prognostic factors for each event were also determined.

Results: One hundred thirty-three consecutive patients (47 males/86 females) were eligible. The median age was 69 years, and the median Karnofsky performance status (KPS) was 90. Sixty-six patients (50%) had no history of EGFR-TKI use at the time of SRS. EGFR-TKI were administered to 85% of EGFR-TKI naïve patients after SRS. One- and 2-year OS rates were 74% and 52%, respectively. One- and 2-year distant BM recurrence rates (per patient) after SRS were 34% and 53%, respectively. One- and 2-year rates of local tumor control (per lesion) were 97% and 95%, respectively. Multivariate proportional hazards analyses showed that being EGFR-TKI naïve was associated with longer OS (HR: 0.42, $P < 0.001$), a lower distant intracranial recurrence rate (HR: 0.61, $P = 0.037$) and a higher local tumor control rate (HR: 0.28, $P = 0.001$).

Conclusions: The present study demonstrated the upfront SRS strategy to offer a minimally invasive and effective treatment option for EGFR-mutant lung adenocarcinoma patients with limited BM. EGFR-TKI naïve patients were found to be a distinct subgroup for which a longer survival time and durable intracranial disease control can be expected.

1. Introduction

Brain metastases (BM) are a significant cause of morbidity and mortality in patients with metastatic cancer. Lung cancer has a high propensity to metastasize to the brain. Approximately 20–40% of patients diagnosed as having lung adenocarcinoma will develop BM during their disease course and this risk is reportedly greater in patients harboring one of the epidermal growth factor receptor (EGFR) mutations [1,2]. Targeted therapies directed against EGFR have reportedly achieved significant clinical improvements in patients with EGFR-mutant lung adenocarcinomas with favorable toxicity profiles [3,4]. Thus, the median overall survival (OS) of patients with BM from EGFR-mutant lung adenocarcinomas has been significantly prolonged [5,6]. Longer survival is, in turn, associated with a higher incidence of BM during the disease course. [7]

To date, local therapies, such as whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or surgical resection, either alone or as part of a multimodality treatment approach are available as strategies

Abbreviations: BM, brain metastases; CI, confidence interval; D95, the dose 95% of the target volume receives; EGFR, epidermal growth factor receptor; HR, hazard ratio; KPS, Karnofsky performance status; LM, leptomeningeal metastases; LQ, linear-quadratic; Lung-molGPA, graded prognostic assessment for lung cancer using molecular markers; MR, magnetic resonance; MST, median survival time; NCI-CTCAE, National Cancer Institute common terminology criteria for adverse events; OS, overall survival; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitors; TV, target volume; WBRT, whole brain radiotherapy

* Corresponding author at: Division of Radiation Oncology, Aizawa Comprehensive Cancer Center, Aizawa Hospital 2-5-1, Honjo, Matsumoto-city, Nagano-prefecture, 390-0814, Japan.

E-mail address: ai.71422@ai-hosp.or.jp (S. Yomo).

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for BM management and the choice of therapy varies depending on patient group and prognosis. The routine use of adjuvant WBRT remains controversial [8]. This is because, despite better distant brain control rates being achieved, there is no survival advantage, and recent studies have suggested adverse effects from WBRT on patient cognition and quality of life [9,10]. SRS has become an established non-invasive ablative therapy [11,12]. The delivery of highly focused radiation with a sharp dose fall-off is theoretically expected to reduce delayed neurotoxicity, and this feature makes it applicable in both the upfront and the salvage setting. Magnuson et al. recently reported a pooled multi-institutional analysis, in which SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT [6]. However, the mechanisms underlying these synergistic effects remain unknown.

We retrospectively investigated the safety and efficacy of SRS for treating BM from EGFR-mutant lung adenocarcinomas in conjunction with EGFR-TKI in 133 consecutive patients. We also explored factors predicting the survival of patients undergoing SRS with EGFR-mutant lung adenocarcinomas.

2. Materials and methods

2.1. Data source and study cohort

The present study was conducted in compliance with the Declaration of Helsinki (sixth revision, 2008), and fulfilled all of the requirements for patient anonymity. The Aizawa Hospital Institutional Review Board approved this retrospective clinical study in April 2017 (No. 2016-033). We analyzed our prospectively maintained institutional radiosurgical database to investigate radiological and clinical outcomes. Between December 2010 and April 2016, 133 consecutive patients with BM which had arisen from EGFR-mutant lung adenocarcinomas who underwent Gamma Knife SRS as upfront treatment were eligible for the present study.

2.2. Radiosurgical indications and techniques

The SRS protocol used in this study was based on the standard of care established at our institution. Patients with up to ten BM principally received SRS [11]. Providing that WBRT had been refused by the patient, SRS was applied for multiple BM, even in cases with more than 10 lesions, when the patient's systemic condition was such that SRS intervention would be tolerable and fully informed consent, based on an explanation that SRS for more than 10 metastases remains an unproven strategy in terms of safety and efficacy, had been obtained. Surgical resection was, in principle, indicated for large tumors with a mass effect. If surgery was apparently contraindicated due to a poor prognosis or advanced systemic disease, 2-session SRS was applied for carefully selected large tumors [13].

Concurrent use of EGFR-TKI was not temporarily interrupted during routine SRS procedures. SRS was performed using the Leksell G stereotactic frame (Elekta Instruments, Stockholm, Sweden). Prior to frame application, non-stereotactic three-dimensional volumetric gadolinium-enhanced T1-weighted and T2-weighted magnetic resonance (MR) images were obtained. The frame was placed on the patient's head under local anesthesia supplemented with adequate sedation. Stereotactic contrast-enhanced computed tomographic images covering the whole skull were routinely used as a reference for co-registration with MR images. An individual treatment plan was generated for each patient employing Leksell Gamma Plan software (Elekta Instruments). Prescribed doses were selected in principle according to the dose protocol of the JLGK 0901 study [11]. The technical details of 2-session SRS were previously described in detail [13]. All radiosurgical interventions were supervised by the senior neurosurgeon (SY) and performed with the Leksell Gamma Knife Model C or Perfexion.

2.3. Post-SRS management and follow-up evaluation

Clinical follow-up data as well as contrast-enhanced MR images were obtained every two to four months. If metachronous distant metastases were identified, they were, in principle, managed with repeat SRS. When miliary metastases (numerous tiny enhanced lesions) and/or leptomeningeal metastases (LM) (linear brain surface enhancement along the sulci) was newly documented, WBRT was then recommended. For local tumor control, we adopted the combined endpoint, imaging and/or clinical worsening of the lesion treated, in order to strictly evaluate the efficacy of SRS. Local control failure was defined as a continuous increase ($> 20\%$ in diameter) in the targeted lesions, taking as a reference the pre-SRS diameter, and/or neurological deterioration irrespective of whether the lesion was a true recurrence or delayed radiation injury. Then, to determine whether salvage management was feasible, we endeavored to meticulously differentiate delayed radiation injury from tumor recurrence, based on the clinical course, serial MR imaging findings [14] and in selected cases ^{11}C-methionine positron emission tomography [15]. Additional SRS was applied provided that the volume of the local tumor recurrence was small enough for single-dose SRS. Surgical removal was indicated when neurological signs became refractory to conservative management, regardless of whether the radiological diagnosis was local tumor progression or radiation necrosis. Any adverse events attributable to SRS procedures were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; ver.4.0).

Before closing the research database for analysis in July 2017, the authors updated the follow-up data of patients who had not visited our outpatient department for more than six months. Inquiries about the date and mode of death were made directly by corresponding with the referring physician and/or the family of the deceased patient, with written permission obtained at the time of undertaking SRS from all patients and/or their relatives, allowing the use of personal data for clinical research. Neurological death was defined as death attributable to central nervous system metastases including tumor recurrence and carcinomatous meningitis. Deaths with unspecified causes were also categorized as neurological deaths in the present study.

2.4. Statistical analysis

The overall survival (OS) rate was calculated by the Kaplan-Meier product limit method. The neurological and non-neurological death rates were calculated employing Gray's test [16], wherein each event was regarded as a competing risk for another event. For the estimation of local control failure rates and distant BM recurrence, Gray's test was similarly applied, with subsequent WBRT for distant recurrence and the patient's death being regarded as competing events, respectively. All of the above analyses were based on the interval from the date of initial SRS treatment until the date of each event. The Cox and Fine-Gray proportional hazards models [17] were appropriately employed to investigate prognostic factors associated with OS and neurological death-free survival, and for distant and local intracranial disease control. Potential prognostic factors were selected with reference to other SRS series. The statistical processing software package "R" version 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. A P-value < 0.05 was considered to indicate a statistically significant difference.

3. Results

3.1. Patient characteristics, concurrent systemic therapy and SRS dose prescription

During the study period, 133 consecutive patients with BM which had arisen from EGFR-mutant lung adenocarcinomas underwent Gamma Knife SRS as upfront treatment. Five patients who had received