GAMMA KNIFE STEREOTACTIC RADIOSURGERY COMBINED WITH TARGETED THERAPY FOR BRAIN METASTASES IN NON-SMALL CELL LUNG CANCER WITH EGFR GENE MUTATIONS

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ABSTRACT

Objectives: Our study aims to evaluate the outcome of Gamma Knife radiosurgery combined TKIs for brain metastasis of non-small cell lung cancer with EGFR gene mutations.

Methods: We analyzed 35 patients with brain metastatic non-small cell lung cancer with EGFR gene mutations from July 2019 to May 2024. Selected patients have brain metastases from 1 to 10 tumors, size ≤ 3cm, KPS score ≥ 60, EGFR gene mutation, first-generation TKI treatment. Patients were treated by stereotactic radiosurgery using Leksell Gamma Knife ICON unit (Elekta AB) with dose of 20 – 24, 18 – 20Gy for lesions measuring < 2, 2.1 – 3 cm, respectively. Patients take st generation TKIs (erlotinib or gefitinib) 1 tablet per day. Patients were assessed for clinical symptoms and imaging response according to RANO criteria at 6, 12 months and survival outcomes.

Results: In our study, cerebral progression-free survival rate at 12 months was 100%, 24 months was 65,6%. Overall survival rate at 12 months was 84%, 24 months was 57,9%, overall survival time was 28 ± 3,7 months.

Conclusion: Combination Gamma Knife radiosurgery with TKIs is an effective treatment for brain metastasis of non-small cell lung cancer with EGFR gene mutations.

Key words: Radiosurgery; brain metastases; non-small cell lung cancer; EGFR gene mutations; TKIs.

1. INTRODUCTION

Lung cancer (LC) is one of the most common malignancies and remains the leading cause of cancer-related death worldwide. According to the International Agency for Research on Cancer (IARC), in 2018, there were approximately 2.09 million new cases and 1.76 million deaths globally. In Vietnam, these figures were estimated at 23.67 thousand new cases and 20.71 thousand deaths[1]. A characteristic feature of advanced-stage lung cancer is its tendency to metastasize to the brain, with approximately 10% of patients diagnosed with advanced non-small cell lung cancer (NSCLC) presenting with brain metastases[2]. Among NSCLC patients, those with brain metastases tend to have a higher rate of EGFR mutations compared to patients without brain metastases. Conversely, among NSCLC patients with EGFR mutations, the incidence of brain metastases (70%) is significantly higher than in the EGFR wild-type group[3]. Historically, brain metastases were considered a poor prognostic factor, with patients rapidly

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deteriorating due to neurological symptoms and having a median overall survival of only 4-6 weeks without treatment. However, with advancements in medical science particularly the emergence of targeted therapies for patients with genetic mutations and the development of local treatments such as stereotactic radiosurgery (SRS), treatment outcomes have markedly improved in terms of both survival and symptom control. Our study aims to evaluate the treatment outcomes of non-small cell lung cancer patients with EGFR mutations and brain metastases treated with a combination of stereotactic radiosurgery and tyrosine kinase inhibitors (TKIs).

2. SUBJECTS AND RESEARCH METHODS

2.1. Study Subjects

2.1.1. Inclusion Criteria

- Non-small cell lung cancer (NSCLC) with brain metastases.

- Number of brain metastatic lesions: 1-10, with each lesion's maximum diameter ≤ 3 cm.

- Presence of EGFR mutation.

- Karnofsky Performance Status (KPS) ≥ 60.

- First-time stereotactic radiosurgery (SRS).

- Liver, kidney and bone marrow functions within acceptable limits.

2.1.2. Exclusion criteria

- Patients previously treated with whole-brain radiotherapy.

- Patients who underwent surgical resection of brain metastases.

- Patients with co-existing cancers or severe acute/chronic illnesses with near-term mortality risk.

2.1.3. Study Period and location

- Study period: From July 2019 to May 2024.

- Location: Vietnam National Cancer Hospital, Vietnam.

2.2. Research Methods

2.2.1. Study design

- Clinical interventional study without a control group.

2.2.2. Sample size

- Convenience sampling method.

- A total of 35 patients were included in the study.

2.2.3. Study procedure

- Patients underwent clinical examination and laboratory testing before treatment

- Stereotactic radiosurgery (SRS) was performed using the Leksell Gamma Knife ICON system (Elekta AB, Sweden). Radiation dose based on RTOG 90-05 protocol, depending on tumor size, number, and location:

+ < 2 cm: 20-24 Gy;

+ 2–3 cm: 18-20 Gy.

- Patients were treated with tyrosine kinase inhibitors (TKIs):

- Erlotinib (Tarceva): 150 mg, 1 tablet/day.

- Or Gefitinib (Bigefinib, Iressa): 250 mg, 1 tablet/day.

- Duration of TKI treatment: minimum of 3 months.

- Follow-up assessment every 3 months: MRI (or contrast-enhanced CT) of the brain, contrast-enhanced CT of the chest and abdomen.

2.2.4. Evaluation Criteria

- Tumor response: assessed based on RANO (Response Assessment in Neuro-Oncology) criteria.

+ Complete Response: all lesions disappear, no corticosteroids required, non-target lesions resolved, clinical condition stable or improved

+ Partial Response: ≥30% reduction in total diameter of target lesions, non-target lesions non-progressive, corticosteroid dose stable or reduced, clinical condition stable or improved

+ Stable Disease: reduction in target lesion size <30% or increase <20%, non-target lesions non-progressive, corticosteroid dose stable or reduced, clinical condition stable or improved

+ Progressive Disease: any of the following: ≥20% increase in target lesion size, progression in non-target lesions, appearance of new lesions, worsening clinical condition.

- Survival analysis: Kaplan–Meier method: OS (Overall Survival), iPFS (Intracranial Progression-Free Survival).

+ Key time points:

• Date of Gamma Knife SRS initiation.

• Date of disease progression per objective response.

• Date of death.

• Date of last follow-up.

• End of study date.

+ Overall Survival (OS): time from treatment initiation to either death or last follow-up.

+ Intracranial Progression-Free Survival (iPFS): time from treatment initiation to brain metastasis progression (increased lesion size or new lesions).

2.3. Data Processing

- All data were coded and processed using SPSS version 20.0.

- Descriptive statistics included mean, median, standard deviation, minimum and maximum values.

- Comparisons of proportions were performed using the Chi-square (χ^2) test.

- Statistical significance was considered at $p < 0.05$.

3. RESULTS

3.1. Patient Characteristics

Table 1. Patient Characteristics

Variable	Result
Total number of patients	35
Age	
Mean	57,5 ± 9,1
Range	32 - 71
Gender	
Male	18 (51,4%)
Female	17 (48,6%)
Neurological symptoms	
Present	27 (77,1%)
Absent	8 (22,9%)
Karnofsky Performance Status	
≥ 90	21 (60%)
≤ 80	14 (40%)
Number of brain metastases	
1 lesion	11 (31,4%)
2 - 5 lesions	20 (57,1%)
6 - 10 lesions	4 (11,4%)
Extracranial metastases	
Present	14 (40%)
Absent	21 (60%)

Remarks: The mean age of the study population was 57.5±9.1 years. The male-to-female ratio was 1.06. A total of 27 patients (77.1%) presented with neurological symptoms. Karnofsky Performance Status (KPS) was ≥ 90 in 21 patients (60.0%). Brain metastases were limited to a single lesion in 31.4% of patients. The rate of extracranial metastases was 40%.

3.2. Treatment Outcomes

3.2.1. Overall Survival (OS)

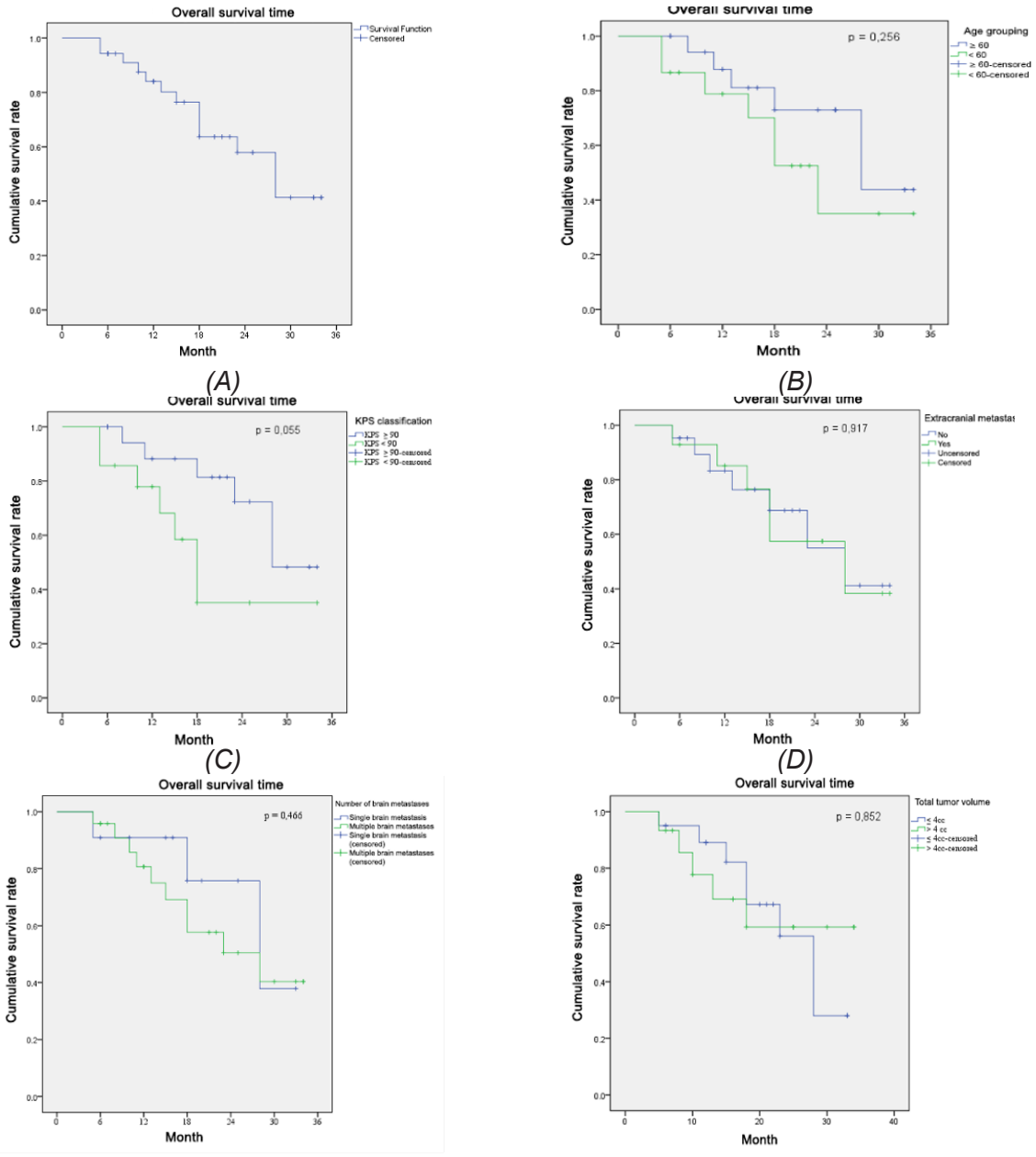
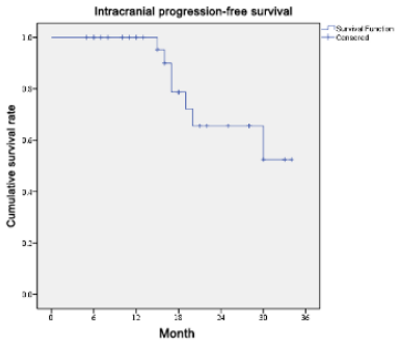


Figure 1. Overall survival (A) and associated factors. (B) Survival by age. (C) Survival by karnofsky performance status (KPS). (D) Survival by presence of extracranial metastases. (E) Survival by number of brain metastases. (F) Survival by total tumor volume

Comments: The median overall survival was 28 ± 3.7 months. The overall survival rates were 84% at 12 months and 57.9% at 24 months. There was no statistically significant association between overall survival and the following factors: Age, Karnofsky Performance Status (KPS), Presence of extracranial metastases, Number of brain metastases, Total tumor volume.

3.2.2. Progression-Free Survival (PFS)

Observation: The median intracranial progression-free survival was 27.8 ± 1.9 months. The intracranial PFS rates at 12 months and 24 months were 100% and 65.6%, respectively. The median extracranial progression-free survival was 19 ± 1.2 months. The extracranial PFS rates at 12 months and 24 months were 64.4% and 35.4%, respectively.



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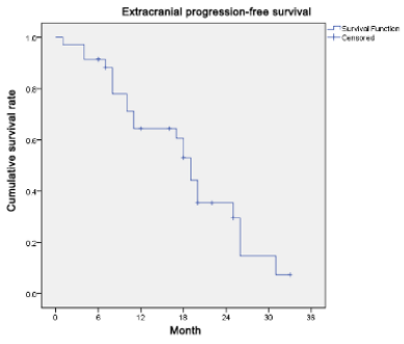

(H)

Figure 2. Progression-Free Survival: (G) Intracranial. (H) Extracranial

4. DISCUSSION

The main treatment strategies for brain metastases include surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS), used either alone or in combination. To date, the optimal treatment strategy remains a matter of debate. Since the advent of first-generation TKIs, brain metastases from lung cancer have become a major focus of therapeutic research. It is undeniable that TKIs with their advantages of low molecular weight, favorable lipid/water ratio, and good permeability have achieved significant results in treating brain metastases compared to traditional therapies. Some authors suggest that TKIs can be used as a standard initial treatment for asymptomatic brain metastases in EGFR-mutant NSCLC patients, with radiotherapy reserved for symptom onset or disease progression. In contrast, other studies support early combination with local therapies such as radiotherapy to improve local control, alleviate local symptoms, enhance the depth of systemic treatment, and thereby extend patient survival[4]. A major concern raised in previous studies is the adverse cognitive effects associated with radiotherapy, especially WBRT. However, most of those studies involved WBRT. The combination of stereotactic radiosurgery and TKIs offers a promising treatment strategy that enhances local control, prolongs survival and minimizes adverse effects.

Regarding intracranial control, Oda's study reported distant brain metastasis recurrence rates of 34% at 1 year and 53% at 2 years, with local control rates of 97% and 95% at 1 and 2 years, respectively[5]. Another study by Dohm on 174 NSCLC patients with brain metastases treated with SRS within 3 months of systemic therapy initiation showed significantly improved intracranial control with TKIs compared to conventional chemotherapy (HR = 0.4; 95% CI: 0.25–0.76; p = 0.04) and also when SRS was given prior to systemic therapy (HR = 0.6; 95% CI: 0.3–0.9; p = 0.03). Local control also improved significantly when patients received SRS prior to (HR = 0.4; 95% CI: 0.2–0.9; p = 0.03) or concurrently with (HR = 0.3; 95% CI: 0.1–0.6;

p = 0.003) systemic therapy[6]. These results are consistent with our findings and other reports, indicating improved control of distant brain metastases when SRS is administered before or during TKI therapy. In our study, intracranial progression-free survival was 100% at 12 months and 65.6% at 24 months.

A 2018 retrospective study by Yomo et al. on 133 EGFR-mutant lung adenocarcinoma patients with brain metastases treated with Gamma Knife SRS followed by TKIs reported 1- and 2-year overall survival (OS) rates of 74% and 52%, respectively, with a median OS of 24.8 months. These results are significantly better than earlier studies, suggesting an increase in survival from 7 months (1985-2005) to 12 months (2006-2014)[5]. Another multi-center retrospective analysis by Magnuson et al. on 351 EGFR-mutant NSCLC patients with brain metastases compared groups treated with SRS followed by TKIs, WBRT followed by TKIs, or TKIs followed by either SRS or WBRT upon progression. The best OS was observed in the group receiving SRS followed by TKIs, with a median survival of 44 months, while avoiding the cognitive decline associated with WBRT[7]. The survival outcomes in our study are consistent with these findings. The 1- and 2-year OS rates were 84% and 57.9%, respectively, with a median OS of 28 months.

5. CONCLUSION

Gamma Knife radiosurgery combined with TKIs is an effective treatment approach for patients with EGFR-mutant non-small cell lung cancer.

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