EGFR mutant status and tyrosine-kinase inhibitors affect the GKRS outcomes for NSCLC brain metastases

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Abstract

Objective Tyrosine kinase inhibitors (TKIs) is the first-line treatment for EGFR-positive non-small cell lung cancer (NSCLC); however, its applicability to patients with wild-type NSCLC remains an issue of contention. This study compared the effects of gamma knife radiosurgery (GKRS) alone versus combining GKRS and TKIs in treating two genetic forms of NSCLC.

Methods This retrospective study examined 479 NSCLC patients with 1982 brain metastases who underwent GKRS and for whom imaging follow-up data or death records were available. All our patients were consecutive. All gene mutations were confirmed by lung biopsy. The three main endpoints in this study were overall survival (OS), local intracranial tumor control (LC), and distal intracranial tumor control (DC).

Results There were 296 NSCLC patients with EGFR positive: TKI treatment (n = 262) and without TKI treatment (n = 34). GKRS + TKIs was more effective than GKRS alone in terms of OS (HR 0.53, p = 0.085) and DC (HR 0.51, p < 0.001). There were 150 NSCLC patients with wild-type EGFR: TKI treatment (n = 50) and without TKI treatment (n = 100). GKRS + TKIs was less effective than GKRS alone in terms of OS (HR 1.82, p = 0.049) and DC (HR: 1.40, p = 0.011). We observed no difference in terms of LC in both genetic groups.

Conclusions Combining GKRS with TKIs proved effective in EGFR positive NSCLC patients; however, we do not observe the similar results when combining GKRS with TKIs for patients with wild-type NSCLC.

Keywords Gamma knife · EGFR · Mutations · Survival · Tumor control · Radiosurgery · Brain metastasis · Tyrosine-kinase inhibitor · Wild type · Non-small cell lung cancer · Stereotactic surgery

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| EGFR | Epidermal growth factor receptor |
| GKRS | Gamma knife radiosurgery |
| Gy | Gray |
| KPS | Karnofsky performance status |
| BM | Brain metastasis |
| MR | Magnetic resonance |
| NSCLC | Non-small cell lung cancer |
| OS | Overall survival |
| TKIs | Tyrosine kynase inhibitors |

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WBRT  Whole brain radiotherapy  
SRS  Stereotactic radiosurgery

Introduction

NSCLC can be divided into three subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1]. Adenocarcinoma poses a higher risk of brain metastasis (BMs) [2], which accounts for one-third of the mortality among patients with NSCLC. In treating NSCLC-related BM, practitioners commonly combine systemic medication to control the primary lung disease as well as a local booster therapy for BM. Local treatment for BMs includes stereotactic surgery (SRS), whole brain radiotherapy (WBRT), craniotomy, and/or laser interstitial thermal therapy. Systemic treatment for BMs includes conventional chemotherapy, TKIs, and/or immunotherapy. The sequence of local treatment and systemic medication remains an issue of controversy; however, recent research has indicated that the outcomes of upfront SRS are superior to those of upfront EGFR-TKI therapy [3–6], and combined treatment appears to be the best choice [7]. Several studies have reported that in non-symptomatic patients with NSCLC oligo-BMs, SRS is the preferred first-line treatment [8, 9], as it provides superior tumor control with fewer complications than other local BM treatments, such as WBRT [6, 10, 11].

TKIs could be the first-line therapy for BMs in cases of EGFR-mutant NSCLC; several studies have reported that combining SRS with TKIs leads to a better outcomes than TKIs alone [7, 12–15]. In cases of EGFR wild-type (EGFR-wt) NSCLC, 2018 ESMO guidelines recommend chemotherapy or immunotherapy as first-line treatment and TKIs (e.g., erlotinib) as a second or third-line treatment [16]. A review in 2016 and an original paper in 2019 challenged the rationale of using TKIs for patients with EGFR-wt [17, 18]. Furthermore, there has been a lack of research on the use of SRS in conjunction with TKIs for the treatment of EGFR-wt patients with NSCLC-BMs.

In this study, we measure other factors' interaction with SRS in EGFR-mutant patients and EGFR-wt patients. Specifically, we identify critical factors affecting overall survival, local tumor control, and distal intracranial tumor control in EGFR-mutant and EGFR-wt NSCLC patients with BMs.

Methods

The retrospective study was based on a review of a GKRS database for the period 2012 to 2021, including 479 patients with 1978 brain metastases. All our patients are consecutive. In accordance with previous studies, the inclusion criteria were as follows: (1) Confirmed EGFR mutation status and a confirmed diagnosis of NSCLC based on lung biopsy or open surgery; (2) Confirmation of BMs via MRI; (3) Treatment involving GKRS; and (4) At least one instance of clinical or neuroimaging follow-up. The exclusion criteria were as follows: (1) Second or third gamma knife treatment in same tumor; (2) No MRI follow-up or death data.

For all patients, we recorded patient profiles, tumor-related data, follow-up and survival time, EGFR gene mutation type, different treatment regimen, and GKRS protocol in Table 1 and Demographics.

Our TKIs use protocol in patients receiving GKRS were as follows: (1) In EGFR positive patients, TKIs was used immediately after diagnosing disease, or within 3 months post GKRS. (2) In EGFR-wt patients, the time of TKIs’ administration was mainly affected by patient’s affordability of immunotherapy, tolerability to chemotherapy and doctor’s clinical advice.

Primary and secondary outcomes were evaluated in terms of survival and intracranial tumor control (local and distal). Local tumor control was defined as follows: (1) Regression, ≥ 10% decrease in tumor volume; (2) Stable, < 10% increase or decrease in tumor volume; and (3) Progression, ≥ 10% increase in tumor volume. Failure in distal intracranial tumor control was defined as the appearance of outfield intracranial tumors following GKRS. Neuroimaging and clinical follow-ups were performed at intervals of 3 months.

All statistical analysis involving descriptive statistics, categorical variables, continuous variables was performed using R Statistical Software. Kaplan–Meier and actuarial methods were used to analyze time-dependent parameters, local tumor control, distal intracranial control, and overall survival. Local tumor control and distal intracranial control curves were compared using the log-rank test. Significance in the efficacy of treatment was defined as a p-value of < 0.05 concurrently with a hazard ratio of > 1.4 or < 0.7.

Results

Demographics

The study included 232 males and 247 females. The median age of the patients was 62.5 years (range: 29.2–91.3 years.).
A total of 131 patients (27.3%) presented with 1 intracranial lesion, 306 patients (63.9%) presented with 2–10 intracranial lesions, and the other patients presented with 11–25 lesions. Extracranial metastasis was reported in 231 patients (48.2%). The median Karnofsky Performance Scale (KPS) score was 90 (range 50–100). The median imaging follow-up period was 12.3 months (range 0.13–114 months), and the median clinical follow-up period was 12.7 months (range 0–120.5 months). The treatment regimens were as follows: Craniotomy prior to GKRS (13.9%), WBRT (13.9%), chemotherapy (44.1%), and TKIs (70.8%). The major tumor type was pure adenocarcinoma (90.0%). Gene mutation distribution was as follows: wild-type EGFR (150 patients), ALK + mutations (25 patients), EGFR mutations (296 patients). Most of the mutations were located at L858R (25.5%), followed by exon 19 (22.3%) and exon 20 (1.9%). Among the deceased patients, the median survival time was 10.9 months and the longest survival time was 122.3 months (Table 1).

### Overall survival after GKRS

The median follow up duration time was 12.7 months. OS rates of all patients in this study (n = 479) were as follows: 12 months (73.8%), 24 months (58.4%), 36 months (52.1%), and 48 months (39.9%) (Fig. 1A). The 2-year survival rate in the two main groups was as follows: EGFR positive patients (62.6%) and EGFR wild-type patients (46.2%) (p = 0.0016, Fig. 1B). As shown in Fig. 1C, among EGFR-positive patients, the 2-year survival rates were 62.6% for EGFR positive patients and 46.2% for EGFR wild-type patients (p = 0.0016). The median survival times were 10.9 months (range 0.3–122.3 months) and 122.3 months, respectively. The 5-year survival rate was 39.9% for all patients, 62.6% for EGFR positive patients, and 46.2% for EGFR wild-type patients. The median survival times were 10.9 months (range 0.3–122.3 months) and 122.3 months, respectively.

Table 1 Clinical characteristics of 1982 brain metastatic tumors in 479 patients with NSCLC

| Characteristics                           | Values | Percentage or range |
|------------------------------------------|--------|---------------------|
| Per patient (n = 479)                    |        |                     |
| Sex (male:female)                        | 232:247| 48.4%-51.6%         |
| Age (years)                              | 62.5   | 29.2–91.3           |
| Median max tumor vol (ml)                | 0.6    | 0.004–39.1          |
| Median total tumor vol (ml)              | 1.5    | 0.014–40.5          |
| Number of intracranial metastases        |        |                     |
| 1 (single lesion)                        | 131    | 27.3%               |
| 2–10                                     | 306    | 63.9%               |
| > 10                                     | 42     | 8.7%                |
| Extracranial metastasis                  | 231    | 48.2%               |
| KPS score (median)                       | 90     | 50–100              |
| Neurological deficits                    |        |                     |
| Long-tract signs                         | 90     | 18.8%               |
| Cerebellar signs                         | 24     | 5%                  |
| Cranial nerve palsy                      | 45     | 9.4%                |
| High cortical dysfunction                | 12     | 2.5%                |
| Asymptomatic                             | 347    | 72.4%               |
| Median image follow-up (mos)             | 12.3   | 0.13–114.0          |
| Median clinical follow-up (mos)          | 12.7   | 0–120.5             |
| Prior craniotomy                         | 67     | 13.9%               |
| WBRT use                                 | 67     | 13.9%               |
| Chemotherapy use                         | 211    | 44.1%               |
| EGFR-TKI use                             | 339    | 70.8%               |
| Tumor histology                          |        |                     |
| Pure adeno CA                            | 431    | 90.0%               |
| Squamous cell CA                         | 7      | 1.4%                |
| AdenoCA and large cell CA                | 1      | 0.2%                |
| AdenoCA and small cell CA                | 1      | 0.2%                |
| AdenoCA and squamous cell CA             | 1      | 0.2%                |
| EGFR mutation type                       |        |                     |
| L858R point mutation                     | 122    | 25.5%               |
| Exon 19 deletion                         | 107    | 22.3%               |
| Exon 20 insertion                        | 9      | 1.9%                |
| G719X point mutation                     | 7      | 1.5%                |
| L861Q point mutation                     | 4      | 0.8%                |
| Exon 21 point mutation                   | 3      | 0.6%                |
| T790M point mutation                     | 3      | 0.6%                |
| S768I point mutation                     | 3      | 0.6%                |
| Exon 18 deletion                         | 1      | 0.2%                |
| Combined mutations                       |        |                     |
| L858R and T790M                          | 17     | 3.5%                |
| Exon 19 deletion and T790M               | 14     | 2.9%                |
| Exon 19 deletion and G719X               | 1      | 0.2%                |
| L858R and S768I                          | 1      | 0.2%                |
| G719X and S768I                          | 2      | 0.4%                |
| Exon 19 deletions and S768I              | 1      | 0.2%                |
| G719X and L861Q                          | 1      | 0.2%                |
| ALK mutation                             | 25     | 6.3%                |
| No mutation                              | 150    | 31.3%               |

Table 1 (continued)

| Characteristics                           | Values | Percentage or range |
|------------------------------------------|--------|---------------------|
| Inconclusive                             | 8      | 1.7%                |
| Median survival (mos) death only         | 10.9   | 0.3–122.3           |
| Per tumor (n = 1982)                     |        |                     |
| Location of tumor                        |        |                     |
| Frontal lobe                             | 656    | 33.1%               |
| Parietal lobe                            | 347    | 17.5%               |
| Temporal lobe                            | 235    | 11.9%               |
| Occipital lobe                           | 270    | 13.6%               |
| Insula                                   | 38     | 1.9%                |
| Basal ganglia and thalamus               | 91     | 4.6%                |
| Brainstem                                | 30     | 1.5%                |
| Cerebellum                               | 285    | 14.4%               |
| Other                                    | 30     | 1.5%                |
| SRS protocol                             |        |                     |
| Radiation volume (ml)                    | 1.26   | 0.002–43.2          |
| Margin dose (Gy)                         | 20.0   | 6.0–27.0            |
| Max dose (Gy)                            | 30.0   | 12.0–45.3           |
| Isodose level (%)                        | 70     | 40–95               |
patients, the 2-year survival rate was as follows: GKRS with TKIs (63.7%) and GKRS alone (44.4%) with a p-value of 0.085 and hazard ratio of 0.53 in multivariate analysis (Table 2). As shown in Fig. 1D, among EGFR wild-type patients, the 2-year survival rate was as follows: GKRS with TKIs (30.9%) and GKRS alone (55.7%) with a p-value of 0.049 and hazard ratio of 1.819 in multivariate analysis (Table 3).

**Intracranial tumor control after GKRS**

The median image follow-up duration time was 12.3 months. Local tumor control of all tumors (n = 1982) was as follows: 6 months (92.0%), 12 months (87.0%), 18 months (84.8%), 24 months (82.3%), and 36 months (80.5%) (Fig. 2A). We did not observe a significant difference between cases of EGFR mutation and EGFR wild-type in terms of local tumor control (p = 0.53) (Fig. 2B). We did not observe a significant difference between treatment modalities (GKRS with TKIs versus GKRS alone) in terms of local tumor control, regardless of tumor type (EGFR positive or wild-type) (Fig. 2C, D).

Distal intracranial tumor control of all tumors was as follows: 6 months (58.0%), 12 months (38.6%), 18 months (28.5%), 24 months (22.2%), and 36 months (10.6%) (Fig. 3A). We did not observe a significant difference between EGFR mutation and EGFR wild-type in terms of distal intracranial tumor control (p = 0.30) (Fig. 3B). Among EGFR positive patients, GKRS with TKIs outperformed GKRS alone: 6 months (60.0 vs 50.8%), 12 months (39.9 vs 29.0%), and 24 months (22.1 vs 14.5%) (Fig. 3C) with a p-value of < 0.001 and hazard ratio of 0.507 in multivariate analysis (Table 2). Among EGFR wild-type patients GKRS with TKIs did not attain the effectiveness of GKRS alone, as follows: 6 months (46.0 vs 64.6%), 12 months (36.4 vs 37.4%), and 24 months (19.2 vs 33.3%) (Fig. 3D) with a p-value of 0.011 and hazard ratio of 1.402 in multivariate analysis (Table 3).

**Other prognostic factors associated with GKRS**

EGFR positive patients benefited from WBRT and chemotherapy in terms of local tumor control; this approach was negatively associated with primary tumor control. TKI treatment proved effective in distal intracranial control; however, prior craniotomy was identified as a negative prognostic factor (Table 2). Among EGFR wild-type patients, prior craniotomy was a positive prognostic factor in terms of OS, whereas TKI use and extracranial metastasis were negative prognostic factors. Undergoing prior craniotomy, WBRT and primary tumor control disclose negative effect on local tumor control. TKIs is the only positive factor under our criteria (Table 3). In the current study, statistically significant treatment effects were
Table 2 Prognostic factors in EGFR positive patients

| Factors                  | Overall survival (EGFR +) | Local tumor control (EGFR +) | Distal intracranial tumor control (EGFR +) |
|-------------------------|---------------------------|-----------------------------|-------------------------------------------|
|                         | Univariate                 | Multivariate                | p Value         | HR   | 95% CI    | p Value         | HR   | 95% CI    | p Value         | HR   | 95% CI |
| Sex                     | 0.371                      | 0.83 | 0.54–1.26 | 0.042 | 0.69 | 0.48–0.99 | 0.055 | 0.68 | 0.46–1.01 | 0.006 | 1.23 | 1.06–1.42 | 0.002 | 1.31 | 1.11–1.55 |
| Age                     | 0.402                      | 1.01 | 0.99–1.03 | 0.005 | 1.02 | 1.01–1.04 | 0.002 | 1.03 | 1.01–1.05 | 0.138 | 1.00 | 0.99–1.00 | 0.039 | 1.01 | 1.00–1.02 |
| KPS score               | 0.001                      | 0.97 | 0.95–0.99 | **0.005** | 0.97 | 0.95–0.99 | **0.031** | 0.98 | 0.96–0.99 | 0.754 | 0.99 | 0.98–1.02 | 0.482 | 1.00 | 0.99–1.01 |
| Prior craniotomy         | 0.113                      | 0.44 | 0.16–1.21 | 0.083 | 0.41 | 0.15–1.12 | 0.884 | 1.04 | 0.63–1.73 | <0.001 | 1.61 | 1.30–1.99 | <0.001 | 1.69 | 1.34–2.12 |
| WBRT use                | **0.129**                  | 1.46 | 0.90–2.38 | 0.218 | 1.36 | 0.83–2.24 | <0.001 | 0.16 | 0.06–0.43 | <0.001 | 0.16 | 0.06–0.45 | **0.122** | 0.51 | 0.38–0.68 |
| TKI use                 | 0.123                      | 0.58 | 0.29–1.16 | 0.085 | 0.53 | 0.25–1.09 | 0.446 | 0.77 | 0.39–1.51 | 0.003 | 0.80 | 0.49–0.93 | **0.001** | 0.77 | 0.65–0.90 |
| Chemotherapy use        | 0.372                      | 1.20 | 0.80–1.81 | <0.001 | 0.38 | 0.25–0.58 | <0.001 | 0.38 | 0.24–0.58 | **0.017** | 1.22 | 1.06–1.42 | 0.192 | 1.11 | 0.95–1.29 |
| Extracranial Metastasis | **0.129**                  | 1.37 | 0.91–2.07 | 0.170 | 1.35 | 0.88–2.07 | 0.205 | 0.81 | 0.58–1.12 | <0.001 | 2.02 | 1.43–2.86 | <0.001 | 2.56 | 1.80–3.66 |
| Primary tumor control   | **0.013**                  | 1.06 | 1.01–1.10 | 0.070 | 1.04 | 0.99–1.09 | **0.001** | 1.05 | 1.03–1.08 | <0.001 | 1.06 | 1.02–1.09 | **0.001** | 1.07 | 1.06–1.10 |
| Lesion number           | **0.013**                  | 0.98 | 0.95–1.04 | 0.945 | 0.97 | 0.90–1.05 | <0.001 | 0.99 | 0.96–1.03 | 0.891 | 0.99 | 0.96–1.03 | 0.922 | 1.00 | 0.99–1.02 |
| Max tumor volume(ml)    | 0.949                      | 0.99 | 0.96–1.04 | 0.655 | 0.99 | 0.96–1.03 | 0.358 | 0.97 | 0.90–1.04 | <0.001 | 0.91 | 0.88–0.94 | **0.016** | 0.95 | 0.91–0.98 |
| Total tumor volume(ml)  | 0.949                      | 0.99 | 0.96–1.04 | 0.655 | 0.99 | 0.96–1.03 | 0.358 | 0.97 | 0.90–1.04 | <0.001 | 0.91 | 0.88–0.94 | **0.016** | 0.95 | 0.91–0.98 |

This table is separated into 3 main columns, which respectively present overall survival, local tumor control and distal intracranial tumor control in EGFR positive patients. In each column, we analyzed factors potentially associated with prognosis using Cox regression analysis. Variables with P < 0.15 in univariate analysis are in bold type and included in multivariate analysis. A hazard ratio (HR) exceeding 1 indicates prognostic factors with negative effects on outcomes.
Table 3  Prognostic factors in EGFR wild-type patients

| Factors                        | Overall survival (EGFR wild-type) | Local tumor control (EGFR wild-type) | Distal intracranial tumor control (EGFR wild-type) |
|-------------------------------|-----------------------------------|--------------------------------------|---------------------------------------------------|
|                               | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
|                               | p Value    | HR         | 95%CI      | p Value    | HR         | 95%CI      | p Value    | HR         | 95%CI      | p Value    | HR         | 95%CI      | p Value    | HR         | 95%CI      |
| Sex                           | 0.761      | 1.09       | 0.64–1.83  | 0.175      | 0.67       | 0.38–1.19  | <0.001     | 0.63       | 0.50–0.80  | 0.028      | 0.75       | 0.58–0.97  |<0.001      | 1.02       | 1.01–1.03  |
| Age                           | 0.001      | 0.95       | 0.93–0.98  | <0.001     | 0.92       | 0.89–0.95  |<0.001      | 1.02       | 1.01–1.03  |<0.001      | 1.02       | 1.01–1.03  |<0.001      | 1.02       | 1.01–1.03  |
| KPS score                     | <0.001     | 0.91       | 0.91–0.96  | <0.001     | 0.87       | 0.83–0.90  |<0.001      | 0.92       | 0.89–0.95  |<0.001      | 1.01       | 0.98–1.02  |<0.001      | 1.02       | 1.01–1.03  |
| Prior craniotomy              | 0.021      | 0.37       | 0.16–0.86  | <0.001     | 0.70       | 4.25–13.97 |<0.001      | 1.87       | 1.89–7.91  | 0.045      | 0.75       | 0.57–0.99  | 0.627      | 0.93       | 0.69–1.25  |
| WBRT use                      | 0.26       | 0.68       | 0.34–1.34  | 0.003      | 2.33       | 1.33–4.01  | 0.037      | 2.12       | 1.05–4.31  | 0.710      | 0.95       | 0.74–1.22  |<0.001      | 1.64       | 1.30–2.07  | 0.011      | 1.40       | 1.08–1.82  |
| TKI use                       | 0.067      | 1.63       | 0.97–2.74  | 0.49       | 1.82       | 1.00–3.30  | 0.790      | 1.08       | 0.62–1.89  | 0.644      | 0.95       | 0.75–1.20  |<0.001      | 1.64       | 1.30–2.07  |<0.001      | 1.40       | 1.08–1.82  |
| Chemotherapy use              | 0.131      | 1.50       | 0.89–2.53  | 0.105      | 1.61       | 0.90–2.85  | 0.313      | 0.75       | 0.42–1.32  | 0.644      | 0.95       | 0.75–1.20  |<0.001      | 1.64       | 1.30–2.07  |<0.001      | 1.40       | 1.08–1.82  |
| Extracranial Metastasis       | <0.001     | 2.90       | 1.70–4.95  | <0.001     | 3.06       | 1.71–5.48  |<0.001      | 1.62       | 0.91–2.88  | 0.413      | 1.32       | 0.68–2.55  |<0.001      | 1.62       | 0.91–2.88  |<0.001      | 1.62       | 0.91–2.88  |
| Primary tumor control         | 0.106      | 0.64       | 0.37–1.10  | 0.355      | 0.77       | 0.44–1.35  | 0.002      | 2.47       | 1.38–4.42  | <0.001     | 3.91       | 1.82–8.37  |<0.001      | 1.62       | 0.91–2.88  |<0.001      | 1.62       | 0.91–2.88  |
| Lesion number                 | 0.096      | 1.05       | 0.99–1.12  | 0.245      | 1.04       | 0.97–1.12  | 0.006      | 0.90       | 0.84–0.97  |<0.001      | 0.81       | 0.72–0.92  | 0.106      | 1.02       | 0.99–1.04  | 0.313      | 1.01       | 0.99–1.04  |
| Max tumor volume(ml)          | 0.998      | 1.00       | 0.95–1.06  | 0.073      | 1.06       | 0.99–1.12  | 0.478      | 0.97       | 0.88–1.06  | 0.039      | 0.95       | 0.90–0.99  | 0.994      | 1.00       | 0.94–1.06  | 0.049      | 0.97       | 0.95–1.00  |
| Total tumor volume(ml)        | 0.881      | 1.00       | 0.95–1.04  | 0.031      | 1.05       | 1.00–1.10  | 0.123      | 1.07       | 0.98–1.17  |<0.001      | 1.10       | 1.04–1.16  | 0.005      | 1.09       | 1.03–1.15  |<0.001      | 1.10       | 1.04–1.16  |
| Margin dose                   | 0.402      | 1.05       | 0.94–1.16  | 0.079      | 0.87       | 0.75–1.02  | 0.278      | 0.92       | 0.78–1.07  |<0.001      | 1.10       | 1.04–1.16  |<0.001      | 1.10       | 1.04–1.16  |<0.001      | 1.10       | 1.04–1.16  |

This table is separated into 3 main columns, which respectively present overall survival, local tumor control and distal intracranial tumor control in EGFR positive patients. In each column, we analyzed factors potentially associated with prognosis using Cox regression analysis. Variables with P<0.15 in univariate analysis are in bold type and included in multivariate analysis. A hazard ratio (HR) exceeding 1 indicates prognostic factors with negative effects on outcomes.
Fig. 2 Kaplan–Meier analysis of local intracranial tumor control rates among patients with NSCLC-BM who underwent GKRS—

A Local tumor control (all mutation types in this study); B Effects of EGFR + , EGFR wild-type mutations; C TKI use versus nonuse among EGFR positive patients; and D TKI use versus nonuse among EGFR wild-type patients

Fig. 3 Kaplan–Meier analysis of distal intracranial tumor control rates among patients with NSCLC-BM who underwent GKRS—

A Distal intracranial tumor control (all mutation types in this study); B Effects of EGFR + , EGFR wild-type mutations; C TKI use versus nonuse among EGFR positive patients; and D TKI use versus nonuse among EGFR wild-type patients
defined as a p-value < 0.05 concurrently with a hazard ratio (HR) of > 1.4 or < 0.7 in multivariate analysis.

Discussion

In this study, cases of EGFR-mutation and EGFR-wt NSCLC were distributed equally, as reported in previous studies [19]. In EGFR mutant patients, we determined that combined therapy of TKIs and SRS was superior to SRS alone or TKIs alone in terms of overall survival and intracranial tumor control. However, in EGFR-wt patients, the effectiveness of combining TKIs as a second/third line therapy with must-do SRS is challenged in our study and we prefer SRS alone in EGFR-wt patients.

Combining SRS and TKIs for EGFR-mutant patients

TKIs is the standard first-line therapy for EGFR-mutant patients, despite the fact that the effectiveness depends on the ability of TKIs to penetrate the blood brain barrier (BBB), which tends to be low. Nonetheless, the new-generation of TKIs (e.g. osimertinib) has largely overcome this issue [20]. This may explain why NSCLC BMs tended not to respond to 1st and 2nd TKIs alone [21], whereas SRS proved effective in terms of tumor control and overall survival [22]. There is a need for randomized trials involving TKIs alone, SRS alone, and combined therapy.

In the current study, combined therapy provided survival outcomes and distal intracranial control superior to SRS alone; however, we did not observe a significant difference in terms of local tumor control. In a meta-analysis of 30 studies, Singh et al. did not observe an obvious difference between combined therapy, radiotherapy alone, or TKIs alone in terms of OS. In that study, combined therapy and radiotherapy presented similar results in terms of intracranial progression free survival with TKI treatment alone falling short [23].

Chiou et al. reported that combined therapy was superior to TKIs alone in terms of tumor control, but not overall survival. They also discussed the synergistic effects of combined therapy in cases of EGFR-positive NSCLC [7]. In 2016, Zhang et al. reported no significant difference between TKIs alone and combined therapy in terms of median OS [24]. Taken together, it appears that in EGFR mutant patients, SRS is effective for local tumor control and TKIs is effective for overall survival, which is highly associated with systemic disease, and new brain metastasis. Thus, combining radiosurgery with TKIs should be the preferred treatment for EGFR-mutant patients [7, 25, 26].

Early SRS intervention for patients with wild-type EGFR

The role of TKIs in EGFR-wt patients remains an issue of debate. Our results do not support combining TKIs with SRS in cases of EGFR-wt NSCLC. According to the European Society for Medical Oncology, erlotinib could potentially be used as a second- or third-line treatment option in cases of unknown EGFR status or EGFR wild-type tumor [16]. Note however that Ciuleanu et al. (TITAN) reported no significant differences in OS between their erlotinib group and docetaxel or pemetrexed group as a second-line treatment. Nonetheless, erlotinib was more easily tolerated than chemotherapy, with no indication of hematologic toxicity [27]. Franchino et al. reported that EGFR-TKIs are effective in treating brain tumors, with a response rate of roughly 10% [28]. By contrast, a meta-analysis of 6 randomized controlled trials by Zhao et al. revealed that in the second-line treatment of EGFR wild-type advanced NSCLC, chemotherapy group was far superior to EGFR-TKIs in terms of local and distal tumor control (p < 0.00001) [29]. Garassino et al. also reported that chemotherapy is more effective than erlotinib as a second-line treatment in cases of EGFR wild-type NSCLC [30]. In the current study, combined therapy proved less effective than SRS alone in terms of overall survival and new intracranial metastasis with no significant difference in terms of local tumor control. Intuitively, the condition of patients taking TKIs should be worse than that of patients who are not taking TKIs, because most of them taking TKIs might be in the further stage. This would explain the poor overall survival; however, it would not explain the high incidence of new intracranial tumor metastases, and we need another mechanism to explain poor distant intracranial tumor control rates.

The ligand-dependent mechanism posited by Yuan et al. in 2019 could explain our results perfectly. As an oncogene, TAZ controls the EGFR pathway in cases of EGFR wild-type NSCLC by promoting amphiregulin (AREG) transcription [31]. As an EGFR ligand, AREG activates the EGFR pathway, and 24 AREG molecules form an AREG exosome, which increases the risk of metastasis [32]. Thus, AREG may accumulate after taking TKIs, such that local tumors are controlled via the blocking of epidermal growth factor receptors. AREG levels are positively correlated with the likelihood of metastasis [32], and tumors expressing TAZ are more likely to survive radiation treatment [33]. Overall, TAZ expression levels in different wild-type NSCLC cell lines. It can be assumed that SRS should increase TAZ expression levels, due to the fact that TAZ negative cells are vulnerable to radiation. Follow-up TKI treatment increases AREG accumulation, which increases the likelihood of metastasis, compared with TKIs alone.
Other prognostic factors in cases of NSCLC of various EGFR status

To understand different confounding factors, such as WBRT, prior craniotomy, chemotherapy, tumor volume or lesion numbers, in NSCLC patients, we used multi-variate analyses to evaluate each factor’s influence. Prior craniotomy and lung tumor control had a positive effect on overall survival in the EGFR positive group (p=0.08; HR 0.41) and EGFR wild-type group (p=0.01; HR 0.27); however, it had a negative effect on local intracranial tumor control. Our results are in line with those published by Tohme et al. [34]. Thus, it is important to confirm the relationship between the neurological sign and tumors’ location, and share the pros and cons of reducing mass versus increasing the risk for metastasis with patients to make further decision. The sensitivity of EGFR positive patients to WBRT has been confirmed [35]; however, in the current study, WBRT was associated with poor local tumor control in patients with wild-type EGFR. In previous studies, EGFR wild-type mutations were resistant to radiotherapy [36], such that WBRT did not bring additional benefit to chemotherapy in patients with BM and EGFR of wild-type or unknown status [37]. Our results indicate that chemotherapy can provide significant benefits in terms of intracranial progression in cases of EGFR-positive NSCLC; however, it has no effect on OS. This is consistent with the results of Blackhall et al. [38]. Note however that confirming our results will require a randomized, double-blinded trial.

Study limitations

The findings in this study should be considered in light of certain limitations. First, this was a retrospective study, which made it difficult to control for patients’ exposure and made it impossible to compare studies based on a unified protocol. Second, the National Health Insurance benefit package lists TKI therapy for EGFR wild-type patients as a second/third-line therapy. Thus, the status of patients with TKI use are worse than TKI naive patients, which may lead to a poor outcome. Still, we cannot exclude the possibility that combining TKIs with SRS had a negative effect in cases of wild-type EGFR. Third, this study spanned more than 10 years, during which time many of the treatments were improved in terms of efficiency and side effects, such that the outcomes would also tend to vary. Therefore, we must mention the 3rd generation tyrosine kinase inhibitors, Osimertinib, which is approved to administer in EGFR+ NSCLC patients resistant to 1st and 2nd TKIs since April, 2020 in our country. Only 10 out of 296 EGFR+ patients used Osimertinib; due to the small population, we will discuss this issue in our next articles.

In terms of radiography, it’s always difficult to distinguish radiation necrosis from tumor progression on MRI. To solve this problem, we used methods as follow: (1) T1, T2 mismatch [39], (2) PET [40], (3) Leakage of contrast pattern [41]. However, for those images hard to differentiate, we regard them as tumor progression to prevent overestimating the efficacy of therapy.

Conclusions

This study examined the effectiveness of combining GKRS and TKIs in cases of NSCLC BM. We confirmed that prior craniotomy increased overall survival in EGFR positive and wild-type groups. We recommend combined therapy involving GKRS and TKIs in cases of EGFR-positive NSCLC with BMs. It appears that TKIs with GKRS in cases of EGFR-wt NSCLC with BMs is less effective in terms of tumor control and overall survival. Further analysis of the mechanism of TKIs in cases of EGFR-wt NSCLC will be required.

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Declarations

Conflict of interest The authors have not disclosed any competing interests.

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