

## Scientific Article

# Neurological Death is Common in Patients With EGFR Mutant Non-Small Cell Lung Cancer Diagnosed With Brain Metastases



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## Abstract

**Purpose:** Brain metastases (BrM) are common in patients with epidermal growth factor receptor (EGFRm) mutant non-small cell lung cancer (NSCLC). We sought to determine the rate of neurologic death (ND) in this population.

**Methods and Materials:** We analyzed data from 198 patients who received a diagnosis of BrM from EGFRm NSCLC between 2004 and 2016, comparing patients whose initial treatment for BrM was stereotactic radiosurgery with or without tyrosine kinase inhibitors (TKI), whole brain radiation therapy (WBRT) with or without TKI, or TKI alone. The incidence of ND was determined using a competing risks analysis. Univariate and multivariate analyses were used to identify clinical variables associated with this outcome.

**Results:** The percentage of patients who initially received stereotactic radiosurgery, whole brain radiation therapy, or TKI alone was 22%, 61%, and 17%, respectively. Median overall survival in these subgroups was 31.1, 14.6, and 24.6 months, respectively ( $P = .0016$ ). The 5-year incidence of ND among all patients was 40% and did not significantly vary according to treatment group. In a

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multivariable model, only leptomeningeal disease at any point in a patient's disease course significantly correlated with ND (hazard ratio 4.75,  $P < .001$ ).

**Conclusions:** Among our cohort of patients with BrM from EGFRm NSCLC, the incidence of ND was significantly higher than suggested by previous reports. BrM should be considered a driver of mortality in many patients with EGFRm NSCLC, and treatments providing better control of BrM, lower neurocognitive side effects, and maintenance of quality of life are needed.

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## Introduction

Brain metastases (BrM) occur in more than 40% of patients with non-small cell lung cancer (NSCLC) and are a major cause of morbidity and mortality. The incidence of BrM in patients with advanced epidermal growth factor receptor mutation positive (EGFRm) NSCLC is particularly high, exceeding 60% in long-term survivors.<sup>1-3</sup>

Radiotherapeutic strategies for managing BrM in EGFRm NSCLC include stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT). Of these, SRS carries a lower risk of neurocognitive toxicity<sup>4</sup> and is most appropriate for patients with a limited number of BrM, the definition of which is the subject of ongoing studies<sup>5</sup> but generally implies  $<5$  BrM.<sup>6-8</sup> In addition, excluding resistant mutations, EGFRm NSCLC BrM generally respond well to systemic tyrosine kinase inhibitors (TKI) when used as a single modality<sup>9</sup> or in combination with radiation therapy.<sup>10</sup> Finally, some large or symptomatic tumors require surgical resection followed by adjuvant therapy.<sup>11</sup> It is not known whether SRS in combination with TKI, WBRT in combination with TKI, or TKI alone results in superior long-term outcomes for patients with EGFRm NSCLC with BrM. In fact, there is uncertainty regarding what outcome is most reasonable and meaningful to evaluate in this context. One large, multi-institutional retrospective effort demonstrated that SRS as first-line treatment for BrM in EGFRm NSCLC patients, compared with WBRT or TKI monotherapy, was associated with superior overall survival (OS).<sup>12</sup> Other published retrospective cohort studies have failed to confirm this effect, and uncertainty prevails.<sup>13-15</sup> Although such results may be due to selection biases, they nonetheless suggest that factors related to BrM or their management strongly influence survival in this population. However, this hypothesis is challenged by prior studies reporting only a 14% to 16% rate of neurologic death (ND) in patients with EGFRm NSCLC with BrM.<sup>16,17</sup>

To examine ND more closely in this population, we compared patient- and disease-specific characteristics and survival rates of patients with BrM from EGFRm NSCLC treated with first-line SRS with or without TKI, WBRT with or without TKI, or TKI monotherapy. Furthermore, we determined the incidence of ND in this cohort and aimed to identify factors associated with that outcome.

## Methods and Materials

With institutional review board approval, we identified patients from a single center prospective registry of approximately 1600 patients who received a diagnosis of and were treated for BrM between 2004 and 2016. From that registry, 198 patients were identified who met eligibility criteria. The single eligibility criterion was the diagnosis of EGFRm NSCLC. This database included a comprehensive record of clinical, histologic, and pathologic data that differentiated each patient's treatment regime and outcome. ND was determined retrospectively based on patient charts. Patients who required surgery as part of their initial treatment for BrM were excluded from the analysis.

All radiosurgical treatments were delivered via Gamma Knife. Prescription dose was based on guidelines from Radiation Therapy Oncology Group trial 9005<sup>7,18</sup> and the preference of the treating physician. The decision to treat with WBRT or SRS was based on quantity ( $<5$ -10 lesions were generally treated with SRS alone, whereas  $>5$ -10 were generally treated with WBRT), BrM size, and other individualized factors. The decision to treat with RT in addition to TKI was made by the medical and radiation oncology teams and on the basis of patient preference, without the use of specified clinical criteria. All patient treatment recommendations were made at a multidisciplinary conference and clinic. The TKIs used in this study included afatinib, erlotinib, gefitinib, nazartinib, osimertinib, and rociletinib. EGFR mutation status was determined through DNA analysis. In some cases, EGFR mutation status was determined subsequent to the initial lung cancer diagnosis (EGFR testing at our institution began in 2008).

Patients were followed from their initial diagnosis of BrM until death or last known follow-up in a multidisciplinary clinic. Magnetic resonance imaging was repeated at 3-month intervals after radiation therapy or TKI treatment.

In keeping with the established definition, ND were exclusively due to BrM, leptomeningeal disease (LMD), or to an unknown cause in patients known to have untreated or growing BrM or LMD on the last imaging before death.<sup>19,20</sup> LMD was defined on the basis of radiologic and cytologic findings.

**Table 1** Patient cohort demographics

| Characteristic   | N = 198    | SRS<br>(N = 43) | WBRT<br>(N = 121) | TKI<br>(N = 34) | P value |
|--|------------|-----------------|-------------------|-----------------|---------|
| Median age (range), y  | 61 (29-86) | 59 (30-85)      | 60 (29-83)        | 64 (40-86)      | .08     |
| Female, n (%)  | 133 (67%)  | 28 (65%)        | 87 (72%)          | 18 (53%)        | .12     |
| Male, n (%)  | 65 (33%)   | 15 (35%)        | 34 (28%)          | 16 (47%)        |         |
| Median DS-GPA (range)  | 2.5 (1-4)  | 3 (1.5-4)       | 2.5 (1-4)         | 2.5 (1.5-3)     | .002    |
| Median follow-up after BrM diagnosis (range), mo                                   | 18 (0-160) | 24 (4-91)       | 14 (0-160)        | 23 (1-56)       | .0029   |
| Alive at last follow-up (%)  | 40 (20%)   | 15 (35%)        | 12 (10%)          | 13 (38%)        | <.001   |
| Median no. of initial BrM (range)*   | 4 (1-120)  | 2 (1-8)         | 7 (1-120)         | 2 (1-50)        | <.001   |
| ECOG at diagnosis of BrM (%)   |            |                 |                   |                 | .52     |
| 0  | 96 (48%)   | 25 (58%)        | 53 (44%)          | 18 (53%)        |         |
| 1  | 90 (45%)   | 15 (35%)        | 60 (50%)          | 15 (44%)        |         |
| 2  | 9 (2%)     | 3 (7%)          | 5 (4%)            | 1 (3%)          |         |
| 3  | 3 (5%)     | 0 (0%)          | 3 (2%)            | 0 (0%)          |         |
| Patients with BrM at diagnosis of lung cancer, n (%)                               | 92 (46%)   | 23 (53%)        | 48 (40%)          | 21 (62%)        | .043    |
| Leptomeningeal disease at diagnosis of BrM of lung cancer, n (%)                   | 18 (9%)    | 0 (0.0%)        | 16 (13%)          | 2 (6%)          | .017    |
| Developed leptomeningeal disease after initial diagnosis of BrM, n (%)             | 19 (10%)   | 3 (7%)          | 12 (10%)          | 4 (12%)         | .74     |
| Extracranial metastases at BrM diagnosis, n (%)                                    | 176 (89%)  | 38 (88%)        | 105 (87%)         | 33 (97%)        | .26     |
| Median no. of extracranial organs/systems involved at BrM diagnosis (range)        | 2 (0-5)    | 2 (0-5)         | 2 (0-4)           | 2 (1-4)         | .61     |
| Patients who had TKI at any point before or immediately after BrM diagnosis, n (%) | 183 (92%)  | 40 (93%)        | 109 (90%)         | 34 (100%)       | <.0001  |
| EGFR mutation status (%)   |            |                 |                   |                 | <.0001  |
| Exon 18  | 1 (1%)     | 0 (0%)          | 1 (1%)            | 0 (0%)          |         |
| Exon 19  | 115 (58%)  | 24 (56%)        | 72 (59%)          | 19 (56%)        |         |
| Exon 21  | 82 (41%)   | 19 (44%)        | 48 (40%)          | 15 (44%)        |         |
| BrM progression after initial treatment, n (%)                                     | 117 (59%)  | 31 (72%)        | 59 (49%)          | 27 (79%)        | <.001   |
| Leptomeningeal disease   | 16 (14%)   | 3 (10%)         | 9 (15%)           | 4 (15%)         |         |
| New BrM  | 56 (48%)   | 22 (71%)        | 19 (32%)          | 15 (56%)        |         |
| New BrM + leptomeningeal disease   | 2 (2%)     | 0 (0%)          | 2 (3%)            | 0 (0%)          |         |
| Progressive disease  | 41 (35%)   | 6 (19%)         | 27 (46%)          | 8 (30%)         |         |
| Progressive disease + leptomeningeal disease                                       | 1 (1%)     | 0 (0%)          | 1 (2%)            | 0 (0%)          |         |
| Unknown  | 1 (1%)     | 0 (0%)          | 1 (2%)            | 0 (0%)          |         |
| Patients who received WBRT (ever), n (%)   | 156 (79%)  | 20 (47%)        | 121 (100%)        | 15 (44%)        | <.001   |
| Median time to first WBRT treatment (range), mo                                    | 11 (4-48)  | 10.5 (4-48)     | 0 (0)             | 12 (5-31)       | .45     |
| Patients with repeat WBRT, n (%)   | 39 (20%)   | 3 (7%)          | 34 (28%)          | 2 (6%)          | <.001   |
| Patients who received SRS (ever), n (%)  | 79 (40%)   | 43 (100%)       | 27 (22%)          | 9 (26%)         | <.001   |
| Median no. of SRS courses (range)  | 0 (0-4)    | 1 (1-4)         | 0 (0-3)           | 0 (0-2)         | <.001   |
| TNM staging (%) <sup>†</sup> at diagnosis, n (%)                                   |            |                 |                   |                 |         |
| T category   |            |                 |                   |                 | .039    |
| 1-2  | 87 (53%)   | 21 (62%)        | 58 (56%)          | 8 (31%)         |         |
| 3-4  | 77 (47%)   | 13 (38%)        | 46 (44%)          | 18 (69%)        |         |
| N category   |            |                 |                   |                 | .14     |
| 0  | 39 (24%)   | 5 (15%)         | 30 (29%)          | 4 (15%)         |         |
| ≥1   | 123 (76%)  | 29 (85%)        | 74 (71%)          | 22 (85%)        |         |
| M category   |            |                 |                   |                 | .012    |
| 0  | 29 (18%)   | 8 (24%)         | 21 (20%)          | 0 (0.0%)        |         |
| 1  | 135 (82%)  | 26 (76%)        | 83 (80%)          | 26 (100%)       |         |
| Overall stage at diagnosis (%) <sup>†</sup>  |            |                 |                   |                 | .16     |
| I or II  | 17 (11%)   | 4 (12%)         | 13 (12%)          | 0 (0.0%)        |         |
| III or IV  | 147 (89%)  | 30 (88%)        | 91 (88%)          | 26 (100%)       |         |

Abbreviations: BrM = brain metastases; DS-GPA = diagnosis-specific Graded Prognostic Assessment; ECOG = Eastern Cooperative Oncology Group Performance Status; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiation therapy.

\* For this analysis, n = 185 patients (SRS = 43, WBRT = 109, and TKI = 33); the missing patients presented with leptomeningeal disease and not a discrete number of BrM.

<sup>†</sup> For this analysis, n = 164 patients (SRS = 34, WBRT = 104, TKI = 26); the missing patients did not have staging details available.

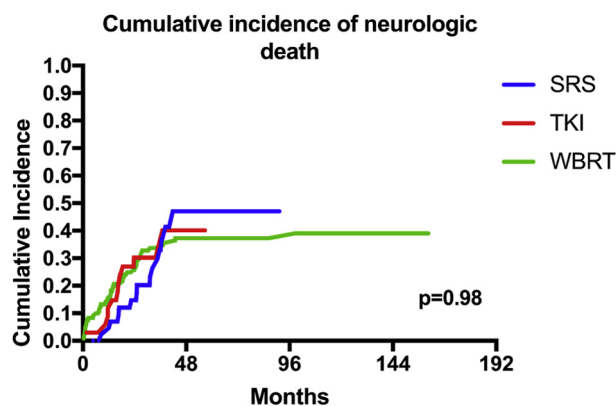
The Kruskal-Wallis test was used to compare continuous variables and treatment type (ie, SRS, TKI, and WBRT). Fisher exact, Brown-Forsythe, and Kruskal-Wallis tests were used for categorical variables. Cox proportional hazard with competing risk methods were used for univariate and multivariate analyses. The competing risk used was systemic death (for estimating the incidence of ND) and ND (for systemic deaths). Lastly, we assessed for differences in survival with Kaplan-Meier plots using the log-rank test and differences in cumulative incidence curves using Gray's test. Survival outcomes were determined using date of BrM diagnosis as the starting point.

## Results

We assessed all 1465 potentially eligible participants seen between January 1, 2004 and September 1, 2016. Ultimately, 198 met inclusion criteria and were enrolled. Follow-up was finalized on August 1, 2017. As shown in Table 1, among patients treated with first-line SRS, WBRT, or TKI monotherapy, some clinical variables were imbalanced. The median diagnosis-specific Graded Prognostic Assessment,<sup>21</sup> median number of BrM at diagnosis, presence of BrM at diagnosis, LMD at BrM diagnosis, and T and M classification were significantly different among our treatment groups.

Of these 198 patients, 71 had ND, 62 died of systemic progression, and 25 died of unclassified causes. The cumulative incidence of ND, accounting for the competing risks of death from other causes, was 33% at 3 years and 40% at 5 years. Among the different treatment groups, there were no statistically significant differences in the incidence of ND ( $P = .98$ ; Fig 1). As a sensitivity analysis, we examined the cohort of patients without LMD at diagnosis ( $n = 180$ ) and also found no difference in the cumulative incidence of ND among treatment groups (Fig E1; available online at <https://doi.org/10.1016/j.adro.2019.11.002>).

We performed univariate analyses to see if selected variables were associated with time to ND, again with other causes of death as a competing risk. Among the variables tested, LMD (at any point in the patient's disease course) was identified as a strong predictor of risk of ND (hazard ratio, 5.14;  $P < .001$ ; Table 2). A multivariable regression model was constructed to examine the effect of clinically selected covariates on ND. Within this model, LMD was also identified as a strong independent predictor of ND (hazard ratio, 4.75;  $P < .001$ ). Given this strong effect, we conducted sensitivity analyses to omit 18 patients with LMD at initial BrM diagnosis; development of LMD was still associated with increased risk of ND in this analysis (Table E1; available online at <https://doi.org/10.1016/j.adro.2019.11.002>).



**Figure 1** Cumulative incidence of neurologic death in patients with epidermal growth factor-mutant non-small cell lung cancer who received a diagnosis of brain metastases or leptomeningeal disease, stratified by initial treatment. Abbreviations: SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor alone; WBRT = whole brain radiation therapy.

Median OS was 20.1 months for the entire cohort. The median time to death in patients who died of nonneurologic causes or neurologic causes was not significantly different at 18.5 versus 16.6 months for systemic and neurologic deaths, respectively ( $P = .1233$ ; Fig E2, available online at <https://doi.org/10.1016/j.adro.2019.11.002>), and median follow-up after BrM diagnosis was 18 months. OS after the diagnosis of BrM varied significantly according to first-line BrM management. Median OS was longer in patients treated with upfront SRS compared with upfront WBRT or TKI alone: 31.1, 14.6, and 24.2 months, respectively ( $P = .0016$ ; Fig 2). When patients with LMD at the time of diagnosis were excluded, this difference was still observed; patients treated with upfront SRS, WBRT, or TKI had median OS of 31.1, 18.3 and 24.2 months, respectively ( $P = .011$ ; Fig E3, available online at <https://doi.org/10.1016/j.adro.2019.11.002>).

The cumulative incidence of intracranial progression after BrM diagnosis differed among treatment groups; for SRS, WBRT, or TKI at 3 years, it was 69%, 47%, and 79%, respectively ( $P < .001$ , Fig 3). Of the patients who did not receive TKI immediately before or after BrM diagnosis, 8 never received TKI treatment at all. In such cases, the patient was either not well enough to receive TKI or there was no evidence of additional metastatic disease after treatment of their BrM. All 8 patients received WBRT.

Finally, the 2-year cumulative incidence of LMD was 17%, with SRS, WBRT, and TKI at 14%, 20%, and 12%, respectively ( $P = .75$ ; Fig E4, available online at <https://doi.org/10.1016/j.adro.2019.11.002>). Of patients who did not have LMD at BrM diagnosis, the 2-year cumulative incidence of LMD was 10%, with SRS, WBRT, and TKI at 14%, 9%, and 6%, respectively ( $P = .2$ ; Fig E5 available online at <https://doi.org/10.1016/j.adro.2019.11.002>).

**Table 2** Univariate and multivariable analyses of covariates associated with time to neurologic death

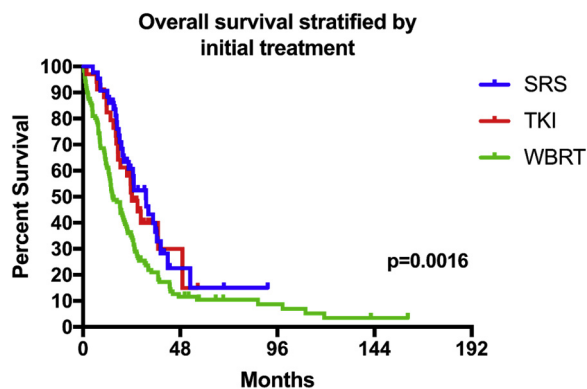
| Univariate analysis           |                  |                | Multivariate analysis*        |                   |                |
|-------------------------------|------------------|----------------|-------------------------------|-------------------|----------------|
| Covariate                     | HR (95% CI)      | Global P value | Covariate                     | HR (95% CI)       | Global P value |
| Ever leptomeningeal (Y/N)     | 5.14 (3.29-8.05) | <.001          | Ever leptomeningeal (Y/N)     | 4.75 (2.93-7.7)   | <.001          |
| Initial local brain treatment |                  | .95            | Initial local brain treatment |                   | .51            |
| SRS                           | Reference        |                | SRS                           | Reference         |                |
| TKI                           | 1.04 (0.5-2.18)  |                | TKI                           | 0.79 (0.34-1.81)  |                |
| WBRT                          | 1.09 (0.63-1.89) |                | WBRT                          | 0.71 (0.39-1.27)  |                |
| Overall stage at diagnosis*   |                  | .071           | Overall stage at diagnosis    |                   | .081           |
| I-II                          | Reference        |                | I-II                          | Reference         |                |
| III-IV                        | 2.84 (0.91-8.85) |                | III-IV                        | 3.22 (0.87-11.95) |                |
| Age at diagnosis              | 0.99 (0.97-1.01) | .3             | Age at diagnosis              | 1 (0.98-1.03)     | .78            |
| Male sex (vs female)          | 1.09 (0.66-1.8)  | .74            | Male sex (vs female)          | 0.96 (0.55-1.69)  | .89            |
| BrM at diagnosis              | 1.17 (0.74-1.85) | .51            | BrM at diagnosis              | 1.11 (0.68-1.8)   | .68            |
| Symptomatic BrM               | 1.45 (0.91-2.31) | .11            | Symptomatic BrM               | 1.77 (0.99-3.18)  | .055           |
| DS-GPA†                       | 0.66 (0.41-1.07) | .095           |                               |                   |                |

Abbreviations: BrM = brain metastases; CI = confidence interval; DS-GPA = diagnosis-specific Graded Prognostic Assessment; HR = hazard ratio; SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiation therapy.

A competing risks method was applied to both analyses, with death from other causes treated as a competing risk.

\* For this analysis, n = 164 patients (SRS = 34, WBRT = 104, TKI = 26); the missing patients did not have staging details available.

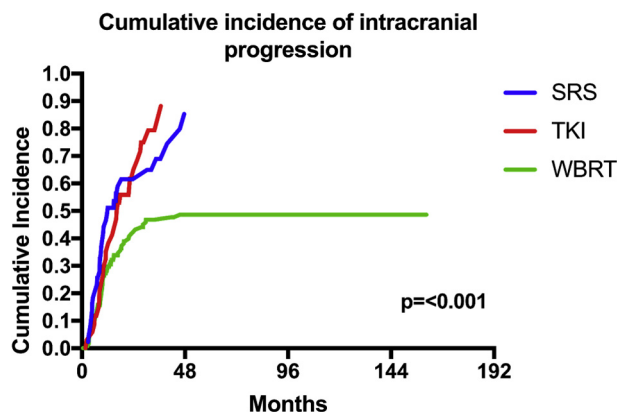
† Treated as a continuous variable in this analysis.



No. at Risk

|      |     |    |   |   |   |
|------|-----|----|---|---|---|
| SRS  | 43  | 3  | 0 | 0 | 0 |
| TKI  | 34  | 2  | 0 | 0 | 0 |
| WBRT | 121 | 12 | 5 | 1 | 0 |

**Figure 2** Overall survival of patients with epidermal growth factor-mutant non-small cell lung cancer diagnosed with brain metastases or leptomeningeal disease according to initial treatment. Abbreviations: SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor alone; WBRT = whole brain radiation therapy.



**Figure 3** Cumulative incidence of intracranial progression after initial treatment for patients with epidermal growth factor-mutant non-small cell lung cancer who received a diagnosis of brain metastases or leptomeningeal disease. Abbreviations: SRS = stereotactic radiosurgery; TKI = tyrosine kinase inhibitor alone; WBRT = whole brain radiation therapy.

## Discussion

9.11.002). Younger age at BrM diagnosis was significantly correlated to the development of LMD ( $P < .001$ ; Table E2, available online at <https://doi.org/10.1016/j.adro.2019.11.002>). Among patients who did not have LMD at diagnosis, median LMD-free survival was 25, 18, and 24 months with SRS, WBRT, and TKI, respectively ( $P = .0014$ ; Fig E6, available online at <https://doi.org/10.1016/j.adro.2019.11.002>).

Patients with EGFRm NSCLC are at particularly high risk for developing BrM. Outcomes of patients with BrM from EGFRm NSCLC, however, are better than the outcomes of patients with BrM from non-oncogene-driven NSCLC.<sup>2,3,16</sup> This is likely due, in part, to the fact that TKIs used to treat EGFRm NSCLC shrink or stabilize BrM in most patients.<sup>9</sup> Nonetheless, we demonstrate here that a significant proportion of patients with EGFRm

NSCLC with BrM die as a result of, or in the presence of, neurologic progression.

The overall rate of ND in our cohort was 33% at 3 years and 40% at 5 years. The strongest predictor of that outcome was LMD, which likely occurs more frequently in patients with EGFRm NSCLC compared with non-EGFRm NSCLC.<sup>22</sup> Although LMD in EGFRm NSCLC sometimes responds to pulsed dosed erlotinib,<sup>23</sup> third-generation EGFR TKIs such as osimertinib,<sup>24</sup> or WBRT,<sup>25</sup> LMD ultimately results in ND in most if not all patients with EGFRm NSCLC and represents a critical endpoint in this disease.

A previous report from our institution describing a cohort of ALK+ and EGFRm patients reported similar rates of OS regardless of first-line BrM treatment.<sup>13</sup> In our present study, patients treated initially with WBRT had the lowest rate of OS, despite the association between WBRT and delayed intracranial progression. SRS was associated with improved OS compared with WBRT or TKI alone. We examined relevant characteristics of each treatment group to determine the ways in which selection bias may affect such survival differences. We noted that patients treated with first-line WBRT had a higher number of BrM at diagnosis and a less favorable graded prognostic assessment score. In addition, patients presenting with LMD, which carries a poor prognosis, were universally treated with WBRT. Patients who presented with more extensive primary tumors or those presenting with BrM or stage IV disease at the time of their diagnosis, all of which are clinical factors that portend worse outcomes, more often received TKI alone as initial management for their BrM.

It is also important to consider the ways in which patients are salvaged after their initial BrM management fails. In our study, nearly half of patients treated with first-line SRS or TKI receive WBRT at some point in their disease course. Approximately one-quarter of patients treated with WBRT or TKI later received SRS. One cannot therefore consider these treatment categories as distinct treatment choices but rather as the first strategy that was used in a particular patient.

Our results are in contrast to those of a previous multi-institutional retrospective study of 235 patients with EGFRm NSCLC BrM, which described a 14% crude rate of ND.<sup>16</sup> There are several possible explanations for this. First, instead of a crude percentage, we report the cumulative incidence of ND. Second, in that previous report, cause of death was not classifiable as either definitively neurologic or nonneurologic in more than half of the 156 patients who died during follow-up, whereas only 13% of the deaths in our study were unclassifiable. Finally, the definition of ND used in that prior study may have differed from ours (theirs was not described). Two recently published series also reported ND in EGFRm NSCLC BrM patients. One group reported a 16% rate of ND in 16 patients who had SRS.<sup>17</sup> Another described 81 patients with EGFRm NSCLC BrM treated with TKI

alone or RT and determined the 2-year cumulative incidences of ND to be 23% and 16%, respectively.<sup>17,26</sup> Finally, a preplanned subanalysis of the FLAURA trial, in which patients with EGFRm NSCLC were randomized to receive osimertinib versus gefitinib or erlotinib as first-line therapy and in which patients with known BrM were analyzed, reported the crude rate of central nervous system (CNS) deaths in the standard therapy arm of 6%.<sup>27</sup> However, this was not actuarial and was after only 10 months median follow-up, at which time >80% patients remained alive, and the definition of CNS-deaths was not defined. In addition to long follow-up, our real-world data were analyzed using a cumulative risks model, which likely explains some of the discrepancy between their results and ours. ND is a difficult outcome to assess and ultimately may not be the ideal way to measure the effectiveness of BrM treatments. However, intracranial progression free survival (iPFS) is also imperfect because progression may represent, for example, a new, single, small brain lesion, which would not necessarily be a significant development in the disease course of a patient with metastatic cancer. Time to WBRT is another potentially attractive outcome; however, it ultimately represents a clinical decision rather than well-defined disease progression.

Ultimately, the optimal upfront management of this patient population remains unclear. Although WBRT appears to improve iPFS, it does not appear to correlate with a decreased incidence of ND.<sup>4</sup> For patients with a limited number of BrM (<4), WBRT is associated with greater neurocognitive decline compared with SRS. Therefore, for patients who require WBRT, hippocampal avoidance and memantine should be strongly considered.<sup>28</sup> Finally, whether SRS offers an advantage over TKI alone is currently the subject of multiple ongoing randomized studies.<sup>29,30</sup>

## Strengths and limitations

There are several potential criticisms of this study beyond the fact that it is retrospective and from a single institution. First, classifying cause of death can be challenging, especially when done retrospectively. We used the definition established by prior, seminal, randomized BrM studies<sup>19,20</sup>: intracranial progression at the time of death, in the absence of a known systemic cause of death. Using this definition, in the European Organisation for Research and Treatment of Cancer 22952-26001 study, Kocher et al described a lower rate of ND (28% vs 44%), depending on whether patients had WBRT in addition to SRS or surgery as first-line treatment for BrM.<sup>19</sup> As with other randomized studies performed in that era, the addition of WBRT to SRS or surgery was not associated with improved OS.<sup>20</sup> Another important concern is that most patients in our study were treated with gefitinib, which has less CNS activity compared with newer agents,

such as osimertinib. In an era where osimertinib is increasingly used in the first-line setting, the applicability of our results to the current clinical environment merits some consideration. Notwithstanding these considerations, we maintain that it is important to study the incidence of ND in EGFRm NSCLC BrM patients so that rates of CNS failure can be meaningfully assessed alongside outcomes such as systemic failures, quality of life, and neurocognitive toxicity.

## Conclusions

Our results indicated that ND is common in patients with EGFRm NSCLC and highlight the need for research and therapeutic interventions specific to patients with BrM. The development of LMD in these patients was associated with a high risk of neurologic death and should be considered as an area for additional research and therapeutic development.

## Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2019.11.002>.

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