Treatment preferences for epidermal growth factor receptor mutation-positive non-small cell lung cancer with brain metastasis: a large-scale survey from Chinese oncologists

Yongfeng Yu, Jie Qian, Lan Shen, Wuxiang Ji, Shun Lu

Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Contributions: (I) Conception and design: Y Yu; (II) Administrative support: J Qian; (III) Provision of study materials or patients: Y Yu, L Shen; (IV) Collection and assembly of data: W Ji; (V) Data analysis and interpretation: W Ji, S Lu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shun Lu. Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West Huaihai Road, Xuhui District, Shanghai 200030, China. Email: shunlu@sjtu.edu.cn.

Background: Radiotherapy combined with tyrosine kinase inhibitor (TKI) has drawn extensive attention as a treatment regimen for patients with epithelial growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) with brain metastases (BMs). However, the optimal regimens and treatment sequence remain unknown. This study sought to investigate the opinions of Chinese oncologists toward the regimen selection and therapeutic timing for patients with EGFR-mutated NSCLC with BMs.

Methods: A survey was developed by the expert group of the Specialty Committee of Lung Cancer of the Chinese Anti-Cancer Association. Between January and March 2018, the survey was distributed in online and paper forms to oncologists working in departments that may receive patients with NSCLC with BMs.

Results: The survey was completed by 1,000 oncologists. When selecting a patient’s therapeutic regimen, respondents were most likely to consider the benefit to overall survival (32%), followed by the benefit to progression-free survival (18%) and quality of life (17%). Radiotherapy combined with EGFR-TKI agents is the leading regimen over monotherapy (46–58%), with rates increasing in patients with neurological symptoms and a higher number of intracranial metastases. For patients with 1–3 BMs, stereotactic radiosurgery (SRS) with TKI was the preferred regimen. For patients with >3 BMs, whole-brain radiotherapy with TKI was the preferred regimen in accordance with the preference towards meningeal BM.

Conclusions: Radiotherapy combined with EGFR-TKI agents is the preferred regimen among Chinese oncologists for the treatment of patients with EGFR mutation-positive NSCLC with BMs. BM number and type may influence the selection of radiotherapy regimen. Randomized controlled trials could be helpful in addressing current disputes regarding treatment regimens.

Keywords: Non-small cell lung cancer (NSCLC); brain; neoplasm metastasis; tyrosine kinase inhibitor (TKI); radiotherapy

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Introduction

Lung cancer is the leading cause of cancer-related death in China and across the world (1). Approximately 733,000 new cases of lung cancer are diagnosed in China every year (2), with non-small cell lung cancer (NSCLC) accounting for 85–90% of these cases (3). Most patients with NSCLC are diagnosed as advanced or metastatic disease (4). The brain is one of the most common distant metastasis sites in lung cancer; 10–20% of patients with NSCLC are diagnosed with brain metastases (BMs) at
presentation, and 25–40% have intracranial metastasis detected during the course of treatment (5,6). The detection rate of BMs from lung cancer is increasing annually and is associated with prolonged survival but also increased morbidity. Prolonging the survival time and improving the quality of life of patients with NSCLC with BMs are important issues in the era of targeted therapy, and more effective treatment approaches are urgently needed.

Epithelial growth factor receptor (EGFR) is a well-established molecular target in NSCLC, and mutations have been identified in 10–15% of Caucasian and up to 50% of Asian patients with adenocarcinoma, the most frequent NSCLC subtype (7). For EGFR-positive advanced or metastatic NSCLC, targeted therapy is the first-line treatment, which has significantly prolonged progression-free survival of these patients compared with chemotherapy. On the other hand, the treatment of EGFR wild-type advanced non-small cell lung cancer is relatively limited. At present, the first-line chemotherapy regimen is mainly dual drug combined chemotherapy based on platinum drugs. After the disease progresses, it is mainly converted to second-line single drug chemotherapy or targeted therapy (8). Patients with NSCLC harboring mutations in the epithelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) rearrangement experience a high incidence of BM (9,10). For patients with NSCLC and EGFR mutations, the incidence of BM is 3.49 times higher than that in patients with NSCLC and wild-type EGFR (11). For patients with NSCLC with EGFR sensitive mutation but without BM at presentation, the incidence of BM at 1 and 2 years after receiving first-generation tyrosine kinase inhibitor (TKI) treatment is 6% and 13%, respectively, which is significantly lower than the incidence among recipients of first-line chemotherapy (12,13). Therefore, it is necessary to discuss personalized treatment regimens for patients with EGFR mutation-positive NSCLC with BMs as a special molecular group in order to improve their prognosis.

Due to controversies regarding the best strategy of treatment for patients with EGFR mutation-positive NSCLC with BMs, further research is needed to determine the optimal regimen and treatment sequence. Previous studies have shown that radiotherapy (RT) followed by TKI therapy, TKI therapy followed by RT, or TKI monotherapy may improve the prognosis of patients with NSCLC with BMs and EGFR mutations (14–19). Yang et al. (20) found that icotinib alone achieved significant intracranial progression-free survival benefit compared with whole-brain RT (WBRT) combined with chemotherapy. As the standard of care for patients with multiple BMs, WBRT can increase the median overall survival of patients by 4–6 months (21). Other studies have reported that delayed brain RT, either with stereotactic radiosurgery (SRS) or WBRT, may result in worse survival for TKI-naïve patients with NSCLC with BMs and EGFR mutations (22). The above-mentioned studies fully demonstrate the importance of RT. With prolonged patient survival, there are increasing concerns among clinicians regarding side effects of RT, such as neurocognitive impairment (23). Unlike first-generation TKIs, third-generation TKIs have good blood-brain barrier (BBB) permeability (24), and therefore offer excellent control of intracranial lesions (25), which may serve as the basis for their use in patients with NSCLC with BMs. Moreover, WBRT may improve the efficacy of TKIs by increasing BBB permeability, while TKIs are considered to be radiosensitizers (26). Therefore, the combination of RT plus targeted drug therapy has drawn extensive attention as a treatment regimen for patients with NSCLC with BMs, but the optimal regimen or treatment sequence remains unknown.

Since China has not yet fully implemented tiered diagnosis and treatment for NSCLC with BMs, this study sought to investigate the opinions of Chinese oncologists regarding regimen selection and therapeutic timing in the treatment of patients with this disease, which mainly based on better overall survival, quality of life, and progression-free survival. Therapeutic attitudes of oncologists were compared across different departments with potential access to patients with NSCLC with BMs. The results of this study for the first time describe the treatment preferences among Chinese oncologist from different departments and analyze their similarities and diversities, which will aid in improving our understanding of the current management status of patients with EGFR-mutant NSCLC with BMs in China and optimizing our treatment strategy for these patients.

We present the following article in accordance with the SURGE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6413/rc).

**Methods**

**Survey design and participants**

This survey study was an initiative of the Specialty Committee of Lung Cancer of the Chinese Anti-Cancer...
Association. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional committee board of Shanghai Chest Hospital (LS2049) and informed consent was taken from all the participants.

The survey covered basic oncologist information, information of admitted patients, general treatment concepts, and treatment concepts. The items of the questionnaire were decided by an expert advisory team, which consisted of committee members. Before the survey was conducted, a draft was produced, discussed, pre-test and revised by the committee members, and different questions had different scoring rules. Between January and March 2018, the questionnaire was distributed in online and paper forms to 1,000 oncologists located across China who were working in departments with potential to receive patients with NSCLC with BMs. Through quota sampling, oncologists from medical oncology (n=350), RT (n=350), respiratory (n=150), and thoracic surgery (n=150) departments were recruited.

Oncologists involved in the diagnosis of patients with NSCLC with BMs were invited to participate in the survey. The exclusion criteria included the following: (I) retired or in-training oncologists; (II) oncologists working in hospitals other than second- or third-class general hospitals or third-class cancer specialist hospitals; (III) oncologists who had mainly worked in departments other than respiratory, medical oncology, RT, or thoracic surgery departments in the past year; (IV) oncologists with less than 5 years of work experience; (V) oncologists not involved in treatment regimen-related decision making for patients with NSCLC, or who had not prescribed TKIs to patients with NSCLC with BMs in the past 3 months.

Completion of the survey

The services of a third-party clinical research organization were employed to enroll oncologists in this study, according to the inclusion/exclusion criteria. Each enrolled oncologist signed an informed consent form. Online questionnaires were distributed via network platforms, while offline questionnaires were distributed by the researchers. Oncologists with no response were reminded by Emails, telephones or WeChat to complete the survey at least 3 times. No financial incentive was provided.

Data management and analysis

Online data were collected directly from the online survey platform. Offline data were entered by registrars using the double-entry method. The quality of collected questionnaires were assessed by response rate (returned surveys/issued surveys), distribution of city levels, hospital types, departments and titles of oncologists, and completeness of questionnaires. Surveys with incomplete data were rejected. Data about patients visiting the included departments were obtained from hospital admission computer systems.

Statistical analysis

Statistical analyses were carried out using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used. For continuous variables, those consistent with normal distribution (according to the Kolmogorov-Smirnov test) were expressed as means ± standard deviations, and those with a skewed distribution were expressed as medians (ranges). Categorical variables were expressed as numbers (percentages).

Results

Recruitment

A total of 1,300 surveys were issued online, and 510 copies were returned (response rate, 39%). According to exclusion criteria relating to the oncologist, hospital, department, title, authority, and prescription type, 46, 70, 30, 35, 15, and 20 respondents were excluded, respectively. A further 27 incomplete surveys were also rejected. Finally, 267 valid online surveys were included for analysis.

A total of 1,200 paper surveys were issued, and 960 were returned (response rate, 80%). According to exclusion criteria relating to the oncologist, hospital, department, title, authority, and prescription type, 11, 23, 10, 62, 46, and 50 individuals were excluded, respectively. A further 25 surveys were rejected due to being incomplete. Finally, 733 valid paper surveys were included for analysis. Therefore, in total, 1,000 valid online and paper surveys were analyzed.

Table 1 presents the characteristics of the included oncologists. Most participants were from second-tier cities (59%), third-class general hospitals (82%), and medical oncology or RT departments (both 35%), and most were
attending physicians (45%). Each oncologist received 25 patients with NSCLC per month. Among those patients, 51% were stage IV, 30% had BMs, and 35% had EGFR mutations.

**Perspectives and perceptions of NSCLC with BMs among oncologists**

Nearly all the oncologists (97%) believed that 1–3 intracranial metastases appeared to be intracranial oligometastases. Acceptance of BM-related treatment concepts was generally similar among oncologists across different departments, with some chemotherapeutic agents generally accepted to be radiosensitizing (7.5–7.8 points). Radiation oncologists more frequently accepted that “Radiotherapy can help the drug penetrate the blood-brain barrier.” than oncologists from other departments. Meanwhile, respiratory oncologists more frequently accepted that “TKI agents can prolong the time before a patient’s BM requires radiotherapy” (Figure 1).

During the selection of therapeutic regimens, the factors considered by the oncologists were (in reverse order) efficacy, safety, price, and accessibility. Specifically, improving overall survival, increasing quality of life, and extending progression-free survival were the main considerations for the oncologists during the development of therapeutic regimens for specific patients with NSCLC and BMs (Figure 2).

**Selecting treatment regimens for patients with neurological symptoms and intracranial metastases**

The survey results indicated that the combined use of RT with antineoplastic agents was increased in patients with neurological symptoms and an increased number of intracranial metastases (Figure 3). The presence of complicating neurological symptoms affected the choice of treatment regimen. The chance of the oncologist choosing RT (RT only or RT plus antineoplastic agents), as opposed to antineoplastic agents only, rose with the presence of neurological symptoms (73% to 81% in 1–3 metastases, 77% to 83% in 4–5 metastases and 79% to 84% in >5 metastases). There were little differences between the departments. Regardless of concomitant neurological symptoms and the number of intracranial metastases, radiation oncologists were more likely to choose RT than oncologists from other departments. Overall, the presence of concurrent neurological symptoms had the greatest effect on the oncologists’ choice of treatment regimen.

For most of the oncologists, RT with concurrent antineoplastic agents was the preferred regimen to treat NSCLC with BMs regardless of whether concurrent neurological symptoms were present (38% to 40% in patients with neurological symptoms; 36% to 37% in patients without neurological symptoms) (Figure 4). The likelihood of this being the first-choice regimen was higher among thoracic surgeons and radiation oncologists than among oncologists from other departments. Regarding the second-choice regimen, for patients without neurological symptoms, the oncologists chose “Upfront antineoplastic agents followed by radiotherapy when achieving optimal efficacy”. For patients with neurological symptoms, the oncologists chose “Upfront radiotherapy followed by antineoplastic agents”; for this option, there was little difference among oncologists across different departments.

The survey results suggested that for patients without neurological symptoms, the most commonly selected drug regimen was TKI therapy (45–48%), followed by chemotherapy (17–25%), best supportive care (14–17%), anti-angiogenic agent + chemotherapy (11–13%), and

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**Table 1 Characteristics of the participating oncologists**

| Characteristics       | Total (n=1,000) [%] |
|-----------------------|---------------------|
| City level            |                     |
| First tier            | 211 [21]            |
| Second tier           | 589 [59]            |
| Third/fourth tier     | 200 [20]            |
| Hospital type         |                     |
| Third-class general hospital | 823 [82]       |
| Third-class cancer hospital | 95 [10]        |
| Second-class general hospital | 82 [8]         |
| Department            |                     |
| Respiratory           | 150 [15]            |
| Medical oncology      | 350 [35]            |
| Radiotherapy          | 350 [35]            |
| Thoracic surgery      | 150 [15]            |
| Title                 |                     |
| Chief                 | 177 [18]            |
| Associate chief       | 369 [37]            |
| Attending             | 454 [45]            |
“The intracranial lesions of patients with brain metastasis are not primary, therefore the prevention of blood-brain barrier against drugs is limited”

“TKIs can prolong the time before patients with brain metastasis require radiotherapy”

“Radiotherapy can help some drugs penetrate the blood-brain barrier”

“Some chemotherapeutic agents may provide similar effects as sensitizers and increase radiotherapy efficiency”

Figure 1: Brain metastasis-related treatment concepts accepted by oncologists across different departments.

Figure 2: Considerations of oncologists during therapeutic regimen selection.
immune modulator therapy (4%). An extremely similar pattern was observed in patients with neurological symptoms, with TKI therapy being the most common drug regimen selected (46–48%), followed by chemotherapy (16–21%), best supportive care (15–18%), anti-angiogenic agent + chemotherapy (12–13%), and immune modulator therapy (4%) (Figure 5A, 5B).

The results also suggested that among RT regimens, SRS (29%) alone was the primary choice for patients with 1–3 BMs and neurological symptoms, whereas WBRT or SRS + WBRT was mostly chosen for patients with >4 BMs. For patients without symptoms, similar pattern could be observed (Figure 5C, 5D).

**Selecting therapeutic regimens for patients with parenchymal and meningeal BMs**

For patients with 1–3 BMs, SRS plus EGFR TKI was the oncologists’ preferred regimen when neurological symptoms were not present; when patients were accompanied by neurological symptoms, the preferred regimen of the medical oncologists was WBRT in addition to SRS plus TKI. For patients with 4–5 BMs without neurological symptoms, the oncologists considered WBRT plus TKI
to be the preferred regimen; when neurological symptoms were present, the preferred regimen of the medical oncologists and thoracic surgeons was SRS in addition to WBRT plus TKI. For patients with >5 BMs, regardless of concomitant neurological symptoms, the preferred regimen of the oncologists was WBRT plus TKI. Overall, regardless of the presence of concomitant neurological symptoms and the number of BMs, the radiation oncologists were more likely than those from other departments to use RT.

**Discussion**

The combination of RT with targeted drugs has drawn extensive attention as a treatment regimen for the management of patients with NSCLC and BMs. However, the optimal regimen and treatment sequence remain unknown. Some authors have concluded that patients with EGFR mutations and BMs do not need upfront WBRT and that oral TKIs are sufficient, but other authors hold different opinions (14-20). The present survey study investigated the therapeutic opinions of Chinese oncologists toward NSCLC with BMs in terms of regimen selection and timing of therapies. It provides insight into Chinese oncologists’ current attitudes regarding the management of EGFR mutation-positive NSCLC with BMs and highlights important differences between different specialists.

Our survey revealed that most oncologists hold the conservative view that both brain RT and TKI are needed. Regarding perspectives and perceptions, 96% of the oncologists believed that 1–3 intracranial metastases were intracranial oligometastasis, and that some chemotherapeutic agents have radiosensitizing effects. When selecting therapeutic regimens, in sequence, the oncologists gave consideration to efficacy, safety, price, and accessibility. Further, RT combined with antineoplastic agents was revealed as the leading regimen for NSCLC with BMs. Regarding the selection and timing of RT, for cases with a small number of BMs, SRS was the optimal option, and for those with a higher number of BMs, the use of WBRT increased. Regardless of concurrent neurological symptoms, the preferred regimen for most oncologists was RT with concurrent antineoplastic agents, with oncologists from thoracic surgery and radiotherapy departments more likely to select this regimen as their first choice. Regarding antineoplastic agents, TKI was the most common approach for patients with EGFR mutations. As the number of BMs increased, the use of third-generation TKIs rose slightly. The presence of concurrent neurological symptoms had
no obvious effect on the selection of antineoplastic agents. Regarding the whole treatment regimen, in cases with a small number of BMs (1–3 metastases), SRS with TKI was the preferred regimen of most oncologists. In cases with a large number of intracranial metastases (>3), WBRT with TKI was the preferred regimen. Besides, the oncologists who considered “radiotherapy + antineoplastic agents” as the preferred regimen, “antineoplastic agents only” was the second optimal regimen, followed by the “radiotherapy + antineoplastic agents” regimen. For patients with meningeal metastases, oncologists from the four departments considered WBRT + TKI to be the preferred regimen, followed by SRS + TKI.

The optimal strategy for the management of patients with NSCLC with BMs is highly controversial, due to the many specialties involved, the number of regimens available, conflicting results between studies, and above all, the high disease heterogeneity between patients. Indeed, the basis of personalized therapy is that the disease of each individual patient is unique. Nevertheless, general patterns and clear trends can be observed in the literature and can be used to guide decision-making (27-30). A meta-analysis showed that delaying RT in TKI-naive patients with EGFR-mutated NSCLC led to worse survival (22). Using a standard regimen of 30 Gy delivered in 10 fractions, WBRT can prolong survival by 4–6 months (21,31). WBRT can permeabilize the BBB, although this permeabilization can be heterogeneous (32). Also, TKIs might have radiosensitizing effects, and thus can potentialize the effect of RT when used in combination (33,34). Studies also show that SRS has better efficacy in cases of small and few BMs (35,36). Overall, the views of oncologists in China generally follow those described in the available literature.

The Greek REASON registry study showed that the main first-line treatment is EGFR-TKI therapy for EGFR-mutated NSCLC and multi-agent chemotherapy for wild-type and metastatic NSCLC (37). In the United States, platinum-based chemotherapy is the most common first-line therapy for metastatic NSCLC (38). Regarding RT, the use of WBRT as a first-line RT for NSCLC with BMs has declined, while that of SRS has doubled (39). A Canadian study reported that 86% of patients with NSCLC with BMs received RT, with 40% of them receiving it near the end of life (38). In British Columbia (Canada), prior to 2018, SRS was mainly offered to patients with <4 BMs, a good performance status, and a good prognosis (40). These results highlight the conflicting practices around the globe and the need for more randomized controlled trials. The current study shows that chemotherapy is the first choice for the treatment of EGFR wild-type patients. EGFR mutation status is related to the efficacy of chemotherapy, but whether the mutation status can determine the choice of chemotherapy remains to be further studied. Targeted therapy or targeted combined chemotherapy schemes, such as crizotinib, bevacizumab combined with paclitaxel + carboplatin, provide more treatment options for EGFR wild-type patients.

The present study has limitations. First, despite the large number of participants, only a small proportion of the oncologists involved in NSCLC management in China participated in our survey. Furthermore, the questionnaire was not validated and its design did not allow for quantitative results to be obtained; future studies should use a validated questionnaire. Finally, the present study did not address the management of toxicities.

Nevertheless, based on the results of this study and previous researches, we suggested that radiotherapy with concurrent EGFR-TKI could be the better choice for the treatment for EGFR-positive NSCLC with BM. Besides, given the highly controversial optimal strategy for the management of patients with NSCLC with BMs, we, as well as the majority of Chinese oncologists, agreed that BM number, type and oncologists’ specialty could affect regimen and timing of RT, reflecting the similarity of Chinese oncologists’ current clinical practice, even with limited evidence from clinical studies on this issue.

Conclusions

This study has provided important insights into the current attitudes of Chinese oncologists regarding EGFR mutation-positive NSCLC with BMs and its management. RT combined with EGFR-TKI agents is the regimen preferred by Chinese oncologists for EGFR mutation-positive NSCLC with BMs. The BM number and type may influence the decision of which RT regimen is used. Due to the narrow time window for such patients to receive treatment, randomized controlled trials could aid in addressing the current disputes in therapeutic regimen selection.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional committee board of Shanghai Chest Hospital (LS2049) and informed consent was taken from all the participants.

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