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

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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

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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 al so 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

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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

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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]

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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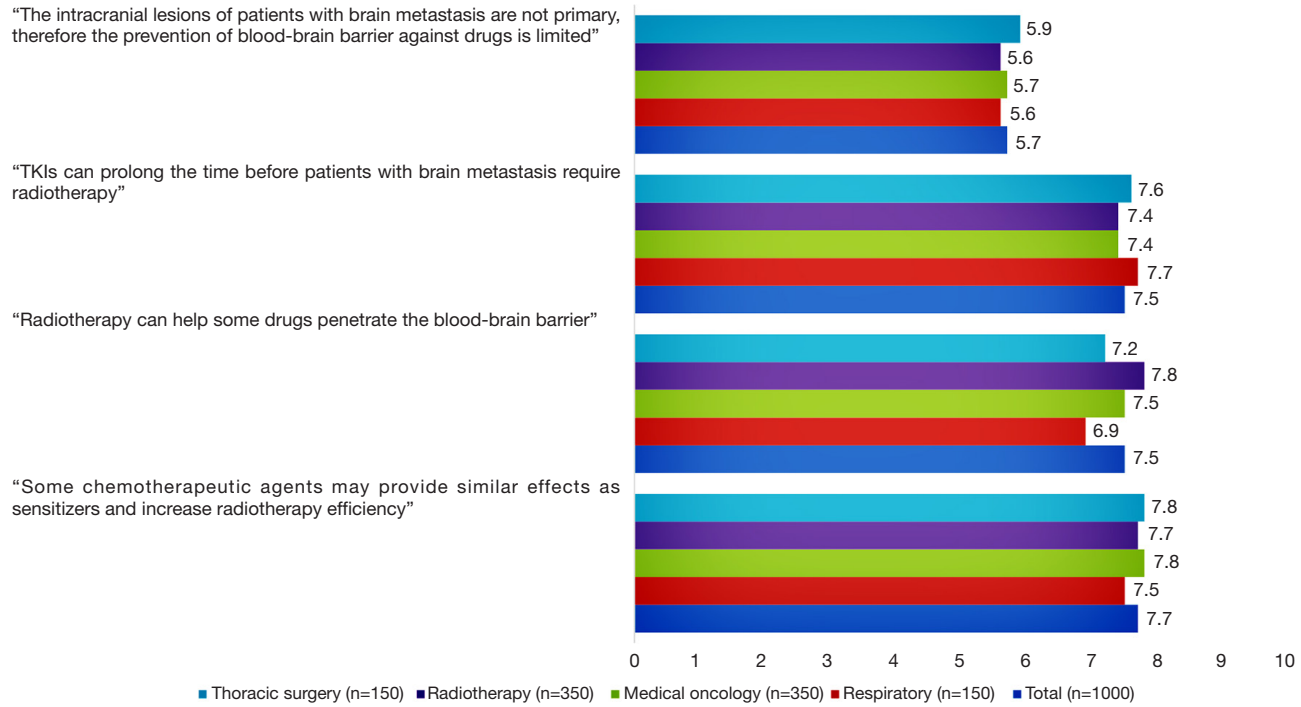

Figure 1 Brain metastasis-related treatment concepts accepted by oncologists across different departments.

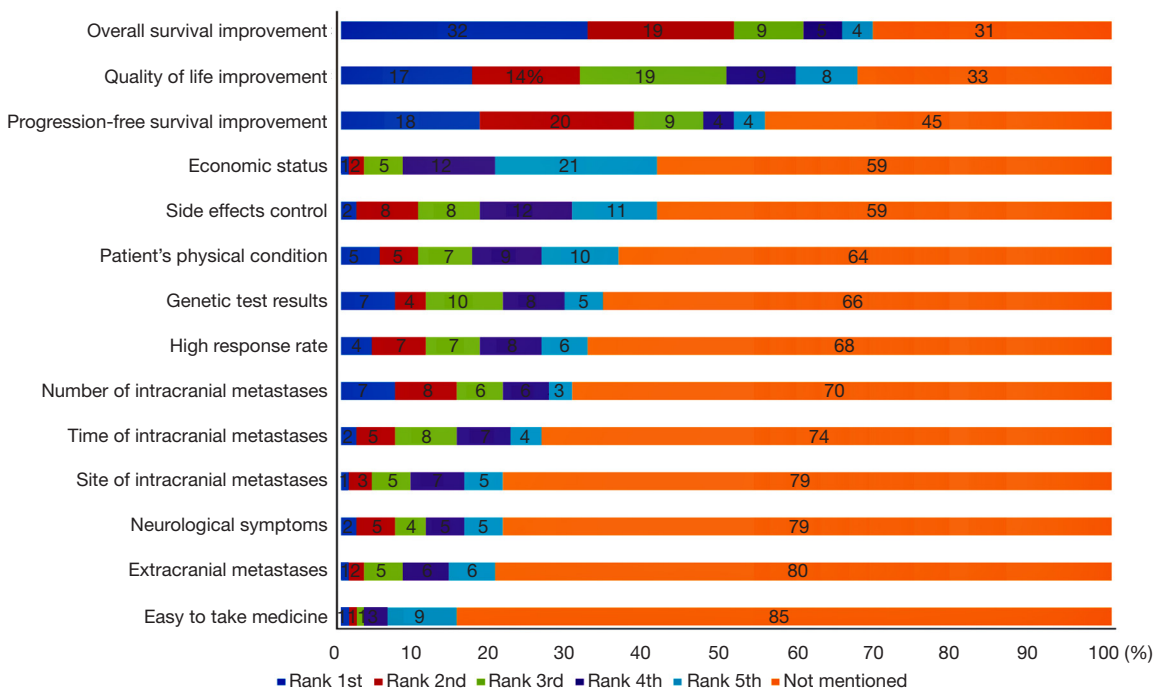

Figure 2 Considerations of oncologists during therapeutic regimen selection.

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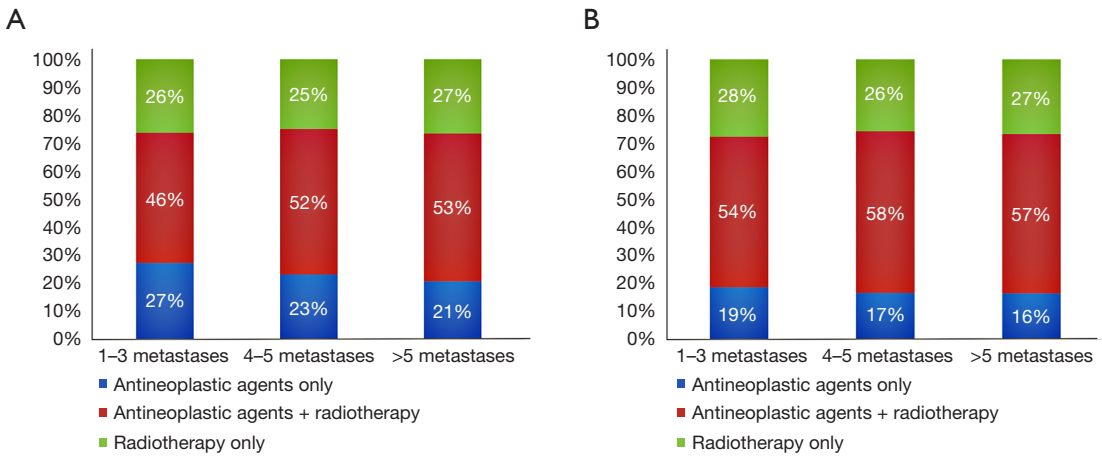

Figure 3 Treatment regimen selection in daily practice based on neurological symptoms and brain metastasis. Treatment regimen selection for patients without (A) and with (B) neurological symptoms.

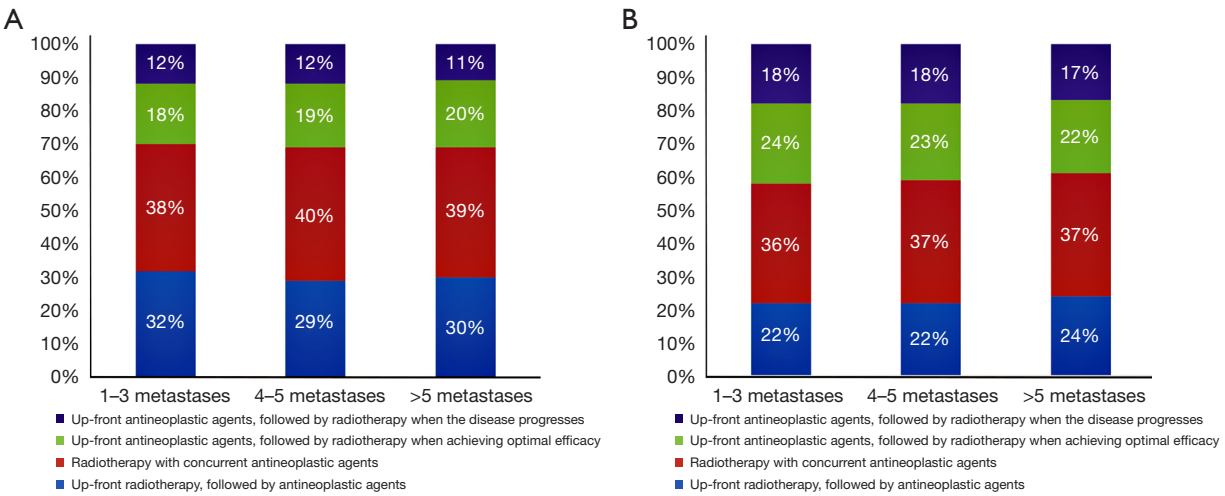

Figure 4 Radiotherapy timing selection for patients receiving radiotherapy and targeted therapy. Radiotherapy timing selection for patients with (A) and without (B) neurological symptoms.

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

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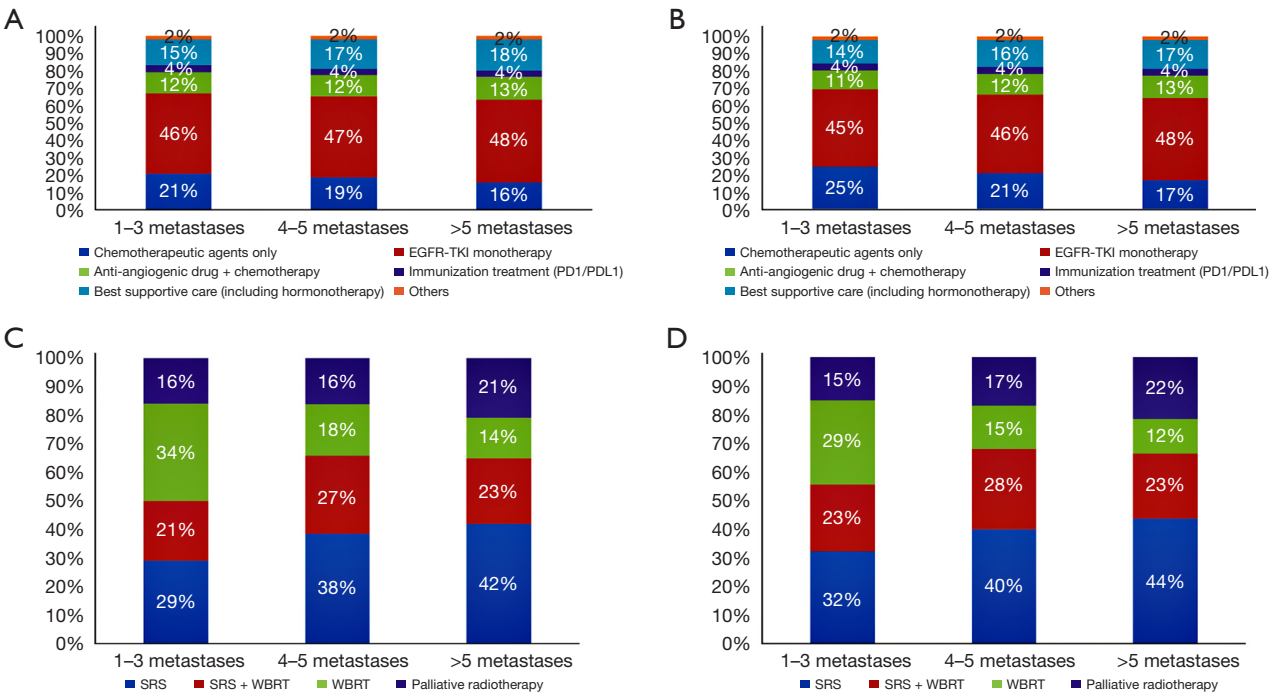

Figure 5 Preferred antineoplastic agent regimens and radiotherapy regimens. Preferred antineoplastic agent regimens for patients with (A) and without (B) neurological symptoms. Preferred radiotherapy regimens for patients without (C) and with (D) neurological symptoms.

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

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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-naïve 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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References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
3. Planchard D, Popat S, Kerr K, et al. Correction to: "Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Ann Oncol 2019;30:863-70.
4. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
5. Dempke WC, Edvardsen K, Lu S, et al. Brain Metastases in NSCLC - are TKIs Changing the Treatment Strategy? Anticancer Res 2015;35:5797-806.
6. Lukas RV, Kumthekar P, Rizvi S, et al. Systemic therapies in the treatment of non-small-cell lung cancer brain metastases. Future Oncol 2016;12:1045-58.
7. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res 2015;4:36-54.
8. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. Mol Cancer 2018;17:38.
9. Preusser M, Berghoff AS, Ilhan-Mutlu A, et al. ALK gene translocations and amplifications in brain metastases of non-small cell lung cancer. Lung Cancer 2013;80:278-83.
10. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015;88:108-11.
11. Shin DY, Na II, Kim CH, et al. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol 2014;9:195-9.
12. Heon S, Yeap BY, Britt GJ, et al. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin Cancer Res 2010;16:5873-82.
13. Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin Cancer Res 2012;18:4406-14.
14. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung

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cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). Ann Oncol 2013;24:993-9.
15. Iuchi T, Shingyoji M, Sakaida T, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. Lung Cancer 2013;82:282-7.
16. Porta R, Sánchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J 2011;37:624-31.
17. Park SJ, Kim HT, Lee DH, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer 2012;77:556-60.
18. Jiang T, Su C, Li X, et al. EGFR TKIs plus WBRT Demonstrated No Survival Benefit Other Than That of TKIs Alone in Patients with NSCLC and EGFR Mutation and Brain Metastases. J Thorac Oncol 2016;11:1718-28.
19. Gerber NK, Yamada Y, Rimner A, et al. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. Int J Radiat Oncol Biol Phys 2014;89:322-9.
20. Yang JJ, Zhou C, Huang Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir Med 2017;5:707-16.
21. Khuntia D, Brown P, Li J, et al. Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 2006;24:1295-304.
22. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naïve Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. J Clin Oncol 2017;35:1070-7.
23. Khalifa J, Amini A, Popat S, et al. Brain Metastases from NSCLC: Radiation Therapy in the Era of Targeted Therapies. J Thorac Oncol 2016;11:1627-43.
24. Ballard P, Yates JW, Yang Z, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. Clin Cancer Res 2016;22:5130-40.
25. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018. [Epub ahead of print]. doi: 10.1200/JCO.2018.78.3118.
26. Chen Y, Wang Y, Zhao L, et al. EGFR tyrosine kinase inhibitor HS-10182 increases radiation sensitivity in non-small cell lung cancers with EGFR T790M mutation. Cancer Biol Med 2018;15:39-51.
27. Okimoto RA, Bivona TG. Recent advances in personalized lung cancer medicine. Per Med 2014;11:309-21.
28. Butts C, Kamel-Reid S, Batist G, et al. Benefits, issues, and recommendations for personalized medicine in oncology in Canada. Curr Oncol 2013;20:e475-83.
29. Yang P. Maximizing quality of life remains an ultimate goal in the era of precision medicine: exemplified by lung cancer. Precision Clin Med 2019;2:8-12.
30. Zhou L, Deng L, Lu Y. Epidermal Growth Factor Receptor Mutations in Non-Small-Cell Lung Cancer With Brain Metastasis: Can Up-Front Radiation Therapy Be Deferred or Withheld? J Clin Oncol 2017;35:1033-5.
31. Khan AJ, Dicker AP. On the merits and limitations of whole-brain radiation therapy. J Clin Oncol 2013;31:11–3.
32. Eichler AF, Chung E, Kodack DP, et al. The biology of brain metastases-translation to new therapies. Nat Rev Clin Oncol 2011;8:344–56.
33. Gow CH, Chien CR, Chang YL, et al. Radiotherapy in lung adenocarcinoma with brain metastases: effects of activating epidermal growth factor receptor mutations on clinical response. Clin Cancer Res 2008;14:162-8.
34. Soon YY, Leong CN, Koh WY, et al. EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: a systematic review and meta-analysis. Radiother Oncol 2015;114:167-72.
35. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-95.
36. Habets EJ, Dirven L, Wiggenraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. Neuro Oncol 2016;18:435-44.
37. Syrigos KN, Georgoulias V, Zarogoulidis K, et al. Epidemiological Characteristics, EGFR Status and Management Patterns of Advanced Non-small Cell Lung Cancer Patients: The Greek REASON Observational Registry Study. Anticancer Res 2018;38:3735-44.
38. Simeone JC, Nordstrom BL, Patel K, et al. Treatment patterns and overall survival in metastatic non-small-cell

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lung cancer in a real-world, US setting. Future Oncol 2019;15:3491-502.
39. Barbour AB, Jacobs CD, Williamson H, et al. Radiation Therapy Practice Patterns for Brain Metastases in the United States in the Stereotactic Radiosurgery Era. Adv Radiat Oncol 2019;5:43-52.
40. Schlijper R, Fraser IM, Regan J, et al. Patterns of Radiotherapy Utilization for Lung Cancer Patients with Brain Metastases: A Population-based Analysis. Cureus 2019;11:e5591.

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