Editorial

Can we omit radiotherapy in case of brain metastases for patients with mutant EGFR lung adenocarcinoma?

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Provenance: This is an invited Editorial commissioned by Guest Section Editor Dr. Shaohua Cui, MD (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Comment on: 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.

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The paper presented by Magnuson *et al.* is a multiinstitutional retrospective study looking to the treatment of brain metastases among patients with tyrosine kinase inhibitor naive epidermal growth factor mutant non-small cell lung cancer: they concluded that deferral of radiotherapy is associated with inferior survival and the best approach is radiosurgery (RS) followed by EGFR-TKI to avoid the neurocognitive toxicity of whole brain radiotherapy (WBRT) (1). This is currently a hot question in the literature with those favoring a combined approach and those favoring only TKI. This is certainly not an easy question as there are many possible endpoints to evaluate the efficacy of the treatment: local response, time to brain progression, quality of life, toxicity and overall survival, the ultimate endpoint. The later will directly be influenced not only by the brain tumor control but also by the extracranial metastatic disease and the response to the systemic treatment which may explain the differences reported in the literature. We also must point out the fact that all studies are retrospective with all the possible biases due to this approach: the choice of treatment is often related to the practitioner both for radiotherapy and the type of treatment (WBRT or RS) and the treatment timing. In a recent paper, Doherty *et al.* has observed a longer time to intracranial progression (TTIP) with WBRT compared to RS or TKI but no difference in survival suggesting that WBRT may be deferred until cranial progression: nevertheless, the rate of patients with brain symptomatic lesions was higher in the WBRT group, 52% *vs.* 16% for RS and 11% for the TKI (2). A similar observation in Byeon series was in favor of only TKI (3). Other series may include only asymptomatic patients such as in Liu's paper (4).

A first comment is certainly the changing pattern of outcome for this group of patients: median overall survival for the three cohorts of patients range from 25 months for the TKI only group to 30 and 46 months for the combined approach with WBRT or RS. This is major improvement in contrast to the results observed in the study of Gaspar *et al.* with patients included in three randomized trials of the RTOG: using the recursive partitioning analysis (RPA) including four variables (age, performance status, control of primary disease and extracranial metastases); a median survival time of 7.7 months was observed for the best group and less than 3 months for the worse (5). In our experience with the Leksell Gamma Knife RS and using the basic score for brain metastases which includes the performance status, the presence or absence of extracranial disease, the control or not of the primary disease, the median survival rose from 2.4 months for the worse subgroup to more than 30 months for the best subgroup (6).This major improvement in patient's survival is partially related to the patient selection but also outline the efficacy of the current systemic treatment, especially the targeted agents in a population with EGFR mutant adenocarcinoma. This was also well illustrated by Sperduto *et al.* analyzing 2,186 patients treated between 2006 and 2014 including in the model of

graded prognostic assessment (GPA), the molecular marker: for the more favorable group, median survival rose from 14.8 months before 2005 to 46.8 months (7). In contrast, for the less favorable group, the general outcome remains poor with median survival between 5 to 7 months.

A second comment is that patient's candidate for RS is already a selected group: usually WBRT is the classical approach for most patients due to the number of lesions, locations, performance status, and meningeal infiltration. This is reflected in the patient selection: the RS group had fewer brain metastases, smaller lesions and less advanced disease than the WBRT group (1). Furthermore, if most patients had a stage IV disease, patients treated with WBRT had more often five brain metastases or more (74%) in contrast to the TKI group (36%) or the RS arm (18%). In contrast, another important prognostic factor was well balanced between the three arms, the ECOG performance status, and a major factor. One advantage of RS is to avoid the WBRT toxicity (hair loss, fatigue, neurocognitive troubles and the impact on the quality of life) and to keep the possibility of repeated treatments in case of new brain lesions. Salvage treatment may have an impact on the results, brain tumor control or even survival: 52% of the patients in the TKI arm had additional brain RT at the time of intracranial progression. Furthermore, patients with a progression but failing to receive RT were excluded from the present study. In the recent series of Doherty *et al.* including 184 patients, 20 patients had a third line cranial nervous system treatment for progressive disease including even surgery, a complete new paradigm in the patient management with brain metastases (2).

Looking to the papers published on the topics, results are conflicting with benefit in term of response for combining RT and TKIs, better brain control but no major differences in survival questioning to start or not with RT or keeping it until progression (2-4,8,9). A meta-analysis by Jiang *et al.* included 15 studies and 1,552 patients: RT plus EGFR TkIs significantly improve the response rate, prolong time to central nervous tumor progression and even median survival at the price of an increase in toxicity (10). In this study, RT refers to WBRT, RS or even the combined approach. The treatment was either concurrent or sequential without any difference in outcome. Most studies included in the analysis were from China.

The question is to use or not RT, RS or WBRT and its timing. This is probably a valid question for naïve and asymptomatic patients and less in case of brain metastases occurring under TKIs. The choice between WBRT, RS or even only steroids depends on the type of brain lesions but also on the evolution of the extracranial disease and the patient's condition. Should we start with TKI and keep RT until brain progression? The risk in case of progression is the development of severe neurological symptoms precluding a local treatment; this may be an important issue in the absence of life threatening extra cerebral lesions. In the study of Magnuson *et al.*, patients failing to receive RT in case of brain progression were excluded from the analysis. The choice should probably be individualized taking into account all the prognostic factors including the performance status, the presence of extensive extra cerebral disease, the location of the brain metastases and the presence of symptoms. In case of deferring RT, the patient should be followed carefully to avoid a dramatic major brain progression leading to permanent damage.

The different trials testing the value of adding to a local treatment (surgery or RS) have showed a better brain tumor control but no impact on survival. Secondary analyses taking into account the GPA have suggested a benefit in median survival in the favorable group, a gain around 6 months in Aoyama and RTOG trials (11,12). Is it possible to reduce the WBRT induced toxicity, especially the neurocognitive toxicity? The hippocampus region plays an important role in the neurocognitive function such as learning and memory. A dose response relationship has been observed: delivering dose above 8 Gy induced this toxicity while keeping the dose below allow avoiding the neurocognitive sequelae (13). The available radiation technique (intensity modulated radiotherapy either static or rotational) allows preserving the hippocampus region. Many trials are on-going to test this approach both for brain metastases and for prophylactic cranial irradiation.

In the absence of a randomized trial, the data suggest a benefit of combining radiation and TKI both in term of response, brain control and also survival for selected patient groups. Once again, the treatment should be individualized taking into account also the patient preference especially in case of WBRT due to the current late effects.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. 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.
2. Doherty MK, Korpanty GJ, Tomasini P, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother Oncol 2017;123:195-202.
3. Byeon S, Ham JS, Sun JM, et al. Analysis of benefit of sequential cranial radiotherapy in patients with EGFR mutant non-small cell lung cancer and brain metastasis. Med Oncol 2016;33:97.
4. Liu S, Qiu B, Chen L, et al. Radiotherapy for asymptomatic brain metastasis in epidermal growth factor receptor mutant non-small cell lung cancer without prior tyrosine kinase inhibitors treatment: a retrospective clinical study. Radiat Oncol 2015;10:118.
5. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745-51.
6. Lorenzoni J, Devriendt D, Massager N, et al. Radiosurgery for treatment of brain metastases: estimation of patients eligibility using three stratification systems. Int J Radiat Oncol Biol Phys 2004;60:218-24.
7. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases An update of the Graded Prognostic Assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol 2017;3:827-31.
8. Zhu Q, Sun Y, Cui Y, et al. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). Oncotarget 2017;8:13304-11.
9. Chen Y, Yang J, Li X, et al. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma. Cancer Sci 2016;107:1800-5.
10. Jiang T, Min W, Li Y, et al. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis. Cancer Med 2016;5:1055-65.
11. Sperduto PW, Shanley R, Luo X, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). Int J Radiat Oncol Biol Phys 2014;90:526-31.
12. Aoyama H, Tago M, Shirato H, et al. Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases: Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial. JAMA Oncol 2015;1:457-64.
13. Gondi V, Hermann BP, Mehta MP, et al. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 2012;83:e487-93.

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