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Comparison of up-front radiotherapy and TKI with TKI alone for NSCLC with brain metastases and EGFR mutation: A meta-analysis

Chunyu Wang[a,1], Xiaotong Lu[a,1], Zhangyan Lyu[b], Nan Bi[a,*], Luhua Wang[a,*]

[a] Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China

[b] Program Office for Cancer Screening in Urban China, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China

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ABSTRACT

Objective: About 50–70% non-small cell lung cancer (NSCLC) patients with EGFR mutation go through brain metastases (BM). Radiotherapy is the standard treatment before the tyrosine kinase inhibitor (TKI) era. However, the TKI has more than 70% intracranial response rate. Here, we performed a meta-analysis to compare clinical outcomes of up-front radiotherapy and TKI with TKI alone for NSCLC with BM and EGFR mutations.

Methods and materials: We searched Embase, Pubmed, Web of Science, Medline, the Cochrane Library and important oncology meetings comparing the up-front radiotherapy (RT) and TKI with TKI alone in NSCLC patients with newly diagnosed BM and EGFR mutation from database inception to December 2017. We conducted meta-analyses evaluating intracranial progression-free survival (iPFS) and overall survival (OS) with hazard ratios (HR) and 95% confidence intervals (CI) based on the HR of individual study.

Results: Seven studies with 1086 patients were eligible for meta-analyses. Compared to TKI alone, up-front RT and TKI showed better iPFS (HR = 0.72, 95%CI: 0.53-0.97, p = 0.028) and OS (HR = 0.70, 95%CI 0.53–0.93, p = 0.015). Meta regression analyses and subgroup analyses demonstrated patients with limited number of brain metastases benefited more from up-front RT on OS (HR: 0.54, 95% CI: 0.41-0.72, p = 0.000).

Conclusion: Compared with TKI alone, up-front RT and TKI had a higher iPFS and OS, especially for patients with limited number of brain metastases. Larger randomized trials evaluating these two treatment arms are needed to identify optimal treatments for specific patients.

1. Introduction

Lung cancer is the leading cause of cancer related death worldwide [1]. The non-small cell lung cancer (NSCLC) comprised more than 80% of that and almost 50% of NSCLC are lung adenocarcinoma [2]. The finding of epidermal growth factor receptor (EGFR) mutations has leading the treatment of lung adenocarcinoma into a new era with tyrosine kinase inhibitor (TKI). Patients with EGFR-mutant have a 50–70% risk for developing brain metastasis (BM) [3]. Traditionally, up-front whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) or surgical resection is the first line treatment of BM, either alone or in combination. However, the single agent of EGFR-TKI showed much pleasing results in TKI naive patients with BM and EGFR mutation with the intracranial response rate (iRR) of 75%-88%, median intracranial progression-free survival (iPFS) is 6.6-14.5 months, and median overall survival is 15.9-21.8 months [4–6]. So can up-front radiotherapy (RT) be deferred or omitted due to the neurotoxicity or stick to the radiation first and mandatory?

Regrettably, no phase III clinical trial has been published to show the comparison of up-front radiotherapy and deferred RT or TKI with no RT. Soon et al. reported a systematic review and meta-analysis based on 12 non-comparative observational studies (n = 363) and reached the conclusion that up-front cranial radiotherapy resulted in improved four-month iPFS and prolonged two-year OS compared to TKI alone in 2015 [7]. Recently, some retrospective analyses have been done with difference indications however. To examine whether up-front RT prolong the iPFS and OS, we reviewed and make a meta-analysis for these retrospective trails that assessed the up-front RT in EGFR mutant BM with deferred RT or no RT.

* Corresponding authors.
E-mail addresses: binan_email@163.com (N. Bi), wlhwq@yahoo.com (L. Wang).
[1] These authors contributed equally to this manuscript.

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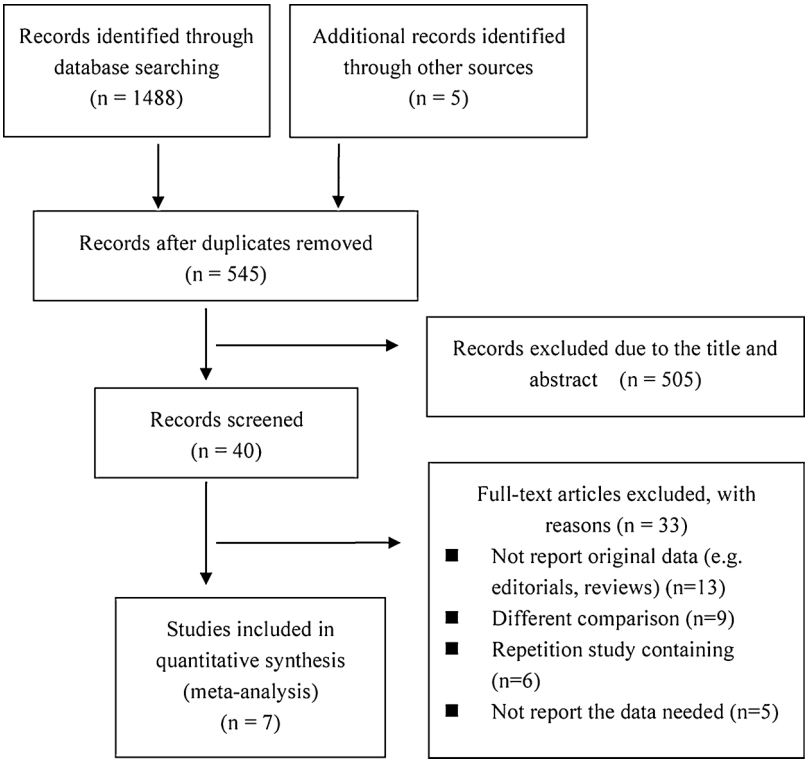

Fig. 1. Study selection process.

2. Materials and methods

2.1. Search strategy and selection criteria

We searched for published articles, abstracts and reviews comparing the up-front RT and TKI with TKI alone (or with salvage RT) in NSCLC patients with newly diagnosed brain metastasis and EGFR mutation. RT followed by TKI or started within 4 weeks after EGFR-TKI initiation were deemed as up-front RT. The salvage RT in the control group started RT after the intracranial failure from the first-line TKI treatment. The study type, prospective or retrospective, was not restricted. All types of RT, including WBRT, SRS, and WBRT with simultaneously integrated boost (SIB) for brain metastasis, were accepted for inclusion.

The inclusion criteria: Patients should aged 18 years older, histologically confirmed with NSCLC, EGFR mutation status confirmed on genetic analysis, newly diagnosed brain metastases visualized on either CT or MRI, no prior radiation to the brain metastases, prior TKI use excluded, ALK mutation excluded, reported outcome of interest (i.e iPFS, OS, objective response rate (ORR) and disease control rate (DCR)) and the original paper was published in English.

We searched Embase, Pubmed, Web of Science, Medline and the Cochrane Library from the date of their inception until December 31, 2017 including terms for lung cancer, brain metastases, EGFR mutation, and radiotherapy (see Appendices 1, 2, 3). The references lists of the reviews were searched with hand. We also searched abstracts from ASTRO, ESTRO, ASCO and ESMO, the most important international oncology meetings.

Two independent reviewers (WCY and LXT) screened the title and abstract of searched articles. Studies that seemed to meet the inclusion criteria were selected for full paper reviewed. Disagreements between the two reviewers were resolved through the third reviewer (BN). When the data of same patient cohort from the same institution were published in multiple reports, the latest study was selected. The study with whole cohort will be selected if another study did a sub-analysis of the same population. The exclusions were documented in detail.

2.2. Data extraction

Two independent investigators extracted study data including: (1) characteristics of trial participants (first author, publication year, country, study design, sample size, patients' baseline, trials' inclusion and exclusion criteria; (2) type of intervention (RT type; TKI with salvage RT or TKI alone); (3) type of outcome. The hazard-ratio (HR) and 95% confidence intervals (CI) needed for meta-analyses were extracted from the paper directly. For studies which presented Kaplan-Meier survival curves, the HR for and OS were calculated through one of the specified outcomes according to a method published [8]. iPFS was defined from the diagnosis date of brain metastases to the date of growth of a previous lesion or the development of a new lesion. OS was counted from the diagnosis date of brain metastases to the date of death. We contacted authors of included studies for information that had not been, or was unclearly, reported. If the information needed for HR calculation is not available, the study will be excluded.

2.3. Statistical analysis

Descriptive statistics were used to summarize the data, including study characteristics, patient characteristics, intervention details, and outcomes of each study. Heterogeneity was defined as statistical significance with an I^2 statistic > 50%, and the random-effects model based on the DerSimonian and Laird method was used in this condition [9]. Otherwise, the fixed-effect model based on the Mantel-Haenszel method was used. Publication bias was evaluated using Egger's linear regression test and Begg's rank correlation test [10,11]. In addition, potential sources of heterogeneity were explored through meta-regression analysis and stratified analysis subsequently. All statistical tests were two-sided and statistical significance was defined as P value less than 0.05. Statistical analyses were performed using STATA (version 12.0).