

Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis

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Background: We performed a meta-analysis to compare overall survival (OS) outcomes in patients with synchronous oligometastatic non-small cell lung cancer (NSCLC) who underwent aggressive thoracic therapy (ATT) with those who did not.

Methods: A systematic review of controlled trials of ATT on survival in synchronous oligometastatic NSCLC was conducted. Hazard ratio (HR) for the main endpoint OS was pooled using a fixed-effects model. Subgroup analysis was performed in patients with single organ metastases, or with different numbers of brain metastases, or with different stages of thoracic disease. Pooled survival curves of OS were constructed.

Results: Seven eligible retrospective observational cohort studies were identified including 668 synchronous oligometastatic NSCLC patients, of whom 227 (34.0%) received ATT. For patients with synchronous oligometastatic NSCLC, ATT was associated with a significant improvement of OS (HR, 0.48; 95% CI, 0.39–0.60; $P < 0.00001$). In subgroup analysis, the association with OS was similar or even strengthened, with a HR of 0.42 (95% CI, 0.31–0.56) in single organ metastases group, 0.49 (95% CI, 0.31–0.75) in solitary brain metastasis group, and 0.38 (95% CI, 0.20–0.73) in thoracic stage I–II group, respectively. The pooled cumulative survival rates for patients received ATT were 74.9% at 1 year, 52.1% at 2 years, 23.0% at 3 years, and 12.6% at 4 years. The corresponding pooled survival for patients who did not receive ATT were 32.3%, 13.7%, 3.7%, and 2.0%, respectively.

Conclusions: Survival benefit from ATT is common in synchronous oligometastatic patients. Selected patients with synchronous oligometastatic NSCLC could also achieve long-term survival with ATT.

Keywords: Synchronous oligometastases; non-small cell lung cancer (NSCLC); aggressive thoracic therapy (ATT); overall survival (OS); meta-analysis

Submitted Sep 22, 2017. Accepted for publication Jan 04, 2017.

doi: 10.21037/jtd.2017.02.21

View this article at: <http://dx.doi.org/10.21037/jtd.2017.02.21>

Introduction

Lung cancer is still the leading cause of cancer death globally. Non-small cell lung cancer (NSCLC) accounts for 85–90% of all cases (1). Almost half of patients diagnosed with

NSCLC have distant metastases at presentation (2) and the prognosis of these patients are poor. Systemic therapy is considered to be the standard treatment for stage IV NSCLC, which results in median survivals of 8–11 months (3).

Targeted therapy have shown efficacy in the treatment of advanced NSCLC, however, most patients progress after a median survival of 12 months because of resistance (4-6).

Hellman and Weichselbaum proposed the existence of a clinically recognisable state termed ‘oligometastases’, which is an intermediate state of metastases characterized by a limited number and site of metastatic tumors. In these selected patients, eradication of oligometastases could be curative (7,8). However, whether the aggressive thoracic therapy (ATT) could potentially improve overall survival (OS) in oligometastatic NSCLC remains unclear. Removal of the primary tumor was shown to improve OS in patients with metastatic renal cancer (9), by contrast, locoregional treatment of the primary tumor did not affect OS in patients with metastatic breast cancer (10). More and more studies reported favorable long-term survivals in oligometastatic NSCLC treated with aggressive local therapy (11-13). However, these studies are retrospective and the validity of the survival benefit are challenging due to patient selection.

Recently, Ashworth *et al.* did a systematic review of literature considering NSCLC patients with 1–5 metastases treated with local therapy and found that definitive treatment of the primary tumor was a good prognostic factor for survival (14). Moreover, they further did an individual patient data (IPD) meta-analysis and found that long-term survival is common in selected patients with metachronous oligometastases, while patients with synchronous metastases and N1/N2 disease experienced the poorest survival (15). In light of these findings, we performed this meta-analysis to determine whether synchronous oligometastatic NSCLC patients might benefit from ATT, and to assess the long-term survival of patients with synchronous oligometastatic NSCLC who received or did not receive ATT.

Methods

Search strategies

A comprehensive systematic search for published articles was carried out by two authors independently up to Aug 3, 2015 among the PubMed, EMBASE, and Cochrane databases. Potential articles were identified using the following keywords combined by “non-small cell lung cancer OR non-small cell lung carcinoma OR non-small cell lung neoplasm OR non-small cell lung tumor OR NSCLC OR pulmonary adenocarcinoma OR lung adenocarcinoma OR adenocarcinoma of the lung OR lung squamous carcinoma OR pulmonary squamous carcinoma OR squamous cell

lung carcinoma” AND “neoplasms/sc OR metast* OR oligomet* OR stage 4 OR stage IV OR stage four OR late stage OR advanced stage” AND “radiotherapy OR radiation therapy OR stereotactic OR SBRT OR SABR OR EBRT OR surgery OR resection OR surgical OR eradication OR ablation OR aggressive therapy” AND “primar*” AND “survive*”. We also searched the bibliography of identified articles manually.

Selection criteria

Studies meeting the following eligibility criteria were included: randomized controlled trial or retrospective or prospective observational cohort studies; studies on NSCLC patients with 1 to 5 synchronous metastases (diagnosed within 2 months after the primary tumor); studies on benefit from ATT (surgery or radiotherapy with a total dose more than 40 Gy); studies with available OS data of observed patients; and studies in English. The exclusion criteria were as followings: review papers, case reports, and non-controlled clinical studies; studies that only reported the therapy of metastases; studies with fewer than 20 patients.

As regard to studies with overlapping patient populations, the most recent investigation using updated data and with the maximum number of individuals was chosen for inclusion.

Data extraction

Data were extracted and recorded in a predefined information sheet by two authors independently, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (16). Study characteristics (first author, country of authors, time period of enrolling patients, number of patients, oligometastatic state, ATT regimens) and outcome data were extracted from the included articles. All discrepancies were discussed to reach consensus by including a third authors. The assessment of the risk of bias in included studies was conducted independently by two authors using Newcastle-Ottawa scale (17).

Statistical analyses

We predefined OS as the primary outcome and a hazard ratio (HR) expressing the intervention effect. For each study, the HR with corresponding 95% confidence intervals (CI) was directly extracted from the research article or estimated using Kaplan-Meier survival curves (18).

The χ^2 test and I^2 test were used to determine the

heterogeneity (19). If the analysis showed significant heterogeneity, defined as $P_{\text{heterogeneity}} < 0.1$ or $I^2 > 30\%$, the random model was used. Otherwise, the fixed model was used. All statistical analyses were performed using the Review Manager analysis software (RevMan, version 5.1.2: The Cochrane Collaboration, <http://ims.cochrane.org/revman>). A P value of less than 0.05 was considered to be statistically significant. Successive monthly pooled estimates of survival

and its standard errors were calculated and then used to yield a pooled measure of cumulative OS for each intervention group, according to the methods suggested by Pereira *et al.* and Takagi *et al.* (20,21). Statistical significance ($P < 0.05$) was assessed for the cumulative survival rate differences between ATT group and no-ATT group at yearly intervals. The statistical method used judges the significance of differences by examining the overlap between confidence intervals, but it does not calculate P values (22).

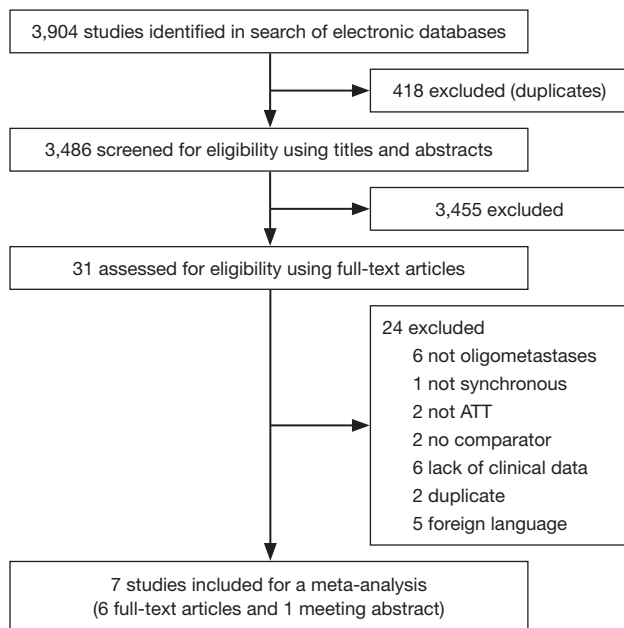


Figure 1 Flowchart of literature identification and screening process.

Results

Study characteristics

A total of 3,904 articles were retrieved from databases search. According to the eligibility criteria for title and abstract, 31 articles were selected for full-text screening. In total, 6 full-text articles (23-28) and 1 meeting abstract (29) were selected for the final analysis. A flow diagram depicting literature screening process is shown in *Figure 1*.

The characteristics of the 7 included studies are summarized in *Table 1*. All the included studies are retrospective observational cohort studies from 1999 to 2015, consisting of 668 synchronous oligometastatic NSCLC patients, among whom 227 (34.0%) received ATT. With regard to ATT regimens, Surgery only was the modality of ATT in one study (26), radiotherapy in one study (23), and surgery combined with radiotherapy or not in the five others articles (24,25,27-29). When stratifying by oligometastatic state, single organ

Table 1 Characteristics of included studies

Study	Country	Year	No. of patients			Oligometastatic state	ATT	Quality score
			Total	ATT	no-ATT			
Xanthopoulos 2015 (23)	USA	1/2004–8/2010	75	25	50	1–4 SO	RT ¹	5*
Guo 2014 (29)	Canada	2005–2012	53	27	26	1–4 SBO	S/RT ²	NR
Gray 2014 (24)	USA	1/2001–1/2011	66	38	28	1–4 SBO	S/RT ³	5*
Parikh 2014 (25)	USA	2002–2012	186	53	133	1–5 SO	S/RT ⁴ or SBRT	6*
Xu 2013 (26)	China	2/2002–10/2010	213	45	168	SSM	S	4*
Flannery 2008 (27)	USA	1993–2006	42	26	16	SSBM	S/RT ³	4*
Chidel 1999 (28)	USA	1982–1996	33	13	20	SSBM	S/RT ¹	4*

*, using the Newcastle-Ottawa scale for non-randomized studies. ATT, aggressive thoracic therapy; SO, synchronous oligometastases; SBO, synchronous brain-only oligometastases; SBRT, stereotactic body radiation therapy; SSM, synchronous solitary metastasis; SSBM, synchronous solitary brain metastasis; S, surgery; RT, radiation therapy; RT¹, radiation therapy with dose >50 Gy; RT², radiation therapy with dose >40 Gy; RT³, radiation therapy with dose >45 Gy; RT⁴, radiation therapy with dose >53 Gy; NR, not reported.

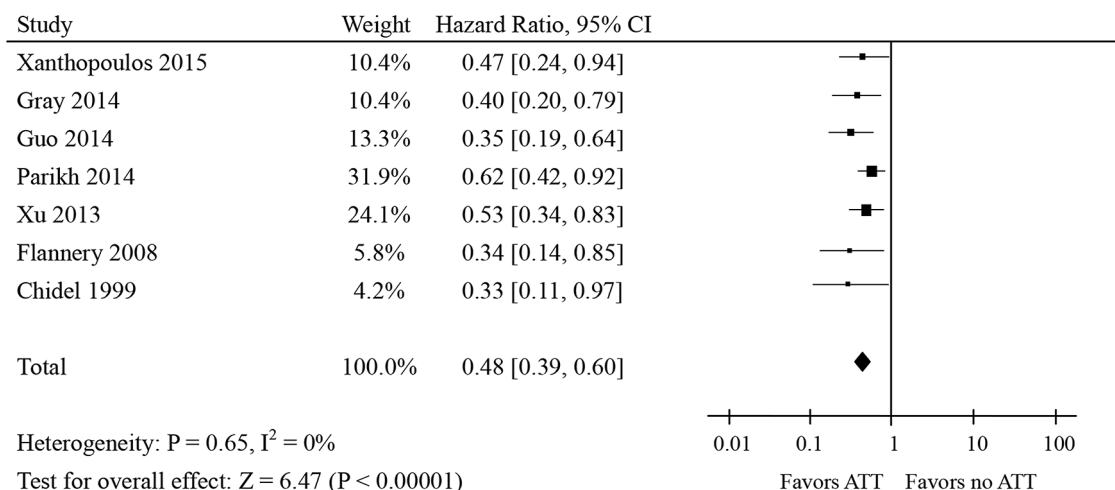


Figure 2 Forest plot of the effect of undergoing aggressive thoracic therapy or not on overall survival in synchronous oligometastatic NSCLC patients.

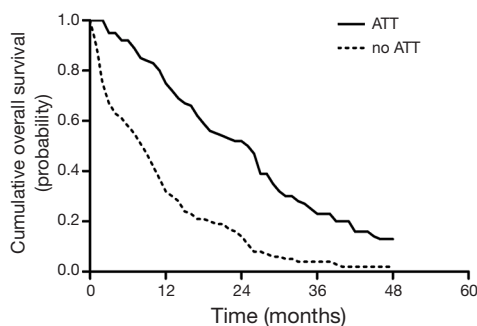


Figure 3 Pooled survival curves of synchronous oligometastatic NSCLC patients received aggressive thoracic therapy or not.

metastases was reported in five studies (24,26-29), of which four included only patients with brain-only metastases (24,27-29).

Benefit of ATT for OS

Incorporating ATT into the treatment of patients with synchronous oligometastatic NSCLC was statistically significantly associated with a 52% reduction in the risk of death (HR, 0.48; 95% CI, 0.39–0.60; $P < 0.00001$; *Figure 2*). No significant statistical heterogeneity was noted for this outcome ($I^2 = 0\%$, $P = 0.65$). No test for funnel plot asymmetry was used, because the power of the tests was too low to distinguish chance from real asymmetry when there were only seven studies included in this meta-analysis (30).

Data for successive monthly pooled estimates of survival

were available from 5 studies (23,24,26-28), consisting of 429 patients, and of whom 155 patients received ATT. The pooled survival curves of OS were displayed graphically as *Figure 3*. The pooled cumulative survival rates for patients received ATT were 74.9% (95% CI, 62.7–87.1%) at 1 year, 52.1% (95% CI, 40.3–64.0%) at 2 years, 23.0% (95% CI, 10.6–35.5%) at 3 years, and 12.6% (95% CI, 3.6–21.6%) at 4 years. The corresponding pooled OS for patients who did not receive ATT were 32.3% (95% CI, 20.8–43.7%), 13.7% (95% CI, 6.7–20.7%), 3.7% (95% CI, 0–8.0%), and 2.0% (95% CI, 0–4.7%), respectively. The 1-, 2-, 3-year cumulative survival rate differences between ATT group and no-ATT group were statistically significant.

Subgroup analyses

In the subgroup with single organ metastases (data of 407 patients was available), the pooled HR for OS was 0.42 (95% CI, 0.31–0.56; $P < 0.00001$; *Figure 4A*). Among the brain-only metastases subgroup, the pooled HR for OS in patients presenting solitary brain metastasis ($n = 108$) was 0.49 (95% CI, 0.31–0.75) compared with a HR of 0.44 (95% CI, 0.26–0.73) in patients presenting 2–4 brain metastases ($n = 33$) (*Figure 4B*). Furthermore, the HR for OS was 0.38 (95% CI, 0.20–0.73; $P = 0.004$) and 0.32 (95% CI, 0.13–0.80; $P = 0.01$) in patients with thoracic stage I–II disease (data of 96 patients was available) and patients with thoracic stage III disease (data of 47 patients was available), respectively (*Figure 4C*).

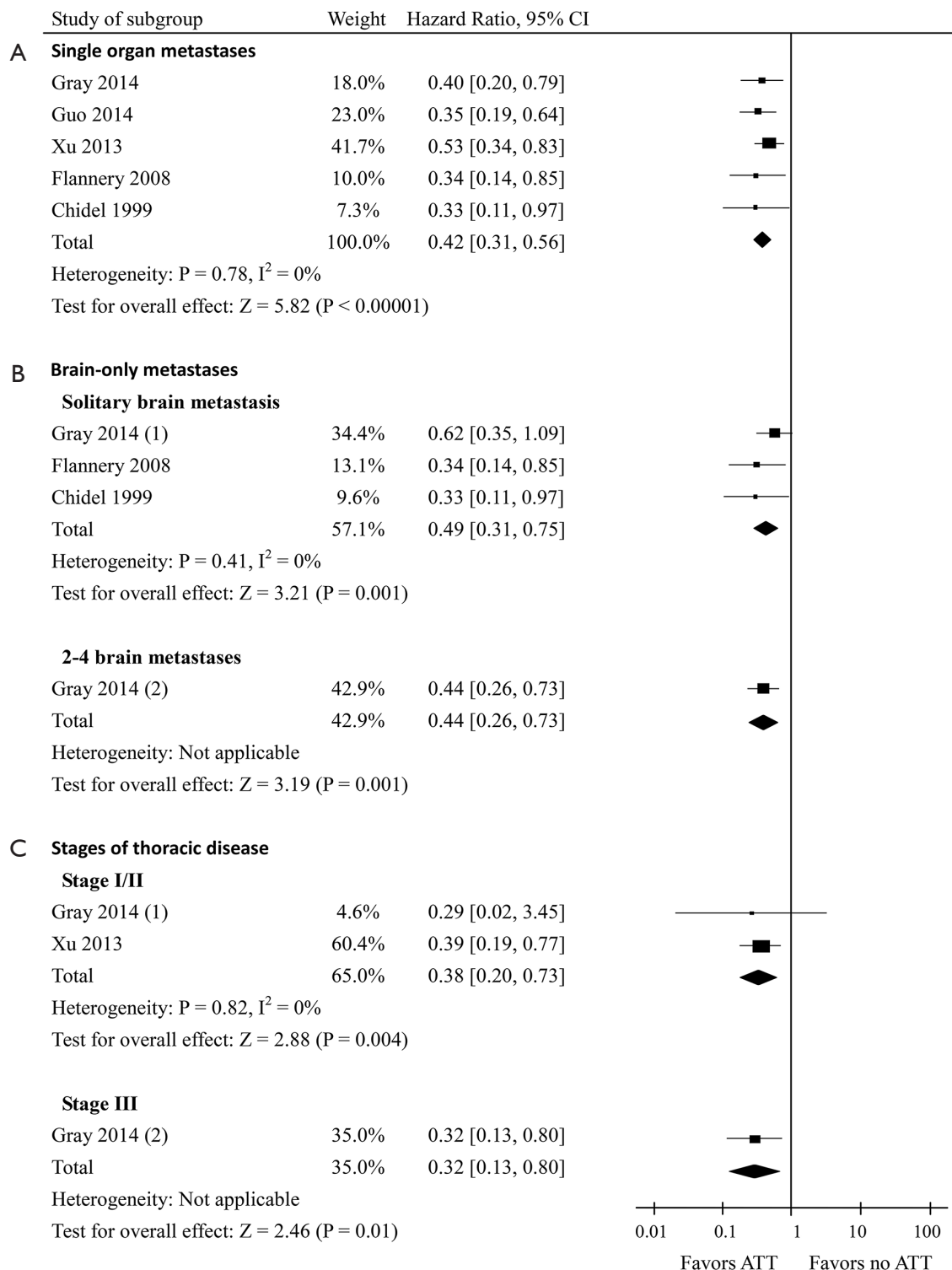


Figure 4 Forest plot of the effect of receiving aggressive thoracic therapy or not on overall survival in subgroups of patients according to (A) numbers of metastatic organ, (B) numbers of brain-only metastases, and (C) stages of thoracic disease.

Discussion

To our knowledge, this is the first meta-analysis to explore the survival benefit of ATT in synchronous oligometastatic NSCLC patients. Using data from 7 retrospective cohort studies including 668 synchronous oligometastatic NSCLC patients, we demonstrated that treatment with ATT is associated with a 52% overall reduction in the risk of death. Pooled 1-, 2-, 3- and 4-year survival for those receiving ATT were 74.9%, 52.1%, 23.0%, and 12.6% respectively *vs.* 32.3%, 13.7%, 3.7%, and 2.0% for those receiving no-ATT.

The definition of oligometastatic state is not uniform and studies included patients with limited number of metastatic foci, varying from 1 to 5. In the other hand, patients with innumerable metastatic lesions and then responded well enough to have a more finite number of lesions after systemic therapy- with no limitation to any duration of disease control will be considered to be with oligometastatic foci as well, leading the term “limited” to be vague (31). In all, we included studies on NSCLC patients with 1 to 5 synchronous metastases at first presentation without treatment.

Brain metastases occur in 30–50% of NSCLC patients and generally have a poor prognosis (32,33). For synchronous brain metastases, a recent study showed that patients with multiple metastases who received ATT had significantly improved survival *vs.* no-ATT, and this trend also was observed in those with a solitary metastasis (24). However, recent European guidelines did not recommend ATT for patients with more than one brain metastasis (34). In our subgroup analysis, aggressive management of thoracic disease improves the survival in NSCLC patients either with solitary brain metastasis or with 2-4 brain metastases. Our subgroup analysis also showed that single organ oligometastatic patients with ATT had a better OS. Due to the lack of survival data detailed by other metastatic organs in present studies, any firm conclusion cannot be drawn yet.

Although the OS benefit from ATT was verified in patients with synchronous oligometastatic NSCLC, it is still unclear who of these patients may benefit more from ATT. Factors affecting survival of synchronous oligometastatic NSCLC patients, such as performance status, N-stage, and thoracic stage, have been revealed in some reports (35-37). However, no study investigated factors predictive of survival specially for patients with ATT. In this meta-analysis, we performed stratified analysis according to intrathoracic disease stage, and concluded that patients of all thoracic stages could benefit from ATT.

It's been reported that primary or metastatic tumors

within lung or liver treated to a nominal dose of 54 Gy or greater had a 3-year actuarial local control rate of 89.3% compared with 59.0% and 8.1% for those treated to 36–53.9 Gy and less than 36 Gy (38), which indicated that radiotherapy dose-dependently improved the local control of primary or metastatic tumors. Guerra *et al.* recently found that receipt of at least 63 Gy to the primary tumor could be delivered safely and was an independent prognostic predictor of favorable outcomes in patients with oligometastatic NSCLC at diagnosis (39). These results implied that improved local control achieved by radiotherapy could be transformed into long-term survival benefit. However, in the included studies, ATT was achieved with radiotherapy only to a dose of more than 40 Gy, which might result in an underestimation of the actuarial survival benefit from ATT. What is more, no study evaluates the association between different therapeutic approaches used in ATT with OS, such as surgery *vs.* radiotherapy.

The gold-standard for synthesising survival data from clinical trials is to obtain IPD from each study (40). However, IPD was not available in our study and we pooled survival curves basing on estimated data alternatively. The pooled survival curves also suggested an OS benefit from ATT over no-ATT in patients with synchronous oligometastatic NSCLC. Limitations of this method were still existed, such as omitted losses to follow-up, a flat tail in the survival curve (20) and so on.

Recently, a phase 2 randomized study found that local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone (41). This study support our findings at some degree, however, we focus aggressive therapy particularly to the primary tumor and patients without treatment before. In general, randomized controlled trials are still warranted to further support our findings.

There are several limitations of the present meta-analysis. First, all the 7 included studies were retrospective cohort studies and there was no randomized controlled trial or prospective cohort study. Second, patients included in our study were selected and especially contains a significantly higher proportion of patients with single brain metastases than is seen in actual clinical practice. Third, being limited by language, we only included studies published in English, and 5 potentially eligible studies were excluded because of language, 2 in German, 2 in Japanese, and 1 in Italian. Additionally, given EGFR and ALK mutation status

unknown for the bulk of the included patients in our study, it remains unclear whether there would be a similar finding in the setting of EGFR or ALK TKIs, such as gefitinib, erlotinib or afatinib, as systemic therapy.

Conclusions

The meta-analysis indicated that ATT may improve OS in patients with synchronous oligometastatic NSCLC. The relative OS benefits of ATT were also seen in patients with brain metastases and patients of all thoracic stages. These findings have important implications for clinical trial design and intervention, however, randomized controlled trials are still warranted to further support our results. Moreover, we suggest further studies to optimize treatment regimen of ATT, and to identify clinical or molecular predictors for the selection of patients who will benefit more from ATT.

Acknowledgements

Funding: This study was funded by National Natural Science Foundation of China (81572279, 81001047), University Excellent Young Teachers Program of Guangdong Province (Yq2013040), Natural Science Foundation of Guangdong Province (2015A030313253), and Pearl River Nova Program of Guangzhou City (2014J2200031).

Footnote

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

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Cite this article as: Li D, Zhu X, Wang H, Qiu M, Li N. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis. *J Thorac Dis* 2017;9(2):310-317. doi: 10.21037/jtd.2017.02.21