RESEARCH ARTICLE

A Systematic Review of Risk Factors for Brain Metastases and Value of Prophylactic Cranial Irradiation in Non-Small Cell Lung Cancer

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Abstract

Background: The incidence of brain metastases (BM) varies in patients with non-small cell lung cancer (NSCLC), calls into question the value of prophylactic cranial irradiation (PCI). It is possible that clinicopathologic characteristics are associated with the development of BM, but these have yet to be identified in detail. Thus, we conducted the present meta-analysis on risk factors for BM and the value of PCI in patients with NSCLC. Methods: Eligible data were extracted and the risk factors for BM and the value of PCI in patients with NSCLC were analyzed by calculating the pooled odds ratio (OR). Heterogeneity was detected using Q and I-squared statistics, and publication bias was tested by funnel plots and Egger's test. Results: Six randomized controlled trials with a focus on the value of PCI and 13 eligible studies with a focus on risk factors for BM were included. PCI significantly reduced the incidence of BM in patients with NSCLC (p=0.000, pooled OR=0.34, 95% confidence interval = 0.37-0.59). Compared with non-squamous cell carcinoma, squamous cell carcinoma was associated with a low incidence of BM in patients with NSCLC (p=0.000, pooled OR=0.47, 95% confidence interval =0.34-0.65). The funnel plot and Egger's test suggested that there was no publication bias in the current meta-analysis. Conclusions: This meta-analysis provides statistical evidence that compared with non-squamous cell carcinoma, squamous cell carcinoma can be used as a predictor for BM in patients with NSCLC, and PCI might reduce the incidence of BM in patients with NSCLC, but does not provide a survival benefit.

Keywords: Meta-analysis - risk factors - brain metastases - prophylactic cranial irradiation - NSCLC

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide. Eighty-five percent of lung cancer patients are diagnosed yearly with non-small cell lung cancer (NSCLC). The central nervous system (CNS) is a frequent site for metastasis in patients with NSCLC. The reported incidence of brain metastases (BM) in patients with NSCLC is 21-54% (Albain et al., 1995; Andre et al., 2001; Chen et al., 2007), and the incidence of BM will be higher as the overall survival (OS) increases.

BM not only leads to the disorder of neurocognitive function (NCF) and the loss of quality of life (QOL), but BM are also the most important factor influencing patient survival. For patients with BM, whole brain irradiation is the most important treatment measure, but whole brain irradiation can only achieve a palliative therapeutic effect. For these patients, even with the most effective therapy, the median survival of patients diagnosed with BM from NSCLC is < 1 year (Patchell et al., 1990; Vecht et al., 1993; Gaspar et al., 1997). Thus, many scholars have proposed prophylactic cranial irradiation (PCI) for patients with lung cancer and conducted a large number of clinical studies. Currently, PCI can significantly improve both OS and disease-free survival in patients with limited stage small cell lung cancer (SCLC) with complete remission or stable disease after multimodality treatment (Aupérin et al., 1999); and it has thus become the standard treatment for patients with SCLC.

For patients with NSCLC, which includes all pathologic types of lung cancer except SCLC, significant differences exist with respect to clinical characteristics and biological behavior, and so the incidence of BM also differs greatly between patients. In the last 30 years, age, clinical stage, gender, and initial treatment are some of the reported BM development-related factors in patients with NSCLC. However, due to the differences in findings, researchers have not always agreed on which factors influence the development of BM. At the same time, the value of PCI in the prevention of BM from NSCLC has

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also been studied in many randomized clinical trials. But due to slow accrual, there have not been a sufficient number of patients in these trials, so the conclusions lack persuasion and the value of PCI is in doubt.

So in this study, we have conducted a systematic review of risk factors for BM in patients with NSCLC and the value of PCI to better characterize BM development-related factors and to obtain a large data set from which to determine the influence of PCI on the incidence of BM and OS of patients with NSCLC. We anticipate that our study can identify BM patterns in patients with NSCLC and provide some clinical guidelines for use of PCI.

Materials and Methods

Literature Collection and Search Strategy

The electronic databases, PUBMED, MEDLINE, EMBASE, and LILACS, along with manual searching of journals, relevant books, and review articles were used to identify potentially eligible studies. The literature for the study was limited to publications between 1 January 1978 and 30 June 2013.

While studying risk factors for BM, the terms retrieved in databases were as follows: (non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC) and (brain metastasis OR brain OR metastasis) and (factor OR risk factor OR influential factor). At same time, the following risk factors were also retrieved to avoid exclusion of some studies: smoking; serum carcinoembryonic antigen (CEA) level; gender; stage; histologic findings; age; Eastern Cooperative Oncology Group performance status (ECOG PS); and response to treatment. No additional restrictions were adopted to achieve an overall inclusion. Using the above search strategy, two reviewers examined the titles and abstracts of all relevant literature to screen the articles in accordance with our study, then the full text articles were procured and screened separately to determine whether or not the articles met the following inclusion criteria.

While studying the value of PCI, the terms retrieved in databases were as follows, then a similar strategy as above was applied: (non-small cell lung cancer OR non-small cell lung carcinoma OR NSCLC) and (brain metastasis OR brain OR metastasis) and (prophylactic cranial irradiation OR PCI).

During the literature search, we also contacted some authors when essential data were not reported in the original papers. Disagreements were resolved with the consensus of a third reviewer.

Inclusion and Exclusion Criteria

The studies included in the meta-analysis had to meet all of the following criteria: (1) published openly in English; (2) patients had to be confirmed with NSCLC by histology or cytology and were treated with radical intent, and there is no radiologic evidence of BM when patients were enrolled in the study; (3) while analyzing risk factors for BM, studies may be prospective or retrospective and the sample size > 100, and intervention factors include smoking, serum CEA level, gender, stage, histologic findings, age, ECOG PS, response to treatment, and outcome event is BM or no BM; (4) while analyzing the value of PCI, only clinical randomized controlled trials (RCTs) were eligible, and intervention measure is PCI or no PCI, and outcome event is the incidence of BM and OS or median survival (MS); (5) duration of follow-up must be long enough and outcome event must be observed; and (6) all studies must provide data on the risk estimates (odds ratio [OR]/hazard ratio [HR]/relative risk [RR]) and the 95% confidential intervals (95% CI) or data that could be used to calculate the OR/HR/RR and 95% CI.

Clinical trials were excluded if the studies did not meet the above criteria. In addition, studies were also excluded, as follows: (1) duplicated publications or literature conducted in the same population; (2) non-original research (e.g., review article and letter to the editor); and (3) results of multivariate analysis while analyzing risk factors for BM.

Quality Assessment

Two reviewers critically assessed the quality of all eligible studies, as follows: (1) basic information of the enrolled patients, including population and ethnicity; (2) information of the disease status of the samples, disease course, and follow-up was detailed; (3) report of study design was provided; (4) duration of follow-up was sufficient; and (5) report of outcome investigation was also included. Otherwise, the studies were removed to ensure the quality of the meta-analysis. Any disagreement between the two reviewers was resolved by third reviewer consensus.

Data Extraction

The data were extracted from identified publications according to standard protocol by two reviewers. The following information from each study was recorded for the meta-analysis: (1) first author's name and year of publication; (2) sample size and number of cases and controls (cases and cohort); (3) stage of included patients; (4) while analyzing risk factors for BM, extracting intervention factors, such as smoking, serum CEA level, gender, stage, histologic findings, age, ECOG PS, response to treatment, and number of BM in different groups or OR and 95% CI; (5) while analyzing the value of PCI, extracting the number of dropouts or withdrawals or exclusions, dose of PCI, primary treatment modality, number of BM in the PCI and no PCI groups during follow-up, and OS and MS as well as P values from original data or data mining.

Statistical Methods

While analyzing risk factors for BM, ORs and 95% CIs were used to estimate the effect of each study. For each study, the OR was estimated depending on the results provided in a previous publication, and the most accurate method was conducted based on the directly reported OR of the original study. If the OR was not available directly, the total number of BM and the number of patients at risk in each group was used to calculate the OR. Then, according to different influencing factors we pooled the estimated effects of studies by using the standard inverse variance weighting method and each study was weighed

Table 1. Main Characteristics of the Studies Included on Risk Factors for BM

Study	Num.	Stage	Smoking OR	ECOG PS	CEA level OR	Gender OR	Stage OR	Histology OR	Age OR	Response to Treat. OR
Ceresoli et al(2002)	112	IIB-IIIA /IIIB					1.16 (0.47, 2.87)	0.45* (0.18, 1.11)	0.22 (0.07, 0.71)	1.15 (0.41, 3.22)
Keith et al(2002)	119	I-IIIA /IIIB		1.14 (0.36, 3.56)		0.22 (0.07, 0.74)	1.00 (0.32, 3.15)	0.40* (0.10, 1.56)	0.31 (0.10, 1.02)	1.42 (0.46, 4.37)
Robnett et al(2001)	150	IIIA/IIIB					0.76 (0.35, 1.64)	0.71* (0.31, 1.62)		
Bajard et al(2004)	305	I-II/III		0.50 (0.20, 1.25)		0.51 (0.22, 1.17)	0.33 (0.19, 0.57)	0.31* (0.18, 0.53)	0.30 (0.17, 0.52)	1.72 (0.87, 3.42)
Petrović et al(2011)	107	IIIA				0.90 (0.41-1.94)		0.66* (0.30-1.43)	2.03 (0.89-4.59)	
Mamon et al(2005)	177	IIIA					NS	0.59* (0.30-1.17)		
Horinouchi et al(2012)	116	III,	0.43 (0.23–0.79)	0.98 (0.53–1.83)	2.17 (1.17–3.99)	0.50 (0.27–0.93)	1.03 (0.57–1.87)		0.65 (0.34–1.21)	
Wang et al(2009)	223	IIIA/IIIB					1.05 (0.51-2.19)	0.50* (0.27-0.93)		
Lee et al(2012)	227	III-IV			4.49 (2.18, 9.25)	0.88 (0.49, 1.58)		1.98** (1.01, 3.88)	1.80 (1.01, 3.21)	
Ding et al(2012)	217	IIIA	0.61 (0.34, 1.08)			0.50 (0.27, 0.92)		0.17* (0.08, 0.35)	0.57 (0.32, 1.03)	
Arrieta et al(2009)	293	III-IV	0.66 (0.40-1.08)		5.03 (2.80-9.03)	1.09 (0.66-1.79)		1.10** (0.65-1.85)	0.51 (0.30-0.85)	
Hubbs et al(2010)	975	I/II				1.46 (0.85, 2.52)	0.29 (0.17, 0.51)	1.14**(0.68, 1.93)or 0.77*(0.44, 1.34)		
Dimitropoulos et al(2011)	161	I-IV				0.83 (0.35-3.67)	NS	0.61** (0.28-1.33)		

*squamous cell carcinoma vs. non-squamous cell carcinoma; **adenocarcinoma vs. non-adenocarcinoma; OR, odds ratio; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; NS, no significance

Table 2. Main Characteristics of the Studies Included on Value of PCI

Study	PCI Dose	Primary Treatment	No. of Participants/ Dropout or Exclude or Withdrawal	Stage	Brain Metastases			Overall Survival	Median Survival
					NO PCI	PCI	*P* Value	(NO PCI vs. PCI)	(NO PCI vs. PCI)
Umsawasdi et al (1984)	30Gy/10fraction	Chemo/RT or Chemo/RT/S	100/3	Advanced	14/51	2/46	0.002	23.5% vs. 22% 3year NS)	NR
Cox et al (1981)	20Gy/10fraction	RT only	410/129	Not given	16/145	7/136	0.038	NR	41.4w* vs. 35.4 w* (P=0.5)
Russell et al (1991)	30Gy/10fraction	RT only	187/0	Advanced	18/94	8/93	0.1	13% vs. 21% (2 years p=0.36)	8.1m** vs. 8.4m** (P=0.36)
Miller et al (1998)	37.5 Gy/15fraction 30Gy/15fraction	Chemo/RT or RT/Chemo	254/28	III	12/111	1/115	0.003	NR	11m** vs. 8m** (p=0.004)
Pöttgen et al (2007)	30Gy/15fraction	Trimodality	106/0	IIIA	9/63	4/43	0.01	18% vs. 16% (5 years P=0.15)	NR
Gore et al (2011)	30Gy/15fraction	Trimodality	356/16	III	36/177	15/163	0.004	76.9% vs. 75.6% (1 year p=0.86)	24.8m** vs. 25.8m** (P=0.86)

*week; **month; PCI, prophylactic cranial irradiation; Chemo, chemotherapy; RT, radiotherapy; S, surgery; NS, no significance; NR, no report

under the inverse square of the logarithm OR. The Z statistic was used to test the pooled effects of studies. Before pooling ORs, the Q statistic was performed to test the heterogeneity and the I-squared value was used to assess the size of heterogeneity among the studies included in meta-analysis. I-squared values ≥50% indicate large heterogeneity among studies, whereas values between 25% and 50% indicate moderate heterogeneity. A P value <0.05 and an I-squared value ≥ 50% were considered statistically significant. The fixed- or random-effects models were used to pool the effect size based on the Mantel–Haenszel and DerSimonian-Laird methods, respectively. These two models provide similar results when between-studies heterogeneity is absent; otherwise, a random-effects model is more appropriate. Funnel plots and Egger's test (linear regression analysis) were used to evaluate publication bias. All of the P values were two-sided. The meta-analysis was carried out using the Stata 12.0 statistical software program (Stata Corp, College Station, TX, USA). Statistically significant differences were considered at a $p<0.05$.

While analyzing the value of PCI, similar statistical methods as above were applied. If the effects of studies could not be pooled, descriptive statistical methods were used to evaluate the results of studies.

Results

Characteristics of the Included Studies

According to the above search strategy, inclusion and exclusion criteria, we selected 13 eligible studies involving risk factors for BM; a total of 3182 patients were enrolled in these studies. Among the studies, four (Wang et al., 2009; Horinouchi et al., 2012; Ding et al., 2012; Lee et al., 2012) recruited participants from Asia, four (Robnett et al., 2001; Mamon et al., 2005; Arrieta et al., 2009; Hubbs et al., 2010) recruited participants from North America, and five (Ceresoli et al., 2002; Keith et al., 2002; Bajard et al., 2004; Petrović et al., 2011; Dimitropoulos et al., 2011) recruited participants from Europe. In addition, 11 studies involved retrospective analyses and 2 studies (Arrieta et al., 2009; Dimitropoulos et al., 2011) involved prospective analyses. With the exception of one study (Horinouchi et al., 2012) that only included adenocarcinoma patients, the

Table 3. Results of Meta-analysis on Different Influential Factors for BM

Risk Factors	I-squared	OR (95%CI)	Z Value	*P* Value
Gender (male vs. female)	61.40%	0.87 (0.60,1.26)	0.75	0.456
Age (old vs. young)	82.10%	0.69 (0.39,1.22)	1.28	0.202
Histology (squamous vs. non-squamous cell carcinoma)	46.00%	0.47 (0.37,0.59)	6.31	0.000
Histology (adenocarcinoma vs. non-adenocarcinoma)	40.90%	1.15 (0.85,1.55)	0.89	0.372

OR, odds ratio; CI, confidential intervals

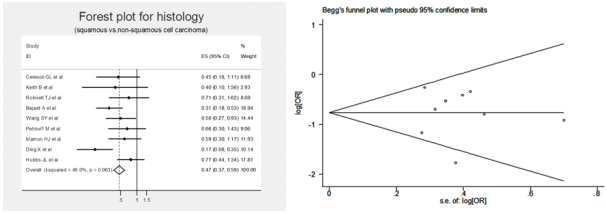

Figure 1. A: Forest Plot of the Association between Histology (Squamous vs. Non-squamous Cell Carcinoma) and Brain Metastases in Non-small-cell Lung Cancer (NSCLC) from Eligible Studies. B: Funnel Plots of Studies Evaluating Publication Bias of Overall Analysis (*p*=0.917)

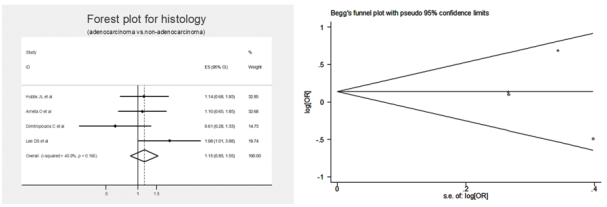

Figure 2. A: Forest Plot of the Association between Histology (Adenocarcinoma vs. Non-adenocarcinoma) and Brain Metastases in Non-small-cell Lung Cancer (NSCLC) from Eligible Studies. B: Funnel Plots of Studies Evaluating Publication Bias of Overall Analysis (*p*=0.734)

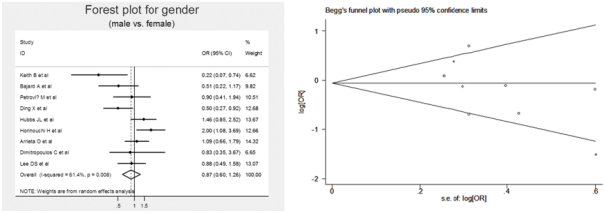

Figure 3. A: Forest Plot of the Association between Gender (Male vs. Female) and Brain Metastases in Non-small-cell Lung Cancer (NSCLC) from Eligible Studies. B: Funnel Plots of Studies Evaluating Publication Bias of Overall Analysis (*p*=0.175)

other studies investigated patients, including all pathologic types of NSCLC. The principal individual characteristics of these different trials and effect values (OR and 95%CI) are listed in Table 1.

While analyzing the value of PCI, previous systematic reviews (Lester et al., 2005; Gore, 2006) identified four RCTs (Cox et al., 1981; Umsawasdi et al., 1984; Russell et al., 1991; Miller et al., 1998) comparing PCI with no PCI in NSCLC patients treated with curative intent. In addition to these four RCTs, we included two other RCTs (Pöttgen et al., 2007; Gore et al., 2011) recently conducted according to the above search strategy. Among these 6 RCTs, 1237 patients were recruited and exceeded the target number of patients (1058) in the Gore et al. study (Gore et al., 2011), which was terminated early due to slow accrual. The principal individual characteristics of these six RCTs and the observability index are listed in Table 2.

Systematic Review of Risk Factors for BM

Among 13 eligible studies of risk factors for BM, 3 reported the influence of CEA levels and response to primary treatment for BM, but the results were not statistically significant. As the cut-off values for the CEA levels and primary treatment modalities were different in each study, the clinical heterogeneity between these studies was evident. Therefore, meta-analysis of the data was inappropriate. Similarly, among the 13 eligible studies, there were also three studies which reported the effects of smoking, although the results of these studies tended to show smoking to be a protection factor; no statistical significance was demonstrated. Because of the clinical heterogeneity in study design and small number of studies, a meta-analysis of the data was not performed. In addition, the effect of ECOG PS was also reported in three studies, but the results lacked consistency and statistical significance; and for the same reasons as above, a meta-analysis of the data was not attempted.

In contrast, among 13 eligible studies, there were more studies analyzing the effects of gender, age, and histologic findings on BM. Because the clinical heterogeneity was small, a meta-analysis for the effects of these factors was conducted. While analyzing the effects of histologic findings on BM, there were nine studies comparing squamous cell carcinoma with non-squamous cell carcinoma and four studies comparing adenocarcinoma with non-adenocarcinoma. Before the meta-analysis, statistical heterogeneity between the studies was tested, and the results showed the statistical heterogeneity was moderate, thus a fixed effects model was used to pool the effect size. The results of the meta-analysis showed that squamous cell carcinoma compared with non-squamous cell carcinoma was a significant protective factor (listed in Table 3 and Figure 1A) and adenocarcinoma compared with non-adenocarcinoma did not produce any influence for BM (listed in Table 3 and Figure 2A). While analyzing the effects of gender and age on BM, the results of the heterogeneity test showed significant statistical heterogeneity (I^2>50%), thus a random effects model was used to pool the effect size. The results of the meta-analysis showed the effects of gender and age on BM were limited (listed in Table 3 and Figure 3A-4A).

Finally, while analyzing the effect of stage on BM, there were seven studies providing detailed data. Among the seven studies, the participants were I-II NSCLC in the

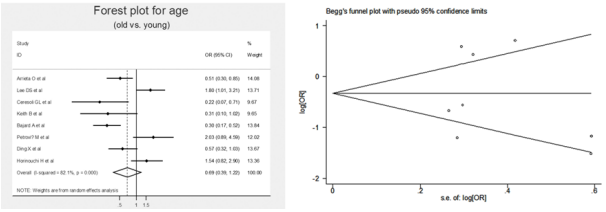

Figure 4. A: Forest Plot of the Association between Age (old vs. young) and Brain Metastases in Non-small-cell Lung Cancer (NSCLC) from Eligible Studies. B: Funnel Plots of Studies Evaluating Publication Bias of Overall Analysis (*p*=1.000)

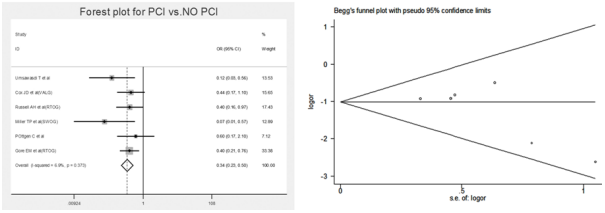

Figure 5. A: Forest Plot of the Association between PCI (PCI vs. NO PCI) and Brain Metastases in Non-Small-Cell Lung Cancer (NSCLC) from Eligible Studies. B: Funnel Plots of Studies Evaluating Publication Bias of Overall Analysis (*p*=0.452)

Hubbs et al. study (Hubbs et al., 2010) and I-III NSCLC in the Bajard et al. study (Bajard et al., 2004); in the remaining five studies the participants were advanced or late stage NSCLC. Thus far, the Hubbs et al. and Bajard et al. studies were two large sample and representative studies on early stage NSCLC, and the results both showed early stage was a significant protective factor for BM. In contrast, the results of five other studies showed no influence of stage on BM. At the same time, clinical heterogeneity in patient selection and stage design invalidated a meta-analysis.

PCI Influence on the Incidence of BM in NSCLC

Among six RCTs involving the value of PCI, five studies (Cox et al., 1981; Umsawasdi et al., 1984; Miller et al., 1998; Pöttgen et al., 2007; Gore et al., 2011) reported that PCI might reduce the incidence of BM; only one study (Russell et al., 1991) showed that PCI had no influence on the incidence of BM in NSCLC. Although there was some clinical heterogeneity in the PCI dose, primary treatment and stage between the six RCTs, statistical heterogeneity was almost absent (I^2=6.9%, p=0.373). Thus, we attempted to pool the effect size of these studies with a fixed effect model. The results of this meta-analysis showed that PCI significantly reduced the incidence of BM in NSCLC (p=0.000, the pooled OR=0.34 and 95% CI=0.23-0.50, Figure 5A).

PCI Influence for Survival in NSCLC

Among all six RCTs involving the value of PCI, the majority studies lacked detailed data on OS and median survival. Even if some studies reported survival results, as the difference of observed end points between studies, the results could not be compared and pooled. Based on existing results, there were significant changes in survival, but except for the results of Miller et al. study (Miller et al., 1998), none of the others showed any influence of PCI for survival in NSCLC.

Evaluation of Publication Bias

To identify the reliability of our results in the meta-analysis, funnel plots and Egger's test (linear regression analysis) were used to evaluate publication bias. The results showed there was no significant publication bias existing in the studies included in the meta-analysis (as showed in Figure 1B-5B).

Discussion

BM frequently occurs in patients with NSCLC, but the incidence of BM varies (Albain et al., 1995; Andre et al., 2001; Chen et al., 2007) as a function of the heterogeneity between NSCLC patients. A number of clinicopathologic characteristics are regarded to be associated with the incidence of BM, and many scholars have conducted research on this issue within the last 30 years, but to date, we have not identified which clinicopathologic characteristics influence the development of BM. Moreover, there is uncertainty regarding the clinical value of PCI in patients with NSCLC. Thus, we conducted this systematic review and expect our study can identify the pattern of BM and our conclusions can provide some clinical guidelines for PCI in patients with NSCLC.

Systematic Review of Risk Factors for BM: In this study, we systematically analyzed the association between the risk factors for BM and the incidence of BM in NSCLC. The results of our meta-analysis showed that squamous cell carcinoma was significantly associated with a low incidence of BM in patients with NSCLC compared with non-squamous cell carcinoma, but adenocarcinoma was not associated with the incidence of BM compared with non-adenocarcinoma. Because good homogeneity existed between studies and the samples were sufficiently large, this conclusion can be regarded as a clinical guideline. The above difference is accounted for by the fact that non-adenocarcinoma includes all other types of NSCLC, such as large cell carcinoma, which has a high incidence of BM; and if we sort it into non-adenocarcinomas, the difference in incidence of BM between adenocarcinoma and non-adenocarcinoma will be masked. Similarly, our study also pooled respectively the effects of gender and age for BM, and the results showed that neither was associated with the development of BM in NSCLC. Thus, we could not use gender or age as a mark to predict the development of BM.

In addition, the effects of some other factors, such as smoking, serum CEA level, stage, ECOG PS, and response to treatment were also reviewed systematically in this study. Based on the clinical heterogeneity of study designs and small number of included studies, a meta-analysis of the data was therefore inappropriate and only a descriptive analysis was performed. Although there was no evidence to support the factors associated with the development of BM in NSCLC, based on the data of the included studies, we were still able to draw

some valid conclusions. For example, even though there were only three studies reporting the effect of the CEA level, the results all suggested that a high CEA level is associated with a high incidence of BM. Among the three studies, two multivariate analyses (Arrieta et al., 2009; Horinouchi et al., 2012) also supported this conclusion. Thus, we conclude that the CEA level might be used to predict BM, but the cut-off value of the CEA level to predict development of BM requires further study. Another example is the influence of stage on BM. Among the included studies, two representative studies (Bajard et al., 2004; Hubbs et al., 2010) showed early stage NSCLC to be associated with a low incidence of BM. With the long duration of follow-up and the sufficient sample sizes in these two studies, their conclusions might serve as a guideline for clinical practice.

Finally, among eligible studies regarding risk factors for BM, individual studies reported the effects of treatment modalities, chemotherapy regimens, mediastinal lymph node status, weight loss during treatment, tumor size, and serum lactate dehydrogenase (LDH) level. As these reported results were not representative and could not serve as a clinical guideline, we did not analyze these conclusions in our study.

Systematic Review regarding the Value of PCI: Regarding the value of PCI, several meta-analyses (Lester et al., 2005; Gore, 2006) have been conducted previously, but these meta-analyses were descriptive and never achieved an agreement on the value of PCI. Thus, the Radiation Therapy Oncology Group (RTOG), with cooperation from other US and Canadian cooperative groups, sponsored a study (RTOG0214) on PCI (Gore et al., 2011) in 2002 for patients with NSCLC after locoregional and systemic treatment, and aimed to evaluate the impact of PCI on OS, the incidence of BM, and disease-free survival. The study aimed to recruit 1058 patients randomized to PCI or observation. Due to slow accrual, only 356 patients were recruited and the trial was terminated early on 30 August 2007. Although RTOG 0214 did not recruit the target number of cases and the significance of the conclusions were diminished, it is still the most recent study with a strict design, comparatively large sample size, and definitely observed end points and detailed reported results that currently can really represent the value of PCI. Thus, in this study we updated eligible RCTs on the basis of the previous meta-analysis, we included RTOG 0214 and another study from Germany (Pöttgen et al., 2007), in which we considered PCI to be randomly allocated as the randomization was between two local therapy options (arms A and B). Thus, our study included all RCTs in the most recent 30 years and the sample size reached 1237, which was more than that of the targeted sample size in RTOG 0214 (n=1058), so our conclusions would have much greater value for clinical application.

While we pooled the effect of PCI on the incidence of BM, some studies with different periods had differences in study design (although there was some clinical heterogeneity between these studies, the statistical heterogeneity was nearly absent), but almost all studies, except the Russell et al. study (Russell et al., 1991) reported PCI might reduce the incidence of BM in NSCLC. The results of our meta-analysis finally confirmed this conclusion. So at present, we can reach an agreement that PCI can reduce the incidence of BM in patients with NSCLC.

Regarding the impact of PCI on survival, in the eligible six RCTs, some studies did not report survival-related data or the observed end point was different and the data was not pooled. In analyzing the existing survival-related data, none of the studies showed that PCI had any significant impact on the OS of NSCLC patients. Thus, we considered PCI might reduce the incidence of BM in patients with NSCLC, but could not provide any survival benefit.

However, several limitations of our meta-analysis should be pointed out. First, as it was difficult to obtain detailed data and uniform risk estimate index, the results of multivariate analysis of risk factors for BM were excluded in this study, but these results may have had a greater persuasion in clinical practice. Second, most eligible studies of risk factors for BM were retrospective, prospective and multicentric studies were lacking, which made the strength of the evidence less. Third, during the targeted therapy era, targeted drugs, such as gefitinib and erlotinib, can effectively reduce the incidence of BM in patients with NSCLC (Ceresoli et al., 2004; Pan et al., 2007; Zhao et al., 2012 ; Zeng et al., 2012), and the value of PCI for reducing the incidence of BM becomes thus uncertain.

In conclusion, this meta-analysis provides statistical evidence supporting an association between squamous cell carcinoma and the low incidence of BM in patients with NSCLC, but gender, age, and adenocarcinoma or non-adenocarcinoma have no relationships with the incidence of BM. Descriptive analysis indicates that a high CEA level is associated with a high incidence of BM and early stage is associated with a low incidence of BM in early-stage NSCLC. Our meta-analysis also confirms that PCI might reduce the incidence of BM in patients with NSCLC, but cannot provide a survival benefit. Some intrinsic biological features might be associated with the incidence of BM and should be studied further.

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