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Risk factors of brain metastasis of lung squamous cell carcinoma: a retrospective analysis of 188 patients from single center

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Abstract

Background: To explore risk factors and the efficacy of treatment strategies for brain metastasis (BM) in squamous cell carcinoma (SCC) of the lung.

Methods: The clinical data of 188 pathologically confirmed as squamous cell carcinoma or adenosquamous carcinoma patients were studied retrospectively. Factors including age (<60 vs. ≥60), gender, stage at diagnosis, T status (T1–2 vs. T3–4), N status (N0–1 vs. N2–3), histology (squamous vs. adenosquamous), smoking history (non-smoker vs. current smoker) and serum tumor markers (normal vs. elevated) were analyzed.

Results: The incidence of BM was 19.1% (36/188) in our cohort. Patients who were female ($p = 0.005$), had advanced disease at diagnosis ($p < 0.001$), had adenosquamous carcinoma histology ($p = 0.033$) or had elevated serum level of CEA at diagnosis ($p < 0.001$) had significantly higher incidence of BM. In multivariate analysis, female ($p = 0.034$, HR = 18.874) and elevated serum level of CEA at diagnosis ($p = 0.009$, HR = 19.824) were independent risk factors of BM. BM patients who received additional systemic therapy after local therapy had significantly longer post-BM survival than those who received local therapy only ($p = 0.004$, HR = 0.058). Gemcitabine/platinum-containing regimen (GP) and taxans/platinum-containing regimen (TP) led to comparable brain-metastasis-free survival (BMFS) ($p = 0.10$).

Conclusions: Females and patients with elevated serum level of CEA at diagnosis had a higher risk of developing BM. The following systemic therapy after local therapy prolonged the survival of BM patient, but the efficacy of GP and TP was comparable in terms of preventing BM.

Keywords: Brain metastasis, Chemotherapy, Non-small cell lung cancer, Risk factor, Squamous cell carcinoma

Background

The brain is one of the most common distant metastasis sites in non-small cell lung cancer (NSCLC). Up to 40% of NSCLC patients develop brain metastasis (BM) during the course of disease [1–4]. BM is associated with a poor quality of life (QOL) and a dismal prognosis; without treatment, the median overall survival (OS) for BM patients is only 4–7 weeks [5–7]. In patients with small cell lung cancer (SCLC), prophylactic cranial irradiation (PCI) is effective in decreasing the incidence of BM and improving OS [8, 9]. PCI has therefore been studied in NSCLC populations. While it decreases the incidence of BM, it does not affect OS [1, 2]. One likely explanation is the heterogeneous risk of BM across pathological subtypes. Most studies of BM in NSCLC suggest that SCC is associated with a lower incidence of BM than adenocarcinoma [10–13]. However, the analysis of BM in SCC is compromised by the inclusion of different histological subtypes in these studies. Furthermore, characteristics other than the incidence of BM in SCC were not examined. There is therefore a need for comprehensive studies specifically addressing the clinical features of BM in SCC.

Local therapies such as whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgical

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resection are the standard of care for patients with BM. However, most patients die from systemic disease rather than intracranial failure. Systemic treatment with novel agents, such as tyrosine kinase inhibitors (TKIs) and pemetrexed, has been shown to be beneficial in patients with BM [14–18]. They could not only shrink the intracranial lesions, but also prolong the survival. But the efficacy was usually seen in patients with non-SCC histology. By far, none agent has previously been studied in SCC with BM. To better characterize the clinical features of BM in SCC and to investigate effective treatment strategy, we conducted a retrospective study that included 188 patients.

Methods

Patients

The clinical data of 188 consecutive patients diagnosed between September 1999 and December 2013 with pathologically confirmed SCC of the lung, were selected from the database and analyzed retrospectively. Before treatment, baseline assessments including blood routine test, biochemical examination, and enhanced-contrast computed tomography (CT) and/or magnetic resonance imaging (MRI) were conducted. The treatment strategy was determined based on the stage at diagnosis. Principally, systemic therapy of platinum-based doublet was recommended post-operatively for patients with operable stage IB to IIIA disease. In fact, it was becoming routine recommendation since 2006, when concrete evidence has been obtained from studies concerning adjuvant chemotherapy. For patients with stage IIIB to IV disease, chemotherapy was recommended. All patients received routine follow-up every 3 to 6 months after the completion of therapy.

Enhanced-contrast MRI was used for BM screening if there was no contraindications. Otherwise, enhanced-contrast CT was considered. At the time of diagnosis, MRI was conducted routinely for all patients. During the time of follow-up, MRI was conducted every 3-6 months. If symptoms of CNS metastasis presented during the follow-up interval, MRI was conducted immediately. Radiation techniques such as SRS was reserved for patients with three or less BM lesions. Otherwise, WBRT would be considered. After the completion of radiotherapy, systemic therapy was recommended routinely. The study protocol was reviewed and approved by the institutional review boards and ethics committees of Beijing Tiantan Hospital affiliated to Capital Medical University. All patients provided informed consent prior to their inclusion in the study according to the Declaration of Helsinki.

EGFR mutation testing

Amplification refractory mutation system (ARMS) was employed to analyze EGFR mutations in paraffin-embedded tissue sections. Briefly, DNA of original tumor tissue, which was obtained from the slides under a dissecting microscope, was isolated with a QIAamp DNA Mini Kit (Qiagen Inc., Valencia, CA, USA). Then, ADx EGFR Mutations Detection Kit (Amoy Diagnostics, Xiamen, China) was employed for EGFR mutations detection. ABI 7500 (Applied Biosystems, Foster City, CA, USA) real-time polymerase chain reaction system was recruited for the assay according to the manufacturer's protocol.

Statistical analysis

IBM SPSS Statistics 19.0 software was used for data analysis. The Kaplan–Meier method was used to estimate survival and the log-rank test was used to detect difference of survival curves. OS was defined as the time from diagnosis to the patients' death of any reason or the last follow-up visit. Brain-metastasis-free survival (BMFS) was defined as the time from diagnosis to the documented BM. Cox regression was employed for multivariate analysis. The incidence of BM between patients with different risk factors was compared using chi-squared test.

Results

Patient characteristics

Patient characteristics were detailed in Table 1. Of the 188 patients enrolled in the study, 86.7% were male and 13.3% were female. The median age at diagnosis was 63 years (range, 32–89 years). At the time of diagnosis, 7.9% of patients had stage I, 12.8% had stage II, 51.1% had stage III and 28.2% had stage IV disease. In terms of histology, 93.1% had SCC and 6.9% had adenosquamous carcinoma. In terms of smoking status, 23.9% were non-smokers, 71.3% were current smokers and the smoking history was unknown for 4.8%. EGFR mutation status was analyzed in 33 patients. Twenty-eight patients had wild-type EGFR, 3 had a mutation at exon 19 and 2 had a mutation at exon 21.

Clinical factors related to BM

Thirty-six patients had documented BM, of which 16 were synchronous and 20 were metachronous (Table 2). Among patients with BM, 24 had one intracranial lesion, 5 had 2–3 lesions, and 7 had >3 lesions. To explore the factors related to the incidence of BM, we analyzed age (<60 vs. ≥60), gender (male vs. female), stage at diagnosis, T status (T1–2 vs. T3–4), N status (N0–1 vs. N2–3), histology (squamous vs. adenosquamous), smoking history (non-smoker vs. current smoker) and serum levels of tumor markers including carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin 19 fragments (Cyfra21-1), and squamous cell carcinoma antigen (SCC). As shown in Table 1, patients who were female (p = 0.002), had advanced disease at diagnosis

Table 1 Patient characteristics

Variables	No.	%	No. of BM	Incidence of BM	*P* value
Median age (years)	63(32-89)		36	19.1	
Age					0.077
< 60	79	42.0	20	25.3	
≥ 60	109	58.0	16	14.7	
Gender					0.002
Male	163	86.7	27	16.6	
Female	25	13.3	9	36.0	
Stage					<0.001
I	15	7.9	1	6.7	
II	24	12.8	1	4.2	
III	96	51.1	12	12.5	
IV	53	28.2	22	41.5	
T status					0.36
T1-2	121	64.4	25	20.6	
T3-4	67	35.6	11	16.4	
N status					0.85
N0-1	65	34.5	13	20.0	
N2-3	123	65.5	23	18.6	
EGFR status					-
Wild-type	28	84.8	5	17.9	
Exon19 mutation	3	9.1	0	0	
Exon 21 mutation	2	6.1	0	0	
Histology					0.033
Squamous cell carcinoma	175	93.1	32	18.3	
Adenosquamous carcinoma	13	6.9	4	30.8	
Smoking history					0.088[a]
Non-smoker	45	23.9	12	26.7	
Current-smoker	134	71.3	23	17.2	
Unknown	9	4.8	1	11.1	
CEA					<0.001
Normal	126	67.1	14	11.1	
Elevated	62	32.9	22	35.5	
NSE		79			1.0
Normal	89	47.3	17	19.1	
Elevated	99	52.7	19	19.2	
Cyfra21-1					0.13
Normal	43	22.8	11	25.5	
Elevated	145	77.2	25	17.2	
SCC		80			0.68
Normal	95	50.5	14	14.7	
Elevated	93	49.5	12	12.9	

Abbreviations: *EGFR* Epidermal growth factor receptor, *BM* Brain metastasis, *CEA* Carcinoembryonic antigen, *NSE* Neuron-specific enolase, *Cyfra21-1* Cytokeratin 19 fragments, *SCC* Squamous cell carcinoma antigen

[a]patients with unknown smoking history were excluded

Table 2 Characteristics of patients with BM

Variables	No.	%
BM		
Synchronous	16	44.4
Metachronous	20	55.6
RPA		
I	8	22.2
II	20	55.6
III	8	22.2
GPA		
0-1	10	27.8
1.5-2.5	17	47.2
3	4	11.1
3.5-4	5	13.9
Number of BM		
1	24	66.7
2-3	5	13.9
> 3	7	19.4
Presence of systemic metastasis at the time of BM		
No	9	25.0
Yes	27	75.0
Treatments after BM		
Local therapy only	15	41.6
Local + systemic therapy	21	58.4
Local therapy		
SRS	27(15)[a]	75.0
WBRT	9(6)	25.0

Abbreviations: *BM* Brain metastasis, *RPA* Recursive partitioning analysis, *GPA* Graded prognostic assessment, *WBRT* Whole brain radiation therapy, *SRS* Stereotactic radiosurgery

[a]Number in the blanket was number of patients receiving additional systemic therapy after local therapy

($p < 0.001$), had adenosquamous carcinoma histology ($p = 0.033$), or elevated serum level of CEA ($p < 0.001$) had a significantly higher incidence of BM. Whilst other factors were not significantly related to the incidence of BM. As BM was not documented in patients with EGFR mutations, the difference in incidence according to EGFR mutation status was not analyzed.

In addition to the incidence of BM, BMFS was employed to evaluate the risk of BM for given patients. For the entire group, the median BMFS was not reached. Single variant analysis demonstrated that female ($p = 0.010$), patients with advanced disease ($p = 0.019$) or elevated serum level of CEA ($p < 0.001$) had significantly shorter median BMFS than their counterparts. However, only females ($p = 0.034$, hazard ratio [HR] = 18.874) and elevated serum level of CEA at diagnosis ($p = 0.009$, HR = 19.824) were proved to be independent risk factors of BM in multivariate analysis.

Survival analysis

In terms of post-BM treatments, 27 received SRS and 9 received WBRT. Sequentially, additional systemic therapy was administrated in 21 patients. The median post-BM survival for patients with BM was 18 months (95% CI 12–23 months). Recursive partitioning analysis (RPA) and graded prognostic assessment (GPA) score are both valuable parameters that were used for prognosis evaluation of BM patients. As it was shown, the median post-BM survival for RPA classes I–III were: 24 months, not reached and 3 months, respectively (Fig. 1). The statistical difference was significant whenever it was calculated in single variant ($p < 0.001$) or multivariate analysis ($p = 0.013$, hazard ratio HR = 23.379). However, the difference of median post-BM survival according to the graded prognostic assessment (GPA) score did not reach significance. Survival analysis also found that, patients who received systemic therapy after the completion of local therapy had a longer post-BM survival than those who received local therapy only (24 months vs. 18 months, $p = 0.084$) (Fig. 2). But the difference was marginal. In multivariate analysis, additional systemic therapy after local therapy was an independent factor that indicated better post-BM survival ($p = 0.004$, hazard ratio HR = 0.058) (Table 3).

Besides, additional analysis was conducted to explore the role of different systemic regimens in BM patients. In patients who received systemic therapy after BM, survival analysis found there was a tendency that patients who received gemcitabine/platinum-containing (GP) regimen ($n = 11$) had longer post-BM survival than those who received taxans/platinum-containing (TP) regimen ($n = 10$) ($p = 0.097$) (Fig. 2). But the difference was not significant. To explore the role of systemic therapy in BM prevention, BMFS was also compared between regimens (patients with synchronous BM were excluded). Altogether, 38 patients received GP, 30 received TP, 16 received both GP and TP, 7 patients received TKIs (EGFR were unknown in 6 patients and mutated at exon 19 in 1 patient.) and 9 patients received other regimens (vinorelbine/platinum, cyclophosphamide/vinblastine/platinum, etoposide/platinum etc.). Survival analysis found that, patients who received both GP and TP before BM had the longest median BMFS than those who received other regimens ($p = 0.013$) (Fig. 3). Further analysis demonstrated that, the median BMFS was different significantly between those treated with both GP and TP and those treated with TP only ($p = 0.009$) or TKIs only ($p = 0.028$), and marginally between those treated with both GP and TP and those treated with GP only ($p = 0.078$). However, the difference in median BMFS between those treated with GP only and those treated with TP only was not significant ($p = 0.10$).

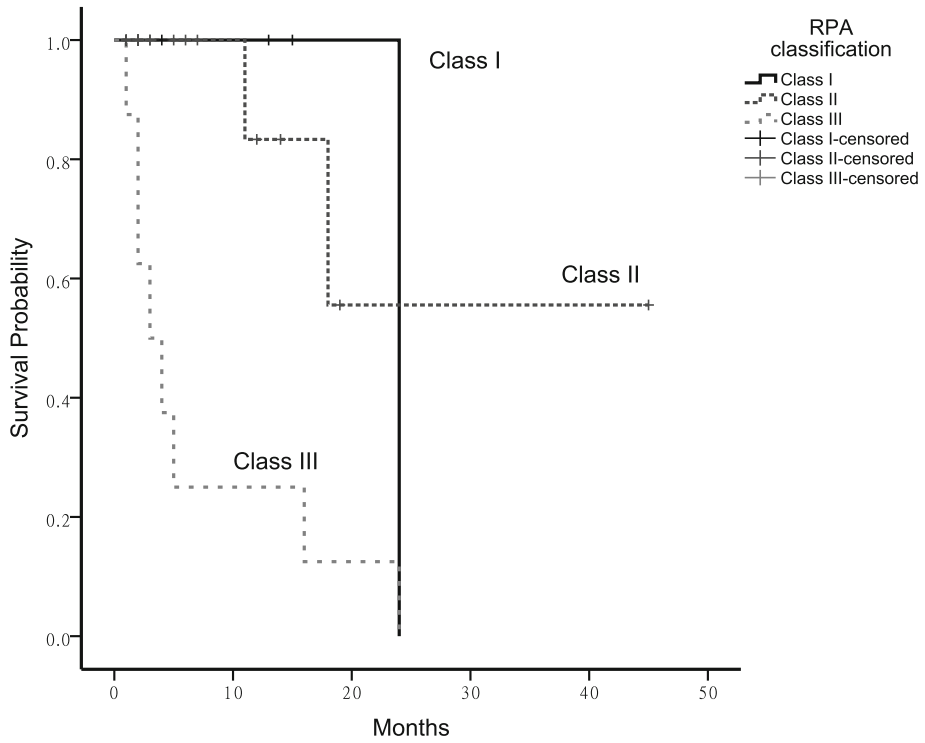

Fig. 1 Post brain metastasis survival by recursive partitioning analysis (RPA) classification ($p < 0.001$)

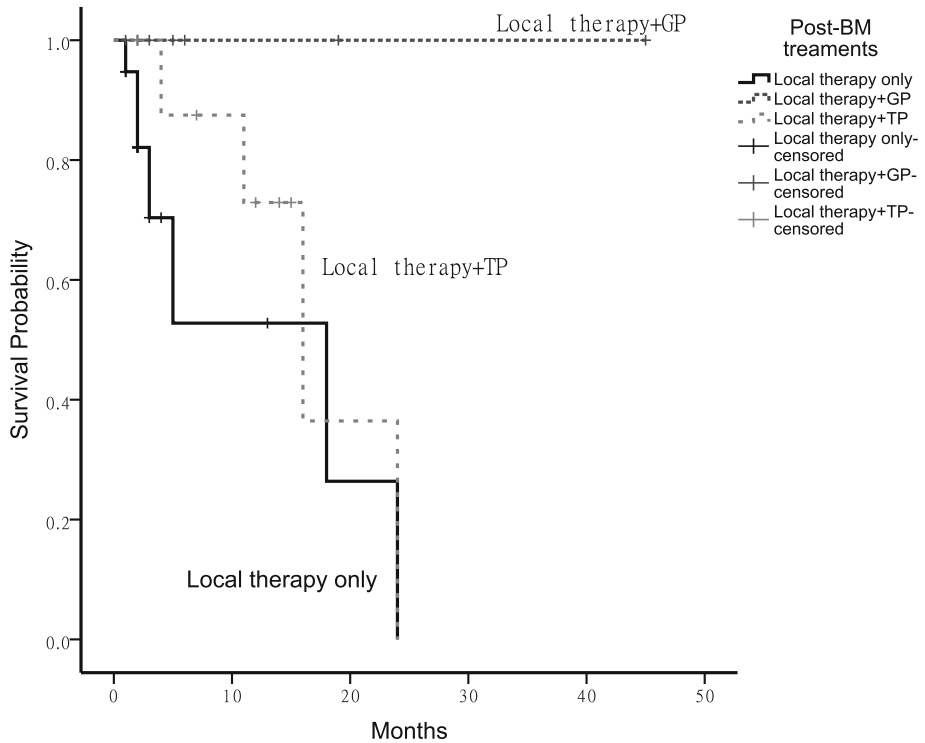

Fig. 2 Post brain metastasis survival by treatment after the occurrence of brain metastasis ($p = 0.055$) (local therapy only vs local therapy plus systemic therapy, $p = 0.084$; local therapy plus GP vs local therapy plus TP, $p = 0.097$)

Table 3 Variants related to post-BM survival

Variants	Single variant analysis		Multivariate analysis		
	Post-BM survival(months)	*P* value	HR	95%CI	*P* value
RPA		<0.001	23.379	1.932-28.805	0.013
I	24				
II	Not reached				
III	3				
GPA		0.087	2.895	0.435-19.285	0.27
0-1	5				
1.5-2.5	18				
3	Not reached				
3.5-4	Not reached				
Treatment after BM		0.084	0.058	0.008-0.410	0.004
Local therapy only	18				
Local + systemic therapy	24				

Abbreviations: *BM* Brain metastasis, *RPA* Recursive partitioning analysis, *GPA* Graded prognostic assessment

Discussion

Patients with SCC have lower incidence of BM. Some studies reported that, the incidence of BM in patients with SCC ranged from 8% to 28%, which was lower than other histological subtypes such as adenocarcinoma, ranging from 20% to 45% [3, 4, 10, 11]. Additionally, previous studies concerning BM in NSCLC included different histological subtypes. As a result, the characteristics of BM in SCC patients have not been fully profiled. Similar to the reports of other studies, only 19.1% of patients in our study had documented BM over a decade. Therefore, it was a great challenge in releasing some convincing results with such relatively smaller samples. However, after careful analysis, there emerged some information which we believed to be worth noticing.

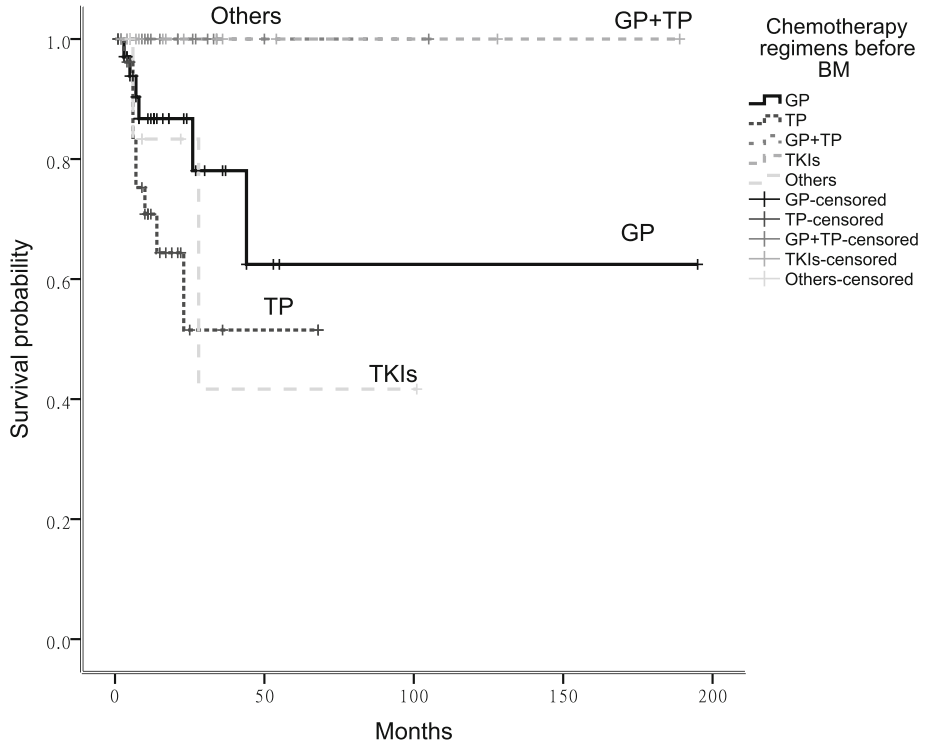

Fig. 3 Brain-metastasis-free survival by different regimens before the occurrence of brain metastasis ($p = 0.013$)

We found that females, those with advanced disease, with adenosquamous histology and elevated serum level of CEA at diagnosis had a significantly higher incidence of BM. Besides, female and abnormal level of CEA were independent factors which indicated higher risk of BM. We are aware of two previous studies investigating the correlation between gender and BM [19, 20]. One showed no such correlation, but the other was in agreement with our findings. The underlying biology of these correlations is unknown. In our study, bivariate analysis found that female gender had a positive correlation with EGFR mutation (p = 0.024). In NSCLC, EGFR mutation is associated with constitutive activation of a downstream signaling pathway implicated in tumor cell growth, local invasion, angiogenesis and metastasis [21–23]. Some researchers have found that, a higher incidence of BM was seen in NSCLC patients with EGFR mutations than those with wild-type EGFR [16, 24, 25]. However, the evidence is stronger for adenocarcinoma than for SCC. In our study, among 33 patients with known EGFR status, only 5 SCC patients were shown to harbor EGFR mutations and none of them developed BM. So it is impossible to draw any conclusions as to whether EGFR mutation contributes to BM in SCC patients. Larger studies are needed to examine the role of EGFR mutation in BM. In addition, the role of other signal transduction pathways should be investigated.

CEA is the most commonly used biomarker for the screening of various malignancies including lung cancer. As it was shown in our study, patients with abnormal serum levels of CEA had not only higher incidence of BM, but also higher risk of BM. In a perspective study enrolling 293 patients with staged IIIB-IV NSCLC also found, CEA ≥ 40 ng/ml was an independent risk factor of BM [26]. In another prospective study conduced by Lee et al., the association of tumor markers including CEA, Cyfra21-1, CA125, CA199 and SCC and BM were studied in 227 patients with advanced NSCLC [27]. As a result, CEA level was the only tumor marker that was found to be significantly different between patients with BM and without BM. Although some studies indicated that the prognostic value of CEA was more specific in adenocarcinoma patients than in SCC patients, it should be noticed that less than one third of patients enrolled in these studies had SCC histology [26, 28]. Since our findings were concluded in SCC patients, we believed that, at least in patients with SCC, those with abnormal serum levels of CEA at diagnosis should be considered as at risk population of BM. More concerns of BM should be paid to these patients during follow-up.

Some studies have suggested that NSCLC patients with local advanced disease have an increased risk of BM. This is confirmed in the current study, in which a higher stage at diagnosis is associated with a higher incidence of BM. Several clinical trials have therefore been carried out to explore the efficacy of PCI in patients with stage III disease [1, 2]. However, while PCI decreased the incidence of BM, no survival advantage was shown. Data from our study showed that, the incidence of BM in patients with SCC and stage III disease was only 12.5%. Even in studies of NSCLC which included patients with varying histological subtypes, the incidence of BM in stage III disease was not much higher, at 13–28% [3, 4, 11, 20]. Hence, stage was not qualified enough to define patients with higher risk of BM, especially when used as single parameter. In addition to incidence, the interval from diagnosis to BM is another factor that should be considered. For NSCLC patients with local advanced disease, the median interval from diagnosis to BM ranges from 5.7 to 12 months [4, 19, 20, 29, 30]. Although some studies have shown that patients with squamous histology have longer intervals of BM [31], our study showed that the median time to BM for SCC patients with metachronous BM was only 7 months (range 5–8 months). This was much shorter than we expected. Furthermore, females and patients with elevated serum levels of CEA at diagnosis had a significantly shorter median BMFS than their counterparts. Thus, although patients with SCC have a lower incidence of BM, those with a higher risk of BM are likely to experience BM early in the course of their disease. Based on all these findings, it is reasonable that patients with higher risk of BM, such as female and patients with abnormal CEA at diagnosis indicated in our study should be the candidates of future studies concerning BM prevention. Furthermore, comprehensive studies are needed to further valid our findings. If possible, exploring risk factors other than clinical ones is also warranted.

RPA and GPA are prognostic systems for BM which includes many clinical factors such as age, Karnofsky performance status (KPS), number of BM and status of extracranial disease at the time of BM. In our study, RPA was found to be an independent prognostic factor for BM patients in multivariate analysis. More importantly, systemic therapy in addition to local therapy was also proved to be an independent prognostic factor which indicated better post-BM survival. Combined with the fact that BM was a kind of hematogeneous metastasis, it is warranted that systemic therapy should be considered after the occurrence of BM, especially for those accompanying extracranial metastasis. A standard systemic treatment regimen has not been established for SCC patients with BM. As a result of the JMDB study, in which subgroup analysis demonstrated superior efficacy of gemcitabine in patients with squamous histology, gemcitabine has become the optimal regimen for treating SCC patients [32]. Many studies have investigated the efficacy of platin-doublets involving a third generation cytotoxic drug as the first-line regimen

for advanced NSCLC [33–35]. These trials have shown no survival benefit for any of these regimens, even when analyzed by histological subtype. In the current study, no significant survival difference was seen between those treated with GP and those treated with TP (p = 0.097), either. But we attribute the negative result more to smaller samples. Furthermore, we also compared median BMFS between different chemotherapy regimens to explore their ability to prevent BM. As a result, patients who received both GP and TP before BM had the longest median BMFS (p = 0.013). However, the difference between GP group and TP group was comparable (p = 0.10). This result suggests that BMFS may not agent-dependent. It may indicate that receiving both GP and TP prolongs BMFS or it may be that those who had a longer BMFS had the opportunity to receive both regimens. In terms of TKIs, since most patients in our study had unknown EGFR status, it is insufficient to evaluate their roles in the current setting. Thus, to date, the most effective agent for BM prevention or treatment in SCC patients remains uncertain.

Conclusions

To our knowledge, this is the first study to explore the risk factors for BM in SCC patients. It is true that our study was limited by retrospective study design and smaller samples of documented BM. But the factors we identified will be useful for the design of future studies to investigate preventative measures, such as PCI. Furthermore, we have shown that the addition of systemic therapy could significantly improve prognosis compared with local therapy alone. However, no agent was clearly superior for BM prevention or treatment in SCC patients.

Abbreviations

BM: Brain metastasis; BMFS: Brain-metastasis-free survival; CEA: Carcinoembryonic antigen; Cyfra21-1: Cytokeratin 19 fragments; EGFR: Epidermal growth factor receptor; GPA: Graded prognostic assessment; KPS: Karnofsky performance status; NSCLC: Non-small cell lung cancer; NSE: Neuron-specific enolase; PBMS: Post-brain-metastasis survival; PCI: Prophylactic cranial irradiation; RPA: Recursive partitioning analysis; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TKI: Tyrosine kinase inhibitor; WBRT: Whole brain radiation therapy

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

LB conceived of the study, participated in its design, performed the statistical analysis and drafted the manuscript. LY and LS participated in the data collection and statistical analysis. QX conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was reviewed and approved by the institutional review boards and ethics committees of Beijing Tiantan Hospital affiliated to Capital Medical University. (KY2014-033-01).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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