Risk factors of brain metastases as initial failure in completely resected stage IIIA(N2) non-small cell lung cancer

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Background: This study aimed to identify the risk factors of brain metastases (BM) as the initial site of failure in patients with completely resected stage IIIA (N2) non-small-cell lung cancer (NSCLC).

Methods: From January 2005 and June 2012, the clinical data of 357 patients with completely resected stage IIIA (N2) NSCLC were reviewed in this study. Kaplan-Meier analysis was used to identify the incidence of BM as the initial site of failure and survival. To assess the risk factors of BM, the log-rank test and Cox regression were used for univariate analysis and multivariate analysis, separately.

Result: Seventy-three (20.4%) patients developed BM; 60 patients had BM as their initial site of failure. The 1-, 3-, and 5-year risk for patients developing BM as the initial site of failure was 9.1%, 27.4% and 35.4%, respectively. Univariate analysis showed adenocarcinoma histology (P=0.000), number of regional LN >4 (P=0.018), multiple N2 stations (P=0.027), multiple region of LN involvement (P=0.010) were significantly associated with an increased risk of developing BM as the initial site of failure. Multivariate analysis showed adenocarcinoma (P=0.001; HR =0.150; 95% CI, 0.047–0.479), multiple regions of LN involvement (P=0.015; HR =2.010; 95% CI, 1.146–3.524) were significantly associated with the high risk of developing BM as the initial site of failure. In patients with adenocarcinoma and multiple regions of LN involvement, the 5-year actuarial risk of BM as the initial failure was 47.6%, respectively.

Conclusions: Adenocarcinoma and multiple regions of LN involvement were independent risk factors for BM as the initial failure in completely resected stage IIIA (N2) NSCLC. Prospective clinical trials are needed to verify the effect of PCI in the highest-risk subset we identified.

Keywords: Brain metastases (BM); non-small cell lung cancer (NSCLC); risk factor; adenocarcinoma and multiple region of LN involvement

Introduction

Approximately 30% of non-small-cell lung cancer (NSCLC) patients are initially diagnosed with locally advanced NSCLC (LA-NSCLC) diseases (1). About 20–50% of patients with NSCLC will develop brain metastases (BM) during their disease course (2-15). BM generally leads to poor prognosis and poor quality of life. In BM patients treated by surgery, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), and systemic therapy either individually or in combination, the median overall survival (OS) was less than 1 year (16-20). The frequency of BM in LA-NSCLC is much higher than that in early stage of NSCLC (4-7,11-13,21). The 5-year risk of developing BM

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was 10% in early stage NSCLC (6), while in the LA-NSCLC and stage IV NSCLC the risk is 30–50% (4-7,11-13,21). Therefore, early BM detection is crucial, which is helpful to select prevention strategies such as prophylactic cranial irradiation (PCI) to improve patient survival and quality of life.

Completely resected NSCLC patients with pathologically confirmed N2 disease are considered to be a heterogeneous population (22,23), with 5-year survival rates ranging from 10% to 30% (24). We aimed at this homogeneous patients with completely resected staged IIIA (N2) of LA-NSCLC, because the frequency of BM in early stage of NSCLC is relatively low, and the rate of locoregional and extracranial recurrence in stage IIIA is lower than that in stage IIIB and stage IV, should not obscure the positive impact of prevention strategies such as PCI on survival.

Radical resection of IIIA (N2) of LA-NSCLC not only can provide accurate pathological stage, but also have more detailed information on lymph node (LN) status. LN status is a major determinant of outcome in patients with NSCLC, but whether or not the LN status is a major determinant of BM is unclear. Different studies have conflicting result and the information about the extent of LN metastases is not very detailed (4,6,7,11). In this study, we focused on completely resected staged IIIA (N2) of LA-NSCLC to explore the correlation between LN status and BM, and identify the risk factor of BM as the initial site of failure and the potential highest risk candidates who may benefit from PCI.

Method

Patients

A retrospective review of patients with surgically staged IIIA NSCLC was conducted. This study was approved by the review board in the hospital. Between January 2005 and June 2012, 357 consecutive patients with pathological IIIA (N2) (pIIIA-N2) who underwent complete resection were identified. The eligibility criteria for the patient records were as follows: (I) lobectomy or ipsilateral pneumonectomy (based on the location of the primary cancer); (II) systematic mediastinal LN dissection or sampling at least three N2 stations (which must include subcarinal LN station); (III) margin-negative resection of all gross disease at microscopic analysis (surgical resection with microscopically tumour-free resection margins including the bronchial, venous and arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or additionally resected tissue); (IV)

negative results of brain magnetic resonance imaging (MRI) as part of their initial staging; (V) histologically confirmed pIIIA-N2 NSCLC (stage pT1-3N2M0) according to the Union for International Cancer Control (UICC) 7th edition of TNM classification (25). Patients were excluded if they had synchronous or sequential second primary tumors.

Patients who received adjuvant chemotherapy or postoperative radiotherapy (PORT) were included in the study. Patients were excluded if they received neoadjuvant therapy (chemotherapy and/or radiotherapy). Adjuvant chemotherapy was routinely administered for the patients. Chemotherapy with platinum-based doublet anticancer drugs was recommended as a standard, but observation or alternative anticancer drugs were selected when patients refused to receive standard chemotherapy or had underlying diseases such asthenia under the advice of physicians. PORT was administered on the judgment of radiation oncologist and referring surgeon. 3D conformal radiation therapy (3D-CRT) technique was employed in all patients who had PORT. The planning target volume (PTV) was determined as the clinical target volume plus 0.5–0.8 cm margins. Radiation for all patients was delivered with 6 MV X-ray from linear accelerator at 1.8/fraction, 5 days/week, to a total dose of 50.4 Gy. Doses were prescribed to the PTV.

Follow-up of patients

Generally, the patients were followed up every 3 months after surgery for 2 years, and every 6 months thereafter. During follow-up, regular evaluations included medical history, physical examination, complete blood count, thoracic CT, and abdominal ultrasound or CT. Other tests, such as PET-CT, were performed as clinically indicated. Brain MRI was not performed during the follow-up period. Contrast-enhanced brain MRI was performed if patients had suspicious symptoms or disease progress. Disease progression was determined by the physician based on available information, including clinical assessments, radiologic examination, and/or pathology reports.

Variables

The demographic and clinic pathologic variables of patients at the time of diagnosis were age, gender, smoking history, histology, histologic grade, tumor stage (T1, T2, T3), IIIA stage (IIIA1-2, IIIA3), laterality, type of surgery, vessel invasion, interstitial fibrosis, extra-capsular extension (ECE), clinical N2 (cN2) factor, the number of regional LNs,

involved N2 stations, distribution of metastatic nodes (skip N2 or non-skip N2), LN ratio (LNR), mediastinal lymph node (MLN) region involved, the presence of LN station 7, the presence of the highest MLN. Treatment-related variables were type of surgery, adjuvant chemotherapy, PORT. The cN2 lesions was defined as the MLN enlargement ≥1 cm in short axis on CT or positive uptake on PET-CT before surgery; The highest MLN was defined as one of the resected MLNs located closest to the head; LNR was defined as ratio of metastatic to examined nodes or LN ratio; skip N2 metastasis was defined as the MLN metastasis without N1 nodal metastasis; Region of LN involvement was divided into superior mediastinal area, sortic area and inferior mediastinal area according to Wang *et al.*'s study (7); Nonsmokers were defined as patients who had smoked <100 cigarettes in their lifetime. In contrast, smokers were categorized as patients who had smoked more than 100 cigarettes in their lifetime.

Data analysis

Progression-free survival (PFS) was defined as the time from surgery to the time of progression, death of any cause, or final follow-up. OS was defined as the time from surgery to death of any cause or final follow-up, with death defined as an event. Disease recurrence at the surgical margin, hilum, mediastinum, and supraclavicular LN regions was considered a local-regional failure. All other sites of failure, outside the local region were considered distant metastasis. Time to BM as their initial site of failure was measured from the date of surgery to the date of BM between the patients who developed distant metastases or both local and distant recurrence as the initial failure, with BM defined as an event. The cumulative incidence of BM and survival were determined using the Kaplan-Meier method. To assess risk factors for BM as their initial site of failure, log-rank test was used for univariate analysis, and cox regression was used for multivariate analysis. All data analyses were conducted with SPSS 18.0 software package. Statistically significant value was P<0.05 (only keeping three digits after the decimal point).

Results

Patient characteristics

A total of 357 patients were included in this study from January 2005 to June 2012. The patients' baseline characteristic was summarized in *Table 1*. There were 219 men and 138 women with a median age 59 years old (range, 34–86 years). Of 357 identified patients, 216 (60.5%) were adenocarcinoma, 177 (49.6%) were smokers, 323 (90.5%) received lobectomy, 315 (88.2%) received adjuvant chemotherapy, and 70 (19.6%) received PORT.

Survival and failure

The median follow-up time for 130 surviving patients was 40.4 months (range, 4.4–132 months). The median PFS was 19.9 months. The 1-, 3-, and 5-year PFS was 69.6%, 29.8% and 17.3%, respectively (*Figure 1A*). The median OS was 43.5 months. The 1-, 3-, and 5-year OS was 91.6%, 55.3% and 35.9%, respectively (*Figure 1B*). Disease progression was identified in 248 (69.5%) patients. 90 experienced local recurrence; 215 developed distant metastases; 192 developed distant metastases (34 had both local and distant failure) as the first site of failure. Time to local recurrence and distant metastasis was showed in *Figure 2*. Of 192 patients who developed distant metastases or both local and distant recurrence as the initial failure, brain was the most common site. *Figure 3* showed the cumulative risk of distant metastases in different sites. The median time from surgery to the diagnosis of BM as the initial site of failure was 13.5 months, and the time to develop extracranial recurrence as the initial site of failure was 14.3 months. Of the 357 patients, 73 (20.4%) patients developed BM: 60 patients had BM as their initial site of failure; 13 patients developing BM at some point during their follow-up. The OS of patients with BM was significant poor than in patients without BM, and the median OS and 5-year OS rates were 36.5 months, 16.7% and 45.6 months, 44.9%, respectively (P=0.021) (*Figure 4A*). The similar was observed between patients with BM as the initial site of failure and without BM as the initial site of failure, the median OS and 5-year OS rates were 31.6 months, 10.1% and 46.6 months, 42.3%, respectively (P=0.004) (*Figure 4B*).

Risk factors BM

The 1-, 3-, and 5-year risk for patients developing BM as the initial site of failure was 9.1%, 27.4% and 35.4%, respectively (*Figure 5*). *Table 1* showed the rate of BM as the initial failure for different clinical and pathological factors and find several risk factors were more likely to develop BM as the initial failure. Univariate analysis showed adenocarcinoma histology (P=0.000), number of

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Table 1 Characteristics of patients

Characteristic	No. of Patients (N=357)	%
Age		
≤60	208	58.3
>60	149	41.7
Gender		
Male	219	61.3
Female	138	38.7
Smoking history		
Never/light smoker	180	50.4
Current/heavy smoker	177	49.6
Histology		
Adenocarcinoma	216	60.5
No- Adenocarcinoma	141	39.5
Tumor differentiation		
Well/moderate	184	51.5
Poor	173	48.5
Pathologic T stage		
T1	80	22.4
T2	239	66.9
T3	38	10.6
IIIA stage		
IIIA1–2	193	54.1
IIIA-3	164	45.9
Tumor location		
Left	163	45.7
Right	194	54.3
Type of surgery		
Lobectomy	323	90.5
Pneumonectomy	34	9.5
Clinical N factor		
N0,1	193	54.1
N2	164	45.9
Number of metastatic LNs		
≤4	192	53.8
>4	165	46.2

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	No. of Patients (N=357)	%
Involved N2 station		
Single	177	49.6
Multiple	180	50.4
Distribution of MLN		
Skip N2	120	33.6
No-skip N2	237	66.4
LNR		
≤20%	172	48.2
>20%	185	51.8
MLN region involved		
Single	254	71.1
Multiple	103	28.9
LN station 7		
Negative	220	61.6
Positive	137	38.4
Highest MLN status		
Negative	197	55.2
Positive	160	44.8
POCT		
No	42	11.8
Yes	315	88.2
PORT		
No	287	80.4
Yes	70	19.6

MLN, mediastinal lymph node, LNR, lymph node ratio (defined as the ratio of metastatic to examined lymph nodes); PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

regional LN >4 (P=0.018), multiple N2 stations (P=0.027), multiple region of LN involvement (P=0.010) were significantly associated with an increased risk of developing BM as the initial site of failure. In multivariate analysis, adenocarcinoma (P=0.001; HR =0.150; 95% CI, 0.047–0.479), multiple regions of LN involvement (P=0.015; HR =2.010; 95% CI, 1.146–3.524) remained as the high risk of BM as the initial site of failure. Incidence of BM in relation to histology and LN status in completely resected staged IIIA (N2) NSCLC showed in *Table 2*. In patients with
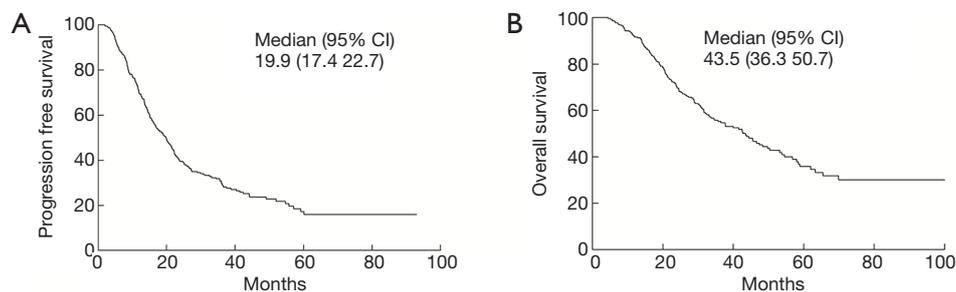
Figure 1 PFS and OS for all the patients. (A) PFS: the median PFS was 19.9 months. (B) OS: the median OS was 43.5 months.
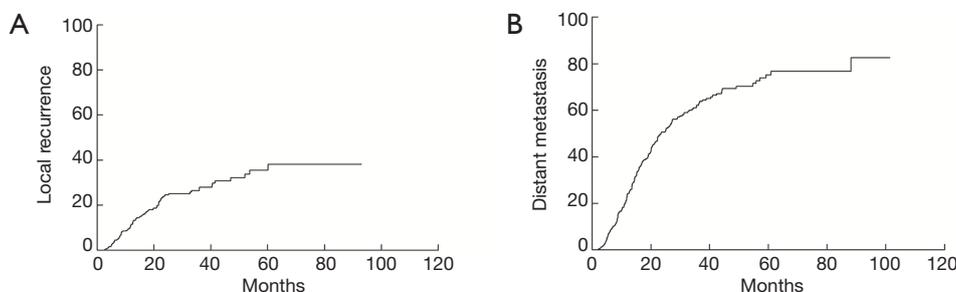

Figure 2 Time to Local recurrence and distant metastasis. (A) local recurrence; (B) distant metastasis.
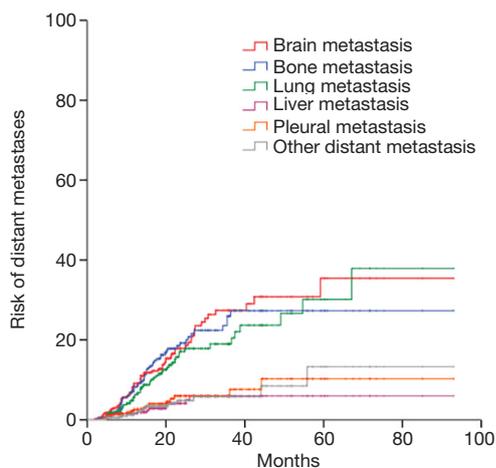

Figure 3 The cumulative risk of distant metastasis in different sites.

adenocarcinoma and multiple regions of LN involvement (n=84), the 1-, 3-, and 5-year actuarial risk of developing BM as the initial site of failure was 19.0%, 47.6%, and 47.6%, respectively. In patients with adenocarcinoma and single region of LN involvement (n=173), the 1-, 3-, and 5-year cumulative risk of BM as the initial site of failure was 8.9%, 28.5%, and 40.6%, respectively. In patients with non-adenocarcinoma and multiple region of LN involvement (n=19) or patients with non-adenocarcinoma and single region of LN involvement (n=81), the 1-, 3-, and 5-year actuarial risk of developing BM was obviously lower than that in patients with adenocarcinoma and single region of LN involvement. The differences among the groups with both, one and none of the two risk factors were statistically significant (P=0.000) (*Figure 6*).

Discussion

Chemotherapy combined with radiotherapy and/or surgery significantly reduces extracranial distant metastases and improves survival among patients with LA-NSCLC; nevertheless, combined-modality therapy does not decrease the relatively high rate of BM. The frequency of BM increases as the survival improved. Systemic chemotherapy does not decrease the relatively high rate of BM, because it is difficult to penetrate the blood–brain barrier and delivery drugs to the BM leaving the brain untreated (18,26-28). High risk of BM has become the critical factor influencing the prognosis of LA-NSCLC patients (11,26,27,29). Because PCI has shown effectiveness in SCLC, some groups conducted large clinical trials to evaluate whether
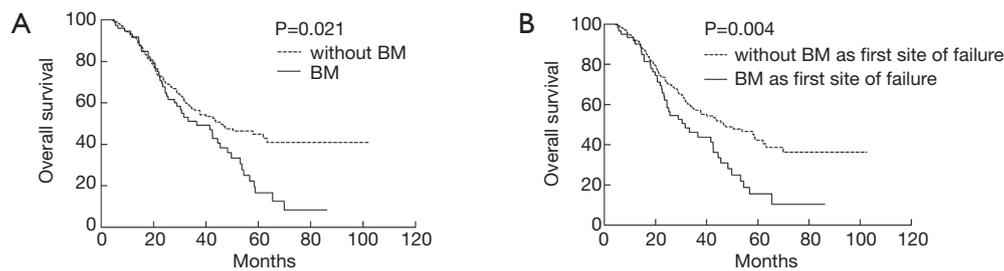
Figure 4 Kaplan-Meier survival curves. (A) the OS in patients with BM or without BM; (B) the OS in patients with BM or without BM as the initial site of failure. BM, brain metastases.
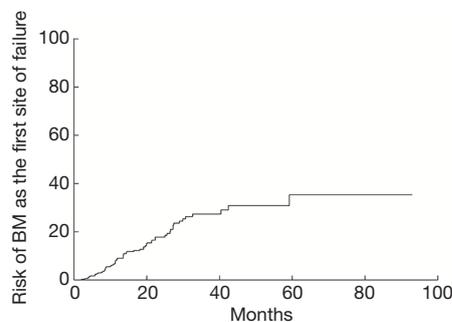

Figure 5 The risk for patients developing BM as the initial site of failure. BM, brain metastases.

LA-NSCLC patients can benefit from PC (30-34). To date, in NSCLC PCI has been proved to reduce the probability and/or delay the BM, but it fails to benefit the survival in several randomized studies (31,35,36)]. PCI also has side effects on mental capacities such as cognition disorders, memory deterioration. Radiation Therapy Oncology Group (RTOG) 0214 also suggests that PCI may not suitable for all patients and assessing PCI in NSCLC should choose high risk of BM patients with relative good locoregional and extracranial control, who are the most likely to derive survival benefit from PCI. Therefore, we focused on patients with completely resected pIIIA-N2 NSCLC, assessed risk factors for developing BM as the initial site of failure, and defined the highest-risk subgroup most likely to benefit from PCI.

Most previous studies aimed at the high risk factors of developing BM at some point during their clinical course, not at the high risk factors of developing BM as their first site of failure in NSCLC. The high-risk patients of BM as their first site of failure are not well defined. In our study, multivariate analysis showed that adenocarcinoma and multiple regions of LN involvement were associated with

high incidence of BM as the first failure. An increased risk in patients with adenocarcinoma or non-squamous cell cancer was also noted by many studies on NSCLC (3-5,7-11,37,38). Our study produced a similar result: adenocarcinoma was an independent risk factor of developing BM as the first failure. But whether or not the LN status (multiple regions of LN involvement) is a major determinant of BM is unclear. Many studies have found that the number and degree of MLN metastases correlated with prognosis of lung cancer, such as the number of resected LNs, the number of regional LNs, LNR, cN2 factor, HM, skip N2 all have been reported as independent prognosis factors in patients with NSCLC (39-49). In pIIIA-N2 NSCLC, the recurrence and the metastasis rate were also affected by the number and degree of MLN metastases (40,43,46,48-50). However, which LN status can predict a high risk of BM is not well defined. So far, different studies have conflicting result and the information about the extent of LN metastases is not very detailed. Ding *et al.* (4) observed that LNR ≥30% associated with an increased risk of BM in completely resected pIIIA-N2. Hubbs *et al.* (6) reported that hilar LN involvement predicts a high risk of BM of patients treated surgically for early stage NSCLC. Wang *et al.* (7) found that multiple LN regions with metastases and the number of metastases LN ≥4 influenced the frequency of BM in resected III-N2 NSCLC. Mamon *et al.* (11) inferred that residual nodal involvement as an important factor in predicting BM in surgically staged IIIA NSCLC treated with combined therapy. Compared with the previous studies, our study included the largest heterogeneous population (357 patients) of complete resected stage IIIA (N2) NSCLC and had more detailed information on LN metastases status and other clinical characteristics. In our study, on univariate analysis, number of regional LNs >4, N2 station, multiple involved N2 stations and multiple regions of MLN involvement were associated with risk of

Table 2 Risk of BM

Factors	Number of patients	Univariate analysis (first BM incidence%)				Multivariate analysis	
		1-	2-	5-	P value	P value	HR, 95% CI
Age					0.332		
≤60	208	8.5	30.2	38.4			
>60	149	10.0	23.0	27.8			
Gender					0.189		
Male	219	9.1	23.1	34.5			
Female	138	8.8	32..1	35.9			
Smoking history					0.181		
No	180	8.1	31.2	37.2			
Yes	177	9.9	21.8	30.5			
Histology					0.000	0.001	0.150 (0.047–0.479)
Adenocarcinoma	216	11.9	33.4	44.0			
Non-adenocarcinoma	141	1.4	9.4	9.4			
Tumor differentiation					0.720		
Well/ Moderate	184	8.6	29.5	37.3			
Poor	173	9.6	25.3	32.3			
Pathologic T stage					0.510		
T1	80	12.3	38.1	53.6			
T2	239	8.5	24.3	29.4			
T3	38	5.3	25.2	25.2			
IIIA stage					0.231		
IIIA1–2	193	8.3	25.1	34.1			
IIIA-3	164	10.0	30.6	36.4			
Tumor location					0.266		
Left	163	8.8	21.2	34.1			
Right	194	9.3	32.6	35.9			
Type of surgery					0.798		
Lobectomy	323	8.5	27.3	35.6			
Pneumonectomy	34	15.1	27.3	27.3			
Clinical N factor					0.231		
N0,1	193	8.3	25.1	34.1			
N2	164	10	30.6	36.4			
N of metastatic LNs					0.018		
≤4	192	5.3	24.1	26.3			
>4	165	13.8	31.8	69.7			

Table 2 (*continued*)

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Table 2 (*continued*)

Factors	Number of patients	Univariate analysis (first BM incidence%)				Multivariate analysis	
		1-	2-	5-	P value	P value	HR, 95% CI
N2 station no.					0.027		
Single	177	5.1	22.9	25.4			
Multiple	180	13.2	32.9	38.0			
Distribution of MLN					0.064		
Skip N2	120	2.8	23.2	27.1			
No-skip N2	237	12.4	29.3	43.7			
LNR					0.110		
≤20%	172	6.4	25.2	27.6			
>20%	185	11.8	29.3	48.2			
MLN region involved					0.010	0.015	2.010 (1.146–3.524)
Single	254	6.1	23.2	32.7			
Multiple	103	17	40.2	40.2			
LN station 7					0.167		
Negative	220	7.0	24.8	29.5			
Positive	137	12.7	31.7	65.8			
Highest MLN status					0.134		
Negative	197	7.7	24.3	31.9			
Positive	160	10.8	31.6	40.5			
chemotherapy					0.723		
No	42	4.9	30.6	42.2			
Yes	315	9.3	25.8	34.3			
PORT							
N0	287	9.9	26.8	31.7	0.974		
Yes	70	6.0	28.9	43.1			

developing BM. On multivariate analysis, only multiple regions of MLN involvement associated with high incidence of BM as the first failure. To our knowledge, our study is the largest retrospective study having the most detailed information on LN metastases from a single institution in studying the risk factors of BM as the initial failure in completely resected pIIIA-N2 patients.

In recent years, many researchers have reported risk factors of developing BM. Adenocarcinoma or non-squamous cell carcinoma is more likely to developing BM. However, it was not consistent with all studies. Some studies did not find a correlation between histology and developing BM (6,13-15,33). There are also other previous studies find different factors correlated with BM in NSCLC; the factors include age (3,14,37,51,52), gender (3), serum levels of tumor markers (carcinoembryonic antigen, neuron-specific enolase, CA125) (8,37), the epidermal growth factor receptor (EGFR) mutation status (2), adjuvant or neoadjuvant therapy (5,7,15), extent of disease (7,15,38), incomplete resection (7). Tumor status is an independent prognosis factors in patients with NSCLC. Tumor size is associated with the risk of BM in NSCLC (6,52). Hubbs
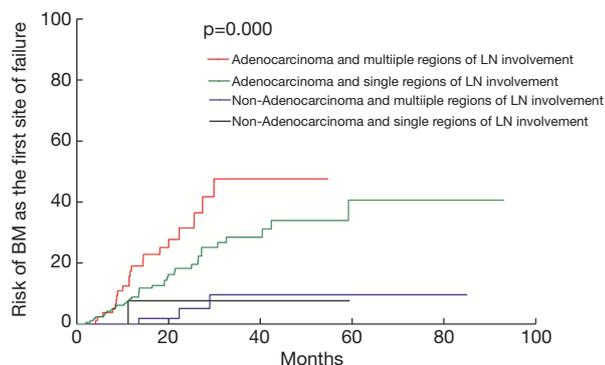
Figure 6 The differences among the groups with both, one and none of the two risk factors.

et al. (6) analyzed of 975 patients with early stage NSCLC, in whom larger tumor size were risk of BM. Mujoomdar *et al.* (9) demonstrated that in a cohort of 264 stage I–IV patients, the probability of BM is correlated with size of the primary tumor. Bajard *et al.* (51) observed that T4 tumor status is a factor factors predictive of BMs in a group of stages I–III NSCLC patients. However, we did not find such a relationship. There are also other investigators who also did not find a relationship between tumor size and BM (4,5,37). Systemic therapy is associated with an increased risk of BM in several previous studies. It is reported that adjuvant chemotherapy or neoadjuvant chemotherapy is a statistically significant factor of BM (7,10). However, many other studies did not find that chemotherapy and TKIs were significantly related with the risk of BM (4,37). In our study, no significant correlation between the system therapy schedule and BM was found. We also did not find age, sex, or primary tumor location etc. correlate with BM. Most of those previous studies often include heterogeneous populations and the results are inconsistent. Our study described 357 patients with stage IIIA (N2) NSCLC treated with complete resection of the primary lesion and LN dissection. All patients in this study were surgically staged. In our study, only adenocarcinoma histology and multiple region of LN involvement were associated with high incidence of BM as the first failure. It also suggests the importance of brain MRI during the follow-up to detect the BM in high-risk patients of brain.

In RTOG 0214, PCI has not been shown to improve OS significantly, one possible explanation is that the high rates of locoregional and extracranial distant relapse overwhelmed any survival benefits from PCI in LA-NSCLC; another possible explanation is that it had a relative low BM risk, only 18% of patients in the observation, it is much lower than that of SCLC, in which PCI has been proved to bring survival benefit. We focused on BM as the initial site of failure in completely resected pIIIA-N2 NSCLC, because the rate of BM significantly higher than early stage of NSCLC, and the locoregional recurrence and extracranial failure is relatively lower than stage IIIB and stage IV NSCLC. Assessment of PCI on this group of patients may not override the positive impact of PCI on survival. In our study, in patients with adenocarcinoma and multiple regions of LN involvement (n=84), the 1-, 3-, and 5-year actuarial risk of developing BM as the initial site of failure was 19.0%, 47.6%, and 47.6%, respectively. The subgroup of patients had sufficient BM rates to identify the high-risk patients who are the most likely to derive a survival benefit from PCI. It is helpful to conduct a future randomized, controlled trial to investigate PCI in the highest-risk group of patients we identified.

Our study also had several limitations. First, this is a retrospective study. The study may have selection bias and the results should be interpreted cautiously. Second, although we targeted a homogeneous largest population with completely resected pIIIA-N2, there was also some heterogeneity in treatment parameters. This heterogeneity was mainly caused by the variability in PORT and adjuvant chemotherapy regimens. Not every patients received PET-CT and/or mediastinoscopy, cannot completely excluded the mediastinal staging considering N3 disease, and criteria for upfront surgery in stage IIIA(N2) tumors mainly depends on clinical staging, and excluding patients who received neoadjuvant therapy the authors are likely excluding patients with poorer risk factors. Third, EGFR mutation status was not known in this study. Two studies have conflicting results about whether or not the EGFR mutations is an independent risk factor of BM. Shin *et al.* (2) found EGFR status had no influence upon the incidence of BM at the diagnosis and after the resection in 3wwwww14 patients of pulmonary adenocarcinoma. Stanic *et al.* (53) demonstrated that non-significant association between EGFR mutation status and BM at the time of diagnosis and no influence upon the cumulative incidence of BM. These two studies include heterogeneous populations with respect to pre/postoperative stage. We are planning to examine EGFR mutation status of patients with staged IIIA (N2) adenocarcinoma to investigate the correlation of EGFR mutations and BM.

Conclusions

This study demonstrated that adenocarcinoma and

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multiple regions of LN involvement were independent risk factors for BM as the initial failure in completely resected pIIIA-N2 NSCLC. Patients with adenocarcinoma and multiple regions of LN involvement are at the highest risk of developing BM as the initial failure, and may receive a greater benefit from PCI. Prospective clinical trials are needed to verify the effect of PCI in the highest-risk subgroup we identified.

Acknowledgments

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Shanghai Chest Hospital. Written informed consent was obtained from all patients.

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