BRIEF REPORT

Incidence of Brain Metastasis at the Initial Diagnosis of Lung Squamous Cell Carcinoma on the Basis of Stage, Excluding Brain Metastasis

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ABSTRACT

Introduction: Current National Comprehensive Cancer Network guidelines recommend routine brain magnetic resonance imaging (MRI) screening in patients with stage II to IV non–small cell carcinoma, regardless of histological subtype. This recommendation might not be universally applicable, however, because brain metastasis (BM) is seen less frequently in patients with lung squamous cell carcinoma (SCC) than in those with a histological diagnosis of nonsquamous cell carcinoma.

Methods: The cases of 564 patients with lung SCC in our institution between January 2012 and December 2013 were reviewed prospectively for comprehensive staging. All subjects' lung SCC, but not their BM, was staged on the basis of the seventh edition of the guidelines of the American Joint Committee on Cancer. We evaluated the incidence of BM across the stages and clinical factors associated with BM.

Results: Of the 564 patients, 28 (5.0%) had BM. BM did not occur in patients with stage Ia or Ib disease; however, it increased significantly as the disease progressed from stage IIa to IV ($p < 0.001$, trend test). Multivariate analysis showed that tumor involvement in N3 lymph nodes and distant metastasis other than BM (M1b) was independently associated with the development of BM.

Conclusions: Routine brain MRI screening in patients with lung SCC in stage II to IV can help to evaluate asymptomatic BM. By contrast, we did not find any evidence supporting routine brain MRI screening in patients with stage I disease.

Keywords: Brain metastasis; Non–small cell lung carcinoma; Squamous cell carcinoma; Neoplasm staging

Introduction

The brain is a common distant site of non–small cell lung cancer (NSCLC) metastasis, and brain metastasis (BM) significantly increases morbidity and mortality in patients with NSCLC.[1–3] Because a considerable proportion of patients with NSCLC have asymptomatic BM, early screening with brain magnetic resonance imaging (MRI) is crucial for the diagnosis and appropriate management in patients with synchronous NSCLC and BM.[4–6] The recently released National Comprehensive Cancer Network guidelines also recommend early screening with brain MRI in patients with stage II to IV NSCLC.[7] Because patients with squamous cell carcinoma (SCC) are at lower risk for the development of BM than are those with a histological diagnosis of nonsquamous cell carcinoma,[8,9] however, the universal application of this recommendation without consideration of histological type needs validation. This study evaluated the incidence of BM on the basis of stage of lung SCC to verify the current brain MRI screening strategy and to explore the clinical factors associated with BM.

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Methods

Patients

On the basis of the results of our previous study, the institutional guidelines of Samsung Medical Center in Seoul, Republic of Korea have, since January 2007, included screening brain MRI in all patients with NSCLC who can receive aggressive anticancer therapies.[10] We conducted a prospective review of the medical records of 631 patients at Samsung Medical Center (a 1961-bed referral hospital) in Seoul, Republic of Korea, in whom primary lung SCC was diagnosed between January 2012 and December 2013. Patients in whom brain lesions such as stroke had occurred within the past 3 months (n = 3), those with synchronous intrathoracic malignancies with nonsquamous histological findings (n = 6) or extrathoracic malignancies (n = 42), those not undergoing positron emission tomography–computed tomography (PET-CT) (n = 14), and those not undergoing brain MRI (n = 2) were excluded. This study was approved by the Institutional Review Board of Samsung Medical Center.

Initial Staging and Diagnosis of BM

All subjects' lung SCC, but not their BM, was staged on the basis of the seventh edition of the guidelines of the American Joint Committee on Cancer.[7,11] The initial NSCLC staging strategy included taking a medical history and conducting a comprehensive physical examination, including neurological examination, chest radiography, chest CT (including of the upper abdomen and adrenal glands), pulmonary function testing, fiber-optic bronchoscopy, PET-CT, and endobronchial ultrasound transbronchial needle aspiration, if applicable. Regarding staging for extracranial lesions, clinical staging was performed in patients who were deemed inoperable and thus staged by imaging studies. In contrast, pathologic staging was conducted in patients who were deemed operable, underwent surgical resection for lung SCC, and were thus staged on the basis of the results of pathologic examination. Pathologic staging was also used for patients who had operable intrathoracic lesions that could be treated by surgical resection and a single BM that could be treatable by surgical resection or gamma knife surgery. We described the detailed method involved in performing brain MRI previously.[10] BM was diagnosed on the basis of the results of brain MRI or cytologic examination of cerebrospinal fluid.

Assessment of the Clinical Usefulness of Routine Brain MRI Screening in Patients with Lung SCC

To investigate the clinical usefulness of routine brain MRI screening, we evaluated the number of occurrences of asymptomatic BM and the number of futile operations that can be prevented by routine brain MRI screening. Patients at potential risk for a futile operation were defined as those who were deemed operable according to staging of their SCC (stage Ia to IIIa) but inoperable according to staging of their BM. Regarding BM being associated with futile operation, we included only asymptomatic patients with multiple occurrences of BM because symptomatic patients can be found without routine brain MRI screening and patients with a single BM and stage Ia to IIIa disease can undergo an operation with the option of treatment of their single BM by surgical resection or gamma knife surgery.

Statistical Analysis

Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as numbers (percentages). Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared with the Pearson chi-square test or Fisher's exact test. The incidence of BM across tumor, node, and metastasis (TNM) staging was compared using the Cochran-Armitage test. To identify independent factors associated with BM, a multivariate logistic regression analysis with backward stepwise selection with a p value less than 0.05 for variable entry and a p value greater than 0.10 for variable removal was performed. The initial candidate variables included age; sex; smoking history; and T, N, and M component. The Bonferroni correction was used for multiple comparisons. All tests were two sided, and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows software, Version 22.0 (Armonk, NY).

Results

Patients

This study included 564 patients, 526 of whom (93.3%) were male; their median age was 67 years. Most subjects (96.8%) were current or ex-smokers with a median smoking history of 40 pack-years. Evaluation of their NSCLC (excluding BM) established it to be at stage Ia in 54 patients (9.6%), Ib in 67 (11.9%), IIa in 83 (14.7%), IIb in 52 (9.2%), IIIa in 158 (28.0%), IIIb in 51 (9.0%), and IV in 99 (17.6%). Twenty-eight patients (5.0%) had BM at the initial diagnosis of their lung SCC. BM was diagnosed in 27 patients on the basis of brain MRI findings and in one patient on the basis of the findings of brain MRI and results of cytologic examination of the cerebrospinal fluid. There was no significant difference between the patients with and without BM (Table 1). As shown in Figure 1, the incidence of BM across stage was 0% in both stage Ia (0 of 54 patients)

Table 1. Baseline Characteristics of the Patients with Lung Squamous Cell Carcinoma

	Total Patients (N = 564)	Patients without Brain Metastases (N = 536)	Patients with Brain Metastases (N = 28)	*p* Value
Median age (range), y	67 (61-72)	67 (61-72)	69 (59-73)	0.804
Male sex, n (%)	526 (93.3)	501 (93.5)	25 (89.3)	0.425
Smoking history				0.238
Never, n (%)	18 (3.2)	16 (3.0)	2 (7.1)	
Current smoker, n (%)	269 (47.7)	258 (48.1)	11 (39.3)	
Former smoker, n (%)	277 (49.1)	262 (48.9)	15 (53.6)	
Median pack-years of smoking (range)[a]	40 (30-50)	40 (30-50)	40 (21-65)	0.820
Staging for extracranial lesions[b]				<0.001
Clinical staging, n (%)	282 (50.0)	256 (47.8)	26 (92.9)	
Pathologic staging, n (%)	282 (50.0)	280 (52.2)	2 (7.1)	

[a]Data for five patients were not available.
[b]Brain metastasis was not included in the staging for extracranial lesions. Clinical staging was used for patients who were deemed inoperable and thus staged clinically. Pathologic staging was used for patients who were deemed operable, underwent surgical resection for lung SCC, and were thus staged on the basis of pathologic examination results.

and stage Ib (0 of 67), 2.4% in stage IIa (two of 83), 3.8% in stage IIb (two of 52), 1.9% in stage IIIa (three of 158), 5.9% in stage IIIb (three of 51), and 18.2% in stage IV (18 of 99). The incidence of BM increased significantly with stage ($p < 0.001$, trend test).

Clinical Characteristics of the Patients with BM

Of the 28 patients with BM, 14 (50.0%) had a single metastasis and 14 (50.0%) had multiple metastases. The most frequent location of the single metastases was the parietal lobe (n = 7), followed by the frontal lobe (n = 5) and cerebellum (n = 2) (Table 2). Whereas 24 patients (85.7%) had no symptoms suggestive of BM, four (14.3%) had symptoms that included dizziness (n = 3), headache (n = 1), and weakness and paresthesia in the left upper extremity (n = 2). Some patients had more than one symptom. Of the four patients with symptomatic BM, one had a single metastasis located in the parietal lobe, one had a single metastasis located in the cerebellum, and two had multiple metastatic lesions.

As shown in Figure 1, TNM staging of four patients with symptomatic BM established that two were in stage IIIa, one was in IIIb, and one was in stage IV. Of the four patients with symptomatic BM, two with stage IIIa disease had a single BM whereas the other two (with stage IIIb or IV disease) had multiple occurrences of BM. In comparison, the TNM staging of the 24 patients with asymptomatic BM identified two in stage IIa, two in stage IIb, one in stage IIIa, two in stage IIIb, and 17 in stage IV. Of the 24 patients with asymptomatic BM, 12 in stage IIa (n = 2), IIb (n = 1), IIIb (n = 2), or IV (n = 7) had a single BM whereas the other 12 in stage IIb (n = 1), IIIa (n = 1), or IV (n = 10) had multiple occurrences of BM.

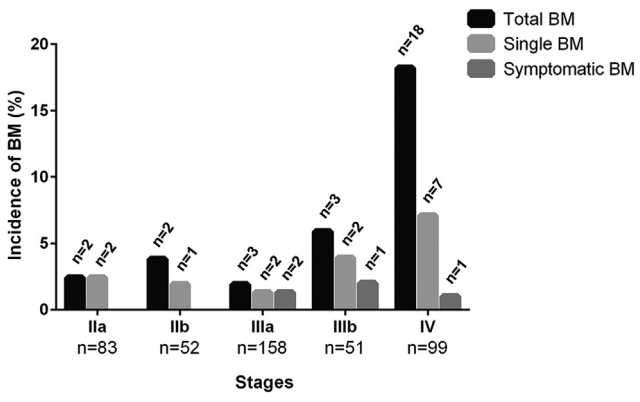

Figure 1. Incidence of brain metastasis (BM) with proportions of single BM and symptomatic BM in patients with lung squamous cell carcinoma across the stages.

Clinical Usefulness of Routine Brain MRI Screening in Patients with Lung SCC

Routine brain MRI screening was useful in finding 4.3% of occurrences of asymptomatic BM (n = 24) in the 564 patients with lung SCC. Of the 414 patients with stage Ia to IIIa disease who were deemed operable (with the exception of BM), 0.5% (n = 2 [one with stage IIb and the other with IIIa disease]) were able to avoid a futile operation because routine brain MRI screening had detected asymptomatic BM in them (see Supplementary Table 1 in the Supplemental Digital Content).

Incidence of BM According to the T, N, and M Components of the TNM Classification of Lung SCC

Table 3 shows the incidence of BM according to the T, N, and M components of the TNM classification of lung SCC. Although the incidence of BM increased significantly

Table 2. Distribution of Brain Metastases in Patients with Symptomatic and Asymptomatic Metastases

	All Patients (N = 28)	Patients with Asymptomatic Brain Metastases (N = 24)	Patients with Symptomatic Brain Metastases (N = 4)
Single metastasis	14	12	2
Parietal lobe	7	6	1
Frontal lobe	5	5	0
Cerebellum	2	1	1
Multiple metastases	14	12	2

with an increase of tumor size (T1a to T2b) ($p = 0.027$, trend test), there was no association between the incidence of BM and an increase in overall T stage ($p = 0.073$, trend test). Regarding an association between the incidence of BM and stage for the N component, BM occurred more frequently in patients with N3 lymph node (LN) involvement than in those with N0, N1, or N2 LN involvement ($p < 0.001$ for N3 versus N0, N1, or N2). The incidence of BM increased with stage for the M component ($p < 0.001$, trend test).

Clinical Factors Associated with BM

As shown in Table 4, a multivariate analysis revealed that the clinical factors associated with BM included disease involving N3 LNs (adjusted OR = 3.6, 95% confidence interval: 1.4–9.4, $p = 0.008$) and metastasis to distant organs other than the brain (M1b, adjusted OR = 8.2; 95% confidence interval: 2.6–26.3, $p < 0.001$).

Table 3. Prevalence of Brain Metastasis According to TNM Staging

	Total Patients, n (%) (N = 564)	Patients with Brain Metastasis, n (%) (N = 28)
T staging		With a specific T component
T1a	28 (5.0)	0 of 28 (0)
T1b	65 (11.5)	2 of 65 (3.1)
T2a	194 (34.4)	6 of 194 (3.1)
T2b	75 (13.3)	7 of 75 (9.3)
T3	133 (23.6)	10 of 133 (7.5)
T4	69 (12.2)	3 of 69 (4.3)
N staging		With a specific N component
N0	188 (33.3)	4 of 188 (2.1)
N1	119 (21.1)	4 of 119 (3.4)
N2	160 (28.4)	3 of 160 (1.9)
N3	97 (17.2)	17 of 97 (17.5)
M staging[a]		With a specific M component
M0	465 (82.4)	10 of 465 (2.2)
M1a	46 (8.2)	4 of 46 (8.7)
M1b	53 (9.4)	14 of 53 (26.4)

[a]Brain metastasis was not included in the staging.
TNM, tumor, node, and metastasis.

Relationship between BM and Distant Metastasis Other than BM

Of the 28 patients with BM, 14 (50.0%) had BM only, whereas 14 (50.0%) had distant metastases in addition to BM. They included bone (n = 7), adrenal gland (n = 6), liver (n = 4), and other organ (n = 9) metastases. Some patients had more than one metastatic site. The incidence of BM increased with the number of involved organs ($p < 0.001$, trend test). BM was present in 60.0% of patients with adrenal metastasis (six of 10), 26.7% of those with liver metastasis (four of 15), and 24.1% of those with bone metastasis (seven of 29).

Discussion

The exact incidence of BM in patients with NSCLC at initial diagnosis is not well known because few studies have evaluated routine brain MRI screening scans at initial diagnosis of NSCLC. Although a recent large population-based study provided a more accurate estimate (approximately 10%),[12] the incidence of BM on the basis of histological findings was not revealed. To our knowledge, ours is the first study reporting the incidence of BM in a relatively large number of patients with lung SCC who underwent routine brain MRI screening at initial staging. The incidence of BM in patients with SCC at initial diagnosis was approximately 5%.

None of the 121 patients in this study with stage Ia or Ib lung SCC had BM. Similarly, an early study evaluating BM in subjects with NSCLC using brain CT showed that subjects with stage I or II SCC had no BM.[13] We provided more accurate data with more patients by using brain MRI because the numbers in the previous study might have been insufficient for detection of rare events and because brain CT is less sensitive than brain MRI for detecting early BM (i.e., BM in subjects with stage II lung SCC).[6]

In line with previous studies,[13,14] the present study found that the incidence of BM increased significantly with an advance in overall staging. Specifically, BM occurred more frequently in patients with lung SCC extending to N3 LNs or involving distant organs (M1b), whereas no relationship existed between BM and extent of the T component. Agreeing with these findings, a previous study showed that patients with lung SCC were more likely to have simultaneous BM and tumor involvement in mediastinal LNs than were patients with adenocarcinoma, although no information on the LN station involved was provided.[8] Another study evaluating clinical predictors of BM in subjects with NSCLC (18% of whom had SCC) reported that the development

Table 4. Clinical Factors Associated with Brain Metastasis

	Any Brain Metastases					
	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* Value	Adjusted OR	95% CI	*p* Value
Age, years	1.0	1.0-1.1	0.967	-	-	-
Sex, male	1.7	0.5-6.0	0.395	-	-	-
Smoking history						
Nonsmoker		Ref				
Current or former smoker	0.4	0.1-1.8	0.238	-	-	-
T staging						
T1		Ref				
T2	2.3	0.4-14.5	0.828	-	-	-
T3	3.7	0.6-24.2	0.288	-	-	-
T4	2.1	0.2-18.9	>0.999	-	-	-
N staging						
N0-2		Ref			Ref	
N3	8.8	4.0-19.5	<0.001	3.6	1.4-9.4	0.008
M staging[a]						
M0		Ref			Ref	
M1a	4.3	1.1-17.1	0.034	2.4	0.6-10.8	0.360
M1b	16.3	6.0-44.4	<0.001	8.2	2.6-26.3	<0.001

[a]Brain metastasis was not included in the staging.
OR, odds ratio; CI, confidence interval; Ref, reference value.

of BM was associated with tumor size and LN stage.[9] Although an increase in overall T stage was not associated with incidence of BM in this study, tumor size (T1a to T2b) was associated with the probability of development of BM ($p = 0.027$, trend test). We also showed that the more the tumor invaded distant organs, the more frequently BM occurred.

Regarding cost per asymptomatic BM detected and futile operation, the cost per asymptomatic BM detected in the overall population was $881.30 and the cost per futile operation in patients with stage Ia to IIIa disease (potentially operable stages) was $7762.50 (see Supplementary Table 1 in the Supplemental Digital Content). The cost of routine brain MRI in our institution was $749. Because patients with a malignancy pay 5% of their medical costs as part of the Republic of Korea's national health insurance plan specific to patients in whom cancer has been diagnosed, we estimated that the actual cost of routine brain MRI per patient who applies to this plan is $37.50. Because no BM was found in patients with stage Ia or Ib lung SCC, we also evaluated the cost per asymptomatic BM detected and the cost per futile operation after excluding the patients with stage I disease. The cost per asymptomatic BM detected among patients with stage IIa to IV disease was $692.20, and the cost per futile operation in patients with stage IIa to IIIa was $5943.80, both of which were significantly lower than those estimated when patients with stage I lung SCC were included ($p < 0.001$ for changes in both costs) (see Supplementary Table 1 in the Supplemental Digital Content).

Although our study showed that BM occurred beginning with stage II lung SCC, this information should not be interpreted as meaning that routine brain MRI screening be mandatory in patients with stage II lung SCC. Although the incidence of BM in stage II lung SCC in this study was relatively low, the cost per futile operation was relatively high. Moreover, since the prognosis of BM in patients with lung SCC is not worse than are those with SCLC or lung adenocarcinoma, the lower prevalence of BM in patients with SCC than in those with SCLC or lung adenocarcinoma should not be emphasized by a worse prognosis for BM due to lung SCC.[15–17] Therefore, the cost-effectiveness of performing routine brain MRI screening in patients with stage II lung SCC should be considered with caution and be based on availability, especially in countries where the cost for routine brain MRI screening is not covered by the medical insurance system.

There are several limitations to this study. First, it was performed in a single center. Second, 93% of the study population was male. The disproportionately high percentage of males in this study may be attributed to the higher rate of smoking in males than in females in the Republic of Korea (which has one of highest rates of smoking in males and lowest rates of smoking in females among all Organisation for Economic Co-operation and Development member countries).[18,19] To evaluate the potential selection bias caused by exclusion, we compared

the percentages of males among those patients who were included and those who were excluded. However, there was no significant difference between the percentages of males in the two groups (93.3% [526 of 564] versus 90.8% [59 of 65], $p = 0.441$). Third, tumor differentiation was not evaluated, so we could not explore its relationship to the differentiation of SCC and BM. Therefore, future studies are needed to explore the impact of tumor grade for the development of brain metastasis. Finally, because half the patients were staged clinically, there might be errors in the stratification of staging. However, PET-CT is the best method for evaluating stage in subjects who cannot undergo pathologic staging.[20]

In conclusion, this study revealed that BM developed in 5.0% of patients with lung SCC and increased significantly as the stage increased. Our study indicates that routine brain MRI screening in patients with stage II to IV lung SCC might help to evaluate asymptomatic BM. By contrast, there was no evidence supporting routine brain MRI screening in patients with stage I disease.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.11.007.

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