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Incidence of brain metastasis in lung adenocarcinoma at initial diagnosis on the basis of stage and genetic alterations

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ABSTRACT

Objective: Patients with lung adenocarcinoma (ADC) are at higher risk of the development of brain metastasis (BM), and genetic alterations are associated with BM.

Patients and methods: A total of 598 patients with lung ADC in our institution between January 2014 and December 2014 were reviewed retrospectively. We evaluated the incidence of BM by stage and genetic alterations.

Results: Of the 598 patients, 97 (16.2%) had BM, which occurred across all stages. The incidence of BM showed a tendency to increase as the stage increased ($p < 0.001$, trend test). Although patients with EGFR mutations had BM across all stages, those with ALK or K- mutations had BM only in stage III and IV diseases. Regardless of types of mutations, the incidence of BM showed a tendency to increase as the T or N staging increased ($p < 0.001$ for each of EGFR, ALK, and K-RAS mutations, trend test). Whereas BM incidence showed a tendency to increase as the M staging increased in patients with EGFR-mutant lung ADC ($p < 0.001$, trend test), there was no linear trend between M staging and ALK ($p = 0.469$, trend test) or K-RAS mutations ($p = 0.066$, trend test). After adjusting covariables, EGFR mutations were associated with BM in never-smokers (adjusted OR = 2.07, 95% CI = 1.02–4.34) and K-RAS mutations were risk factors for BM in males (adjusted OR = 3.86, 95% CI = 1.01–14.43).

Conclusions: BM occurred in approximately 16% of lung ADC patients, including 3% with stage I diseases. Whereas EGFR-mutant lung ADC had BM across all stages, ALK- or K-RAS-mutant lung ADC had BM only in advanced stages. EGFR mutations were risk factors for BM among never-smokers and K-RAS mutations were risk factors among males.

1. Introduction

Brain metastasis (BM) is common in patients with non-small cell lung cancer (NSCLC) and is associated with increased morbidity and mortality [1–3]. Since approximately 10–20% of patients with NSCLC present with BM at initial presentation and these patients often have no symptoms [1,4,5], routine BM screening is important for the appropriate diagnosis and management of NSCLC patients. However, there is still considerable controversy regarding routine BM screening in patients with NSCLC.

Previous reports have recommended that brain imaging not be performed in all patients with NSCLC [6–8], and recently released guidelines, such as the National Comprehensive Cancer Network and the American College of Chest Physicians guidelines, do not recommend routine screening of BM in clinical stage I NSCLC patients who are asymptomatic [9,10]. On the other hand, recent studies have revealed that BM can occur even in patients with early stage disease or in those without any symptoms [11–13]. Consistent with these results,

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the European Society of Oncology guidelines announced that routine BM screening may be useful for patients considered for curative therapies [14].

Because patients with lung adenocarcinoma (ADC) are at higher risk of the development of BM [15,16] and certain genetic alterations, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and K-RAS, are associated with BM in NSCLC, especially in ADC [5,17–19], information on BM according to the histologic subtype and genetic alterations should be considered for the recommendation of BM screening in NSCLC. However, information regarding this issue is limited. Therefore, the aim of the current study was to evaluate the incidence of BM based on the stage of lung ADC and genetic alterations.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the medical records of 660 patients at Samsung Medical Center (a 1961-bed referral hospital) in Seoul, Republic of Korea, in whom primary lung ADC was diagnosed between January 2014 and December 2014. Since January 2007, the institutional guidelines of Samsung Medical Center have required brain magnetic resonance imaging (MRI) screening in all patients with resectable lung cancer or systemic therapy. Patients in whom brain lesions, such as stroke, had occurred within the past 3 months (n = 3), those with synchronous intra-thoracic malignancies with non-squamous histological findings (n = 16), those not undergoing positron emission tomography-computed tomography (PET-CT) and did not follow-up in our institution (n = 39), and those not undergoing brain MRI (n = 4) were excluded. A total of 598 patients were included in the study, which was approved by the Institutional Review Board of Samsung Medical Center (IRB number 2018-08-052).

2.2. Initial staging

All subjects' lung ADC, but not their BM, was staged on the basis of the 8th edition of the guidelines of the American Joint Committee on Cancer [20,21]. Pre-treatment staging included a clinical and medical history, physical examination (including neurological examination), blood tests, chest X-ray, chest CT scan (including liver and adrenal glands), pulmonary function test, PET-CT, and brain MRI. Flexible bronchoscopy was recommended when it is needed for staging or diagnostic purpose. Pathologic confirmation was also performed in all patients. In patients who could not undergo surgical resection, clinical stage was determined based on imaging findings and endobronchial ultrasonography-transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy. The detailed method involved in performing brain MRI was described previously [22]. BM was diagnosed on the basis of the results of brain MRI or cytologic examination of cerebrospinal fluid.

2.3. Genetic alterations

In this study, the mutational analyses of EGFR (exons 18–21) and K-RAS (exons 2 and 3) were performed using directional sequencing of polymerase chain reaction (PCR) fragments amplified from genomic DNA from paraffin-embedded. The detailed method involved in performing PCR was previously described [23,24]. The results were marked as mutation-positive if a mutation was detected in both the forward and reverse DNA strands. Testing for ALK rearrangement was performed using immunohistochemistry (IHC) as previously described [25,26]. An IHC score was assigned as follows: 0 (no staining), 1+ (faint cytoplasmic staining in ≥10% of tumor cells), 2+ (moderate, smooth cytoplasmic staining), and 3+ (intense, granular cytoplasmic staining). A positive ALK rearrangement was defined as an IHC score of 2+ or 3+ according to the findings of previous studies showing a high correlation between ALK fluorescence in stiu hybridization (FISH) and an ALK IHC score of 2+ or 3+ [27].

2.4. Statistical analysis

All data are presented as medians with interquartile ranges (IQRs) for continuous variables, and as numbers with percentages for categorical variables. Data were compared using the Mann-Whitney *U* test for continuous variables and the Pearson χ^2 test or Fisher's exact test for categorical variables. 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 multivariable logistic regression analysis was performed after adjusting for clinical variables, including age, sex, smoking history, and T, N, and M components. To determine whether a certain genetic alteration is associated with BM, we performed multivariable logistic analyses after adjusting for age, sex, smoking history, and T, N, and M component for the subgroup population with a specific genetic alteration. A two-sided p value < 0.05 was considered to reflect statistical significance in all analyses. All statistical analyses were performed using SPSS statistical software (ver. 23.0; IBM Corp., Armonk, NY, USA) and R (ver. 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients

Baseline characteristics of the study population are summarized in Table 1. The median age of the 598 patients was 61 years (IQR, 55–69 years), 294 patients (49.2%) were male, and 349 patients (58.4%) were never-smokers. Ninety-seven patients (16.2%) had BM at initial diagnosis. Of the 501 patients without BM, 276 (55.1%) were clinically staged and 225 (44.9%) were pathologically staged. Of the 97 patients with BM, most (97.9%, n = 95) were clinically diagnosed using EBUS-TBNA, mediastinoscopy, and biopsy of metastatic lesions.

Patients with BM were more likely to have advanced diseases than those without BM ($p < 0.001$ for each of overall stage, T, N, and M staging). There were no significant differences in the types of mutations between the patients with and without BMs in terms of EGFR (54.2% vs. 49.2%, p = 0.431), ALK (7.8% vs. 6.6%, p = 0.419), and K-RAS (11.3% vs. 8.0%, p = 0.339) mutations.

As shown in Supplemental Table 1, patients with K-RAS mutations were more likely to be older than those with EGFR or ALK mutations (median 72 years, 60 years, and 57 years; p = 0.001). However, there were no significant differences in sex, smoking history, staging methods regardless of type of mutations.

3.2. Distribution of BM

Of the 97 patients with BM, 26 (26.8%) had single metastasis and 71 (73.2%) had multiple metastases. The most frequent location of the single metastases was the frontal lobe (n = 8), followed by the cerebellum (n = 6). While 75 patients (77.3%) had no symptoms suggestive of BM, 22 (22.7%) had symptoms. Of the 22 patients with symptomatic BM, 20 (90.9%) had multiple BM (Supplemental Table 2).

3.3. Incidence of BM according to the T, N, and M components of TNM staging

As shown in Fig. 1, the incidence of BM across stage was 1.3% in stage I (3 of 224 patients), 9.2% in stage II (6 of 65), 22.9% in stage III (24 of 105), and 31.4% in stage IV (64 of 204) ($p < 0.001$, trend test). The incidence of BM showed a tendency to increase with an increase of tumor size (T1a to T4) ($p < 0.001$, trend test) and nodal staging (N0 to N3) ($p < 0.001$, trend test). According to the M component, 7.5% (29/388), 6.8% (5/73), 53.8% (7/13), and 45.2% (56/124) had BM in patients with M0, M1a, M1b, and M1c disease, respectively ($p < 0.001$,

Table 1
Baseline characteristics of the patients with lung adenocarcinoma.

	Total (N = 598)	Patients without brain metastases (N = 501)	Patients with brain metastases (N = 97)	p value
Median age (IQR), y	61 (55-69)	61 (55-69)	62 (56-71)	0.523
Male sex, n (%)	294 (49.2)	254 (50.7)	40 (41.2)	0.111
Smoking history				0.001
Never, n (%)	349 (58.4)	287 (57.3)	62 (63.9)	
Current smoker, n (%)	167 (27.9)	153 (30.5)	14 (14.4)	
Ex-smoker, n (%)	82 (13.7)	61 (12.2)	21 (21.6)	
Median pack-years of smoking (IQR)	0 (0-30.0)	0 (0-30.0)	0 (0-20.0)	0.254
Staging for extra-cranial lesions[a]				< 0.001
Clinical staging, n (%)	371 (62.0)	276 (55.1)	95 (97.9)	
Pathologic staging, n (%)	227 (38.0)	225 (44.9)	2 (2.1)	
Staging[a], n (%)				< 0.001
IA1	45 (7.5)	45 (9.0)	0 (0)	
IA2	49 (8.2)	49 (9.8)	0 (0)	
IA3	85 (14.2)	84 (16.6)	1 (1.0)	
IB	45 (7.5)	43 (8.6)	2 (2.1)	
IIA	23 (3.8)	21 (4.2)	2 (2.1)	
IIB	42 (7.0)	38 (7.6)	4 (4.1)	
IIIA	50 (8.4)	43 (8.6)	7 (7.2)	
IIIB	43 (7.2)	31 (6.2)	12 (12.4)	
IIIC	12 (2.0)	7 (1.4)	5 (5.2)	
IVA	78 (13.0)	70 (14.0)	8 (8.2)	
IVB	126 (21.1)	70 (14.0)	56 (57.7)	
T staging, n (%)				< 0.001
T1a	9 (1.5)	9 (1.8)	0 (0)	
T1a (mi)	36 (6.0)	36 (7.2)	0 (0)	
T1b	75 (12.5)	67 (13.4)	8 (8.2)	
T1c	156 (26.1)	139 (27.7)	17 (17.5)	
T2a	104 (17.4)	86 (17.1)	18 (18.6)	
T2b	74 (12.4)	59 (11.8)	15 (15.5)	
T3	82 (13.7)	67 (13.4)	15 (15.5)	
T4	62 (10.4)	38 (7.6)	24 (24.7)	
N staging, n (%)				< 0.001
0	305 (51.0)	292 (58.3)	13 (13.4)	
1	41 (6.8)	31 (6.2)	10 (10.3)	
2	117 (19.6)	91 (18.1)	26 (26.8)	
3	135 (22.6)	87 (17.4)	48 (49.5)	
M staging[a], n (%)				< 0.001
M0	388 (64.9)	359 (71.6)	29 (29.9)	
M1a	73 (12.2)	68 (13.6)	5 (5.2)	
M1b	13 (2.2)	6 (1.2)	7 (7.2)	
M1c	124 (20.7)	68 (13.6)	56 (57.7)	
Type of genetic alterations, n (%)				
EGFR mutation (n = 539)	270/539 (50.1)	218/443 (49.2)	52/96 (54.2)	0.431
ALK mutation (n = 528)	36/528 (6.8)	29/438 (6.6)	7/90 (7.8)	0.419
K-RAS mutation (n = 334)	29/334 (8.7)	21/263 (8.0)	8/71 (11.3)	0.339

IQR, interquartile range; T = tumor; N = node; M = metastasis.
[a] Brain metastasis was not included in the staging for extra-cranial lesions. Clinical staging was defined in a patient who was deemed inoperable, and thus staged clinically. Pathologic staging was defined in a patient who was deemed operable and underwent surgical resection for lung adenocarcinoma, and thus staged by pathologic results.

trend test, Table 2).

3.4. Incidence of BM according to stages and types of mutations

The incidence of BM was 19.3% (52/270), 19.4% (7/36), and 27.6% (8/29) in patients with lung ADC with EGFR, ALK, and K-RAS mutations, respectively (p = 0.565). While patients with EGFR mutations had BM across all stages (Fig. 2A) (2.7%, 8.0%, 22.9%, and 39.8% in stage I, II, III, and IV, respectively), those with ALK (Fig. 2B) (33.3% in stage III and 18.8% in stage IV) or K-RAS (Fig. 2C) (50.0% in stage III and 46.1% in stage IV) mutations had BM only in stage III and IV diseases. However, there were no significant differences in the incidence of BM between EGFR-, ALK-, and K-RAS-mutant lung ADCs by stages (p > 0.999, p > 0.999, p = 0.354, and p = 0.242 for stage I, II, III, and IV, respectively). Regardless of types of mutations, the incidence of BM showed a tendency to increase with an increase of stage (Stage IA to IV) (p < 0.001, for each of EGFR, ALK, and K-RAS mutations, trend test).

3.5. Incidence of BM according to T, N, M components of TNM staging and types of mutations

As shown in Supplemental Table 3, there were no significant differences in the incidence of BM by T, N, M components of TNM staging and types of mutations. Regardless of types of mutations, the incidence of BM showed a tendency to increase as the T or N staging increased (p < 0.001 for each of EGFR, ALK, and K-RAS mutations, trend test). However, whereas BM incidence showed a tendency to increase as the M staging increased in patients with EGFR-mutant lung ADC (p < 0.001, trend test), there was no linear trend between M staging and ALK (p = 0.469, trend test) or K-RAS mutations (p = 0.066, trend test).

3.6. Clinical factors associated with BM

As shown in Table 3, multivariable analysis revealed that the clinical factors associated with BM were T4 diseases (adjusted odds ratio [OR] = 2.29, 95% confidence interval [CI] = 1.04–5.07), disease involving any lymph node (LN) involvement (adjusted ORs [95% CI] = 5.35 [1.96–14.20], 3.65 [1.65–8.27], and 6.19 [2.90–13.77] for N1, N2, and N3, respectively), and diseases with M1b/M1c diseases (adjusted OR = 4.52, adjusted OR = 2.53–8.20).

3.7. Association of genetic alterations and the occurrence of BM

Table 4 shows the association between genetic alterations and the occurrence of BM. In overall population, there were no significant association between genetic alterations and BMs. However, the impact of genetic alterations was different according to sex and smoking histories; whereas male patients with K-RAS mutations were 3.86 (95% CI = 1.01–14.43) times more likely to have any BMs compared to those without K-RAS mutation, there were no significant genetic alterations associated with BMs among female patients. Among never-smokers, patients with EGFR mutations were 2.07 (95% CI = 1.02–4.34) times more likely to have any BMs compared to those without EGRF mutations. However, there were no significant genetic alterations associated with BMs among the smokers.

4. Discussion

The exact incidence of BM in patients with lung ADC at initial diagnosis has not been well elucidated due to a lack of studies evaluating BM using routine brain imaging studies at initial diagnosis of lung cancer. Although recent studies using the National Cancer Data Base registry data [16] or the Surveillance, Epidemiology, and End Results (SEER) data [28] revealed that the prevalence of BM in lung ADC is

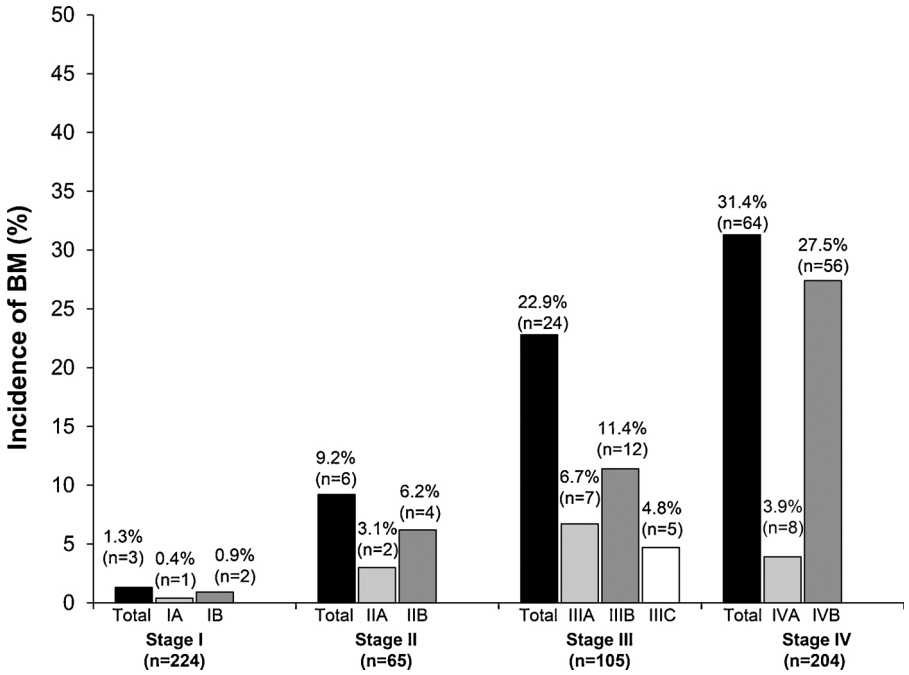

Fig. 1. Incidence of brain metastasis according to stage.

Table 2
Incidence of brain metastasis according to TNM staging.

	Total patients, n (%) (N = 598)	With brain metastasis, n (%) (N = 97)
T staging		With a specific T component
T1a(mi)	36 (6.0)	0 of 36 (0)
T1a	9 (1.5)	0 of 9 (0)
T1b	75 (12.5)	8 of 75 (10.7)
T1c	156 (26.1)	17 of 156 (10.9)
T2a	104 (17.4)	18 of 104 (17.3)
T2b	74 (12.4)	15 of 74 (20.3)
T3	82 (13.7)	15 of 82 (18.3)
T4	62 (10.4)	24 of 62 (38.7)
N staging		With a specific N component
N0	305 (51)	13 of 305 (4.3)
N1	41 (6.8)	10 of 41 (24.4)
N2	117 (19.6)	36 of 117 (30.8)
N3	135 (22.6)	48 of 135 (35.6)
M staging[a]		With a specific M component
M0	388 (64.9)	29 of 388 (7.5)
M1a	73 (12.2)	5 of 73 (6.8)
M1b	13 (2.2)	7 of 13 (53.8)
M1c	124 (20.7)	56 of 124 (45.2)

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

approximately 13% and 11%, respectively. However, BM data were not available in approximately 10% of the study population in the former study, and patients who were indicative of radiation therapy was diagnosed of having BM in the latter study. Therefore, brain imaging studies may have been performed more frequently in symptomatic patients, which could have resulted in a relatively lower incidence of BM than expected. From this perspective, with the advantage of using routine brain MRI screening at initial diagnosis of lung cancer, our study showed that approximately 16% of patients with lung ADC have BM at initial stating.

As shown in previous studies evaluating BM of NSCLC by staging [16,29–32], the incidence of BM in lung ADC increased with an advance in overall staging. Regarding the T component, more advanced T staging, especially T4, was significantly associated with an increased incidence of BM. Although BM occurred more frequently in patients with T2 or T3 diseases, this association disappeared in multivariable analyses. Regarding the N or M component, BM occurred more frequently in patients with lung ADC involving any LNs or metastasizing to distant organs (M1b/c), whereas no relationship existed between BM and local thoracic metastasis (M1a).

Another important finding of the current study is that lung ADC can metastasize to the brain even in an early stage (from stage IA2 lung ADC) with relatively low tumor burden. Although previous studies have suggested patients with ADC are at higher risk of BM, and NSCLC can metastasize to brain in an early stage, no studies have clearly shown stage I lung ADC can metastasize to BM, since previous studies did not evaluate histologic subtypes [4,8]. Furthermore, our results showed that only EGFR mutations are detected in stage I lung ADC with BM, implicating its crucial role in the occurrence of BM. Lee et al., recently revealed that angiogenesis-associated genetic expression affects the pathogenesis of ground-glass nodular ADC [33]. In that study, as the size and solid proportion of ground-glass nodular lung ADC increased, the expression of EGFR mutation increased along with angiogenesis-related gene expression. These results suggest that EGFR mutation may promote BM through enhanced angiogenesis in lung ADC, even in early stage. However, since the number of patients was small, further studies with a larger number of patients are needed to confirm this finding.

In patients with otherwise radically treatable NSCLC harboring EGFR or ALK mutations, identification of CNS disease might change the treatment paradigm and results in uncertainty on optimal management in the era of highly CNS penetrant tyrosine kinase inhibitors (TKIs). In this study, among 5 EGFR-mutant ADC patients with resectable stage except for BM, one patient with stage IA3 with single BM underwent lobectomy and gamma knife surgery, three patients (stage IB, stage IIA, and stage IIB) with less than three BMs were treated with EGFR TKIs and gamma knife surgery, and one patient with multiple BMs were treated with EGFR TKI and whole brain radiotherapy. Except for one patient with multiple BMs who died after 10 months, other patients are still alive. Given the limited sample size, further studies are needed to determine the role of curative surgery in early stage of EGFR-mutant NSCLC with single BM and the role of upfront use of CNS penetrant EGFR TKIs without radiotherapy to the brain.

Several studies have shown that EGFR mutation is closely associated with distant metastasis including BM rather than progression to the

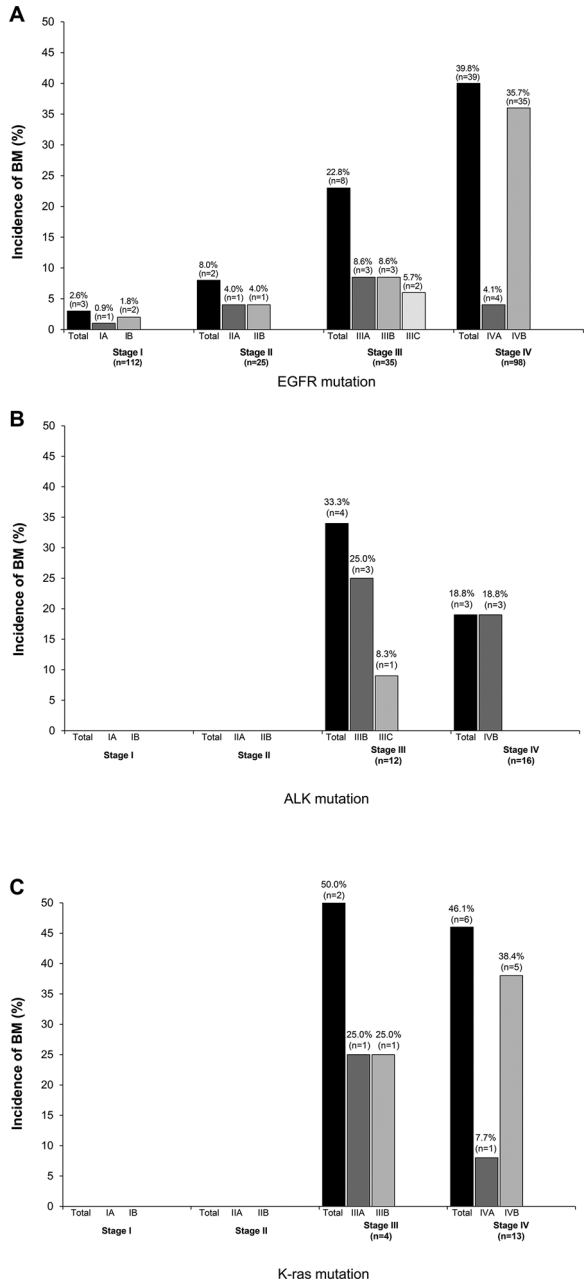

Fig. 2. Incidence of brain metastasis by stage in patients with EGFR mutations (A), ALK reaarangement (B), and K-RAS mutations (C).
EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

regional lesions [34]. A recent meta-analysis showed that EGFR mutation is a risk factor for BM in lung ADC [17], and another study evaluating the association between EGFR mutation and BM in NSCLC showed that EGFR mutation is linked to a higher likelihood of BM [35]. However, in the former, the proportion of studies evaluating patients with advanced lung ADC was higher and brain imaging was not performed as a routine protocol, which may have resulted in selection bias. In the latter study, not only lung ADC, but also other pathologic types were included. Overcoming these limitations and examining a relatively large number of subjects with lung ADC where BM was evaluated by a routine MRI protocol, our study showed that EGFR mutation is associated with BM in lung ADC, especially in never-smokers.

Regarding the Association between types of EGFR mutation and the occurrence of BM, previous studies showed that there were no significant differences in BM incidence between the patients with exon 21 mutations and those with 19 mutations [17]. However, the incidence of BM in patients with lung ADC with exon 20 mutations was higher than in those with other EGFR mutations [36]. Agreeing with these results, in our study, the incidence of BM was the highest among tumors with exon 20 mutations (33.3% [4/12]), followed by 22.2% (2/9) with exon 18 mutations, 19.5% (24/123) with exon 21 mutations, and17.5% (22/126) with exon 19 mutations. Howeever, proably due to relatively small number of involved cases, this difference did not reach a statistical significance.

Two opposing positions have been articulated regarding the relationship between K-RAS mutation and BM in NSCLC. A study evaluating stage IV NSCLC patients reported that oncogenic status, including K-RAS mutation, was not associated with BM [37]. In contrast, another study showed that alteration of K-RAS may be a risk factor for BM in surgically resected NSCLC [38]. However, the number of patients in those two studies was relatively small and the study population was confined to a specific stage. Overcoming these limitations by evaluating a larger number of patients across all stages, our results support the latter position. More specifically, we found a gender-specific association between K-RAS mutation and BM in lung ADC. Although K-RAS is a hallmark of smoking history, there was no association between K-RAS mutation and BM among smokers, consistent with a recent study evaluating KRAS mutation and distant metastases in lung ADC [39]. It is well known that K-RAS mutation drives malignant transformation, proliferation, and metastases in lung ADC [40]. Although these characteristics of K-RAS-mutant tumors are believed to contribute to BM, the exact mechanism by which K-RAS mutation contributes to BM should be elucidated in future studies.

In the current study, there was no relationship between ALK rearrangement and BM. This phenomenon could be explained by the unique characteristics of tumors with ALK rearrangement. Lung ADC with ALK rearrangement is more likely to advance locally rather than metastasize to distant organs compared to those without ALK rearrangement [34]. Another study also revealed that ALK rearrangement is associated with loco-regional metastasis in patients with stage IA lung ADC who underwent lung resection [41]. However, it should be also mentioned that a considerable proportion of patients with ALK rearrangement has BM at initial staging. Thus, no association between ALK rearrangement and BM in this study might have been caused by a relatively small number of lung ADC with ALK rearrangement. Thus, future studies with large number of patients are needed to confirm this issue.

There are several limitations to this study. First, this study was performed in a single center in South Korea. The pattern of BM may show racial differences and may not be uniformly applicable to another study population. Second, in our institution, molecular analysis for lung cancer was performed according to the discretion of attending physicians. Thus, several factors, such as age, sex, and smoking history might have influenced this decision. Third, tumor differentiation was not evaluated. Fourth, ALK rearrangement was assessed by IHC, not by ALK FISH. In South Korea, the cost for ALK FISH is only covered when it is used to determine the use of (TKIs). Thus, it is likely that the number of lung ADC patients with ALK rearrangement may have been underestimated. However, considering the results of our previous study showing a high correlation of ALK IHC with 2+ or 3+ with ALK FISH [42], this may not have affected the relationship between ALK rearrangement and BM.

In conclusion, the present study showed that BM occurred in approximately 16% of lung ADC patients including, 3% with stage I lung ADC. Large tumor size, LN involvement, and distant metastases were closely associated with BM. While EGFR mutations were risk factors for BM among never-smokers, K-RAS mutations were risk factors for males.

Author contributions

Conception and design: B.Y., H.L., and H.K. Data analysis,

Table 3
Clinical factors associated with brain metastasis.

	Any brain metastases					
	Univariable analysis			Multivariable analysis[b]		
	OR	95% CI	p value	Adjusted OR	95% CI	p value
Age, y	1.01	0.98-1.03	0.637	1.01	0.99-1.03	0.444
Female sex	1.47	0.95-2.29	0.089	1.58	0.70-3.67	0.279
Smoking history						
Nonsmoker	Ref			Ref		
Current or ex-smoker	0.76	0.48-1.18	0.226	0.88	0.38-2.06	0.757
T staging						
T1	Ref			Ref		
T2/T3	2.27	1.37-3.86	< 0.001	1.36	0.75-2.48	0.317
T4	6.34	3.29-12.29	< 0.001	2.29	1.04-5.07	0.040
N staging						
N0	Ref			Ref		
N1	7.25	2.88-17.88	< 0.001	5.35	1.96-14.20	< .001
N2	6.42	3.22-13.38	< 0.001	3.65	1.65-8.27	0.002
N3	12.39	6.60-24.83	< 0.001	6.19	2.90-13.77	< .001
M staging[a]						
M0	Ref			Ref		
M1a	14.65	4.63-47.90	< 0.001	0.37	0.12-0.98	0.062
M1b/M1c	10.34	6.33-17.15	< 0.001	4.52	2.53-8.20	< .001

OR = odds ratio; CI = confidence interval; Ref = reference value; T = tumor; N = node; M = metastasis.
[a] Brain metastasis was not included in the staging.
[b] Factors entered into the model included age, sex, smoking history, T, N, and M staging.

Table 4
Unadjusted and adjusted odds ratio of genetic alterations for the development of brain metastasis.

	Any brain metastases					
	Univariable analysis			Multivariable analysis[c]		
	OR	95% CI	p value	Adjusted OR	95% CI	p value
Total						
Genetic alterations						
EGFR (n = 539)	1.22	0.78-1.90	0.379	1.26	0.75-2.13	0.383
K-RAS (n = 334)	1.46	0.59-3.34	0.386	1.40	0.50-3.365	0.505
ALK (n = 528)	1.19	0.47-2.66	0.692	0.67	0.25-1.61	0.371
Male						
Genetic alterations						
EGFR (n = 261)	0.79	0.37-1.61	0.526	0.78	0.34-1.72	0.546
K-RAS (n = 157)	2.98	0.84-9.70	0.074	3.86	1.01-14.43	0.043
ALK (n = 261)	0.33	0.02-1.67	0.285	0.18	0.01-1.08	0.121
Female						
Genetic alterations						
EGFR (n = 278)	1.42	0.76-2.71	0.280	2.12	1.00-4.52	0.052
K-RAS (n = 177)	0.75	0.17-2.47	0.662	0.38	0.07-1.77	0.244
ALK[a](n = 267)	2.21	0.74-6.00	0.132	1.08	0.32-3.34	0.899
Never-smoker						
Genetic alterations						
EGFR (n = 321)	1.63	0.91-3.04	0.112	2.07	1.02-4.34	0.048
K-RAS (n = 195)	0.93	0.25-2.74	0.896	0.72	0.16-2.85	0.654
ALK (n = 310)	1.42	0.50-3.53	0.481	0.63	0.20-1.78	0.398
Current or ex-smoker						
Genetic alterations						
EGFR (n = 218)	0.60	0.24-1.35	0.239	0.63	0.24-1.52	0.325
K-RAS (n = 139)	2.88	0.70-10.47	0.114	3.48	0.77-14.76	0.090
ALK[b](n = 219)	0.57	0.03-3.12	0.596	0.47	0.02-3.00	0.500

OR = odds ratio; CI = confidence interval; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinas.
[a] Due to absence of smokers with ALK rearrangement, smoking was not included in the multivariable analyses.
[b] Due to absence of females with ALK rearrangement, sex was not included in the multivariable analyses.
[c] Factors entered into the multivariable analysis included age, sex, smoking history, T, N, and M staging, and each type of genetic alteration.

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Appendix A. Supplementary data

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References

[1] J. Sanchez de Cos, M.A. Sojo Gonzalez, M.V. Montero, M.C. Perez Calvo, M.J. Vicente, M.H. Valle, Non-small cell lung cancer and silent brain metastasis. Survival and prognostic factors, Lung Cancer 63 (2009) 140–145.
[2] F. Ampil, G. Caldito, S. Milligan, G. Mills, A. Nanda, The elderly with synchronous non-small cell lung cancer and solitary brain metastasis: does palliative thoracic radiotherapy have a useful role? Lung Cancer 57 (2007) 60–65.
[3] A. Sekine, H. Satoh, T. Iwasawa, K. Tamura, K. Hayashihara, T. Saito, et al., Prognostic factors for brain metastases from non-small cell lung cancer with EGFR mutation: influence of stable extracranial disease and erlotinib therapy, Med. Oncol. 31 (2014) 228.
[4] T. Matys, R. Drury, S. David, D.M. Rassl, W. Qian, R.C. Rintoul, et al., Routine preoperative brain CT in resectable non-small cell lung cancer - ten years experience from a tertiary UK thoracic center, Lung Cancer 122 (2018) 195–199.
[5] F. Hsu, A. De Caluwe, D. Anderson, A. Nichol, T. Toriumi, C. Ho, EGFR mutation status on brain metastases from non-small cell lung cancer, Lung Cancer 96 (2016) 101–107.
[6] F.H. Cole Jr., J.E. Thomas, A.B. Wilcox, H.H. Halford, 3rd, Cerebral imaging in the asymptomatic preoperative bronchogenic carcinoma patient: is it worthwhile? Ann. Thorac. Surg. 57 (1994) 838–840.
[7] Y. Ichinose, N. Hara, M. Ohta, A. Motohiro, T. Maeda, T. Nobe, et al., Preoperative examination to detect distant metastasis is not advocated for asymptomatic patients with stages 1 and 2 non-small cell lung cancer. Preoperative examination for lung cancer, Chest 96 (1989) 1104–1109.
[8] A.A. Balekian, J.M. Fisher, M.K. Gould, Brain imaging for staging of patients with clinical stage IA non-small cell lung cancer in the national lung screening trial: adherence with recommendations from the choosing wisely campaign, Chest 149 (2016) 943–950.
[9] D.S. Ettinger, D.E. Wood, D.L. Aisner, W. Akerley, J. Bauman, L.R. Chirieac, et al., Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Canc. Netw. 15 (2017) 504–535.
[10] G.A. Silvestri, A.V. Gonzalez, M.A. Jantz, M.L. Margolis, M.K. Gould, L.T. Tanoue, et al., Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest 143 (2013) e211S–e250S.
[11] D. Ferrigno, G. Buccheri, Cranial computed tomography as a part of the initial staging procedures for patients with non-small-cell lung cancer, Chest 106 (1994) 1025–1029.
[12] A.A. Shi, S.R. Digumarthy, J.S. Temel, E.F. Halpern, L.B. Kuester, S.L. Aquino, Does initial staging or tumor histology better identify asymptomatic brain metastases in patients with non-small cell lung cancer? J. Thorac. Oncol. 1 (2006) 205–210.
[13] T. Ando, H. Kage, M. Saito, Y. Amano, Y. Goto, J. Nakajima, et al., Early stage non-small cell lung cancer patients need brain imaging regardless of symptoms, Int. J. Clin. Oncol. 23 (2018) 641–646.
[14] S. Novello, F. Barlesi, R. Califano, T. Cufer, S. Ekman, M.G. Levra, et al., Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 27 (2016) v1–v27.
[15] Z. Ji, N. Bi, J. Wang, Z. Hui, Z. Xiao, Q. Feng, et al., Risk factors for brain metastases in locally advanced non-small cell lung cancer with definitive chest radiation, Int. J. Radiat. Oncol. Biol. Phys. 89 (2014) 330–337.
[16] S.N. Waqar, P.P. Samson, C.G. Robinson, J. Bradley, S. Devarakonda, L. Du, et al., Non-small-cell lung cancer with brain metastasis at presentation, Clin. Lung Cancer 19 (2018) e373–e379.
[17] L. Li, S. Luo, H. Lin, H. Yang, H. Chen, Z. Liao, et al., Correlation between EGFR mutation status and the incidence of brain metastases in patients with non-small cell lung cancer, J. Thorac. Dis. 9 (2017) 2510–2520.
[18] I. Zhang, N.G. Zaorsky, J.D. Palmer, R. Mehra, B. Lu, Targeting brain metastases in ALK-rearranged non-small-cell lung cancer, Lancet Oncol. 16 (2015) e510–521.
[19] F. Petrelli, C. Lazzari, R. Ardito, K. Borgonovo, A. Bulotta, B. Conti, et al., Efficacy of ALK inhibitors on NSCLC brain metastases: a systematic review and pooled analysis of 21 studies, PLoS One 13 (2018) e0201425.
[20] D.E. Wood, National Comprehensive Cancer network (NCCN) clinical practice guidelines for lung cancer screening, Thorac. Surg. Clin. 25 (2015) 185–197.
[21] P. Goldstraw, K. Chansky, J. Crowley, R. Rami-Porta, H. Asamura, W.E. Eberhardt, et al., The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer, J. Thorac. Oncol. 11 (2016) 39–51.
[22] H.Y. Park, Y.H. Kim, H. Kim, W.J. Koh, G.Y. Suh, M.P. Chung, et al., Routine screening by brain magnetic resonance imaging decreased the brain metastasis rate following surgery for lung adenocarcinoma, Lung Cancer 58 (2007) 68–72.
[23] S.E. Park, J.M. Noh, Y.J. Kim, H.S. Lee, J.H. Cho, S.W. Lim, et al., EGFR mutation is associated with short progression free survival in patients with stage III non-squamous cell lung cancer treated with concurrent chemoradiotherapy, Cancer Res. Treat. (2018).
[24] S. Lee, Y. Kim, J.M. Sun, Y.L. Choi, J.G. Kim, Y.M. Shim, et al., Molecular profiles of EGFR, K-ras, c-met, and FGFR in pulmonary pleomorphic carcinoma, a rare lung malignancy, J. Cancer Res. Clin. Oncol. 137 (2011) 1203–1211.
[25] A. Marchetti, A. Di Lorito, M.V. Pace, M. Iezzi, L. Felicioni, T. D'Antuono, et al., ALK protein analysis by IHC staining after recent regulatory changes: a comparison of two widely used approaches, revision of the literature, and a new testing algorithm, J. Thorac. Oncol. 11 (2016) 487–495.
[26] C.M. Conklin, K.J. Craddock, C. Have, J. Laskin, C. Couture, D.N. Ionescu, Immunohistochemistry is a reliable screening tool for identification of ALK rearrangement in non-small-cell lung carcinoma and is antibody dependent, J. Thorac. Oncol. 8 (2013) 45–51.
[27] E.S. Yi, J.M. Boland, J.J. Maleszewski, A.C. Roden, A.M. Oliveira, M.C. Aubry, et al., Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH, J. Thorac. Oncol. 6 (2011) 459–465.
[28] P.H. Goncalves, S.L. Peterson, F.D. Vigneau, R.D. Shore, W.O. Quarshie, K. Islam, et al., Risk of brain metastases in patients with nonmetastatic lung cancer: analysis of the Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) data, Cancer 122 (2016) 1921–1927.
[29] H. Lee, S.H. Jeong, B.H. Jeong, H.Y. Park, K.J. Lee, S.W. Um, et al., Incidence of brain metastasis at the initial diagnosis of lung squamous cell carcinoma on the basis of stage, excluding brain metastasis, J. Thorac. Oncol. 11 (2016) 426–431.
[30] A. Salvatierra, C. Baamonde, J.M. Llamas, F. Cruz, J. Lopez-Pujol, Extrathoracic staging of bronchogenic carcinoma, Chest 97 (1990) 1052–1058.
[31] R. Salbeck, H.C. Grau, H. Artmann, Cerebral tumor staging in patients with bronchial carcinoma by computed tomography, Cancer 66 (1990) 2007–2011.
[32] A. Mujoomdar, J.H.M. Austin, R. Malhotra, C.A. Powell, G.D.N. Pearson, M.C. Shiau, et al., Clinical predictors of metastatic disease to the brain from non–small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases, Radiology 242 (2007) 882–888.
[33] H. Lee, J.-G. Joung, H.-T. Shin, D.-H. Kim, Y. Kim, H. Kim, et al., Genomic alterations of ground-glass nodular lung adenocarcinoma, Sci. Rep. 8 (2018) 7691.
[34] C.M. Choi, M.Y. Kim, H.J. Hwang, J.B. Lee, W.S. Kim, Advanced adenocarcinoma of the lung: comparison of CT characteristics of patients with anaplastic lymphoma kinase gene rearrangement and those with epidermal growth factor receptor mutation, Radiology 275 (2015) 272–279.
[35] T. Iuchi, M. Shingyoji, M. Itakura, S. Yokoi, Y. Moriya, H. Tamura, et al., Frequency of brain metastases in non-small-cell lung cancer, and their association with epidermal growth factor receptor mutations, Int. J. Clin. Oncol. 20 (2015) 674–679.
[36] V. Noronha, A. Choughule, V.M. Patil, A. Joshi, R. Kumar, D. Susan Joy Philip, et al., Epidermal growth factor receptor exon 20 mutation in lung cancer: types, incidence, clinical features and impact on treatment, Onco. Ther. 10 (2017) 2903–2908.
[37] R.C. Doebele, X. Lu, C. Sumey, D.A. Maxson, A.J. Weickhardt, A.B. Oton, et al., Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer, Cancer 118 (2012) 4502–4511.
[38] N. Zhao, M.D. Wilkerson, U. Shah, X. Yin, A. Wang, M.C. Hayward, et al., Alterations of LKB1 and KRAS and risk of brain metastasis: comprehensive characterization by mutation analysis, copy number, and gene expression in non-small-cell lung carcinoma, Lung Cancer 86 (2014) 255–261.
[39] Z. Lohinai, T. Klikovits, J. Moldvay, G. Ostoros, E. Raso, J. Timar, et al., KRAS-mutation incidence and prognostic value are metastatic site-specific in lung adenocarcinoma: poor prognosis in patients with KRAS mutation and bone metastasis, Sci. Rep. 7 (2017) 39721.
[40] I.A. Prior, P.D. Lewis, C. Mattos, A comprehensive survey of Ras mutations in cancer, Cancer Res. 72 (2012) 2457–2467.
[41] S.H. Shin, H. Lee, B.H. Jeong, Y.S. Choi, M.H. Shin, S. Kim, et al., Anaplastic lymphoma kinase rearrangement in surgically resected stage IA lung adenocarcinoma, J. Thorac. Dis. 10 (2018) 3460–3467.
[42] I.H. Choi, D.W. Kim, S.Y. Ha, Y.L. Choi, H.J. Lee, J. Han, Analysis of histologic features suspecting anaplastic lymphoma kinase (ALK)-expressing pulmonary adenocarcinoma, J. Pathol. Transl. Med. 49 (2015) 310–317.