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A diagnostic model to detect silent brain metastases in patients with non-small cell lung cancer ☆

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ABSTRACT

We aimed to discriminate subgroups according to the risk of brain metastases in patients with non-small cell lung cancer (NSCLC) lacking neurological symptoms. We performed a retrospective review of 433 patients with NSCLC who underwent chest computed tomography (CT), brain magnetic resonance imaging (MRI) and bone scans at an initial staging work-up between April 2003 and April 2007. Brain metastases were determined by MRI. Patients were stratified into groups according to the number of risk factors (0–3) identified by multivariate analysis. In multivariate analysis, histopathology with non-squamous cell carcinoma, nodal stage $\geqslant 2$ on CT and presence of bone metastases were three risk factors for brain metastases. Patients were divided into four groups according to the number (0–3) of these predictive factors. The proportions of patients with brain metastases in the four groups were 2%, 3%, 17% and 35%, respectively, and these differences were significant ($P < 0.001$). When analysis was performed in patients with localised disease, the number of risk factors was correlated with the prevalence of brain metastases ($P = 0.013$) but stage was not ($P = 0.153$). Although this diagnostic model should be validated through further studies, our data suggest that the number of risk factors might be a useful tool to identify silent brain metastases in patients with NSCLC.

1. Introduction

Lung cancers, of which more than 80% show non-small cell histology, form a leading cause of death worldwide.[1,2] Initial presentations with distant metastases are common.[3] Extra-thoracic staging of non-small cell lung cancers (NSCLCs) is important for prognostic estimation and treatment strategy.[4,5] The brain is one of the most frequent sites of extra-thoracic metastases.[6]

Although positron emission tomography (PET) scans have been introduced as a useful tool for staging of NSCLCs,[7] it is not yet widely available. Moreover, PET is not a practical tool to evaluate brain metastases due to high background activity in brain tissue.[8] Therefore, computed tomography (CT) scans

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or magnetic resonance imaging (MRI) is recommended for cranial staging.[9] However, fewer than 10% brain metastases have been detected in patients with negative neurological signs and symptoms,[10] and the cost-effectiveness of routine screening for brain metastases is not clear.[11]

Routine screening for brain metastases in asymptomatic patients has not yet reached a consensus in practice guidelines. Whereas the American Thoracic and European Respiratory Societies advocate no routine screening in asymptomatic patients,[12] the American Society of Clinical Oncology recommends cranial screening for patients with stage III cancers who are being considered for local treatment.[13] However, other studies suggest that cranial scanning should be performed routinely.[14,15] Furthermore, some investigators have reported that some types of pathology that are not considered in current guidelines[12,13] are associated with risks of brain metastases.[16–18]

Traditionally, the blood–brain barrier has been considered as a limiting factor of chemotherapeutic agents in treating patients with brain metastases.[19] Local treatment such as radiation or surgery has been applied to control metastatic brain lesions.[20] Although some investigators have reported the effectiveness of a chemotherapeutic agent for brain metastases,[21] their role has not been established. Therefore, even in patients with advanced stages, detection of brain metastases may be useful to determine therapeutic strategies.

It has been suggested that diagnostic accuracy of MRI is superior to CT in patients with brain metastasis.[22,23] Brain MRI is a useful technique for the evaluation of small lesions with brain metastases in patients with NSCLC.[10] Although clinical benefits of its application remain unclear in asymptomatic patients with NSCLC,[10] detection of brain metastases could reduce the discomfort and the unnecessary risks caused by invasive procedures such as mediastinoscopy or aggressive local treatment. Also, it could be helpful to determine the additional local treatment for brain lesions in advanced stages. The selected application of brain MRI in high-risk patients could lead to an improvement in cost-effectiveness. Therefore, stratification of patients with newly diagnosed NSCLCs, using risk factors for brain metastases, could be useful in making a decision to proceed to cranial staging. We launched this retrospective study to identify predictive factors and to discriminate subgroups according to the risk of brain metastases in patients with NSCLC lacking neurological symptoms.

2. Patients and methods

2.1. Patient population

We evaluated patients with NSCLCs who were consecutively diagnosed at our hospital between April 2003 and April 2007. Four hundred forty-six patients met the following entry criteria: Brain MR, chest CT and bone scans were applied at diagnosis. Patients without neurological symptoms, which were defined using criteria as described in a previous study,[16] and histopathology were reviewed at Korea Cancer Center Hospital in Seoul. Amongst these patients, we excluded seven with sarcomatoid carcinomas and six with adenosquamous cell carcinomas. A total of 433 patients were included. All medical records including images were reviewed.

Chest CT scans were performed as a part of the diagnostic work-up using one of the two helical scanners (Volume Zoom; Siemens Medical Systems, Erlangen, Germany, or HiSpeed CT/i; GE Medical Systems, Milwaukee, WI, USA). The CT scans were obtained from the supraclavicular regions through the upper abdomen following intravenous administration of a contrast agent using 5 or 10 mm thick sections.

Brain MRI scanning was performed using a 1.5-T unit (Signa 1.5-T; GE Medical Systems). Spin-echo T1-weighted images (500/8 repetition time/echo time, two signals acquired, 256×192 matrix, 20 cm field of view) and T2-weighted images (6000/84 repetition time/echo time, one signal acquired, 512×256 matrix, 20 cm field of view) were obtained in the axial plane with 7 mm sections and 0.1 mm intersection gap. Axial, coronal and sagittal T1-weighted images were obtained for contrast MR studies after intravenous administration of gadopentetate dimeglumine (0.1 mmol/kg).

Whole body bone scans using a gamma camera were obtained 3–4 h after injection of 20 mCi methylene diphosphonate labelled with 99 mTC. Bone scans were used to diagnose bone metastases[24] if they showed multiple hot uptakes consistent with metastases or if they showed increased uptakes showing typical findings in additional studies (i.e. radiography, CT or MRI scans). Brain metastases were diagnosed based on brain MRI scans interpreted by one neuroradiologist (T.H.L., with five years of experience). Stage was classified using the TNM (tumour, node, metastasis) system.[25] T and N factors were decided based on findings of CT with or without additional fiberoptic bronchoscopy. One thoracic radiologist (D.H.C., with 10 years of experience) reviewed the CT images. Mediastinal lymph nodes larger than 1 cm on transaxial CT images were considered positive. Adrenal masses, except for benign-looking lesions showing low attenuation (<10 Hounsfield unit) on unenhanced CT scans, that were performed if indicated clinically, were considered metastases.[16,26] The institutional review board at the Korea Cancer Center Hospital reviewed and approved the study protocol.

2.2. Statistical analysis

Predictive factors for brain metastases were evaluated by univariate analysis using Pearson's Chi-squared test or Fisher's exact test. Using the median value of diameter, primary cancers were categorised into large ($\geqslant$median) or small tumours (<median). Multivariate logistic regression analysis with stepwise forward selection was performed to identify the predictors of brain metastases. A model using the number of risk factors identified by multivariate analysis was constructed and compared with one using TNM staging alone. The Bayesian information criteria (BIC) statistics, inversely correlated with a model's fit, were used to compare the two models and Raftery's guidelines were used to interpret BIC differences between the two models.[27] Briefly, BIC differences of 0–2, 2–6, 6–10, >10 were assumed to provide weak, positive, strong and very strong evidence for the new model giving a smaller BIC, respectively. A multilevel likelihood ratio (LR) for stage or number of predictors was calculated according to previously as described.[28]

Stata version 9.0 software (Stata Corp., College Station, TX, USA) was used for statistical analyses. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All *P*-values were derived from two-sided tests and $P < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

Data from 433 patients were analysed and Table 1 shows their characteristics. The median age was 66 years and 77% of the patients were men. The sizes of primary lung tumours ranged from 1 to 9 cm (median 3.6 cm). Of these patients, 47% had squamous cell carcinomas and 41% had adenocarcinomas. On CT scans, 162 patients had N2 or N3 nodes. Most of the extrapulmonary metastatic lesions were in bone (12%), the adrenal gland (3%) and the liver (2%). Thirty-two patients (7%) had brain metastases. The maximum size of brain lesions ranged from 0.2 to 2.3 cm with a median of 0.9 cm.

3.2. Risk factors for brain metastases

Results of the univariate analysis are listed in Table 2. Tumour size (large versus small) was a risk factor in this analysis ($P = 0.027$). When the tumour stage was analysed as T, N or M factors, the T factor did not affect brain metastases ($P = 0.689$), but both N and M factors did ($P < 0.001$). Compared with squamous cell carcinoma, the risk of brain metastases in patients with non-squamous cell carcinoma was increased significantly ($P = 0.004$). The presence of bone metastases together with metastases in the lung and other distant sites was associated with brain metastases by univariate analysis. However, amongst those significant clinical features identified by univariate analysis, when we used multivariate analysis, histology (squamous cell carcinoma or not), N stage (0–1 versus 2) and the presence of bone metastases were significantly associated with brain metastases. The TNM stage did not remain significant when subjected to multivariate logistic regression.

3.3. Diagnostic model for brain metastases

Next, we attempted to categorise patients using the risk factors defined by the multivariate analysis (i.e. non-squamous cell carcinoma, nodal stage $\geqslant 2$, bone metastases). The 433 patients were allocated to four groups according to the number of risk factors: 124 patients with none; 202 patients with one; 81 patients, with two and 26 with three. The proportions of patients with brain metastases in these four groups were 2%, 3%, 17% and 35% (Table 2) and its difference was significant ($P < 0.001$). In receiver operating curve analysis, the area under the curve (AUC) for the number of risk factors was similar to that for stage (0.77 and 0.74, respectively). However, the difference in the partial AUC for a false positive rate <20% was 0.05 (95% CI, 0.02–0.08), which suggests diagnostic superiority of the proposed model when high sensitivity is of great importance. Considering the similar frequency of brain metastases between stage II and III, we combined the data on these two stages. Similarly, data on patients with two or three risk factors were merged (Fig. 1A). We then calculated the LRs and their 95% CIs in these groups (Fig. 1B). In the stage-based model, the LR in stage II or III was 0.8 (95% CI, 0.5–1.3), which suggests a limited diagnostic ability. Furthermore, the BIC statistics (difference of 9.3) showed 'strong' evidence favouring the model constructed using the number of risk factors compared with the model using the TNM stage alone.

Table 1 – Patient characteristics

Characteristic	Number of patients (%)
Age (years)	
Median	66 (range 39–84)
⩽66	224 (52)
>66	209 (48)
Sex	
Male	333 (77)
Female	100 (23)
Histology	
SCC	202 (47)
ADC	178 (41)
Large cell carcinoma	7 (2)
NOS	45 (10)
PS	
⩽1	397 (92)
>1	36 (8)
Tumour size	
Small (⩽3.6 cm)	217 (50)
Large (>3.6 cm)	216 (50)
T stage	
T1–2	337 (78)
T3–4	96 (22)
N stage	
N0–1	274 (63)
N2–3	159 (37)
M stage[a]	
M0	334 (77)
M1	99 (23)
Metastatic sites	
Bone	52 (12)
Lung	41 (9)
Adrenal gland	12 (3)
Liver	10 (2)
Not classified[b]	7 (2)
Stage[a]	
I	163 (38)
II	60 (14)
III	111 (26)
IV	99 (23)
Brain metastases	
Yes	32 (7)
No	401 (93)
Maximal size of brain metastases, cm	
Median (range)	0.9 (0.2–2.3)

NOS, not otherwise specified; PS, performance status; SCC, squamous cell carcinoma; ADC, adenocarcinoma.
a Brain metastases were not considered in staging.
b Skin, kidney or lymph node.

Table 2 – Risk factors for brain metastases

Characteristic	Number of patients with a brain metastasis (%)	P	OR in multivariate analysis (95% CI)	P
Age, years		0.102	NI	
⩽66	21 (9)			
>66	11 (5)			
Sex		0.790	NI	
Male	25 (7)			
Female	8 (8)			
Histology		0.004		
SCC	7 (3)		Reference	0.020
Others	25 (11)		2.9 (1.2–7.2)	
PS		0.120	NI	
⩽1	27 (7)			
>1	5 (14)			
Tumour size			NI	
Small (⩽3.6)	10 (5)	0.027		
Large (>3.6)	22 (10)			
T stage			NI	
T1–2	24 (7)	0.689		
T3–4	8 (8)			
N stage				
N0–1	9 (3)	<0.001	Reference	0.001
N2–3	23 (14)		4.1 (1.8–9.5)	
M stage			NI	
M0	13 (4)	<0.001		
M1	19 (19)			
Metastasis to bone				0.004
No	19 (5)	<0.001	Reference	
Yes	13 (25)		3.4 (1.5–7.9)	
Metastasis to lung			NI	
No	25 (6)	0.013		
Yes	7 (17)			
Metastasis to other sites			NI	
Yes	27 (7)	0.022		
No	5 (19)			
Stage (except brain)			NI	
I	3 (2)	<0.001		
II	3 (5)			
III	7 (6)			
IV	19 (19)			
Number of risk factors[a]		<0.001		
0	3 (2)			
1	6 (3)			
2	14 (17)			
3	9 (35)			

CI, confidence interval; NI, not included; PS, performance status; SCC, squamous cell carcinoma; ADC, adenocarcinoma.
a Significant factors in multivariate analysis.

When we performed a statistical analysis in patients with stage I–III, the difference according to the number of risk factors (0, 1 and 2) was statistically significant (3%, 3% and 12%, respectively; $P = 0.013$). Meanwhile, the difference in the prevalence of brain metastases by stage (I, II and III) did not reach statistical significance (2%, 5% and 6%, respectively; $P = 0.153$).

4. Discussion

This retrospective study evaluated the risk factors of brain metastases in patients with NSCLC lacking neurological symptoms. Based on the number of risk factors, patients could be stratified with different risks for showing brain metastases. Although the brain is one of the most common sites for metastatic lesions, the routine cranial staging of silent brain metastases is controversial.[12–15] Cranial staging is recommended based on the stage alone in one practical guideline.[13] In this study, the diagnostic model included the N2 factor amongst TNM stage along with histopathology and bone metastases. Importantly, our data suggest that this model could predict silent brain metastases better than one including TNM stage alone.

The prevalence and risk factors of silent brain metastases should be interpreted cautiously considering the different methods of studying brain metastases and various proportions of advanced stages or pathologies.[18,29,30] The prevalence of silent brain metastases in our study (7%) is consistent with the previous reports.[18,29] As in other studies, patients with

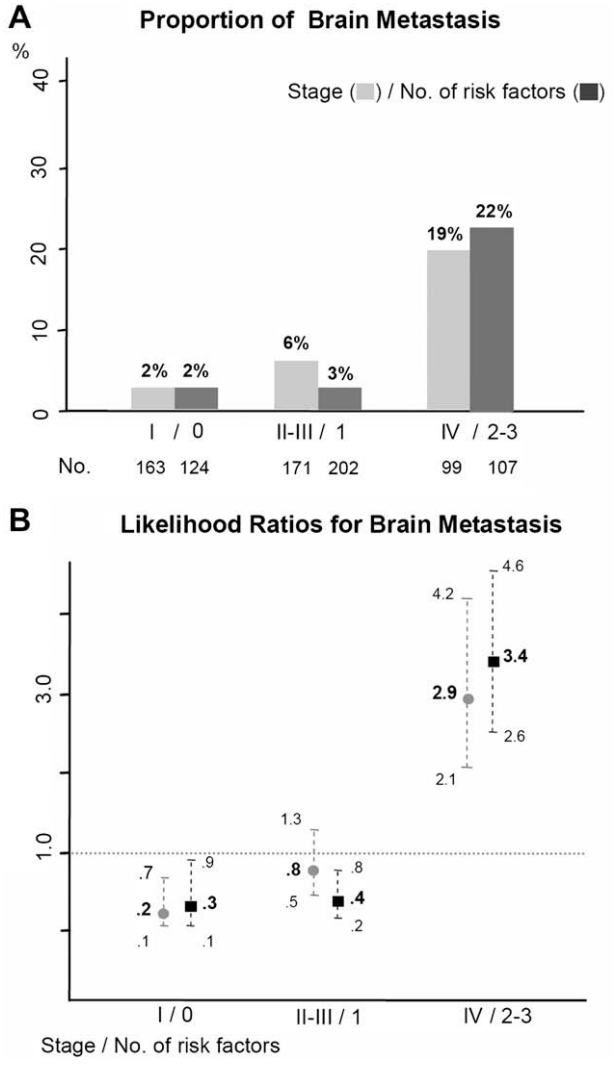

Fig. 1 – (A) The proportions of patients with brain metastases related to stage and number of risk factors. (B) Multilevel likelihood ratios (LR) and their 95% confidence intervals according to stage and number of risk factors, respectively.

non-squamous cell carcinomas were associated with an increased risk of brain metastases.[18,31–33] The high-risk of brain metastases in patients with N2 or N3 stage is also in line with the previous studies.[17,34]

Although the TNM stage was significantly associated with brain metastases, the T factor was not a risk factor, in contrast with N and M factors. One report suggested that the T stage might be a risk factor for having brain metastases.[17] However, this finding was not suggested in other studies.[35,36] In our data, tumour size was linked with brain metastases by univariate analysis. Although this finding is consistent with the results of a previous study,[37] our multivariate analysis suggests that tumour size might not be an independent risk factor. The design of our study focusing on neurologically asymptomatic patients 'at diagnosis' might explain the disparity between the studies.[17,35,36] The clinical significance of T stage and tumour size for the actual risk of brain metastases should be defined through further studies.

Consistent with a previous pilot study, we observed a link between the two metastatic sites.[38] Simply, the high-risk of brain metastases in patients with bone metastases could be due to the extent of tumour spread. In addition, adenocarcinoma histology, a risk factor of both brain and bone metastases,[16] might explain such a link. However, it should be noted that bone metastases, compared with non-skeletal metastases, were associated with an increased risk of brain metastases when analysed by multivariate analysis. Further studies should be followed to confirm this finding.

In addition to the BIC statistics, LRs were used to compare the predicting model based on the number of risk factors with the stage-based one. LRs, alternative statistics for diagnostic accuracy, provide information about the probability that a patient has a given target disease.[39] The further LR is from 1.0, the greater its effect is on the presence or absence of a target disease.[39] Conversely, an LR close to 1.0 indicates uselessness as a diagnostic test. Therefore, in the proposed model, three groups could be considered to have an increased or decreased probability of brain metastases based on their LRs. In contrast, diagnostic ability in stage II or III seems to be limited in the stage-based model (Fig. 1B). Moreover, for localised disease, the stage-based model could not discriminate patients with brain metastases, but the proposed model could. However, in this study, the proposed model, using a small number of patients with silent brain metastases, was constructed without an external validation. Therefore, the proposed model needs to be validated through further studies with a sufficient sample size.[40]

Our data should be interpreted cautiously given the retrospective natures of this study. Although a false positive rate of 11% using brain CT has been reported in patients with a single brain metastasis,[41] the multiple tumourous lesions in patients with NSCLC that were confirmed by pathology seem to support this method for making a diagnosis of brain metastases. In our data, 15/32 (47%) patients with brain metastases had multiple lesions on brain MRI. Amongst 17 patients with a single brain lesion, nine underwent follow-up brain MRI scans at least three months later, and progressing lesions in the brain were observed in six of them. Although the results of our study could be biased by false positive interpretations of brain metastases, it should be noted that MRI is more accurate for the diagnosis of brain metastases than CT.[10,23] A substantial change in the incidence of brain metastases is not likely to occur.

Although the brain has been considered as a pharmacological sanctuary site because of the blood–brain barrier,[19] some authors have reported favourable responses in treating brain lesions with front-line chemotherapy.[21] However, small lesions in asymptomatic patients might have a less disrupted blood–brain barrier.[19] This idea is partly supported by a study suggesting a low response rate of brain lesions to systemic chemotherapy in asymptomatic patients with small cell lung cancers.[42] Therapeutic benefits of chemotherapy, compared with radiation therapy, are not completely understood. Therefore, additional local treatments for asymptomatic brain lesions could be considered in patients with advanced stages. Future studies are essential to establish suitable treatments for such patients. Our findings in respect to identification of high-risk patients could be useful in the design of clinical trials.

These results suggest that a diagnostic model using several risk factors may be useful to identify silent brain metastases in patients with NSCLC at presentation. In addition, our study indicates that this proposed model is able to discriminate high-risk patients accurately compared with a stage-based model. These results suggest that the number of risk factors could be helpful in clinical practice and in designing future studies. Further studies are recommended to validate this diagnostic model.

Conflict of interest statement

None declared.

REFERENCES

1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;**2**(9):533–43.
2. Lee C-T. Epidemiology of lung cancer in Korea. *Cancer Res Treat* 2002;**34**(1):3–7.
3. Quint LE, Tummala S, Brisson LJ, et al. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. *Ann Thorac Surg* 1996;**62**(1):246–50.
4. Quinn DL, Ostrow LB, Porter DK, Shelton Jr DK, Jackson Jr DE. Staging of non-small cell bronchogenic carcinoma. Relationship of the clinical evaluation to organ scans. *Chest* 1986;**89**(2):270–5.
5. Pope RJ, Hansell DM. Extra-thoracic staging of lung cancer. *Eur J Radiol* 2003;**45**(1):31–8.
6. Hillers TK, Sauve MD, Guyatt GH. Analysis of published studies on the detection of extrathoracic metastases in patients presumed to have operable non-small cell lung cancer. *Thorax* 1994;**49**(1):14–9.
7. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *New Engl J Med* 2003;**348**(25):2500–7.
8. Marom EM, McAdams HP, Erasmus JJ, et al. Staging non-small cell lung cancer with whole-body PET. *Radiology* 1999;**212**(3):803–9.
9. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003;**123**(1 Suppl):137S–46S.
10. Yokoi K, Kamiya N, Matsuguma H, et al. Detection of brain metastasis in potentially operable non-small cell lung cancer: a comparison of CT and MRI. *Chest* 1999;**115**(3):714–9.
11. Colice GL, Birkmeyer JD, Black WC, Littenberg B, Silvestri G. Cost-effectiveness of head CT in patients with lung cancer without clinical evidence of metastases. *Chest* 1995;**108**(5):1264–71.
12. The American Thoracic Society and The European Respiratory Society. Pretreatment evaluation of non-small-cell lung cancer. *Am J Respir Crit Care Med* 1997;**156**(1):320–332.
13. Pfister DG, Johnson DH, Azzoli CG, et al. American society of clinical oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;**22**(2):330–53.
14. Ferrigno D, Buccheri G. Cranial computed tomography as a part of the initial staging procedures for patients with non-small-cell lung cancer. *Chest* 1994;**106**(4):1025–9.
15. Bilgin S, Yilmaz A, Ozdemir F, Akkaya E, Karakurt Z, Poluman A. Extrathoracic staging of non-small cell bronchogenic carcinoma: relationship of the clinical evaluation to organ scans. *Respirology* 2002;**7**(1):57–61.
16. Metintas M, Ak G, Akcayir IA, et al. Detecting extrathoracic metastases in patients with non-small cell lung cancer: is routine scanning necessary? *Lung Cancer* 2007;**58**(1):59–67.
17. Bajard A, Westeel V, Dubiez A, et al. Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* 2004;**45**(3):317–23.
18. Shi AA, Digumarthy SR, Temel JS, Halpern EF, Kuester LB, Aquino SL. Does initial staging or tumor histology better identify asymptomatic brain metastases in patients with non-small cell lung cancer? *J Thorac Oncol* 2006;**1**(3):205–10.
19. Postmus PE, Smit EF. Chemotherapy for brain metastases of lung cancer: a review. *Ann Oncol* 1999;**10**(7):753–9.
20. Kvale PA, Selecky PA, Prakash UB. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed.). *Chest* 2007;**132**(3 Suppl.):368S–403S.
21. Cortes J, Rodriguez J, Aramendia JM, et al. Front-line paclitaxel/cisplatin-based chemotherapy in brain metastases from non-small-cell lung cancer. *Oncology* 2003;**64**(1):28–35.
22. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol* 1999;**44**(3):275–81.
23. Davis PC, Hudgins PA, Peterman SB, Hoffman Jr JC. Diagnosis of cerebral metastases: double-dose delayed CT vs. contrast-enhanced MR imaging. *AJNR Am J Neuroradiol* 1991;**12**(2):293–300.
24. Erturan S, Yaman M, Aydin G, Uzel I, Musellim B, Kaynak K. The role of whole-body bone scanning and clinical factors in detecting bone metastases in patients with non-small cell lung cancer. *Chest* 2005;**127**(2):449–54.
25. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;**111**(6):1718–23.
26. Kim HK, Choi YS, Kim K, Kim J, Shim YM. Preoperative evaluation of adrenal lesions based on imaging studies and laparoscopic adrenalectomy in patients with otherwise operable lung cancer. *Lung Cancer* 2007;**58**(3):342–7.
27. Kass R, Raftery A. Bayes factors. *J Am Stat Assoc* 1990;**90**(430):773–95.
28. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *J Clin Epidemiol* 1991;**44**(8):763–70.
29. de Cos Escuin JS, Menna DM, Gonzalez MA, Quirantes JZ, Vicente CD, Calvo MC. Silent brain metastasis in the initial staging of lung cancer: evaluation by computed tomography and magnetic resonance imaging. *Arch Bronconeumol* 2007;**43**(7):386–91.
30. Hochstenbag MM, Twijnstra A, Hofman P, Wouters EF, ten Velde GP. MR-imaging of the brain of neurologic asymptomatic patients with large cell or adenocarcinoma of the lung. Does it influence prognosis and treatment? *Lung Cancer* 2003;**42**(2):189–93.
31. Mamon HJ, Yeap BY, Janne PA, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol* 2005;**23**(7):1530–7.
32. Komaki R, Cox JD, Stark R. Frequency of brain metastasis in adenocarcinoma and large cell carcinoma of the lung: correlation with survival. *Int J Radiat Oncol Biol Phys* 1983;**9**(10):1467–70.
33. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007;**109**(8):1668–75.
34. Ceresoli GL, Reni M, Chiesa G, et al. Brain metastases in locally advanced nonsmall cell lung carcinoma after

multimodality treatment: risk factors analysis. *Cancer* 2002;**95**(3):605–12.
35. Tang SG, Lin FJ, Leung WM. Impact of prophylactic cranial irradiation in adenocarcinoma of the lung. *J Formos Med Assoc* 1993;**92**(5):413–9.
36. Jacobs RH, Awan A, Bitran JD, et al. Prophylactic cranial irradiation in adenocarcinoma of the lung. A possible role. *Cancer* 1987;**59**(12):2016–9.
37. Mujoomdar A, Austin JH, Malhotra R, 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* 2007;**242**(3):882–8.
38. Earnest Ft, Ryu JH, Miller GM, et al. Suspected non-small cell lung cancer: incidence of occult brain and skeletal metastases and effectiveness of imaging for detection – pilot study. *Radiology* 1999;**211**(1):137–45.
39. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet* 2005;**365**(9469):1500–5.
40. Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol* 2003;**56**(9):826–32.
41. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *New Engl J Med* 1990;**322**(8):494–500.
42. Seute T, Leffers P, Wilmink JT, ten Velde GP, Twijnstra A. Response of asymptomatic brain metastases from small-cell lung cancer to systemic first-line chemotherapy. *J Clin Oncol* 2006;**24**(13):2079–83.