ORIGINAL ARTICLES

Silent Brain Metastasis in the Initial Staging of Lung Cancer: Evaluation by Computed Tomography and Magnetic Resonance Imaging

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OBJECTIVE: Brain metastases are common in patients with lung cancer and influence both prognosis and treatment decisions. The aim of this study was to evaluate the incidence of silent brain metastasis during the initial staging of lung cancer using cranial computed tomography (CT) and magnetic resonance imaging (MRI).

PATIENTS AND METHODS: We performed a retrospective analysis of lung cancer patients with no neurologic signs or symptoms who were evaluated by cranial CT, MRI, or both at the time of diagnosis. Results were checked using data obtained during systematic monitoring of progression. The incidence of brain metastasis was analyzed by sex, age, histology, and TNM stage.

RESULTS: Silent brain metastasis was detected in 8.3% of the 169 patients with lung cancer. The detection rate was 7.9% in the cranial CT group and 11.3% in the cranial MRI group. The percentage of false positives and false negatives was 0% and 1.9%, respectively. Cranial MRI performed better than CT in detecting multiple brain metastases (72.8% vs 50%) and metastases smaller than 1 cm (36.3% vs 16.7%). The incidence of brain metastasis was lower in patients aged over 70 years and higher in patients with adenocarcinoma (20% compared to 5.3% to 5.9% for other histologic subtypes, *P*=.01). No association was found with TNM stage.

CONCLUSIONS: The incidence of silent brain metastasis is high in patients under 70 years of age, particularly in patients with adenocarcinomas, even in initial stages. This should be taken into consideration when planning staging procedures. Cranial MRI seems to be more accurate than cranial CT for detecting multiple metastases and small metastases.

Key words: *Lung cancer. Silent brain metastasis. Computed tomography. Magnetic resonance imaging.*

Metástasis encefálicas silentes en la estadificación inicial del cáncer de pulmón. Evaluación mediante tomografía computarizada y resonancia magnética

OBJETIVO: Las metástasis cerebrales (MC) son frecuentes en el cáncer de pulmón (CP) y tienen influencia pronóstica y terapéutica. El objetivo del trabajo ha sido evaluar la incidencia de MC silentes en la estadificación inicial del CP mediante tomografía axial computarizada y resonancia magnética craneales (TACC y RMC).

PACIENTES Y MÉTODOS: Análisis retrospectivo de los pacientes con CP que tenían un estudio craneal mediante TACC y/o RMC en ausencia de síntomas/signos neurológicos en el momento del diagnóstico. Para verificar los resultados se usó como criterio la evolución mediante un seguimiento frecuente. Se comparó la incidencia de MC según sexo, edad, histología y estadio TNM.

RESULTADOS: Se detectaron MC silentes en el 8,3% de 169 pacientes con CP: un 7,9% en el grupo de TACC y un 11,3%, en el de RMC. La tasa de resultados falsos positivos fue del 0% y la de falsos negativos, del 1,9%. La RMC detectó más MC múltiples (un 72,8 frente a un 50%) y menores de 1 cm (un 36,3 frente a un 16,7%) que la TACC. La incidencia de MC fue menor en mayores de 70 años y superior en adenocarcinomas (un 20 frente a un 5,3-5,9%; p = 0,01). No hubo relación con el grado de extensión.

CONCLUSIONES: En pacientes menores de 70 años y especialmente en adenocarcinomas, la incidencia de MC silentes es elevada, incluso en estadios iniciales, lo que debería considerarse al planificar las pruebas de estadificación. La RMC parece más exacta para detectar MC múltiples y de pequeño tamaño.

Palabras clave: *Cáncer de pulmón. Metástasis cerebrales silentes. Tomografía computarizada. Resonancia magnética.*

Introduction

Lung cancer is often diagnosed in advanced stages given its high propensity to metastasize. The brain is often the site of metastasis from the lung,[1] and in fact most brain metastases are caused by a primary lung tumor.[2] The detection of brain metastasis generally affects treatment decisions, unless the patient's general state of health is so

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poor that palliative care is the only option. There is widespread agreement that diagnostic tests should be performed in patients with signs or symptoms suggestive of brain metastasis because of the poor positive predictive value of clinical evaluation (around 50%).[3] Several years ago, the European Respiratory Society and the American Thoracic Society recommended performing cranial computed tomography (CT) in patients with neurologic symptoms[4] but there are doubts as to whether this approach is of value in the absence of such manifestations.[5,6] The American Society of Clinical Oncology has made minor changes to its recommendations and now states: "Head CT or magnetic resonance imaging (MRI) with and without infusion of contrast material is recommended in patients who have signs or symptoms of central nervous system disease, *as well as* asymptomatic patients with stage III disease who are being considered for aggressive local therapy (*chest surgery or radiation*)"[7] (italics added). The recent guidelines issued by the American College of Chest Physicians make the same recommendation but do not include patients with stage I and II disease with a negative clinical evaluation.[5] None of these important guidelines specify whether other factors such as histologic type, sex, and age should be considered when deciding whether or not to perform cranial imaging studies (CT or MRI). Most of the evidence used to draw up these initial guidelines was based on cranial CT studies and, as Silvestri and colleagues[5] pointed out, the systematic use of MRI in the staging of non-small cell lung cancer has not yet been adequately studied. Several studies, however, mostly involving small samples, have demonstrated the value of MRI for detecting silent brain metastasis, particularly when an aggressive treatment approach is being considered.[8-11]

The present study aimed to evaluate the effectiveness of cranial CT and MRI in detecting silent metastasis during the initial staging of lung cancer and also to assess their value according to other factors such as age, sex, histology, and TNM stage.

Patients and Methods

We performed a retrospective study of lung cancer patients evaluated by cranial CT or MRI during initial staging between January 2000 and June 2005. We excluded patients with neurologic symptoms and signs that were suggestive of brain metastasis. The final study group comprised 169 patients, all of whom had lung cancer that had been confirmed by cytology or histology. Seventy-two of the patients underwent cranial CT, 93 cranial MRI, and 4 both procedures.

The cranial CT study was performed on a Tomoscan AV scanner (Philips Medical Systems, Best, The Netherlands) using contiguous 5-mm to 10-mm slices, and the images were contrast enhanced with 50 mL of iopromide (Clarograph; Juste SAQF, Madrid, Spain). Cranial MRI was performed on a 1.5-T NT Gyroscan scanner (Philips Medical Systems). T1-weighted precontrast images (repetition time of 600 ms and echo time of 17 ms) and T2-weighted images (repetition time of 4900 ms and echo time of 120 ms) were acquired. The field of vision was 20 cm × 20 cm and the matrix 256 mm × 256 mm. Section thickness was 6 mm, with a 1-mm intersection gap. The T1-weighted images were repeated following the administration of 0.2 mL/kg of a paramagnetic gadolinium-based contrast agent (Magnograph, Juste SAQF).

The first step in the evaluation of patients with suspected lung cancer in the respiratory medicine department at our hospital involves history taking, a general physical examination, and standard tests (chest radiograph, electrocardiogram, basic blood and biochemistry analyses). In a second phase, the patients are normally scheduled for fiberoptic bronchoscopy and a CT scan of the chest and upper abdomen. Furthermore, at this initial stage (before the CT, cytology, and histology results have been received), potential candidates for aggressive treatments such as chest surgery or radiotherapy are scheduled for a cranial CT, even if they have no neurologic signs or symptoms. A systematic evaluation is not conducted by a neurologist. Other tests such as ventilation—perfusion scintigraphy, bone scans, or a transthoracic needle aspiration biopsy are performed depending on the patient's symptoms or on the type or location of the lesion observed in the radiograph. We were able to use both cranial CT and MRI during the study period (from 2000 to 2005) and the choice of procedure depended on the availability of the equipment at the time of testing. Four CT patients also underwent MRI to gain a more accurate picture of certain images that were not clear on the CT scans. To determine the incidence of brain metastasis and disease stage, we grouped the patients according to TNM stage,[12] determined without considering possible brain involvement.

Lung cancer patients in the respiratory medicine department at our hospital are systematically followed, meaning that we were able to repeat the cranial CT or MRI study in patients who initially had no brain metastasis but later displayed suggestive neurologic signs and symptoms and in patients who had been treated for brain metastasis at the outset. In the second group, the repeat imaging was to evaluate the efficacy of treatment. We also used the data collected during this follow-up stage to check the accuracy of the initial positive and negative results.

The study was approved by the hospital's ethics committee and informed consent was obtained from all patients prior to performing the tests.

Percentages were compared using χ^2 test or the Fisher exact test.

Results

Of the 596 patients diagnosed with lung cancer at our hospital during the study period (January 2000 to June 2005), 226 underwent cranial imaging. On reviewing the medical records of these 226 patients, we determined that 57 had been referred for imaging because they had displayed neurologic signs and/or symptoms during clinical evaluation. We excluded these patients from our study. The remaining 169 patients, who were neurologically asymptomatic at the time of diagnosis, were sent for imaging to determine whether they were potential candidates for chest surgery or aggressive radiotherapy. Their characteristics are shown in Table 1. The subgroup of other non-small cell lung cancer included 5 undifferentiated large-cell carcinomas, 3 adenosquamous carcinomas, 1 bronchioloalveolar carcinoma, and 36 cancers that were nonspecific.

Silent brain metastasis was detected in 14 patients (8.3%). The detection rate was 7.9% for the 76 cranial CT patients and 11.3% for the 97 cranial MRI patients. The sum of the patients in the 2 groups is 17 rather than 14 because 4 of the patients underwent both tests. The tests produced similar results in 3 patients and different results in 1 (Table 2).

TABLE 1
Patient Characteristics*

	Cranial CT (n=72)	Cranial MRI (n=93)	Cranial CT and MRI (n=4)
Sex			
Male	64	90	4
Female	8	3	–
Age, y			
Mean (range)	67.5 (38-82)	67.8 (37-88)	59.5 (47-67)
<70	38	58	4
≥70	34	35	–
Histology			
Adenocarcinoma	12	21	2
Squamous cell cancer	18	19	1
Other non-small cell cancer	24	21	–
Small cell cancer	18	32	1
TNM stage (not considering brain study)			
I and II	12	26	1
IIIA	10	16	1
IIIB	27	27	1
IV	23	24	1

MRI indicates magnetic resonance imaging; CT, computed tomography.

TABLE 2
Neurologically Asymptomatic Patients With Brain Metastasis Detected by Cranial Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)*

	Cranial CT, No. (%)	Cranial MRI, No. (%)	Total, No. (%)	*P*
Patients examined	76†	97†	169†	NS
Patients with brain metastasis	6 (7.9)	11 (11.3)	14 (8.3)	
False positives	0 (0.0)	0 (0.0)	0 (0.0)	
False negatives	2 (2.9)	1 (1.2)	3 (1.9)	
No. of brain metastases				NS
1	3 (50.0)	3 (27.2)	3 (21.4)	
2	1 (16.7)	7 (63.7)	8 (57.1)	
>2	2 (33.3)	1 (9.1)	3 (21.4)	
Largest diameter of the metastatic brain tumor, cm				NS
<1	1 (16.7)	4 (36.3)	5 (35.7)	
1-2.5 cm	5 (83.3)	7 (63.7)	9 (64.3)	

*NS indicates not significant.
†The total (n=169) does not coincide with the sum of the 2 groups (n=173) because 4 patients underwent both CT and MRI. The results of the 2 tests were similar for 3 of the 4 patients (2 had a solitary lesion, and the third had none). In the fourth patient, CT and MRI revealed 1 and 2 lesions, respectively.

The percentage of patients identified as having multiple metastases (≥2) was greater in the MRI group than in the CT group (72.8% vs 50%, respectively). Although all of the lesions were small (≤2.5 cm), there was a higher percentage of very small lesions (<1 cm) in the MRI group (Table 2).

Follow-Up and Verification of Results

1. Patients with positive results. In 1 patient who underwent neurosurgery, brain metastasis was confirmed by examination of the excised surgical tissue. Eleven patients received whole-brain radiotherapy. The remaining 2 patients rejected this treatment and received only corticosteroids and chemotherapy. Neurologic symptoms returned quickly (<3 months after initial staging) in 6 of the 13 patients who did not undergo surgery (the 2 who had received chemotherapy and 4 from the whole-brain radiotherapy group). Moreover, a second imaging study (CT or MRI) in 3 of these patients revealed that their lesions had grown. The other 7 patients, who had all received whole-brain radiotherapy, achieved complete or partial remission, confirmed by a second imaging study. We concluded from these follow-up findings that all our positive results had been true positives.

2. Patients with negative results. Four patients with no evidence of brain metastasis following initial staging (3 from the cranial CT group and 1 from the cranial MRI group) later developed neurologic symptoms, and signs of brain metastasis were found during a second radiographic study. The symptoms appeared in under 6 months in 3 of the patients and within 17 months in the fourth. The results for the first 3 patients were considered to be false negatives, corresponding to a false negative rate of 1.9% (3/155) for the initial tests (Table 2).

TABLE 3
Distribution of Brain Metastases According to Age, Sex, Histology, and TNM Stage12 Without Consideration of Possible Brain Involvement*

	Total, No.	Patients With Metastasis, No. (%)	*P*
Sex			NS
Female	11	2 (18.2)	
Male	158	12 (7.6)	
Age, y			NS
< 70	100	11 (11.0)	
≥ 70	69	3 (4.3)	
Histology			0.01
Adenocarcinoma	35	7 (20.0)	
Squamous cell cancer	38	2 (5.3)	
Other non-small cell cancer	45	2 (5.9)	
Small cell cancer	51	3 (5.9)	
TNM Stage			NS
I and II	39	4 (10.2)	
IIIA	27	2 (7.4)	
IIIB	55	2 (3.6)	
IV	48	6 (12.5)	
Total	169	14 (8.3)	

*NS indicates not significant.

Table 3 shows the distribution of patients with brain metastasis by sex, age, TNM stage, and histology. Female gender, age of under 70 years, and adenocarcinoma were all associated with a higher percentage of brain metastasis, although the association was only statistically significant for tumor type: 20% of adenocarcinomas metastasized compared to 5.3% to 5.9% for the other histologic types. We did not find a tendency towards a higher rate of brain metastasis in patients with more advanced stages of disease.

Table 4 shows the distribution of TNM staging for all the patients studied and those with brain metastasis by histology. The distribution of TNM stage was similar for all the histologic types except non-small cell lung cancer. Only in non-small cell lung cancer was there an association between stage IV disease and brain metastasis, although the small size of these subgroups limits comparisons.

In addition to characteristic metastatic lesions, we also found other types of brain lesions, including punctate foci indicating ischemia (n=16), small lacunar infarctions (n=5), intraparenchymatous hematoma (n=1), and leukoariosis (n=2). These lesions are generally easy to distinguish from metastatic ones.

Discussion

The incidence of brain metastasis detected during the initial staging of lung cancer is high. In a cohort of patients from a European population-based cancer registry, the incidence of brain metastasis at the time of diagnosis and during the following month was 7.8%.[2] Using cranial CT systematically in the initial staging of lung cancer, Salbeck and colleagues[13] and Ferrigno and Buccheri[14] found incidences of 14% and 13.6%, respectively. The corresponding rates for the subgroup of patients with no neurologic symptoms were 10.8% and 8.7%, respectively. In a study of neurologically asymptomatic patients with operable primary lung cancer, Yokoi and colleagues[9] detected brain metastasis in 7.8% of the patients (3.4% prior to surgery and 3.4% in the following 12 months) with the systematic use of cranial MRI. Although we report a higher rate of silent brain metastasis (8.3%), our patients, unlike those of Yokoi and colleagues, were not all potentially operable, and many of them had an advanced-stage disease. As our hospital does not have a chest surgery department, it is essential to stage lung cancer as quickly as possible using noninvasive techniques to avoid unnecessary surgical procedures or interventions such as mediastinoscopy or thoracoscopy. We therefore performed cranial CT or MRI on all patients who were provisionally thought to have TNM stage III disease (ie, before receipt of chest CT results) but who in fact were shown to have stage IV disease, without consideration of the state of the central nervous system. If we had requested the imaging study at the end of the full evaluation process (once in possession of all the results), we would not have had to perform some of the studies. While this may seem like a more rational approach, in our setting it would mean prolonging, often excessively, the diagnostic process.

TABLE 4
Distribution of TNM Stages According to Histology

Histological Type	TNM I and II, No. (%)	TNM IIIA and B, No. (%)	TNM IV, No. (%)	Total, No. (%)
Adenocarcinoma				
Patients examined	10 (28.6)	19 (54.3)	6 (17.1)	35 (100)
Patients with brain metastasis	2	4	1	7
Squamous cell cancer				
Patients examined	11 (28.9)	18 (47.4)	9 (23.7)	38 (100)
Patients with brain metastasis	1	–	1	2
Other non-small cell cancer				
Patients examined	14 (31.1)	20 (44.4)	11 (24.4)	45 (100)
Patients with brain metastasis	1	–	1	2
Small cell cancer				
Patients examined	4 (7.8)	25 (49.0)	22 (43.1)	51 (100)
Patients with brain metastasis	–	–	3	3
Total				
Patients examined	39 (23.1)	82 (48.5)	48 (28.4)	169 (100)
Patients with brain metastasis	4	4	6	14

MC: metástasis cerebrales.

As in other studies,[9,13-15] we did not request a special neurological evaluation of asymptomatic patients. (This evaluation increases the negative predictive value of clinical examination.[5]) We cannot, therefore, completely rule out the possibility that patients classified as having silent brain metastasis might have had a slight clinical abnormality that could only have been detected by an exhaustive neurological examination. This seems unlikely, however, in view of our findings from the follow-up period.

We did not find a positive association between tumor stage and the rate of brain metastasis (Table 4), in contrast with the findings of many other studies that have found metastasis to be more common in patients with more advanced stages of disease.[11,13,15,16] Our results, however, may have been influenced by the design of our study, as by focusing on neurologically asymptomatic patients, we excluded many advanced-stage patients with brain metastasis.

Cranial MRI detected more cases of multiple metastases than did cranial CT, and the differences between the 2 tests in the group of 4 patients who underwent both MRI and CT were important in 1 patient in whom MRI revealed 2 metastases whereas CT revealed just 1 (Table 2). Using MRI, Schellinger and colleagues[17] found multiple brain metastases in 31% of patients shown to have solitary metastasis by CT, suggesting that MRI should be the test of choice for screening for brain metastasis in patients with extracranial tumors. Recent case series have shown that 65% to 80% of brain metastasis, of whatever origin, detected by cranial MRI are multiple. The percentage reported for cranial CT previously was about 50%.[18,19] The difference is probably due to the presence of very small lesions and/or infratentorially located lesions as these can only be detected by MRI.[17] The ability to correctly differentiate between solitary and multiple metastatic lesions is essential to choosing the best therapeutic strategy. In this study, the proportion of lesions smaller than 1 cm detected by MRI and CT was 36.3% and 16.7%, respectively, confirming that MRI is more sensitive than CT in the detection of small lesions.

Although a diagnosis of brain metastasis should be made with caution in the case of solitary lesions due to the risk of false positives (Patchell[1] reported a false positive rate of 11% in such circumstances), multiple lesions in patients with a confirmed primary tumor are a clear indication of brain metastasis. In our study, we were able to rule out the occurrence of false positives by closely following our patients. Like Yokoi and colleagues,[9] we calculated our approximate false-positive rate by repeating tests frequently during the follow-up period, although it is often difficult to distinguish between a false negative result and a new brain metastasis. Following the approach taken by Kormas and colleagues,[15] we only repeated radiologic studies during the follow-up period in patients with neurologic signs and symptoms. Like those authors and also Ferrigno and Buccheri,[14] we defined false negatives as cases in which a brain metastasis was detected (by new symptoms and a positive CT or MRI result) within 12 months of the first negative test result. Our false-negative rate was 2.9% for CT and 1.2% for MRI. Hochstenbag and colleagues[11] established an interval of 6 months for calculating the false-negative rate.

We observed a higher incidence of brain metastasis among women than among men, although this finding is not conclusive given the small number of women in our series (consistent with the epidemiological pattern of lung cancer in Spain).[20] We also observed a lower percentage of brain metastasis in patients over 70 years old (4.3% vs 11%); although the difference was not statistically significant, the tendency was consistent with the findings of Schouten and colleagues.[2] We believe this might be a reflection of the less aggressive form that cancer takes in elderly patients.

Our findings with respect to histologic type are consistent with those of many studies that have reported a higher incidence of brain metastasis in patients with adenocarcinoma.[3,11,13-16,21] Salbeck et al[13] and Salvatierra et al,[16] for example, using cranial CT, detected an incidence of 12.1% and 32%, respectively. Using MRI, Hochstenbag and colleagues[11] diagnosed brain metastasis in 13/91 (14%) neurologically asymptomatic patients with adenocarcinoma or undifferentiated large-cell tumors. Twenty percent of all the silent brain metastases we detected were in patients with adenocarcinoma. This rate was significantly higher than the 5.6% found for the other tumor types (Table 3) and the difference was not due to variations in the distribution of stages (Table 4). We therefore believe that, in addition to provisional tumor stage, histology should also be considered when scheduling tests to detect metastasis in lung cancer patients. If a solitary brain tumor is found, for example, neurosurgery is the treatment of choice if the patient is in good condition or a potential candidate for lung surgery.[1,19,21] If multiple or inoperable metastatic brain lesions are found, however, radiosurgery is an option if the lesions are smaller than 3 cm.[19,22] In most cases, however, whole-brain radiotherapy is the only alternative.[1]

In conclusion, we believe that the incidence of silent brain metastasis in our setting (8.3%) is sufficiently high to justify the use of exploratory imaging procedures. Although these images increase costs, they are noninvasive and can substantially alter treatment decisions. Changes in treatment strategies can be particularly important in patients with up to TNM stage III disease and in potential candidates for surgery or combined treatment (chemotherapy and radiotherapy). The higher incidence of brain metastasis in patients under the age of 70 years, and particularly in persons with adenocarcinoma, suggests that age and histology should be taken into account when planning staging procedures. Cranial MRI detected a slightly higher percentage of silent brain metastasis and very small lesions than did cranial CT, and it also provided a more accurate count of the number of lesions. Although the differences were not statistically significant, altogether the results seem to indicate that MRI is more accurate than CT and should therefore be the method of choice for diagnosing brain metastasis in potential candidates for neurosurgery or radiosurgery.

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