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Detecting extrathoracic metastases in patients with non-small cell lung cancer: Is routine scanning necessary?

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Summary There is controversy over whether to scan extrathoracic sites for metastases in patients with non-small cell lung cancer (NSCLC).

We tested the efficiency of clinical factors to determine whether metastasis has occurred, and whether routine scanning for NSCLC is required. Nine hundred and forty five patients scanned for extrathoracic metasates were included. Clinical factors indicating metastasis were determined using multivariate analysis.

Of the 945 cases, 377 (39.9%) had metastasis. Bone metastases were determined by focal skeleton pains, elevated serum alkaline phosphatase levels, adenocarcinoma, KPS $\leq$ 70, sensitivity of 90.6, specificity of 12.7, PPV of 16.3, NPV of 87.8, and silent metastases rate (SMR) of 9.4%. Brain metastases were determined by neurological symptoms, adenocarcinoma, hematocrite <40 for men and <35 for women, KPS $\leq$ 70, sensitivity of 89.9, specificity of 7.9, PPV of 9.2, NPV of 88.3, and SMR of 10.1%. Abdominal metastases were determined by abdominal pain/tension, hepatomegaly, elevated GGT levels, serum LDH levels >500 IU, a N2 or N3 case, KPS $\leq$ 70, sensitivity of 95.9, specificity of 7.1, PPV of 13.3, NPV of 92.1 and SMR of 4.1%. Of the 224 patients with stage I and II disease, 73 had metastasis with a rate of 10.9% silent metastasis.

We concluded that routine scanning of NSCLC for staging is necessary.

1. Introduction

Non-small cell lung carcinoma (NSCLC) is responsible for approximately 80% of all lung cancers, with one million new cases occurring each year [1]. Appropriate staging of non-

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small lung cancer is essential for prognostic estimations and therapeutic options [2,3], as well as rationale designing for clinical trials [4]. There are two primary issues regarding lung cancer. First, the incidence of metastatic disease is so high that distant metastases are found in more than 40% of patients at the time of diagnosis [5,6]. Second, in approximately 60% of patients, cancer recurrence appears from extrathoracic micrometastatic involvement at presentation [7]. Thus, the critical issue during management of patients with lung cancer is the detection of distant metastases [8].

A good physical examination can exclude a high percentage of patients with extrathoracic disease by examining for supraclavicular nodal involvement, axillary lymph nodal involvement, an enlarged liver or palpable mass on the liver, and nodular involvement of the skin [9]. Although the brain, liver, adrenal glands, and bone are common metastatic sites in lung cancer patients [10,11], the signs and symptoms of systemic metastases at these sites carry a substantial false-positive (FR) rate [12,13]. Thus, the issue of whether to perform routine scans is controversial [14]. Some studies suggest that scanning should be routinely performed in all patients with lung cancer at the time of diagnosis [15—18]. Others recommend that investigations of distant metastases should be restricted to patients who manifest with symptoms or signs of metastasis [3,13,19]. International medical associations are also in disagreement about this issue. The Canadian Lung Oncology Group suggests full scanning for metastatic disease in patients with non-small cell lung cancer even if they lack symptoms or signs of metastatic disease [14]. The American Thoracic and European Respiratory Societies advocate for no preoperative imaging of the brain or skeleton in NSCLC patients without symptoms or signs of distant metastases [20].

In spite of recent practice guidelines [7,20,21] and meta-analyses [11,22,23], these imaging modalities are commonly performed in asymptomatic patients, especially those being considered for aggressive local therapy like surgery or radical radiation [24]. The reliability of these decisive results are still under discussion. In addition, some recent studies using newly developed devices have made different findings. One study found that as many as 30% of patients who undergo resection have silent metastases [25]. In another study, unexpected distant metastases were indicated in 8% of stage I and 18% of stage II lung cancer patients by PET analysis [26]. Although PET-CT systems, developed using a combination of PET and computed tomography (CT) scanning, have provided a new perspective and the use of these systems has been gradually increasing, PET-CT is not a commonly used technique throughout the world.

There is also a strong need for studies to examine the relationship between primary tumor histology, intrathoracic tumor stage, and asymptomatic metastasis rate [22]. There are a limited number of studies on this subject and data obtained thus far is still preliminary. The aims of this study are to determine the distribution of metastasis in NSCLC cases with respect to intrathoracic tumor (T) and node (N) staging and histologic cell types, to test the efficiency of criteria that indicate which metastases have occurred, to determine whether there are any new and more efficient clinical and laboratory criteria that could determine metastasis, to determine the ratio of cases that are diagnosed as silent metastasis by routine scanning, to examine the relationship between histology of the tumor and intrathoracic tumor stages and the rate of asymptomatic metastases, and to determine when routine scanning is required for NSCLC cases.

2. Materials and methods

This study was planned at the beginning of 1990. Lung cancer patients who were diagnosed at our clinic from February 1990 onwards, or were sent to our clinic after being diagnosed elsewhere, were clinically evaluated before a treatment decision was made. In this evaluation, epidemiological anamneses of patients were taken and recorded during diagnosis, and clinical interrogations and examinations were performed and recorded. White blood cell counts, hemoglobin levels, platelet values, hourly sedimentation rates, total biochemical serum parameters, electrocardiography, two-way conventional chest X-ray graphies (X-RGs), and contrast enhancement thoracic CT scans were obtained. Following histopathological diagnosis, all patients were scanned for distant organ metastasis using brain, abdominal, and bone imaging methods. Mediastinal lymph nodes were evaluated at the first stage by contrast enhancement thoracic CT and mediastinoscopy was performed when necessary. The patients were staged using a panel including two chest disease experts and a chest radiologist after the examined patients had been evaluated. Patients whose Karnofsky performance score (KPS) and cardiopulmonary physiologic evaluations had been performed were evaluated using the board of thoracic tumors, and therapies were recommended. The study protocol was closed in January 2005. Data from all lung cancer patients included in the study were documented between April 2005 and December 2006.

2.1. Patients

One thousand three hundred and forty lung cancer patients received follow-up between 1990 and 2005. Patient cell types were as follows: 559 squamous cells (41.7%), 357 small cells (26.6%), 249 adenocancers (18.6%), 45 large cells (3.4%), 15 mixed (1.1%) and 115 undefined cell types (reported as non-small cells) (26.6%). Nine hundred and eighty three patients with non-small cell lung cancer were included in the study.

2.2. System scanning and metastasis diagnosis

Contrast enhancement head and abdomen CT and radionuclide bone scan (RBS) were routinely used to evaluate metastases of patients included in the study. CT scans of the chest, brain, and abdomen were performed with a 3 s scanning time and a 1 cm slice thickness. All scans were performed by intravenous injection of contrast material. Whole-body bone scans were performed 2—4 h after intravenous injection of 20 mCi MDP labeled with ^{99m}TC and whole-body images of the anterior and posterior body positions were obtained. Scanning was done using a gamma camera.

Bone metastasis decisions [16,27,28] were made as follows: (1) If an RBS showed multiple areas of uptake consistent with metastases, no further evaluation was necessary. However, an isolated area of uptake required further evaluation. (2) An RBS was interpreted as positive for bone metastases if the findings could not be explained by arthritic changes, previous fractures or additional studies (i.e. radiography and CT scanning). (3) If there was skeletal pain or sensitivity, or if an imaging method, including conventional X-RG, resulted in findings consistent with bone metastases, that location was considered positive for bone metastases even if the RBS was negative. (4) If serum alkaline phosphatase and serum Ca^{2+} levels exceeded the upper limit and an imaging method, including conventional X-RG, resulted in findings consistent with bone metastases, that location was accepted as a bone metastasis even if the RBS was negative. A bone biopsy is seldom necessary for definitive diagnosis [20].

Contrast enhancement head CT was routinely used to evaluate brain metastasis. Head cerebral magnetic resonance imaging (MRI) was performed when the CT was normal in the case of suspicious situations or clinically neurological complaints [24].

While the abdomen was being evaluated with contrast enhancement CT, non contrast CT scanning was used to evaluate adrenal masses, with benign adrenal lesions tending to be lower in density—<10 Hansfield units (HU) [20,29]. Adrenal gland biopsies were performed on any undetermined adrenal masses. When a final decision could not be made on liver metastases by CT scan, contrast enhancement CT and ultrasonography were utilized to distinguish benign cysts from hemangioma of the liver. Percutaneous biopsy was used to examine liver lesions suspicious for metastatic disease [20]. The patients were followed for at least 2 years to validate clinical staging [28].

2.3. Organ-specific clinical factors (signs, symptoms, laboratory findings) indicating metastasis

Factors suggestive of M disease were defined according to the literature [7,13,18,19,22], as follows:

- *Brain*: Neurologic symptoms: headaches, syncope, extremity weaknesses, focal weakness and paresthesia, mental changes, nausea or vomiting, loss of sight, and neurologic abnormalities including papilledema.
- *Abdomen*: Abdominal pain or tension, hepatomegaly, increased serum gamma-glutamyltransferase (GGT) and glutamicoxalonacetic transaminase (SGOT) levels.
- *Bone*: Focal bone, muscle, or skeletal pains, bone tenderness, elevated alkaline phosphatase and/or serum Ca^{2+} levels.

2.4. Organ-non-specific clinical factors indicating metastasis that may indicate an advanced stage of disease [7,19,22]

Weight loss >10%, hematocrite <40 for men, <35 for women.

2.5. Silent metastases

Metastases in patients without organ-specific and organ-non-specific factors were defined as *silent metastases*.

2.6. Additional clinical factors that suggest metastasis by univariate and multivariate analysis, as well as organ-specific and organ-non-specific clinical factors

Gender, age group, asbestos exposure, familial cancer history, occupational and environmental risk factors, smoking, symptom duration, KPS, sedimentation rate, white blood cell counts, platellet counts, serum amylase, billirubin, LDH, uric acid, protein, albumin levels, existence of exudative pleural fluid, existence of paraneoplastic syndrome, vena cava syndrome, Claude Bernard Horner syndrome, peripheral or central lesion localization on chest X-RG, T status (T1, 2, 3, 4) and N status (N0, 1, 2, 3) [30], tumor histologies.

2.7. Statistics

Multivariate analysis was employed to evaluate the efficiencies of current clinical and laboratory findings still used to indicate organ-specific metastasis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of significant findings regarding metastases, and the ratios of silent metastases were determined. Other potential clinical and laboratory factors were then evaluated by multivariate analysis, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of significant findings regarding metastasis, and the ratios of silent metastasis were determined.

3. Results

Nine hundred and eighty three patients who were histopathologically diagnosed as NSCLC and available for follow-up were included in the study (T evaluated: 962, N evaluated: 950, M evaluated: 945). The number of patients and metastasis distribution with respect to cell types is shown in Table 1. The distribution of metastasis according to T and N status is shown in Table 2.

A fully extrathoracic metastasis examination was possible in 945 cases. Five hundred and sixty eight cases had no metastases (60.1%), and 377 cases had metastasis (39.9%).

Based on T staging, metastasis frequency was of no importance ($p = 0.190$). However, metastasis frequency increased as N increased ($p < 0.001$). The ability of organ-specific and organ-non-specific clinical factors to diagnose metastasis following logistic regression analysis with our patients' data is presented in Table 3.

As shown in Table 3, the organ-specific and organ-non-specific clinical factors that are still in use today [19,22] were unable to determine brain and bone metastases in 10% or more of cases. While searching for organ-specific metastases relevant to our series, it was found that the sensitivity was 97.5% for abdominal metastases, while the rate of silent metastases was fixed at 2.5%. When carefully checked, criteria that originally increased sensitivity and

Table 1 Number of patients and metastasis distribution according to cell type

Cell types	Patient number	Brain		Liver		Adrenal		Bone	
		n	%	*n*	%	*n*	%	*n*	%
Epidermoid	532	35	6.6	45	8.5	20	3.8	62	11.7
Adenocarcinoma	245	30	12.2	28	11.4	10	4.1	63	25.7
Large cell	42	4	9.5	5	11.9	3	7.1	6	14.3
Mixed	14	2	14.3	2	14.3	—	—	—	—
Non-small cell	112	18	16.1	9	8.0	9	8.0	18	16.1
Total	945	89	9.4	89	9.4	42	4.4	149	15.7

Table 2 Distribution of metastasis according to T and N status

T, N	Patient number	Brain		Liver		Adrenal		Bone	
		n	%	*n*	%	*n*	%	*n*	%
.T1	9	1	11.1	0	—	0	—	4	44.4
.T2	173	16	9.2	18	10.4	4	2.3	24	13.9
.T3	290	35	12.1	30	10.3	19	6.6	46	15.9
.T4	466	37	7.9	40	8.6	19	4.1	73	15.7
.N0	322	27	8.4	22	6.8	10	3.1	54	16.8
.N1	62	2	3.2	4	6.5	1	1.6	5	8.1
.N2	361	31	8.6	36	10.0	10	2.8	51	14.1
.N3	191	29	15.2	26	3.6	21	11.0	37	19.4

NPV were considered ''organ-non-specific factors''. In this case, PPV decreased.

In addition to the factors mentioned above, we also determined whether other factors were effective at emphasizing metastasis while the study was being planned, or whether more effective factors existed compared to the current ones being used. Combined univariate and multivariate analyses were performed. Details are shown in the Methods section, and factors that were able to emphasize organ-specific metastases are shown in Table 4.

The sensitivity, specificity, PPV and NPV of clinical and laboratory findings determined in our study, for detection

Table 3 The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical and laboratory findings that are currently being used to detect brain, abdominal, and bone metastases

Organ	Sensitivity	Specificity	PPV	NPV	Rate of silent metastasis
Brain					
Organ-specific clinical factors for brain metastasis	30.3	96.7	49.1	93	69.7
Organ-specific clinical factors for brain metastasis + organ-non-specific clinical factors[a]	87.6	15.7	9.8	92.4	12.4
Abdomen					
Organ-specific clinical factors for abdominal metastasis	63.1	92.2	20.9	92.2	36.9
Organ-specific clinical factors for abdominal metastasis + organ-non-specific clinical factors[a]	97.5	5.2	13.2	93.5	2.5
Bone					
Organ-specific clinical factors for bone metastasis	49.7	67	22	87.7	50.3
Organ-specific clinical factors for bone metastasis + organ-non-specific clinical factors[a]	89.9	12.6	16.1	87	10.1

[a] Organ-non-specific clinical factors: weight loss >10%, hematocrite <40 for men, <35 for women.

Table 4 Clinical factors indicating metastasis using univariate and multivariate analyses

Organ	Clinical factors indicating metastasis using univariate and multivariate analyses
Brain	Neurological symptoms, signs and/or findings; having adenocarcinoma; hematocrite <40 for men, <35 for women; KPS $\leq$ 70
Abdomen	Abdominal pain or tension; hepatomegaly; elevated serum GGT levels, serum LDH level >500 IU; having an N2 or N3 case; KPS $\leq$ 70
Bone	Focal bone, muscle, skeletal pain and/or sensitivity; elevated serum alkaline phosphatase levels; adenocarcinoma; KPS $\leq$ 70

Table 5 Abililty of clinical and laboratory factors to determine organ metastasis

Organ	Sensitivity	Specificity	PPV	NPV	Rate of silent metastasis
Brain	89.9	7.9	9.2	88.3	10.1
Abdomen	95.9	7.1	13.3	92.1	4.1
Bone	90.6	12.7	16.3	87.8	9.4

of brain, abdominal, and bone metastasis are shown in Table 5.

The silent brain metastasis rate was 10.1%, the silent abdomen metastasis rate was 4.1%, and the silent bone metastasis rate was 9.4%. These rates were accepted as better rates than the ones still in use (Table 3).

As shown in Table 6, 224 individuals with stage I and II disease were available for surgical treatment upon application of the clinical and laboratory criteria that diagnosed metastasis. Of these patients, 73 had metastases. Eight of the 73 (10.9%) had silent metastasis based on the clinical and laboratory criteria we established (Table 6). When 19 T3N1 cases were added to these 224 cases, 8 (10.4%) of the 77 metastases were determined to be stage I or II, and the T3N1 cases were silent metastases.

Silent metastasis was not observed in T1N0. Two of the 24 metastases (8.3%) from the T2N0 cases, and 5 of the 43 metastases (11.6%) from the T3N0 cases were silent metastases. Twenty of the 224 patients with stage I and II cancer had brain metastasis. One had silent metastasis. In the same patient group, 24 were abdominal metastasis, four of which were silent (16.7%), and 29 were bone metastases, three of which were silent (10.3%). Two of the 25 metastases from the stage I cancers (8%), and 6 of the total 47 metastases from the stage II cancers (12.8%) were silent metastases. No differences in metastasis frequency and silent metastasis rate were observed between the stage I, II, and T3N1 cases.

4. Discussion

Surgical treatment and other anti-tumor treatment options combined with surgical treatment significantly prolongs the lifespan of lung cancer patients, and surgical treatment alone prolongs lifespan in early stages that are suitable for resection [8,24]. The prognosis of patients with lung cancer varies according to stage, with 5-year survival rates for 42% of stage I patients, 23% of stage II patients, 11% of stage IIIa patients, 5% of stage IIIb patients, and 1% of stage IV patients [31]. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable but will benefit from radiation therapy and/or chemotherapy [8]. It is clear that clinical trials should be based on a definite and effective staging system [8,24,32].

Staging NSCLC is based on the TNM (tumor, nodal involvement, distant metastasis) system, of which the 1997 classification is the latest version [33]. T staging for lung cancers can be easily carried out using contrast enhancement CT and bronchoscopy. Fields that are highly debated are mediastine staging and the determination of extratho-

Table 6 Rate of silent metastasis with respect to T and N status

T—N	Patient number	Brain		Abdomen		Bone	
		M	SM	M	SM	M	SM
.T1 N0	3	1		0		1	
.T2 N0	77	6	1	8	1	10	
.T1 N1	2	0		0		0	
.T2 N1	18	1		2		1	1
.T3 N0	124	12		14	3	17	2
.T3 N1	19	1		1		2	
Total	243	21	1	25	4	31	3

M, metastasis; SM, silent metastasis.

racic metastases. Extrathoracic metastases are commonly observed, and approximately 40% occur during the diagnosis stage [5,6]. The brain, liver, adrenal glands, and skeletal system are the most likely sites of metastatic disease in patients with lung cancer [7,10,11]. In our study, 40% of patients (377/945) had metastasis during the diagnosis, many of which were in these organs. Until recently, metastasis scans in these areas were being conducted by abdominal CT or ultrasonography, RBS, and head CT or MRI. These examinations are still being used for patients who are scanned for metastases. However, it is controversial as to whether all staging studies should be done routinely for NSCLC patients with early stage disease who have no evidence of distant metastasis [14,22,30,34—37]. Most cases have signs, symptoms, physical examination findings, laboratory findings related to metastatic organ, or issues like weight loss that indicate a systemic disease. In patients with these problems, the existence of metastasis should be considered and organ scanning made a common practice. Although the specificities and PPV of these clinical factors is low, the possibility of metastasis in these patients is high [11—13,18,22].

In patients with a negative history, a negative physical examination, and a negative initial laboratory screeining, what is the incidence of metastatic disease? Recommendations differ for this patient group. Some authors advocate proceeding immediately to thoracotomy. Since the discovery of distant metastases is more than three times higher in patients with clinical or laboratory signs of disease before imaging [18] and in patients with a negative history, physical examination and a laboratory test, the incidence of metastatic disease is much lower [11]. Others suggest a more aggressive approach to rule out clinically occult but detectable metastases [18]. In accordance with these authors, the silent metastasis rate is not as low as it was originally thought. In many studies the reported incidence of silent metastases varies from 2.7 to 26.6% in the brain [13,38—41], 1.7—17.8% in the adrenal glands [42,43], and up to 30.3% in the bone [16,17,30]. The incidence of liver metastases is 9.3% for asymptomatic patients and 25% for symptomatic patients [13]. In this study authors claimed that 21% of brain metastases are asymptomatic, and 61% of patients with hepatic metastasis had no organ-specific factors suggesting metastases [13]. In another study, lung cancer patients who underwent surgery as a curative procedure had a high incidence of extrathoracic metastases. In this series, 23 patients (25.5%) had extrathoracic metastases in at least one organ [18]. In another study the silent bone metastasis rate was 17% [16]. On the other hand, in the management of non-small cell lung cancer, the recurrence rate after curative surgical procedures remains high [34,44]. This may be the result of treatment failure. Some studies have concluded that as many as 3% of patients who undergo resection for cure have silent metastases [25].

In early stage non-small cell lung cancer patients, medical institutions share different opinions regarding whether these patients should be scanned for routine metastasis. While The Canadian Lung Oncology Group suggests a full investigation for metastatic disease in patients with non-small cell lung cancer without symptoms or signs of metastatic disease [14], the American Thoracic and European Respiratory Societies do not require preoperative scanning of the brain or skeleton of NSCLC patients who have no symptoms or other evidence of distant metastases [20].

The most important meta-analysis of lung cancer patients was published in 1995 [22]. In this analysis, studies using the clinical factors for brain, abdomen, and bone metastasis that suggest metastatic disease were separately assessed. Thirteen studies of brain metastasis were collected. In these studies, the efficiency of median prevalence was 16% (range: 13—27), sensitivity was 79% (*r*: 65—83), specificity was 91% (*r*: 78—98), PPV was 58% (*r*: 26—88), NPV was 94% (*r*: 91—97). The median silent metastasis rate was 21% in this meta-analysis. For seven cases of bone metastasis in the same series, median prevalence was 20% (*r*: 13—27), sensitivity was 90% (*r*: 89—91), specificity was 46% (*r*: 40—98), PPV was 40% (*r*: 36—50), NPV was 92% (*r*: 84—100), and the median silent metastasis rate was 10%. In the same study, median NPV for the abdominal metastasis was 97% [22]. Clinical metastatic disease was considered based on the meta-analysis of this research, and NVP aided in the decision of whether a routine scanning is necessary to establish metastasis when these findings are non-existent. However, when these studies were individually examined, different observations were made. We observed that the NPV was high in some parts of the silent metastasis rate, making the usability of this measurement highly skeptical. For instance, in meta-analysis that assessed brain metastasis, the NPV in a study of 84 cases was 97% and the silent metastasis rate was 16.7% [45], the NPV in a study of 145 cases was 94% and the silent metastasis rate was 34.8% [46], the NPV in a study of 279 cases was 91% and silent metastasis rate was 17.4% [47], the NPV in a study of 66 cases was 90% and the silent metastasis rate was 62.5% [40], and the NPV in a study of 146 cases was 97% and the silent metastasis rate was 21.1% [13]. In all these studies, the NPV was between 90 and 97% and the silent metastasis rate was between 16.7 and 62.5% [22]. Thus, no matter how high the NPV gets, silent metastases rates around between 16 and 30% should be ignored, indicating that NPVs are not very helpful in diagnosis. In the same study, the meta-analysis of bone metastases showed that while metastasis prevalence in a study of 146 cases was 13%, with the NPV being 97%, and the silent metastasis rate being 21% [13], metastasis prevalence in a study of 150 cases was 34%, with the NPV being 83%, and the silent metastasis rate being 11.7% [16]. If metastasis prevalence, NPV, and silent metastasis rates in these two studies are considered, and the NPV is low (83%), then we should expect to find only 11.7% silent metastasis by scanning. However, if we trust the high NPV (97%) and do not carry out a scanning, we could miss 21% of silent metastases [22].

The problem is that NPV is highly affected by prevalence. If the prevalence is low, NPV has a tendency to increase [22]. However, as the above-mentioned examples illustrate, a change in NPV does not fully reflect silent metastasis rates. Thus, it may not always be appropriate to act based on NPV levels while studying clinical factors that suggest metastasis. Instead, it would be better to use the silent metastasis rate. In a recent meta-analysis carried out on a higher number of cases, in which the efficiency of clinical factors suggesting metastases was assessed in order to determine brain metastases, the NPV was 94% in a total of 1784 cases, and the silent metastasis rate was 24% [23]. When abdominal metastasis was evaluated in the same study, the NPV was 95% in

1201 cases, and the silent metastasis rate was 8%. When bone metastasis was assessed, the NPV was 90% in 633 cases and silent metastasis was 13% [23].

In addition, there were several problems with the meta-analyses. Patient populations were not homogenous and there was great variation in the methodology of individual studies, including differences in the scanning methods [48]. An assessment was not conducted based on the tumor cell types and stages. Thus, comparing the NPVs obtained by these meta-analyses is not appropriate. In fact, when common clinical factors were used to suggest metastasis in our study, we observed that the NPV and silent metastasis rates did not necessarily correlate. In our series, the NPV of the clinical factors for brain metastasis was 92% and the silent metastasis rate was 12%, the NPV for abdominal metastasis was 94% and silent metastasis rate was 2.5%, and the NPV for bone metastasis was 87% and the silent metastasis rate was 10.1%. In accordance with studies determined as the subject matter of the above-mentioned meta-analyses, silent metastasis rates were lower. This rate was 2.5% for abdominal metastasis, which is quite good. The median rate was 8% among 23 cases. Thus, silent metastasis rates would be more suitable than NPVs for clinical factors that suggest metastasis. The silent metastasis rate for brain and bone is >10%, but the silent metastasis rate for abdominal metastasis could have a low rate which also needs to be considered. At this point, there are two questions to be addressed: (1) Could more effective clinical factors that are suggestive of metastases be found? (2) Are these factors related to the cell type and spreading within the inner thorax? What are the silent metastasis rates be at stage I and II required for direct referral for surgical treatment?

In this study, we assessed the ability of common organ-specific and organ-non-specific clinical factors to indicate metastasis, in combination with other factors that have not yet been tested to suggest metastasis by univariate and multivariate analysis. Clinical factors proven to be meaningful at suggesting organ-specific metastases are shown in Table 4. Of those factors, the presence of adenocarcinoma, a KPS >70, LDH levels >500 IU, and the presence of N2 or N3 cases proved meaningful. Weight loss, serum Ca^{2+} and SGOT levels were not observed as meaningful. In assessments carried out by both groups using data obtained from cases, clinical factors determined to be meaningful gave less silent metastasis rates (Table 4).

Unique studies that examine the relationship between histological type and silent metastasis are quite rare. In our series, the metastasis rate in lung cancer patients with a non-squamous histology was relatively higher, and bone metastases were more frequently observed in adenocarcinoma cases than others (Table 1). The metastasis rate was high in some adenocarcinoma cases, and in some non-squamous histologies [22,15,49,50]. Some studies found silent brain metastasis in adenocarcinoma cases are higher than in other cell types, indicating that adenocarcinoma is a risk factor for silent brain metastasis [13,22,51]. Adenocarcinoma was observed to be a factor that posed risk for both silent brain and silent bone metastases.

In our study, N2 and N3 disease and serum LDH levels >400 were considered risk factors. There are a few studies that determine high LDH as a risk factor [13]. LDH is probably manifested as a symptom related to liver damage. The relationship between intrathoracic tumor stage, especially N status, and asymptomatic metastases, was only available in a few studies [22]. More scan abnormalities were detected in stage N2 disease in which asymptomatic metastases have been documented. In that study there was a higher rate of asymptomatic metastases than expected [52]. However, there are some controversies about this feature. Jung et al. report that tumour type and N status do not correlate with the prevalance of extrathoracic metastasis [53]. In another study, the authors found no relationship between the clinical T, N stage and metastasis frequency [18]. In this report, we show that T status and metastasis frequency remains the same, but metastasis frequency increases as N progresses (Table 1). Similarly, Table 6 shows that stage I, II, and IIIa did not manifest a meaningful difference in terms of the metastasis frequency and silent metastasis rate for the T3N1 groups. Our study established that only having N2 and N3 disease was a risk factor for abdominal metastasis.

In our study, 224 individuals had stage I and II disease and of these, 73 had metastasis. Of the metastatic patients, eight (10.9%) had silent metastasis using the clinical and laboratory criteria we established (Table 6). When 19 T3N1 cases that would directly undertake surgical treatment were added to these 224 individuals, 8 of 77 metastases (10.4%) in the stage I, II, and T3N1 cases were silent metastases. Two of the 25 metastases (8%) in stage I, and 6 of the 47 metastases (12.8%) in stage II were silent metastases.

As a result, we concluded that the criteria in Table 4 are the most efficient clinical factors that suggest lung cancer metastasis. When these criteria are applied, the silent metastasis rate in the abdomen is only 2.5%, which is quite low and may not necessitate scanning. Even when these criteria are applied for brain and bone, the silent metastasis rate would be slightly above 10%. Thus, we are not as comfortable for these two organs as we are for the abdomen, and would recommend brain CT or MRI, and bone RBS as routine tests for these organs. Contrast enhancement thoracic CT, which is already routine for the abdomen, could easily manifest in the upper abdomen with the help of an additional dose of contrast substance when it reaches the diaphragm level. Thus, additional scanning is unneccesary.

In a recent issue of the American Society of Clinical Oncology Treatment of Unresectable Non-Small-Cell Lung Cancer Guideline: Update 2003, ASCO recommends in an article entitled ''Staging distant metastatic disease'' that ''for the staging of distant metastatic disease, an FDG-PET scan is recommended when there is no evidence of distant metastatic disease on CT scan of the chest'' [24].

PET-CT is more efficient at assessing metastasis of both mediastinal and extrathoracic regions compared to standard methods [8,54—57]. However, PET-CT has some restrictions. (1) FDG-PET scans do not often extend below the pelvis, thereby neglecting the detection of bone metastases in the long bones of the lower extremities [24]. (2) CT or MRI imaging of the brain is still required since the high glucose metabolism of the brain makes FDG-PET a poor imaging test [57]. (3) There may be some indeterminate findings on PET imaging that may require a battery of additional interventions [57]. (4) There is still a need for ascertaining standards from PET-CT scans that could be widely accepted, and it could take approximately 5 years for these studies to be recommended as standard applications. (5) PET-CT is still

restricted to a number of centers, and these scannings could take many years to become widespread. (6) PET-CT is 4—5 times the cost of abdominal and brain CT and bone scintigraphy combined. Thus, CT or MRI, and radionuclide bone scanning could be used to detect lung cancer metastases for years to come.

Conflict of interest

Authors state that they have no conflict of interest.

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