研究成果報告書

EBM を用いた放射線診断のガイドライン作成に関する研究

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研究代表者　高橋雅士（滋賀医科大学医学部）

研究組織

研究代表者	高橋雅士	(滋賀医科大学・医学部、助教授)
研究分担者	村田喜代史	(滋賀医科大学・医学部、教授)
研究分担者	新田哲久	(滋賀医科大学・医学部、助手)
研究分担者	高櫻竜太郎	(滋賀医科大学・医学部、助手)

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Research Title:

Survey for the Establishment of Imaging Procedure Guideline using EBM Approach

Principle investigator:

Masashi Takahashi, M.D. Shiga University of Medical Science

EBM (Evidence Based Medicine) was first proposed by Guyatt GH in 1991 and has been widely accepted in the medical field during past decade. EBM is conducted using the following five steps; 1. Asking Answerable Questions 2. Finding the Best Evidence 3. Critically Appraising the Evidence 4. Acting on the Evidence 5. Evaluating your Performance. On the other hand, many clinical guidelines have already been published. Recently, the establishments of these guidelines are usually based on the EBM approach. In Japan, the introduction of EBM approach in establishing clinical guideline was strongly recommended by Ministry of Health, Labour

and Welfare. However in the field of radiology, especially the diagnostic imaging, the use of EBM approach is not sufficiently used and the comprehensive clinical guideline has not been published. The purpose of this study is to collect the basic information regarding EBM approach of diagnostic imaging, especially in the field of chest radiology. The study is composed of two main categories; A) diagnostic guideline of the search for the metastasis in the cases with non-small cell bronchogenic carcinoma, B) diagnostic guideline of the imaging for the community acquired pneumonia.

A. diagnostic guideline of the search for the metastasis in the cases with non-small cell bronchogenic carcinoma

A-1. Introduction

The prognosis of bronchogenic carcinoma is usually defined by the local control rate, as well as, the management of distant metastases. It is widely accepted that the incidence of metastasis in the cases with bronchogenic carcinoma is extremely high if compared to other types of malignancy. Auerbach et al(1) has reported the incidence of distant metastasis based on the 662 autopsy cases in which it was observed that metastaseis to the brain, adrenal gland and bone were observed in almost 30-50% of cases including the microscopic diagnosis. Quint et al. has reported

that the metastases were found on imaging diagnosis in 72 of 348 cases(21%) with bronchogenic carcinoma. The organ metastasized were markedly varied as following; brain (65.2%), bone(50%), liver(30.6%), adrenal gland (20.8%), body wall(18.1%), lung(15.3%), spleen(8.3%), abdominal LN(8.3%), axillary LN(5.6%), spinal cord (4.2%), pancreas (1.4%)(2). The small lung cancers have become frequently found probably because of the improvement of imaging diagnosis. The risk of distant metastases of these cancers are considered to be low. However, Jung et al(3) has reported that 90 cases with T1 NSCLC have revealed that 13%(12/90) already had the distant metastasis at the initial establishment of diagnosis and newly developed metastases were observed at 1 year follow up in 11%(10/90). Therefore, even with the small lung cancer, the risk of distant metastasis is still a significant problem. On the other hand, the validity of the variable medical procedures are now re-evaluated using the EBM technique. Major reason for this tendency is the high medical cost in advanced nations and the increased interests of the population toward the quality of the medicine. The appropriateness of the methods to search the metastatic lesion in the cases with lung cancer is also debated from the EBM aspect. In this study, the validity of the procedure for searching metastatic lesion in the cases with NSCLC will be reviewed. The following two major guideline regarding the clinical practice of bronchogenic carcinoma have already been published; ASCO(American Society of Clinical Oncology): Unresectable non-small cell lung cancer(1997)(4), ATS/ERS(American Thoracic Society/European Respiratory Society):

Pretreatment evaluation of non-small-cell lung cancer(5). Also in Japan, the clinical guideline of the lung cancer with using EBM procedure was recently published(6). In this review, the guidelines of these major English publications will be mainly introduced. The level of evidence and the level of the recommendation which used in the guideline of ASCO are shown in table 1 and 2.

A-2. Importance of clinical pictures

Recently, two meta-analysis have been published regarding the search for the metastatis in the cases with bronchogenic carcinoma(7,8). According to these articles, although the concept or the method to search the metastatic lesion are markedly varied among the institutes, it is noted that every guideline emphasize the importance of clinical pictures of the patients before performing the examination of metastatic lesion. If the patient does not demonstrate any subjective symptoms, the possibility of the metastasis is extremely low. Silvestri et al. have reported that the negative predictive value of the clinical pictures regarding brain, abdomen and bone metastases are extremely high, 95%,94% and 89%, respectively(8). On the other hand, the imaging modalities are frequently used regardless with the patient symptoms to search the metastatic lesions in Japan. Table 3 shows the standard clinical examination and signs suspected to have metastasis in the cases with bronchogenic carcinoma.

A-3. Brain

ASCO: Head CAT or brain MRI with and without infusion of contrast material should be obtained only in patients who have signs or symptoms of CNS disease. (Level of evidence II, grade of recommendation B)

ATS/ERS: The recommendation is to perform head CT only in patients with newly diagnosed NSCLC who have positive findings on clinical evaluation or in patients with nonspecific findings that suggest widespread disease, if metastatic disease has not been documented elsewhere. The use of routine MRI of the head has not been adequately studied and is not recommended at this time.

The incidence of distant metastasis is increased when the tumor size exceeds 3cm, especially in adenocarcinoma(8,9). The incidence of discovering metastatic foci in the cases with respectable lung cancer without symptoms are generally 3 to 8%(10,11). The most important issue is whether the imaging procedures to search metastatic lesion should be performed for all the patients with lung cancer or not.

In most of the institutes in Japan, brain CT or MRI are considered as a routine imaging procedure as a preoperative evaluation. The results of following articles are consistent with these trends. Ferringno et al have performed retrospective comparative study in which the clinical

significance of brain CT as a preoperative evaluation for the 184 newly diagnosed patients with NSCLC(12). In this study, the cases that neurological symptoms appeared within 6 months after CT were considered as true positive, and the cases whose CT were normal and no neurological symptoms at 12months follow up after the CT were considered as true negative. The obtained sensitivity, specificity and accuracy were 92%, 99% and 98% respectively. There was no relationship between the existence of neurological symptoms and that of brain metastasis. Among the 25cases with positive CT findings, 16 cases did not demonstrate any neurological findings(64%). Among 31patients with respectable lung cancers, 3 cases(10%) were proven to have brain metastases. From these data, they have concluded that brain CT should be performed in all the patients with resectable lung cancer. Butler et al. also supported this opinion from the aspect of cost-benefit(11). Earnest et al(9). have executed the brain MRI with contrast for the 27 patients with NSCLC staged more than T1N0M0 and observed whether the newly metastasis has appeared during 12 months follow up or not with comparison to the 110 patients to whom MRIs were not performed. Among them, 22% of patients(6/27) were proven to be brain metastases and they were free from neurological symptoms. No false positive was found in the cases with contrast MRI group and there was no newly appeared brain metastasis observed during 12 months in the patients whose initial MRI did not show any abnormality. According to these results, it can be concluded that MRI with contrast should be performed as the pre-operative examination.

On the other hand, there are a lot of manuscripts which insisted that it is questionable to perform imaging study for the patients without any neurological symptoms. Silvestri et al(8). have reported that the incidence of discovering brain metastasis in the cases with asymptomatic NSCLC were only 3% and the negative predictive value of neurological symptoms are extremely high as 95%. Cole et al(13). have reported that brain CT with contrast for 43 NSCLC patients without any neurological symptoms did not any imaging findings suggesting brain metastases. Among them, 30 MRI with contrast were also performed, however no additional information were obtained. These authors have negative opinions for the use of CT or MRI if the patients are neurologically normal.

Low specificity of the brain CT as a preoperative evaluation was indicated by Patchell et al.(14) Among the fifty-four cases in whom the solitary mass lesion was found on pre-operative CT examination for malignancy including lung cancer, 6 cases(11%) were proven to be non-metastatic lesion such as primary brain tumor, brain abscess or non-specific inflammation.

The relationship between the incidence of brain metastasis and metastasis to other organ was discussed in a several papers. Kormans et al.(15) have reported that among 158 cases with asymptomatic NSCLC, pre-operative CT have found 6 brain masses including 5 cases of metastases and 1 case with glioma. 12 months follow up has revealed 5 cases with brain metastases, most of which are N2 cases and adenocarcinoma. Therefore they have concluded that brain CT should be

performed as a pre-operative examination if the histology is adenocarcinoma associated with high-grade N factor. Grant et al.(16) analyzed the findings of chest, abdomen and brain CT in 114 resectable NSCLC. Among 10 cases with brain metastases, 9 cases simultaneously demonstrated metastases to mediastinal lymphnodes or abdominal organ. Among the 9 cases with abdominal metastases, 7 cases were combined with brain of mediastinal lymphnode metastases. Brain metastases are strongly related with the metastases to extracranial metastases and pre-operative comprehensive research will prevent the unnecessary operation.

From the cost-benefit aspect, Colice et al.(17), with decision analysis model, have compared the cases with routine use of brain CT and the cases in whom the CT is indicated only the neurological symptoms are observed. They found the poor cost-benefit ratio in the former cases.

The diagnostic capability was compared between the CT and MRI by a several authors. Kumasaki et al.(18) have studied 218 lung cancer cases and 38 cases with brain metastases were found. Among them, 24 cases to whom the CT and MRI were simultaneously performed were selected and detectability of the metastases were compared. In 24 cases that contrast MRI showed brain metastasis, CT could not detect metastases in 7 patients. Yokoi et al.(19) have compared the usefulness of MRI and CT in the detection of brain metastases during preoperative evaluation and postoperative follow-up. Of 332 patients with potentially operable NSCLC who were free of neurological signs and symptoms, brain CT was performed preoperatively on 155 patients (CT

group) and brain MRI on 177 patients (MRI group). Patient characteristics in both groups were comparable. In 279 patients with complete resection of the primary lung tumor, intensive follow-up with CT and MRI was performed in the respective groups. The preoperative detection of brain metastases, postoperative intracranial recurrence rates, and characteristics of detected brain tumors were compared between the two groups. The survival of patients with brain metastases was also compared. Results: From the first evaluation to 12 months after surgery for primary lung cancer, brain metastases were observed in 11 patients (7.1%) from the CT group and 12 patients (6.8%) from the MRI group. MRI detected brain metastases preoperatively in 6 of the 12 patients (3.4% of the total MRI group), whereas CT detected brain metastases preoperatively in 1 of the 11 patients (0.6% of the total CT group). MRI showed a tendency toward a higher preoperative detection rate of brain metastases than CT ($p = 0.069$). Furthermore, the mean (+/- SD) maximal diameter of the brain metastases was significantly smaller in the MRI group (12.8+/-9.1 mm) than in the CT group (20.3+/-7.0 mm) ($p = 0.041$). However, the median survival time and 2-year survival rate after treatment of detected brain metastases, respectively, were 10 months and 27% in the CT group and 17 months and 28% in the MRI group. There was no significant difference between the groups in survival time. From these data, they concluded that preoperative evaluation and intensive follow-up with MRI could facilitate early detection of brain metastases in patients with potentially operable lung cancer.

Regarding the post-operative follow up, Yokoi et al. (20) studied 128 patients with completely resected non-small cell lung cancer. Follow-up computed tomographic scans were obtained every 2 to 6 months over 24 postoperative months in 69 patients and every 2 months for 6 postoperative months in 59. Brain metastases were discovered in 11 patients (8.6%), and 7 patients were neurologically asymptomatic when the metastases were diagnosed. Single metastasis was found in 5 patients and multiple metastases in 6. The maximal size of all but one lesion was less than 25 mm. The median survival time and 5-year survival rate in all 11 patients with brain metastases were 10 months and 24%, respectively. Furthermore, those in 7 asymptomatic patients were 25 months and 38%, respectively. They have concluded that intensive follow-up with computed tomography to be worthwhile for early detection and effective treatment of brain metastases in patients with completely resected lung cancer.

A-4. Bone

ASCO: A bone scan should be performed only in patients who complain of bone pain, chest pain, or who have an elevated serum calcium level or an elevated serum alkaline phosphatase level. (Level of evidence III, grade of recommendation C)

ATS/ESR: Any one of the following findings are presented in patients with NSCLC should prompt a

radionuclide bone scan; common clinical findings of bone metastases include bone pain, pathologic fractures, and/or an elevated alkaline phosphatase or serum calcium level. If the clinical evaluation is negative, a radionuclide bone scan should not be performed. If a radionuclide scan shows multiple areas of uptake consistent with metastase, no further evaluation is necessary. An isolated area of uptake may require further evaluation.

Bone metastases are found in 9-15% of patients with newly diagnosed NSCLC(21,22). The spine is a predominant site and the histology of adenocarcinoma and coexistence with a metastasis to mediastinal lymphnode are the predisposing factors. Bone scintigraphy is considered as the most sensitive method, however the relatively high rate of false positive is a major concern.

Michel et al.(21) prospectively studied 110 consecutive patients referred for initial staging of non-small cell lung cancer and assessed the sensitivity of a group of clinical indicators (chest pain, skeletal pain, bone tenderness on physical examination, serum alkaline phosphatase, and serum calcium) for the presence of skeletal metastases as determined by bone scanning. The final staging result was validated with follow up data over at least three years. At the initial staging 37 of 110 bone scans (34%) showed areas of increased uptake, of which only nine were confirmed to be metastases (by tomography, computed tomography, or biopsy). Half the patients (55) had at least one clinical indicator suggesting skeletal metastases, including all patients with proved skeletal

metastases. Thus the sensitivity of these clinical indicators was 100% and the specificity 54%. Within one year three of 27 patients with non-confirmed positive bone scans had skeletal metastases, one of which was in the area that had shown increased uptake initially. All these patients had clinical indicators for skeletal metastases and all had inoperable advanced tumours. Four of 69 patients with an initially negative bone scan developed skeletal metastases within one year. From these results, they have concluded that in non-small cell lung cancer bone scanning can be restricted to patients with clinical indicators for skeletal metastases(23,24).

A-5. Adrenal gland

ASCO: The finding of an isolated adrenal mass on ultrasound or CT requires biopsy to rule out metastatic disease if the patient is considered to be potentially respectable. (Level of evidence III, grade of recommendation C)

ATS/ERS: CT of the thorax should include the adrenals. Contrast administration is not required. Biopsy should be performed in any indeterminate adrenal mass that is not shown to contain fat by either CT or MRI.

Adrenal metastasis is found in 18-38% of the patients with lung cancer (25). However the

almost two-thirds of adrenal masses observed in the cases with NSCLC are adenoma. Oliver et al(26) and Ettinghausen et al.(27) have reported the similar results; although the adrenal masses were found 7.5% and 4.1% of 330 and 243 cases with NSCLC, respectively, metastases were proven only 2.4% and 1.6%, respectively. Gillams et al.(28) found 22 cases(4%) with adrenal masses in 546 lung cancer patients, and among them, only 5 cases were proven to be metastases. Silverman et al. reported the accuracy of 96% of percutaneous biopsy for adrenal mass(29).

It is indispensable to consider the technical performance of CT scanner if the indication of CT to the adrenal is discussed. As a recent fast CT scanner, such as MDCT, made it possible to cover the wide area of the body with thin slice and a short time, whether the level of adrenal should be covered or not is no-longer unimportant issue. However, the following articles which published almost one decade before were discussing the clinical significance of adrenal CT as an independent procedure. Silvestri et al. (30)studied 173 patients with lung cancer and reviewed abnormalities in three clinical categories (signs, symptoms, and routine laboratory tests) and the presence of extrapulmonary tumor spread including adrenal involvement by CT. They found that adrenal metastases are found in patients with a large tumor burden who have clinical indicators of widespread disease. There is no evidence of adrenal metastases by CT in any patient with a normal clinical evaluation. It is concluded that CT scans through the adrenal glands are unnecessary when staging newly diagnosed bronchogenic carcinoma if the findings from the initial clinical evaluation

are normal. Eggesbo et al.(31) have surveyed the CT scans of brain, chest and abdomen which were performed on 96 patients with lung cancer, and evaluated the correlation with the incidence of adrenal mass, TNM staging, and histology. Most of the patients with adrenal metastases showed distant metastases to non-adrenal gland or advanced nodal metastases. Therefore, routine CT examination of adrenal gland has no clinical significance.

Burt et al.(32) have evaluated the accuracy of magnetic resonance imaging in distinguishing a benign from a malignant adrenal mass in patients with otherwise operable NSCLC. The higher signal than the liver or contra lateral adrenal is considered as metastases. The result showed that the false-negative rate was 0% and the false-positive rate was 67%. They have concluded that most adrenal masses in patients with operable NSCLC are benign and currently available magnetic resonance imaging methods cannot replace biopsy. Porte et al.(33) have reported the similar tendency of MRI and stated that 100% of sensitivity and specificity can be achieved by CT guided biopsy. The detection of fat within the adrenal mass is markedly significant when the adrenal mass is encountered. McNicholas et al.(34) have suggested that , for the management of adrenal mass less than 5cm, if the CT value is less than 0HU, it should be diagnosed as adenoma, if 0-20HU, chemical shift MR imaging should be performed, and if more than 20HU, biopsy should be performed. From the cost-benefit analysis, Remer et al.(35), with using decision analysis model, showed that the criteria of less than 10HU is justifiable to diagnose

adenoma and chemical shift imaging should be used as an additional option.

A-6. Liver

ASCO: The finding of an isolated hepatic mass on ultrasonographic or computed tomographic exam requires a biopsy to rule out matastatic disease if the patientis otherwise considered to be potentially respectable. (Level of evidence III, grade of recommendation C)

ATS/ESR: The role of liver imaging as part of the initial staging chest CT for the detection of liver metastases is controversial. Most liver lesions are benign, and contrast is required to discriminate benign lesions, such as cysts and hemangiomas, from metastatic tumor. Standard contrast-enhanced CT requires extra scanning time and increased radiation dosage and is therefore not recommended if the clinical evaluation is negative. However, helical or spiral CT permits evaluation of both the thorax and the entire liver with a single bolus of contrast in a much reduced scan time. Percutaneous biopsy, if clinically indicated, is recommended for liver lesions suspicious for metastatic disease.

The incidence of liver metastasis from NSCLC is about 5% (36). Although there is some augments about the indication of the liver CT, the recent fast CT, including MDCT, can cover to the lower edge of the liver with an additional few seconds and therefore it is meaningless to discuss its

indication. Remer et al. have also stated that chest CT including adrenal and liver is a standard protocol as a pre-operative study for lung cancer.

A-7. Cost-benefit analysis

There are a several important papers published regarding the cost-benefit analysis for the search for the extrathoracic metastases.

The Canadian Lung Oncology Group (37) have tried to clarify the optimal approach to the investigation of possible distant metastases in patients with apparently operable non-small cell lung cancer who do not have symptoms suggesting metastatic disease. They conducted a randomized, controlled trial in thoracic surgery services at mainly academic tertiary- and secondary-care general hospitals. They recruited 634 patients with apparently operable, suspected or proven non-small cell carcinoma of the lung without findings on history, physical examination, laboratory testing, or imaging suggesting extrathoracic metastases. Patients were randomly allocated to receive either mediastinoscopy and computed tomography of the chest and then, depending on the results, immediate thoracotomy or bone scintigraphy and computed tomographic scanning of the head, liver, and adrenal glands. The relative risk of thoracotomy without cure (the combination of open and closed thoracotomy, incomplete resection, and thoracotomy with subsequent recurrence) in the full investigation group versus the limited investigation group was 0.80 (95% confidence interval [CI],

0.56 to 1.13; p = 0.20). Forty-three patients in the full investigation group and 61 patients in the limited investigation group underwent a thoracotomy but subsequently had recurrence (relative risk, 0.70; 95% CI, 0.47 to 1.03; p = 0.07). Patients in the full investigation group were more likely to have avoided thoracotomy because of extrathoracic metastatic disease than those in the limited investigation group (22 patients versus 10 patients, respectively; relative risk, 2.19; 95% CI, 1.04 to 4.59; p value = 0.04). The total number of negative invasive tests was six in the full investigation group and one in the limited investigation group (relative risk, 6.1; 95% CI, 0.72 to 51.0; p = 0.10) and the total number of invasive tests, 11 versus six, respectively (relative risk, 1.84; 95% CI, 0.68 to 4.98; p = 0.23). The full investigation strategy cost $823 less per patient (95% CIs 2,482 to -725). CONCLUSIONS: Full investigation for metastatic disease in patients with non-small cell lung cancer without symptoms or signs of metastatic disease may reduce the number of thoracotomies without cure. The higher the threshold for considering symptoms to suggest metastatic disease, the more likely it is that investigation will spare patients futile thoracotomy.

This conclusion is contradictory to the results in the previously published meta-analysis(7,8) and the statement from ASCO(4) and ATS/ESR(5). On the other hand, the following papers were also found which support the statement of ASCO and ATS/ESR. Osada et al.(38)have evaluated how much time and money could be saved without compromising overall results in treating lung cancer with retrospectively evaluating 318 patients for T- and M-factors and

335 for N-factor. If bronchoscopy failed to diagnose a mass lesion believed to be malignant in x-ray computed tomography (CT), they proceeded to direct thoracotomy without needle or video-assisted biopsy. When mediastinal nodes were negative in CT, they proceeded to direct thoracotomy without mediastinoscopy. They searched routinely for distant metastasis with brain and abdominal CTs and bone scans. Lesions suspected of malignancy in CT were pathologically malignant in 93%. A total of 82.8% of patients with CT-negative mediastinum were without metastasis. The remainder, with metastasis, had a postoperative 5-year survival of 23.5%. Brain CT scans were positive in only 2.2%, abdominal CT scans in 2.4%, and bone scans in 5.0%, for patients with a cT1/T2 non-cN2 lesion. From these data, they have concluded that brain and abdominal CT scans and bone scans may be omitted for cT1/T2 and non-cN2 lesions in CT. CT-negative mediastinum then leads to direct thoracotomy. The vast majority of patients may thus undergo surgery earlier with less physical and financial burden. The cost saving was calculated to be 59.4% per cT1/T2 non-cN2 patient, or US$666,815, for population evaluated based on cost-effectiveness. The similar evaluation was also executed by Tanaka et al.(39). They did a retrospective analysis of 755 patients with non-small-cell lung cancer in clinical stage T1-2 N0 between 1982 and 1996. The patients all had a full series of imaging procedures, based on the staging protocol. Their medical records were reviewed with respect to how often distant metastasis was detected by these procedures and whether the patients showed any symptoms and laboratory abnormalities indicating extrathoracic metastasis. The

incidence of distant metastasis detected by the imaging procedures was 2.1% (nine of 419) in T1 N0 cases and 5.4% (18 of 335) in T2 N0 cases. Silent metastasis was found only in 0.5% (2 of 419) of the T1 N0 cases and 0.9% (3 of 335) of the T2 N0 cases. The cost of these staging procedures was approximately one million dollars. Therefore, considering the cost and time savings, staging procedures are not warranted for patients with non-small-cell lung cancer stage T1-2 N0 with negative clinical evaluations.

A-8 Summary

How is the imaging diagnosis used in searching for extrathoracic metastases are mainly divided into the following two ways in English literatures.

1) The indication should be considered when the clinical symptoms are suspicious of having metastasis. T and N factor also influences the incidence of extrathoracic metastases, as well as, the indication of imaging examination. (ASCO, ATS/ESR)

2) The imaging search for extrathoracic metastases should be performed regardless whether the symptoms are existed or not. (The Canadian Lung Oncology Group)

It should be careful when considering the cost-effective analysis that state of medical insurance system or medical economy is markedly variable among the countries and the indication of the imaging evaluation for the metastasis in lung cancer is also different. Although the

diagnostic accuracy and its contribution to the survival rate should be considered, it is needed to establish the guideline with considering the variable social factors including medical insurance system or medical economy of Japan.

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Table 1 Level of Evidence

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples

Table 2 Grade of Recommendation

A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

Table3

STANDARDIZED CLINICAL EVALUATION FOR METASTATIC DISEASE IN PATIENTS PRESENTING WITH PRIMARY LUNG CANCER

Symptoms elicited in history

- Constitutional: weight loss
- Musculoskeletal: focal skeletal pain, chest pain
- Neurological: headaches, syncope, seizures, extremity weakness, recent change in mental status

Signs found on physical examination

- Lymphadenopathy (>1 cm)
- Hoarseness
- Superior vena cava syndrome
- Bone tenderness
- Hepatomegaly
- Focal neurologic signs: papilledema
- Soft tissue mass

Routine laboratory tests

Hematocrit <40% in males

Hematocrit<35% in females

Elevated alkaline phosphatase, GGT, SGOT, calcium

B. Guideline of the imaging for the management of community acquired pneumonia

B-1. Introduction

Pneumonia is still one of the leading cause of death not only in the developing nations but also in the advanced ones. Because there is a lot of influence on the healthcare and its cost, there have been many guidelines of community acquired pneumonia(CAP) derived from the EBM approach published through the world (1-6). Although the radiological evaluation is one of the important diagnostic approach for the pneumonia, most of those are limited to the chest radiography and the CT is not considered as a routine technique. On the contrary, in Japan, the CT tends to be frequently used in daily clinical practice and even so for the CAP. This tendency probably related to the large number of CT units and the relatively less expensive fee for CT examinations in Japan. However, there have been no consensus regarding how the CT should be used for the patients suspected to have CAP. In this study, a retrospective article survey was conducted with EBM approach against for the clinical question " Is CT needed for the management of CAP?".

B-2. Materials and Methods

To solve this clinical question, an evaluation of previously published articles which mainly discussed the diagnosis of CAP were surveyed using the conventional EBM approach. Database

which we employed were PubMed(National Libraly of Medicine) from 1966 to 2004 and Ichushi Web basic mode version3 (Japana Centra Revuo Medicina) from 1983 to 2004. Retrieved citations after inputting search terms were then transferred to bibliography software (iPubMed maker 7 version2.5, Kinichi Yokota, MD,PhD Health Care Center, Kitami Institute of Technology, Japan, File maker Pro7.0; Filemaker ,Inc). On this software, the abstracts of articles were browsed and the articles in which the diagnostic procedures or its implications for CAP were mainly discussed were selected. "Abstract form" was made using commercially available database software(File maker pro 7.0, Filemaker ,Inc). "Abstract form" includes the following information; clinical question, key words, used database, titles of manuscript, title of journal, authors, objective of the research, design of research, materials, methods, assessed items, used statistical method, results, specific comment and the evidence level of manuscript. The evidence level of the manuscript was rated as followings (Agency for Health Care Policy and Research (AHCPR).1992)(7);

1a: Evidence obtained from meta-analysis of randomized controlled trials.

1b: Evidence obtained from at least one randomized controlled trial.

2a: Evidence obtained from at least one well-designed controlled study without randomization.

2b: Evidence obtained from at least one other type of well-designed quasi-experimental study.

3: Evidence obtained from well-designed nonexperimental studies, such as comparative studies,

correlational studies, and case studies.

4: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Addition to these databases, widely used guidelines through the world regarding the management for CAP were analyzed from the point of view for the imaging diagnosis of CAP.

Analysis was executed on these abstract forms and previously published world-wide guidelines to address the following inquiries; 1) How should chest radiography(CXR) be used for the CAP? 2)Is CT needed to manage CAP? 3)Are there any difference in terms of imaging diagnosis of CAP among the published guidelines?

B-3.Results

1. Retrieve and selection of the articles

A total of 336 articles were found at "Pub Med" from 1966 to 2004.Aug when the search terms "CAP and management" were put. These abstract data were transferred to "iPubMed" maker and finally 76 articles were selected. In the same manner, a total of 699 articles were found when the search terms "Pneumonia and CT" were used and 92 articles were selected. When the term "pneumonia and CT and management" were used, 48 abstracts were found and 9 articles of

them were selected. When the term "pneumonia and imaging and management" were used, 57 abstracts were found and 9 articles of them were selected.

A total of 4 articles were found at "Ichu-shi Web" from 1983 to 2004.Aug when the search terms "CAP and management" were put. However, there was no applicable articles found which described the imaging procedure for the CAP. No articles were retrieved when the the search terms "pneumonia and CT and management" or "pneumonia and imaging and management" were used.

2. Evaluation of the articles and its evidence levels

A total of 186 articles were analyzed from the perspective of the imaging for CAP and, as a result, a total of 34 articles in which acceptable descriptions regarding the imaging diagnosis for the CAP were found. The contents of these articles were summarized using the "abstract form". The evidence levels of these articles were summarized on the table1. There have been no articles which could be rated above 2b. To evaluate the validation the published guidelines, the search terms "pneumonia and guideline and validation" were put on "PubMed". There have been no article found which performed a comprehensive validation for each guideline.

3. Summary of the retrieved articles regarding the imaging diagnosis for CAP.

1) Indication of chest radiography for the patients suspected to have CAP

Most of the articles have stated that chest radiography should be obtained for all the patients suspected to have CAP as an initial diagnostic procedure(8). The diagnosis of CAP is based primarily on the clinical findings and confirmed by chest radiography(9,10). Main purpose of chest radiography is the evaluation whether the infiltrative shadows are present or not. The differentiation from viral bronchitis is extremely important because antibiotics abuse is a serious concern especially in the United States(3,11). Therefore many guidelines include the presence of infiltrative shadows as the essential diagnostic clue for the pneumonia(1-6,9). Another purposes of chest radiography includes the exclusion of other combined pulmonary diseases such as pulmonary embolism, congestive heart failure and bronchogenic carcinoma(9). An assessment of disease severity is another role of chest radiography such as pleural effusion, cavity formation and multilobar involvement(9). In some guidelines, the indication of chest radiography is strictly defined. European Respiratory Society(ERS) guideline recommends that chest radiography should be considered only for the severe or complicated cases to whom hospital management must be considered(6). The incidence of infiltrative shadow in the patients who have symptoms consistent with pneumonia is only 3% in outpatient services and 28% in ER(3,12). Many articles have mentioned some limitations of chest radiography for diagnosing pneumonia(9). Radiographic

finding is not reliable for confirmation the causative organism(9). Additionally, inter- and intra-observer variation is frequently observed in the interpretation of chest radiography(9,13). There is no established statement regarding how the chest radiograph should be obtained in the treatment process of CAP. Young non-smokers who are healthy at a 6-week follow up visit generally do not need radiography to show pneumonia resolution(14).

2) Indication of chest CT for the patients suspected to have CAP

There have been few articles describing the indications of CT for the patients suspected to have CAP(8,9,15,17,18,20). Although we have found 11 articles describing the CT indication, there have been no recommendation that CT should be used for the cases suspected to have CAP(8,9,11,13,15-21). Three of eleven articles have denied or suspended the conclusion about the usefulness of CT in the management of CAP(11,16,19). One article has stated that CT provides no useful information in differentiating causative organism excepts for Pneumocystis Carinii pneumonia(PCP) and Mycoplasma pneumonia(19). Five articles were describing the CT indications for the patients suspected to have CAP(8,9,17,18,20). These articles have stated that CT should be used only for the cases with the complicated states or whose chest radiography is normal while with the symptoms suspected to have pneumonia. One article showed the detailed indication of CT including; 1) to differentiate pleural lesion from pulmonary lesion, 2) to evaluate the

case whose x-ray shows suspicion of lymphadenopathy, 3) to evaluate the subphrenic disease, 4) to evaluate the cavitary disease in early phase, 5) to evaluate the position of the chest tube and 5) to evaluate the chest wall invasion by the special orgasm such as actinomycosis(20).

3) Described imaging procedures in previously published guidelines(Table 2)

a. Japanese Respiratory Society (2000)(1)

-Pneumonia is diagnosed by the clinical symptoms and acutely appeared infiltrative shadow on chest radiography or chest CT.

-CT is extremely useful in differentiating pneumonia from other conditions, evaluating the character and the extent of shadows.

-As one of the assessment method for disease severity, the evaluation of disease extension on the chest radiography is employed; " mild, moderate and severe.

-Chest radiography cannot identify the causative organism. CT can demonstrates the early and small disease or hidden disease, however the exact roll is not established yet.

b. American Thoracic Society(2001)(2)

-All patients with CAP should have a chest radiograph to establish the diagnosis and the presence of complications(pleural effusion, multi-lobar disease).

-Standard PA and lateral chest radiographs are valuable in patients whose symptoms and physical examination suggest the possibility of pneumonia, and every effort should b e made to obtain this information.

-The radiograph can be useful in differentiating pneumonia from other conditions that may mimic it.

-The radiographic findings may suggest specific etiologies or conditions such as lung abscess or tuberculosis.

-The radiograph can also identify coexisting conditions such as bronchial obstruction or pleural effusion.

-The radiograph is also useful for evaluating severity of disease.

-Clinical value of CT for the CAP is uncertain.

c. Infectious Disease Society of America (2000)(3)

-Chest radiograph should be considered as a baseline assessment to substantiate diagnosis of pneumonia, to detect associated lung diseases, to gain insight into causative agent, to assess severity, and as baseline to assess response. (Grade of recommendation A, level of evidence II)

Categories for ranking recommendations and quality of evidence in IDSA

Strength of recommendation

A Good evidence to support a recommendation for use

B Moderate evidence to support a recommendation for use

C Poor evidence to support a recommendation

D Moderate evidence to support a recommendation against use

E Good evidence to support a recommendation against use

Quality of evidence

I Evidence from at least 1 randomized, controlled trial

II Evidence from at least 1 well-designed clinical trial without randomization

III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

-Clinical significance of CT is unclear. The IDSA panel does not endorse the routine use of this technology because of the preliminary nature of the data and high cost of the procedure.

d. British Thoracic Society (2001)(4)

・All patients referred to hospital with CAP should have a chest radiograph.

-There are no characteristic features of the chest radiograph in CAP that allow a confident prediction of the likely pathogen (recommendation level II)

· CT lung scan may be useful in subjects where the diagnosis is in doubt (III), but in general there seems little role for CT scanning in the usual investigation of CAP.

Evidence level Definition in British Thoracic Society

Ia A good recent systematic review of studies designed to answer the question of interest

Ib One or more rigorous studies designed to answer the question, but not formally combined

II One or more prospective clinical studies which illuminate, but do not rigorously answer, the question

III One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question

IVa Formal combination of expert views

IVb Other information

e.Canadian Infectious Diseases Society and the Canadian Thoracic Society(2000)(5)

-Chest radiography is recommended for the routine evaluation of a patient suspected of

having pneumonia (II).

-The advantage of chest radiography is that the diagnosis of pneumonia is strengthened (but not confirmed) by the presence of an infiltrate. Occasionally, information regarding etiology and prognosis may be obtained and alternative diagnoses may be entertained.

-The panel realizes that in some instances a chest radiograph might not be obtained; for example, when the patient is in a nursing home or when access to radiographic equipment is limited. The panel recognizes that under these circumstances a trial of empirical therapy without radiographic confirmation of the diagnosis is a reasonable approach (III).

-HRCT can detect additional infiltrates, however the significance of the improved sensitivity of the HRCT was not studied; whether this improved sensitivity made a difference in the management or outcome of the cases remains to be determined.

-Chest radiography is less sensitive than HRCT scans in detecting pulmonary infiltrates, but the significance of this observation remains to be determined.

Evidence level Definition in the Canadian Task Force on the Periodic Health Examination

well-conducted randomized, controlled trials constitute strong or level I evidence

well-designed controlled trials without randomization (including cohort and case-control

studies) constitute level II or fair evidence

expert opinion, case studies, and before-and-after studies are level III (weak) evidence.

f. European Respiratory Society (1998)(6)

-Chest radiography is not recommended for the patients with no risk factors including high age, alcoholism and a various co-morbidities.

-Chest radiography is recommended for the patients to whom hospital management has to be considered, including with risk factors for severity, risk factors for particular microorganism and failure of first-line antibiotic therapy.

B-4. Discussion

Our article survey has revealed the following consensus in terms of imaging diagnosis for patients suspected having CAP.

1. Chest radiography should be performed for the patients suspected having CAP.

2. The diagnosis of pneumonia is established when the clinical signs and newly appeared infiltrative shadows are co-existed.

3. There are no characteristic features of the chest radiograph in CAP that allow a confident prediction of the likely pathogen.

4. There has been no systematic study conducted concerning the CT indication for the CAP. Although CT provides more detailed information than chest radiography, its clinical significance is uncertain.

It is no doubt that chest radiography is an indispensable tool for diagnosing CAP. Chest radiography is less expensive and is easily available in almost all medical facilities. On the contrary, in most of countries, CT is not considered as a routine workup for CAP. There is one manuscript from Finland describing the indication of CT for CAP(15). Syrjala H et al. have reported the usefulness of HRCT in diagnosing CAP(15). They compared chest radiographs with HRCT for 47 patients with clinical symptoms and signs suspicious for CAP. HRCT identified all 18 CAP cases (38.3%) apparent on radiographs as well as eight additional cases (i.e., 55.3%); P =.004. The corresponding figures for bilateral involvement were six by chest radiography (33.3%) and 16 by HRCT (61.5%), P=.001. Chest radiography did not show changes particularly affecting the upper and lower lung lobes and the lingula. Bronchopneumonia was visualized by chest radiography in all cases (61.1%) and by HRCT in 22 cases (84.6%). The corresponding figures for airspace pneumonia were four (22.2%) and one (3.8%), respectively. The use of HRCT seems to increase the number of CAP cases confirmed by imaging and to improve the accuracy of diagnosing and typing of CAP. Low dose technique gives solution for radiation exposure. The problem is the medical cost; $180 vs. 27$(15).

Although the systematic research has not been conducted in Japan, "The Japan Respiratory Society guideline for management of CAP in adult" showed that pneumonia is diagnosed by the clinical symptoms and acutely appeared infiltrative shadow on chest radiography or chest CT(1). These generous acknowledgement for the use of CT in CAP in Japan guideline is specific and is markedly contrast to those in western countries. In general, CT is frequently used in clinical practice in Japan, probably due to its wide availability and low cost compared to the foreign countries. According to the published data from Shrimpton et al.(22), almost 670000000 examinations were done by the approximately 20000 CT units through the world in 1997. Among them, almost half number of CT scanners in the world have been used and almost half number of CT examinations have been performed in Japan. According to the United Nation(23) and Nishizawa' et al.(24), number of CT units has been increased from 712 in 1979 to 11050 in 2000 in Japan. Although the actual number of CT examinations is not obtained, Nishizawa et al. has speculated that 36550000 examinations were performed in Japan annually(24). This is consistent with a mean of 290 examinations per 10000 populations. In addition, there is no regulation by health insurance system in Japan when the patient with pneumonia is subjected to CT scan.

Pneumonia is still listed as the 4th leading cause of death in Japan regardless with the development of its managing procedure(25). Pneumonia is still considered as one of the dangerous common disease in daily clinical practice. In the Unite States, six million immunocompetent

people are suffered from bacterial pneumonia annually and pneumonia is listed as the 6th leading cause of death(14,26). Annually, 2–3 million cases of CAP result in～10 million physician visits, 500,000 hospitalizations, and 45,000 deaths in the United States(3). The incidence of CAP that requires hospitalization is estimated to be 258 persons per 100,000 population and 962 per 100,000 persons aged >65 years(3). The cost of inpatient care, estimated at more then $9 billion a year, is up to 20 times higher than that of outpatient care(3,27). It is estimated that it increases 20 billion $ if the lost wages during admission is added(14). Therefore the establishment of accurate diagnosis and treatment for pneumonia is crucial not only from the healthcare aspect but also from the economical one. The establishment of the appropriate way for the imaging approach in pneumonia is also extremely important. However, in Japan, there has been no study of technology assessment regarding the cost-effectiveness of imaging diagnosis of CAP. The medical cost for CT examination is enormously large and therefore there is a lot of influence on health insurance system in Japan. Although the DPC(Diagnosis Procedure Combination) system has been introduced in national university or hospital recently, the outpatient is not indicated in this system. Most of the initial diagnostic procedure for the patients suspected to have CAP including imaging procedure is usually performed in outpatient service. Therefore medical cost for the outpatient suspected to have pneumonia is still the important issue.

It is obvious that CT will provide the more detailed information than chest radiography in

the case with pneumonia(15,28,29). CT has an ability to demonstrate the subtle abnormality which chest radiography cannot demonstrate(15,28,29). Some infectious disease shows specific CT findings which helps physician in managing pneumonia(28). Additionally, the technological development of CT enables us to obtain a large number of thin-slice images in a remarkable short time. This tends to accelerate the frequent use of CT even in the CAP management. However, there have been no evidence reported that CT can contribute the management of CAP more efficiently than the chest radiography alone. It is needed that more strict guideline about the use of CT in the management of CAP from the standpoint of technology assessment. This is because not only from the economical aspect but also from the radiation concern to the patients. Nishizawa et al. have reported the result from the survey of CT practice in Japan with estimating the collective effective dose for the population(23). This survey has revealed that the CT examinations including chest is almost 30% of all CT examinations(23). These data means that the contribution of chest CT examinations in Japan for the collective effective dose for the population is significant. Although the low dose technique is quite feasible in chest CT for evaluating lung field, it is not routinely used for adults in daily practice.

In conclusion, this study has revealed that no work with highly rated evidence has conducted about the use of CT for the patient with CAP. In Japan, it is needed that strict guideline for the use of CT in CAP is established from the aspects of medical cost and radiation exposure.

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Table 1 : Evidence levels of retrieved articles(n=34)

level of evidence	Number of articles
1a	0
1b	0
2a	0
2b	0
3	9
4	25

Table2 : Comparison among descriptions regarding the imaging procedures for CAP in published guidelines

Guideline	chest radiography	chest CT
Japanese Respiratory Society (2000)	#Pneumonia is diagnosed by the clinical symptoms and acutely appeared infiltrative shadow on chest radiography or chest CT. #The disease severity is evaluated by the extension of the shadows on the chest radiography as; " mild, moderate and severe.	#Pneumonia is diagnosed by the clinical symptoms and acutely appeared infiltrative shadow on chest radiography or chest CT. #CT is extremely useful in differentiating pneumonia from other conditions, evaluating the character and the extent of shadows. #CT can demonstrates the early and small disease or hidden disease, however the exact roll is not established yet.
American Thoracic Society (2001)	# All patients with CAP should have a chest radiograph to establish the diagnosis and the presence of complications (pleural effusion, multi-lobar disease). # Standard PA and lateral chest radiographs are valuable in patients whose symptoms and physical examination suggest the possibility of pneumonia, and every effort should b e made to obtain this information. # The radiograph can be useful in differentiating pneumonia from other conditions that may mimic it. # The radiographic findings may suggest specific etiologies or conditions such as lung abscess or tuberculosis. # The radiograph is also useful for evaluating severity of disease.	#Clinical value of CT for the CAP is uncertain.
Infectious Disease Association of America (2000)	# Chest radiograph should be considered as a baseline assessment to substantiate diagnosis of pneumonia, to detect associated lung diseases, to gain insight into causative agent, to assess severity, and as baseline to assess response.	# Clinical significance of CT is unclear. The IDSA panel does not endorse the routine use of this technology because of the preliminary nature of the data and high cost of the procedure.
British Thoracic Society (2001,2004)	# All patients referred to hospital with CAP should have a chest radiograph. # There are no characteristic features of the chest radiograph in CAP that allow a confident prediction of the likely pathogen	#CT lung scan may be useful in subjects where the diagnosis is in doubt (III)*, but in general there seems little role for CT scanning in the usual investigation of CAP.

Canadian Infectious Diseases Society and the Canadian Thoracic Society(2000,2003)	# Chest radiography is recommended for the routine evaluation of a patient suspected of having pneumonia (II)**. # The advantage of chest radiography is that the diagnosis of pneumonia is strengthened (but not confirmed) by the presence of an infiltrate. Occasionally, information regarding etiology and prognosis may be obtained and alternative diagnoses may be entertained. # The panel realizes that in some instances a chest radiograph might not be obtained; for example, when the patient is in a nursing home or when access to radiographic equipment is limited. The panel recognizes that under these circumstances a trial of empirical therapy without radiographic confirmation of the diagnosis is a reasonable approach (III)**.	# HRCT can detect additional infiltrates, however the significance of the improved sensitivity of the HRCT was not studied; whether this improved sensitivity made a difference in the management or outcome of the cases remains to be determined. # Chest radiography is less sensitive than HRCT scans in detecting pulmonary infiltrates, but the significance of this observation remains to be determined.
European Respiratory Society (1998)	# Chest radiography is not recommended for the patients with no risk factors including high age, alcoholism and a various co-morbidities. # Chest radiography is recommended for the patients to whom hospital management has to be considered, including with risk factors for severity, risk factors for particular microorganism and failure of first-line antibiotic therapy.	Not described

*Evidence level Definition in British Thoracic Society

Ia A good recent systematic review of studies designed to answer the question of interest

Ib One or more rigorous studies designed to answer the question, but not formally combined

II One or more prospective clinical studies which illuminate, but do not rigorously answer, the question

III One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question

IVa Formal combination of expert views

IVb Other information

** Evidence level Definition in the Canadian Task Force on the Periodic Health Examination

well-conducted randomized, controlled trials constitute strong or level I evidence

well-designed controlled trials without randomization (including cohort and case-control studies) constitute level II or fair evidence

expert opinion, case studies, and before-and-after studies are level III (weak) evidence.