な臨床試験が必要である．Ph陽性MPALに対して*ABL*チロシンキナーゼ阻害剤の有効性が期待されるが，まとまった治療成績がないため現時点では不明である．

今後の課題と展望

WHO分類2008による診断基準により，MPALはEGIL基準に比べてより厳密に診断できると考えられるが，その新基準の妥当性や有効性の評価は明らかではない．本稿で触れたように，MatutesらによりWHO分類2008で診断されたMPALの臨床学的特徴と治療成績がはじめて報告され，今後のMPALの病態解明へのアプローチや治療法開発の参考になるものと期待される．一方で，Ph陽性や*MLL*遺伝子再構成を有するMPALが，これらの異常を有するALLと生物学的・臨床学的にどう違うかなど，解明すべき点は山積している．今後，MPALが真に独立した疾患として治療法が確立されるためには，現在の分類だけでは限界があり，さらなる分子遺伝学的なアプローチにより診断と治療の鍵となる分子マーカーを見出していく必要があると思われる．

おわりに

WHO分類2008によるMPALの臨床像について，EGIL基準のBALと比較しながら最近の知見を交えて解説した．MPALに対する至適な治療戦略を確立するために，今後，厳密な診断に基づいた患者コホートを対象に，前方視的な大規模臨床試験や分子遺伝学的アプローチによる病態解明が進められることを期待したい．

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Original Article

Comparison of Long-Term Clinical Outcomes of CHOP Chemotherapy between Japanese Patients with Nodal Peripheral T-Cell Lymphomas and Those with Diffuse Large B-Cell Lymphoma in the Study Group of the Tohoku Hematology Forum

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To clarify the clinical outcome of peripheral T-cell lymphomas (PTCLs), we conducted a retrospective review comparing the outcomes of patients with PTCL (nodal peripheral T-cell lymphoma, unspecified, n = 34 ; angioimmunoblastic T-cell lymphoma, n = 12) to those with diffuse large B-cell lymphoma (DLBCL, n = 48). All patients received CHOP-based chemotherapy without rituximab. PTCL patients presented at a more advanced clinical stage (91% vs. 65%, $P < 0.002$) with a poorer performance status (26% vs. 17%, $P < 0.002$) than DLBCL patients. The complete response rate among PTCL patients was significantly lower than among DLBCL patients (39% vs. 67%, $P < 0.008$), as was the 3-year overall survival rate (26% vs. 50%, $P = 0.005$), and Cox multivariate analysis revealed immunophenotype, performance status, and extranodal site involved to be significantly associated with shorter overall survival ($P = 0.045$, $P = 0.007$, and $P = 0.034$, respectively). Our findings suggest that PTCL patients tend to have a poor prognosis associated with several initial risk factors. Moreover, the T-cell phenotype itself appears to have a significant impact on overall survival. Thus, standard CHOP chemotherapy may be inadequate for PTCLs, especially in patients with high-risk factors. The development of newly stratified therapies for the treatment of PTCLs would be highly desirable. [*J Clin Exp Hematopathol 51(1) : 29-35, 2011*]

Keywords: peripheral T-cell lymphomas, diffuse large B-cell lymphoma, survival, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)

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INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are relatively uncommon malignancies, accounting for only 10-15% of non-Hodgkin's lymphomas (NHLs) in large international studies.[1,2] However, their incidence shows significant geographical and racial variation, such that they are much more common in Asia, including Japan, than in North America or Europe.[3,4] The most common PTCL subtypes are peripheral T-cell lymphoma, unspecified (PTCL-u or PTCL, not otherwise specified) (25.9%), angioimmunoblastic T-cell lymphoma (AITL) (18.5%), and anaplastic large cell lymphoma (ALCL) [anaplastic lymphoma kinase (ALK)-positive ALCL, 6.6% ; ALK-negative ALCL, 5.5%].[5] Patients with PTCL usually present with systemic lymphadenopathy and frequent

involvement of extranodal tissues, including bone marrow, skin, and spleen, and a majority have advanced disease with B symptoms.[6] Moreover, PTCLs include primary extranodal T-cell lymphoma, especially cutaneous peripheral T-cell lymphomas. However, this subtype is a different entity from nodal PTCLs by clinical features or etiology.

PTCLs have an aggressive clinical course with a poor response to therapy. When stratified on the basis of international prognostic index (IPI), treatment of PTCLs using standard anthracycline-based regimens results in significantly poorer outcomes within each risk group than when the same regimens are used to treat diffuse large B-cell lymphoma (DLBCL).[2,7,8] Indeed, long-term disease-free survival (DFS) is achieved in only 20-30% of patients with PTCL.[2,6-10] However, these results showed substantial heterogeneity due to the inclusion in the PTCL group of patients with ALK-positive ALCL, which has a significantly better outcome than DLBCL.[11-13] To clarify the clinical outcome of PTCLs, we conducted a retrospective review of patients with PTCL, including nodal PTCL-u (n = 34) and AITL (n = 12), who were treated using a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone). A cohort of consecutive patients with primary nodal DLBCL, which is the same aggressive lymphoma as PTCLs, also treated with a CHOP regimen (without rituximab) served as a reference group for comparison.

PATIENTS AND METHODS

Patients

A total of 46 Japanese patients with PTCL, including nodal PTCL-u (n = 34) and AITL (n = 12), were treated as members of the study group of the Tohoku Hematology Forum (THF) from April 1998 to December 2005. A consensus diagnosis for each patient was obtained using the World Health Organization (WHO) classification (2001).[14] A diagnosis was confirmed hematopathologically by pathologists at each institute and R.I. We specifically excluded from the study patients with extranodal PTCL-u, ALK-positive ALCL, HTLV-1-positive T cell lymphoma, extranodal NK/T-cell lymphoma, and the other subtypes of mature T-cell lymphoma. Clinical stage was defined according to the Ann Arbor classification. The IPI was calculated on the basis of age, performance status (PS), serum lactate dehydrogenase (LDH) value, number of involved extranodal sites, and clinical stage. The treatment response was assessed according to the WHO response criteria. A complete response (CR) was defined as no evidence of residual disease. All patients were newly diagnosed, were previously untreated, and were treated using a CHOP regimen. The median follow-up period was 11.5 months (range, 3-60 months). Consecutive patients with primary nodal DLBCL that received the aforementioned CHOP regimen without rituximab were identified from the database of Aomori Prefectural Hospital and were selected as a control group. Patients with extranodal DLBCL (n = 7), who had been treated using high-dose chemotherapy following auto stem cell transplantation (n = 2) or who had been treated using chemotherapy without anthracycline because of old age (more than eighty years old ; n = 3) were excluded from the control group. Given these considerations, the control group was composed of 48 patients who received the CHOP regimen between April 1998 and December 2005, which was before we started routinely using rituximab as first-line therapy. The median follow-up period of the control group was 15.0 months (range, 6-60 months). The present study was conducted under approval of the institutional review board of Akita University Hospital in accordance with the Declaration of Helsinki.

Statistical Analyses

All statistical analyses were performed using SPSS statistical software (SPSS Japan Inc., Tokyo, Japan, version 17.0). Data are presented as means±SD, unless indicated otherwise. Differences between two groups were evaluated using Student's t-test (parametric analysis). The χ^2 test or Fisher's exact test was used to compare the proportions of patients. Disease-free survival (DFS) for patients who achieved CR was calculated from the date of the first documentation of response to the date of recurrence or death. Overall survival (OS) was calculated from the date chemotherapy was initiated to the date of death from any cause or to the date of last contact. DFS and OS were analyzed using the Kaplan-Meier method. The statistical significance of differences in survival was assessed using the Log-rank test. The effects of potential prognostic variables on survival (significance threshold, $P = 0.1$) were assessed in stepwise fashion according to the Cox regression method. Values of P less than 0.05 were considered significant.

RESULTS

Patient Characteristics

The main clinical characteristics of the 46 patients with PTCL and 48 with DLBCL (control) are shown in Table 1. As was carried out previously,[2] we evaluated age, PS, clinical stage, serum LDH values, and the number of involved extranodal sites as prognostic factors. The median age of the PTCL patients was 65 years (range 35-89 years), while that of the DLBCL patients was also 65 years (range 17-83 years). There was no significant difference between the two groups with respect to age, gender, serum LDH values, or the number of involved extranodal sites. On the other hand, more PTCL patients presented at an advanced clinical stage (91% vs.

Table 1. Patient characteristics and prognostic factors

Characteristics	PTCLs (n=46)	DLBCL (n=48)	*P*
Age (years)	64.9±11.1 65y (35-89)	63.6±11.0 65y (17-83)	0.549[a] 0.555[b]
Sex (male/female)	24/22	22/26	0.539
Performance status (2-4)	12	8	<0.002
Clinical stage (III+IV)	42	31	<0.002
Serum LDH (<UNL)	33	32	0.595
Extranodal sites (>2)	11	7	0.251
IPI (HI+H)	30	20	0.022

PTCLs, peripheral T-cell lymphomas ; DLBCL, diffuse large B-cell lymphoma ; LDH, lactate dehydrogenase ; UNL, upper normal limit ; IPI, international prognostic index ; HI, high-intermediate ; H, high ; [a], Student's t-test ; [b], Mann-Whitney test

Table 2. Clinical response to CHOP regimen and survival

Outcomes	PTCLs (%)	DLBCL (%)	*P*
Complete response	18/46 (39%)	32/48 (67%)	<0.008
Relapse	10/18 (56%)	13/32 (41%)	0.309
3-year disease-free survival	40%	49%	0.253[a]
3-year overall survival	26%	50%	0.005[a]

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone ; PTCLs, peripheral T-cell lymphomas ; DLBCL, diffuse large B-cell lymphoma ; [a], log-rank test

65%, $P<0.002$), with a poorer performance status (26% vs. 17%, $P<0.002$), and with a higher international prognostic index (IPI) (65% vs. 42%, $P=0.022$) than DLBCL patients.

Response to Treatment and Survival

We assessed the impact of immunophenotype on clinical response and survival. A significantly lower CR rate was observed among the PTCL patients initially treated with the CHOP regimen than among the DLBCL patients (39% vs. 67%, $P<0.008$, Table 2). As shown in Table 2, 10 of the 18 (56%) PTCL patients who achieved CR relapsed, whereas only 13 of 32 (41%) DLBCL patients relapsed. Thus, PTCLs appear to recur more frequently than DLBCL, although the difference was not significant ($P=0.309$).

When we then compared the DFS curves between PTCL and DLBCL patients (Fig. 1), we found that the frequency of 3-year DFS tended to be lower among PTCL patients than DLBCL patients (40% vs. 49%, Log-rank test : $P=0.253$). Similarly, comparison of the OS curves (Fig. 2) showed the 3-year OS rate to be significantly lower among PTCL patients than DLBCL patients (26% vs. 50%, Log-rank test : $P=0.005$). In addition, Cox multivariate analysis revealed that immunophenotype, performance status, and extranodal site involved were all significantly associated with shorter OS ($P=0.045$, $P=0.007$, and $P=0.034$, respectively ; Table 3).

DISCUSSION

We found that PTCL patients presented at a more advanced clinical stage and with poorer performance status than DLBCL patients. Consequently, the IPI among the patients was significantly higher than among DLBCL patients. This finding is consistent with earlier Japanese studies, which reported that high-risk groups (High + High-intermediate) accounted for 72.2% or 74% of Japanese patients with PTCL.[15,16] In Western countries, by contrast, high-risk groups account for only 42-46% of patients with PTCL.[2,9,17] Although the IPI for PTCLs appears to be higher in Japan than in Western countries, international studies with large patient populations will be required to confirm the racial differences in the clinical characteristics of PTCLs.

A significantly lower CR rate was observed among PTCL patients initially treated with a CHOP regimen than among DLBCL patients administered the same treatment. This finding was consistent with earlier reports in which CR rates for PTCLs ranged from 31% to 69%.[2,6,7,9,15,16] Furthermore, in the pre-rituximab era, the long-term remission rate was 50-60%, which is consistent with our result. If rituximab were combined with the CHOP regimen for CD20-positive DLBCL, the difference in CR rates between PTCLs and DLBCL would be expected to increase, as most studies have suggested that primary regimens containing rituximab improved the CR rate and long-term outcomes of DLBCL patients.[18-21]

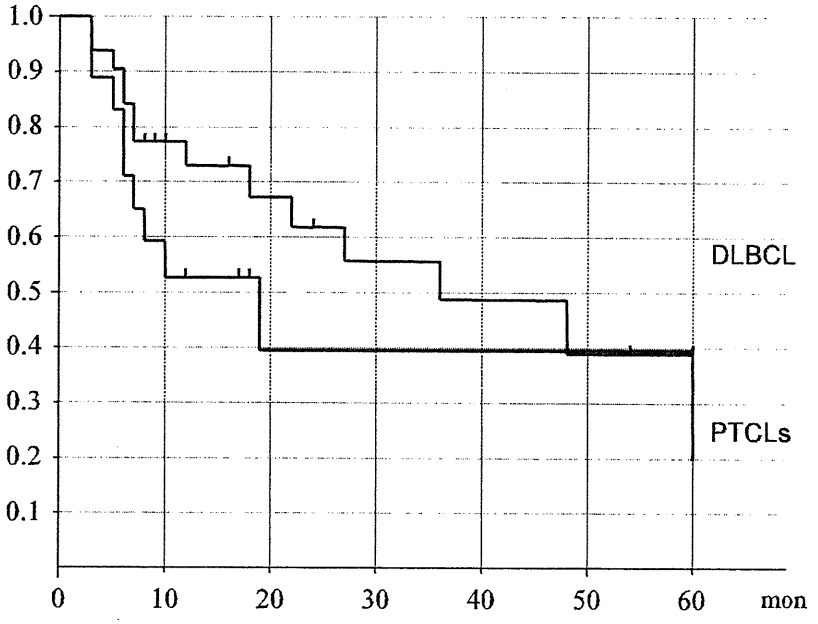

Fig. 1. Disease-free survival curves for patients with nodal peripheral T-cell lymphoma, unspecified (n = 32), or diffuse large B-cell lymphoma (n = 18) were analyzed using Kaplan-Meier methods. The Log-rank test revealed no significant difference between the two groups ($P = 0.253$).

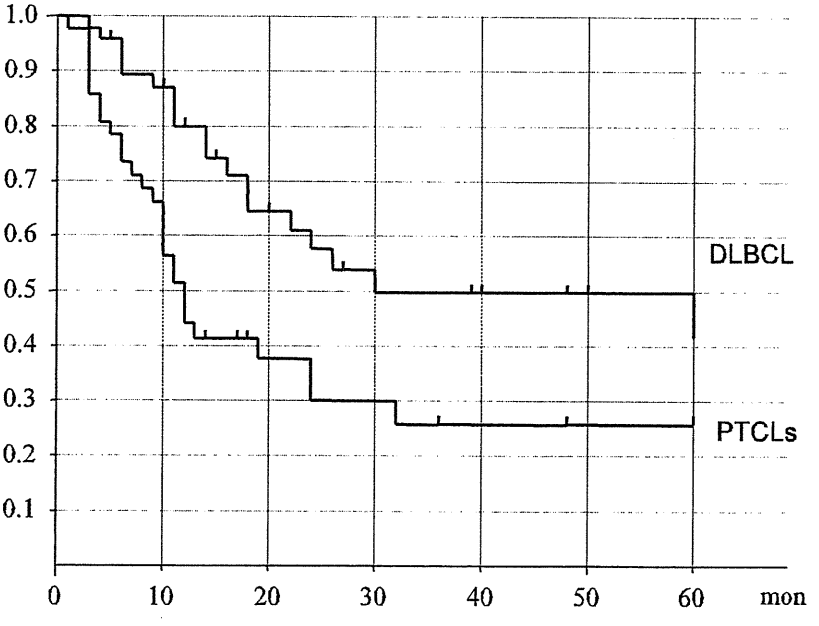

Fig. 2. Overall survival curves for patients with nodal peripheral T-cell lymphoma, unspecified (PTCL-u), or diffuse large B-cell lymphoma (DLBCL). Data from all patients with PTCL-u (n = 46) or DLBCL (n = 48) were analyzed using Kaplan-Meier methods. The Log-rank test revealed a statistically significant difference between the two groups ($P = 0.005$).

Table 3. Prognostic factors and overall survival

Variable	Median OS (mon)	Univariate *P*-value[a]	Multivariate *P*-value[b]	RP (95% CI)
Sex (male/female)	14/31	0.033	0.280	—
Age (<60/>60)	14/24	0.838	—	—
Immunophenotype (PTCLs/DLBCL)	12/30	0.005	0.045	0.53 (0.29-0.99)
Performance status (0-1/2-4)	32/6	<0.001	0.007	2.91 (1.34-6.33)
Clinical stage (I-II/ III-IV)	n.r./14	0.001	0.322	—
Serum LDH (<UNL/>UNL)	32/14	0.029	0.881	—
Extranodal sites (0-1/2-)	30/6	<0.001	0.034	2.30 (1.07-4.98)
IPI (L-LI/ HI-H)	12/60	<0.001	0.579	—

OS, overall survival ; mon, months ; [a], Log-rank test ; [b], Cox regression analysis ; RR, risk ratio ; CI, confidence interval ; PTCLs, peripheral T-cell lymphomas ; DLBCL, diffuse large B-cell lymphoma ; n.r., not reached ; LDH, lactate dehydrogenase ; UNL, upper normal limit ; IPI, international prognostic index ; L, low ; LI, low-intermediate ; HI, high-intermediate ; H, high

Although the immunophenotype itself was an independent risk factor affecting OS in the present study, several earlier studies reported that there was no difference in OS between B-cell and T-cell lymphomas.[22-24] Moreover, Morabito *et al.* reported that, although the OS curves associated with the T-cell and B-cell immunophenotypes significantly differed from each other (5-year OS, 42% vs. 56% ; median OS, 39 months vs. 94 months, P = 0.0012), multivariate analysis did not detect an association between OS and immunophenotype.[17] It seems likely that we were able to identify immunophenotype as an independent risk factor because we excluded patients with ALCL, which have more favorable outcomes than those with PTCL-u, and we compared nodal PTCLs with nodal DLBCL treated with the same standard CHOP regimen. Moreover, although they were small patient populations, we compared OS among patients with a high IPI index (14 of PTCLs, 10 of DLBCL). There was a significant difference between the two groups (50% OS, 4 months vs. 11 months ; Log-rank test P = 0.038). This finding might be associated with three potential prognostic variables, including immunophenotype, performance status, and extranodal sites, which we analyzed by multivariate analysis.

Recently, the International T-Cell Project reported a cohort of 1,314 cases, including PTCLs, organized from 22 centers, worldwide. It was concluded that, unlike in DLBCL, the use of an anthracycline-containing regimen was not associated with improved outcomes in PTCLs.[5] On the other hand, the outcomes were equivalent in patients treated with high-dose sequential chemotherapy followed by autologous transplantation (ASCT).[25-30]

It has been reported that there is marked variability in the 5-year relative survival rate across PTCL subtypes, and that there has been no clear improvement in survival among PTCL patients over time.[31] This finding is in sharp contrast to the improvement in OS seen for B-cell NHLs over the same time period,[18-21] which is due mainly to advances in therapy, particularly the addition of immunotherapy using anti-CD20 rituximab. CD52 antigen appears to be a suitable target for chemo-immunotherapy protocols for PTCLs, given the availability of anti-CD52 alemtuzumab. Prospective multicenter clinical trials have been designed to explore both the efficacy and the safety of a chemo-immunotherapeutic approach based on the combination of alemtuzumab and a standard-dose CHOP regimen as the first-line treatment for patients with PTCLs.[32,33] For patients who have high IPI score at the time of diagnosis, better therapeutic regimens are needed to improve the outcome of PTCLs.

Although this study was retrospective with only a small patient population, we found the prognosis of PTCL patients receiving the standard CHOP regimen to be poorer than that of DLBCL patients receiving the same therapy. This difference in clinical outcome seemed to depend on the phenotype itself, even in the era before rituximab, as well as on the more advanced clinical stage of the PTCL patients at the time of diagnosis. Thus, standard CHOP chemotherapy may be inadequate for PTCLs, especially in patients with high-risk factors. The development of new stratified therapies for the treatment of PTCLs would be highly desirable.

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Increase of Ascites and Pleural Effusion Misleading Assessment of Antitumor Response to Erlotinib in Adenocarcinoma of the Lung

Case Report

A 71-year-old nonsmoking man was diagnosed with metastatic adenocarcinoma of the lung. Computed tomography (CT) showed a left lower lobe mass with multiple metastases to the lung and liver, left pleural effusion, and some ascites. Pleural fluid cytology revealed adenocarcinoma, which was compatible with histopathologic examination of a specimen obtained by bronchoscopy. Positive status for epidermal growth factor receptor (EGFR) mutation (L858R) was revealed. After pleurodesis, the patient received pemetrexed (500 mg/m^2) as first-line chemotherapy because of an Eastern Cooperative Oncology Group performance status of 2. However, disease progression continued after first-line treatment (Figs 1A, 1B).

Erlotinib (Tarceva; Genentech, South San Francisco, CA) was administered daily as second-line chemotherapy. Therapy was started at a dosage of 100 mg because of mild liver dysfunction (AST, 1.5 × upper limit of normal) and Eastern Cooperative Oncology Group performance status of 2. Because treatment was well tolerated, we increased the dosage to 150 mg from day 7. The general condition of the patient improved markedly, and the tumor size decreased. However, after 11 days of erlotinib administration, he suddenly developed high-grade fever followed by dyspnea. CT of the chest showed no interstitial lung changes but demonstrated marked worsening of ascites and pleural effusion despite the decreasing size of tumors (Figs 2A, 2B). We drained 2 L of ascites and examined the fluid. Bacteriology of ascites did not yield any bacterial growth, and no malignant cells were apparent cytologically. Up to 92% of the cells in the fluid were lymphocytes. Because we judged that erlotinib seemed to have no severe adverse effects, therapy was continued. However, ascites fluid and pleural effusion increased (Fig 3A), and fever was not alleviated. We drained the fluid repeatedly and obtained similar cytologic results. We attributed this phenomenon to an immune reaction to the acute lysis of cancer cells after erlotinib therapy. Administration of prednisolone (PSL) was started at 30 mg/d from day 40, achieving control of fluid and improved general condition (Fig 3B). The PSL dose was gradually tapered, and the patient was discharged on day 91. CT evaluation showed dramatic reductions in the sizes of the primary tumor and metastases and decreases in both ascites and pleural effusion despite tapering of PSL (Fig 3C).

Discussion

Malignant pleural effusion is a complication that occurs in 35% of lung cancers. As for ascites, 85% result from liver disease, and one of the other causes is related to malignancy. Peritonitis carcinomatosis from lung cancer is uncommon, with only 1.2% of patients with advanced lung cancer developing peritoneal carcinomatosis, according to retrospective analysis.[1] The amount of effusion from these sources usually decreases along with improvements in the underlying disease in response to systemic anticancer treatment.

In our patient, the fluid increased against the dramatic effects of erlotinib. These symptoms suddenly occurred on day 11 after starting erlotinib. The effects and adverse effects of EGFR tyrosine kinase inhibitors (TKIs) have been reported to occur commonly within 1 month. Kataoka et al[2] reported that the median time to onset of interstitial lung disease (ILD) related to gefitinib was 15 days, and inflammatory or immune responses to EGFR TKIs have been suggested as one mechanism underlying ILD. Because the onset phase of symptoms resembled that of ILD in our patient, we attributed this phenomenon to an inflammatory response to EGFR TKIs.

The following factors account for our hypothesis: first, unexpected fluid reaction for erlotinib; second, accompanying fever and

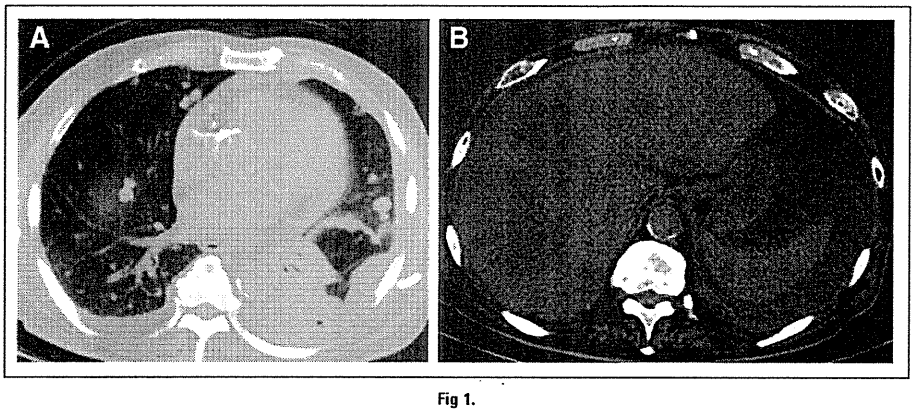

Fig 1.

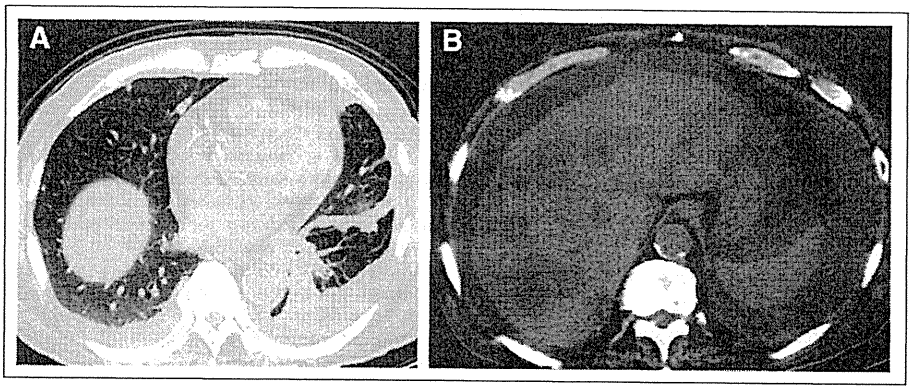

Fig 2.

inflammatory laboratory data; third, most ascites were filled with lymphocytes; and fourth, no clinical evidence of infection. We thus speculated that corticosteroids might have good effect in controlling effusion. Actually, administration of PSL improved ascites and pleural effusion. This reaction to PSL in itself also supported the theory that the fluid phenomenon involved an immune response. Besides, because this patient had mild liver dysfunction, and tumor volume was huge, this phenomenon was apparent. Miller et al[3] reported that patients with hepatic dysfunction should be treated at a reduced dose consistent with their reduced clearance. Our patient had mild dysfunction because of metastasis to the liver, so there was a possibility that this effect was strong. Also, we supposed that because of the bulk of tumor, there was a large amount of tumor lysis, and this caused strong immune response.

Differential diagnosis for the increase in fluid was as follows: either portal hypertension resulting from the rapid decrease in liver volume or adverse effects of erlotinib itself, as with docetaxel. The first possibility was ruled out, because we were unable to find any evidence of portal hypertension on CT. As for the second possibility, to our knowledge, increasing nonmalignant effusion as an adverse effect of EGFR TKI administration has not been reported before. Peripheral edema and nonmalignant effusion have been reported with docetaxel treatment, explained as a result of microtubule disruption causing capillary protein leak syndrome into the interstitial space.[4-6] This effusion occurs without inflammatory responses such as fever or elevation of C-reactive protein levels.

Toh et al[7] reported the first case of worsening pleural effusion with erlotinib and attributed this finding to inflammatory response. They examined interleukin (IL) levels in pleural fluid and discovered elevated levels of IL-8 and IL-10. We also examined ascites fluid, detecting IL-8 and IL-10 even after 2 weeks of administration of PSL. IL-8 and IL-10 levels were 25.4pg/mL and 44pg/mL, respectively, whereas IL-2, IL-12, and interferon γ were not detected at all. IL-8 is a proinflammatory molecule that has been shown to promote lymphocyte chemotaxis in the pleural space in patients with cancer.[8] IL-10 is a

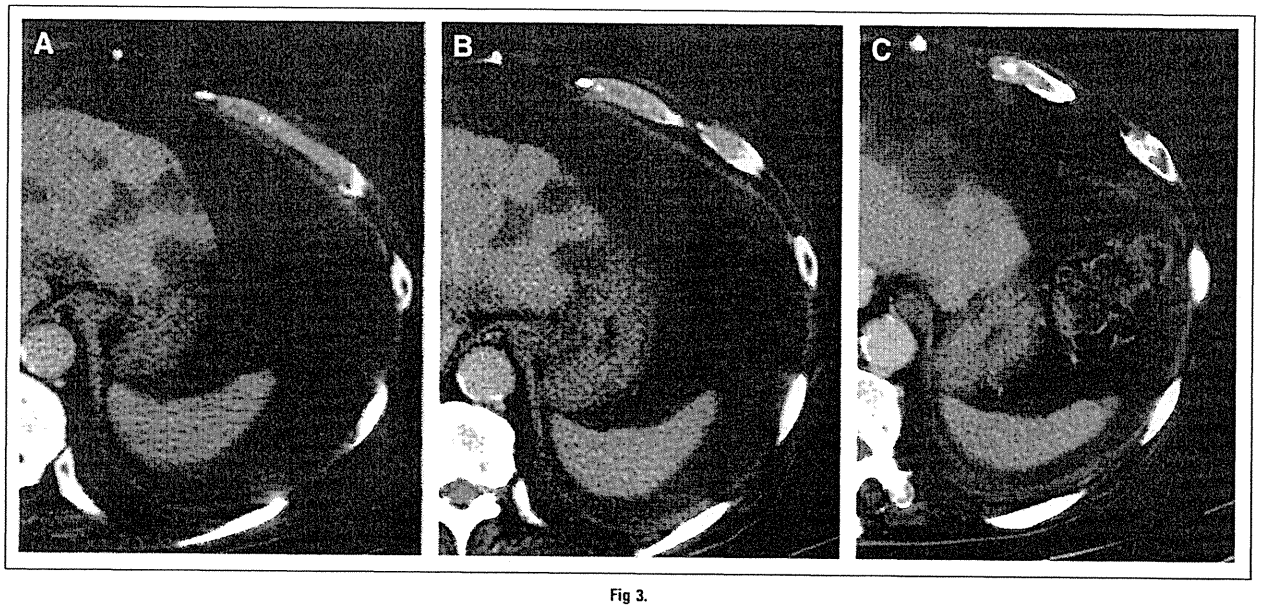

Fig 3.

mediator of T-helper (Th) 2 cell response and inhibits cytokine production by Th1 cell response. Our data suggest that Th2 cell response predominated. We finally concluded that the increased ascites and pleural effusion resulted from an immune response to the acute lysis of cancer cells by erlotinib.

We report a case of marked increases in both ascites and pleural effusion despite good response to erlotinib and show the efficacy of corticosteroids in controlling these fluid levels. Although this phenomenon is infrequent, it is important to recognize that not all instances of increased effusion during treatment with EGFR TKIs are manifestations of disease progression. Moreover, corticosteroids may be effective in controlling increased effusion in such cases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL ARTICLE

Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomised trial

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ABSTRACT

Background Bronchoscopy using endobronchial ultrasound (EBUS) can help to diagnose small peripheral pulmonary lesions. However, although biopsy sites can be confirmed, a bronchoscope cannot be guided in EBUS. Virtual bronchoscopic navigation (VBN) can guide a bronchoscope with virtual images, but its value has not been confirmed.

Methods This prospective multicentre study examines the value of VBN-assisted EBUS for diagnosing small peripheral pulmonary lesions. 199 patients with small peripheral pulmonary lesions (diameter ≤30 mm) were randomly assigned to VBN-assisted (VBNA) or non-VBN-assisted (NVBNA) groups. A bronchoscope was introduced into the target bronchus of the VBNA group using the VBN system. Sites of specimen sampling were verified using EBUS with a guide sheath under fluoroscopy.

Results The diagnostic yield was higher for the VBNA than for the NVBNA group (80.4% vs 67.0%; p=0.032). The duration of the examination and time elapsed until the start of sample collection were reduced in the VBNA compared with the NVBNA group (median (range), 24.0 (8.7–47.0) vs 26.2 (11.6–58.6) min, p=0.016) and 8.1 (2.8–39.2) vs 9.8 (2.3–42.3) min, p=0.045, respectively). The only adverse event was mild pneumothorax in a patient from the NVBNA group.

Conclusions The diagnostic yield for small peripheral pulmonary lesions is increased when VBN is combined with EBUS.

Clinical trial number UMIN000000569.

Key messages

What is the key question?

- Can virtual bronchoscopic navigation improve the bronchoscopic diagnostic yield for small peripheral pulmonary lesions?

What is the bottom line?

- Bronchoscopy using endobronchial ultrasound (EBUS) can help to diagnose peripheral pulmonary lesions; however, EBUS cannot navigate the bronchoscope itself, so small lesions cannot always be reached.

Why read on?

- This multicentre, randomised study shows that the diagnostic yield for small peripheral pulmonary lesions is increased when virtual bronchoscopic navigation is combined with EBUS.

INTRODUCTION

Lung cancer is the leading cause of cancer death in Europe, the USA and Japan.[1–3] Although imaging modalities including CT, MRI and positron emission tomography have been applied, pathological findings remain the benchmark for a diagnosis of lung cancer. The increased frequency of high quality CT application has allowed the identification of much smaller and far more pulmonary lesions than before.[4]

Suspected malignant pulmonary lesions can be diagnosed by bronchoscopy, but the sensitivity of detecting small peripheral lung cancer varies from 36% to 86% depending on the size of the lesion.[5–7] According to the lung cancer diagnosis and treatment guidelines issued by the American College of Chest Physicians (ACCP),[8] the diagnostic sensitivity of bronchoscopy for peripheral pulmonary lesions is 78%, whereas that for lesions <2 cm is 34%. In comparison, the reported diagnostic sensitivity of transthoracic needle aspiration (TTNA) is 90%, and TTNA is recommended for diagnosing lesions <2 cm. Consequently, TTNA is frequently applied in many countries, but the incidence of complications is fairly high. The British Thoracic Society (BTS) guidelines state that the incidence of pneumothorax is 0–61%, with chest tube drainage required in 3.3–15%, intrapulmonary haemorrhage in 5–16.9% and haemoptysis in 1.25–5%.[9] The ACCP guidelines state with respect to bronchoscopy that, '…in expert hands, a radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of <20 mm in size. Its use can be considered prior to referring the patient for TTNA.' The given grade of recommendation is 2B.[8] Target lesions can be directly visualised by EBUS before attempting biopsies that raise the diagnostic yields for peripheral lesions[10]; reported diagnostic yields are 58.3–80%.[10–13] However, EBUS cannot navigate the bronchoscope itself, so lesions cannot be reached in 8–20.8% of cases.[11 13]

Navigational bronchoscopy has recently improved the diagnostic approach to peripheral small lesions. Electromagnetic navigation (EMN) is

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one of two methods that are currently in clinical use, and one EMN system (inReach System; superDimension, Minneapolis, Minnesota, USA) has been marketed mainly in Europe and in the USA.[14] Bronchoscopists navigate EMN systems using a positional sensor that determines direction based on an electromagnetic field generated around the patient's chest. Reported diagnostic yields of EMN for variously sized peripheral pulmonary lesions range from 69% to 74%.[15–17] A randomised study has shown that EMN-assisted bronchoscopy combined with EBUS is more sensitive than either modality alone (diagnostic yield, 88% vs 69% and 59%, respectively).[18]

Virtual bronchoscopic navigation (VBN) is another method in which virtual bronchoscopic images of the bronchial path to a peripheral lesion are generated and used as a guide to navigate the bronchoscope.[19] Since virtual bronchoscopic (VB) and bronchoscopic images are similar, the bronchoscope can be advanced near a target lesion according to the bronchial pathway displayed on the VB images. A VBN system has been developed that allows the automatic production of virtual images of the bronchial path that are matched with actual images for reliable bronchoscopic navigation to sampling sites.[20 21] However, the value of VBN has not yet been clearly and statistically demonstrated. The present multicentre, prospective, randomised study examines the value of VBN-assisted EBUS for diagnosing small peripheral pulmonary lesions of suspected lung cancer.

METHODS

Participants

We enrolled 199 patients who were referred to three Japanese medical centres between April 2006 and August 2007 with peripheral pulmonary lesions (mean diameter ≤3 cm calculated from axial CT images) suspected to be cancer that were not pathologically confirmed. Peripheral pulmonary lesions were defined as those that are surrounded by normal lung parenchyma and thus unlikely to be visualised by bronchoscopy. Most of these lesions were discovered by plain chest x-rays and/or CT images acquired for reasons other than the symptoms caused by the lesions. Eligible patients were men and women ≥20 years old who could tolerate bronchoscopy. The exclusion criteria comprised evidence of endobronchial disease revealed by chest CT, percutaneous oxygen saturation <90%, a range of known severe co-morbid conditions (unstable angina, acute myocardial infarction within the past 3 months, severe asthma or uncontrolled pulmonary infection), pregnancy and unable to proceed without anticoagulant or antiplatelet medications. We monitored the course of lesions that were <10 mm with ground-glass opacity confirmed by CT and excluded them from the study.

Randomisation and intervention

Eligible patients were randomly assigned to VBN-assisted (VBNA) or non-VBN-assisted (NVBNA) groups. Because others have shown that bronchoscopic diagnostic yield is associated with lesion size[8] and physician skill, randomisation was based on lesion size (mean diameter <2 cm or 2–3 cm) and bronchoscopists used a randomised block design to ensure that these factors were balanced in the study arms. Independent, blinded, trial staff randomly assigned the patients before bronchoscopy.

Scan data from multidetector chest CT (16- or 64-row; slice width, 0.5–2 mm) were acquired from all patients without using contrast medium before bronchoscopy. Individual CT data sets from the VBNA group were transferred to a workstation on which VBN software automatically created virtual bronchoscopic images[21] within 20 min. The consecutive images could be moved forwards and backwards and rotated like a bronchoscope in a monitor positioned beside the video-bronchoscopic screen in the endoscopy suite. As assistant physician controlled the virtual bronchoscopic images[20] during bronchoscopy and a bronchoscopist inserted an endoscope as instructed (figure 1). All patients were locally anaesthetised with lidocaine and examined using a thin video-bronchoscope (type P260F; outer diameter, 4.0 mm; Olympus Medical Systems, Tokyo, Japan). Additional pentazocine hydrochloride or hydroxyzine chloride was administered as required.

Bronchoscopic insertion was assisted using the VBN system in the VBNA group. The bronchoscope was introduced into the bronchus of the NVBNA group without VBN support and with reference only to CT axial images. Lesions were visualised in both groups by inserting a 20 MHz mechanical radial-type EBUS probe (external diameter, 1.4 mm; UM-S20-17S; Olympus Medical Systems) with a guide sheath (K-201; Olympus Medical

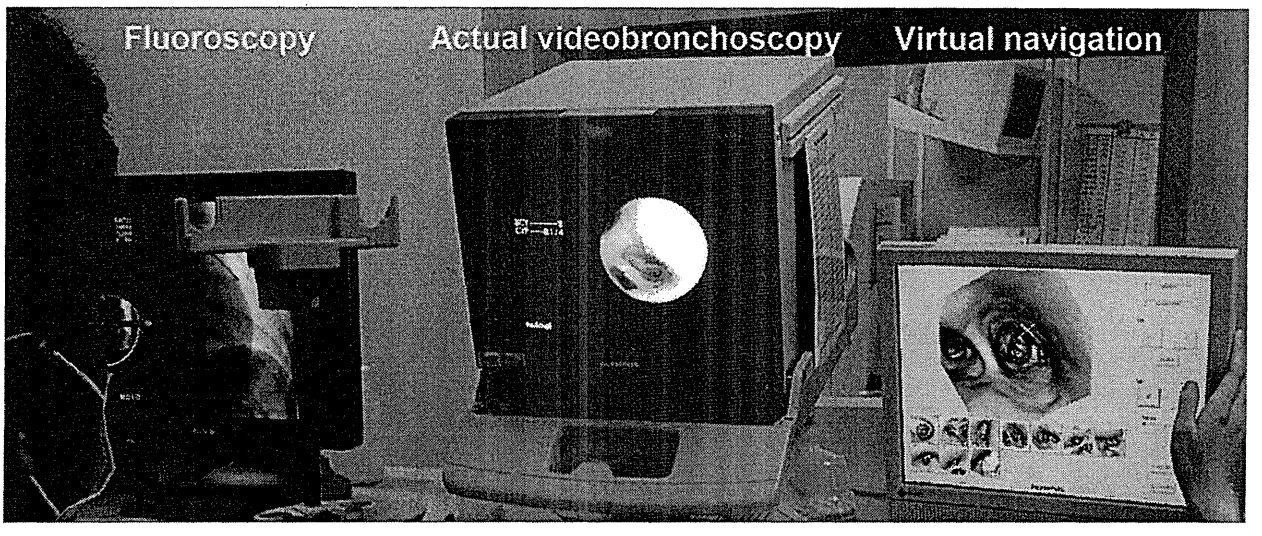

Figure 1 Virtual bronchoscopic navigation. An assistant physician controls virtual bronchoscopic images of the path leading to a peripheral lesion and a bronchoscopist inserts an endoscope as instructed.

Systems) through an endoscopic channel. This probe was withdrawn as soon as the lesion was visualised. Pathological samples were collected using forceps and/or a brush introduced into the guide sheath.[12] If the lesion was not visualised by EBUS, the approach to sampling was decided by the bronchoscopist. The area around the bronchial target was washed as determined by the bronchoscopist with 20 ml of saline as a supplementary procedure. Biopsy samples were immediately fixed in formalin, brush smears on glass slides were immediately fixed in alcohol, and pathologists who were blinded to the results of randomisation processed and evaluated all specimens using standard procedures. The presence of bacteria was assessed in some portions of brush smears and/or lavage. All patients were positioned on an x-ray table, correct device placement was confirmed and sampling was conducted under fluoroscopy.

Outcomes

The primary end point was bronchoscopic diagnostic yield defined as all instances in which the results matched the final diagnosis confirmed by pathological and/or bacterial assessment of bronchoscopic samples. The key secondary end point was total examination duration, which was calculated as the interval between the moment the endoscope passed the vocal cords until its withdrawal from the trachea. Other secondary end points were the interval until the start of sample collection, duration of x-ray fluoroscopy and the generation number of the inserted bronchi. A segmental bronchus was defined as third generation. Safety end points of interest included severe haemorrhage, pneumothorax, hypoxaemia, lidocaine intoxication, arrhythmia, pneumonia and other serious adverse events. Retrieved blood loss >50 ml mixed with or without saline lavage was defined as significant. The safety of all patients was assessed.

Study follow-up

If a lesion was undiagnosed by bronchoscopy, we recommended that the patient consider undergoing other diagnostic procedures, including CT-guided fine needle aspiration (FNA) or surgical intervention. If an undiagnosed patient refused further intervention, follow-up was considered as the second best strategy. Thus, this study continued until the last enrolled patient had been followed up for 2 years. Follow-up information was derived from outpatient clinics, by telephone or by fax contact.

Statistical analysis

Sample size was calculated based on the primary end point. The estimated diagnostic yields in the VBNA and NVBNA groups based on published records were 70% and 50%, respectively.[13 21 22] Thus, at 80% power and α=0.05, we calculated that 190 patients would be required (n=95 in each group) to determine whether diagnostic yield improved with the addition of VBNA. We planned to enrol 200 patients to account for incomplete data or undiagnosed patients.

We analysed the diagnostic yield and safety of the entire intent-to-treat population. Data from the per-protocol population that included all randomised patients with planned bronchoscopic procedures for peripheral lesions were also statistically analysed. Primary and secondary variables were analysed using

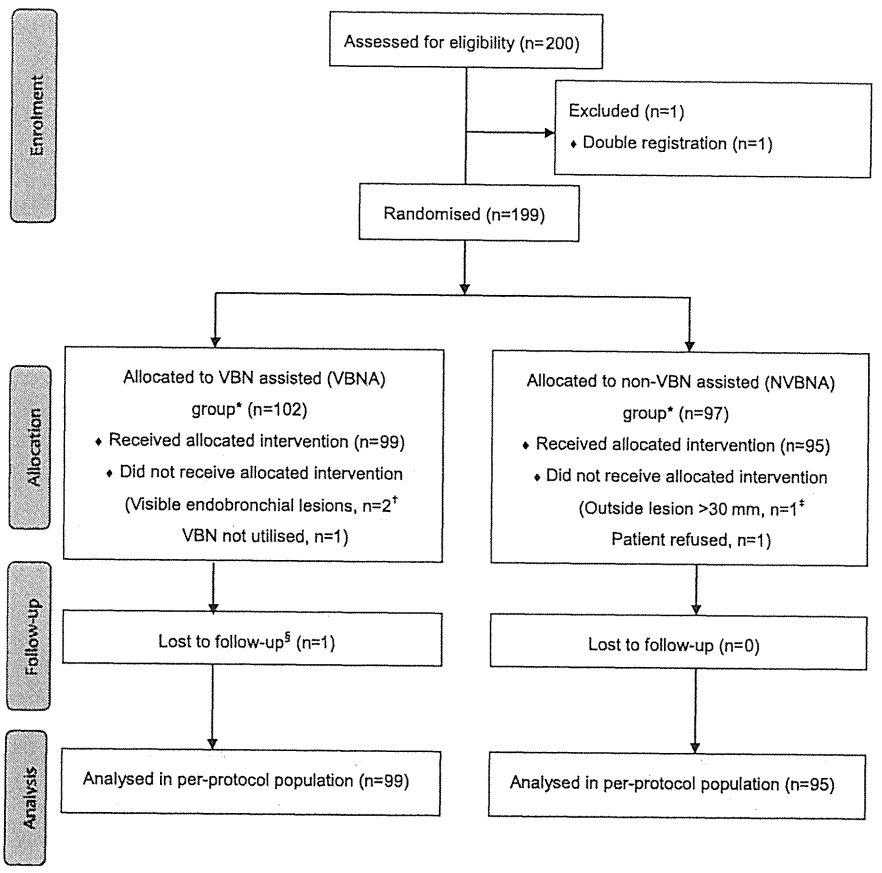

Figure 2 CONSORT flow diagram. *All allocated patients were included in the intention-to-treat population. †Diagnoses established without operating virtual bronchoscopic navigation (VBN). ‡The bronchoscopic procedure was performed according to protocol. §Final diagnosis of this patient was not established; however, this patient was included in the per-protocol analysis.

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the Pearson χ^2 test and the Mann–Whitney U test. Continuous variables were assessed for normality in distribution and the Mann–Whitney test/description as medians was used. All p values were two-sided. A p value of <0.05 indicated statistical significance. All data were statistically analysed using IBM SPSS Statistics, V 18.

RESULTS

We randomly assigned 102 and 97 patients to the VBNA and NVBNA groups. One and two patients in the NVBNA and VBNA groups, respectively, with endobronchially visible malignant or large (>3 cm) lesions were ineligible. We could not use VBN in one patient in the VBNA group and another refused bronchoscopy after assignment to the NVBNA group. We excluded these five patients from the per-protocol populations. The trial profile is shown in figure 2. Age, sex, lesion size and location in patients at baseline were similar between the groups (table 1).

The proportions of primary lung cancer, other malignancies and non-malignant diseases were similar between the groups. Non-malignant diseases comprised tuberculosis, non-tuberculous mycobacterial infection, fungal disease, organising pneumonia, hamartoma and lipoma. Among bronchoscopically undiagnosed patients, 23 (44.2%) of 52 underwent video-assisted thoracoscopy and/or surgery and 8 (15.4%) were diagnosed by CT-guided FNA or repeated bronchoscopy. Twenty of the 21 patients who refused further intervention were followed up for 2 years.

The results indicated a significant difference in diagnostic yield between arms both in the intent-to-treat (all randomly assigned patients, n=199) and the per-protocol populations (finally analysed patients, n=194). Diagnostic yield was significantly higher for the VBNA than for the NVBNA groups in both the intent-to-treat (82 (80.4%) of 102 vs 65 (67.0%) of 97; p=0.032) and per-protocol (80 (80.8%) of 99 vs 64 (67.4%) of 95; p=0.032; table 2) populations.

Diagnostic yield did not differ significantly according to lesion size between the groups in the per-protocol population (table 3).

Table 1 Baseline characteristics and final diagnoses

	VBNA group (n=102)	NVBNA group (n=97)
Age (years, median; range)	69 (21–85)	67 (27–82)
Male, n (%)	64 (62.7)	57 (58.8)
Lesion size (mm, median; range)	18.0 (9.5–30.0)	18.0 (7.0–30.0)
<20 mm, n (%)	59 (57.8)	59 (60.8)
20–30 mm, n (%)	43 (42.2)	38 (39.2)
Lesion location		
Rt. upper lobe, n (%)	32 (31.4)	35 (36.1)
Rt. middle lobe, n (%)	12 (11.8)	6 (6.2)
Rt. lower lobe, n (%)	23 (22.5)	18 (18.6)
Lt. upper lobe, n (%)	25 (24.5)	21 (21.6)
Lt. lower lobe, n (%)	10 (9.8)	17 (17.5)
Final diagnosis		
Malignant disease n (%)		
Primary lung cancer n (%)	69 (67.6)	76 (78.4)
Other malignant disease n (%)	10 (9.8)	4 (4.1)
Non-malignant disease n (%)		
Infectious disease n (%)	17 (16.7)	8 (8.2)
Other benign condition n (%)	5 (4.9)	9 (9.3)
Undetermined n (%)	1 (1.0)	0 (0)

Lt., left; NVBNA, non-virtual bronchoscopic navigation-assisted; Rt., right; VBNA, virtual bronchoscopic navigation-assisted.

Table 2 Diagnostic yields in the intent-to-treat and per-protocol populations

	Bronchoscopic diagnosis		
	VBNA	NVBNA	p Value
Full intent-to-treat	82/102 (80.4)	65/97 (67.0)	0.032
Per-protocol	80/99 (80.8)	64/95 (67.4)	0.032

Data are shown as numbers of lesions/total lesions (%).
NVBNA, non-virtual bronchoscopic navigation-assisted; VBNA, virtual bronchoscopic navigation-assisted.

Of the virtual images constructed based on data from the VBNA group, 98% agreed with actual images of the shape of each bronchial bifurcation on the route. The median generation of virtual bronchial images was six (range, 4–12 bronchi).

The VBN system thus allowed insertion of the endoscope into significantly further generations of bronchi (VBNA vs NVBNA median (range): 4 (2–8) vs 4 (2–7); p<0.001; table 4). The endoscope was also accurately positioned in the VBNA group, with more targets being confirmed by EBUS (VBNA vs NVBNA: 92/99 (92.9%) vs 77/95 (81.1%); p=0.014). Numbers of biopsies and brushings/washes did not differ significantly between the groups. Total examination duration was significantly shorter in the VBNA than in the NVBNA group (median (range): 24.0 (8.7–47.0) vs 26.2 (11.6–58.6) min; p=0.016). The interval to starting sample collection was significantly shorter in the VBNA versus the NVBNA group (8.1 (2.8–39.2) vs (9.8 (2.3–42.3) min; p=0.045). The duration of x-ray fluoroscopy exposure did not differ significantly between the groups. No severe or moderate adverse events were associated with bronchoscopy except for mild pneumothorax that did not require chest drainage in a patient from the NVBNA group.

DISCUSSION

This is the first prospective, multicentre, randomised trial to examine the value of using a VBN system to assist radial EBUS. The findings showed that VBN-assisted EBUS with a guide sheath significantly improved the diagnostic yield of small pulmonary peripheral lesions to 80.4%, which was 13% higher than that in the NVBNA group (67.0%). The diagnostic yield for similar lesions in our previous study using a conventional or thin bronchoscope assisted by VBN under fluoroscopy was 62.5%.[23] The diagnostic yield was 58.3% in another of our studies using EBUS.[13] The high diagnostic yield in the present study was achieved by combining these two procedures. Moreover, although the study cohort was small and diagnostic yields for lesions <20 mm did not differ significantly, the diagnostic yield with VBNA was nevertheless high at 75.9%. Comparison is difficult since x-ray fluoroscopy was used in this study, but the diagnostic yield with EBUS + VBN was comparable with that reported by Eberhardt *et al*.[18] One advantage of VBN compared with EMN is simplicity. Operations such as steering the sensor

Table 3 Diagnostic yield according to lesion size in the per-protocol population

	Bronchoscopic diagnosis		
Lesion size	VBNA	NVBNA	p Value
<20 mm	44/58 (75.9)	35/59 (59.3)	0.056
20–30 mm	36/41 (87.8)	29/36 (80.6)	0.382
Total	80/99 (80.8)	64/95 (67.4)	0.032

Data are presented as numbers of lesions/total lesions (%).
NVBNA, non-virtual bronchoscopic navigation-assisted; VBNA, virtual bronchoscopic navigation-assisted.

Table 4 Bronchoscopic outcomes in the per-protocol population

	VBNA	NVBNA	p Value
Endoscopically inserted bronchial generation (n, median) (range)	4 (2–8)	4 (2–7)	<0.001
EBUS-visualised peripheral lesion, n (%)	92 (92.9)	77 (81.1)	0.014
Sampling by biopsy, (n, median) (range)	5 (0–12)	4 (0–12)	0.113
Sampling by brushing/washing (n, median) (range)	3 (0–6)	3 (0–5)	0.42
Duration			
Total examination (min, median) (range)	24.0 (8.7–47.0)	26.2 (11.6–58.6)	0.016
Initial sampling (min, median) (range)	8.1 (2.8–39.2)	9.8 (2.3–42.3)	0.045
x-ray fluoroscopy exposure (min, median) (range)	9.7 (1.5–22.7)	11.0 (1.3–31.0)	0.058

EBUS, endobronchial ultrasound; NVBNA, non-virtual bronchoscopic navigation-assisted; VBNA, virtual bronchoscopic navigation-assisted.

probe or registration during tests are not required to superimpose the electromagnetic sensor position and CT information as with EMN.[14] Furthermore, the bronchoscope is advanced together with virtual image indications in VBN, which is essentially identical to conventional bronchoscope manipulation.[19] Thus, bronchoscopists with basic skills can easily operate this system after practice on a simulator. Locatable guides attached to the EMN sensor probe are single use, which imposes a cost burden of US$700–1000 per patient depending on market price.[24]

The diagnostic sensitivity of TTNA differs depending on the technique and lesion size, but it is 92% with FNA under CT guidance[6] and 82–90% even for lesions ≤2 cm. However, the main complication with FNA under CT guidance is pneumothorax, which occurs at an incidence of 15–42% [25–27] and is quite frequent with small lesions or emphysema.[27] Reported complications comprise bronchial haemorrhage,[25] needle tract implantation and air embolism.[28] In contrast, the complication rate with transbronchial lung biopsy is 0.2–5% for pneumothorax and 1.2–9% for haemorrhage.[9 29 30] Pneumothorax or other complications have not been found in other studies of EBUS + VBN to date, including the present study.[21 22] The diagnostic sensitivity of EBUS + VBN may not be as high as that with CT-guided FNA, but it is considerably higher than the diagnostic sensitivity of normal bronchoscopy indicated in the ACCP guidelines.[8] Therefore, considering the low rate of complications, VBN combined with EBUS may be a viable option for diagnosing small peripheral lesions.

To our knowledge, this is the first report to describe the duration of navigational bronchoscopy, and that the amount of time required for guidance was decreased in the VBNA group. Moreover, VBN improved diagnostic yield while decreasing the overall duration of the examination by ~2 min. This is thought to be significant in terms of patient comfort, especially considering that patients endured the procedure under local anaesthesia. Although the time required for fluoroscopy tended to decrease in the VBNA group, the difference did not reach statistical significance. Fluoroscopy duration before and after initial sampling was not measured in this study, but almost all of the fluoroscopic exposure was taken up by specimen sampling to confirm proper device use, such as forceps opening and cutting, as well as brushing at adequate sites. Steinfort *et al* reported that radiation exposure from fluoroscopy used together with EBUS does not pose a clinical problem.[31] However, we found that radiation exposure accounted for ~40% of the total duration of the examination. More reliable sampling devices are needed for EBUS with a guide sheath.

We identified the following limitations. The precision of VB decreases when CT data are inadequate during VB; for example, the branch order that can be visualised is lower when slices are too thick.[32] Under such circumstances, repeat CT might be required, which imposes additional cost. Many of the patients in this study were referred from private clinics after abnormalities on plain x-rays had been identified. Therefore, row CT data with a slice thickness of ≤2 mm were collected from the start with multidetector CT instruments at the institution where the present study was conducted and, as a result, virtual images could be created up to sixth generation bronchi. In contrast, the amount of CT data increases with thinner slices and more time is required to create VB images. Most of the time required to create VB images in this study was due to PC processing, but the VB images were created over a period of ~20 min. This depends to some extent on the performance of the software and PC hardware, which could be further enhanced. The VBN system used in the present study (Bf-NAVI; Cybernet Systems, Tokyo, Japan) has been promoted mainly in Japan. The automatic tracking system for the VBN system used herein will allow automatic synchronisation of the virtual to the actual bronchoscopic view.[33] Another VBN system with an automatic tracking system has recently been developed.[24 34] This study showed that diagnostic yield improved with VBN when combined with EBUS which is still not globally applied. We also combined VBN with fluoroscopy, and confirmed lesions in 83% of patients with plain x-rays. Although VBN has been applied without fluoroscopy,[24] when not combined with EBUS it is usually combined with CT[20 35] or fluoroscopy[23] to confirm lesions. Randomised studies with each of these combinations may be necessary to define the diagnostic value of VBN.

Author footnote

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Competing interests FA, HM, KY, TI and Olympus Medical Systems Corporation co-developed the VBN system. FA, HM, KY and TI legally transferred all patent rights to Olympus Corporation without compensation. TI, FA and NS have received speaker fees of less than three hundred thousand yen (~US$3500) per year each from the Olympus Corporation as invited guests to academic medical meetings. All other authors declare that they have no conflict of interest.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of each of the following institutions: Gifu Prefectural General Medical Center, Gifu, Japan, Hokkaido University School of Medicine, Sapporo, Japan and Fukushima Medical University, Fukushima, Japan.

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Q17 小分子化合物7 ソラフェニブ

回答：福島県立医科大学附属病院 臨床腫瘍センター 石田 卓（いしだ たかし）

point

- ソラフェニブは経口投与可能なマルチキナーゼ阻害薬であり，細胞内キナーゼと受容体型チロシンキナーゼ活性を阻害して，腫瘍増殖抑制効果と血管新生阻害作用を示す．
- 現在我が国では，外科治療や局所治療の対象にならない肝細胞がんと腎細胞がんに適応がある．
- 頻度が高い副作用として手足症候群，高血圧，下痢がみられ，重篤な副作用としては消化管出血，間質性肺炎・急性呼吸不全がある．
- ソラフェニブの効果を予測するバイオマーカーは確立されていない．
- 安全・適正な使用にはチームでの医療体制が必要である．

Q ソラフェニブは，どのような薬剤ですか？

A ソラフェニブ（ネクサバール®）は経口のマルチキナーゼ阻害薬です．分子量は637.03 g/molの低分子化合物で，当初は細胞内キナーゼであるc-RAFなどのセリン・スレオニンキナーゼ活性の阻害薬として研究されていました．その後の研究で受容体型チロシンキナーゼであるc-KIT，VEGFR（血管内皮増殖因子レセプター vascular endothelial growth factor receptor）-2，PDGFR（血小板由来増殖因子受容体 platelet derived growth factor receptor）-βなどのチロシンキナーゼ活性も阻害することがわかってきました（表1）．前者は腫瘍細胞内のMAPキナーゼカスケードにおける細胞増殖シグナル伝達を阻害することによる増殖抑制効果をもたらし，後者は血管内皮細胞・周皮細胞に働き血管新生を抑制する効果をもたらすと考えられています[1]（図1）．

表1 ソラフェニブにより阻害される分子

部位	分類	阻害される分子/受容体
細胞内	セリン・スレオニンキナーゼ活性阻害	C-RAF B-RAF
細胞外	チロシンキナーゼ活性阻害	C-KIT FLT-3 VEGFR-1 VEGFR-2 VEGFR-3 PDGFR-β RET

VEGFR：血管内皮増殖因子受容体，PDGFR：血小板由来増殖因子．

2185-5684/11/¥400/論文/JCOPY

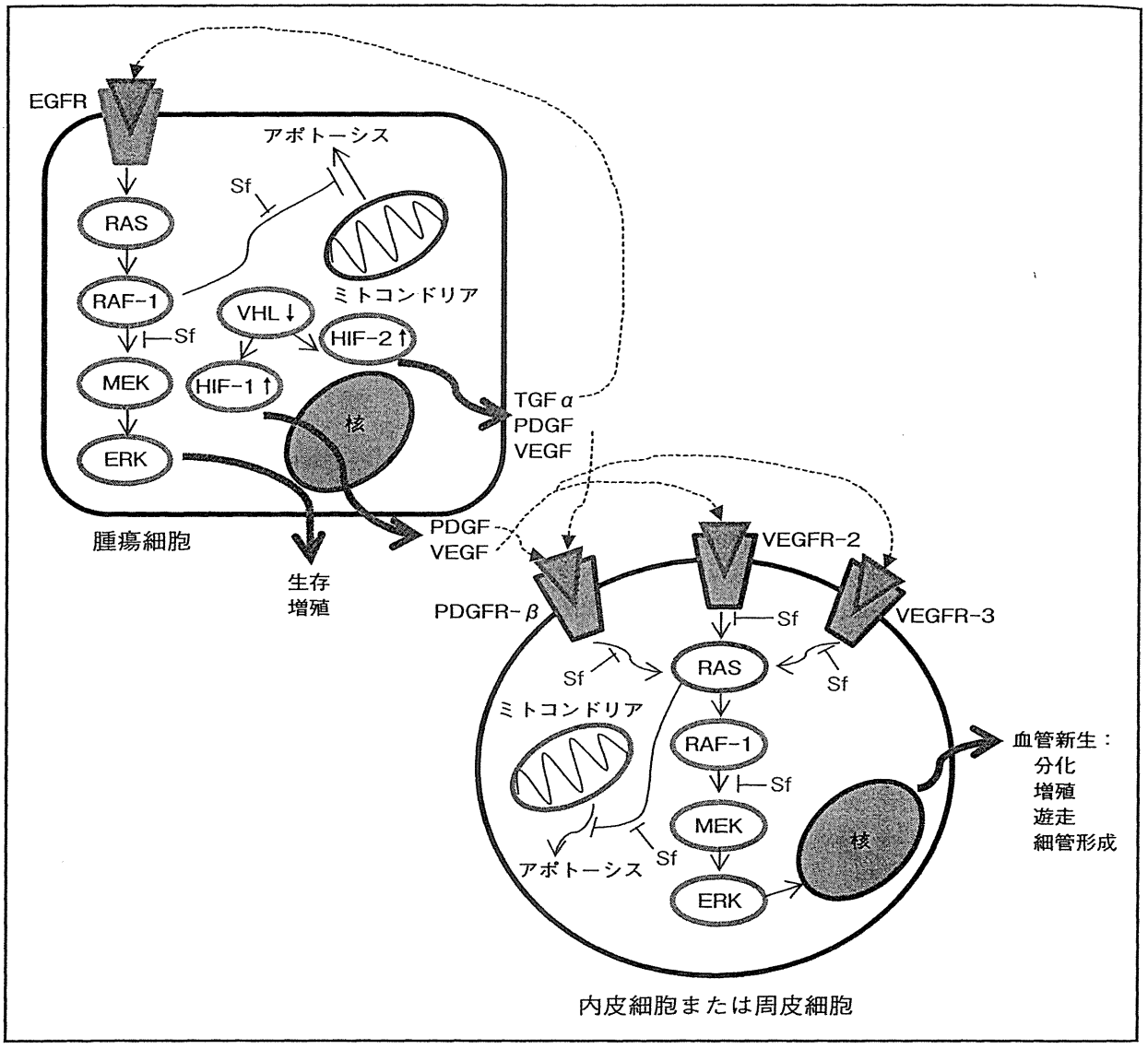

図1　ソラフェニブの作用機序
Sfはソラフェニブ.

Q ソラフェニブの用法用量，減量基準は，どのようになっていますか？

A 発売されている製剤（ネクサバール®錠）は1錠にソラフェニブ200 mgを含有しています．成人には1回400 mgを1日2回経口投与します．1段階減量する場合，1回400 mgを1日1回投与し，2段階減量する場合は1回400 mgを隔日投与します．増量の規定はなく，また他の抗悪性腫瘍薬との併用のエビデンスもありません．デキサメタゾンのように肝のCYP3A4を誘導する薬剤はソラフェニブの血漿中濃度を低下させる可能性があります．一方，ワーファリンの作用を増強させる可能性があります．