Table 3 Thrombocytopenia Incidence

Thrombocytopenia	N	Overall	1/2 Cycles	≥ 3 Cycles
Grade 3/4	31	2/3 (16.2%)	1/1 (6.5%)	1/2 (9.7%)

Nadir platelet counts in 5 cases with grade > 3 thrombocytopenia ($\times 10^4$) were 1.5, 2, 2.5, 3.9, and 4.9.

Among the first 6 patients, 5 had ≥ 3 treatment cycles without treatment delay (4, 3, 2, 8, 4, and 4 cycles for the first, second, third, fourth, fifth, and sixth patients, respectively). Final analysis revealed that 21 of 31 patients received ≥ 3 treatment cycles, but 8 of these patients experienced treatment delay in the first 3 cycles. The treatment completion rate was not sufficiently high at 42%. Ten patients were withdrawn from the study early; the reason for withdrawal was progressive disease for 2 patients, hematologic toxicity for 3 (all were neutropenic but did not have thrombocytopenia), and nonhematologic toxicity for 5 (grade 3 depression in 1 patient and grade 3 rash in 4 patients; 1 was caused by carboplatin, and the others were caused by gemcitabine).

Discussion

Third-generation chemotherapy, consisting of a platinum agent and a third-generation chemotherapeutic agent, including gemcitabine, is considered a standard treatment for advanced-stage NSCLC worldwide. Many studies were carried out to compare the toxicity and efficacy of each regimen of third-generation chemotherapy. According to the ECOG 1594 study, a significant difference in efficacy is difficult to demonstrate among the regimens.[41] In contrast, the profiles of toxicities were demonstrably different among the regimens.

Although platinum compounds, such as cisplatin and carboplatin, are still key drugs in chemotherapy for NSCLC, a recent metaanalysis suggested that treatment with regimens containing gemcitabine showed small but statistically significant improvement in patient survival.[42] With its mild toxicity and easiness in administration, gemcitabine is becoming another key drug in chemotherapy for NSCLC. In a Japanese phase III trial in which gemcitabine/vinorelbine/paclitaxel in combination with a platinum agent were compared with irinotecan/cisplatin, a Japanese standard for NSCLC, gemcitabine/cisplatin exerted the best result; however, the difference was not statistically significant.[35] Recent trials showed that the gemcitabine/carboplatin improved patient survival compared with gemcitabine alone and mitomycin/ifosfamide/cisplatin.[43,44] Taking these results together, gemcitabine/carboplatin is a reasonable combination and becoming widely used for NSCLC.

Early studies of gemcitabine/carboplatin used a 28-day schedule in which gemcitabine was administered on days 1, 8, and 15 and carboplatin was administered on day 1.[23-29] However, because of a high incidence of severe thrombocytopenia, 2 alternate schedules were proposed: one is a 21-day schedule treatment in which gemcitabine is administered on days 1 and 8 with carboplatin administered on day 1,[31] and the other is a 28-day schedule in which gemcitabine is administered on day 1 and 8 with carboplatin on day 8.[30] Obasaju et al conducted a randomized phase II study comparing these 2 schedules.[45] Although the study was not powered to show a statistically significant difference between these 2 regimens, the 21-day schedule seemed to be superior to the 28-day schedule in terms of efficacy. However, grade 3/4 thrombocytopenia was observed in 14% of cycles in the 21-day schedule, higher than that in the 28-day schedule. The 21-day schedule has been used in several other studies, in which thrombocytopenia was still the main problem, accompanied by bleeding episodes, although not frequently.[27,46,47] In the Japanese phase II study described previously, thrombocytopenia was again a major issue, resulting in a high incidence of dose reduction and early withdrawal from the study.[33] Nevertheless, good median survival time of the patients treated with gemcitabine/carboplatin (432 days) and low incidences of nonhematologic toxicities were impressive. Meanwhile, the 28-day schedule in which carboplatin was administered on day 8 appeared to be less myelotoxic than the 21-day schedule but has the problem of low dose intensity.

Table 4 Nonhematologic Toxicities

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	2	1	1	0
Rash	0	2	4	0
Depression	0	0	1	0
Fever (Absence of Neutropenia)	1	0	0	0
Transaminase	3	0	0	0

Our study was designed to evaluate the feasibility and efficacy of gemcitabine/carboplatin in a modified administration schedule. Gemcitabine/carboplatin were administered at 1000 mg/m^2 on days 1 and 8 and at AUC 5 on day 8 of each 21-day cycle, respectively. The main aim of this study was to decrease the severity of thrombocytopenia with minimal effect on dose intensity. The low incidence of grade 3/4 thrombocytopenia was notable, observed in only 2 of 31 patients in the first 2 cycles. This result suggested that the nadir of thrombocytopenia of gemcitabine and carboplatin occur around day 15, and that incidence of severe thrombocytopenia could be decreased even in a 21-day schedule by delaying administration of carboplatin until day 8. We were concerned whether this 3-weekly chemotherapy would become possible by adopting looser criteria (leukocyte count > 2500/μl and platelet count > 75,000/μL) to start new cycles. Other hematologic and nonhematologic toxicities were also mild, and altogether, the treatment was well tolerated. The incidence of stressful toxicities represented by nausea/vomiting, neurologic toxicities, and alopecia was relatively low in the gemcitabine/carboplatin combination.

The planned dose intensities and actual dose intensities were 667 mg/m^2 per week and 638 mg/m^2 per week (95.7% of planned dose intensity) for gemcitabine and 1.67 mg/

minute/mL per week and 1.56 mg × minute/mL per week (93.4% of planned dose intensity) for carboplatin AUC, respectively. Dose intensity for each drug in the 28-day schedule described previously[30,32] was estimated to be 550 mg/m^2 per week for gemcitabine and 1.25 mg × minute/mL per week for carboplatin AUC, respectively. The median cycles of delivery were 3, which was comparable with those of platinum-doublet chemotherapy.[35] Therefore, our main purpose to decrease the incidence of thrombocytopenia and increase dose intensity was achieved, although there are still problems to be solved.

Drug administrations were frequently delayed, treatment time tended to be protracted, and the treatment completion rate we defined was 42%. Unfortunately, early withdrawal from the study was seen in 10 patients (32%). Among these patients, 3 experienced grade > 2 leukopenia (leukocyte count < 3000/μL) on day 8 of the first course, and the other 3 patients developed grade 3 rash after administration of day 1 gemcitabine. For these 6 patients, gemcitabine/carboplatin chemotherapy was considered inappropriate regardless of the schedule. This schedule, which delays carboplatin administration until day 8, would enable early exclusion of the patients who are inappropriate for this combination chemotherapy, avoiding severe hematologic and nonhematologic toxicities. Response rate, median TTP, and median survival time were favorable. However, this might be biased by the small number of patients and the high percentage of patients with good prognostic factors such as female sex and PS of 0 in this study.

Recently, prolonged administration of gemcitabine combined with carboplatin has been tested.[48,49] Because gemcitabine/carboplatin combination chemotherapy has become a widely used regimen, further improvement of this regimen is necessary.

Conclusion

The present study suggests that carboplatin administered on day 8 in a 21-day schedule of gemcitabine/carboplatin reduces severity of thrombocytopenia without having a detrimental effect on efficacy. However, further evaluation is still needed to estimate the efficacy and feasibility of this regimen. The ongoing randomized phase II study compares day-1 and day-8 administration of carboplatin in a 21-day schedule of gemcitabine/carboplatin. In clinical practice, this regimen will be one of the treatment options suitable for outpatients.

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High-Dose-Rate Brachytherapy for Small-Sized Peripherally Located Lung Cancer

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Background: The demand for minimally invasive therapies is increasing in the treatment of small peripheral non-small cell lung cancer (NSCLC).

Patients and Methods: Twelve patients with T1–2 N0 M0 peripheral NSCLC were treated by high-dose-rate brachytherapy with ^{192}Ir radioactive source.

Results: A ^{192}Ir source was introduced into the tumors percutaneously in five patients (percutaneous brachytherapy) or transbronchially in seven patients (transbronchial brachytherapy). Whereas irradiation was performed with a single fraction of 20 Gy in percutaneous brachytherapy, it was hypofractionated from 5 × 5 Gy to 2 × 12.5 Gy in transbronchial brachytherapy. Complications were generally mild in all patients, although focal radiation pneumonitis was observed in most patients. Primary recurrence occurred in three patients, including one with a T2 tumor and one treated by brachytherapy as a salvage treatment for recurrence after conformal radiotherapy. When brachytherapy is evaluated as a primary treatment for T1 N0 M0 NSCLC, local control rate is 88.9% and estimated 5-year survival rate is between 60% and 70%.

Conclusion: Brachytherapy has a potential to be a method to treat peripheral T1 N0 M0 NSCLC.

Key Words: Lung cancer · Brachytherapy · T1 N0 M0 · Peripheral · Transbronchial · Percutaneous

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High-Dose-Rate-Brachytherapie bei kleinem peripheren Bronchialkarzinom

Hintergrund: Das Erfordernis minimalinvasiver Eingriffe in der Behandlung kleiner, peripherer, nichtkleinzelliger Bronchialkarzinome (NSCLC) nimmt zu.

Patienten und Methodik: Zwölf Patienten mit peripherem NSCLC der Stadien T1–2 N0 M0 erhielten eine High-Dose-Rate-Brachytherapie mit radioaktiver ^{192}Ir-Quelle.

Ergebnisse: Die ^{192}Ir-Quelle wurde bei fünf Patienten über einen perkutanen Zugang (perkutane Brachytherapie) und bei sieben Patienten über einen bronchialen Zugang (transbronchiale Brachytherapie) eingeführt. Bei der perkutanen Brachytherapie wurde die Bestrahlung mit einer Einzeitdosis von 20 Gy durchgeführt, bei der transbronchialen Brachytherapie hypofraktioniert mit 5 × 5 Gy bis 2 × 12,5 Gy. Komplikationen waren im Allgemeinen geringgradig ausgeprägt, allerdings wurde bei den meisten Patienten eine fokale Strahlenpneumopathie beobachtet. Bei drei Patienten trat ein Lokalrezidiv auf (zwei Patienten mit T2-Tumor und ein Patient mit Brachytherapie als Salvage-Behandlung wegen eines Rezidivs nach konventioneller Strahlentherapie). Für die Brachytherapie in der Primärbehandlung von NSCLC des Stadiums T1 N0 M0 beträgt die lokale Kontrollrate 88,9%, und die geschätzte 5-Jahre-Überlebensrate liegt bei 60–70%.

Schlussfolgerung: Die Brachytherapie ist eine effektive Behandlungsmethode bei peripherem NSCLC des Stadiums T1 N0 M0.

Schlüsselwörter: Bronchialkarzinom · Brachytherapie · T1 N0 M0 · Peripher · Transbronchial · Perkutan

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Introduction

Although surgical resection is a standard treatment for stage I non-small cell lung cancer (NSCLC), the aging of population requires minimally invasive therapies in its treatment. Conventional external radiation of 55–75 Gy is an alternative in this setting, but it associates with an unacceptably low 5-year survival rate, around 20% [1–3, 6, 10].

Brachytherapy is a radiation therapy using a small radioactive source to treat various cancers, and has the potential advantage of providing the tumor-bearing area with a higher radiation dose relative to doses received by the surrounding normal tissues. We have already reported a patient with peripheral T1 N0 M0 pulmonary adenocarcinoma who was successfully treated by CT-guided single-fraction interstitial brachytherapy alone [5]. After confirming the safety and efficacy of brachytherapy in the peripheral lung through the observation of this patient over 5 years, we have built on our experiences of brachytherapy for peripheral NSCLC.

Patient and Methods

From April 1996, twelve patients with peripheral T1–2 N0 M0 NSCLC received CT-guided brachytherapy (Table 1). A transbronchial approach was applied to eight patients, but failed in one patient because of poor access to the tumor. Five patients including this patient were treated by the percutaneous method. The patients were relatively high-aged (53–85 years old), and mostly medically inoperable due to concomitant medical illnesses or refusal of surgical treatment. Respiratory function of the patients was generally poor.

A ^{192}Ir source was tentatively introduced into the lesions either percutaneously (percutaneous brachytherapy) or transbronchially (transbronchial brachytherapy; Figure 1). In percutaneous brachytherapy, tumors were punctured percutaneously with a 21-G needle under fluorography and CT guidance in local anesthesia, and an applicator tube with an open edge was connected to the needle. In transbronchial brachytherapy, an applicator tube with a blind edge was directly introduced into the tumor via bronchoscope under fluorography and CT guidance (Figure 2).

Target volumes and reference points were defined by CT examination before each treatment. Gross tumor volume (GTV) was defined as the mass shadow depicted on CT images in lung window. Clinical target volume (CTV) was equal to GTV without including regional lymph nodes, and margins of 1 cm were added to contour planning target volume (PTV). In transbronchial brachytherapy, a dummy wire was inserted into the applicator before treatment, and the reference point was determined as the furthest point in the tumor from the dummy wire. The dwell positions were determined on chest X-ray and CT images to treat PTV adequately; the dwell time was calculated to deliver the prescribed dose to the reference point without optimization. Thereafter, the real source was pushed into the applicator by step-backward design with step sizes of the source length. In percutaneous brachytherapy, the reference point was determined as the furthest point in the tumor from the needle. Planning and treatment were performed similarly.

The dose distribution was calculated by Cadplan BT (version 1.1.15) till 2003 and later by BrachyVision (version 6.1.13). Brachytherapy was performed using a ^{192}Ir radioactive source, which was equipped with a wire of 0.635 mm diameter connected to a computer-driven remote afterloader (Varisource, Varian Medical System). The diameter and length of a ^{192}Ir source were 0.52 mm and 10 mm, respectively, in the beginning, but later a ^{192}Ir source of 5 mm length became available. In transbrochial brachytherapy, irradiation by five fractions of 5 Gy (total 25 Gy) was first adopted, then was hypofractionated, and currently, irradiation by two fractions of 12.5 Gy (total 25 Gy) is being done. In percutaneous brachytherapy, single 20-Gy fraction irradiation was performed. To avoid pneumothorax, transbronchial brachytherapy was generally selected as the first-choice treatment.

Table 1. Patient characteristics. BI: Brickman index; SCLC: small cell lung carcinoma.

Tabelle 1. Patientencharakteristika. BI: Brickman-Index; SCLC: kleinzelliges Bronchialkarzinom.

	Patients (n)
Mean age	74.5 years (53–85 years)
Male/female	10/2
Stage	
• T1 N0 M0	11
• T2 N0 M0	1
Number of cancers (synchronous)	
• Single	6
• Double	4 (3)
• Quartet	2 (1)
Histology	
• Adenocarcinoma	5
• Squamous cell carcinoma	6
• SCLC	1
Tumor size, mean 25.4 mm	
• ≤ 20 mm	5
• 21–30 mm	6
• ≥ 31 mm	1
Smoking (BI)	400–2,400 (median 1,200)
Primary reason for selecting this treatment	
• Impaired cardiopulmonary function	6
• Inoperable	3
• Refusal of surgery	2
• Recurrence of tumor	1
Introduction of radioactive source	
• Percutaneous	5
• Transbronchial	8 (including 1 failure[a])
Pretreatment to the lesion	
• None	11
• Conformal irradiation	1

[a] successfully treated by percutaneous brachytherapy

However, since the percutaneous approach is easier to access lesions than the transbronchial one, percutaneous brachytherapy was done for the patients who had negligible risk of pneumothorax or were acceptable for pneumothorax.

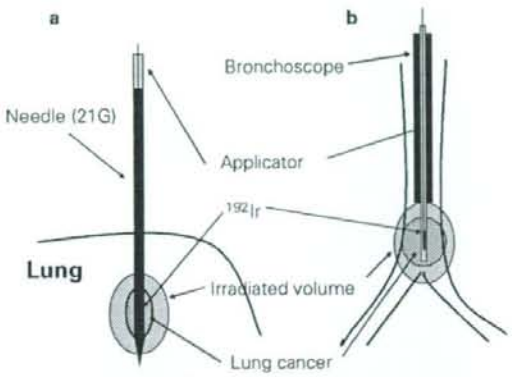
Complete (CR) and partial regression (PR) of the tumor were defined as reduction by 100% and > 50% of maximal tumor area lasting for at least 1 month, respectively; progressive disease (PD) was defined as increment by > 25% of maximal tumor area. Stable disease (SD) was defined as the change that met neither CR, PR, nor PD. The evaluation of response was planned at 1, 3, 6, and 12 months following treatment, and every 6 months thereafter.

Results

Although moderate radiation pneumonitis appeared in one patient who had undergone conformal radiotherapy for the same tumor previously and mild pneumothorax was observed in one patient who received percutaneous brachytherapy, brachytherapy was safe and radiation pneumonitis was generally mild. We have already reported that our first percutaneous single-fraction brachytherapy for peripheral T1 N0 M0 NSCLC resulted in no appreciable short-term complications [5]. Follow-up of this case showed that the tumor and surrounding normal lung irradiated formed a nodule that remained similar-sized for approximately 7.5 years (Figure 3). The lung parenchyma surrounding the nodule seems to shrink, but no appreciable radiation pneumonitis has been observed during the entire observation period. The nodule is possibly focal radiation fibrosis, although pathologic examination was not performed.

The therapeutic parameters were shown in Table 2. The radiation time period was 518 ± 399 s, ranging between 123 and 1,559 s, depending on several factors including tumor size, location of an applicator in the tumor, and activity of radioactive source. V_{100} had a tendency to be smaller in percutaneous (20 ± 15 ml) than in transbronchial (49 ± 37 ml) brachytherapy.

Three (25%), four (33.3%), and five patients (41.7%) showed CR, PR, and SD, respectively, resulting in a response rate of 58.3%. So far, three patients have experienced dis-



Figures 1a and 1b. Schema of percutaneous and transbronchial brachytherapy. The radioactive iridium source is introduced via needle into the tumor (a), or it reaches the tumor through an applicator tube via bronchoscope (b).

Abbildungen 1a und 1b. Schematische Darstellung der perkutanen und der transbronchialen Brachytherapie. Die radioaktive Iridium-Quelle wird mit Hilfe einer Nadel in den Tumor eingeführt (a) oder erreicht ihn über einen bronchoskopisch eingeführten Applikator (b).

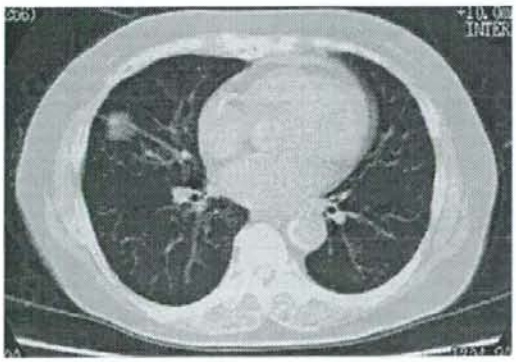


Figure 2a – Abbildung 2a

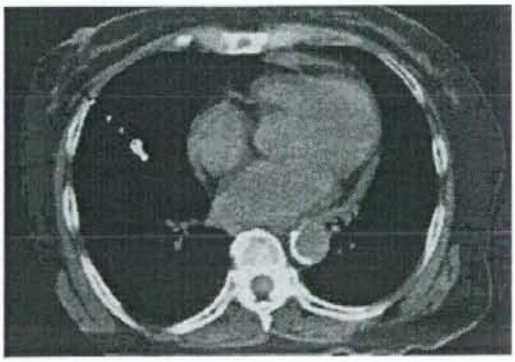


Figure 2b – Abbildung 2b

Figures 2a and 2b. Transbronchial brachytherapy. T1 N0 M0 pulmonary adenocarcinoma is present in right S4 (a). An applicator tube is introduced into the tumor via bronchoscope (b).

Abbildungen 2a und 2b. Transbronchiale Brachytherapie. Es liegt ein T1 N0 M0-Adenokarzinom der Lunge rechts in S4 vor (a). Der Applikator wird bronchoskopisch in den Tumor gebracht (b).

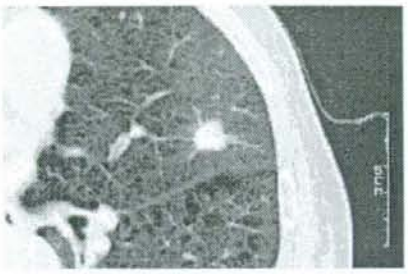


Figure 3a – Abbildung 3a

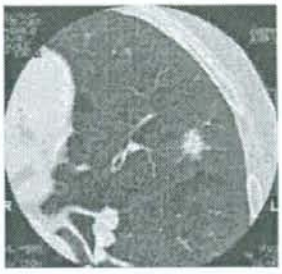


Figure 3b – Abbildung 3b

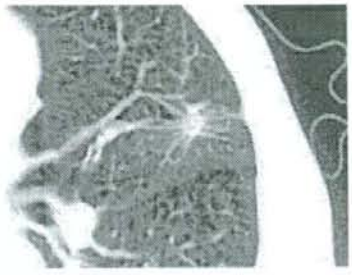


Figure 3c – Abbildung 3c

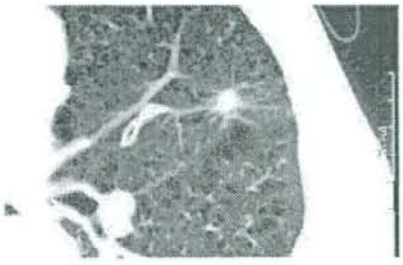


Figure 3d – Abbildung 3d

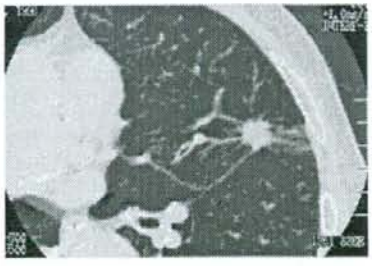


Figure 3e – Abbildung 3e

Figures 3a to 3e. Clinical course of the lesion treated by percutaneous brachytherapy. A nodule in the left middle lobe was irradiated by brachytherapy (a). 3 months (b) and 9 months (c) after the treatment, the nodule stayed in similar size, whereas the surrounding pulmonary parenchyma showed a tendency to shrink. During 7.5-year observation (d, e), the nodule has remained almost stable in size.

Abbildungen 3a bis 3e. Klinischer Verlauf nach perkutaner Brachytherapie eines Karzinoms. Ein Knoten im linken Mittellappen wurde brachytherapeutisch bestrahlt (a). Drei (b) und neun (c) Monate nach der Behandlung war die Größe des Knotens kaum verändert, während das umgebende Lungenparenchym eine Tendenz zum Schrumpfen zeigte. Während der Nachbeobachtungszeit von 7,5 Jahren (d, e) blieb die Größe des Karzinoms fast stabil.

ease recurrence, which occurred at 32 months, 12 months, and 13 months after the treatment, respectively. When brachytherapy was evaluated as an initial treatment for T1N0M0 NSCLC, local relapse occurred in one patient. Projected 5-year survival rate of all cases is about 50% and that of the patients in T1N0M0 between 60% and 70% (Figure 4).

Table 2. Parameters in brachytherapy. SD: standard deviation; V_{100}: volume irradiated at the dose over that at the reference point.

Tabelle 2. Parameter der Brachytherapie. SD: Standardabweichung; V_{100}: Volumen, das mit einer höheren als der Referenzpunkt-Dosis bestrahlt wird.

Fractionation		
Transbronchial		
• 5 Gy × 5 fractions	1	
• 4 Gy × 2 fractions + 5 Gy × 2 fractions	1	
• 7 Gy × 3 fractions	3	
• 12.5 Gy × 2 fractions	2	
Percutaneous		
• 20 Gy × 1 fraction	5	
Irradiation time per fraction	**Mean ± SD**	**Range**
Transbronchial	500 ± 491 s	
Percutaneous	542 ± 276 s	
Overall	518 ± 399 s	123–1,559 s
V_{100}[a]	**Mean ± SD**	**Range**
Transbronchial	49 ± 37 ml	
Percutaneous	20 ± 15 ml	
Overall	37 ± 33 ml	5–102 ml

[a]mean ± SD in each approach

Discussion

This study showed that brachytherapy was safe and effective in the treatment of peripheral small NSCLC. One patient experienced minimal pneumothorax due to percutaneous puncture, but no treatment was necessary. Radiation pneumonitis was mild and focal, reflecting limited distribution of radiation dose in brachytherapy. Whereas brachytherapy for central airway tumors is reported to sometimes induce necrotizing bronchitis and severe hemoptysis, no hemoptysis was observed in our study. Percutaneous brachytherapy has an advantage in that a ^{192}Ir needle can be introduced almost in the center of tumors. In transbronchial brachytherapy, a ^{192}Ir needle is in the bronchial tree, and therefore, it is difficult to put the radioactive source in the center of tumor.

Primary recurrence was observed in three patients. In one of them, brachytherapy was performed as a salvage treatment for recurrence after conformal radiotherapy and in an-

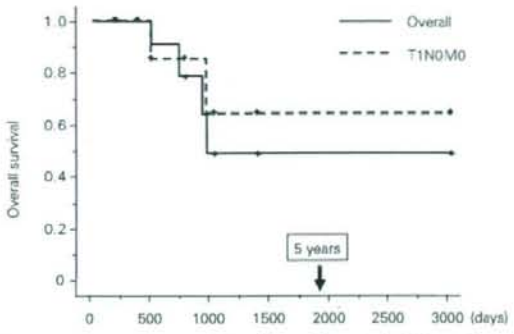


Figure 4. Kaplan-Meier analysis of overall survival of the patients treated by brachytherapy alone. A dotted line is a survival curve of the patients with T1 N0 M0 lung cancer. Projected 5-year survival rates are around 50% in all patients and between 60% and 70% in the patients with T1 N0 M0 tumor, respectively.

Abbildung 4. Kaplan-Meier-Analyse des Gesamtüberlebens der ausschließlich brachytherapeutisch versorgten Patienten. Die gestrichelte Linie ist die Überlebenskurve der Patienten mit T1 N0 M0-Lungenkrebs. Die prospektiven 5-Jahres-Überlebensraten liegen für alle Patienten bei rund 50%, und zwischen 60% und 70% bei Patienten mit T1 N0 M0-Karzinom.

other with T2 tumor. In the latter systemic recurrence was also observed. The local control rate for primary T1 N0 M0 NSCLC by brachytherapy is 90% (9/10), and no systemic recurrence has occurred.

Recently, stereotactic (SRT) or conformal radiotherapy (CRT) is widely used for inoperable T1 N0M0 NSCLC, and radiofrequency ablation is also applied. The comparison of brachytherapy with these methods is necessary. Although brachytherapy for centrally located NSCLC is studied extensively [7], reports on its application to peripheral NSCLC are still limited [4, 9, 12, 14]. Recently, image-guided brachytherapy is being developed for the tumors in several organs [4, 8, 11, 13]. Considering the multifocal nature of NSCLC sometimes seen in certain patients, overlap of radiation beams will become a serious problem in CRT and SRT. Because of the steep gradient of radiation doses, brachytherapy is especially useful in the treatment of patients with poor respiratory reserve or multiple early lung cancer.

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Improved Diagnostic Efficacy by Rapid Cytology Test in Fluoroscopy-Guided Bronchoscopy

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Background: Fluoroscopy-guided bronchoscopy is a safe and routine method used to obtain a histologic or cytologic specimen of peripheral lung nodules, but it has low sensitivity in diagnosing malignant tumors. Although feedback from rapid cytology tests are expected to improve diagnostic rates, the value of the routine use of rapid cytology tests has not been established.

Materials and Methods: We prospectively studied 657 patients with suspected peripheral malignant lung lesions on chest computed tomography who underwent fluoroscopy-guided bronchoscopy between January 2002 and December 2004. Rapid on-site cytopathologic examinations (ROSE) were performed during bronchoscopic examinations. The additional approach to the lesions was performed immediately after conventional bronchoscopic examinations when ROSE was not considered diagnostic.

Results: There were 528 patients diagnosed as having malignant lesions. In 477 of these patients (90.3%), final malignant diagnosis was established by the initial bronchoscopy. Among these, 84 patients (15.9%) were diagnosed only with the additional feedback from ROSE. Of 240 peripheral lesions ≤2 cm, 174 were found to be malignant. Without ROSE, 110 (63.2%) of peripheral malignant lesions were diagnosed by bronchoscopy. The integration of ROSE enabled us to diagnose an additional 40 patients (23.0%) by bronchoscopy. ROSE improved diagnostic yield independent of the site and histology of the lesions and experience of the operators.

Conclusion: ROSE increased the diagnostic yield of bronchoscopy from 74.4% to 90.3% and therefore is an effective reinforcement in bronchoscopic diagnosis of peripheral pulmonary malignancies. The use of ROSE in routine bronchoscopy should be encouraged.

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Examinations used to diagnose pulmonary malignant lesions should be safe, accurate, and optimal for obtaining adequate information. A flexible fiberoptic bronchoscope has become prevalent in obtaining specimen from lung lesions. Although central visible tumors can be diagnosed at high sensitivity, it is reported that the diagnostic rate for peripheral lung lesions is low, from 62% to 86%, even in combination with various techniques.[1–4] Brush, curette, forceps, and aspiration needles have been investigated as tools to obtain diagnostic specimens. Other reports recommend rapid on-site cytopathologic examinations (ROSE) in transbronchial needle aspiration of lymph nodes.[5–7] However, ROSE has not been introduced for diagnosing peripheral lung lesions. Recently, the combination of ultra-fast Papanicolaou staining and multiplanar reconstruction images has been recommended to improve diagnostic accuracy and safety in fluoroscopy-guided transbronchial biopsy.[8] In this prospective study, we integrated ROSE into routine bronchoscopy and evaluated the benefit of bronchoscopy combined with ROSE.

BRONCHOSCOPY

In our hospital, we foremost recommend bronchoscopy with a flexible bronchoscope in the diagnosis of pulmonary nodules because of its safety. If the lesions are not bronchoscopically invisible, procedures to obtain diagnostic materials are performed under fluoroscopic guidance. Transcutaneous fine-needle biopsy (TCNB) is recommended for patients with a negative result of preceding bronchoscopy or with negligible risk of pneumothorax by percutaneous puncture, such as those with lesions invading the thoracic wall. Video-assisted thoracic surgery (VATS) is usually recommended for patients with negative results of bronchoscopy and/or TCNB or lesions unrecognizable under fluoroscopy. For pure GGO, we recommend computed tomographic (CT) follow-up, otherwise VATS.

In bronchoscopy, the specimen for cytology was obtained by curetting or brushing. The material was smeared on two glass slides: one was subjected to ROSE (ROSE sample) and the other to conventional Papanicolaou staining. During ROSE, forceps biopsy was performed to obtain the specimen for histology and cytology. When ROSE was not diagnostic, additional bronchoscopic examinations, such as transbronchial needle aspiration (TBNA), bronchial washing, or ultrathin bronchoscopy, were performed to obtain additional samples just after conventional bronchoscopy. For the analysis, we defined both the material subjected to Papanicolaou staining and the material obtained by biopsy as conventional

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samples. The material obtained by additional bronchoscopic examinations after ROSE was defined as additional samples.

CYTOLOGY AND HISTOLOGY EXAMINATION

We used rapid Shorr stain as a rapid cytology test, which we have recently developed by modifying the Shorr stain.[9] Rapid Shorr stain completes staining very fast (approximately 1 minute) and presents similar coloring to Papanicolaou staining; therefore, it is familiar to the cytoscreeners in our institute. The cytopathologist was able to provide a preliminary diagnosis within a few minutes. Papanicolaou staining was performed after bronchoscopic examination. Tissue specimens obtained by forceps biopsy were fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. Additional specific staining was performed when necessary.

PATIENTS

We performed 1900 flexible bronchoscopic examinations between January 2001 and December 2004. Based on the results of chest radiograph and CT, 795 patients were thought to have central lesions and underwent bronchoscopy without fluoroscopy; 1105 patients underwent fluoroscopy-guided bronchoscopy. ROSE was not performed in the examinations to obtain samples for bacterial testing, for visible lesions, or to evaluate lesions diagnosed before, etc. ROSE was not used for the patients entered into another study performed during the same period in which ROSE was not integrated. Other patients' samples were not subjected to ROSE because only a single trial to obtain bronchoscopic material was possible because of patients' stress during bronchoscopy. Excluding these from the 1105 patients who underwent fluoroscopy-guided bronchoscopy, 657 patients received fluoroscopy-guided bronchoscopy with ROSE. ROSE was repeated when we thought it possible and necessary. Despite negative ROSE results, the lesions of very likely malignant or difficulty except for bronchoscopy, we tend to repeat ROSE. If a diagnosis could not be made via bronchoscopy, further work-up for the lesions included surgical procedures, TCNB, follow-up by bronchoscopy, chest radiograph and CT, and sputum investigations.

RESULTS

Bronchoscopic examinations with ROSE were performed under fluoroscopic guidance for 657 peripheral lung lesions. Patient characteristics are listed in Table 1. The final diagnosis of malignant and benign disease was determined in 528 and 117 lesions, respectively. The remaining 12 lesions were not diagnosed and subjected to careful follow-up. Malignant lesions consisted of adenocarcinoma (n = 328), squamous cell carcinoma (n = 87), small cell carcinoma (n = 32), carcinoid (n = 20), large call carcinoma (n = 7), lymphoma (n = 3), metastatic carcinoma (n = 22), and other malignancies (n = 29).

As shown in Table 2, 393 lesions were diagnosed as malignant by using conventional samples alone. ROSE definitively detected malignant cells in 357 malignant lesions but failed to detect atypical cells in 36 malignant lesions. The false-negative rate of ROSE was 9.2% compared with diagnosis based on conventional samples. In ROSE, a limited time period is permitted for screening and diagnosis. However, cancer cells were detected in only one sample with a negative ROSE result by subsequent re-diagnosis with sufficient time. There was no false-positive result in ROSE. However, final diagnosis was obtained with the additional samples in 84 of 135 malignant lesions that were not diagnosed with conventional samples alone. Therefore, the integration of ROSE into bronchoscopic examination improved the diagnostic sensitivity from 74.4% to 90.3% (Figure 1*A*). The improvement of sensitivity was statistically significant ($p < 0.05$) and enabled effective diagnosis for peripheral lung lesions.

TABLE 1. Patient characteristics

Sex	All patients	Patients with malignancy
Male	411	344
Female	246	184
Age (year)		
Range	25–89	27-87
Average	65.7	66.5
Chance of discovery		
Annual screening	250	183
Tests for other diseases	223	176
Subjective symptoms	163	151
Others	21	18
Smoking status		
Smoker	223	190
Ex-smoker	161	136
Non-smoker	210	156
Unknown	63	46

Additional samples for diagnosis were collected by brushing, curetting, forceps biopsy, TBNA, ultra-thin-bronchoscopy, and washing from the same or other bronchi. Sometimes, several methods were combined for obtaining a specimen. The methods to obtain additional specimens were determined based on the bronchoscopic access to the lesions and the condition of patients. We analyzed additional approaches contribute to the improvement of diagnostic accuracy (Table 3). Whereas brushing showed low diagnostic yield, curetting or forceps biopsy from the other branch, TBNA, and forceps biopsy with ultra-thin bronchoscope yielded more than a 65% positive rate in additional approaches. Washing was also useful for diagnosis in additional approaches, but malignant cells were usually detected by the other methods conducted at the same time.

Surprisingly, ROSE provided more benefit for the diagnosis of small-sized lesions (≤2 cm) (Figure 1*B*). With conventional samples, 110 of 174 small-sized malignant lesions (63.2%) were diagnosed by bronchoscopy. With the help of ROSE, 40 lesions (23.0%) were diagnosed only with an additional sample. Improvement of diagnostic rate for small lesions was significantly greater than that for larger lesions (23.0% versus 12.4%; $p < 0.05$). No significant improvement was observed among the other factors in exam-

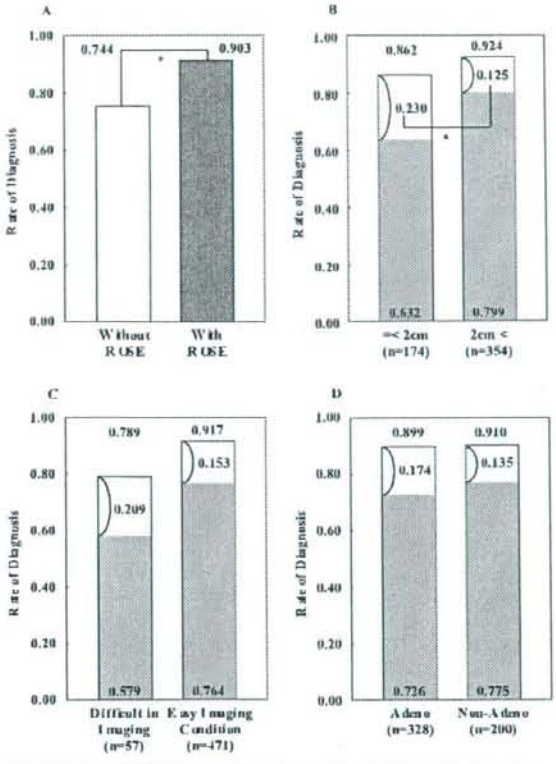

FIGURE 1. ROSE improved diagnostic yield and lesion features. *A*, ROSE improved diagnostic sensitivity. The *gray bar* shows the diagnostic sensitivity of fluoroscopy-guided bronchoscopy with ROSE; the *white bar* shows the diagnostic sensitivity of bronchoscopy without ROSE. The sensitivity is significantly different ($p < 0.05$). *B*, Tumor size and improvement of diagnostic sensitivity by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. The improvement in small lesions was better than that in large lesions ($p < 0.05$). *C*, Imaging conditions of the lesions under fluoroscopy revealed diagnostic yield but little difference in improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. *D*, Histology type made little difference in diagnostic sensitivity and improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE.

inations (Figure 1, *C* and *D*). Examination of poorly visible lesions in fluoroscopy had low sensitivity (n = 57, 78.9%) compared with that of clearly visible lesions (n = 471, 91.7%). The improvement by ROSE was slightly higher in examinations for poorly visible lesions (21.1% versus 15.3%), although the difference was not statistically significant. Little improvement by ROSE was shown between histology types of the lesions: adenocarcinoma 52.3%, squamous cell carcinoma 56.3%, small cell carcinoma 50%, and metastatic carcinoma 40.0% of ROSE-negative lesions. Our results also showed the difficulty in diagnosing lesions in the upper lobe and S6, especially in right lung with conventional samples. However, a comparable improvement of diagnostic yield was achieved with ROSE in most areas (from 40% to 60% of ROSE-negative lesions). We calculated the diagnostic yields with conventional samples and additional samples for each examiner to determine the effect of skill level of examiners on usefulness of ROSE. Although the skill level of the examiner tends to correlate to diagnostic yield with conventional samples, improved diagnosis by ROSE was observed similarly in almost all of the examiners (approximately 40% to 52% of ROSE-negative cases).

ROSE was repeated to make a decision for further examinations when access to the lesion was not satisfactory and an additional approach was considered to be possible. We calculated the effect of repeated ROSE on the diagnostic yield of peripheral lung cancer by fluoroscopy-guided bronchoscopy and found that a diagnostic improvement of 89.4% was attained by the first ROSE and 3.2% by the second ROSE (Table 4). Repeated ROSE improved diagnosis in only five of 107 examinations.

DISCUSSION

Bronchoscopic examination with fluoroscopic guidance is often used to obtain a diagnostic specimen of lung nodules. However, most reports have shown relatively low accuracy of diagnosing peripheral lesions by bronchoscopy.[10–12] Bandoh et al.[8] reported refined accuracy up to 91% by combining multiplanar reconstruction images and ultra-fast Papanicolaou staining. They used a historical control for comparison and multiplanar images for another tool. Our study was designed to improve the bronchoscopic diagnosis of peripheral malignant lesions by introducing only ROSE and was performed prospectively in routine bronchoscopic examinations. Therefore, more precise analysis could be performed to estimate ROSE's effectiveness. Our result shows that diagnostic sensitivity of peripheral malignant lesions was improved from 74.4% to 90.3% with ROSE only.

To obtain rapid diagnosis during bronchoscopy, the staining method should be convenient and fast and should present suitable coloring for diagnosis. Several staining methods are applied in ROSE.[8,14,15] We selected rapid Shorr staining for ROSE that we established recently[9] because it is simple, rapid, and similar in coloring to Papanicolaou staining, which is familiar to cytoscreeners and cytopathologists. Additionally, rapid Shorr staining requires only a small area for staining. Rapid Shorr staining is reliable, with low false-positive and false-negative rates.

To improve sensitivity, a method for obtaining additional samples should be carefully determined. When another visible bronchus could be a suitable path to the lesion, we selected this path. When the visible route to the lesion could not be improved, we changed the method for approaching to lesions to TBNA, ultra-thin bronchoscopy, or washing. Comparison among the methods indicates that TBNA and ultra-thin bronchoscopy were most effective in the approach through the same bronchus. In the approach through different bronchi, curetting and biopsy were effective for diagnosis, whereas TBNA was a good alternative (Table 3). Therefore,

TABLE 2. Results of bronchoscopic examinations with ROSE

ROSE	Final diagnosis	Diagnosis by conventional samples	Diagnosis by additional samples	Diagnosis by different examinations
Negative	279			
Malignant	154	26	80	48
Benign	113	13	2	98
Unknown	12	0	0	12
Positive suspected	21			
Malignant	17	10	4	3
Benign	4	1	0	3
Unknown	0	0	0	0
Positive	357			
Malignant	357	357	0	0
Benign	0	0	0	0
Unknown	0	0	0	0

ROSE, rapid on-site cytopathologic examinations.

TABLE 3. Methods of additional sampling for diagnosing malignant lesions

	Tested lesions	Sole positive	Positive
Brushing	16	0 (0.0%)	4 (26.7%)
(from other branch)	4	0 (0.0%)	1 (25.0%)
Curetting and forceps	101	33 (32.7%)	51 (50.5%)
(from other branch)	14	12 (85.7%)	13 (92.9%)
TBNA	35	16 (45.7%)	25 (71.4%)
(from other branch)	7	4 (57.1%)	6 (85.7%)
Washing	29	3 (10.3%)	12 (41.4%)
(from other branch)	4	1 (25.0%)	2 (50.0%)
Forceps with ultra-thin bronchoscope	20	14 (70.0%)	20 (100%)
Washing with ultra-thin bronchoscope	16	0 (0.0%)	11 (68.8%)

TABLE 4. Diagnostic yield of malignant lesions by repeated ROSE

ROSE	Bronchoscopic examinations	Additional examination	Diagnostic yield	Accumulated sensitivity
0	657		393	74.4%
1	657	214	79	89.4%
2	126	94	3	90.0%
3	20	12	2	90.3%
4	1	1	0	90.3%

ROSE, rapid on-site cytopathologic examinations.

alternative routes or methods such as TNBA or ultra-thin bronchoscopy should be considered when ROSE is not diagnostic. We do not recommend brushing and washing.

It has been reported that the size of the lesion has negative correlation to the sensitivity of bronchoscopy. Our results also showed low sensitivity for small lesions (≤2 cm). Surprisingly, however, improvement of diagnostic yield by ROSE was more prominent in diagnosing small lesions (Figure 1*B*). We analyzed the relationship between the size of lesions and the methods by which diagnosis could be made with additional samples. There was no distinct difference in frequency of usage of each method and its ability to yield additional diagnoses between the small and large lesions. Therefore, the reason why diagnostic yield improved more in smaller lesions is not known. One possible explanation is poor fluoroscopic targeting for smaller lesions in bronchoscopy. We used biplane fluoroscopy, but not CT, to determine whether the tip of sampling tools reached the lesions. It is reasonable that the error in targeting by this method is greater for small lesions than for large lesions. ROSE may have improved diagnostic yield partly by correcting the error in targeting.

There are several factors other than the size of tumors related to diagnostic yields. The experience of the examiners relates to the diagnostic sensitivity of bronchoscopic examinations.[16] The location of the lesion, histology type, and visibility under fluoroscopy can influence the yield. We analyzed the relationship between these factors and diagnostic yield. Experience of examiners, location of the lesion, and fluoroscopic visibility of lesions showed some relation to the diagnostic yield. However, improvement of diagnosis by ROSE was similarly observed for all examiners. Diagnostic yield of the lesions in the upper lobe and S6 was relatively low. However, we did not observe a clear difference of improvement by ROSE by location. Examinations for poorly

visible lesions under fluoroscopy showed low sensitivity compared with clearly visible lesions. The improvement by ROSE was slightly higher in the examinations for poorly visible lesions, although not statistically significant. Comparison among histology types of the lesions showed little difference in sensitivity and improvement by ROSE. We encourage the use of ROSE for diagnosing peripheral lesions, especially those of small size, regardless of their location, fluoroscopic visibility, or experience of the examiners.

We usually performed curetting and forceps biopsy only once before ROSE. Although repeated curetting and biopsy were thought to improve sensitivity, we repeated the collection of specimens only in negative ROSE cases, including false negatives. We performed additional examinations for only 214 cases with ROSE and showed an increased sensitivity by 14.9% instead of performing repeated curetting and biopsy in most of the 657 cases without ROSE. ROSE enabled us to avoid unnecessary examinations, even including false-negative cases. Considering the low effectiveness of repeated ROSE, single ROSE is recommended. Recently, CT screening and positron emission tomography have been experimentally introduced for the early detection of lung cancer.[16–18] We expect to diagnose peripheral lung nodules more safely and accurately in the future. The combination of ROSE with fluoroscopy-guided bronchoscopy is encouraged as a conventional method to enhance its safety and sensitivity.

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Case Reports

Relapse of Stage I Small Cell Lung Cancer Ten or More Years after the Start of Treatment

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Most patients with small cell lung cancer (SCLC) usually show relapse within 1 or 2 years. Relapses after a 5-year disease-free survival are extremely rare. This report describes two patients with stage I SCLC in whom the disease recurred 10 or more years after the start of initial therapy. Because the recurrence of SCLC was noted in the mediastinal lymph nodes of the same side, we concluded that the patients had a late relapse of SCLC rather than a metachronous lung cancer.

Key words: 10-year disease-free survival – late relapse – second malignancy – small cell lung cancer

INTRODUCTION

Small cell lung cancer (SCLC) is characterized by early and widespread metastases, but good responsiveness to both chemotherapy and radiotherapy. The percentage of long-term disease-free survival was reported in 1983 (1) to be in the range of 15–20% in cases of limited disease (LD) and only a few percent in those with extensive disease, and a recent report suggested an expected 5-year survival rate of ~25% in cases with LD SCLC (2). Previous analyses of long-term disease-free survivors of SCLC (3,4) revealed that relapses usually occurred by 1.5 years after the beginning of combination chemotherapy. However, recent data indicate that as many as one-fourth of the patients who are disease-free at 30 months after the initial therapy develop late relapses (5). Furthermore, in his series, Vogelsang et al. (6) reported that 18 of the 25 long-term survivors (>2 years) eventually showed relapse, sometimes as late as 8 years after the initial diagnosis. In 1993, we reported the course of a patient with SCLC who showed relapse 9.4 years after the initial treatment (7). In this paper, we report two cases of SCLC in whom relapse occurred after 10 or more years' disease-free survival, along with a review of the total of seven cases of SCLC reported until now, who developed a second SCLC or relapse after 10 years' disease-free survival.

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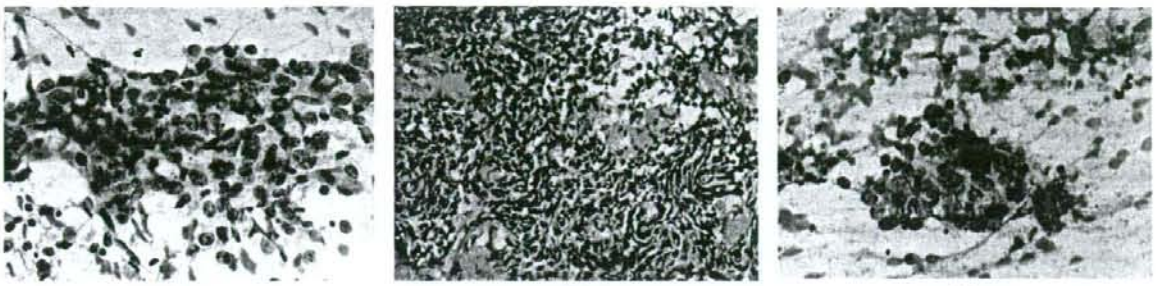
CASE REPORTS

CASE 1

A 61-year-old man participated in a mass screening for lung cancer by chest roentgenography (CXR) in June 1994. The Brinkman index was 1200, however, he stopped smoking after the first diagnosis. Fiberoptic bronchoscopy with transbronchial tumor biopsy confirmed the diagnosis of SCLC (Fig. 1a and b). The primary tumor was located in the B^{1+2} segment of the left upper lobe (Fig. 2a). Surgical resection of the left upper lobe was conducted, followed by combination chemotherapy with four cycles of cisplatin and etoposide. Pathologically, the tumor was determined to be stage IA SCLC and had no components of non-SCLC or large cell carcinoma with neuroendocrine properties.

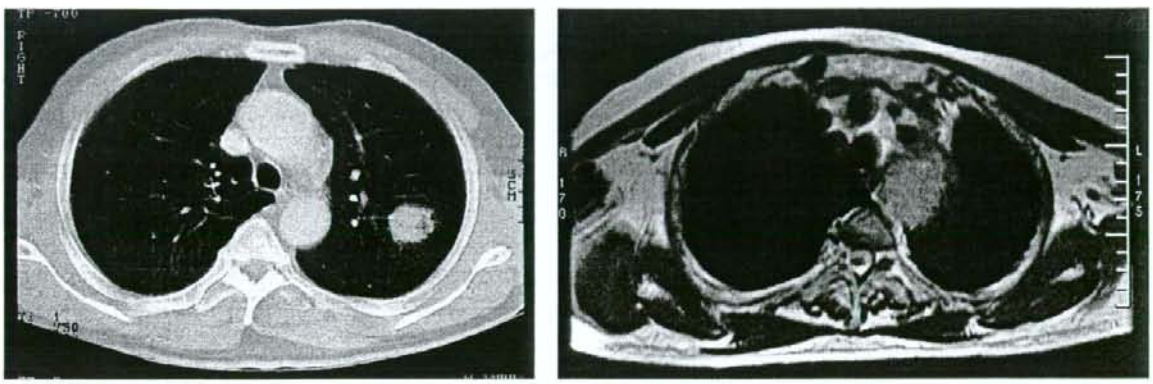
The patient underwent transurethral resection for early-stage bladder cancer (second malignancy) in January 2002 and received radiotherapy (75 Gy) for A2 (early) prostate carcinoma (third malignancy) in March 2004.

In June 2004, when he was 71 years old, a follow-up chest computed tomography (CT) and MRI (Fig. 2b) revealed para-aortic mediastinal lymphadenopathy (40 × 50 mm in size). The serum levels of pro-gastrin-releasing peptide, neuron-specific enolase (NSE) and carcinoembryonic antigen



(a) (b) (c)

Figure 1. Cytological (a) and histological (b) appearance of the first tumor in July 1994 and aspiration biopsy (c) of cervical lymph node in September 2005 at relapse in Case 1.



(a) (b)

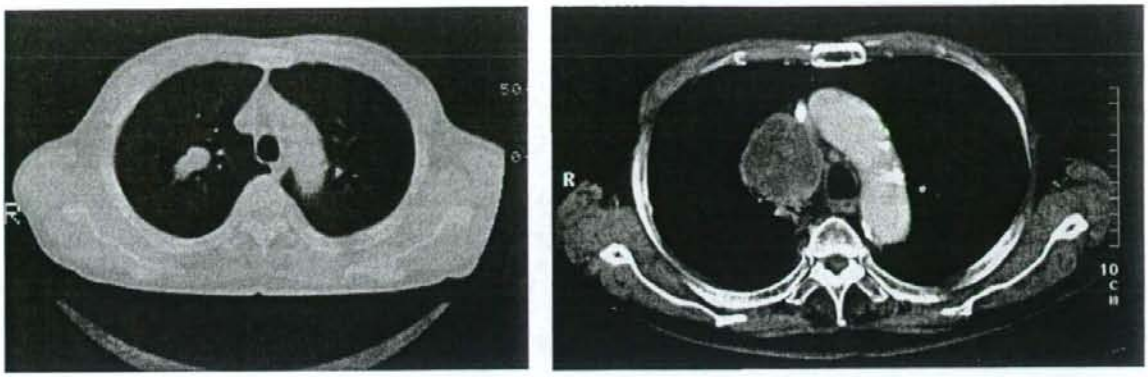
Figure 2. Findings on Chest CT (a) at diagnosis in July 1994 in Case 1. Findings on MRI (b) at relapse in 2004. There is mediastinal lymph node enlargement; size, 40 × 50 mm.

(CEA) were 360 pg/ml (normal range <46 pg/ml), 14.9 ng/ml and 1.4 ng/ml, respectively. The performance status on the Eastern Cooperative Oncology Group (ECOG) scale was zero, because he complained only of hoarseness and the serum lactate dehydrogenase (LDH) was normal. The standard staging procedures and upper gastro-intestinal screening by endoscopy revealed no evidence of metastases. Because of the poor pulmonary function of the patient and high metastatic potential of the disease, no surgery or chest irradiation was planned at this time. He was started on combination chemotherapy with irinotecan (CPT-11) at 60 mg/m^2 on day 1 and etoposide at 80 mg/m^2 on days 1–3, along with granulocyte-colony stimulating factor support on days 4–17 for one cycle, however, he developed severe neutropenia. The tumor regrew within 6 weeks of the treatment-free interval given to allow for his bone marrow recovery. He received CPT-11 at the dose of 50 mg/m^2 alone bi-weekly and enjoyed prolonged partial response (PR). In March 2005, multiple bone metastases were observed, along with left cervical adenopathy. Aspiration biopsy of the cervical lymph nodes revealed the typical histologic features of SCLC (Fig. 1c). Brain metastasis occurred in July 2005, and in September 2005, the serum NSE level rose to 245 ng/ml. He died of cancer in October 2005.

Case 2

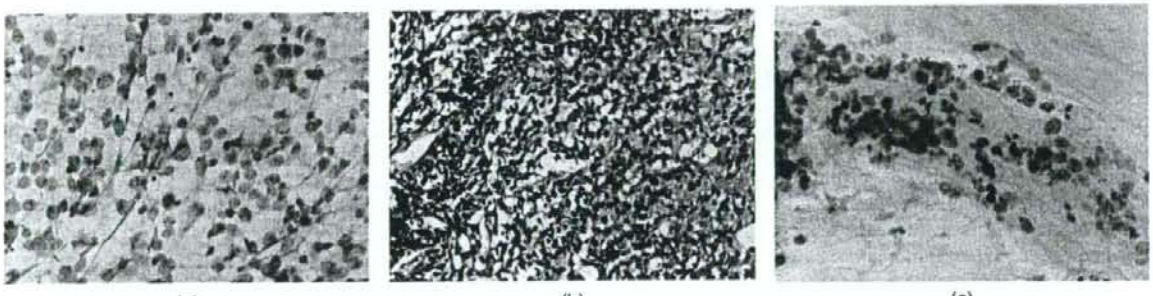
In April 1987, a 72-year-old man visited our hospital with a month's history of productive cough and blood-streaked sputum. He had smoked one packet of cigarettes a day for 52 years; however, he stopped smoking at the first diagnosis of lung cancer. A CXR showed a right upper lobe mass, which was confirmed on chest CT (Fig. 3a). Fiberoptic bronchoscopy with tumor biopsy confirmed the diagnosis of SCLC (Fig. 4a and b). The patient was determined to have stage IB (T2N0M0) SCLC. Chemotherapy was administered with cyclophosphamide, doxorubicin and vincristine alternating with cisplatin-etoposide, for six cycles. Thereafter, sequential chest radiotherapy was administered.

In September 1998, when he was 82 years old and 11.4 years had passed since the initial treatment of SCLC, the patient complained of shortness of breath on walking even as little



(a) (b)

Figure 3. Findings on Chest CT (a) in Case 2 at diagnosis in April 1987. A mass measuring 31 × 13 mm in size in the right upper lobe. Chest CT (b) findings at relapse in 1998.



(a) (b) (c)

Figure 4. Findings on transbronchial biopsy [cytology (a), and histology (b)] in Case 2 at diagnosis. Sputum cytology (c) at relapse in 1998.

as one block, and hemoptysis. His performance status on the ECOG scale was 3. The serum levels of LDH, NSE and CEA were all within normal range. The sputum cytology result was consistent with the diagnosis of SCLC (Fig. 4c). Chest CT revealed multi-stage mediastinal lymphadenopathy, especially on the ipsilateral side (Fig. 3b). There was no evidence of metastasis elsewhere, as confirmed by brain CT. Because of his poor performance status, the patient received two cycles of monotherapy with oral etoposide (50 mg/body/day for 14 days), with no shrinkage of the tumor. He died of worsened SCLC on 2 May 1999.

Table 1 shows a review of adequately documented cases of recurrence and/or second SCLC after 10 years of disease-free survival. All the patients received systemic combination chemotherapy followed by thoracic irradiation.

DISCUSSION

Jacobs et al. (8) stated that there were continued relapses of disease until 39 months. Jacoulet et al. (5) reported that the risk of recurrence was <30% beyond 3 years and <10% beyond 5 years. In the treatment of SCLC, 5-year disease-free survival has usually been considered as a benchmark of cure (9,10). However, Niiranen (11) described a case with relapse at the primary site, in the central nervous system and in the skin 11 years after the diagnosis of SCLC.

Brigham et al. (12) estimated that the clinical doubling time of SCLC ranged from 25 to 160 days (median, 77 days; log mean, 81 days; arithmetic mean, 91 days) on the basis of chest radiographic findings. He suggested that highly effective therapy which reduces the residual tumor burden level to that approaching a single cell can be followed by disease-free intervals of more than 6 years before apparent clinical recurrence (>30 doublings). If the longer doubling time of 160 days were used for the calculation, potential relapse of SCLC may not be expected until 13 years after successful induction therapy with complete response as suggested by Al-Ajam et al. (10). It is usually difficult to ascertain whether a second SCLC is a late relapse of the first SCLC or a second primary tumor after a long disease-free survival. Some authors (9,13) suggested that the second diagnosis of SCLC after a long period of survival following the first diagnosis of SCLC should be considered as representing a second primary SCLC, whereas others (14,15) interpret it as representing a relapse of the first SCLC. The

Table 1. Patients of SCLC with 10 years or greater disease-free survival before the second diagnosis of SCLC

Author	Year of publication	Age/ Sex	Stage	Location of initial tumor	Initial therapy	DFI (years)	First relapse site	Treatment after relapse	Survival after relapse (months)
Niiranen[12]	1988	60/M	LD (I)	NR	RT (60 Gy)	11	Lung, Brain, Skin	NR	2 dead
Lassen[15]	1995	65/F	NR	NR	NR	10.9	Lung, Brain, Kidney	NR	2 dead
Johnson[16]	1995	69/M	LD	LLL	CT+RT	12.2	LLL, LH, L-pl, ML	NR	NR
Kitamoto[13]	2002	56/M	LD (IIIB)	LLL	CT+RT*	10.4	LUL, LH	CT+RT***	10 live
Al-Ajam[11]	2005	52/M	LD	RUL	CT+RT**	10	RUL, Brain	Whole brain RT, CT[$]	17 alive
Present case 1		61/M	LD (IA)	LUL	OP+CT[#]	10	ML	CT[$$]	14 dead
Present case 2		72/M	LD (IB)	RUL	CT +RT[##]	11.4	ML	CT[$$$]	8 dead

DFI, disease-free interval; NR, not reported; LLL, left lower lobe; LUL, left upper lobe; RUL, right upper lobe; LD, limited disease; ED, extensive disease; ML, mediastinal lymph node; L-pl, left pleural effusion; LH, left hilum lymph node; CT, chemotherapy; RT, chest irradiation; *chemotherapy with cisplatin, etoposide and doxorubicin, and concurrent chest irradiation at 40 Gy in 20 fractions; **CAV (cyclophosphamide + adriamycine + vincristine) and sequential chest irradiation, [#]Left upper lobectomy and adjuvant chemotherapy with PE (cisplatin + etoposide), [##]chemotherapy with CAV alternating with PE and sequential chest irradiation (45 Gy twice daily), ***PE sequential RT, [$]PE, [$$]etoposide + CPT and CPT alone, [$$$]oral etoposide.

latter contention may be valid if the tumor arose at the same anatomic site as the initial SCLC, although the possibility of a new second primary tumor can still not be completely excluded. Kitamoto et al. (13) considered the second diagnosis of SCLC as a second malignancy, because the primary tumor was located in a different lobe of the lung in his patient. We believe that our patients may have had a relapse rather than a second primary tumor, because the second SCLC developed at the same site as the first tumor in one case, and in the ipsilateral mediastinal nodes in the other, and the specimens at diagnosis and at relapse showed an identical cytological or histological appearance in our patients (Figs 1 and 4).

Wistuba et al. (16) reported of observing genetic damage in the adjacent normal and hyperplastic bronchial epithelium in cases of SCLC. Tucker et al. (17) reported that continued smoking increased the risk of second primary cancers in patients treated for SCLC, and the cumulative risk of development of a second primary lung cancer made this cancer a common cause of death. Despite the decreasing incidence of recurrent SCLC with time, the longevity of long-term disease-free survivors continues to be compromised by increasing incidence of second primary smoking-related cancers. Since cigarette smoking cessation after successful therapy is associated with a decreased risk for a second smoking-related primary cancer, the simplest and most important intervention should be to encourage patients to quit smoking (18).

Although the standard therapy for late recurrent disease has not been established, retreatment with chemotherapy similar to the initial treatment (reinduction therapy) is reported to often achieve second responses up to 1 year or longer (19). Sekine et al. (20) also reported a relative good prognosis of patients after late relapse. The median survival time after relapse in their 13 patients was 7.4 months. This may be explained in part by good response to reinduction treatment in these patients or by very sluggish growth in these tumor cells.

Although only seven cases of late relapses after a 10-year disease-free survival have been reported until now, including our two patients, there is still a chance of such rare recurrence occurring beyond this interval. Therefore, careful follow-up is necessary to detect malignant lesions as early as possible in these long-term survivors.

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ORIGINAL ARTICLE

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Phase I study of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy in patients with locally advanced non-small-cell lung cancer

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Abstract

Background. The combination of chemotherapy and thoracic radiation therapy (TRT) is considered as a standard treatment for locally advanced non-small-cell lung cancer (NSCLC). Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, the daily administration of these agents is complicated. We therefore used weekly administration of these agents, and conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

Methods. Patients with locally advanced NSCLC were enrolled in this study. Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36. The total dose of TRT was 60 Gy. The dose of cisplatin was fixed at 20 mg/m^2 per week. The starting dose of vinorelbine was 15 mg/m^2 per week (dose level 1).

Results. Nine patients were enrolled in this study. All three patients at dose level 1 experienced DLTs. We decreased the dose of vinorelbine to 10 mg/m^2 per week (dose level 0). Two of the six patients at dose level 0 experienced DLTs. Therefore, dose level 1 was considered as the MTD, and dose level 0 as the recommended dose. The DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia.

Conclusion. The recommended dose of cisplatin is 20 mg/m^2 per week and that of vinorelbine is 10 mg/m^2 per week with standard TRT. A phase II study of this treatment is warranted.

Key words Cisplatin · Vinorelbine · Chemoradiotherapy · Non-small-cell lung cancer

Introduction

Lung cancer is a leading cause of cancer mortality in Western industrialized countries.[1] Approximately 80% of lung cancer is of the non-small-cell histologic type, such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Surgery, if possible, is the mainstay of treatment for patients with non-small-cell lung cancer (NSCLC); however, the majority of NSCLC is considered as unresectable due to the local or systemic spread of the cancer. Approximately 30% of NSCLC is locally advanced, unresectable stage IIIA or IIIB disease. The American Society of Clinical Oncology (ASCO) published their guideline (update 2003) for the treatment of unresectable NSCLC.[2] This guideline recommends the following treatment for locally advanced NSCLC: chemotherapy in association with definitive thoracic irradiation is appropriate for selected patients with unresectable, locally advanced NSCLC; radiation therapy should be included as part of the treatment for selected patients with unresectable locally advanced NSCLC; and chemotherapy given to

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The results of this study were presented in part at the 43rd Annual Meeting of the Japan Lung Cancer Society in Fukuoka, Japan, November 21–22, 2002.

NSCLC patients should be a platinum-based combination regimen.

The combination of cisplatin and vinorelbine is more effective than single-agent cisplatin, or cisplatin plus vindesine, for advanced NSCLC.[3,4] Furthermore, some randomized trials have shown that cisplatin plus vinorelbine is as effective as carboplatin plus paclitaxel, cisplatin plus gemcitabine, or cisplatin plus irinotecan.[5-7] Therefore, the cisplatin plus vinorelbine combination is considered as one of the standard platinum-based chemotherapy regimens.

There are two possible advantages of the combination of chemotherapy and radiation therapy. One is spatial cooperation (which means that radiation is effective against the loco-regional tumor, and chemotherapy eradicates micrometastases independently) and the other is the radiosensitizing effects.[8-10] Cisplatin is one of the anticancer agents whose radio-sensitizing effects have been studied extensively, and many preclinical studies have shown that cisplatin enhanced the cytotoxic effects of irradiation.[11] The European Organization for Research and Treatment of Cancer (EORTC) performed a randomized trial comparing the following three arms: thoracic radiation therapy (TRT) alone, TRT combined with weekly cisplatin, and TRT combined with daily cisplatin, for locally advanced NSCLC.[12] The survival rate was 54% at 1 year, 26% at 2 years, and 16% at 3 years for the TRT+daily-cisplatin group, as compared with 44%, 19%, and 13% for the TRT+weekly-cisplatin group, and 46%, 13%, and 2% for the TRT-alone group, respectively. The EORTC concluded that TRT+daily cisplatin had the greatest survival benefit of the three treatment arms and this benefit was due to the improvement of local control. On the other hand, some preclinical studies have shown that vinorelbine also had radio-sensitizing effects.[13-15] Vinorelbine is a potent inhibitor of mitotic microtubule polymerization, and this effect synchronizes cells at the G2/M phase of the cell cycle. This phase is considered as the most radio-sensitive phase; thus, vinorelbine can exhibit radio-sensitizing effects.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, daily administration of these agents is complicated. Weekly administration is more convenient than daily administration. Therefore, we conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT for locally advanced NSCLC. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

Patients and methods

Eligibility criteria

Patients with histologically or cytologically confirmed locally advanced NSCLC were enrolled in this study. All patients were deemed suitable for definitive TRT by a radiation oncologist (T.T.). Other eligibility criteria included the following: age, 20 years or older; Eastern Cooperative Oncology Group (ECOG) performance status, 0 or 1; unresectable stage IIIA or IIIB; absence of malignant pleural or pericardial effusion; absence of involvement of contralateral hilar lymph nodes; no prior chemotherapy or TRT; adequate bone marrow function (leukocyte count ≥4000/μl, neutrophil count ≥2000/μl, hemoglobin level ≥10 g/dl, and platelet count ≥100000/μl), renal function (creatinine level ≤ upper limit of normal and creatinine clearance ≥50 ml/min), hepatic function (aspartate aminotransferase/alanine aminotransferase [AST/ALT] ≤ twice upper limit of normal and bilirubin level ≤ upper limit of normal), and pulmonary function (arterial partial pressure of oxygen [PaO_2] ≥70 mmHg); absence of interstitial pneumonitis or pulmonary fibrosis, or other serious illnesses; and no pregnancy or lactation. Written informed consent was obtained from all patients. This protocol was approved by the institutional review board of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. All patients received the protocol treatment at the same institution.

Chemotherapy

Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36 (Fig. 1). The doses of cisplatin and vinorelbine are described later. Cisplatin was administered as a 60-min infusion with adequate hydration (at least 1000 ml of fluid). Antiemetic drugs, such as 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists and dexamethasone 8 mg, were given intravenously before the administration of cisplatin. Vinorelbine was administered as a 5-min infusion. The minimum requirements for the administration of cisplatin and vinorelbine were as follows: leukocyte count 2000/μl or more, neutrophil count 1000/μl or more, platelet count 50000/μl or more, nonhematological toxicity grade 2 or less, and no suspension of TRT.

Subsequently, consolidation chemotherapy was given, starting 1 week after the completion of irradiation. If creatinine clearance was 60 ml/min or greater, cisplatin 80 mg/m^2 was given intravenously as a 60-min infusion on day 1 and vinorelbine 20 mg/m^2 was given intravenously as a 5-min infusion on days 1 and 8 of a 3-week cycle. Standard hydration and antiemetics were also given. If creatinine clearance was less than 60 ml/min, vinorelbine 25 mg/m^2 was given intravenously as a 5-min infusion on days 1, 8, and 15 of a 4-

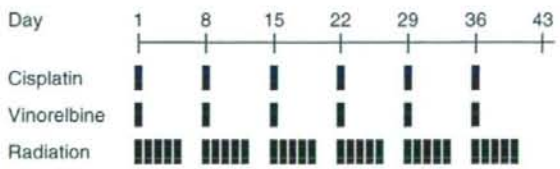

Fig. 1. Treatment schedule of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy