Accuracy of ^{18}F Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Staging of Pediatric Sarcomas

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Summary: The present study was conducted to clarify the diagnostic accuracy of ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography (PET)/computed tomography (CT) in the staging in pediatric sarcomas. Fifty pediatric patients with histologically proven sarcomas who underwent ^{18}FDG PET/CT before treatment were evaluated retrospectively for the detection of nodal and distant metastases. Diagnostic accuracy of ^{18}FDG PET/CT in detecting nodal and distant metastases was compared with that of ^{18}FDG PET and conventional imaging (CI). The images were reviewed and a diagnostic consensus was reached by 3 observers. Reference standard was histologic examination in 15 patients and confirmation of an obvious progression in size of the lesions on follow-up examinations. Nodal metastasis was correctly assessed in 48 patients (96%) with PET/CT, in contrast to 43 patients (86%) with PET, and 46 patients (92%) with CI. Diagnostic accuracies of nodal metastasis in 3 modalities were similar. Using PET/CT, distant metastasis was correctly assigned in 43 patients (86%), whereas interpretation based on PET alone or CI revealed distant metastasis in 33 patients (66%) and 35 patients (70%), respectively. Diagnostic accuracy of distant metastasis with PET/CT was significantly higher than that of PET ($P = 0.002$) or CI ($P = 0.008$). False negative results regarding distant metastasis by PET/CT in 7 patients (14%) were caused by subcentimetric lesions (n = 4), bone marrow lesion (n = 2), and soft tissue lesions (n = 1). PET/CT is more accurate and probably more cost-effective than PET alone or CI regarding distant metastasis in pediatric sarcomas.

Key Words: PET/CT, pediatric sarcoma, stage

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Pediatric sarcoma remains uncommon neoplasm but contributes significantly to the burden of morbidity and mortality. The success of aggressive therapy with multiagent chemotherapy and radiotherapy resulted in a significant improvement of the prognosis. However, patients with metastasis continue to have a poor prognosis.[1–3] Therefore, the diagnosis of nodal and distant metastases is crucial to determine the therapeutic plan and prognosis in patients with pediatric sarcomas.

The conventional imaging (CI) for initial staging of bone and soft tissue sarcomas consists of clinical examination, magnetic resonance imaging (MRI) of the primary lesion, chest x-ray, computed tomography (CT), and bone scintigraphy. Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}FDG) has been used in the evaluation of bone and soft tissue sarcomas,[4–11] and most of these studies report that ^{18}FDG PET is advantageous in the assessment of grading and therapy monitoring compared with CI. A hybrid imaging of PET/CT can allow accurate anatomic localization of tumors, and thus has an important advantage over ^{18}FDG PET alone for the staging of tumors.[12]

However, the exact role of ^{18}FDG PET/CT in the staging of pediatric sarcomas has not been elucidated. To further clarify the role of ^{18}FDG PET/CT, the comparison with ^{18}FDG PET/CT, PET alone, and CI are needed. The aim of the current study was to clarify diagnostic accuracy of ^{18}FDG PET/CT for the staging of pediatric sarcomas.

MATERIALS AND METHODS

Patient

We retrospectively reviewed ^{18}FDG PET/CT images since June 2005 to August 2006 for staging (n = 40, 80%) and restaging (n = 10, 20%) of pediatric sarcomas. ^{18}FDG PET/CT was performed for initial staging in all patients. The study population consisted of 26 males and 24 females with a mean age of 13 years (range, 3 to 17 y). The clinical records of all the patients were available for review. This study was conducted in accordance with the amended Helsinki declaration and the protocol was approved by the Institutional Review Board. All the patients had provided their written

informed consent to participate in the present study and to review their records and images.

PET/CT

PET/CT was performed within mean 2 weeks (range, 0 to 2 wk) before therapy and mean 6 weeks (range, 4 to 11 wk) after initiation of therapy. We used premedication with oral intake of chloral hydrate in 4 patients. Scans were acquired with a PET/CT device (Aquiduo; Toshiba Medical Systems, Tokyo, Japan) that consisted of a PET scanner (ECAT HR+; CTI, Knoxville, TN) and 16-section CT scanner (Aquilion V-detector; Toshiba Medical Systems) with a whole-body mode implemented as the standard software. Before PET/CT study, the patients fasted for at least 6 hours. CT was performed from the skull vertex to the toes according to a standardized protocol with the following setting: axial 3.0-mm collimation × 16 modes; 120 kVp; 80 mAs; and a 0.5-second tube rotation, 11.0 mm/s table speed. Patients maintained normal shallow respiration during the acquisition of CT scans. No intravenous or oral contrast material was administered. Emission scans from the skull vertex to the toes were obtained starting mean 67 minutes (range, 55 to 86 min) after the intravenous administration of mean 7 mCi (range, 2 to 10 mCi) of ^{18}FDG. The acquisition time for PET was 2 minutes per table position. Images were reconstructed with attenuation-corrected ordered-subset expectation maximization with 2 iterations and 8 subsets using emission scans and CT data.

CI

Patients in the present study underwent CI studies, which were performed within a week of PET/CT either before or after therapy. CI studies included ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy, chest radiography, diagnostic CT of the chest and abdomen, and locoregional MRI. ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy was obtained with a dual-headed gamma camera (E.CAM; Siemens). Diagnostic CT was performed separately from PET/CT using a multidetector scanner (Aquilion V-detector; Toshiba Medical Systems) with the following setting; axial 4.0-mm × 4 modes; 120 kVp, automated electric current; 0.5-second tube rotation; and 5.0 mm/s table speed. Images were reconstructed with 10.0-mm slice thickness by means of a standard algorithm. Intravenous contrast agent was administered in all patients. Nonionic contrast material (Oiparomin 370 mg of iodine/mm; Konica-Minolta, Tokyo, Japan) was administered intravenously. The injection dose was 2.0 mL/kg of body weight with an upper limit of 100 mL. No oral contrast material was administered. Scan delay was set at 60 seconds after injection of contrast media. CT images were reviewed in lung, bone, and soft tissue windows in each patient. MRI of the primary site was performed using a 1.5 Tesla system (Signa Horizon; GE Medical Systems; Milwaukee, WI or Visart; Toshiba Medical Systems). Pulse sequences comprised T1-weighted spin echo (SE) or fast SE images, T2-weighted fast SE images, and also postcontrast T1-weighted SE images with fat suppression after injection of 0.1 mmol/kg of gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany).

Imaging Analysis

All images were reviewed and a diagnostic consensus was reached by 2 board-certified radiologists and a nuclear medicine physician who were unaware of any clinical or other radiologic information using a multimodality computer platform. In attempt to reduce bias of image analysis, review process was performed in random order and the interval between reviews of various studies on each patient was 2 weeks. PET and coregistered PET/CT images were analyzed with dedicated software (e-soft; Siemens). The initial review of the attenuation-corrected PET images was performed using transaxial, coronal, and sagittal planes. A pixel region of interest was outlined in the peak activity within regions of increased ^{18}FDG uptake and measured on each transaxial, coronal, and sagittal slice. For quantitative interpretations, maximum standardized uptake value (SUV max) was determined according to the standard formula, with activity in the region of interest given in Bq/mL/injected dose in Bq/weight (kg). However, time decay correction for whole-body image acquisition was not conducted.

Image Interpretation

The presence or absence of nodal or distant metastasis was evaluated for study analysis. The assessment of the T stage was verified histopathologically using specimens obtained by surgical resection of the primary tumors in all patients. For bone tumors, T1 is assigned when the tumor is less than or equal to 8 cm in greatest dimension and T2 is assigned when the tumor is greater than 8 cm in greatest dimension. For soft tissue tumor, T2b is assigned when the deep tumor is greater than 5 cm in greatest dimension. The reference standard of nodal and distant metastases was histologic examination in 15 patients and confirmation of an obvious progression in size of the lesions on follow-up examinations in 35 patients. The reviewers recorded the presence or absence of nodal or distant metastasis and nodal stations and metastatic organs for each modality. For diagnosing bone marrow metastasis, bone marrow biopsy was used as the reference standard in all patients. The presence or absence of abnormal uptake at a site where bone marrow biopsy had been performed was also recorded. Focal ^{18}FDG uptake was considered to be abnormal when it was substantially greater than that of the surrounding normal tissue. The SUV max of the lesion was categorized by comparing with that of normal adjacent tissue: slight uptake was assigned when the SUV max of the lesion was less than 1.5 times that of surrounding normal adjacent tissue; moderate uptake was assigned when the SUV max of the lesion was greater than or equal to 1.5 times but less than 3.0 times that of surrounding normal adjacent tissue; marked uptake was assigned when the SUV max of the lesion was greater than or equal to 3.0 times that of

surrounding normal adjacent tissue. Lymph nodes with abnormal uptake were deemed positive for metastases even when they were smaller than 10.0 mm in short axis nodal diameter. Lung nodules without abnormal uptake but depicting multiple well-defined or ill-defined nodules throughout parenchyma on the chest CT were considered to be positive for metastases. For interpretation of abnormal nodes on CI, the presence of lymph nodes greater than 10.0 mm in short axes was considered positive.

Statistical Analysis

All valuables were assessed on patient-by-patient basis. The McNemar test was used for paired comparisons between 3 modalities. To address the problem of multiple comparisons, Bonferroni correction was applied. Statistical analysis was performed with the SPSS version 11 software program (SPSS Inc, Chicago, IL).

RESULTS

In 50 patients, there were 26 bone sarcomas (52%) and 24 soft tissue sarcomas (48%, Table 1). Among 20 Ewing sarcomas, 8 tumors were bone origin and 12 tumors were soft tissue origin. All patients had increased ^{18}FDG uptake of the primary lesion [average SUV max ± standard deviation (SD); 7.6 ± 3.7: range; 1.7 to 19.0]. Clinical T stages of primary staging tumors (n = 40, 80%) were as follows: T1 (n = 12, 24%), T2 (n = 15, 30%), and T2b (n = 13, 26%). Nodal metastases in 5 patients (10%) and distant metastases in 10 patients (20%) were confirmed by pathologic examinations using biopsy specimens. For suspected nodal metastases in 2 patients (4%) and suspected distant metastasis in 14 patients (28%), diagnosis was confirmed by an obvious progression in size of the lesions on follow-up examinations. The mean follow-up period was 8 months (range, 0 to 14 mo).

TABLE 1. Patient Characteristics

Parameter	Value (%)
Age	
Mean ± SD	13 ± 4
Range	3-17
Sex	
M/F	26 (52)/24 (48)
Primary site	
Bone tumor	26 (52)
Femur	8 (16)
Tibia	8 (16)
Rib	4 (8)
Vertebra	2 (4)
Others*	4 (8)
Soft tissue tumor	24 (48)
Back	6 (12)
Head and neck	4 (8)
Thigh	3 (6)
Groin	2 (4)
Chest wall	2 (4)
Calf	2 (4)
Others†	5 (10)
Histologic diagnosis	
Ewing sarcoma	20 (40)
Osteosarcoma	18 (36)
Synovial sarcoma	5 (10)
Rhabdomyosarcoma	3 (6)
Fibrosarcoma	1 (2)
Epithelioid sarcoma	1 (2)
Pleomorphic MFH	1 (2)
Angiosarcoma	1 (2)

The numbers of the parentheses are percentages.
*Others include mandible (n = 2), ilium (n = 1), and humerus (n = 1).
†Others include abdomen (n = 1), abdominal wall (n = 1), scalp (n = 1), and hand (n = 1).
MFH indicates malignant fibrous histiocytoma.

Among 7 patients with nodal metastasis, the lesion was found only in soft tissue sarcomas: Ewing sarcoma (n = 2), synovial sarcoma (n = 2), rhabdomyosarcoma (n = 2), and angiosarcoma (n = 1). Using CI, nodal metastasis was correctly assigned in 46 patients (92%). On the other hand, nodal metastasis was correctly diagnosed by PET/CT in 48 patients (96%) and by PET in 43 patients (86%, Table 2). The average SUV max ± SD of nodal metastasis was 6.5 ± 1.0 (range, 4.9 to 9.5). One patient was understaged by PET/CT, 2 patients by PET, and 3 patients by CI, respectively (Table 3). Lymph node, which could not be discriminated from the adjacent primary tumor, was a cause of an understage by all modalities. The causes of an understage on CI were due to lymph nodes whose diameter of the short axis were less than 8 mm. The causes of nodal understage by PET were due to a lack of FDG avidity or inability to localize the activity to a lymph node. PET/CT revealed 1 patient with an overstage, while overstaged patients were identified by PET (n = 5) and by CI (n = 1). Reason for an overstage was due to inflammatory reactive lymph nodes on PET/CT, PET, and CI. There was no significant difference found in diagnostic accuracy of nodal metastasis between 3 modalities. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were summarized in Table 2.

Among 24 patients with distant metastasis, the lesion was correctly assigned in 43 patients (86%) with PET/CT. The average SUV max ± SD of distant metastasis was 4.2 ± 0.5 (range, 3.0 to 8.0). Distant metastasis was correctly diagnosed in 33 patients (66%) by PET and 35 patients (70%) by CI. The numbers of understaged patients were 7 on PET/CT, 17 on PET, and 15 on CI (Table 3). Reasons for patients of an understage by PET/CT were pleural or peritoneal metastases (n = 4), bone marrow metastasis (n = 2), and soft tissue metastasis (n = 1). The causes of an understage by PET were lung metastases (n = 6), soft tissue metastases (n = 6), pleural or peritoneal metastases (n = 3), and bone marrow metastasis (n = 2). The causes of an understage by CI were due to soft tissue metastases (n = 6), pleural or peritoneal metastases (n = 4), bone metastases (n = 3), and bone marrow metastasis (n = 2). The understage of distant metastases by PET/CT, PET, or CI was due to a lack of FDG avidity or inability to localize the activity to the lesion. Three patients with pleural or peritoneal metastases, 2 patients with bone marrow metastases, and

TABLE 2. Diagnostic Accuracy of Nodal and Distant Metastases in Pediatric Sarcomas

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT					
Nodal metastasis	6/7 (86)	42/43 (98)	6/7 (86)	42/43 (98)	48/50 (96)
Distant metastasis	17/24 (71)*†	26/26 (100)	17/17 (100)	26/33 (79)	43/50 (86)*†
PET					
Nodal metastasis	5/7 (71)	38/43 (88)	5/10 (50)	38/40 (95)	43/50 (86)
Distant metastasis	7/24 (29)*	26/26 (100)	7/7 (100)	26/43 (60)	33/50 (66)*
CI					
Nodal metastasis	4/7 (57)	42/43 (98)	4/5 (80)	42/45 (93)	46/50 (92)
Distant metastasis	9/24 (38)†	26/26 (100)	9/9 (100)	26/41 (63)	35/50 (70)†

Data of the parentheses are percentages.
Significant difference was found between 2 modalities by McNemar test with Bonferroni correction (*$P = 0.002$; †$P = 0.008$).
NPV indicates negative predictive value; PPV, positive predictive value.

1 patient with soft tissue metastasis were not detected by any modality. In 2 patients with bone marrow metastasis, the iliac crest where bone marrow biopsies had been performed was also negative on PET or PET/CT. No patients were overstaged by PET/CT, PET, or CI. Diagnostic accuracy of distant metastasis by PET/CT was significantly higher than that of PET ($P = 0.002$) or that of CI ($P = 0.008$). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were summarized in Table 2.

DISCUSSION

We have demonstrated a significant difference in diagnostic accuracy for the detection of distant metastasis by PET/CT, PET, or CI in pediatric sarcomas. The improvement of diagnostic accuracy in detecting distant metastasis can affect tumor stage before treatment.

The magnitude of diagnostic accuracy of PET/CT in detection of distant metastasis is unclear, because its efficacy and performance in staging of pediatric sarcomas is still limited.[12–16] In our study, 8 of the 50 patients (16%) had distant metastases detected by PET/CT which were not identified by PET alone or CI. McCarville et al[12] described that PET/CT was useful in identifying and localizing unusual sites of soft tissue and bony metastases not appreciated by CI. These results from the previous studies were consistent with our results.

TABLE 3. Diagnostic Performance in Nodal and Distant Metastases in Pediatric Sarcomas

Parameter	CI	PET	PET/CT
Nodal metastasis			
Correct	46 (92)	43 (86)	48 (96)
Overstaged	1 (2)	5 (10)	1 (2)
Understaged	3 (6)	2 (4)	1 (2)
Distant metastasis			
Correct	35 (70)	33 (66)	43 (86)
Overstaged	0	0	0
Understaged	15 (30)	17 (34)	7 (14)

The numbers of the parentheses are percentages.

There was a significant difference in diagnostic sensitivity, reflected by the 42% difference between PET/CT and PET and 33% difference between PET/CT and CI. PET/CT device permits sequential acquisition of anatomic CT and functional PET images in a single scanning session. Morphologic characterization of active lesions by PET/CT resulted in a lower percentage of equivocal interpretations compared with that of PET alone. This may have been causally linked to the improvement of sensitivity to detect distant metastases in the present study.

In the present study, correct diagnosis of distant metastasis was found in 43 patients (86%) by PET/CT. However, false negative results by an understage were caused by pleural or peritoneal metastasis, bone marrow metastasis, and soft tissue metastasis. Importantly, 3 patients with pleural or peritoneal metastasis, 2 patients with bone marrow metastases, and 1 patient with soft tissue metastasis were not detected by any modality. It is difficult to detect such distant metastases when the lesion gets smaller in size, owing to limited spatial resolution of PET or PET/CT. However, further studies are needed to be conducted for addressing the ability of PET or PET/CT to evaluate metastasis of pleura, peritoneum, bone marrow, and soft tissue in patients with pediatric sarcomas.

We failed to demonstrate a significant improvement in diagnostic accuracy to detect nodal metastasis by any modality. This may be explained by the small numbers of patients with nodal metastasis in the patient population. Lymph nodes whose diameter in the long axis less than 8 mm resulted in understaged patients on both PET and CI. In the present study, nodal metastasis was found in 7 patients (14%) who had soft tissue sarcomas in the primary sites. The causes of nodal understage by PET were due to a lack of FDG avidity or inability to localize the activity to a lymph node. Most histologic subtypes of sarcomas have a tendency to spread via the vascular system to the lung. However, a few histologic types including epithelioid sarcoma[17] and angiosarcoma[18,19] are often accompanied by nodal metastasis at the initial presentation. Although the exact reasons for rarity of nodal metastasis in sarcomas are unclear, further studies

are needed to clarify the clinical implications of PET/CT for diagnosing nodal metastasis in pediatric sarcomas.[20]

Our study has limitations. Patients enrolled in this study may be relatively small population for specific types of bone and soft tissue sarcomas. Our study was intended to examine the diagnostic accuracy of nodal and distant metastases as a potential role of PET/CT, compared with PET or CI. A study with a larger patient population would clarify the clinical impact of PET/CT on initial staging. In our study, all the lesions were not confirmed by pathologic examination. In 14 patients (28%) with suspected nodal and distant metastatic lesions, diagnosis was based on an obvious progression in size of the lesions on follow-up examinations. This might be sampling bias in the statistical analysis.

In summary, we demonstrate that the use of PET/CT in patients with pediatric sarcomas increases the diagnostic accuracy of distant metastasis compared with PET alone or CI. Further studies are required to assess the exact role and clinical impact of PET/CT on initial staging of pediatric sarcomas.

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ORIGINAL PAPER

Prediction of response and prognostic factors for Ewing family of tumors in a low incidence population

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Abstract
Purpose There is some unknown reason Ewing family of tumors (EFTs) is much less common on Asia and Africa than in the Western Caucasian population. This study analyzed the prediction of response and prognostic factors for Ewing family of tumors (EFTs) in an Asian population with a low incidence.
Methods We retrospectively reviewed 94 patients with EFTs between 1978 and 2006. Fifteen patients received local therapy only. Statistical analyses were performed for 79 patients, including those who received systemic chemotherapy, to identify factors related to chemotherapy responsiveness, event-free survival, and overall survival.
Results Of the 79 patients whose records were analyzed, the 5-year event-free rate and overall survival (OS) rate were 41 and 54%, respectively. The response rate to first-line chemotherapy was 61% in 70 patients with assessable lesions. A significant predictor of response was existence of a non-pelvic primary tumor ($P = 0.04$). Significant prognostic factors for OS were age, performance status, and metastases at the time of diagnosis ($P < 0.01$, respectively). Fifty-four patients had disease progression or recurrence after first-line treatment. The time to progression was 3.4 months after salvage treatment. Progression during first-line treatment was significantly associated with time to progression after salvage treatment ($P = 0.01$). All patients treated without chemotherapy in first-line treatment were recurred with poor prognosis.
Conclusion A non-pelvic primary tumor was a favorable predictor of responsiveness to chemotherapy. Chemoresistant patients might less benefit from second line chemotherapy. Chemotherapy in first-line treatment should not be omitted, even if primary tumor was extirpated completely.

Keywords Ewing family of tumors · Predictive factor · Prognostic factor · Response · Chemotherapy · Asian population

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Introduction

The Ewing family of tumors (EFTs) is a group of rare malignant tumors that mostly arise in bone, although a significant proportion of patients have soft tissue primaries. EFTs share histological, immunohistochemical and

cytogenetic characteristics; in the past, they have also been identified as Ewing sarcomas of bone or soft tissue, malignant peripheral primitive neuroectodermal tumors, primitive neuroepitheliomas or Askin tumors. (Miser et al. 1987) The vast majority of these tumors arise in children and young adults. The treatment of EFTs consists of a multidisciplinary approach including surgery, radiotherapy, and combination chemotherapy. During the past three decades, the prognosis of patients with EFTs has improved considerably, as shown in several clinical trials, mainly because of improved chemotherapy regimens (Burgert et al. 1990; Grier et al. 2003; Jurgens et al. 1988; Nesbit et al. 1990; Paulussen et al. 2001; Sluga et al. 2001).

For reasons that remain unknown, EFTs rarely occurs in Asian and African-American populations. The incidence of EFTs in Asian populations is lower than in Western populations (Guo et al. 1999) According to the Japanese Musculoskeletal Tumor Committee, 473 patients with EFTs of bone were registered during 1972–2003, the population of Japan is 120 million (The JOA Musculo-Skeletal Tumor Committee 2003a) Registration of malignant soft tissue tumor had starting from 2003, and 11 patients with EFTs of extra-osseous primary were registered in 2003. (The JOA Musculo-Skeletal Committee 2003b) Only three reports on the clinical outcome of Japanese patients with EFTs have been made (Obata et al. 2007; Ozaki et al. 2002; Yamada et al. 2006). It is controversy that the prognosis of patients with EFTs were relatively poorer compared with the major Euro-American studies. However, the recent report described the clinical outcome of patients with localized EFTs of bone were virtually equivalent (Obata et al. 2007).

Several clinical and biologic characteristics can assist in determining the prognosis and directing the intensity of therapy. These characteristics include age, primary tumor location and size, the presence or absence of metastases, the serum lactate dehydrogenase level, and the response to therapy (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). Although chemotherapeutic regimens and treatment strategies based on prognostic factors have been advanced, previous reports from developing countries indicate that similar results were not obtained in non-western population (Cardenas-Cardos et al. 1999; Jenkin et al. 2002; Villarroel et al. 1997) Thus, previously reported prognostic factors may not have the same influence on clinical outcome in patients belonging to populations with a low incidence, even if developed countries.

The aim of this study was to analyze the clinical characteristics and prognostic factors of EFTs in an Asian population with a low incidence.

Methods

Patients

We retrospectively reviewed the records of 94 patients with EFTs; all records were retrieved from a database of patients treated at the National Cancer Center Hospital (Tokyo, Japan) between September 1978 and April 2006. Two experienced musculo-skeletal pathologists (T.H. or K.S.) had diagnosed or reviewed all biopsy or surgical specimens after performing histological or immunohistochemical examinations. Molecular genetic studies such as PCR or FISH had been performed in cases with available specimens (Yamaguchi et al. 2005).

Treatment

In the present study, all the patients had received single modality therapy or various combinations of multi-modality therapy. Therapy for local control was individualized: surgery alone, radiation therapy alone or a combination of surgery and radiotherapy was performed, as suitable. Various systemic chemotherapy regimens were used. The 94 patients were classified into four groups according to their first-treatment systemic therapy regimen: group I consisted of patients treated with systemic chemotherapy, including vincristine, doxorubicin, and cyclophosphamide with or without actinomycin D; group II consisted of patients treated with multi-drug chemotherapy regimens, including vincristine, doxorubicin, actinomycin D and ifosphamide (VAIAdr) or vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide (VAdrC/IE); group III consisted of patients treated with systemic treatment including various chemotherapy regimens (Meyers et al. 1995, 1998) (T9 protocol, $n = 1$; T11 protocol, $n = 3$; T12 protocol, $n = 1$; vincristine plus etoposide plus cyclophosphamide plus cisplatin, $n = 2$; vincristine plus ifosfamide plus cisplatin, $n = 1$; doxorubicin plus cisplatin, $n = 2$; and etoposide plus cisplatin, $n = 1$); group IV consisted of patients receiving local therapy, including surgery or radiotherapy, without systemic chemotherapy. Some patients received high-dose consolidation therapy and peripheral blood stem cell transplantations or autologous bone marrow transplantations. Salvage treatment after recurrence was classified in the same manner as the first-line treatments.

Response assessment

Objective responses were evaluated according to the WHO criteria (World Health Organization 1979) Patients with no bidimensionally measurable lesions were considered ineligible for the objective response evaluation and were classified as not evaluable (NE). Systemic chemotherapy was

discontinued if clinical or radiological evidence of progression was present.

Statistical analysis

Event-free survival was measured from the first day of treatment until the observation of evidence of the first local, regional, or distant recurrence or progression of the tumor or the final day of follow-up without recurrence. Time to progression was measured from the first day of salvage treatment until disease progression or the final day of follow-up without disease progression, and the overall survival was measured from the first day of treatment until death or the final day of follow-up.

After excluding patients treated with local therapy only, pretreatment and treatment variables were investigated for their relation to event-free survival, and overall survival using both univariate and multivariate Cox regression analyses. The variables were selected after considering the possible effects on prognosis indicated by our experience and previous investigations (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). The variables were followed as: gender (male versus female), age (<15 years vs. 15≤), Eastern Cooperative Oncology Group performance status (0 vs. 1≤), primary tumor type (bone versus soft-tissue), primary tumor site (non-pelvic as extremities or axial sites versus intra-thoracic or abdominal), primary tumor size (≤8 cm vs. 8<), disease type (localized versus metastatic), serum lactate dyhydrogenase level (elevated vs. normal or unknown), serum neuron-specific enolase level (elevated vs. normal or unknown). The median event-free survival, time to progression, and overall survival were estimated using the Kaplan–Meier method. We used univariate and multivariate logistic regression analysis to assess the relationship between pretreatment and treatment variables and the response to chemotherapy. A statistical analysis was also performed to identify factors associated with the time to progression in patients treated with salvage therapy. The statistical analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, NC, USA), and the significance level was set at $P = 0.05$ (two-sided).

Results

Patient characteristics

Fifty-five men and 39 women with a median age at the time of diagnosis of 22 years (range 2–70 years) were enrolled in this study. The median Eastern Cooperative Oncology Group performance status was 0 (range 0–2). Forty-nine patients (52%) had primary tumors in bone and the others had primary tumors in soft tissue. The primary tumor sites are listed in Table 1. Sixty-four primary tumors (68%) were located in the trunk, and the remaining 30 tumors were located in extremities. The median largest dimension of the primary tumor was 7 cm (range 1.5–29 cm). Twenty-two patients had metastasis at the time of diagnosis. The median number of sites involved in each of the 22 patients with metastases was 2 (range 1–4).

Treatment

Of the 94 patients, 79 had received chemotherapy as their first-line treatment and the remaining 15 patients had been treated without chemotherapy (2 patients had undergone a combination of surgery and radiation therapy, 11 patients had undergone surgery, and 2 patients had undergone radiation therapy). When grouped according to their chemotherapy regimen, 4 patients received group I treatments, 62 patients received group II treatments, and 13 patients received group III treatments. Twenty-two patients received high-dose chemotherapy as their first-line chemotherapy treatment (1 patient in group I, 20 patients in group II, and 1 patient in group III). Among the patients that received chemotherapy, 9 patients received chemotherapy in an adjuvant setting (7 patients in group II, including 2 patients who received high-dose chemotherapy; and 2 patients in group III). Among the 79 patients who received chemotherapy, 23 patients also underwent a combination of surgery and radiation therapy, 26 patients underwent surgery, 17 patients underwent radiation therapy, and 13 patients did not undergo local therapy.

Response to chemotherapy

The response rate of 70 patients whose response to chemotherapy was assessable was 61% [95% confidence interval

Table 1 Sites of primary tumors in 94 patients with EFT

Tumor location	N	%
Osseous	49	
Skull	3	3.2
Trunk	13	13.8
Pelvic	14	14.9
Upper extremities	8	8.5
Lower extremities	11	11.7
Extra-osseous	45	
Head and neck	4	4.2
Trunk	8	8.5
Intra-thoracic	5	5.3
Intra-abdominal	17	18
Upper extremities	3	3.2
Lower extremities	8	8.5

(CI): 50 to 73%; 6 complete responses (CR), 37 partial responses (PR), 17 no changes (NC) or NE, and 10 progressive diseases (PD)]. Performance status, primary tumor size, and primary tumor site were significantly associated with response in univariate analysis. A multivariate logistic regression analysis indicated that the only significant predictor of response was a non-pelvic primary tumor [hazard ratio (HR), 3.01; 95% CI, 1.02–8.91; $P = 0.04$).

Outcome

Of the 79 patients, the 5-year event-free rate and overall survival rate were 41 and 54%. The median event-free survival and overall survival were 2.0 and 6.1 years, respectively (Fig. 1). Among the 57 patients without metastasis, the 5-year event-free rate and overall survival rate were 47 and 68%, respectively. And the 22 patients with metastasis, the 5-year event-free rate and overall survival rate were 30 and 37%, respectively. Age, primary tumor size, primary tumor site, and disease type were significantly associated with event-free survival in univaliate analysis. And a multivariate Cox regression analysis disclosed that metastasis at the time of diagnosis was a significant adverse prognostic factor of event-free survival ($P = 0.02$, Table 2). Age, primary tumor size, performance status, and disease type were significantly associated with OS in univariate analysis. And Cox regression analysis disclosed significant adverse prognostic factors for OS were an age ≥15 years, a performance status ≥1, and metastasis at the time of diagnosis, respectively ($P < 0.01$, Table 2).

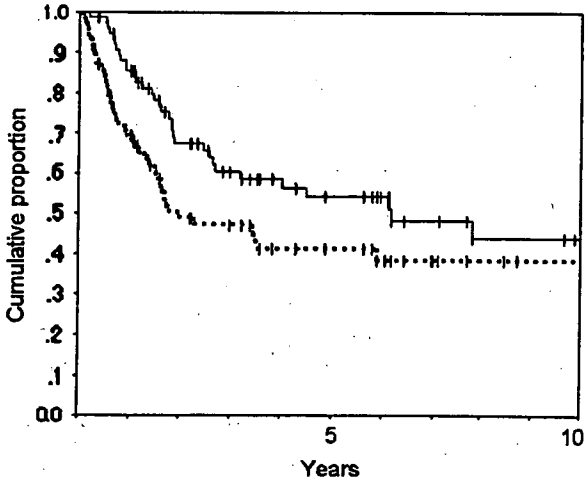

Fig. 1 Kaplan–Meier analysis of event-free survival (*dotted line*) and overall survival (*solid line*) in 79 patients who received chemotherapy. The *vertical bars* indicate censored cases

Salvage treatment

Of the 94 patients, 54 had received second line treatment for disease progression or recurrence. The median number of disease sites was 1 (range 1–3). The most common disease sites were the lung ($n = 24$), bone ($n = 15$), primary tumor site ($n = 11$), lymph node ($n = 7$), liver ($n = 5$), peritoneum ($n = 4$), soft-tissue ($n = 4$), and brain ($n = 2$). The majority of patients (85%) had received chemotherapy, and eight patients had received local therapy—including one patient who had undergone surgery. When grouped according to their chemotherapy regimen, 4 patients received group I treatments, 21 patients received group II treatments, and 21 patients received group III treatments, including 5 patients who received high-dose chemotherapy as a second line treatment (2 patients in group II, 3 patients in group III). The time to progression was 3.4 months after second line treatment. Progression during first-line treatment was significantly associated with time to progression after second line treatment (HR, 2.56; 95% CI, 1.21–.39; $P = 0.01$). The duration of the event-free survival was not significantly associated with the time to progression.

After second line treatment, 53 patients had developed progression. In these patients, 37 patients had received third line treatment including 20 patients had been treated by chemotherapy, 1 patients received group I treatments, 3 patients received group II treatments, and 16 patients received group III treatments. The other 17 patients had been treated by local therapy, 13 patients received radiation therapy, 4 patients received surgery. After third line treatment, 12 patients had been treated with chemotherapy and 7 patients had received local therapy in forth line treatment. Although 5 patients had received further treatment, all heavily treated patients had died.

Table 2 Multivariate analyses in 79 patients treated with chemotherapy

Variables	Event-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Metastasis at the time of diagnosis	2.34	1.16–4.72	0.02	2.71	1.31–5.65	<0.01
Age ≥ 15	–	–	–	4.76	1.60–14.2	<0.01
PS ≥ 1	–	–	–	2.91	1.55–5.43	<0.01

HR Hazard ratio, 95% CI, 95% confidence interval, *PS* ECOG performance status

Patients treated without chemotherapy in first-line treatment

In this study, 15 patients did not receive chemotherapy as part of their first-line treatments. The median age of these patients was 39 years (range 20–53 years). None of these patients had metastasis, and most of the patients (87%) had extra-osseous primary tumors. Two-thirds of the patients had a primary tumor size $\leq$80 mm. Nine patients had pelvic primary tumors, and only two patients had primary tumors in their extremities. A univariate analysis indicated that age, percentage of extra-osseous primary tumor sites, and percentage of pelvic primary tumor sites were significantly different among these 15 patients, compared with the other 79 patients. Two-thirds of these cases were admitted during the last 5 years of the study period. Regrettably, all patients had recurred, 13 patients had developed systemic recurrence and the other had local recurrence. The median time to recurrence was 9.4 months. The most common systemic disease sites was lung ($n = 6$), liver ($n = 5$), bone ($n = 4$), lymph nodes ($n = 3$), and miscellaneous ($n = 2$). In 13 patients with systemic recurrence, all patients had received group II treatment, including 5 patients had received additional local therapy (3 patients in radiation therapy and 2 patients in surgery). Despite chemotherapy in group II was performed for systemic recurrence, 12 of 13 patients had died and only 1 patient survived over 2 years after systemic recurrence. In patients with local recurrence (intra-thoracic and lower extremities in each patient), they had received group II treatment. Although patient with intra-thoracic tumor had progression again, the patient treated with group III treatment and survives over 2 years after local recurrence. The other patient survives over 1 year without recurrence. The median overall survival of these patients was 2.9 years, significantly shorter than that of the other 79 patients ($P = 0.03$, log-rank test).

Discussion

This retrospective study revealed that predictive factor of response in first-line chemotherapy and the progressive disease in first line chemotherapy was associated with outcome of second line treatment. The prognostic factors and prognosis in EFTs patients with low incidence may be similar to that of patients in previous reports. This study suggested that appropriate timing of systemic chemotherapy was important to achieve good prognosis, even if local therapy as surgery had successful in patients with localized disease of EFTs.

The incidence of EFTs in Asian countries is generally lower than that of Caucasian populations (Guo et al. 1999). Previous studies have described the background characteristics and treatment results in Japanese populations, which have a low incidence of EFTs (Obata et al. 2007; Ozaki et al. 2002; Yamada et al. 2006). Two studies of EFTs were small sample size less than 20 patients, and the largest study of EFTs of bone included 243 patients. Recent study suggested the there was no considerable differences in clinical background in patients with EFTs of bone. (Obata et al. 2007) When comparing the present study with reports from Western countries, the present study showed a higher frequency of soft-tissue primary tumors. Our hospital is a specialist orthopedic cancer referral center, and the present study describes no small sample to be reported in an Asian population. Differences among populations are difficult to judge because of selection biases. Previous studies reporting different frequencies of genetic aberrations may explain the different incidences and prognoses among populations (de Alava et al. 1998; Ozaki et al. 2002). We had insufficient material for statistical analyses of any possible relation between genetic alteration in our patients' tumors and their prognosis.

Limitations of this study were retrospective nature and the considerable heterogeneity of the treatment regimens. However, the majority of the patients had received multidrug-chemotherapy regimens consisting of VAIAdr or VAdrC/IE. Thus, the treatment outcome among the patients who received chemotherapy, adjusted for the presence of metastasis, was probably representative.

Advances in systemic chemotherapy have generally contributed to the improvement of treatment results (Sluga et al. 2001). In the present study, some of the patients were treated without chemotherapy, within the last 5 years. These patients were relatively older and had higher incidences of soft-tissue and pelvic primary tumors. Although none of these patients had metastatic disease at the time of their diagnosis, the prognosis of the patients without chemotherapy was clearly poorer. Present study demonstrates that even in patients with small primary tumors had been completely extirpated with sufficient margin, appropriate timing of systemic chemotherapy has an important role for cure. Population with low incidence leads to less experienced physicians. However, EFTs arouses from various site and adult patients with atypical primary tumors have a particularly poor prognosis. Therefore, promoting of multimodality treatment strategy and education for physicians will improve clinical outcome.

Although it is not a true prognostic factor that can be assessed at the time of diagnosis, the radiologic response to initial chemotherapy appeared to be a strong predictor of overall survival. (Sluga et al. 2001) The present study indicated that patients with non-pelvic primary tumors responded well to chemotherapy. Thus, this favorable subset of patients with EFTs may have a better prognosis. Previous report attributed the poor prognosis in pelvic primary

tumors to difficulties in local therapy, especially surgical resection (Catterill et al. 2000). This problem associated with primary site will not be solved easily. Biological and molecular characteristics may be explored among patients with pelvic primary tumors, and new molecular targeted therapy should be developed to prolong survival in this group.

The prognosis of patients with relapsed disease is poor. Many reports have investigated chemotherapy regimens that can be effective in producing temporary disease control in second line settings (El Weshi et al. 2004; Shankar et al. 2003) In addition, high-dose chemotherapy and peripheral blood stem cell transplantation have been studied as second line treatments for patients with relapsed EFTs (Burdach et al. 1993; Stewart et al. 1996). Although a subgroup of patients benefit from these treatments, both the role and indications for second line treatment remain uncertain. A previous study reported that patients with a short first remission derived little benefit from second line therapy. (Shankar et al. 2003) Although the duration of remission was not associated with the time to progression in the present study, the patients who had progressive diseases during their first-line treatments were significantly associated with a poor outcome after second line treatment. Therefore, patients with these poor prognostic factors should receive palliative therapy, rather than aggressive second line treatment.

Previous reports mostly including EFTs of bone have analyzed prognostic factors such as metastatic disease, patient age, tumor size, and pelvic primary tumor location (Bacci et al. 2000; Catterill et al. 2000; Obata et al. 2007; Rodriguez-Galindo et al. 2003; Sluga et al. 2001). Although the outcome of treatment in the present study was slightly worse than that reported in Western populations, the prognostic factors for event-free and overall survival identified in the present report were similar to those mentioned in previous reports. The current staging system (localized or metastatic) is clearly important for categorizing patients. In addition, risk-adapted strategies using prognostic factors should help to clarify the best treatment strategy in each risk group.

Much remains to be done to improve the outcome of patients with EFTs, especially in countries with low incidences. Because of the difficulty of conducting clinical trials in populations with low incidences, joining nationwide treatment study or international study group would be important to develop a common staging system and common treatment guideline in worldwide.

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Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan

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KEYWORDS
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Survey;
PORT meta-analysis

Summary To investigate the practice process of postoperative radiation therapy for non-small-cell lung cancer (NSCLC) in Japan. Between April 2002 and March 2004, the Patterns of Care Study conducted an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data on treatment process of 627 patients with NSCLC who received radiation therapy were collected. Ninety-nine (16%) patients received postoperative radiation therapy between 1999 and 2001 (median age, 65 years). Pathological stage was stage I in 8%, II in 17%, IIIA in 44%, and IIIB in 20%. The median field size was 9 cm × 11 cm, and median total dose was 50 Gy. Photon energies of 6 MV or higher were used for 64 patients, whereas a cobalt-60 unit was used for five patients. Three-dimensional conformal treatment was used infrequently. Institutional stratification influenced several radiotherapy parameters such as photon energy and planning target volume. Smaller non-academic institutions provided worse quality of care. The study confirmed continuing variation in the practice of radiotherapy according to stratified institutions. Outdated equipment such as Cobalt-60 units was used, especially in non-academic institutions treating only a small number of patients per year.

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1. Introduction

Postoperative radiation therapy (PORT) decreases the risk of local–regional recurrence in patients with resected non-small-cell lung cancer (NSCLC) [1–3]. However, reduction in the frequency of local recurrence has not translated into a survival benefit in most studies. In 1998, the impact of PORT for NSCLC was analyzed in a meta-analysis of phase III trials [4]. After publication of the PORT meta-analysis, which emphasized deleterious effects in patients receiving PORT for completely resected N0-1 cases, much of the clinical focus on adjuvant therapy shifted to chemotherapy [5,6]. Thus, the role of PORT for patients at high risk for locoregional failure such as those with N2 disease remains unclear. Adjuvant chemotherapy trials have often permitted use of PORT as an option for patients with N2 disease [5,7]. One clinical study reported promising results for combined PORT and chemotherapy for patients with pathologic stage II or IIIA disease [8]. The results of these trials imply that PORT delivered using modern radiotherapy techniques may potentially provide a survival advantage for selected high-risk patients.

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice for cancer patients during a specific period [9,10]. In April 2002, the PCS started a nationwide survey for patients with NSCLC treated with radiation therapy in Japan. In the present report, we provide results of analyses focused on patients who received PORT for NSCLC during the study period. The objectives of this study were to reveal clinical practice patterns regarding PORT after publication of the PORT meta-analysis and to assess variation in clinical practice according to stratified institutions.

2. Materials and methods

Between April 2002 and March 2004, the PCS conducted a national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format and performed an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data collection consisted of two steps of random sampling. Prior to random sampling, all institutions were classified into one of four groups. Criteria for stratification have been described elsewhere [10]. Briefly, the PCS stratified Japanese institutions as follows: A1, academic institutions such as university hospitals or national/regional cancer center hospitals treating $\geq$ 430 patients per year; A2, academic institutions treating <430 patients; B1, non-academic institutions treating $\geq$130 patients per year; and B2, <130 patients. The cut-off values in number of patients treated per year between A1 and A2 institutions and B1 and B2 institutions, respectively, were increased from those used in the previous PCS study because of the increase in the number of patients treated by radiation therapy in Japan [10]. Eligible patients had 1997 International Union Against Cancer (UICC) stage I–III NSCLC that was treated with PORT between 1999 and 2001, a Karnofsky Performance Status (KPS) >50 prior to start of treatment, and no evidence of other malignancies within 5 years. The current PCS collected specific information on 627 patients (A1:157, A2:117, B1:214, B2:139) who were treated with radiation therapy between 1999 and 2001. Of those, 99 (16%) patients (A1:15, A2:17, B1:45, B2:22) who received PORT constitute the subjects of the present analysis. The practice of PORT was investigated by reviewing items in each medical chart such as demographics, symptoms, history, work-up examinations, pathology, clinical stage, treatment course including radiation therapy, surgery and chemotherapy, and radiotherapy parameters. In addition, simulation films and linacgraphy of each patient were also reviewed by surveyors.

The PCS surveyors consisted of 20 board-certified radiation oncologists. For each institution, one radiation oncologist visited and surveyed data by reviewing patient charts. In order to validate the quality of collected data, the PCS utilized an internet mailing-list among all surveyors. In situ real-time check and adjustment of data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data "unknown". We combined "missing" and "unknown" in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with missing or unknown values were included when both the percentage and significance value were calculated. Statistical significance was tested by the χ^2 test. A p-value less than 0.05 was considered statistically significant. Overall survival was assessed from the day of surgery and was estimated by the Kaplan–Meier product limit method using the Statistical Analysis System, Version 6.12.

3. Results

3.1. Patient and tumor characteristics

Patient and clinical tumor characteristics are shown in Table 1. Of the 99 patients who received PORT, 32 were treated at academic institutions and 67 at non-academic institutions. The proportion of patients with NSCLC who received PORT was significantly higher in non-academic institutions than in academic institutions (19% versus 12%, $p = 0.013$). Overall, median age was 65 years (range, 39–82), and the male to female ratio was 4:1. Ninety-three percent of patients had a KPS greater than or equal to 80%. Preoperative examinations included chest computed tomography (CT) in 97% of patients, bronchoscopy in 87%, brain CT or magnetic resonance imaging (MRI) in 75%, abdominal CT in 75%, bone scintigraphy in 83%, and mediastinoscopy in 4%. The primary tumor site was the upper lobe in 62 patients, middle lobe in 7, and lower lobe in 27. The remaining 2 patients had a primary tumor near the border of the upper and middle lobes that involved both lobes, and they were allocated to "others". Peripheral tumors were twice as common as central tumors. When tumors were analyzed by laterality, the ratio of right to left side primary site was 1.5. Clinical T- and N-classifications were T1 in 28 patients, T2 in 35, T3 in 24, T4 in 11, and N0 in 33, N1 in 19, N2 in 40, and N3 in 6, resulting in clinical stage I in 27 patients, II in 14, IIIA in 41, and IIIB in 16. The numbers less than 99 are due to missing or unknown data.

Table 1 Patient and tumor characteristics

No. of patients	99
Men	79
Women	20
Age (years)	
Median	65
Range	32–89
% KPS ≥ 80	93
Preoperative work-up (%)	
Chest CT	97
Bronchoscopy	87
Brain CT or MRI	75
Abdominal CT	75
Bone scan	83
Mediastinoscopy	4
Primary tumor site	
Upper lobe	62
Middle lobe	7
Lower lobe	27
Other	2
Missing	1
Tumor location	
Central	30
Peripheral	60
Missing	9
Laterality	
Left lung	38
Right lung	59
Missing	2
Clinical T factor	
TX	1
T1	28
T2	35
T3	24
T4	11
Clinical N factor	
NX	1
N0	33
N1	19
N2	40
N3	6
Clinical stage	
IA	14
IB	13
IIA	7
IIB	7
IIIA	41
IIIB	16
Missing	1

KPS, Karnofsky performance status score.

3.2. Surgery and tumor pathology characteristics (Table 2)

The primary surgical procedure was a lobectomy in 78 patients, pneumonectomy in 12, and segmentectomy in 9.

Table 2 Surgical procedure and tumor pathology characteristics

Type of surgery	
Lobectomy	78
Pneumonectomy	12
Segmentectomy	9
Histopathology	
Squamous cell carcinoma	47
Adenocarcinoma	43
Large cell carcinoma	7
Adenosquamous carcinoma	2
Surgical margin status	
Negative	55
Positive	31
Missing	13
Pathological T factor	
T1	22
T2	35
T3	23
T4	18
Missing	1
Pathological N factor	
N0	15
N1	19
N2	56
N3	4
Missing	5
Pathologically involved mediastinal nodes (%)[a]	
No. 1	16
No. 2	23
No. 3	26
No. 4	34
No. 5	28
No. 6	5
No. 7	34
No. 8	12
Pathological stage	
IA	4
IB	5
IIA	9
IIB	8
IIIA	45
IIIB	20
Missing/unknown	8

[a] Nearly half of the data for this item were "missing/unknown".

Among all 99 patients, complete resection was accomplished for 55 patients. Surgical margin status was positive in 31 patients. Histopathology was squamous cell carcinoma in 47 patients, adenocarcinoma in 43, large cell carcinoma in 7, and adenosquamous carcinoma in 2. Predominantly involved mediastinal nodes confirmed pathologically to contain tumor were No. 7 (34%), No. 4 (34%), No. 5 (28%), and No. 3 (26%) according to the lymph node mapping system of the Japan Lung Cancer Society [11], although nearly half of the data for this item were "missing/unknown." The pathological T-

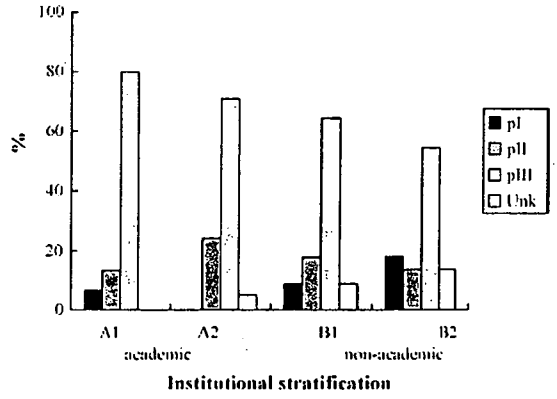

Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

Table 3 Pathological stage in patients with complete surgery according to the stratified institution

Pathological stage	Institutional stratification				Total
	A1	A2	B1	B2	
I–II	2	4	8	4	18
III	5	6	18	8	37
Total	7	10	26	12	55

and N-classifications were pT1 in 22 patients, pT2 in 35, pT3 in 23, and pT4 in 18, and pN0 in 15 patients, pN1 in 19, pN2 in 56, and pN3 in 4. Pathological stage was stage I in 9 patients, II in 17, IIIA in 45, and IIIB in 20, respectively. The proportion of pathological stage III patients tended to be higher in large academic institutions (Fig. 1, $p = 0.13$). Breakdown of pathological stage in 55 patients who underwent complete surgery according to the stratified institution group was shown in Table 3. As for the proportion of pathological stage III patients, no significant difference was observed between institutions.

3.3. Radiotherapy parameters (Table 4)

A CT-simulator was used for planning for 26 patients. Ninety-one patients were treated with opposed AP-PA fields, and field reduction during the course of radiotherapy was done for 48%. Three-dimensional treatment was used in only 2 patients. Photon energies of less than 6 MV were used for 34 patients (34%). Dose prescription by isodose line technique was performed for only 8 patients (8%). The median field size was 9 cm × 11 cm, and the median total dose was 50 Gy. The planning target volume included the ipsilateral hilus in 80%, ipsilateral mediastinum in 86%, contralateral mediastinum in 68%, contralateral hilus in 9%, ipsilateral supraclavicular region in 30%, and contralateral supraclavicular region in 22%. Institutional stratification was found to influence several radiotherapy parameters. A photon energy of 6 MV or higher was used for 73% of patients in A1, 77% in A2, and 80% in B1 institutions, whereas it was used for only 23% of patients in B2 institutions (Fig. 2, $p < 0.0001$). A Cobalt-60 unit was used only in 5 B2 institutions. The planning target volume included the contralateral mediastinum for more than 70% of patients in A1 to B1 institutions, whereas it was included in only 46% of patients treated in B2 institutions ($p = 0.011$).

Table 4 Radiotherapy parameters

Simulation method	
CT-simulator	26
X-ray simulator	38
X-ray simulator + CT	26
Missing	7
Treatment technique	
AP-PA	91
Oblique	2
Three-field	1
Three-dimensional conformal	2
Other	2
Missing	1
Photon energy	
60 Co	5
<6 MV	29
≥6 MV	64
Missing	1
Dose prescription	
Isodose line	8
Point	91
Total dose	
≤3000 cGy	1
3001–4000 cGy	6
4001–5000 cGy	49
5001–6000 cGy	37
6001–7000 cGy	6
Missing	1
Median total dose (cGy)	5000
All fields treated each day (%)	83
Median field size (cm)	
Left-right	9 (range, 5–23)
Cranio-caudal	11 (range, 5–20)
Field reduction during radiotherapy (%)	48
Field included (%)	
Ipsilateral hilus	80
Ipsilateral mediastinum	86
Contralateral mediastinum	68
Contralateral hilus	9
Ipsilateral supraclavicula	30
Contralateral supraclavicula	22

3.4. Use of chemotherapy

Thirty patients (31%) received systemic chemotherapy. For 21 patients, chemotherapy and PORT were administered concurrently, mainly using a platinum-based, two-drug combination. For 9 of the 30 patients, platinum-based chemotherapy was used as induction therapy. Oral fluorouracil was used for 9 patients.

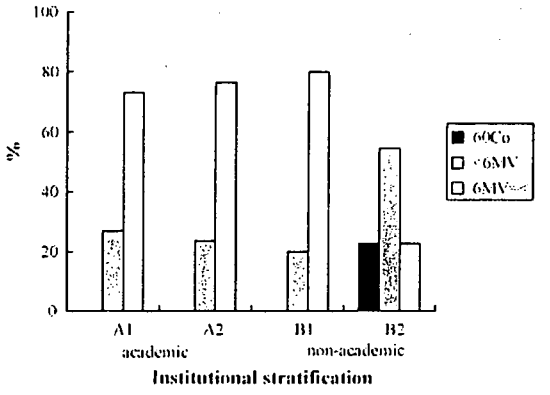

Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

3.5. Failure pattern and preliminary clinical outcome

The site of first failure was local in 6, regional in 5, and distant in 31. Of the patients who developed failure, the median time to first failure was 7 months. Although the current PCS has limitations in terms of outcome analysis due to a short follow-up period and significant variations in follow-up information according to institutional stratification [10,12], overall survival for the entire group was 88% at 1 year and 63% at 3 years, with a median follow-up period after PORT of 1.7 years.

4. Discussion

The results of the present PCS reflect national practices for PORT for NSCLC in Japan. However, when interpreting our data, it is important to note that they were limited to patients who received radiation therapy. We have no information about patients who did not receive radiation therapy after surgery. Thus, we have no data concerning the percentage of patients who underwent radiation therapy after surgery. Analysis of the national practice process for all patients with NSCLC in the adjuvant setting is beyond the scope of this study.

All eligible patients in this study received radiation therapy after publication of the PORT meta-analysis that emphasized deleterious effects in patients receiving PORT, especially for patients with completely resected N0-1 disease [4]. Since then, the clinical focus on adjuvant treatment has largely shifted to chemotherapy, which has become part of the postoperative standard of care for patients with NSCLC [5,6,8]. In the United States, use of PORT has substantially declined due to the lack of proven survival benefit [13]. However, PORT was still incorporated as an option in recent clinical trials that recruited patients with pathological N2 disease [5,7]. The recent analysis of Surveillance, Epidemiology, and End Results (SEER) data in the United States demonstrated that PORT was associated with improved survival for patients with N2 disease [14,15]. In addition, a recent clinical study has reported promising results for combined PORT and chemotherapy using modern radiotherapy techniques [7,8]. Thus, the current clinical question is whether adjuvant chemotherapy combined with PORT improves survival for patients at high risk for locoregional failure compared with adjuvant chemotherapy alone. Taking all of the evidence together, we conclude that PORT still plays an important role in the adjuvant setting. We believe that this PCS study provides basic data of current practice regarding PORT in Japan.

Results of the present study demonstrated that patients who received PORT accounted for 16% of all patients with NSCLC who received radiation therapy in Japan between 1999 and 2001. Of all 99 patients, 65 had pathological stage III disease (45, stage IIIA; 20, stage IIIB). Using a median field size of 9 cm × 11 cm, a median total dose of 50 Gy was delivered mainly through opposed AP-PA fields. Three-dimensional conformal treatment was infrequently used. Field size reduction during the course of radiotherapy was done for almost half of the patients. A dedicated CT-simulator was used for 26 patients. The PORT meta-analysis was criticized because the authors included several old studies in which a cobalt machine was used for radiotherapy. It was pointed out that suboptimal administration of PORT using outdated techniques counterbalanced the beneficial locoregional effects of PORT treatment in the meta-analysis [16]. Because of potential pulmonary/cardiac toxic effects of mediastinal radiotherapy, PORT should be delivered with modern radiotherapy techniques using CT-based three-dimensional conformal treatment planning, a technique with which target volumes and normal tissue constraints are precisely defined. Although the patients included in this PCS survey were treated between 1999 and 2001, the modern radiotherapy era, 34% of all patients were treated using photon energies <6 MV, including five patients who were treated using a cobalt machine. Institutional stratification influenced several radiotherapy parameters in PORT for NSCLC. As shown in the previous report for small-cell lung cancer in Japan [17], smaller non-academic institutions (B2) provided a lower quality of care for their patients. Planning target volume typically included the ipsilateral hilus, ipsilateral mediastinum, and contralateral mediastinum in A1 to B1 institutions, whereas the contralateral mediastinum was included for only 46% of patients treated in B2 institutions. Although there is controversy concerning prophylactic nodal irradiation in the setting of definitive radiation therapy, PORT for patients with pN2 NSCLC should include the contralateral mediastinum. Proportion of patients with pathological stage I–II who underwent complete surgery did not differ between stratified institution groups. Thus, it was considered that omission of treating the contralateral mediastinum in B2 institutions was not caused by unbalance in stage distribution. We speculate that this discrepancy in care was due mainly to the extremely small number of radiation oncologists in B2 institutions. We also found that obsolete equipment such as Cobalt-60 units were still used, especially in non-academic institutions treating only a small number of patients per year. The proportion of patients treated with 6 MV or higher photon energies was significantly higher in A1 to B1 institutions than in B2 institutions. A Cobalt-60 unit was used only in B2 institutions. The present study again confirms differences in the practice of radiotherapy according to institutional stratification status.

We consider that the structure of radiation oncology is a domestic problem specific to each country. The results represent intrinsic problems with the structure of radiation therapy in Japan. Considering the current immaturity of the Japanese structure of radiation oncology, PCS still perform an important role in monitoring structure and process, as well as providing essential information not only to medical staff and their patients but also to administrative policy makers.

5. Conclusions

Through the audit survey and subsequent data analyses, the PCS established nationwide basic information on the practice of PORT for NSCLC in Japan. Even after the publication of the PORT meta-analysis, PORT was used for a considerable proportion of patients receiving radiotherapy. However, this PCS documented that outdated modalities such as cobalt-60 units were still used in small non-academic institutions during the study time frame. Thus, the current PCS confirmed the continuing existence of variation in the practice of radiotherapy according to institution stratification.

Conflict of interest

We have no conflict of interest in connection with this paper.

Acknowledgments

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Phase I Study of Cisplatin Analogue Nedaplatin, Paclitaxel, and Thoracic Radiotherapy for Unresectable Stage III Non-Small Cell Lung Cancer

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Background: The standard treatment of unresectable stage III non-small cell lung cancer is concurrent chemoradiotherapy in patients in good general condition, but where the optimal chemotherapeutic regimen has not been determined.
Methods: Patients with unresectable stage III non-small cell lung cancer received nedaplatin (80 mg/m^2) and paclitaxel on day 1 every 4 weeks for 3–4 cycles and concurrent thoracic radiotherapy (60 Gy/30 fractions for 6 weeks) starting on day 1. The dose of paclitaxel was escalated from 120 mg/m^2 in level 1, 135 mg/m^2 in level 2 to 150 mg/m^2 in level 3.
Results: A total of 18 patients (14 males and 4 females, with a median age of 62.5 years) were evaluated in this study. Full cycles of chemotherapy were administered in 83% of patients in level 1, and in 50% of patients in levels 2 and 3. No more than 50% of patients developed grade 4 neutropenia. Transient grade 3 esophagitis and infection were noted in one patient, and unacceptable pneumonitis was noted in three (17%) patients, two of whom died of the toxicity. Dose-limiting toxicity (DLT), evaluated in 15 patients, noted in one of the six patients in level 1, three of the six patients in level 2 and one of the three patients in level 3. One DLT at level 2 developed later as radiation pneumonitis. Thus, the maximum tolerated dose was determined to be level 1. The overall response rate (95% confidence interval) was 67% (41–87%) with 12 partial responses.
Conclusion: The doses of paclitaxel and nedaplatin could not be escalated as a result of severe pulmonary toxicity.

Key words: non-small cell lung cancer – chemoradiotherapy – paclitaxel – nedaplatin – pneumonitis

INTRODUCTION

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA disease with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions, and/or involvement of the mediastinal or supraclavicular lymph nodes, and occult systemic micrometastases (1). Concurrent chemoradiotherapy, recently shown to be superior to the sequential approach in phase III trials, is the standard medical care for this disease (2–4). Chemotherapy regimens used concurrently with thoracic radiotherapy in these randomized trials were second-generation platinum-based chemotherapy, such as combinations of cisplatin, vindesine and mitomycin, cisplatin and vinblastine, and cisplatin and etoposide. The third-generation cytotoxic agents including vinorelbine and paclitaxel, which provided a better survival rate in patients with disseminated disease than second-generation agents, must be reduced when administered concurrently with thoracic radiotherapy (5–7). Thus, the optimal chemotherapy for concurrent chemoradiotherapy has not been established.

Nedaplatin (*cis*-diammine-glycolate-O,O′-platinum, II, 254-S) is a second-generation platinum derivative that has an

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antitumor activity comparable to that of cisplatin but is less toxic to the kidney as shown in preclinical experiments (8). Nedaplatin produced a promising response rate for NSCLC, especially for squamous cell lung cancer (9,10). In addition, this drug can be safely administered with full-dose thoracic radiation, as shown in patients with esophageal cancer (11). Paclitaxel is another promising drug for the treatment of stage III NSCLC, as shown by the favorable response rate and survival in phase II trials in combination with platinum and thoracic radiation (6,7).

Our previous study of the nedaplatin and paclitaxel combination in patients with systemic disease showed that the recommended dose of these drugs was 80 mg/m^2 and 180 mg/m^2, respectively, repeated every 3–4 weeks. A promising response rate of 55% was achieved in patients with squamous cell lung cancer (12). The objectives of the present study were primarily to evaluate the toxicity of nedaplatin, paclitaxel and concurrent thoracic radiotherapy and determine the recommended dose of these two drugs for a phase II trial, and secondarily to observe the antitumor effect of this regimen in patients with stage III NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease indicated for curative radiotherapy; no previous treatment; measurable disease; the percentage of the normal lung volume receiving 20 Gy or more (V_{20}) (13) expected to be 30% or less; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status (14) 0 or 1; adequate bone marrow function (12.0 × 10^9/L ≥ white blood cell (WBC) count ≥ 4.0 × 10^9/L, neutrophil count ≥ 2.0 × 10^9/L, hemoglobin ≥ 10.0 g/dL and platelet count ≥ 100 × 10^9/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ twice the upper limit of the normal value), and renal function (serum creatinine ≤ 1.5 mg/dL and creatinine clearance ≥ 60 mL/min); and a PaO_2 of 70 torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan, and radionuclide bone scan.

Treatment Schedule

Paclitaxel and nedaplatin were administered as previously described (12). Briefly, paclitaxel diluted in 500 ml of 5% glucose was administered as a 3-h intravenous infusion with premedication consisting of dexamethasone, ranitidine and diphenhydramine. Nedaplatin diluted in 250 ml of normal saline was administered in a 1-h intravenous infusion. This treatment was repeated every 4 weeks for 3–4 cycles. The dose of paclitaxel was escalated as follows: 120 mg/m^2 (level 1), 135 mg/m^2 (level 2), and 150 mg/m^2 (level 2). The dose of nedaplatin was 80 mg/m^2 through the levels 1–3.

Thoracic radiation therapy was given with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV. The total dose of 60 Gy was delivered at a single dose of 2 Gy once daily Monday through Friday for 6 weeks without interruption beginning on day 1 of the chemotherapy. Three-dimensional conformal radiotherapy technique was used in all patients. The gross target volume (GTV) included the primary lesion (GTV1) and involved lymph nodes whose short diameter was 1 cm or larger (GTV2) based on conventional chest X-ray and CT scans. The clinical target volume (CTV) consisted of CTV1 and CTV2, identical to GTV1 and GTV2, respectively, and CTV3, the ipsilateral hilum and bilateral mediastinum area. The contralateral hilum was excluded from the CTV. The supraclavicular fossa was also excluded unless it was involved. The planning target volume (PTV) for the initial dose up to 40 Gy consisted of CTV1-3 with the superior and inferior field margins extended to 1–2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The PTV for the boost 20 Gy included only CTV1-2 based on the second CT scans with the same margins. The spinal cord dose was limited to 44 Gy by using oblique parallel opposed fields.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations and a chest X-ray were performed once a week during the course of treatment. Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count <3.0 × 10^9/L, neutrophil count <1.5 × 10^9/L, platelet count <100 × 10^9/L, serum creatinine level ≥1.6 mg/dL, infection ≥ grade 2, elevated hepatic transaminase level or total serum bilirubin ≥ grade 2, pneumonitis ≥ grade 2, peripheral neuropathy, musculoskeletal pain ≥ grade 3, fever ≥ 38°C, or performance status ≥ 2. Chemotherapy was terminated if the toxicities did not

recover within 2 weeks. The doses of nedaplatin and paclitaxel were reduced by 25% in all subsequent cycles if any of the dose-limiting toxicities (DLTs) defined below were noted. The dose of nedaplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: fever $\geq 38^{\circ}C$, infection $\geq$ grade 2, esophagitis of grade 3, performance status ≥ 3, or radiation pneumonitis was suspected. Thoracic radiotherapy was terminated if radiation pneumonitis that required corticosteroid administration was noted, or radiotherapy was not completed within 60 days. Both chemotherapy and thoracic radiotherapy were terminated if any of the following was noted: disease progression, any of the grade 4 non-hematological toxicities except abnormal electrolytes, performance status of 4, patient refusal to receive subsequent treatment, protocol violation, or patient death of any cause. Granulocyte colony-stimulating factor and antibiotics were administered if febrile neutropenia was noted.

DLT, Maximum Tolerated Dose (MTD), and Recommended Dose For Phase II Trials

The DLT was defined as a grade 4 leukopenia, grade 4 neutropenia lasting 7 days or longer, febrile neutropenia, platelet count $<20 \times 10^9$/L, grade 3 or a more severe non-hematological toxicity other than nausea, vomiting and transient electrolyte abnormality, and treatment termination before two cycles of chemotherapy and thoracic radiotherapy were completed. Dose levels were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If none to two of the six patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If three or more of the six patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15).

Study Design, Data Management and Statistical Analyses

This study was designed as a phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 2 years and a follow-up period of 3 years were planned. Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method (16). Overall survival time was measured from the date of registration to the date of death from any cause or last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression or death from any cause or last follow-up. Patients who were lost to follow-up without event were censored at the date of their most known follow-up. A confidence interval for the response rate was calculated using methods for exact binomial confidence intervals. Response rates among patients with squamous cell carcinoma and those with non-squamous carcinoma were assessed with the χ^2 test. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of The Patients

From October 2003 to July 2004, six patients were registered at dose level 1, eight patients at dose level 2 and five patients at dose level 3. Two patients at dose level 2 were excluded from the DLT evaluation, because they discontinued receiving the treatment early because of disease progression and anaphylactic shock, respectively. Initially, DLT was noted in only two of the six patients at dose level 2, and therefore, patient registration at dose level 3 was started. However, severe radiation pneumonitis developed 5 weeks after the end of radiotherapy in another patient at dose level 2 and this pneumonitis was counted as DLT. Thus, because DLT was finally noted in three of the six patients at dose level 2, patient registration at dose level 3 was stopped. One patient at dose level 3 was found to be ineligible because the radiation treatment planning showed that the V_{20} exceeded 30%. The patient did not receive the current treatment and was excluded from the analysis. Thus, a total of 18 patients were subjects of this study and their detailed demographic characteristics are listed in Table 1.

Treatment Delivery

The planned three to four cycles of chemotherapy were administered in 83% of patients in level 1 and in 50% of patients in levels 2 and 3. Radiation delivery was generally well maintained and it did not differ among the three dose levels (Table 2).

Toxicity, DLT and MTD

Hematological toxicity was generally mild. No more than 50% of patients developed grade 4 neutropenia, and no one developed grade 2 or higher thrombocytopenia (Table 3). Non-hematological toxicity other than lung toxicity was also well tolerated. One patient developed transient grade 3 esophagitis and grade 3 infection not associated with neutropenia, which were considered DLTs. Another patient developed grade 4 anaphylactic shock 1 min after the second cycle infusion of paclitaxel, but soon recovered with fluid