Table 3. Process of thoracic radiation therapy for patients with limited-stage small-cell lung cancer

Median total dose (Gy)	50
Median spinal cord dose (Gy)	42
Use of CT simulator (%)	40
Three-dimensional conformal therapy (%)	12
Beam energy (%)	
^{60}Co	1.4
<6 MV	10.8
≥6 MV	88
Median field size (cm)	12 × 14
Field reduction during treatment (%)	61
IRB-approved protocol treatment (%)	4.4
Twice-daily radiotherapy (%)	44
Prophylactic cranial irradiation (%)	8.6
Area included in planning target volume (%)	
Ipsilateral hilus	96
Ipsilateral mediastinum	96
Contralateral mediastinum	84
Contralateral hilus	17
Ipsilateral supraclavicula	25
Contralateral supraclavicula	15
Systemic chemotherapy (%)	93
Concurrent chemotherapy and thoracic radiotherapy (%)	68

Abbreviations: CT = computed tomography; IRB = institutional review board.

Comparison of preliminary outcomes between studies

There are known limitations in survival analyses in this type of retrospective survey study. Still, preliminary outcome data in the two studies could be compared. Overall survival rates of the entire patient pool in each study are shown in Fig. 1. Two-year survival rates in PCS 95-97 and PCS 99-01 were 34% and 45%, with a median follow-up of only 11 months in both studies, respectively. Median survival times of the patient pools in PCS 95-97 and PCS 99-01 were 14 and 17 months, respectively. These differences did not reach a statistically significant level.

Table 4. Process of thoracic radiation therapy influenced by institutional stratification

	Stratification of institutions					
Characteristics	A1	A2	B1	B2	Total	*p*-value
Photon energy						0.0006
^{60}Co	0	0	0	2	2	
<6 MV	1	1	7	6	15	
≥6 MV	35	22	47	18	122	
Twice-daily fractionation used						0.0012
Yes	18	11	28	4	61	
No	18	12	26	22	78	
Treatment planning						0.011
Use of CT simulator (%)	52	65	34	17	40	
Prophylactic cranial irradiation used						0.0002*
Yes	7	2	3	0	12	
No	29	17	48	24	118	
Unknown/missing	0	4	3	2	9	

Abbreviation: CT = computed tomography.
* A1 vs. A2–B2; $p = 0.0073$.

Table 5. Comparison of treatment modalities between two studies

Background and treatment process	PCS 95-97 ($n = 174$)	PCS 99-01 ($n = 139$)
SCLC/all lung cancer (%)	16	18
Median age (y)	65	69
KPS > 70 (%)	70	73
Stage III (%)	87	88
Median total dose (Gy)	50	50
Photon energy <6 MV or ^{60}Co (%)	20	12
Use of CT-simulator (%)	NA	40
Twice-daily thoracic radiotherapy (%)*	15	44
Chemotherapy used (%)	92	93
Concurrent chemoradiation (%)†	34	68
Prophylactic cranial irradiation (%)‡	1.9	8.6
Survival at 2-years (%)	34	45

Abbreviations: PCS = Patterns of Care Study; SCLC = small-cell lung cancer; KPS = Karnofsky Performance Status; CT = computed tomography; NA = not available.
* $p < 0.0001$ by chi-square test.
† $p < 0.0001$ by chi-square test.
‡ $p = 0.0045$ by chi-square test.

DISCUSSION

Results of the present PCS reflect national treatment trends for TRT for patients with LS-SCLC in Japan between 1999 and 2001. Through this second nationwide audit survey and data analysis, PCS established the general patterns of care for patients with LS-SCLC in Japan. Results also show the influence of the structure of radiation oncology on the process of TRT and how state-of-the-art cancer care supported by clinical trial results has penetrated into the national practice process during the study period.

During the study period, TRT for LS-SCLC constituted less than one fifth of all radiation therapy for patients with lung cancer. This result was similar to data from the United States (6). Use of such staging studies as chest CT, bone scan, and PET scan for patients with SCLC was in line with guidelines (7) and very similar to the report from the United States (6). A PET scan in clinical use was still scarce. Only a small fraction of patients participated in clinical trials similar to those observed in the United States. In Japan, twice-daily TRT was used more frequently and PCI was used less frequently compared with the United States. However, it should be noted that subjects of the PCS in the United States were treated between 1998 and 1999, preceding the results of key studies that supported the use of twice-daily radiation therapy and PCI.

The study shows that more suitable photon energies were used in TRT at academic institutions. Thirty-one percent of patients in B2 institutions were treated with a linear accelerator with less than 6 MV or a ^{60}Co machine that did not meet the standard of care for equipment to treat patients with lung

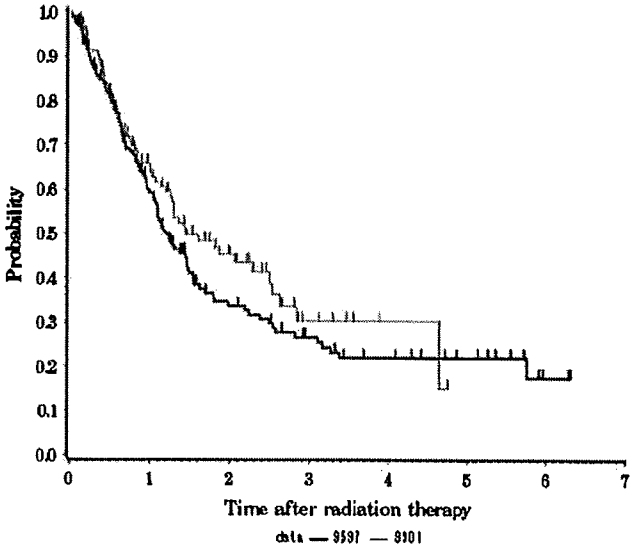

Fig. 1. Kaplan-Meier estimate of overall survival of patients with Stages I–III small-cell lung cancer surveyed in the 1995–1997 (dark line) and 1999–2001 (bright line) Patterns of Care Studies in Japan.

cancer, although this rate decreased from PCS 95-97 (>40% in B2) and was somewhat favorable compared with postoperative radiation therapy for patients with lung cancer in the same period (8). The availability of CT simulators was greater than 50% in academic institutions, but only one third in B1 and even lower in B2 institutions. In modern radiation therapy, CT-based treatment planning is essential for TRT to achieve optimal target coverage while reducing the dose to normal tissue. Twice-daily TRT was used more frequently for patients in A1 to B1 institutions than patients in B2 institutions. The PCI was used for 19% of patients in A1 institutions, but only 4.9% of patients in the remaining institutions. Although the general quality of radiation oncology improved from PCS 95-97, results of the present study show that institutional stratification still influences the structure and process of radiotherapy, such as availability of CT simulators, the flexibility of external beam energy selection, and use of evidence-based cancer care in Japan.

During the past 20 years, survival prolongation in patients with LS-SCLC was attained mainly by clinical trials that studied some aspect of radiation therapy, such as integration of TRT (9, 10), optimization of timing and fractionation of TRT (11), and introduction of PCI (12). The TRT is an essential component of the standard management of patients with LS-SCLC. Two meta-analyses showing the advantage of the addition of TRT to systemic chemotherapy, published in 1992 (9, 10), preceded our first national survey (PCS 95-97). In PCS 99-01, although 43% of all surveyed patients were older than 70 years and 23% of all patients had KPS of 70% or less, 93% of all patients received chemotherapy. This percentage is very similar to that in PCS 95-97 (2, 3).

When interpreting our data, it is important to note that they are limited to patients who received TRT as part of their overall treatment regimen. However, these two surveys showed that use of systemic chemotherapy was reasonably high in Japanese practice. Based on several studies published during the past 10 years, CCRT up front has emerged as a standard of care generating the highest survival rates (11, 13, 14). A landmark study supporting twice-daily TRT was published in 1999 after the previous PCS 95-97 (11). In that study, Turrisi *et al.* (11) showed a significant benefit in 5-year survival rate with the use of twice-daily TRT (45 Gy in 1.5 Gy fractions twice daily) concurrent with chemotherapy compared with once-daily TRT (45 Gy in 1.8 Gy fractions every day). Use of CCRT in PCS 99-01 (68%) was twice as high as in PCS 95-97 (34%). Similarly, there was a notable increase in the use of twice-daily TRT after PCS 95-97. In the present study, 44% of patients received twice-daily TRT, nearly three times as high as in PCS 95-97. Although it is still unclear whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose of 60–70 Gy delivered by using more standard fractionation, it seems that diffusion of twice-daily TRT to Japanese practitioners was rapid. It seems likely that the marked increase in use of twice-daily TRT with concurrent chemotherapy in Japan contributed to the widespread use (95%) of inpatient treatment in PCS 99-01. In general, once-daily treatment is better accepted for outpatient care, whereas twice-daily scheduling is convenient for the care of inpatients, but at greater cost. Marked increases in the use of CCRT and twice-daily TRT indicates greater acceptance of these treatment modalities by radiation oncologists across Japan.

However, PCI has yet to be systematically adopted in Japanese practice. Despite the 1999 publication of another landmark trial that showed the survival advantage of PCI for complete responders (12), only 8.6% of all patients received this intervention. At the time of PCS 95-97, the role of PCI had not been established and it was used for only 1.9% of all patients (2). Before the present survey, it was expected that the percentage of patients who received PCI would be greater on the basis of the meta-analysis. Although a slight increase in use of PCI was observed, the rate was still extremely low in Japan. Information about the number of complete responders was outside the audit. However, a complete response rate of at least 50% is expected for study subjects (15). Whether this is caused by the small number of radiation oncologists in Japan or the small number of patients who received radiation therapy for cancer treatment is unknown. We reported previously that the number of full-time radiation oncologists is low, especially in nonacademic institutions in Japan (2). According to cancer statistics in Japan, radiation therapy was used for only 11.3% of all patients with cancer in 1999 compared with medical (27.5%) and surgical treatment (69.9%) (16). It is not clear why evidence-based PCI has not yet been widely accepted in Japan as opposed to the rapid diffusion of CCRT and twice-daily TRT in clinical practice. It appears that physicians in Japan hesitate to use PCI, and their patients are reluctant to receive PCI even if it is beneficial. Results of the ongoing third national survey in Japan will be particularly interesting in this regard.

Nonsignificant survival improvement in patient outcome was observed between PCS 95-97 and PCS 99-01. The current PCS has limitations in terms of outcome analysis because of a short follow-up period, significant variations in follow-up information according to institutional stratification (4, 17), and difficulties in outcome survey. One of the ultimate goals of the PCS is to determine how structure and processes of radiation therapy affect patient outcomes, including local control, survival, and quality of life. However, since 2006, personal information is strictly protected by law and outcome surveys are difficult to perform in Japan, even for patients with cancer. Cancer is not yet a reportable disease in Japan. Currently, limitations in data accumulation concerning patient outcomes in this type of survey encouraged us to develop new health care data collection systems and linkages among systems that make systematic recording and analysis of structure/process and outcome data part of routine quality monitoring (Japanese National Cancer Database, funded by the Ministry of Health, Labor, and Welfare Japan).

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Local Control of Regional and Metastatic Lesions and Indication for Systemic Chemotherapy in Patients with Non-Small Cell Lung Cancer

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ABSTRACT

Systemic chemotherapy is the mainstay of treatment in patients with advanced non-small cell lung cancer. Local control of regional and metastatic lesions may be needed before systemic therapy can be started in patients with pleural effusions or bone or brain metastases. The indication for systemic chemotherapy depends on the symptoms and performance status of the patient. In addition, a risk assessment considering complications such as hemodynamic and respiratory compromise by effusions, pathological bone fractures, and neurologic deterioration caused by brain metastases is critical in selecting which patients should receive first-line systemic chemotherapy before local therapy, although predictive factors for these complications have not yet been established. Chemotherapy has been considered to have only a limited role in the treatment of patients with pleural effusions and brain and bone metastases, but recently developed anticancer agents have shown substantial antitumor effects in these types of patients with a good general condition. *The Oncologist* 2008:13(suppl 1):21–27

INTRODUCTION

The majority of patients with non-small cell lung cancer (NSCLC) develop distant metastases either by the time of the initial diagnosis or during recurrence following surgery for the primary lesion. While systemic chemotherapy is the mainstay of treatment in patients with advanced NSCLC, local control of regional and metastatic lesions may be needed before systemic therapy can be used in patients with pleural effusions, bone metastases, or brain metastases. The general rule about whether local control should precede systemic chemotherapy varies according to the performance status (PS) of a patient and the responsiveness of the tumor to chemotherapy. If possible, systemic chemotherapy should be employed early in patients with malignant lymphoma and germ-cell tumors, as they are highly responsive and can be cured even at an advanced stage. It is unlikely that small-cell lung cancer can be cured, but because it responds well to chemotherapy, chemotherapeutic agents are frequently given prior to local therapy. In patients with advanced NSCLC, however, local therapy is often required before chemotherapy is administered because of the limited efficacy of chemotherapy in these patients.

PLEURAL EFFUSIONS

Malignant pleural effusions are a common clinical problem in patients with neoplastic disease, and may be the first presenting sign in as many as 10% of patients. Indeed, approximately 15% of lung cancer patients present with malignant pleural effusions at diagnosis [1]. In fact, lung cancer is the most common cause of malignant pleural effusions,

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accounting for 17%–56% of cases [2]. Dyspnea is the most common symptom in patients with malignant effusions, occurring in more than half of cases, followed by cough and chest pain, although 5%–25% of patients have no respiratory complaints [3].

PS is significantly associated with survival in patients with pleural effusions [4]. Pleural effusions have been treated with the aim of palliation because NSCLC patients with pleural effusions are advanced stage by definition; massive effusions can cause hemodynamic and respiratory compromise, and the development of a symptomatic pleural effusion can drastically alter the quality of life and survival of patients [2]. Recently, however, as a result of the availability of ultrasound, computed tomography (CT), and positron emission tomography scans, NSCLC patients with small, asymptomatic pleural effusions can now be identified, and the treatment approach can be reconsidered in the setting of systemic disease control because relatively effective chemotherapy regimens have been developed.

It should be noted that pleural effusions can affect drug pharmacokinetics: methotrexate administered i.v. to patients with massive effusions is slowly released from third-space fluid, resulting in prolongation of the terminal half-life of the drug in the plasma, and potentially also increasing its toxicity [5, 6]. Similarly, levels of 5-fluorouracil decline rapidly in the plasma, but persist for longer in the effusion [7]. The pharmacokinetics of other drugs in patients with effusions are poorly studied, but drugs may accumulate in effusions and only slowly be redistributed throughout the body [8].

Patients with a small pleural effusion causing no symptoms can be treated with primary systemic chemotherapy, although there is a risk that the effusion will become symptomatic and require therapy. Patients with effusion-related dyspnea and those with a massive pleural effusion should be treated with a therapeutic thoracentesis; a large-volume thoracentesis allows rapid relief of symptoms in many patients. If systemic disease progression is a significant concern, an initial thoracentesis may create a window of opportunity in which to gain control over symptoms before starting chemotherapy. For patients whose effusions recur rapidly, more aggressive interventions may be required to achieve durable palliation, including chest tube drainage followed by chemical pleurodesis, and thoracoscopy with talc poudrage [8]. If patients gain durable palliation and are restored to a good PS by these treatments, then systemic chemotherapy is indicated. If not, their condition is suggestive of terminal-stage disease with a very short life expectancy.

Patients with NSCLC and pleural effusions are commonly included in chemotherapy clinical trials while they retain a good PS. Although the control of effusions by systemic chemotherapy has rarely been described, the efficacy of chemotherapy in treating effusions is considered to be comparable to the systemic response to chemotherapy. A retrospective study of 34 NSCLC patients with malignant pleural effusions treated with cisplatin, ifosfamide, and irinotecan showed that effusions disappeared for >4 weeks in 13 (38%) patients, while a partial response in measurable primary or metastatic lesions was obtained in 25 (66%) patients [9]. Active mutations of epidermal growth factor receptor (EGFR) have been detected in samples of pleural effusion fluid, and in patients with NSCLC they were associated with a clinical response to gefitinib, an EGFR tyrosine kinase inhibitor [10]. These results suggest that, in the near future, investigation of pleural effusion fluid could be important in selecting a chemotherapy regimen in patients with advanced NSCLC.

Brain Metastases

Lung cancer is the most common primary source of brain metastases, which develop in 10%–64% of lung cancer patients during the clinical course of the disease [11]. Even among newly diagnosed, asymptomatic patients with potentially operable NSCLC, routine brain scans identify brain metastases in 3%–10% of patients [12]. It is believed that the incidence of brain metastases is increasing as a result of an aging population, better control of extracerebral disease by more active systemic therapy, and better detection of small metastases following the development of imaging modalities such as magnetic resonance imaging (MRI).

Two thirds of cancer patients found to have brain metastases at autopsy had experienced neurologic symptoms resulting from the metastases, with only 10% of patients diagnosed by CT or MRI between 1973 and 1993 being asymptomatic [13]. Symptoms include headache, focal weakness, nausea, vomiting, and altered mental status. Seizures occur in about 20% of patients with brain metastases. When lung cancer patients are routinely screened, only 10% present to the physician with symptoms of brain metastases [12]. Thus, although the exact percentage is unknown, there are many patients with NSCLC who have brain metastases but no neurologic symptoms. The prognosis for patients with brain metastases is influenced largely by PS, age, and control of the primary and extracranial tumors. Whole brain radiotherapy (WBRT), with or without stereotactic irradiation, has been the treatment of choice for most patients with brain metastases, with a median survival time of 3–6 months after radiotherapy. This relatively short survival is related to progressive systemic disease rather than the brain metastases [11]. Therefore, systemic chemotherapy can be administered in many patients with brain metastases and is in fact important for their survival.

Chemotherapy has not been thought to have a major role in the treatment of patients with brain metastases because of a poor PS in many cases and the prevailing belief that the blood–brain barrier (BBB) may play a role in limiting delivery of chemotherapeutic agents to the central nervous system. However, the accumulation of contrast medium during CT or MRI assessments and the development of edema surrounding metastatic lesions suggest that tumor-induced vessels do not possess normal anatomical and physiological properties, and the BBB at the site of established brain metastases may be partly disrupted [14]. While one study demonstrated that the concentration of cisplatin in the brain metastases of patients who received the agent before surgery did not differ from that found in extracranial metastases [15], another study found that paclitaxel concentration in brain metastases was in the therapeutic range, while in brain tissue the concentration was below the limit of detection [16]. This observation is supported by objective response rates of brain metastases to systemic chemotherapy of 27%–50% in previously untreated patients with NSCLC, which are comparable to systemic response rates (Table 1) [17–23]. Gefitinib has also been shown to be effective against brain metastases arising from NSCLC; objective responses were obtained in 13 of 25 case reports of gefitinib use in such patients [24]. Thus, systemic chemotherapy is an important treatment option for NSCLC patients with brain metastases, as long as a good PS is maintained without neurologic symptoms.

The advantages of administering chemotherapy before radiotherapy can be summarized as follows: (a) it is useful to judge the tumor's response to chemotherapy; (b) radiotherapy decreases blood supply to the tumor and thus may hamper the ability of chemotherapeutic agents to reach the metastases; and (c) chemotherapy delivered before radiotherapy may be less toxic to the brain than chemotherapy after radiotherapy, because radiotherapy may open the BBB and allow the entry of potentially neurotoxic agents. Evidence for this is available for methotrexate treatment, and may also apply to other agents [25]. A randomized phase III trial of cisplatin plus vinorelbine followed by WBRT (arm A; $n = 86$) versus the same chemotherapy with early concurrent WBRT (arm B; $n = 85$) in NSCLC patients with brain metastases showed that the respective intracranial response rates evaluated after two cycles of chemotherapy were 27% and 33%, and that the overall response rates were 21% and 20%. The median survival time was 5.5 months in arm A and 4.8 months in arm B ($p = .83$). There was no difference between the arms in terms of hematologic and neurologic toxicities. These results suggest that chemotherapy is effective against brain metastases arising from NSCLC, and that the timing (early or delayed) of WBRT does not influence the survival of these patients [21].

Bone Metastases

Bone metastases are common in patients with lung cancer, with an incidence of 30%–55% at autopsy. These metastases are usually osteolytic, and are distributed mainly in

Table 1. Chemotherapy in previously untreated non-small cell lung cancer patients with brain metastases

Study	Chemotherapy regimen	*n* of patients	Response rate (%)		Median survival time (months)
			Intracranial	Systemic	
Minotti et al. (1998) [17]	CDDP + TNP	23	35	30	4.8
Crinò et al. (1999) [18]	CDDP + IFM + MMC	120	39	23	NA
	CDDP + GEM	123	41	37	NA
Franciosi et al. (1999) [19]	CDDP + ETP	43	30	75	7.4
Fujita et al. (2000) [20]	CDDP + IFM + CPT	30	50	62	12.6
Robinet et al. (2001) [21]	CDDP + VNR	86	27	35	5.5
Bernardo et al. (2002) [22]	CBDCA + VNR + GEM	20	45	45	7.6
Cortes et al. (2003) [23]	CDDP + PTX + VNR or GEM	25	38	50	4.9

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; CPT, irinotecan; ETP, etoposide; GEM, gemcitabine; IFM, ifosfamide; MMC, mitomycin-C; NA, not available; PTX, paclitaxel; TNP, teniposide; VNR, vinorelbine.

the spine, pelvis, ribs, and extremities. The most common symptom of bone metastases is pain, which is either diffuse or localized. It is characteristically described as dull and constant in presentation, worsening at night. The pain gradually increases in intensity, and can be exacerbated by certain movements or positions, such as standing, walking, or sitting [26]. However, up to 25% of patients with bone metastases are free of pain, and patients with multiple bone metastases typically report pain in only a few sites. The factors that convert a painless lesion to a painful one are unknown [27]. As bone destruction progresses, mechanical weakness and loss of structural integrity lead to pathological fracture; spinal instability, defined as mechanical instability in the spine related to extensive bone destruction [28]; cord compression, and hypercalcemia [26, 29]. The prognosis for patients with bone metastases varies among the different tumor types. The median survival time from diagnosis of bone metastases in patients with prostate cancer or breast cancer is measurable in years, whereas for lung cancer it is only 6–7 months [29]. The second most important prognostic factor in patients with bone metastases is PS; the median survival time for patients with a Karnofsky PS score of <50, 50–70, or 80–100 who received radiotherapy to the metastatic site was 2–3 months, 5 months, and 12 months, respectively [30, 31].

Bone destruction and its complications severely limit the activity and mobility of patients. For patients with a high risk for these complications, radiotherapy is the treatment of choice and orthopedic interventions may be necessary in some cases [26, 29].

Pathologic fractures occur in 8%–30% of all cancer patients, with the ribs, vertebrae, and long bones being the most frequent fracture sites [26, 29]. A long-bone fracture, especially when located at the proximal part of the femur, has a detrimental effect on the quality of life of patients with advanced cancer. Important factors in predicting an impending fracture of the long bones are pain that is exacerbated by movement and radiographic findings such as a predominantly osteolytic appearance, a large lesion, and axial cortical involvement [32, 33].

Spinal instability is the cause of back pain in 10% of patients with advanced cancer [26]. It can cause unbearable pain that is mechanical in origin, and frequently the patient is only comfortable when lying still [26]. Neither radiation therapy nor chemotherapy, even if successful in controlling the tumor, will alleviate the pain. As in the treatment of pathological fractures of the long bones, stabilization of the vertebral segments is required for pain relief [28]. However, major surgery is associated with significant morbidity and mortality, and good results can be obtained only in carefully selected patients. Percutaneous vertebroplasty provides rapid and effective relief from the pain associated with spinal instability.

Spinal cord compression occurs in 2%–5% of cancer patients [34]. The incidence varies with the type of cancer, and is 2.6% for NSCLC [35]. The cumulative incidence for all cancers decreases with age: it is 4.4% for patients aged 40–50 years, 3.9% for patients aged 50–60 years, 2.9% for patients aged 60–70 years, 1.7% for patients aged 70–80 years, and 0.5% for those aged >80 years [34]. About 60%–80% of spinal cord compressions occur in the thoracic region, 15%–30% in the lumbar region, and 10% in the cervical region. Multiple compression sites occur in approximately 7%–14% of cases [26, 34]. Early diagnosis and treatment are important for successful rehabilitation, but 48%–96% of patients present with motor weakness, bladder dysfunction, and inability to walk. In 83%–96% of patients, the first symptom is pain at the affected site, which may have been present from as little as 1 day to as long as 2 years, with a median duration of 8 weeks. It is generally exacerbated by coughing, sneezing, and straining, and typically increases in intensity over several weeks. Thus, the development of back pain in a cancer patient is a warning sign for possible spinal cord compression [26, 34].

Asymptomatic patients with bone metastases are potentially candidates for initial systemic chemotherapy, unless they show no risk factors for structural complications in radiographic assessments. These patients have been included in clinical trials of systemic chemotherapy; however, only limited information is available on the efficacy of chemotherapy for bone metastases, mainly because it is difficult to assess response to treatment in the bone, and bone metastases are defined as nontarget lesions in the Response Evaluation Criteria in Solid Tumors [36]. In patients with breast cancer, objective response rates of osteolytic lesions to standard chemotherapy regimens vary in the range of 20%–60% [37]. There are currently no reports on the objective response of bone metastases to chemotherapy in patients with NSCLC, but pain relief has been observed in 30%–61% of NSCLC patients receiving cisplatin-based chemotherapy, gemcitabine, or gefitinib [38-40].

Bisphosphonates, pyrophosphate analogues with a phosphorus–carbon–phosphorus (P–C–P)-containing central structure that promotes binding to the mineralized bone matrix, provide an additional treatment strategy for metastatic bone disease. Approximately 25%–40% of i.v. administered bisphosphonates are excreted by the kidney, and the remainder binds avidly to exposed bone mineral around resorbing osteoclasts, leading to inhibition of bone resorption and apoptosis of osteoclasts [26]. In addition to clinical use for hypercalcemia of malignancy, bisphos-

phonates are a routine treatment to prevent skeletal-related events (SREs) in patients with metastatic breast cancer and multiple myeloma. A recent meta-analysis evaluating randomized trials in these patients that lasted for 6 months or longer showed that bisphosphonates led to a significantly lower risk, versus placebo, for vertebral fractures (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.57–0.84), nonvertebral fractures (OR, 0.65; CI, 0.64–0.99), radiotherapy (OR, 0.67; CI, 0.57–0.79), and hypercalcemia (OR, 0.54; CI, 0.36–0.81). In contrast, trials of <6 months' duration did not show any significant results for any skeletal morbidity outcome [41]. In patients with NSCLC, however, the role of bisphosphonates in the treatment of bone metastases has been less investigated. A recent phase III trial of zoledronic acid, a new generation bisphosphonate that has 100-1,000 times the potency of pamidronate in vitro, showed that 4 mg zoledronic acid led to a significantly lower annual incidence of SREs (1.74 per year versus 2.71 per year; $p = .012$) and longer median time to first SRE (7.8 months versus 5.1 months; $p = .009$) compared with placebo in 773 patients with lung cancer and other solid tumors [42, 43]. There are no criteria regarding the indication and duration of bisphosphonate therapy in patients with NSCLC. Evidence of bone destruction on plain radiographs, which is suggestive of receiving a benefit of bisphosphonates in patients with breast cancer [44], also may be an important factor in patients with NSCLC.

The presence or absence of bone pain should not be a factor in initiating bisphosphonates in patients with breast cancer [44], but no reports are available on this issue in patients with NSCLC. Because a relatively long duration of treatment (>6 months) is required for patients to get a benefit from bisphosphonates, patient prognosis is considered another factor to determine the indication of this type of agent [26].

Treatment Algorithm

Pleural effusions, brain metastases, bone metastases, and their associated morbidities give rise to a vexing clinical problem in patients with advanced NSCLC. Approaches to treating these patients are illustrated in Figure 1. The use of systemic chemotherapy depends on the symptoms and PS of the patients. In addition, a risk assessment looking at complications is critical in selecting which patients should receive first-line systemic chemotherapy, although factors predictive of these complications have not yet been established. Chemotherapy has previously been considered to have only a limited role in the treatment of patients with pleural effusions and brain and bone metastases, but recently developed anticancer agents have been shown to have substantial antitumor effects in patients with a good general condition.

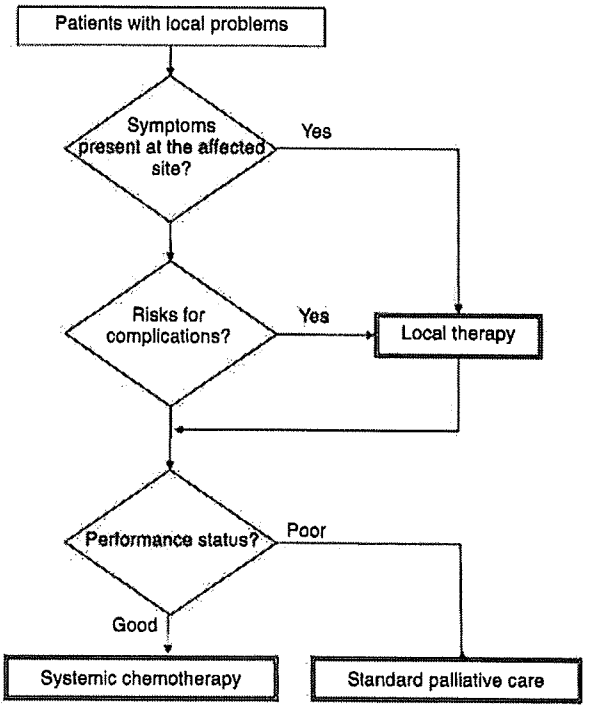

Figure 1. Treatment approaches for patients who have advanced non-small cell lung cancer with local problems.

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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
Non-small-cell lung cancer;
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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-

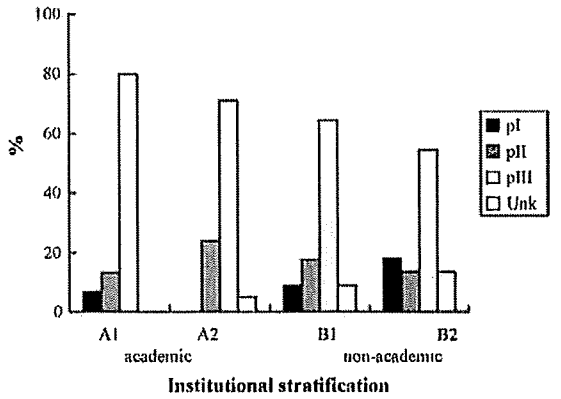

Fig. 1 Proportion of patients with pathologic stage III disease tended to be higher in large academic institutions ($p = 0.13$).

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

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

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 ($p = 0.011$).

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.

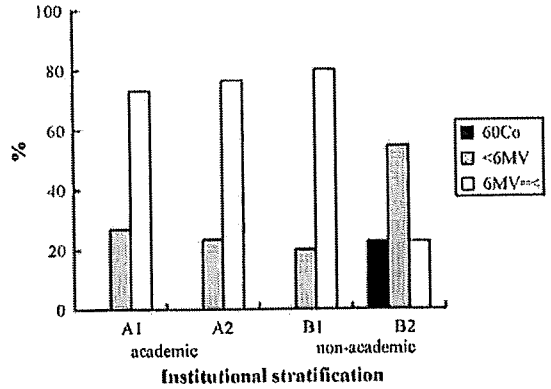

Fig. 2 A photon energy of 6 MV or higher was used for 73% of patients in A1 institutions, 77% in A2, and 80% in B1, whereas only 23% in B2 institutions ($p < 0.0001$). A Cobalt-60 unit was used only in B2 institutions.

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.

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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 $\times$ 10^9/L $\geq$ white blood cell (WBC) count $\geq$ 4.0 $\times$ 10^9/L, neutrophil count $\geq$ 2.0 $\times$ 10^9/L, hemoglobin $\geq$ 10.0 g/dL and platelet count $\geq$ 100 $\times$ 10^9/L), liver function (total bilirubin $\leq$ 1.5 mg/dL and transaminase $\leq$ twice the upper limit of the normal value), and renal function (serum creatinine $\leq$ 1.5 mg/dL and creatinine clearance $\geq$ 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 $\times$ 10^9/L, neutrophil count $<$1.5 $\times$ 10^9/L, platelet count $<$100 $\times$ 10^9/L, serum creatinine level $\geq$1.6 mg/dL, infection $\geq$ grade 2, elevated hepatic transaminase level or total serum bilirubin $\geq$ grade 2, pneumonitis $\geq$ grade 2, peripheral neuropathy, musculoskeletal pain $\geq$ grade 3, fever $\geq$ 38°C, or performance status $\geq$ 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 ≥ 38°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

Table 1. Patient characteristics

	n	(%)
Number of patients	18	
Gender		
male	14	(78)
female	4	(22)
Age		
median (range), years	62.5	(46–69)
PS		
0	11	(61)
1	7	(39)
Body weight loss		
< 5%	15	(83)
5–9%	2	(11)
≥ 10%	1	(6)
Clinical stage		
IIIA	10	(56)
IIIB	8	(44)
Histology		
adenocarcinoma	8	(44)
squamous cell carcinoma	6	(33)
non-small cell, not specified	4	(22)

PS, performance status.

replacement and oxygen therapy. This patient was excluded from DLT evaluation. One patient in level 1 and another patient in level 2 developed grade 4 pneumonitis after completion of two cycles of chemotherapy and thoracic radiotherapy and they died of the pneumonitis. The V_{20} and mean lung dose (MLD) of these patients were 23% and 30%, and 1341 cGy and 1675 cGy, respectively.

Table 2. Treatment delivery

Dose level	Level 1	Level 2	Level 3
	(*n* = 6)	(*n* = 8)	(*n* = 4)
Number of chemotherapy cycles			
3–4	5	4	2
2	1	3	1
1	0	1	1
Total radiation dose (Gy)			
60	6	7	3
50–59	0	1	0
NE	0	0	1
Radiotherapy delay (days)			
0–4	5	7	2
5–9	1	0	1
NE	0	1	1

NE, not evaluable.

Table 3. Toxicity in all patients

Dose level	Level 1 (*n* = 6)			Level 2 (*n* = 8)			Level 3 (*n* = 4)		
Toxicity grade	2	3	4	2	3	4	2	3	4
Leukopenia	2	3	0	3	3	0	1	2	1
Neutropenia	0	4	1	2	3	1	0	2	2
Anemia	0	0	0	2	0	0	2	0	0
GPT elevation	1	0	0	2	0	0	0	0	0
Total bilirubin elevation	1	0	0	1	0	0	1	0	0
Infection	0	0	0	1	1	0	0	0	0
Allergic reaction	1	0	0	2	0	1	0	0	0
Anorexia	1	0	0	2	0	0	0	0	0
Nausea	0	0	0	1	0	0	0	0	0
Constipation	0	0	0	2	0	0	0	0	0
Esophagitis	1	0	0	2	1	0	0	0	0
Pneumonitis	0	0	1*	1	0	1*	0	0	0
Musculoskeletal pain	1	0	0	1	0	0	1	0	0
Alopecia	4	0	0	4	0	0	0	0	0

GPT, glutamic pyruvic transaminase.
*Pneumonitis was fatal in these patients.

Both patients were former heavy smokers with a smoking index of 520 and 1680, respectively. The chest CT scan of the former patient disclosed mild emphysematous, but no interstitial changes. A spirometry analysis showed a vital capacity (VC) of 3480 ml (104% of predicted), and a forced expiratory volume one second percent (FEV1.0%) of 82%. The lung diffusing capacity measurement using carbon monoxide (DL_{CO}) was not done in this patient. The PaO_2 was 93.3 torr. The serum LDH level before treatment was 241 IU/l (the upper limit of the normal value was 229 IU/l). The chest CT scan of the latter patient disclosed slight changes in the dorsal portion of the both lungs, which were considered the gravitation effect, or fibrotic changes. The VC was 3810 ml (107% of predicted), % DL_{CO} was 111%, and PaO_2 was 99.7 torr. The serum LDH level before treatment was 147 IU/l. Another patient in level 2, whose V_{20} and MLD were 15% and 822 cGy, respectively, developed grade 2 pneumonitis when he received 52 Gy of radiotherapy and the subsequent protocol treatment was stopped. The chest CT scan of this patient before treatment showed no abnormal findings except for lung cancer. Pulmonary function test values were all within normal limits. The serum LDH level before treatment was 178 IU/l. Thus, in total three (17%) of 18 patients developed unacceptable severe pneumonitis induced by the current treatment, which was counted as DLT.