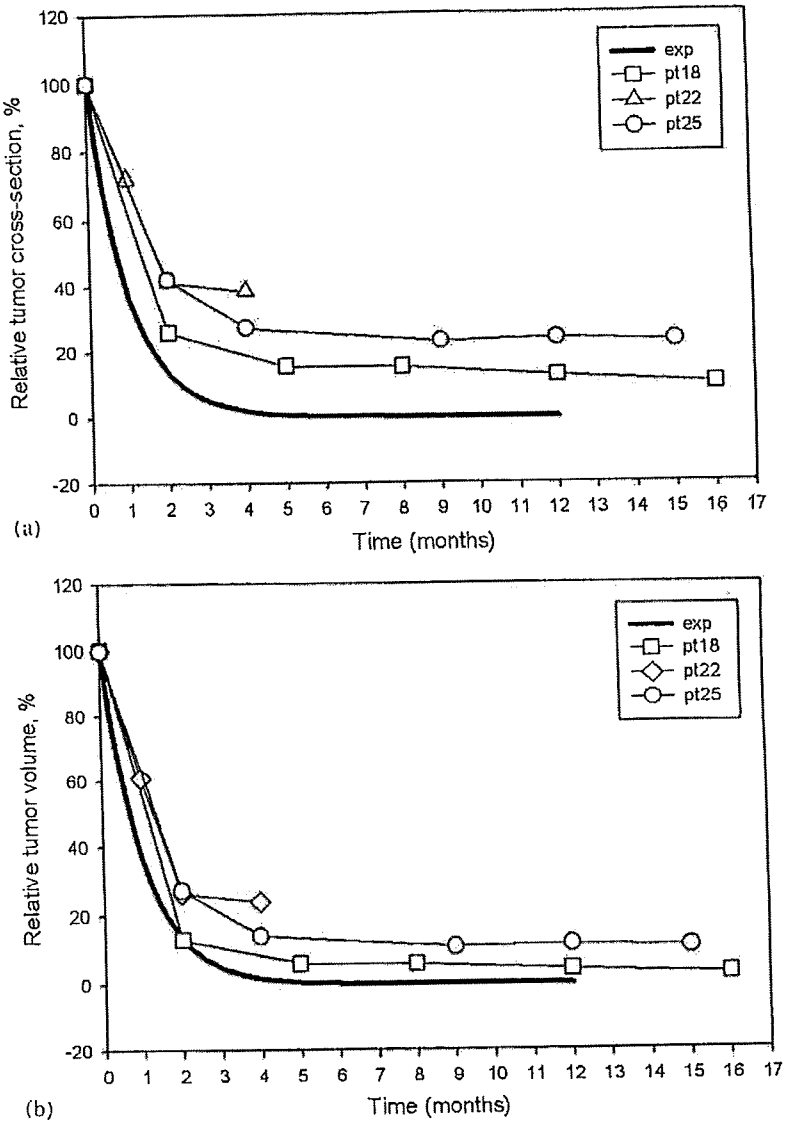

Figure 1. Comparison of relative tumor size variation after stereotactic body radiotherapy of lung as measured by Aoki *et al* with an exponent function $\exp(-t)$. (a) Clinical data for largest tumor cross-section; (b) approximation of clinical data to tumor volume.

The fitting of the exponential function was done using the least-squares minimization based on a version of a quasi-Newton method called the L-BFGB-B algorithm (Byrd *et al* 1995). This code is widely used in the medical physics community for solving different radiotherapy optimization problems of different complexity (Chvetsov *et al* 2007). The mathematical function which has been used for the fitting has been presented as a weighted linear combination of an exponent function and a constant function

$$f(t) = (1 - w)\exp(-\mu_0 t) + w, \tag{7}$$

where w is a constant value between 0.0 and 1.0. This has been done to subtract the constant saturation value in the clinical data during the optimization process.

The results of the fitting are shown in figure 2 for adenocarcinoma and in figure 3 for SCC. We have obtained the average value of half-life $T_{1/2} = 28.2$ days and standard deviation $\sigma = 8.6$ days for SCC and the average value of half-life $T_{1/2} = 72.4$ days and standard

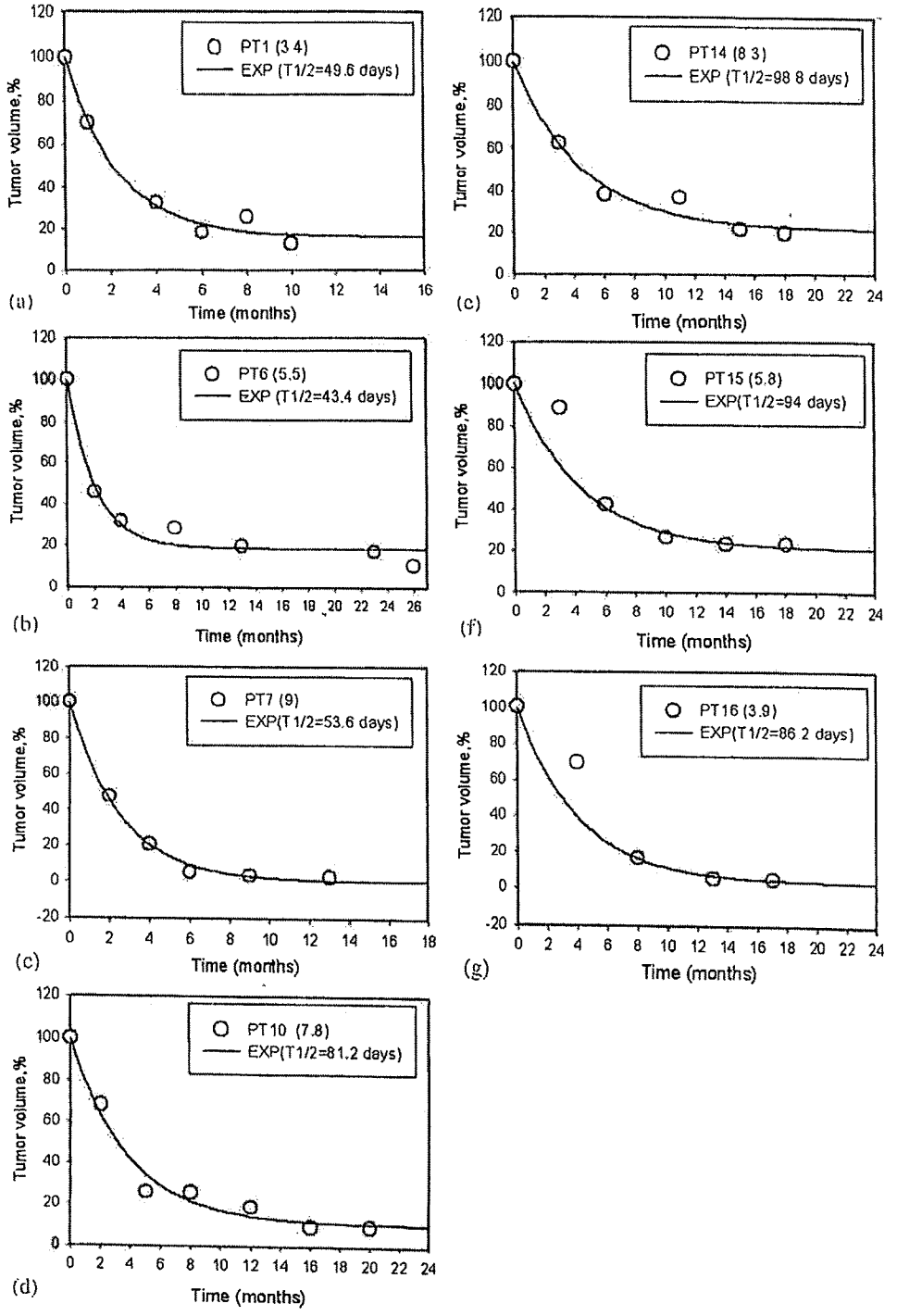

Figure 2. Comparison of the lung adenocarcinoma volume after stereotactic body radiotherapy in clinical data of Aoki *et al* with the function $(1 - w)\exp(-\ln 2t/T_{1/2}) + w$: (a)–(g) patients 1–7. Tumor size (cm^2) is shown for each patient in parentheses.

deviation $\sigma = 22.8$ days for adenocarcinoma. Assuming that the potential doubling time T_{pot} is 7.7 days for adenocarcinoma and 8.5 days for SCC according to the data published by Shibamoto and Hara (2005), we obtain the average value of the disintegration parameter $b = 9.4$ for adenocarcinoma and $b = 3.3$ for SCC. These data indicate that an adenocarcinoma cell cycling approximately three times longer after lethal radiation damage than a SCC cell before it disintegrates. Using the half-life we can also evaluate the mean life of a single cell if

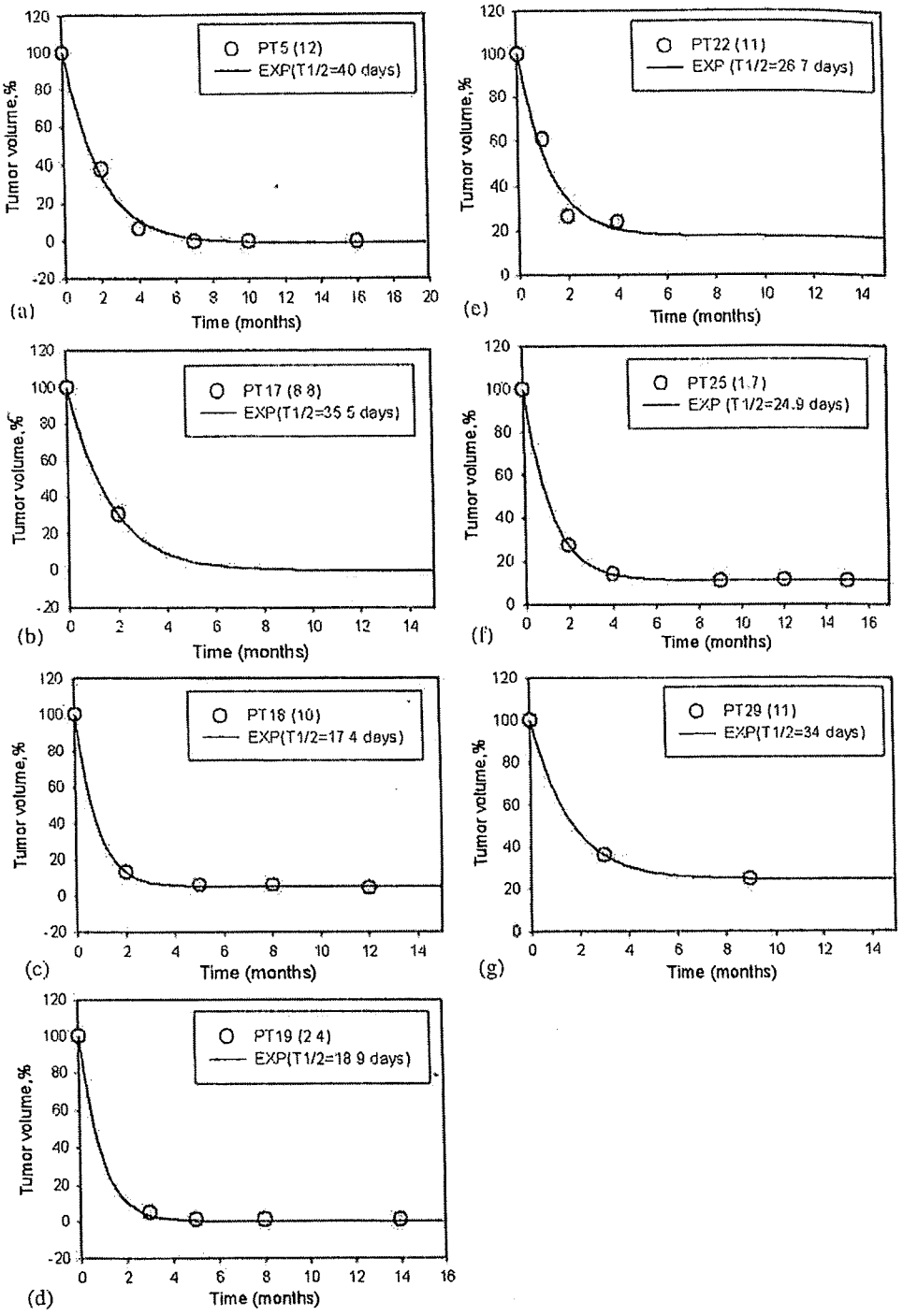

Figure 3. Comparison of the lung squamous cell carcinoma volume after stereotactic body radiotherapy in clinical data of Aoki *et al* with the function $(1-w)\exp(-\ln 2t/T_{1/2})+w$: (a)–(g) patients 1–7. Tumor size (cm^2) is shown for each patient in parentheses.

it suffers radiation damage. The mean life is given by $T_a = T_{1/2}/\ln 2$; therefore, we obtain the average mean life of $T_a = 40.7$ days for SCC and $T_a = 105.5$ days for adenocarcinoma.

The standard deviation of the half-life for both adenocarcinoma and SCC is approximately 30% of the average value. This relatively large value can be explained by several reasons: (1) patient heterogeneity is usually a reason of large standard deviation of radiobiological parameters (Wigg 2001, Keall and Webb 2007); (2) small number of cases in our evaluation

and (3) lung tumors may not be completely reoxygenated at the end of SBRT because this treatment is relatively short; therefore, lethally damaged oxygenated and hypoxic cells may be present in tumors. Hypoxic cells are practically removed from the dividing population of cells in the tumor because they are resting in the Go phase. Hypoxic cells can remain in Go phase for days, weeks or years, but can be stimulated to return to the cell division cycle. Therefore, the disintegration of lethally hypoxic cells may depend on tumor reoxygenation rate and the residual tumor hypoxia may affect heterogeneity of the measured half-life value. According to the data of Rasey *et al* (1996) obtained using PET fluoromisonidazole, the hypoxia for non-small lung cancer can be relatively large with the median value of 47.6% and the maximum value of 94.7%.

4. Discussion

In this paper, we attempted to study the kinetics of the disintegration of tumor cells damaged by radiation and, therefore, unable to proliferate. The radiobiological analysis for radiotherapy treatment planning usually involves the kinetics of proliferating cells because they define the optimal fractionation schedules and treatment outcomes given by TCP and NTCP (Moiseenko *et al* 2005, Stewart and Li 2007). In this radiobiological analysis, a cell is considered instantaneously gone from the system if it is lethally damaged by radiation.

However, the development of new imaging systems has led to more evidence that volumetric tumor changes during radiotherapy can affect tumor dosimetry in highly conformal therapies like proton therapy (Bucci *et al* 2007). Volumetric tumor changes are defined by both proliferating cells and lethally damaged cells which are not able to proliferate. Lethally damaged cells will disintegrate with time and their kinetics will affect the dynamics of tumor mass and volume. The cell loss mechanism has been addressed in the studies discussing tumor growth and its relationship to the potential doubling time and volume doubling time (Fowler 1991). However, quantitative modeling of the tumor volume variation during or after radiotherapy has not been emphasized in radiotherapy treatment planning.

Modeling the volumetric tumor response is a complicated mathematical and radiobiological task because several cell subpopulations should be considered, including proliferating and damaged cells. Many radiobiological processes such as cell survival, reoxygenation, repopulation and reassortment should be modeled. Therefore, we began with the simple task of modeling with a tumor with only one subpopulation, which could be found at the end of the radiotherapy treatment after all living cells were destroyed by ionizing radiation. The tumor at the end of the therapy consisted only of the population of damaged cells which could not proliferate; however, they did make up the bulk of the tumor. These cells disintegrate at the first or a subsequent division after irradiation and their debris is removed.

In this study, we proposed and validated a simple mathematical formula for cell disintegration in tumors treated with ionizing radiation. The parameters of the model have been obtained using clinical data on tumor size variation after stereotactic radiotherapy of solitary lung tumors. To study the cell kinetics based on the volumetric measures, we assumed a linear relationship between the cell number and the tumor volume. We have shown that many complicated processes such as mitotic cell death and diffusion of cell debris can be described as a simple exponential decay. We believe that this model can lead to further development of a fast computational radiobiological model to predict the tumor volume variation during fractionated radiotherapy. To simulate tumor volume during radiotherapy, this model should additionally include an analysis of subpopulations of live cells governed by radiobiological mechanisms such as the LQ survival model, exponential repopulation, reoxygenation and reassortment.

We believe that a radiobiological model for volumetric tumor response is needed for qualitative and quantitative analyses of the most recent clinical results on anatomical changes in the human body during radiation therapy (Barker *et al* 2004, Kupelian *et al* 2005, Siker *et al* 2006, Bucci *et al* 2007). These clinical results indicate that volumetric tumor changes during radiotherapy can affect treatment planning dosimetry for highly conformal radiotherapeutic modalities like IMRT and proton beams. The radiobiological model for volumetric tumor variation can be used in 4D treatment planning for evaluating dose distribution variations which may be due to time-dependent density variations in highly conformal radiotherapeutic modalities like IMRT and proton therapy (Mohan *et al* 2005). The cell disintegration model which we have proposed in this paper can be used in more complicated models for tumor volumetric response during radiotherapy which should include kinetics of living and lethally damaged cells. If these models would be developed they would allow one evaluate dose variations due to time-dependent density variations thus improving 4D treatment planning. The ability to model tumor volume during radiotherapy can especially improve and optimize 4D treatment planning for IMRT and proton therapy, which is a laborious and time-consuming process.

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Lung cancer RT

Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses

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ABSTRACT

Introduction: The role of elective nodal irradiation of non-small-cell lung cancer (NSCLC) patients treated with radiotherapy remains unclear. We investigated the significance of treating clinically uninvolved lymph nodes by retrospectively analyzing the relationship between loco-regional failure and the irradiated volume.

Methods: Between 1998 and 2003, patients with IA–IIIB NSCLC were treated with radiotherapy. The eligibility criteria for this study were an irradiation dose of 60 Gy or more and a clinical response better than stable disease. Typical radiotherapy consisted of 40 Gy/20 fr to the tumor volumes (clinical target volume of the primary tumor [CTVp], of the metastatic lymph nodes [CTVn], and of the subclinical nodal region [CTVs]), followed by off-cord boost to CTVp+n to a total dose 60–68 Gy/30–34 fr. The relationship between the sites of recurrence and irradiated volumes was analyzed.

Results: A total of 127 patients fulfilled the eligibility criteria. Their median overall and progression-free survival times were 23.5 (range, 4.2–109.7) and 9.0 months (2.2–109.7), respectively. At a median follow-up time of 50.5 months (range, 14.2–83.0) for the surviving patients, the first treatment failure was observed in 95 patients (loco-regional; 41, distant; 42, both; 12). Among the patients with loco-regional failure, in-field recurrence occurred in 38 patients, and four CTVs recurrences associated with CTVp+n failure were observed. No isolated recurrence in CTVs was observed.

Conclusions: In-field loco-regional failure, as well as distant metastasis, was a major type of failure, and there was no isolated elective nodal failure. Radiation volume adequacy did not seem to affect elective nodal failure.

 Radiotherapy and Oncology 91 (2009) 433–437

Radiation therapy is an integral component of the multi-modal treatment of non-small-cell lung cancer (NSCLC). Recent phase III studies have demonstrated that concomitant chemoradiotherapy improves survival, and this has resulted in the general acceptance of concurrent chemoradiotherapy as one of the standard treatments for locally advanced NSCLC [1]. Despite the improved survival, however, most patients die from their disease as a result of local or distant failure.

Local failure remains a major challenge when treating NSCLC with radiotherapy. A number of studies of dose escalation to the gross tumor volume (GTV) have been conducted as a means of improving local control [2–5]. The conventional radiation fields for NSCLC typically encompass the entire mediastinum and ipsilateral hilum (elective nodal region) to deliver a dose of 40 Gy, even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV. However, the conventional treatment has added considerable morbidity and can limit the dose escalation. In phase I–II dose escalation studies, there is a trend toward omitting the practice of elective nodal irradiation (ENI) after their experiences with toxicity, which is not based on direct evidence [2–5]. According to those studies, omitting ENI has not sacrificed treatment outcomes so far. They also analyzed patterns of recurrence in relation to irradiated volume in a dose escalation setting [6].

By contrast, the current literature provides limited information regarding patterns of failure when conventional fields and doses are used [7,8]. Since it is important to know whether loco-regional failure is within or outside the irradiation field, we retrospectively analyzed patterns of failure after radiation therapy for NSCLC, especially in regard to the relationship between local failure and irradiated volume.

Methods and materials

Patients

Between January 1998 and March 2003, 263 patients with newly diagnosed NSCLC were treated with thoracic radiation therapy,

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with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

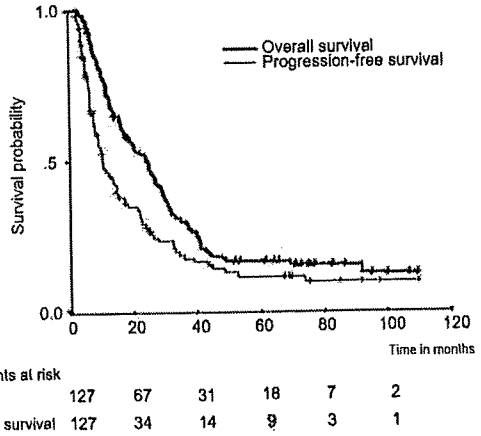

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

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Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

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with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in

43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics

Characteristics	Female ($n = 44$)		Male ($n = 160$)		P value
	N	%	N	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		P value
		N	%	N	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

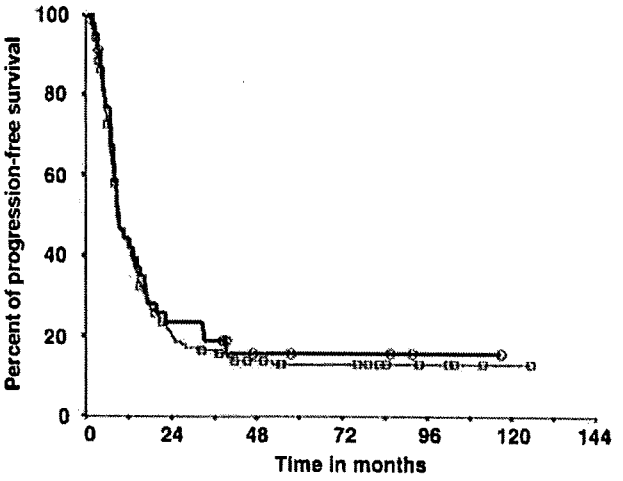

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

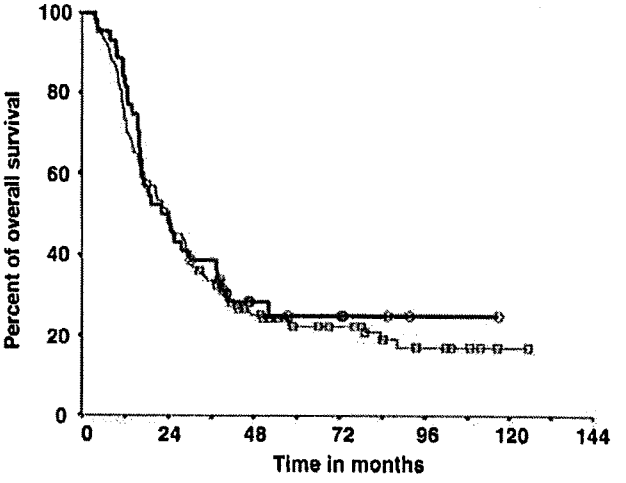

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
≤4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Lung**

CHANGES IN PATTERNS OF CARE FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS OF THE 99-01 PATTERNS OF CARE STUDY—A NATIONWIDE SURVEY IN JAPAN

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Background: This study was undertaken to analyze the practice process of thoracic radiotherapy (TRT) and evaluate changes in patterns of care for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan.
Methods and Materials: The Patterns of Care Study (PCS) conducted the second nationwide survey of care process for patients with LS-SCLC treated by using TRT between 1999 and 2001.
Results: The PCS collected data for 139 patients with LS-SCLC (man-woman ratio, 5:1; median age, 69 years; age > 70 years, 43%; Karnofsky Performance Status > 70, 73%; and Stage III, 88%). Median total dose was 50 Gy. Twice-daily TRT was used in 44% of patients. Median field size was 12 × 14 cm. The most commonly used photon energy was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV comprised 12%. Three-dimensional conformal therapy was used with 12% of patients. Computed tomography simulation was performed in 40% of cases. Only 12 patients (8.6%) received prophylactic cranial irradiation (PCI). Concurrent chemotherapy and TRT (CCRT) was used for 94 patients (68%). Only 6 patients (4.4%) entered clinical trials. Compared with the previous PCS 95-97, significant increases in the use of CCRT (34–68%; $p < 0.0001$), twice-daily TRT (15–44%; $p < 0.0001$), and PCI (1.7–8.6%; $p = 0.0045$) were observed, although the absolute number of patients receiving PCI was still extremely low.
Conclusions: Evidence-based CCRT and twice-daily TRT has penetrated into clinical practice. However, PCI is not yet widely accepted in Japan. © 2008 Elsevier Inc.

Patterns of Care Study, Small-cell lung cancer, Thoracic radiation therapy, Nationwide survey, Practice process.

INTRODUCTION

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice processes for selected malignancies during a specific period (1). In addition to documenting practice processes, the PCS is important in developing and spreading national guidelines for cancer treatment. In Sept 1998, the Japanese PCS conducted the first nationwide survey for patients with lung cancer treated using thoracic radiotherapy (TRT) between 1995 and 1997 (PCS 95-97). The main findings from the PCS 95-97 are summarized as follows. First, the use of TRT for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan is predominantly influenced by institutional characteristics, rather than age group. Second, patient age significantly influenced the use of chemotherapeutic modality, such as etoposide and cisplatin for patients with LS-SCLC (2, 3).

Because results of several key clinical studies of patients with LS-SCLC were reported between 1997 and 1999, it seems meaningful to evaluate whether practice processes in Japan were changed accordingly. The second PCS for lung cancer investigated patient characteristics, workup studies, the process of TRT, and use of chemotherapy in patients with LS-SCLC treated by using TRT between 1999 and

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2001. The objectives of the present study are as follows. First, compile processes in TRT for patients with LS-SCLC treated between 1999 and 2001, and second, compare patient characteristics and treatment modalities between the PCS 95-97 and PCS 99-01 in Japan.

METHODS AND MATERIALS

Between July 2002 and August 2004, the PCS conducted a second national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format for patients with lung cancer. The PCS performed an extramural audit survey for 73 (38 academic and 35 nonacademic institutions) of 556 institutions by using stratified two-stage cluster sampling and collected data for 768 eligible patients with lung cancer. Data collection consisted of two steps of random sampling. Before random sampling, all institutions were classified into one of four groups. Criteria for stratification were described elsewhere (2, 4). Briefly, the PCS stratified Japanese institutions as follows: A1, such academic institutions as university hospitals or national/regional cancer center hospitals treating 430 or more patients per year; A2, academic institutions treating fewer than 430 patients; B1, nonacademic institutions treating 130 or more patients per year; and B2, those treating fewer than 130 patients per year. Cutoff values for numbers of patients treated per year between A1 and A2 institutions and B1 and B2 institutions were increased from those used in the previous PCS because of the increase in number of patients treated using radiation therapy in Japan (4).

Eligible patients included those with 1997 International Union Against Cancer Stages I–III lung cancer treated by using TRT between 1999 and 2001, with Karnofsky Performance Status (KPS) greater than 50 before the start of treatment and no evidence of other malignancies within 5 years. The International Union Against Cancer staging system was used because the PCS comprehensively surveyed patients with non-SCLC and those with SCLC. As mentioned, Stages I–III SCLC do not precisely match the definition of LS-SCLC by Mountain (5). However, no definition of this term has been universally accepted. The PCS survey of TRT charts showed that for patients with SCLC, the tumor could be encompassed within the TRT field. Thus, in the present study, all patients were regarded as having LS-SCLC.

The aims of this study are to provide patterns of practice concerning: (*1*) patient background; (2) workup studies; (*3*) TRT, including photon energies, total dose, spinal cord dose, field arrangements, prescription point, and use of prophylactic cranial irradiation (PCI); and (*4*) chemotherapy, including agents, number of chemotherapy cycles, sequence of chemotherapy, and TRT. Patient background included demographics and medical status, such as KPS, comorbidities, stage, and whether treated on an outpatient basis. In addition, practice patterns of the PCS 99-01 were compared with those of the PCS 95-97.

To validate the quality of collected data, the PCS used the Internet mailing list among all the surveyors. *In situ* real-time check and adjustment of the 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 unknown values were included when both percentage and significance values were calculated. Statistical significance was tested by using chi-square test. A $p < 0.05$ was considered statistically significant. Overall survival, assessed from the first day of radiation therapy, was estimated by using the Kaplan-Meier product-limit method, and differences were evaluated using log-rank test.

RESULTS

Patient backgrounds

There were 141 patients with SCLC, which constituted 18% of all patients with lung cancer surveyed. Of those, 2 patients underwent initial surgical resection and adjuvant postoperative irradiation. Thus, in the present study, the PCS analyzed the remaining 139 patients who did not undergo surgery (Table 1).

There were 116 men and 23 women with an age range of 36–85 years (median, 69 years). Patients older than 70 years constituted 43% of the patient population. For that elderly patient pool, the institutional breakdown was as follows: 31% in A1, 39% in A2, 50% in B1, and 50% in B2 ($p = 0.037$). For comorbidities, the most frequent adverse medical conditions were cardiovascular disease (34%) and diabetes (14%). Seventy-three percent had KPS of 80% or greater. Comparison of four institutional groups failed to show differences in terms of patient background other than patient age and KPS. Patients with KPS of 80 or greater comprised 89% of A1, 55% of A2, 74% of B1, and 65% of B2 strata ($p = 0.0071$). A majority of patients (88%) had Stage III disease. There were no significant differences in distributions of T and N classifications or clinical stages between institutional groups. Only 5% of all patients were treated on an outpatient basis.

Workup studies

Workup studies are listed in Table 2. Pretreatment workup included chest computed tomography (CT) in 96%, bronchoscopy in 93%, brain CT or magnetic resonance imaging in 86%, and bone scan in 79% of surveyed patients. Chest/abdominal CT and bone scan were used for a majority of patients, whereas positron emission tomography (PET) was used for an extremely small number of patients. Comparison of four institutional groups failed to show differences in terms of workup studies.

Practice process of TRT

Thoracic radiotherapy methods are listed in Table 3. Median total dose of TRT was 50 Gy, and median field size was 12 × 14 cm. Median dose to the spinal cord was 42 Gy. A CT simulator was used for planning in 40% of patients. Three-dimensional conformal therapy was used in 12%. The planning target volume included the ipsilateral hilus in 96%, ipsilateral mediastinum in 96%, contralateral mediastinum in 84%, contralateral hilus in 17%, ipsilateral supraclavicular region in 25%, and contralateral supraclavicular region in 15%. Field reduction during the course of TRT was done for 61%. Twice-daily radiotherapy was used for 44%. Photon energy generally was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV were used for 12%. Only 12 patients (8.6%) received PCI. Median dose of PCI was 25 Gy. Only 6 patients (4.4%) entered clinical trials.

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions A1	A2	B1	B2	Total	*p*-value
No. of patients	36	23	54	26	139	
Age (y)						0.037
Range	44–85	36–81	40–81	54–85	36–85	
Median	69	68	71	71	69	
>70 (%)	31	39	50	50	43	
Sex						0.780
Men	30	18	47	21	116	
Women	6	5	7	5	23	
Karnofsky performance status						0.013
≥80 (%)	89	55	74	65	73	
Clinical stage/UICC 1997						0.475
I	0	1	2	2	5	
IIA, IIB	3	3	4	1	11	
IIIA	10	6	19	10	45	
IIIB	23	13	28	13	77	
Unknown/missing	0	0	1	0	1	
T classification						0.569
T1–2	14	11	25	14	64	
T3–4	22	12	28	12	74	
Unknown/missing	0	0	1	0	1	
N classification						0.551
N0–1	7	4	9	6	26	
N2–3	29	19	44	20	112	
Unknown/missing	0	0	1	0	1	

Abbreviation: UICC = International Union Against Cancer.

Institutional stratification influenced several radiotherapeutic parameters (Table 4). Photon energy of 6 MV or greater was used for 97% of patients in A1, 96% in A2, 87% in B1, and 69% in B2 institutions ($p = 0.0006$). The ^{60}Co machines were not used in any A1 to B1 institutions. Twice-daily radiotherapy was used for 57 of 113 patients in A1 to B1 institutions, but only 4 of 26 patients in B2 institutions were treated in that manner ($p = 0.0012$). The PCI was used for 7 of 36 patients (19%) in A1 institutions, but only 5 patients (4.9%) in the remaining institutions ($p = 0.0073$). Use of a CT simulator was more frequent in A1 (52%) and A2 (65%) compared with B1 (34%) and B2 (17%) institutions ($p = 0.011$).

One hundred twenty-nine patients (93%) received systemic chemotherapy. Of those, platinum-based chemotherapy constituted 98%. Concurrent chemotherapy and TRT (CCRT) was used for 68% (73% of patients who received systemic chemotherapy). Median number of chemotherapy cycles was four. Median times from the first day of systemic chemotherapy to the first date and last date of TRT were 3 and 44 days, respectively. Proportions of patients who received chemotherapy were 97% in A1, 96% in A2, 91% in B1, and 89% in B2 institutions ($p = 0.49$).

Comparison between two PCS studies

Patient backgrounds and practice patterns in PCS 99-01 were compared with those in PCS 95-97. Differences between the two studies are listed in Table 5. Based on two-stage cluster sampling, the ratios of academic to nonacademic institutions were almost equal in the two surveys. Although median age in PCS 99-01 was slightly older than that in PCS 95-97, patients' backgrounds were similar in the studies. Use of obsolete treatment equipment (photon energy < 6 MV and ^{60}Co) decreased from 20% in PCS 95-97 to 12% in PCS 99-01 ($p = 0.06$). The greatest differences were seen in the use of twice-daily TRT and CCRT. Twice-daily TRT increased from 15% in PCS 95-97 to 44% in PCS 99-01 ($p < 0.0001$). Use of CCRT in PCS 99-01 was twice as high as in PCS 95-97 (68% vs. 34%; $p < 0.0001$). Although a significant increase in the use of PCI was observed (1.7–8.6%; p = 0.0045), the rate was still extremely low in Japanese practice.

Table 2. Percentage of patients examined by using each diagnostic technique in the course of staging

Chest CT	96%
Chest MRI	7%
Bronchoscope	93%
Bone scan	79%
Abdominal CT	88%
Positron emission tomography	2%
Brain CT or MRI	86%

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.