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

Please cite this article in press as: Sanuki-Fujimoto N et al., Relation between elective nodal failure and irradiated volume in non-small-cell ..., Radiother Oncol (2009), doi:10.1016/j.radonc.2008.12.013

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.

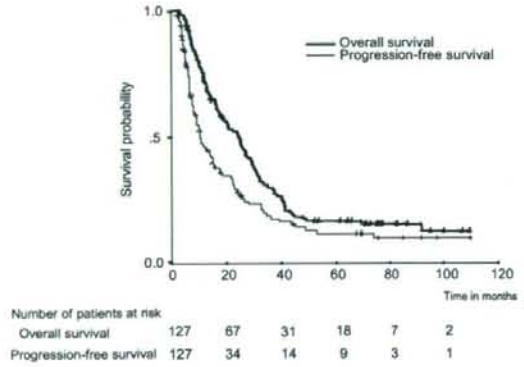

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

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 sys-

Please cite this article in press as: Sanuki-Fujimoto N et al., Relation between elective nodal failure and irradiated volume in non-small-cell ..., Radiother Oncol (2009), doi:10.1016/j.radonc.2008.12.013

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

temic 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.

References

[1] Penland SK, Socinski MA. Management of unresectable stage III non-small cell lung cancer: the role of combined chemoradiation. Semin Radiat Oncol 2004;14:326–34.
[2] Belderbos JS, De Jaeger K, Heemsbergen WD, et al. First results of a phase I/II dose escalation trial in non-small cell lung cancer using three-dimensional conformal radiotherapy. Radiother Oncol 2003;66:119–26.
[3] Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. Int J Radiat Oncol Biol Phys 2002;54:348–56.
[4] Socinski MA, Morris DE, Halle JS, et al. Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: a dose-escalation phase I trial. J Clin Oncol 2004;22:4341–50.
[5] Wu KL, Jiang GL, Liao Y, et al. Three-dimensional conformal radiation therapy for non-small-cell lung cancer: a phase I/II dose escalation clinical trial. Int J Radiat Oncol Biol Phys 2003;57:1336–44.
[6] Rosenzweig KE, Sura S, Jackson A, et al. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007;25:5557–61.
[7] Kepka A, Szajda SD, Jankowska A, et al. Risk of isolated nodal failure for non-small cell lung cancer (NSCLC) treated with the elective nodal irradiation (ENI) using 3D-conformal radiotherapy (3D-CRT) techniques – A retrospective analysis. Acta Oncol 2008;47:95–103.
[8] Emami B, Mirkovic N, Scottc C, et al. The impact of regional nodal radiotherapy (dose/volume) on regional progression and survival in unresectable non-small cell lung cancer: an analysis of RTOG data. Lung cancer 2003;41:207–14.
[9] Izbicki JR, Passlick B, Hosch SB, et al. Mode of spread in the early phase of lymphatic metastasis in non-small-cell lung cancer: significance of nodal micrometastasis. J Thorac Cardiovasc Surg 1996;112:623–30.
[10] Oda M, Watanabe Y, Shimizu J, et al. Extent of mediastinal node metastasis in clinical stage I non-small-cell lung cancer: the role of systematic nodal dissection. Lung cancer 1998;22:23–30.
[11] Keller SM, Adak S, Wagner H, et al. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. Ann Thorac Surg 2000;70:358–65 [discussion 365–366].
[12] Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. World J Surg 1998;22:290–4 [discussion 294–295].

Please cite this article in press as: Sanuki-Fujimoto N et al., Relation between elective nodal failure and irradiated volume in non-small-cell ..., Radiother Oncol (2009), doi:10.1016/j.radonc.2008.12.013

[13] Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Ann Surg 1998;227:138–44.
[14] Izbicki JR, Thetter O, Habekost M, et al. Radical systematic mediastinal lymphadenectomy in non-small cell lung cancer: a randomized controlled trial. Br J Surg 1994;81:229–35.
[15] Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected non-small cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers Bronchiques. Cancer 1999;86:265–73.
[16] Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000;343:1217–22.
[17] Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11–9.
[18] Rowell NP. Postoperative radiotherapy in non-small-cell lung cancer. Lancet 1998;352:1384 [author reply 1385–1386].
[19] Asamura H, Nakayama H, Kondo H, et al. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. J Thorac Cardiovasc Surg 1999;117:1102–11.
[20] Asamura H, Nakayama P, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125–34.
[21] Komaki R, Scott CB, Bynandt R, et al. Failure patterns by prognostic group determined by recursive partitioning analysis (RPA) of 1547 patients on four radiation therapy oncology group (RTOG) studies in inoperable nonsmall-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1998;42:263–7.
[22] Komaki R, Scott CB, Sause WT, et al. Induction cisplatin/vinblastine and irradiation vs. irradiation in unresectable squamous cell lung cancer: failure patterns by cell type in RTOG 88-08/ECOG 4588. Radiation Therapy Oncology Group. Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 1997;39:537–44.
[23] Movsas B, Scott C, Sause W, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999;45:1143–9.
[24] Suzuki K, Nagai K, Yoshida J, et al. Clinical predictors of N2 disease in the setting of a negative computed tomographic scan in patients with lung cancer. J Thorac Cardiovasc Surg 1999;117:593–8.
[25] Vansteenkiste J, Fischer BM, Booms C, et al. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol 2004;5:531–40.
[26] Grills IS, Yan D, Martinez AA, et al. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. Int J Radiat Oncol Biol Phys 2003;57:875–90.
[27] Senan S, Burgers S, Samson MJ, et al. Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. Int J Radiat Oncol Biol Phys 2002;54:999–1006.
[28] Senan S, De Ruysscher D, Girard P, et al. Literature-based recommendations for treatment planning and execution in high-dose radiotherapy for lung cancer. Radiother Oncol 2004;71:139–46.
[29] Yuan S, Sun X, Lim L, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol 2007;30:239–44.
[30] Zhao L, Chen M, Ten Haken R, et al. Three-dimensional conformal radiation may deliver considerable dose of incidental nodal irradiation in patients with early stage node-negative non-small cell lung cancer when the tumor is large and centrally located. Radiother Oncol 2007;82:153–9.

Please cite this article in press as: Sanuki-Fujimoto N et al., Relation between elective nodal failure and irradiated volume in non-small-cell ..., Radiother Oncol (2009), doi:10.1016/j.radonc.2008.12.013

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 414–419, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.10.018

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

TAKASHI UNO, M.D.,* MINAKO SUMI, M.D.,† YOSHITOMO ISHIHARA, M.S.,‡ HODAKA NUMASAKI, M.S.,‡ MICHIHIDE MITSUMORI, M.D.,§ AND TERUKI TESHIMA, M.D.,‡ FOR THE JAPANESE PCS WORKING SUBGROUP OF LUNG CANCER

* Department of Radiology, Chiba University Graduate School of Medicine, Chiba, Japan; † Division of Radiation Oncology, National Cancer Center, Tokyo, Japan; ‡ Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Osaka, Japan; and § Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine Kyoto University, Kyoto, Japan

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

Reprint requests to: Takashi Uno, M.D., Department of Radiology, Chiba University Graduate School of Medicine, Inohana 1-8-1, Chuou-ku, Chiba City, Chiba 260-8670, Japan. Tel: (+81) 43-226-2100; Fax: (+81) 43-226-2101; E-mail: unotakas@faculty.chiba-u.jp

Presented in part at the Second USA/Japan PCS Workshop, Tokyo, Japan, February 17–19, 2003; and the 13th European Cancer Conference, Paris, France, October 30–November 3, 2005.

Supported by Grants-in-Aid for Cancer Research No. 10-17 and 14-6 from the Ministry of Health, Labor, and Welfare and by the Research Fund in 1999 and 2000 from the Japan Society of Therapeutic Radiology and Oncology.

Conflict of interest: none.

Acknowledgments—The authors thank all radiation oncologists and staff for their support and cooperation in this study.

Received Sept 11, 2007, and in revised form Oct 11, 2007. Accepted for publication Oct 11, 2007.

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					*p*-value
	A1	A2	B1	B2	Total	
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.

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

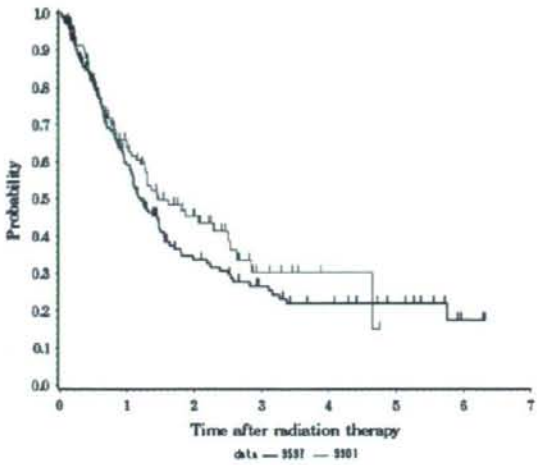

Fig. 1. Kaplan-Meier estimate of overall survival of patients with Stages I–III small-cell lung cancer surveyed in the 1995–1997 (dark line) and 1999–2001 (bright line) Patterns of Care Studies in Japan.

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).

REFERENCES

1. Hanks GE, Coia LR, Curry J. Patterns of care studies. Past, present and future. *Semin Radiat Oncol* 1997;7:97–100.
2. Uno T, Sumi M, Ikeda H, *et al.* Radiation therapy for small-cell lung cancer: Results of the 1995-1997 Patterns of Care process survey in Japan. *Lung Cancer* 2002;35:279–285.
3. Uno T, Sumi M, Sawa Y, *et al.* Process of care and preliminary outcome in limited-stage small-cell lung cancer: Results of the 1995-1997 Patterns of Care Study in Japan. *Int J Radiat Oncol Biol Phys* 2003;55:626–632.
4. Teshima T. Japanese PCS Working Group. Patterns of Care Study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
5. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–1717.
6. Movsas B, Moughan J, Komaki R, *et al.* Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol* 2003;21: 4553–4559.
7. National Comprehensive Cancer Network: Oncology Practice Guidelines, version 3, 2003. Available at: http://www.nccn.org. Accessed December 21, 2004.
8. Uno T, Sumi M, Kihara A, *et al.* Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999-2001 Patterns of Care Study nationwide process survey in Japan. *Lung Cancer* 2007;56:357–362.
9. Pignon JP, Arriagada R, Ihde DC, *et al.* A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–1622.
10. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992;10:890–895.
11. Turrisi AT III, Kim K, Blum R, *et al.* Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–271.
12. Auperin A, Arriagada R, Pignon JP, *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med* 1999;341:476–484.
13. Murray N, Coy P, Pater JL, *et al.* The importance of time for thoracic radiation in the combined modality treatment of limited stage small-cell lung cancer. *J Clin Oncol* 1993;11:336–344.
14. Takada M, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: Results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–3060.
15. Gaspar LE, Gay EG, Crawford J, *et al.* Limited-stage small-cell lung cancer (stage I-III): Observations from the National Cancer Data Base. *Clin Lung Cancer* 2005;6:355–360.
16. Editorial Board of the Cancer Statistics in Japan. Methods of treatment at National Cancer Center Hopital, Japan, *Cancer Statistics in Japan 2001*. Tokyo: Foundation of Cancer Research; 2001. 50–51.
17. Sugiyama H, Teshima T, Ohno Y, *et al.* The Patterns of Care Study and regional cancer registry for non–small-cell lung cancer in Japan. *Int J Radiat Oncol Biol Phys* 2003;56: 1005–1012.

The Oncologist®

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

IKUO SEKINE,[a] MINAKO SUMI,[b] NAGAHIRO SAIJO[c]

[a]Division of Internal Medicine and Thoracic Oncology, and
[b]Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan;
[c]Division of Internal Medicine, National Cancer Center Hospital East, Kashiwa, Japan

Key Words. Non-small cell lung cancer • Chemotherapy • Pleural effusion • Bone metastasis • Brain metastasis

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

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,

Correspondence: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Telephone: 81-3-3542-2511; Fax: 81-3-3542-3815; e-mail: isekine@ncc.go.jp
Received August 28, 2007; accepted for publication November 5, 2007. 1083-7159/2008/$30.00/0 doi: 10.1634/theoncologist.13-S1-21.

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.

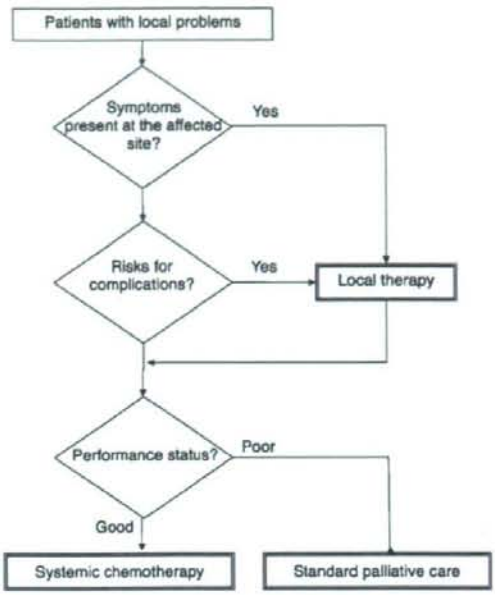

Figure 1. Treatment approaches for patients who have advanced non-small cell lung cancer with local problems.

Acknowledgment

We thank Mika Nagai for invaluable assistance in the collection and arrangement of the large number of papers.

References

1 Wozniak A, Gadgeel S. Clinical presentation of non-small cell carcinoma of the lung. In: Pass H, Carbone D, Minna J et al., eds. Lung Cancer: Principles and Practice, Third Edition. Philadelphia: Lippincott Williams & Wilkins, 2005:291–303.

2 Fenton KN, Richardson JD. Diagnosis and management of malignant pleural effusions. Am J Surg 1995;170:69–74.

3 DeCamp MM Jr, Mentzer SJ, Swanson SJ et al. Malignant effusive disease of the pleura and pericardium. Chest 1997;112(4 suppl): 291S–295S.

4 Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: An assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest 2000;117:73–78.

5 Evans WE, Pratt CB. Effect of pleural effusion on high-dose methotrexate kinetics. Clin Pharmacol Ther 1978;23:68–72.

6 Li J, Gwilt P. The effect of malignant effusions on methotrexate disposition. Cancer Chemother Pharmacol 2002;50:373–382.

7 Wagner T. [Pharmacokinetics of 5-fluorouracil and its permeation in pleural effusions in the therapy of metastatic breast cancer.] Onkologie 1984;7:22–26. German.

8 Spira A, Brahmer J. Effusions. In: Abeloff M, Armitage J, Niederhuber J et al., eds. Clinical Oncology, Third Edition. Philadelphia: Elsevier Churchill Livingstone, 2004:1179–1212.

9 Fujita A, Takabatake H, Tagaki S et al. Combination chemotherapy in patients with malignant pleural effusions from non-small cell lung cancer: Cisplatin, ifosfamide, and irinotecan with recombinant human granulocyte colony-stimulating factor support. Chest 2001;119:340–343.

10 Kimura H, Fujiwara Y, Sone T et al. EGFR mutation status in tumour-derived DNA from pleural effusion fluid is a practical basis for predicting the response to gefitinib. Br J Cancer 2006;95:1390–1395.

11 Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: A comprehensive review. Crit Rev Oncol Hematol 2004;52:199–215.

12 Gavrilovic IT, Posner JB. Brain metastases: Epidemiology and pathophysiology. J Neurooncol 2005;75:5–14.

13 Nussbaum ES, Djalilian HR, Cho KH et al. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781–1788.

14 van den Bent MJ. The role of chemotherapy in brain metastases. Eur J Cancer 2003;39:2114–2120.

15 Stewart DJ, Molepo JM, Green RM et al. Factors affecting platinum concentrations in human surgical tumour specimens after cisplatin. Br J Cancer 1995;71:598–604.

16 Heimans JJ, Vermorken JB, Wolbers JG et al. Paclitaxel (Taxol) concentrations in brain tumor tissue. Ann Oncol 1994;5:951–953.

17 Minotti V, Crino L, Meacci ML et al. Chemotherapy with cisplatin and teniposide for cerebral metastases in non-small cell lung cancer. Lung Cancer 1998;20:93–98.

18 Crino L, Scagliotti GV, Ricci S et al. Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: A randomized phase III study of the Italian Lung Cancer Project. J Clin Oncol 1999;17:3522–3530.

19 Franciosi V, Cocconi G, Michiara M et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: A prospective study. Cancer 1999;85:1599–1605.

20 Fujita A, Fukuoka S, Takabatake H et al. Combination chemotherapy of cisplatin, ifosfamide, and irinotecan with rhG-CSF support in patients with brain metastases from non-small cell lung cancer. Oncology 2000;59:291–295.

21 Robinet G, Thomas P, Breton JL et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Français de Pneumo-Cancérologie (GFPC) Protocol 95-1. Ann Oncol 2001;12:59–67.

22 Bernardo G, Cuzzoni Q, Strada MR et al. First-line chemotherapy with vinorelbine, gemcitabine, and carboplatin in the treatment of brain metastases from non-small-cell lung cancer: A phase II study. Cancer Invest 2002;20:293–302.

23 Cortes J, Rodriguez J, Aramendia JM et al. Front-line paclitaxel/cisplatin-based chemotherapy in brain metastases from non-small-cell lung cancer. Oncology 2003;64:28–35.

24 Katz A, Zalewski P. Quality-of-life benefits and evidence of antitumour activity for patients with brain metastases treated with gefitinib. Br J Cancer 2003;89(suppl 2):S15–S18.

25 Grimm S, DeAngelis L. Brain metastases. In: Kufw D, Bast R, Hait W et al., eds. Cancer Medicine, Seventh Edition. Hamilton, Canada: BC Decker Inc., 2006:1065–1070.

26 Coleman R, Rubens R. Bone metastases. In: Abeloff M, Armitage J, Niederhuber J et al., eds. Clinical Oncology, Third Edition. Philadelphia: Elsevier Churchill Livingstone, 2004:1091–1128.

27 Cherny N, Portenoy R. Cancer pain: Principles of assessment and syndromes. In: Wall P, Melzack R, eds. Textbook of Pain, Fourth Edition. Edinburgh, UK: Churchill Livingstone, 2002:1017–1064.

28 Galasko CS, Norris HE, Crank S. Spinal instability secondary to metastatic cancer. J Bone Joint Surg Am 2000;82:570–594.

29 Selvaggi G, Scagliotti GV. Management of bone metastases in cancer: A review. Crit Rev Oncol Hematol 2005;56:365–378.

30 van der Linden YM, Steenland E, van Houwelingen HC et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 2006;78:245–253.

31 Chow E, Fung K, Panzarella T et al. A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. Int J Radiat Oncol Biol Phys 2002;53:1291–1302.

32 Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res 1989:256–264.

33 Van der Linden YM, Dijkstra PD, Kroon HM et al. Comparative analysis of risk factors for pathological fracture with femoral metastases. J Bone Joint Surg Br 2004;86:566–573.

34 Prasad D, Schiff D. Malignant spinal-cord compression. Lancet Oncol 2005;6:15–24.

35 Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clin Oncol (R Coll Radiol) 2003;15:211–217.

36 Kimura M, Tominaga T. Outstanding problems with response evaluation criteria in solid tumors (RECIST) in breast cancer. Breast Cancer 2002;9:153–159.

37 Harvey HA. Issues concerning the role of chemotherapy and hormonal therapy of bone metastases from breast carcinoma. Cancer 1997;80(8 suppl):1646–1651.

38 Vansteenkiste J, Vandebroek J, Nackaerts K et al. Influence of cisplatin-use, age, performance status and duration of chemotherapy on symptom control in advanced non-small cell lung cancer: Detailed symptom analysis of a randomised study comparing cisplatin-vindesine to gemcitabine. Lung Cancer 2003;40:191–199.

39 Ellis PA, Smith IE, Hardy JR et al. Symptom relief with MVP (mitomycin C, vinblastine and cisplatin) chemotherapy in advanced non-small-cell lung cancer. Br J Cancer 1995;71:366–370.

40 Zhang XT, Li LY, Wang SL et al. Improvements in quality of life and disease-related symptoms in patients with advanced non-small cell lung cancer treated with gefitinib. Chin Med J (Engl) 2005;118:1661–1664.

41 Ross JR, Saunders Y, Edmonds PM et al. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ 2003;327:469.

42 Rosen LS, Gordon D, Tchekmedyian S et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol 2003;21:3150–3157.

43 Rosen LS, Gordon D, Tchekmedyian NS et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: A randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613–2621.

44 Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042–4057.

Radiotherapy and Oncology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Dose–response relationship and dose optimization in radiotherapy of postoperative keloids

Takashi Sakamoto [a,b,*], Natsuo Oya [a,b], Keiko Shibuya [b], Yasushi Nagata [b], Masahiro Hiraoka [b]

[a] Department of Radiation Oncology, Kumamoto University, Japan
[b] Department of Radiation Oncology and Image-applied Therapy, Kyoto University, Japan

ARTICLE INFO

Article history:
Received 18 November 2007
Received in revised form 30 December 2008
Accepted 31 December 2008
Available online xxxx

Keywords:
Postoperative keloid
Irradiation therapy
Radiotherapy
Dose relationship
Dose optimization

ABSTRACT

Background and purpose: The treatment dose and fractionation dose that are considered in postoperative keloids had been reported in the previous studies. We performed retrospective analysis to elucidate the factors influencing the treatment outcome.
Materials and methods: From 1979 to 1994, 194 lesions in 119 patients received postoperative radiotherapy after excision with the total dose ranging from 16 Gy/8 fr to 40 Gy/8 fr (mean: biologically effective dose (BED) 33.5 Gy). Kilo-voltage X-rays (55 or 100 kVp) or electron beams (4 or 6 MeV), including entire keloid scars, and any suture/puncture holes with a margin around the lesion were used. The median follow-up period was 36 months (range 12–164 months).
Results: Symptomatic pain and itching relief were achieved in 96% and 91%, respectively. The relapse rate was 11% at 20 Gy in five fractions or higher dose, while 43% at less than 20 Gy. On the other hand, the incidence of adverse effects was significantly higher for patients receiving more than 20 Gy in five fractions.
Conclusion: There was a significant correlation between the relapse rate and the total dose of irradiation, and between adverse effects and the total dose. To correlate local control and adverse effects, we proposed 20 Gy in five fractions as the optimal dose for the postoperative of keloids. A significant correlation between relapse rate and the interval time between excision and radiotherapy was not found in our current study.

There is no universally effective treatment method for keloids and hypertrophic scars. The recurrence rates after surgical excision alone vary from 50% to 80%, thus leading to the development of many adjuvant therapeutic modalities [1]. Several therapeutic techniques have been tested, including continuous pressure after surgery, corticosteroid injections [2], carbon dioxide laser [3], NdYaG laser [4], silicone gel [5], retinoic acid [6], and silastic sheet coverage [7]. However, these methods seem unsatisfactory for preventing keloid recurrence; the recurrence rate is reported to be above 50%.

The value of radiation therapy in the treatment of keloids has been known for many years. In a randomized trial, Sclafani et al. [8] observed a higher recurrence of keloids after surgery and steroid injections than after surgery and radiotherapy. After the total excision of keloids and hypertrophic scars, radiation therapy has been demonstrated as one of the most effective treatment methods to prevent recurrence, showing a recurrence rate around 20% [9–12].

In this study, we reviewed keloids treated with postoperative radiotherapy in our hospital, and retrospectively analyzed in regard to long-term control, symptomatic relief and adverse effects to elucidate the factors influencing the treatment outcome.

Materials and methods

Patients

From September 1979 to July 1994, 194 lesions in 119 patients received postoperative radiotherapy at Kyoto University Hospital. The characteristics of the patients and lesions are summarized in Tables 1 and 2. All patients were Asian, 35 men and 84 women, aged 4–75 years with a median age of 25 years. Fifty-seven of the 194 lesions had been treated previously with surgical excision and/or local steroid injection, but none had received radiotherapy previously.

Treatment methods

The treatment parameters are summarized in Table 3. Various dose schedules were used, with the total dose ranging from

* Corresponding author. Address: Department of Radiation Oncology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan.
E-mail address: stakashi@kumamoto-u.ac.jp (T. Sakamoto).

0167-8140/$ - see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.radonc.2008.12.018

Table 1
Characteristics of 119 patients.

	Number of patients
Sex	
Male	35
Female	84
Age	
<10	3
10–19	32
20–29	44
30–39	10
40–49	10
50–59	10
60–69	5
70⩽	5
Median (range) 25 (4–75)	
Keloid lesions	
1	84
2	19
3	5
4	6
5	1
6	2
7	1
12	1
Median (range) 1 (1–12)	
Total	119

Table 2
Characteristics of 194 keloids.

	Number of keloids
Previous treatment	
(−)	137
(+)	57
Size (cm)	
<2.0	10
2.0–3.9	44
4.0–5.9	34
6.0–7.9	26
8.0–9.9	23
10.0–14.9	26
15.0–19.9	17
20⩽	14
Site	
With high stretch tension	149
Sternum	68
Shoulder	40
Chest wall	23
Arm	11
Back	7
Without high stretch tension	45
Neck	15
Upper abdomen	11
Lower abdomen	10
Ear	4
Lower limbs	4
Face	1
Etiology	
Minor stimulations	109
Acne	44
Varicella	16
Vaccination	15
Insect wound	7
Herpes	1
Unknown	26
Major stimulations	85
Surgery	48
Burn	17
Trauma	17
Abscess	5
Total	194

16 Gy in 8 fractions to 40 Gy in 8 fractions. The total treatment time ranged from 5 days to 47 days, with a median of 9 days. The interval from excision to irradiation ranged from 1 day to 72 days, with a median of 7 days. Four fractions of 4 Gy in 8–10 days were the most common treatment schedule for postoperative radiotherapy.

In most cases, either 55 kVp (10 mA, 1.0 mm Be and 0.78 mm Al filters) or 100 kVp (8 mA, 1.0 mm Be and 1.7 mm Al filters) X-ray at a dose rate of 1–11 Gy/min was used. For only six lesions, 4 or 6 MeV electron beams were used. The choice of radiation source depended on the height, size, and position of the lesion. The 90% isodose target area included the entire postoperative scar and any suture/puncture hole with a margin of 3–5 mm around the lesion. Non-target areas were shielded by an individually cut 1–2 mm lead sheet.

Evaluation of treatment response and adverse effect

The initial response to treatment was evaluated in all 194 lesions at the first follow-up examination (1–6 months after the end of radiation treatment). Symptomatic relief was assessed if the lesion had caused pain and/or itching before treatment. A judgment of recurrence was made when the height of a lesion began to increase even just a little.

The existence of moderate to severe skin hyperpigmentation and/or telangiectasis with depigmentation was regarded as a positive adverse effect. Mild or transitory pigmentation, which disappeared within a year after treatment and did not affect cosmesis, was not regarded as a positive adverse effect.

Our follow-up policy for patients with keloids consists of a 6-month observation for at least 2 years after radiotherapy. We used telephone interviews for some patients who could not visit our hospital. All keloids were enrolled in the present study were followed up for 12 months or longer. The follow-up time ranged from a minimum of 12 months to a maximum of 164 months, with a median follow-up of 36 months.

Statistical analysis

In long-term recurrence rate and the positive adverse effect rate, univariate analysis using the logrank test and multivariate analysis using the Cox proportional hazard model were performed with the following factors: gender, patient age, involved site, etiology, keloid size, previous treatment, affliction time, interval from excision, source of radiation, and total dose. Various dose schedules were used, instead of the total dose, so we calculated biologically effective dose (BED) according to Kal et al. [13]. All calculations were with Stat View J 5.0 software (SAS Institute Inc, Chicago, IL). Differences with a *p-value* of less than 0.05 were considered statistically significant.

Results

Symptomatic relief is summarized in Table 4. Itching and pain relief was achieved in 91% and 96% of symptomatic keloids, respectively.

We calculated BED according to Kal et al. [13], and plotted the control rates as a function of BED. We showed a dose–response relationship in Fig. 1a. Long-term recurrence rates of postoperative keloids are shown in Fig. 1b. At 36 months, 64 of 194 keloids treated with excision and radiotherapy had relapsed (33%). The univariate and multivariate analyses are shown in Table 5. Univariate analysis showed that the recurrence rate was significantly higher

Please cite this article in press as: Sakamoto T et al. Dose–response relationship and dose optimization in radiotherapy ... Radiother Oncol (2009), doi:10.1016/j.radonc.2008.12.018