Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

Ikuo Sekine, Hiroshi Nokihara,* Minako Sumi,† Nagahiro Saijo,‡ Yutaka Nishiwaki,§ Satoshi Ishikura,|| Kiyoshi Mori,¶ Iwao Tsukiyama,# and Tomohide Tamura**

Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) ($p = 0.035$ by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

(*J Thorac Oncol.* 2006;1: 810–815)

Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

Divisions of *Internal Medicine and Thoracic Oncology, and †Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; Divisions of ‡Internal Medicine, §Thoracic Oncology, and ||Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan; and Divisions of ¶Thoracic Oncology and #Radiotherapy, Tochigi Cancer Center, Utsunomiya, Japan.

Address for correspondence: Ikuo Sekine, Division of Thoracic Oncology and Internal Medicine, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

ISSN: 1556-0864/06/0108-0810

dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter ≥ white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were breast feeding. All patients gave their written informed consent.

Pretreatment Evaluation

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

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

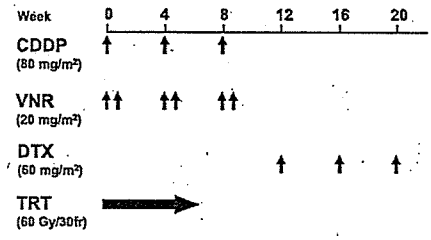


FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment (≥6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1; WBC count ≥3.0×10^9/liter, neutrophil count ≥1.5×10^9/liter, hemoglobin ≥9.0 g/dl and platelet count ≥100×10^9/liter, total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1:-WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dl or higher. The dose of vinorelbine or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. Thoracic radiotherapy was terminated if any of the following were noted: grade 4 esophagitis, grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

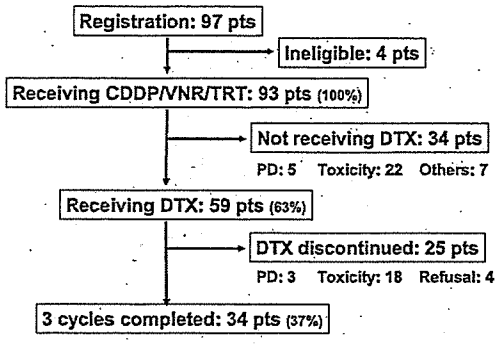


FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

Toxicity	Grade 3	Grade 4	Grade 3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

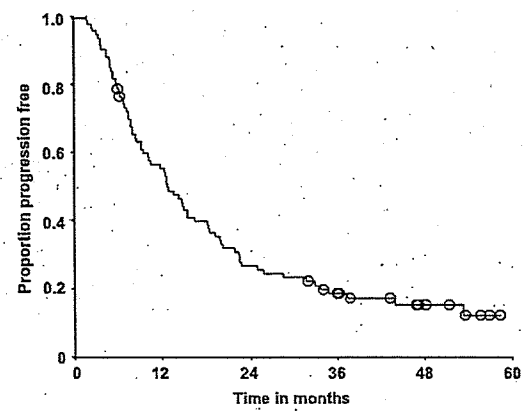


FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

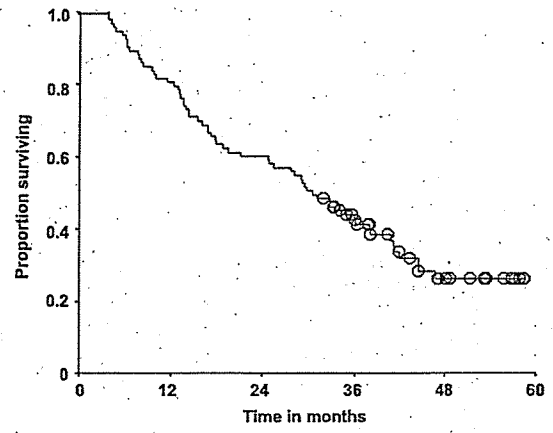


FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

ACKNOWLEDGMENTS

We thank residents and staff doctors in the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center for their care of patients and valuable suggestions and comments on this study. We would also like to thank Fumiko Koh, Yuko Yabe, and Mika Nagai for preparation of the manuscript.

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

1. Vokes EE, Crawford J, Bogart J, et al. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2006;11:5045s–5050s.
2. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.
3. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupeqqfrancaisqqqq de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2006;23:5910–5917.
4. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
5. Curran W, Scott CJ, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621 (abstr 2499).
6. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
7. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
9. Fossella FV, Lee JS, Shin DM, et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995;13:645–651.
10. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21:2004–2010.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
12. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
13. Armitage P, Berry G, Matthews J. Survival analysis. In Armitage P, Berry G, Matthews J (eds.), *Statistical Methods in Medical Research* (4th ed.). Oxford: Blackwell Science Ltd, 2002, pp. 568–590.
14. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2006;23:5883–5891.
15. Carter D, Keller A, Tolley R, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by either weekly paclitaxel or observation in patients with stage III non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2006;22:635s (abstr 7076).
16. Mac Manus MP, Hicks RJ, Matthews JP, et al. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2006; 49:95–108.

日放腫会誌 J Jpn Soc Ther Radiol Oncol 18: 107-112, 2006

JASTRO平成15・16年度研究課題報告 医療実態調査研究による放射線治療施設構造基準化（案）の改訂（日本版ブルーブック）

日本PCS作業部会
手島 昭樹[*1]，立崎 英夫[*2]，光森 通英[*3]，三橋 紀夫[*4]，宇野 隆[*5]，
中村 和正[*6]，角 美奈子[*7]，鹿間 直人[*8]，戸板 孝文[*9]，小口 正彦[*10]，
権丈 雅浩[*11]，小泉 雅彦[*12]，大西 洋[*13]，高橋 豊[*14]，古平 毅[*15]，
山内 智香子[*3]，芦野 靖夫[*16]，小川 和彦[*9]，井上 俊彦[*17]

REVISION OF GUIDELINE FOR STRUCTURE OF RADIATION ONCOLOGY BY THE PATTERNS OF CARE STUDY

Japanese PCS Working Group
Teruki Teshima[*1], Hideo Tatsuzaki[*2], Michihide Mitsumori[*3], Norio Mitsuhashi[*4], Takashi Uno[*5], Katsumasa Nakamura[*6], Minako Sumi[*7], Naoto Shikama[*8], Takafumi Toita[*9], Masahiko Oguchi[*10], Masahiro Kenjo[*11], Masahiko Koizumi[*12], Hiroshi Onishi[*13], Yutaka Takahashi[*14], Takeshi Kodaira[*15], Chikako Yamauchi[*3], Yasuo Ashino[*16], Kazuhiko Ogawa[*9], and Toshihiko Inoue[*17]

(Received 20 February 2006, accepted 11 April 2006)

Abstract: "Guidelines for Structure of Radiation Oncology in Japan" was revised by referring to annual change of structure and process in Japan and to other international guidelines. These results were published as so called "Japanese Blue Book Guidelines". Number of cancer patients who require radiation is increasing by more than 7% annually. The standard guidelines for annual patient load per FTE radiation oncologist were set at 200 (warning level 300), those per FTE radiation technologist 120 (warning level 200), and those per one external beam equipment 250-350 (warning level 400). As the standards of process, establishment of verifiable information system like radiotherapy database and hospital cancer registration was proposed. Economic analysis showed that enough profit to meet with these guidelines became available recently in most radiotherapy institutions except for the smallest group.

Key words: Patterns of Care Study, Radiation Oncology, Structural Guideline, Japanese Blue Book Guideline

[*1] 大阪大学大学院医学系研究科医用物理工学講座（〒565-0871 大阪府吹田市山田丘 1-7）
Department of Medical Physics & Engineering, Osaka University Graduate School of Medicine (1-7 Yamadaoka, Suita, Osaka 565-0871, JAPAN)
[*2] 放射線医学総合研究所国際室 International Cooperation Section, National Institute of Radiological Sciences
[*3] 京都大学大学院医学研究科放射線医学講座放射線腫瘍学・画像応用治療学
Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine Kyoto University
[*4] 東京女子医科大学放射線科 Department of Radiology, Tokyo Women's Medical University
[*5] 千葉大学大学院医学研究院放射線医学 Department of Radiology, Graduate School of Medicine, Chiba University
[*6] 九州大学大学院医学研究院臨床放射線科学 Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University
[*7] 国立がんセンター中央病院放射線治療部 Radiation Oncology Division, National Cancer Center Hospital
[*8] 信州大学医学部画像医学講座 Department of Radiology, Shinshu University School of Medicine
[*9] 琉球大学医学部放射線医学教室 Department of Radiology, University of the Ryukyus School of Medicine
[*10] 癌研究会附属病院放射線治療科 Department of Radiation Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research
[*11] 広島大学大学院医歯薬総合研究科病態情報医科学講座
Division of Medical Intelligence and Informatics, Hiroshima University Graduate School of Biomedical Sciences
[*12] 京都府立医科大学大学院放射線医学教室 Department of Radiology, Kyoto Prefectural University of Medicine
[*13] 山梨大学医学部放射線医学教室 Department of Radiology, University of Yamanashi, School of Medicine
[*14] 癌研究会癌研究所物理部 Department of Physics, Cancer Institute, Japanese Foundation for Cancer Research
[*15] 愛知がんセンター中央病院放射線治療部 Department of Radiology, Aichi Cancer Center Hospital
[*16] シー・エム・エス・ジャパン株式会社 CMS Japan, Co., Ltd.
[*17] 大阪大学名誉教授 Professor Emeritus, Osaka University

Table 1 Forecast of irradiation equipment and staff required for radiotherapy (10 years later: 2015).

		2005年との差
放射線治療機器	1,200台	450+更新350
放射線腫瘍医	1,800人	1,300
医学物理士/放射線治療品質管理士	900人	830×1.5–2
治療専任技師	2,400人	1,400
治療専任看護師	1,200人	
事務員	600人	

た．本稿では紙幅の制約上，概要を述べるに留める．

放射線治療に必要とされる照射機器とスタッフの将来予測（2015年：10年後）

Figure 1より将来需要から放射線治療機器1,200台（2005年との差450台+更新350台），放射線腫瘍医1,800人（同1,300人），物理士/放射線治療品質管理士900人（同830人），治療専任技師2,400人（同1,400人），治療専任看護師1,200人，事務員600名（Table 1）必要と試算した．物理士/放射線治療品質管理士に関しては，欧米並みの研究開発要員を含めるとさらに1.5～2倍の人員を要すると想定された．

放射線治療に必要な設備及びスタッフに関する基準

年間治療患者数/治療装置の実態を施設層毎に分布させてみると，小規模施設B2を除いて平均250～300人/台の治療を施行していた．現場の作業負荷のシミュレーションからも確認し，この値を基準値とした（Fig. 2）．しかし，上位1/4の施設では400名を超えて治療していた．これは過大な負荷であり，事故等発生のリスクがあると判断し，このレベルを改善警告値とした．尚，この分布はPCSの調査終了の2002年辺りのデータである．現状は患者数がさらに増加しているため悪化していると推定される．

一方，放射線治療の診療内容の質も装置のエネルギーやマルチリーフコリメータ（MLC）装着等のスペックに強く依存している．一施設ですべてを揃えることは必ずしも効率的とはいえず，地域医療における施設間での設備の共用ならびに患者紹介についても提言した（Fig. 3）．

年間治療患者数/FTE（full time equivalent：週40時間治療専任業務）放射線腫瘍医の分布を施設層毎にみると，小規模施設B2を除いて平均200名以上であった．米国の10数年以上前の基準（ブルーブック）も200名であり[6]，この値を基準値とした．しかし昨今の複雑な高精度放射線治療計画業務も放射線腫瘍医が受け持っている現状ではこれでもかなり厳しい条件といえるかもしれない．上位1/4の施設では300名以上治療していた．過大な負荷であり，このレベルを改善警告値とした（Fig. 4）．同様に放射線治療技師の場合は120名を基準値とし，200名を改善警告値とした．

放射線治療の質的保証

過程に関する基準ではstaging work-up等の診断や治療法の詳細な情報の管理を含んでいる．特に重要であるのは各

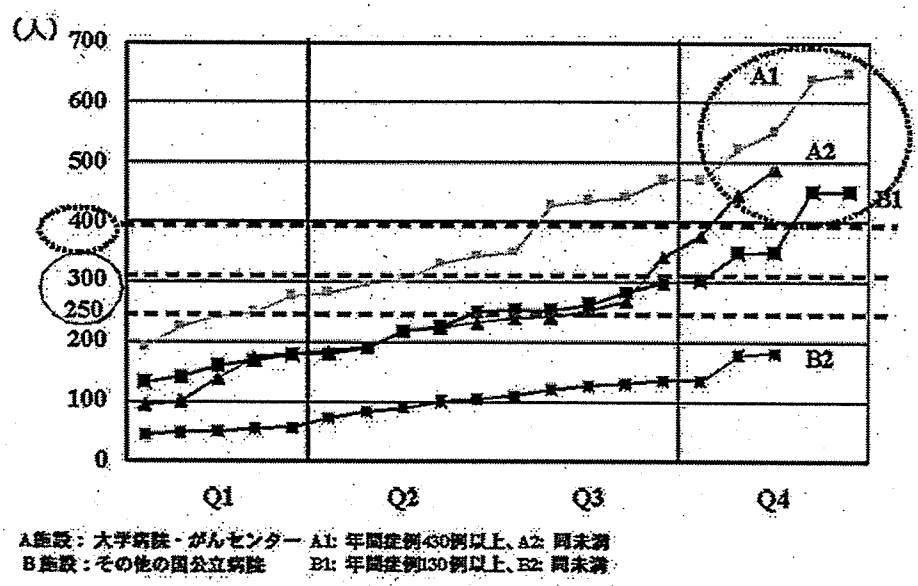


Fig. 2 Distribution of annual number of patients treated/external treatment equipment, by stratification of facility. Horizontal axis represents facilities arranged in order of increasing value of annual number of patients treated/treatment equipment within facilities in each stratum (A1, A2, B1, B2). Q1: 0-25%, Q2: 26-50%, Q3: 51-75%, Q4: 76-100%. Apart from B2 facilities, 26-75% of A2 and B1 facilities (Q2, Q3) treated approximately 250 patients per unit. At A1 facilities, the figure was approximately 350 patients. At A1-Q4 facilities, more than 450 patients/unit were treated. These facilities should consider additional equipment and staff increases (warning level).

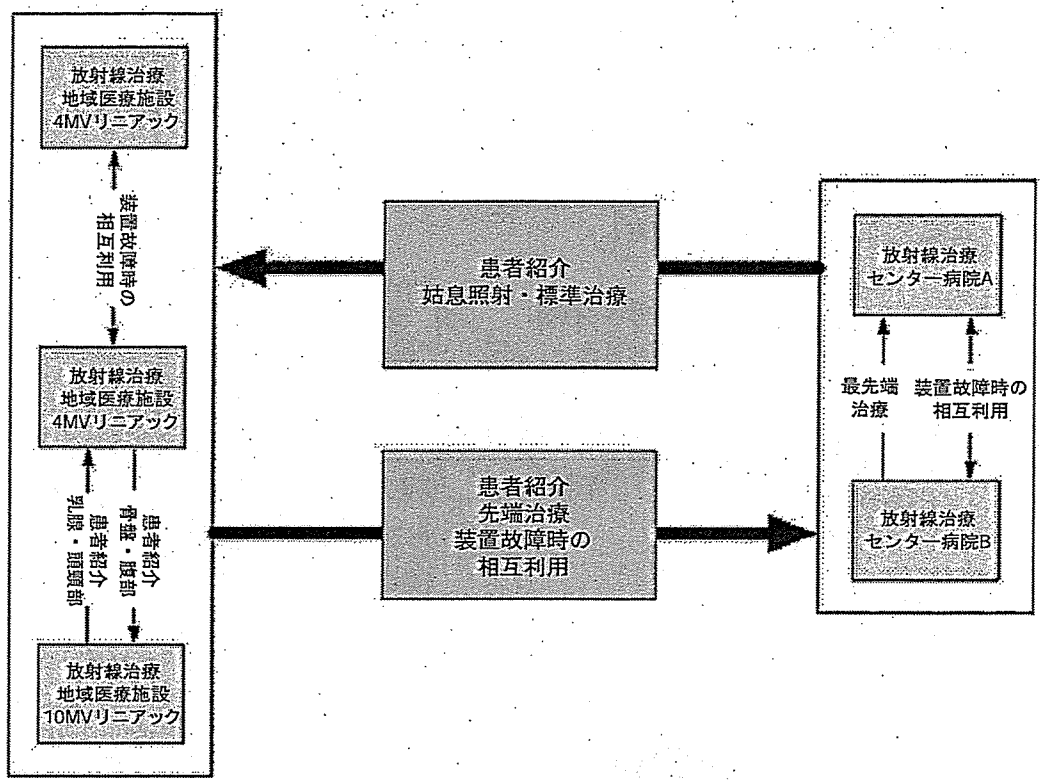


Fig. 3 Shared use of equipment and patient referral among facilities in regional treatment (example).

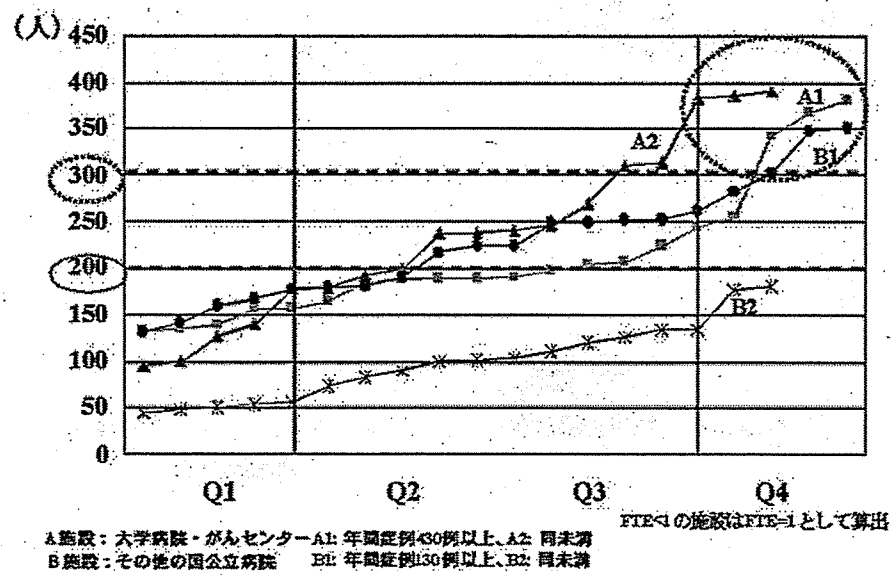


Fig. 4 Distribution of number of patients per year/number of FTE radiation oncologists at PCS 1999-2001 survey facilities. To avoid overestimation, facilities with FTE<1 were calculated as FTE=1. Apart from B2 facilities, approximately 200 patients/FTE individual were treated at 26-75% of facilities. In Q4 facilities (highest 25%), 300 or more patients were treated (warning level). In B2 facilities, the value was low, at <150, but treatment was performed by non-full time radiation oncologist (median value FTE 0.3).

放射線治療部門での診療内容が検証可能な形で確実に保存され，将来の治療成績分析を常時可能にすることである．既に実現できている先進的施設はあるが，少数である．これからの全国的な放射線治療施設の標準的インフラ整備にとって必須である．外科や内科部門に先駆けて情報系を整備することにより，evidenceを持って対峙できるだけでなく，患者や国民に放射線治療の真実の姿を示すことが可能となる．デジタルの定量データの多い放射線治療部門は患

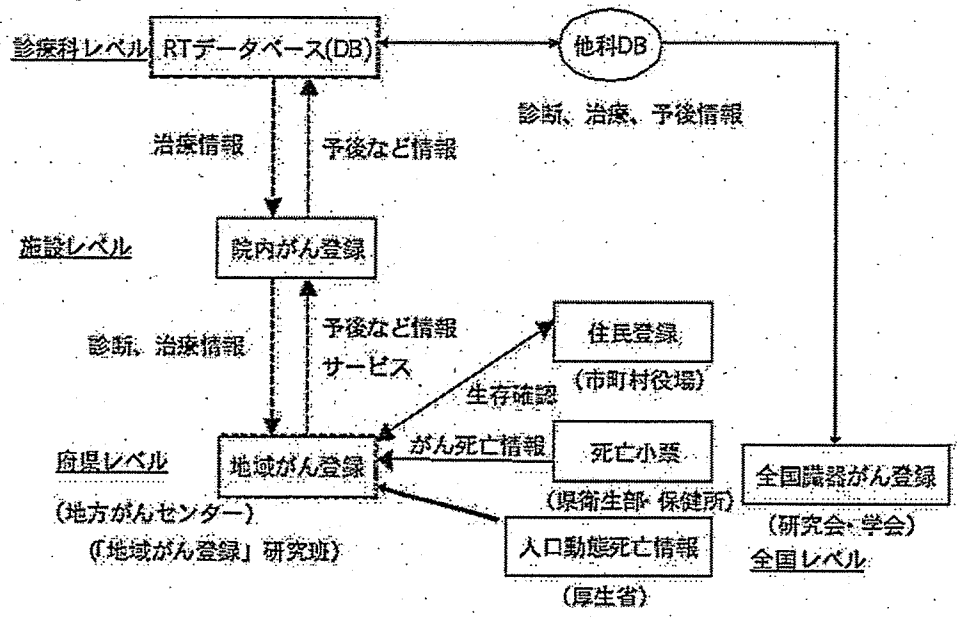
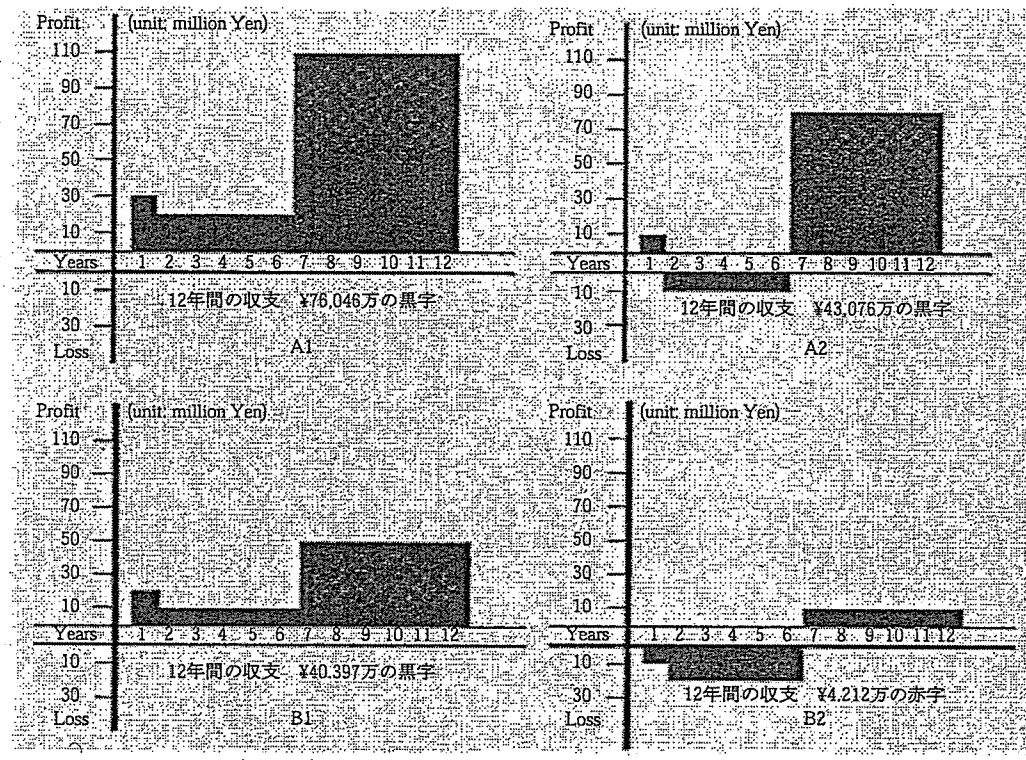


Fig. 5 Relationship between radiotherapy (RT) database and cancer registration/other database.



芦野靖夫氏CMS Japanの分析

Fig. 6 Economic analysis shows the balance of annual profit and cost in a facility with average numbers of staff and patients in each stratum. However due attention should be paid to the fact that these calculations do not include expenses such as real estate and construction costs and insurance for employees. Current break-even point was considered as approximately 150 patients/year.

者への将来の情報開示を先取りする形で，情報系を精力的に整備すべきである．現時点で整備すべき入力項目の詳細をこの章では挙げている．Figure 5 にはこれら整備された情報を最終的な結果分析に導く際に必要となる情報の流れを提示している．各施設での院内がん登録整備と同時に診療科データベースを開発していくことが鍵となる．

経済分析

PCSで測定した現有の平均的な施設構造別に長期的な収支を分析した（Fig. 6）．ただし，この分析には土地・建屋のコストは入っていない．現状では小規模施設B2を除いて黒字であり，これらの基準を実現する経済的バックグラウンドは徐々に確保されつつある．

まとめ

PCSによる十分な現地調査を行い，放射線治療実施施設でのスタッフや装置にかかる患者負荷までを考慮して従来の放射線治療施設基準化（案）を見直し，日本版ブルーブックの形で改訂した．経済分析によって本基準がより安全で質の高い放射線治療を提供するために決して過大な要求ではないことも明らかにした．

【謝辞】

本研究の機会を与えていただいた日本放射線腫瘍学会研究調査委員会各位，厚生労働省がん研究助成金阿部班（8-27），池田班（8-29），井上班（10-17），手島班（14-6）PCSの訪問調査を受け入れていただいた全国の先生各位，PCS訪問調査チームの先生各位に感謝申し上げる．本研究は日本放射線腫瘍学会平成15・16年度研究調査助成金および厚生労働省がん研究助成金手島班（14-6）の支援を受けた．

文　献

1) 阿部光幸，永田　靖，平岡眞寛，他：放射線治療施設の基準化に関する提案．日放腫会誌 **10**: 249-257, 1998.
2) 手島昭樹，井上俊彦，山下　孝，他：医療実態調査研究による放射線治療施設の基準化（案）の検証．日放腫会誌 **13**: 175-179, 2002.
3) 井上俊彦，他：特集　PCS（Patterns of Care Study）による放射線治療の現状．癌の臨床 **47**: 615-722, 2001.
4) Teshima T, Japanese PCS Working Group: Patterns of Care Study. *Jpn J Clin Oncol* **35**: 497-506, 2005.
5) 日本PCS作業部会：がんの集学治療における放射線腫瘍学―医療実態調査研究に基づく放射線治療の品質確保に必要とされる基準構造―．厚生労働省がん研究助成金計画研究班　14-6.
6) Inter-Society Council for Radiation Oncology (ISCRO): Radiation Oncology in Integrated Cancer Management. Report of the Inter-Society Council for Radiation Oncology. ACR Publications; 1991.（日本語訳，廣川　裕，池田　恢，井上俊彦，共訳，統合的癌治療における放射線腫瘍学，放射線科専門医会，1993）

要旨：PCSによる構造と過程の実態の経年変化と他の国際基準を分析し，「放射線治療施設の基準化（案）」を改訂し，その成果を「日本版ブルーブックガイドライン」として出版した．放射線治療患者数が年７％以上の割合で増加しており，主な構造基準として放射線腫瘍医への年間負荷：200名（同改善警告値：300名），技師：120名（同200名），治療装置１台：250～300名（同400名）とした．診療過程基準として検証可能な診療科データベースを含む情報システム整備を提唱した．経済分析で小規模施設を除いて多くの施設で黒字であり，これらの基準を実現する経済的バックグラウンドは徐々に整備されつつある．

放射線肺臓炎の臨床

角 美奈子* 池田 恢*

Lecture Key Notes

- 放射線肺臓炎は照射開始後週～月単位で進行し，咳・息切れ・発熱などの症状を示す．肺線維症は肺臓炎に比較し緩徐に月～年単位で進行する肺の変化であり呼吸機能の変化も徐々に出現する．
- 三次元放射線治療計画では正常な肺の線量軽減の検討が容易となり，dose-volume histogram (DVH) の検討により，20 Gy や 30 Gy が照射される正常肺の体積 (V_{20} や V_{30}) や肺の平均線量などが検討され，臨床的な肺の有害事象の発現との相関が明らかとなってきた．

はじめに

肺癌の罹患率の上昇とともに高齢者や合併症を有する症例も増加している．医療実態調査法 Patterns of Care Study (PCS) にみるわが国の肺癌の特徴の一つとして，放射線治療を施行された患者における高齢者の増加が指摘されている．放射線治療施行例の年齢中央値は 1991～2001 年治療症例を対照とした調査 (PCS 9901) では 70 歳に達しており，1995～97 年治療症例を対照とした調査 (PCS 9597) では，41%であった 70 歳以上の比率は PCS 9901 では 46%と増加していた[1]．年齢の高齢化とともに問題となるのが合併症の存在であり，何らかの合併症の記載がある症例は PCS 9901 では 56%に達しており，放射線治療の実施に際し問題となる間質性肺炎または肺線維症が 5%，肺気腫は 14%で認められていた．治療戦略を考慮するうえで，高齢者や合併症を有する症例における治療の選択は，今後さらに重要性が高くなると考えられる．

key words
放射線治療
肺の有害事象
放射線肺臓炎
三次元治療計画

放射線治療においては治療効果の向上とともに良好な生活の質 (QOL) を得るための治療の確立が急がれているが，本稿ではとくに肺癌のみならず食道癌など胸部の放射線治療において QOL に重大な影響を及ぼす有害事象である放射線肺臓炎の臨床像についてまとめる．

1. 放射線肺臓炎と肺線維症の特徴とは

局所進行非小細胞肺癌の治療ガイドラインでは放射線

*Sumi Minako, Ikeda Hiroshi／国立がんセンター中央病院 放射線治療部

表❶ 肺に関する有害事象（有害事象共通用語規準v3.0日本語訳JCOG版より）

	Grade				
	1	2	3	4	5
咳	症状があり，非麻薬性薬剤のみを要する	症状があり，麻薬性薬剤を要する	症状があり，睡眠や日常生活に顕著な支障がある	—	—
呼吸困難（息切れ）	労作時呼吸困難，ただし休息をとらずに階段を1階分登ることができる	労作時呼吸困難，ただし階段を1階分上る，または市街地の1区画（0.1 km）を歩く際に休息を要する	日常生活動作に伴う呼吸困難あり	安静時呼吸困難；挿管/人工呼吸器を要する	死亡
気道閉塞/狭窄	症状がなく，検査/内視鏡/画像により確認される閉塞または狭窄	症状があるが（例：呼吸時の気道雑音），呼吸障害を伴わない；内科的管理を要する（例：ステロイド）	日常生活に支障あり；喘鳴ありまたは内視鏡的処置を要する（例：ステント，レーザー）	生命を脅かす；気管切開または挿管を要する	死亡
肺臓炎/肺浸潤	症状がなく，画像所見のみ	症状あり，日常生活に支障がない	症状があり，日常生活に支障あり；**酸素吸入を要する**	生命を脅かす；人工呼吸を要する	死亡
肺線維症（画像上の変化）	画像上わずかな所見あり（または斑状病変や両側肺底部の変化），ただし画像所見上，線維化が総肺容積の<25%を占めると推定される	画像所見上，線維化が総肺容積の25－<50%を占めると推定される斑状病変または両側肺底部の変化	画像所見上，線維化が総肺容積の50－<75%を占めると推定される濃いまたは広範囲の浸潤/硬化	画像所見上，線維化が総肺容積の≧75%を占めると推定される；蜂巣肺	死亡

治療に関して，PSが良好で適切な肺機能を有する症例においては標準分割照射で60 Gy以上照射が勧められている[2)3)]．しかし，この線量では放射線肺臓炎（radiation pneumonitis）や肺線維症（pulmonary fibrosis）といった肺の有害事象（RT-induced lung injury）が生じてくる．

通常分割の放射線治療では各臓器に耐容線量が存在し，それ以上の線量では非可逆的遅発性放射線反応が出現する可能性が高まるとされている．各臓器は放射線による非可逆的遅発性反応の出現のタイプにより，臓器の一部分でも放射線による非可逆的反応が出現した場合に臓器機能を失う直列臓器〔serial organ（脊髄，食道，気管など）〕と，臓器全体のなかである一定の割合で非可逆的反応がおきた場合に臓器機能が不十分となる並列臓器〔parallel organ（肺，肝臓，腎臓など）〕に分けられている．Parallel organである肺については，肺を単位構造の集合と捉え，単位構造あたりの線量が一定以上になると，その単位構造には肺臓炎が発生するとされている．

放射線肺臓炎の発生時期としては照射開始後週～月単位で進行し，多くの症例は治療開始後6ヵ月頃までに咳・息切れ・発熱などの症状を示すが，肺機能検査では変化が生ずる場合と明らかでない場合がある[4)]．肺線維症は肺臓炎に比較し，より緩徐に月～年単位で進行する肺の変化であり，呼吸機能の変化も徐々に出現する．表❶にNCI-CTC有害事象共通用語規準v3.0（日本語訳JCOG版）による肺に関する有害事象と関連する項目を示すが[5)]，肺線維症の注釈に“肺線維症は放射線または集学的治療（手術を含む）より，通常>3ヵ月後にみられる“遅発性の影響”である肺組織の瘢痕化/線維化を意味する。放射線または集学的治療より，通常3ヵ月以内にみられる肺臓炎との鑑別が困難なこともある。”と記載されている．根治的放射線治療症例では照射野内に多くの症例で画像上の変化が生じてくることもあり，放射線肺臓炎と肺線維症の臨床上区別が困難であることがしばしばある．肺機能検査上の変化は症状より高頻度に認められ，CTや単一光子放射型コンピュータ断層法（single-photon-emission computed tomography：SPECT）およびポジトロン断層法（positron emission tomography：PET）上の所見が多かれ少なかれ認められる[6)]．早期診断を目的に研究されてきた指標として，インターロイキン（IL）-1αとIL-6，可溶性細胞間接着分子-1（Soluble

表❷ 非小細胞肺癌症例における症状を呈する放射線肺臓炎の臨床的因子

Author	No.	Increased risk	No change in risk	Decreased risk
Brooks *et al*, 1986[32]	80	Chemotherapy	Age KPS	
Schaake-Koning *et al*, 1992[18]	331		Chemotherapy	
Jeremic *et al*, 1996[33]	131		Chemotherapy	
Lee *et al*, 1996[21]	79	Chemotherapy		
Byhardt *et al*, 1998[34]	461	Concurrent chemotherapy		
Monson *et al*, 1998[19]	83	Smoking	Chemotherapy	Surgery
Yamada *et al*, 1998[17]	60	Tumor location Concurrent chemotherapy		
Robert *et al*, 1999[35]	43	Chemotherapy		
Quon *et al*, 1999[36]	608		Age	
Robnett *et al*, 2000[16]	148	Women Low KPS	Chemotherapy timing Tumor site	
Hernando *et al*, 2001[12]	201		Age Tumor location	Smoking
Rancati *et al*, 2003[20]	84		Age Chemotherapy	Surgery
Claude *et al*, 2004[37]	96	Age	Gender KPS Smoking Surgery Chemotherapy	

intracellular adhesion molecule-1：SICAM-1)，サイトケラチン19フラグメント（CYFRA 21-1)，血清ムチン様糖蛋白抗原KL-6（Serum mucin-like glycoprotein antigen KL-6)，呼気一酸化窒素（Exhaled nitric oxide)，肺サーファクタント蛋白D(SP-D)，transforming growth factor（TGF)-β1などがある．transforming growth factor beta（TGF-β）は肺の線維化により血液中に増加することが指摘されており[7]，IL-1αおよびIL-6は肺臓炎の早期のマーカーとして有用とする報告[8]もあり，早期診断への期待が寄せられている．

中ないし高度の放射線肺臓炎は，放射線治療および化学放射線療法後10～20%に生ずることが報告[9)-14)]されており，高度の放射線肺臓炎では死亡率が50%に達するという報告[15]もあり，高度の放射線肺臓炎を伴う症例は軽度の症例より予後不良であることが示唆されている[16]．しかし，肺の有害事象研究の課題の一つは診断基準であり，画像上の変化と臨床症状の評価により過小評価や過大評価を生じやすく，臨床研究では定義を明確にする必要がある．

2. 放射線肺臓炎の危険因子の検討がさまざまにおこなわれている

放射線肺臓炎は発生時期も治療開始後数ヵ月と長期にわたり，積極的な治療方法が確立しておらず，治療後の経過観察上の重要な要素の一つであるため，危険因子の解析もさまざまに施行されている．表❷に非小細胞肺癌症例における症状を呈する放射線肺臓炎の臨床的因子についてまとめた．放射線治療にかかわる事項については次項にまとめる．

患者側因子としては年齢やKarnofsky PS (KPS)，喫煙歴，腫瘍の位置が関係しているという報告があり，治療因子としては化学療法や手術の施行が報告されている．しかし，お互いに相反する報告も少なくない．腫瘍の位置としては，Yamadaら[17]は60例の解析で中・上葉に比し下葉で高率であったと報告しているが，Robnettら[16]は上葉と中・上葉で差はなかったとしている．放射線治療前の低肺機能も肺臓炎の発生率に関与するという報告[15)16)19)]もあり，Inoueら[16]は肺癌191例の解析で

PaO_2<80で高度の肺臓炎の発生率が有意に高かったと報告している（19% vs. 5%，p=0.034）．化学療法の関与も報告により異なる．Leeら[21]の5つの臨床試験に参加した非小細胞肺癌461症例の検討では，Grade 3以上の肺の有害事象の発生率は導入化学療法後に同時化学放射線療法施行群で高く（通常照射群で21%，多分割照射群で20%），導入化学療法後の放射線治療群では10%であったと報告している．使用される薬剤による差異も報告されており，化学療法のタイミングのみでなく薬剤による発生率の差異が検討されている．

3. 放射線肺臓炎のRisk管理に三次元治療計画の検討がはじまっている

肺癌の放射線治療ではエネルギーが低く半影の大きなコバルトによる治療は不適切とされている[21]．肺の線量増加による有害事象のリスクを高くしないためには6 MV以上のエネルギーでの放射線治療が望ましいとされている．日本における6 MV以上のX線の使用率はPCS 9597の74%よりPCS 9901では87%と増加しており，より適切な治療装置の使用が増加していることは歓迎すべき変化である．

非小細胞肺癌に対する放射線治療の進歩としては，三次元放射線治療（Three-dimensional conformal radiotherapy：3D-CRT）の応用がある．ターゲットの形状に則した照射野や線量分布の設定による周囲正常組織の線量の軽減は，治療成績の向上と有害事象の軽減をもたらしうる．ターゲットの決定において重要な役割を果たすのは画像診断であり，CTやMRI，PETなどの応用で腫瘍の浸潤・残存範囲や正常組織の機能を考慮した治療計画の可能性が実現されている．

放射線治療後の肺の有害事象に関する因子としては，1回線量や総線量が検討されてきた．二次元治療計画では照射野サイズと有害事象は比例しないとされたが[18][22]，三次元治療計画の進歩により照射体積を含む新たな指標の検討がはじまった．二次元治療計画と比較し三次元治療計画では，正常な肺の線量軽減を目的とした治療計画の比較検討が容易となっている．具体的な指標として，dose-volume histogram（DVH）の検討により，20 Gyや30 Gyが照射される正常肺の体積（V_{20}やV_{30}）や肺の平均線量などが検討されてきた（表❸）．これらの指標は臨床的な肺の有害事象の発現とよく相関している．

Grahamら[23]はV_{20}（the percent volume of the total lung exceeding 20 Gy）が，肺臓炎の良好な指標であると報告した．Grade 2以上の肺臓炎発生はV_{20}とよく相関しており，V_{20}が22%未満の症例では発症はなく，Grade 2の発生率はV_{20}が22～31%であった症例で7%（Grade 3は0%）であり，V_{20}が32～40%では13%（Grade 3は5%）と増加し，V_{20}が40%を超えると36%（Grade 3は23%）に達していた．RTOG 9311（Phase I/II）はV_{20}で層別化し，予防的リンパ節照射をしない3D-CRTで総線量増加をおこなう多施設共同臨床試験である[24]．V_{20}が25%未満の症例では83.8 Gyまで，V_{20}が25～36%であった症例では77.4 Gyまで安全な総線量増加が可能であったと報告された．RTOG L-0117（Phase I/II）では，3D-CRTを応用したdose escalationと同時併用化学療法の臨床試験が実施された．

平均肺線量（単位構造あたりの線量の全肺平均）に関しては症状を伴うSWOG grade 2以上の放射線肺臓炎との相関関係が示され，平均肺線量19 Gyで20%の患者にGrade 2以上の放射線肺臓炎がおきると報告[25]されている．Grade 3以上の放射線肺臓炎については，さらに高い線量で同様な関係があると考えられる．

現時点では放射線治療後の肺の有害事象に関する指標間の優劣の評価は一定していないが，有害事象のリスクの検討や治療計画の比較にその有用性を発揮している．体積のみでなく腫瘍の位置の重要性を指摘する報告[26]もあり，今後よりよい有害事象検討の指標の確立が望まれている．

4. 放射線肺臓炎の治療法とは

放射線肺臓炎に対する標準的な治療方法は確立されていない．Millerら[27]は，経過観察に際し腫瘍の状況とともに，肺の有害事象の判断のために咳・息切れ・発熱などの症状の確認と感染症や肺梗塞，基礎疾患としての肺疾患の急性増悪の診断の重要性を指摘している．CTや肺機能検査や気道狭窄の確認のための気管支鏡を適切に施行すべきであり，ステロイド使用前に感染症の除外が重要であるとしている．急性期の肺臓炎は典型的にはス

表❸ 放射線治療による肺の有害事象と parameter

	No.	Lung Injury End Point	V Dose Subgroup	V Dose Rate	Mean Lung Dose Subgroup	Mean Lung Dose Rate
Kwa *et al*, 1998[38]	400	Grade≧2			0-8 Gy	5%
					8-16 Gy	11%
					16-24 Gy	18%
					24-36 Gy	43%
Graham *et al*, 1999[23]	99	Grade≧2	V20 Gy<22%	0%	<10 Gy	0%
			V20 Gy 22-31%	7%	11-20 Gy	9%
			V20 Gy 32-40%	13%	21-30 Gy	24%
			V20 Gy≧40%	36%	>30 Gy	25%
Hernando *et al*, 2001[12]	201	All grades	V30 Gy≦18%	6%	<10 Gy	10%
			V30 Gy>18%	24%	10-20 Gy	16%
					21-30 Gy	27%
					>30 Gy	44%
Tsujino *et al*, 2003[39]	71	Grade≧2	V20<20%	8.7%		
			V20 21-25%	18.3%		
			V20 26-30%	51%		
			V20>31%	85%		
Seppenwoolde *et al*, 2003[25]	382	Grade≧2	V13<20%	4.2%	0-8 Gy	0%
			V13 20-30%	6.3%	8-16 Gy	4.5%
			V13 30-40%	9.6%	16-24 Gy	19.7%
			V13 40-50%	15.9%	24-36 Gy	26.9%
			V13>50%	32.0%		

＊図より計算

テロイドに反応するためプレドニゾロンで40ないし60 mg/日を数週投与したのち，10 mg/日程度を週単位でゆっくり減量していく方法や，ステロイドによるパルス療法が応用されている．遅発性の肺有害事象は照射後数ヵ月ないし数年単位で慢性の呼吸困難として発症し，照射された肺の線維化を伴っている．線維化の時期にはステロイドへの反応性は低下していることが多く，対応としては必要に応じて酸素の補給をおこなう．放射線治療後の肺の有害事象はサイトカインによる急性炎症や，ゆっくりとした線維化の過程の進行により生じてくるとされ[28]，その治療方法は確立していない．

現在臨床試験が実施されている他の方法としては放射線防護剤の検討があり，Amifostine に関しては Komaki ら[29]は Grade 3 以上の肺臓炎の発生を 16%より 0%へ減少させたと報告しており，適切な使用により肺の有害事象対策として有効であることが示されている．他にもさまざまな薬剤が現在検討されており，今後積極的な放射線肺臓炎対策としての確立が期待されている．

おわりに

肺癌の放射線治療に関しては従来の二次元治療計画による 70 Gy 以上の照射は，正常組織の線量を考慮すると不適切とする報告[30]があり，放射線肺臓炎の発生率の低減に関しては 3 D-CRT を応用した治療計画による Risk 管理が期待されている．米国の肺癌放射線治療においては 3 D-CRT が根治治療症例の多くで施行されており[31]，わが国においても普及が進んでいる．PCS 9901 では CT を用いた治療計画は，非小細胞肺癌の放射線治療においては 67%で施行されていた．3 D-CRT の実施には Multi-leaf Collimator による照射野形状の作成など，治療装置のハード面での対応も必要である．治療計画装置の進歩と治療計画の複雑化は，放射線治療の精度管理と質的保証を必要としている．放射線治療では治療装置や治療計画装置の進歩とともに，線量測定・線量計算および装置の受入れ時や日常業務のなかでの定期点検など，品質管理の重要性を認識し適切な管理のもとに治療を実施する必要がある．

また，放射線肺臓炎の管理にはそのメカニズムの解析および治療方法の開発・適正化のみならず，予防方法の研究が必要である．臨床的には，放射線治療にあたる放射線腫瘍医のみならず看護師や腫瘍内科医・外科医を含めた情報交換が必要であり，肺癌診療のシステムとチーム医療の確立を推進する必要がある．

文献

1) Sumi M *et al*：The Patterns of Care Study for Non-small Cell Lung Cancer Treated with Radiation Therapy in Japan；Analyses of Age. *Int J Radiat Oncol Biol Phys* **60**：S 526, 2004
2) Pfister DG *et al*：American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline：update 2003. *J Clin Oncol* **22**：330-353：2004
3) EBMの手法による肺癌の診療ガイドライン策定に関する研究班編：EBMの手法による肺癌診療ガイドライン2005年版．金原出版，東京，2005
4) Mehta V：Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer：pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* **63**：5-24, 2005
5) 有害事象共通用語規準v3.0日本語訳JCOG版（JCOGホームページ：http://www.jcog.jp）
6) Seppenwoolde Y *et al*：Radiation dose-effect relations and local recovery in perfusion for patients with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* **47**：681-691, 2000
7) Anscher MS *et al*：Changes in plasma TGF beta levels during pulmonary irradiation as a predictor of the risk of developing radiation pneumonitis. *Int J Radiat Oncol Biol Phys* **30**：671-676, 1994
8) Chen Y *et al*：Radiation pneumonitis and early circulatory cytokine markers. *Semin Radiat Oncol* **12**：26-33, 2002
9) Roach M 3rd *et al*：Radiation pneumonitis following combined modality therapy for lung cancer：analysis of prognostic factors. *J Clin Oncol* **13**：2606-2612, 1995
10) Segawa Y *et al*：Risk factors for development of radiation pneumonitis following radiation therapy with or without chemotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* **39**：91-98, 1997
11) Fu XL *et al*：Hyperfractionated accelerated radiation therapy for non-small cell lung cancer：clinical phase I/II trial. *Int J Radiat Oncol Biol Phys* **39**：545-552, 1997
12) Hernando ML *et al*：Radiation-induced pulmonary toxicity：a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* **51**：650-659, 2001
13) Schaake-Koning C *et al*：Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* **326**：524-530, 1992
14) Sause WT *et al*：Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588：Preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* **87**：198-205, 1995
15) Wang JY *et al*：Outcome and prognostic factors for patients with non-small-cell lung cancer and severe radiation pneumonitis. *Int J Radiat Oncol Biol Phys* **54**：735-741, 2002
16) Inoue A *et al*：Radiation pneumonitis in lung cancer patients：a retrospective study of risk factors and the long-term prognosis. *Int J Radiat Oncol Biol Phys* **49**：649-655, 2001
17) Yamada M *et al*：Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* **34**：71-75, 1998
18) Robnett TJ *et al*：Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* **48**：89-94, 2000
19) Monson JM *et al*：Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. *Cancer* **82**：842-850, 1998
20) Rancati T *et al*：Factors predicting radiation pneumonitis in lung cancer patients：a retrospective study. *Radiother Oncol* **67**：275-283, 2003
21) Lee JS *et al*：Concurrent chemoradiation therapy with oral etoposide and cisplatin for locally advanced inoperable non-small-cell lung cancer：Radiation Therapy Oncology Group protocol 91-06. *J Clin Oncol* **14**：1055-1064, 1996
22) Byhardt RW *et al*：The influence of field size and other treatment factors on pulmonary toxicity following hyperfractionated irradiation for inoperable non-small cell lung cancer (NSCLC)-analysis of a Radiation Therapy Oncology Group (RTOG) protocol. *Int J Radiat Oncol Biol Phys* **27**：537-544, 1993
23) Graham MV *et al*：Clinical dose-volume histogram analysis for pneumonitis after 3 D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* **45**：323-329, 1999

24) Bradley J *et al* : Toxicity and outcome results of RTOG 9311 : a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* **61** : 318-328, 2005
25) Seppenwoolde Y *et al* : Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. *Int J Radiat Oncol Biol Phys* **55** : 724-735, 2003
26) Yorke ED *et al* : Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small cell lung cancer patients treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* **54** : 329-339, 2002
27) Miller KL *et al* : A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. *Semin Radiat Oncol* **14** : 298-307, 2004
28) Vujaskovic Z *et al* : Radiation-induced hypoxia may perpetuate late normal tissue injury. *Int J Radiat Oncol Biol Phys* **50** : 851-855, 2001
29) Komaki R *et al* : Effects of amifostine on acute toxicity from concurrent chemotherapy and radiotherapy for inoperable non-small-cell lung cancer : report of a randomized comparative trial. *Int J Radiat Oncol Biol Phys* **58** : 1369-1377, 2004
30) Armstrong JG *et al* : Three-dimensional conformal radiation therapy may improve the therapeutic ratio of high-dose radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys* **26** : 685-689, 1993
31) Moysas B *et al* : Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol* **21** : 4553-4559, 2003
32) Brooks BJ Jr *et al* : Pulmonary toxicity with combined modality therapy for limited stage small-cell lung cancer. *J Clin Oncol* **4** : 200-209, 1986
33) Jeremic B *et al* : Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer : a randomized study. *J Clin Oncol* **14** : 1065-1070, 1996
34) Byhardt RW *et al* : Response, toxicity, failure patterns, and survival in five Radiation Therapy Oncology Group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small-cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* **42** : 469-478, 1998
35) Robert F *et al* : Phase I/II a study of concurrent paclitaxel and cisplatin with radiation therapy in locally advanced non-small cell lung cancer : analysis of early and late pulmonary morbidity. *Semin Radiat Oncol* **9** : 136-147, 1999
36) Quon H *et al* : The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. *Int J Radiat Oncol Biol Phys* **43** : 39-45, 1999
37) Claude L *et al* : A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer : clinical and dosimetric factors analysis. *Radiother Oncol* **71** : 175-181, 2004
38) Kwa SL *et al* : Evaluation of two dose-volume histogram reduction models for the prediction of radiation pneumonitis. *Radiother Oncol* **48** : 61-69, 1998
39) Tsujino K *et al* : Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* **55** : 110-115, 2003

角美奈子 : SUMI Minako
国立がんセンター中央病院 放射線治療部 医長

1986年 熊本大学医学部 卒業
同 放射線医学教室
1993年 同 大学院 卒業
国立がんセンター中央病院 放射線治療部
2002年より現職
専門分野・研究テーマ : 放射線腫瘍学

池田 恢 : IKEDA Hiroshi
国立がんセンター中央病院 放射線治療部 部長

1967年 大阪大学医学部 卒業
1973年 同 放射線医学教室
1981年 ロスアラモス・メイ中間子治療施設
1990年 大阪大学医学部 集学放射線治療学講座 助教授
1993年 国立がんセンター中央病院 放射線治療部 医長
1994年 同 部長
2002年より現職
専門分野・研究テーマ : 放射線腫瘍学

Breast Cancer
Vol. 12 No. 2 April 2005

Symposium

Treatment Outcome of Breast-Conserving Therapy in Patients with Positive or Close Resection Margins: Japanese Multi Institute Survey for Radiation dose Effect

Kumiko Karasawa*[1,2], Michihide Mitsumori*[1,3], Chikako Yamauchi*[1,3], Kotaro Gomi*[1,4], Masaaki Kataoka*[1,5], Takayoshi Uematsu*[1,6], Takeshi Kodaira*[1,7], Michitaka Yamakawa*[1], Katsuyuki Karasawa*[1], Toshikazu Watanabe*[1], Kayoko Tsujino*[1], and Masahiro Hiraoka*[1,3]

*[1]*Japanese Radiation Oncology Study Group, ICS convention design,* *[2]*Department of Radiology, School of Medicine, Juntendo University,* *[3]*Department of Therapeutic Radiology and Oncology, Graduate School of Medicine, Kyoto University,* *[4]*Department of Radiation Oncology, Cancer Institute Hospital,* *[5]*Department of Radiology, Shikoku Cancer Center,* *[6]*Division of Diagnostic Radiology and Breast Care Unit, Shizuoka Cancer Center Hospital,* *[7]*Department of Radiology, Aichi Cancer Center, Japan.*

Background: The relationship between a positive resection margin and the risk of ipsilateral breast tumor recurrence (IBTR) is controversial. To evaluate the radiation dose and other factors influencing the ipsilateral breast tumor control (IBTC) in patients with positive or close resection margins after breast conserving surgery (BCS), the Japanese Radiation Oncology Study Group (JROSG) S-99-3 study group conducted a multi-institute survey of these patients.

Methods: The patients with less than 5 mm tumor-free margins after BCS were eligible for this study. A total of 971 patients from 18 institutes were enrolled in the analysis. The final pathological margin status was classified into 3 groups. Radiation doses to the tumor bed were less than 60 Gy in 252 patients, 60 Gy in 456 patients and more than 60 Gy in 233 patients.

Results: IBTR was observed in 55 patients (5.8%). The IBTC rates at 5 and 10 years by the Kaplan Meier method were 95.6% and 87.3%, respectively. There was no significant difference in 10-year IBTC rates according to marginal status; 85.9% in positive margin patients, 91.0% in equal or less than 2 mm margin patients and 87.0% in 2.1-5 mm margin patients. Radiation dose to the tumor bed was a marginally significantly associated with the 10-year IBTC rate (≧60 Gy 90.8% vs <60 Gy 84.2%, $p = 0.057$). In patients with positive margins, IBTC with radiation dose equal to or more than 60 Gy was significantly better ($p = 0.039$). The other factors influencing the IBTC were age (≧35 years vs <35 years: $p < 0.0001$), menopausal status ($p < 0.0001$) and tumor size ($p = 0.023$).

Conclusions: In patients with positive margins, IBTC with radiation dose equal to or more than 60 Gy was significantly better than the others. We recommend that the tumor bed be irradiated with at least 60 Gy in the patients with positive margins. Further follow-up is necessary to draw final conclusions.

Breast Cancer 12:91-98, 2005.

Key words: Breast conserving therapy, Resection margin, Radiotherapy

Breast conserving therapy that consisting of gross tumor excision followed by breast irradiation is a well-recognized standard therapy for local treatment of early-stage breast cancer. There continues to be controversy as to which factors predict an increased risk of IBTR. The association between pathologic resection margin status and IBTR is a well discussed but controversial matter. Many retrospective studies have reported a significantly increased rate of IBTR in positive margin patients compared with negative margin patients, but some have not. Singletary and Freedman *et al.*

Reprint requests to Kumiko Karasawa, Department of Radiology, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.
E-mail: kkarasaw@med juntendo.ac.jp

Abbreviations:
IBTR, Ipsilateral breast tumor recurrence; IBTC, Ipsilateral breast tumor control; BCS, Breast conserving surgery; JROSG, Japanese Radiation Oncology Study Group; EIC, Extensive intraductal component; UICC, Union Internationale Centre le Cancer; ER, Estrogen receptor; BCT, Breast conserving therapy; n.s., not significant; DFM, Disease-free margin

reviewed the articles examining the relationship between resection margins and IBTR[1,2]. Singletary reported that margin detections were very heterogeneous, as some assessments were based on gross assessment during surgery, and some were based on detailed microscopic examination. Furthermore, it is also unclear what factors are associated with positive margins and IBTR in margin positive or close margin patients. Some authors reported that positive margins were associated with large tumor size, young age, axillary node-positive status, presence of lymphovascular invasion, and the presence of extensive intraductal component (EIC)[3]. It is also unclear whether high doses of boost radiation influence outcome in margin positive or close patients. Optimal breast irradiation after BCS remains an unresolved issue in those cases.

JROSG was established in 1997 as a multi-institutional cooperative organization, a national cancer study research group that studies radiotherapy either alone or in conjunction with surgery and/or chemotherapy. The members consisted of radiation oncologists nation-wide in Japan.

To evaluate the effect of the radiation dose and the other factors influencing IBTC in patients with positive or close resection margins after BCS, the JROSG S-99-3 study group conducted a multi-institutional survey of these patients. This protocol has been studied since 1999. This article evaluates the results of the study.

Materials and Methods

Since 1999, registration forms were sent to the members of JROSG. Patients were eligible for this study if they met the following entry criteria: histological documentation of carcinoma of the breast, clinical stage 0 to II, tumor diameter less than 3 cm, no extensive intraductal spread or multiple tumor foci, focally positive or close (less than 5 mm) resection margins after BCS, whole breast irradiation was performed and a follow-up period longer than 2 years or until the time of recurrence. The clinical, pathological and treatment features investigated in this study were age, menopasal status, primary tumor size, UICC clinical stage, pathologic nodal status, histologic type, hormone-receptor status, marginal status (focally positive, less than 2 mm, 2.1-5 mm), surgical method, total radiation dose to the whole breast, total radiation dose to the tumor bed and the use of adjuvant systemic therapy.

Table 1. Participating Institutes and Person in Charge

Kyoto Univ.	Mitsumori M., Yamauchi C.
Cancer Institute	Gomi K.
Shikoku Cancer Center	Kataoka M.
Tokyo Women's Medical Univ.	Karasawa Ku.
Niigata Cancer Center	Uematsu T., Sugita T.
Aichi Cancer Center	Kodaira T.
Gunma Univ.	Yamakawa M., Sakurai H.
Tokyo Met. Komagome Hosp.	Karasawa Ka.
Saku Gentral Hosp.	Watanabe T.
Hyogo Medical Center for Adults	Tsujino K.
Isezaki Municipal Hosp.	Shiojima K.
Tohoku Univ.	Kakutou Y.
Tokyo Met. Fucyu Hosp.	Kita M.
Okayama Univ.	Kobayashi Ma.
Shiga Uni. of Medical Science	Syo K.
Tokai Univ.	Oizumi Y.
Rinku General Medical Center	Shioura H.
Jikei Univ.	Kobayashi Mi

Table 2. Patients' Characteristics

Characteristics		No. of patients (%)
Age	24-35	64 (7)
	35-44	236 (25)
	45-54	391 (42)
	55-64	166 (18)
	65-74	68 (7)
	75-83	16 (2)
Menopause	Pre	514 (55)
	Term	108 (11)
	Post	319 (34)
Stage	0	13 (1)
	I	506 (54)
	II	419 (45)
T Stage	Tis	13 (1)
	T1	506 (54)
	T2	419 (45)
n Stage	n0	663 (70)
	n1	278 (30)
ER	Negative	221 (23)
	Positive	369 (39)
	Unknown	351 (37)

Between 1999 and 2002, 1007 patients from 18 institutions were registered (Table 1). Among them, 66 were ineligible due to a short follow-up period or a tumor more than 3 cm, so a total of 941 were enrolled in this analysis. The years of treatment for the study population were 1986 to 2000. The range of follow-up for surviving patients was 2