Table 1. Study protocols of PCS and OCR

	PCS	OCR
Purpose	Standardization and improvement of the quality of radiotherapy in Japan	To calculate the number of incident cases (rate) and survival rate To assist in planning and evaluating the cancer control programs
Primary contractor	Japanese PCS group supported by Ministry of Health, Labor, and Welfare	Osaka Prefecture Government, the OMA, and the OMCCCD
Covered area	Nationwide	Prefecture-wide
Starting year	1996	1962
Object treatment	Radiotherapy with/without surgery or chemotherapy	Surgery, radiotherapy, chemotherapy, hormone therapy, TAE, immune therapy, ethanol therapy, laser, and hyperthermia
Cancers	Esophagus, lung, breast, cervix, and prostate	All cancer sites (ICD-10)
Sampling method	Two-staged cluster sampling Oncologists visit the sampled hospital to collect the new patient data obtained by random sampling. The patients with distant metastasis, prior radiotherapy, and other cancer are excluded	Complete count survey Each doctor mails a registration form of cancer patients to the OCR via the OMA. Cancer death certificate data are transferred to the OCR from health centers
Follow-up method	1. Early prognosis for some patients was followed up when a radiation oncologist visited an institution to collect new data 2. Longer follow-up information was obtained by mailing method or reaudit	Three steps are taken to obtain information on the prognosis of registered cases: 1. Collation with the cancer death file 2. Collation with the death certificate file in Osaka 3. Confirmation of the case's living status by referring to registers of habitants in local municipality offices
Staging criteria	UICC TNM classification	Five categories: 1. CIS 2. Localized 3. Spread to regional lymph nodes 4. Spread to adjacent tissue 5. Metastasis to distant organ

Abbreviations: PCS = Patterns of Care Study; OCR = Osaka Cancer Registry; OMA = Osaka Medical Association; OMCCCD = Osaka Medical Center for Cancer and Cardiovascular Diseases; TAE = transcatheter arterial embolization; CIS = carcinoma *in situ*.

tion in radiotherapy. The PCS has gathered data by using a two-stage cluster sampling method (2). It is thus essential to determine whether the PCS reflects the actual conditions of radiotherapy on a national scale. In Japan, there was no nationwide database that reflected the actual state of radiation therapy except the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) structure database, which only deals with equipment and personnel patterns. On the other hand, the Osaka Cancer Registry (OCR) database is well-established and has played an important role in monitoring and predicting cancer incidence since 1965; furthermore, it has been frequently used for government policy making in Japan. The OCR database contains important information on demographics, stage, and treatment. Although perfect matching of the two databases is impossible because of the different protocols used, this comparison is useful as an initial step for an introduction of PCS into Japan.

In the current study, the patients registered in the PCS as having non–small-cell lung cancer (NSCLC) were compared with those registered in the OCR, which is the largest regional cancer registry in Japan, as the prototype of a national database that eventually could accurately reflect national practice for cancer patients in Japan (3).

Methods and patients

The study protocols of the PCS and OCR are shown in Table 1.

PCS

The Japanese PCS is a retrospective and comprehensive study of the patterns of care in clinical and research cancer radiotherapy. To improve the quality of radiation oncology nationwide, the PCS was brought to Japan from the United States courtesy of the American College of Radiotherapy, Philadelphia, PA. The PCS has been in effect since July 1996, with the job of accumulating data for patients with esophagus, lung, breast, cervix, and prostate cancer treated with radiation (1, 4). The study covers the demographics of patients, workups, treatments, types of hospital where patients have been or are being treated, and follow-up information for calculating survival and complication rates.

To compensate for the skewing that occurs in data sampling, national averages (NAs) of the PCS process were calculated using Sedransk's equation (4–6). This method calculates the average from a limited number of data, and it was modified for the Japanese PCS data by Tanisada *et al.* The PCS working group stratifies all institutions into four groups (A1, A2, B1, and B2) according to their characteristics (academic or nonacademic, the number of patients treated with radiation per year) and then randomly samples institutions from each stratum as the first stage. In the second stage, patients were randomly sampled from all eligible patients in each institution sampled. This sampling method originated as the two-stage cluster sampling of the U.S. PCS. To compensate for the imbalance in PCS data sampling, NAs in the PCS process were calculated by using the total number of institutions in each stratum and the total number of eligible cases in each sampled institution. Therefore, the actual state of the process of radiation oncology at the national level could be assessed with a limited number of patients. The NAs were calculated for mean age, rate of males, stage distributions, the rate of combined treatments, and rate of the institution by type.

The first follow-up survey was carried out in an audit between September 1998 and March 2000. The second follow-up survey was done between July 2000 and March 2001 either by mailing method or by a reaudit. In this study, we analyzed data on 906 patients with NSCLC who had been treated with radiation between 1995 and 1997 in the PCS survey. The patients with distant metastasis or other concurrent or precedent (5 years) malignancy were ineligible.

OCR

The OCR has been operating since 1962 under close cooperation between the Osaka Prefectural Environmental and Public Health Department and the Department of Cancer Control and Statistics of the Osaka Medical Center for Cancer and Cardiovascular Disease (7, 8). Registration is a passive process where each patient diagnosed with cancer living in Osaka Prefecture is registered in the OCR by his or her physician. The registry covers background data such as patient's birth, sex, and regional residential code, cancer site and stage, information on treatment and workup, type of the hospital where the patient has been or is being treated, last follow-up date, and, in the case of a patient's death, the type of hospital where the patient died and the date of death (9).

Follow-up surveys were conducted 5 years after diagnosis for cases diagnosed after 1975 and 10 years after diagnosis for cases diagnosed after 1980 (10). The subjects of our study were 845 patients treated with radiotherapy and registered as having NSCLC between 1988 and 1992, because these patients were the latest group to have received a 5-year follow-up check after diagnosis.

Comparison

Age and sex distribution were examined among the background data of the patients. Stage, type of hospital where the patients had been or were being treated, and the ratio of combined treatments (surgery and chemotherapy) were also investigated. For the PCS, the dates of the start of treatment with radiation and surgery are known. In the OCR database, on the other hand, only the date of diagnosis is recorded. Therefore, the ages of the PCS patients were calculated from earlier dates, on which either surgery or radiotherapy was performed or started, whichever occurred earlier. The ages of the OCR patients were calculated at the date of diagnosis of NSCLC.

For the OCR, the stages are classified into five categories, namely, carcinoma *in situ* (CIS), localized, spread to regional lymph nodes, spread to adjacent tissues, and metastasis to distant organs (7). The clinical cancer stages of each patient were recorded by the physician on the basis of the staging criteria in OCR as shown in Table 2. This table is based on the UICC TNM classification (11) and the Comparative Staging Guide in Surveillance, Epidemiology, and End Results Program (12), and is presented in Guidelines on Population-Based Cancer Registration in Japan (13). The PCS has been using the TNM classification by UICC for cancer stages, or the General Rule for Clinical and Pathology Record of Lung Cancer by the Japan Lung Cancer Society (4). The stages of the PCS patients were adjusted to OCR stages by a radiation oncologist (T.T.). The patients with T1, T2, T3, and N0 in the PCS group were classified into the "localized" category of OCR. Those with T4 were classified into the "spread to adjacent tissue" categories. Finally, those patients with T and ≤N1 were classified into the "spread to regional lymph nodes" category. The patients with distant metastasis and other primary cancers were excluded from the OCR dataset, because the PCS has not collected data for such patients (4).

In the PCS, the institutions in which the patients are treated with radiation are stratified into four groups: A1, A2, B1, and B2. A1 and A2 are academic institutions such as university hospitals or cancer centers, whereas B1 and B2 are nonacademic institutions such as national, prefectural, and municipal hospitals. The difference between A1 and A2 or B1 and B2 is determined by the number of patients treated with radiation per year, according to the 1995 structure survey made by JASTRO (A1 and A2, ≥300 and <300; B1 and B2 ≥120 and <120) (14). In the OCR, on the other hand, the institutions in which patients are treated are

Table 2. The definition of the OCR staging criteria based on UICC and SEER programs

The staging criteria in the OCR	Clinical stage of primary tumor			Lymph nodes	
	Primary site	Spread to adjacent tissue	Distant metastasis	Regional lymph nodes	Distant lymph nodes
Localized	+	−	−	−	−
Spread to regional lymph nodes	+	−	−	+	−
Spread to adjacent tissue	+	+	−	+/−	−
Metastasis to distant organs	+	+/−	+·−		−·+

Abbreviations: OCR = Osaka Cancer Registry; UICC = International Union Against Cancer; SEER = Surveillance, Epidemiology, and End Results; + = presence; − = absence; / = or.
+ · − and − · + indicate that either or both of distant metastasis and distant lymph nodes is/are +.

divided into "university hospitals and cancer centers," "large hospitals (number of beds ≥400)," "medium-sized hospitals (≤150 to <400)," and "small hospitals (≤20 to <150)" (9). Therefore, A1 and A2 in the PCS and university hospitals and cancer centers in the OCR are classified as "academic institutions," whereas B1 and B2 in the PCS and other institutions in the OCR are classified as "nonacademic institutions."

Survival time for the PCS was calculated from the start of treatment until the latest follow-up. For the OCR patients, the date of diagnosis was used instead of the date of the start of treatment. For the PCS patients, the follow-up rate was defined as the percentage of patients whose prognostic information had been completed at 3 years after diagnosis, because the PCS started the second follow-up survey in July 2000. For the OCR patients, the follow-up rate was defined as the percentage of patients who were followed 3 years after the diagnosis. Accordingly, the rates of prognosis were compared based on the follow-up performed 3 years after diagnosis. Moreover, the backgrounds of the patients were compared according to surgery group or nonsurgery group to examine the prognosis conditions of the two groups.

The ages listed in the two databases were compared by the *t* test, and sex distribution, stage distribution, and ratio of treatment combined with surgery or chemotherapy were compared by the chi-square test. Survival rates in the two databases were analyzed with Kaplan-Meier method and compared by the Wilcoxon test in terms of treatment combined with surgery or not.

RESULTS

Background and process

The mean age ± SD of the PCS patients was 67.3 ± 10.1 years and that of the OCR patients was 64.4 ± 11.0 years (Table 3). The mean age of the PCS patients was significantly higher than that of the OCR patients ($p = 0.000$). NA of the PCS patients was 67.2 years old. The male ratio in the PCS was 84.2% and that in the OCR was 84.0% ($p = 0.411$); the NA was 84.1%.

The numbers and ratios of the stages of the PCS and OCR patients and PCS NAs were, respectively: 219 (24.2%), 132 (15.6%), and 21.1% with localized tumors; 396 (43.7%), 309 (36.6%), and 40.1% with spread to regional lymph nodes; and 281 (31.0%), 352 (41.7%), and 31.6% with spread to adjacent tissues. The stage of 50 patients in the OCR was unknown, but there were no such patients in the PCS. The ratio of PCS patients with localized tumor was higher than that for OCR patients, whereas the reverse was true for patients in the advanced stage ($p = 0.001$), as shown in Table 4.

Ratio of combined treatment

The ratio of radiotherapy combined with surgery was significantly lower for PCS patients than for OCR patients ($p = 0.026$), at 24.2% and 28.9%, respectively, whereas PCS NA was 25.3%. The ratios of radiotherapy combined with chemotherapy for the PCS and OCR patients were 50.1% and 67.5% ($p = 0.001$), respectively, whereas PCS NA was 47.4%.

Table 3. Backgrounds of patients of PCS and OCR

	PCS	OCR	*p* value	PCS NA
Diagnosed year	1995–1997	1988–1992		
Number of patients	906	845		
Mean age (SD), years	67.3 (±10.1)	64.4 (±11.0)	0.000	67.2
Number of males (%)	763 (84.2)	710 (84.0)	0.411	(84.1)

Abbreviations: PCS = Patterns of Care Study; OCR = Osaka Cancer Registry; NA = national average; SD = standard deviation.
p value was calculated except missing data.

Table 4. Distribution of stage and combined treatment of PCS and OCR

	PCS No. patients (%)	OCR No. patients (%)	*p* value	PCS NA
Stage				
CIS	10 (1.1)	2 (0.2)		
Localized	219 (24.2)	132 (15.6)		(21.1)
Spread to regional lymph node	396 (43.7)	309 (36.6)	0.001	(40.1)
Spread to adjacent tissues	281 (31.0)	352 (41.7)		(31.6)
Unknown	0 (0)	50 (5.9)		
Combined treatment				
Combined with surgery	219 (24.2)	244 (28.9)	0.026	(25.3)
Combined with chemotherapy	454 (50.1)	570 (67.5)	0.001	(47.4)

Abbreviations: PCS = Patterns of Care Study; OCR = Osaka Cancer Registry; NA = national average; CIS = carcinoma in situ.
p value was calculated except missing data.

Type of institution

In the PCS and OCR, 51.8% and 21.1% of patients, respectively, were treated with radiation in academic institutions (Table 5). Because the PCS sampled the patients according to type of institution, the ratios of the samples were almost equal. The ratio of OCR patients treated with radiation in medium-sized hospitals was the highest.

Outcome

In the surgery group, the 3-year survival rate for the PCS was 52.5% and that of the OCR was 42.2% ($p = 0.057$); the respective follow-up rates were 64.8% and 99.2%, as shown in Fig. 1. The number of the patients who underwent surgery in the PCS was 219, and that in the OCR 244, whereas the mean age of the PCS patients was 65.2 years and that of the OCR patients 59.6 years. The mean age of the PCS patients was higher than that of the OCR patients ($p = 0.005$), but the sex distributions were almost the same ($p = 0.211$). Stage distributions were different for the two databases. The ratio of patients in the localized stage in the PCS was 37.9% and that in the OCR was 20.5%, whereas more patients in the advanced stage were registered in the OCR than in the PCS ($p = 0.001$) (Table 6).

In the nonsurgery group, the 3-year survival rate in the PCS was 20.3%, and that of the OCR was 11.3% ($p = 0.001$); the respective follow-up rates were 67.3% and 99.8%, as shown in Fig. 2. The number of patients in the nonsurgery group in the PCS was 687 and that in the OCR was 601, whereas the respective mean ages were 69.0 and 66.4 years. The mean age of the PCS patients was higher than that of the OCR patients ($p = 0.000$). Sex distribution in the two databases was almost the same ($p = 0.089$), but the distributions of stages were different ($p = 0.001$) (Table 6).

DISCUSSION

In this article, PCS data were compared with OCR data to determine whether the data collected by the PCS reflect actual conditions of the radiotherapy process for NSCLC patients in Japan. The characteristics condition of the two databases were adjusted and aligned as much as possible.

Regarding the background of the patients with NSCLC, the mean age of the PCS patients was significantly higher than that of the OCR patients. However, between 1980 and 1996, the mean age of the patients with NSCLC registered in the OCR changed from 65.2 to 67.5 years, which suggests that the difference in the mean age between the two databases may not be critical but reasonable. Furthermore, this difference might to be partially the result of the different time points used for calculating age: it was the start of treatment for PCS patients and the date of diagnosis for OCR patients. The sex distribution in the two databases was almost the same. In terms of age and sex distribution; therefore, we assume that PCS sampling is similar to that by the OCR.

Table 5. Type of institution of PCS and OCR

PCS		OCR	
Type of institution	No. patients (%)	Type of institution	No. patients (%)
A1	283 (31.2)	University hospital and cancer center	179 (21.2)
A2	187 (20.6)	Large hospitals (number of beds ≥400)	260 (30.8)
B1	261 (28.8)	Medium sized hospitals (≥150, <400)	403 (47.7)
B2	175 (19.3)	Small hospitals (≥20, <150)	1 (0.1)
		Missing	4

Abbreviations: PCS = Patterns of Care Study; OCR = Osaka Cancer Registry.

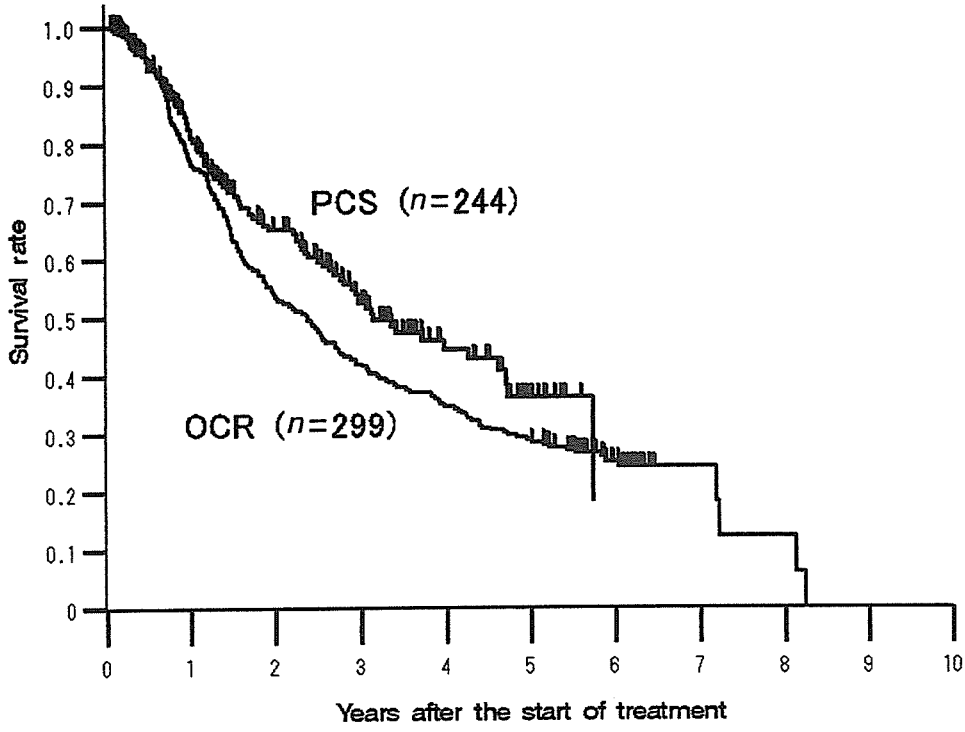

Fig. 1. Survival curves in surgery groups in Patterns of Care and Osaka Cancer Registry studies.

As for the stage, it was difficult to carry out precise comparisons because of the difference in classification criteria of the two databases. The main result showed that the ratio of patients with localized cancer was higher in the PCS than in the OCR, whereas the reverse was true for the ratio of patients in the advanced stage. The reason why more patients with more advanced stages were observed in the OCR than in the PCS is unknown. Each PCS data item was

Table 6. Background, stage, survival rate, and follow-up rate of patients in surgery group and nonsurgery group of PCS and OCR

		PCS	OCR	*p* value
Surgery group				
Number of patients		219	244	
Mean age (years)		65.2	59.6	0.005
Number of males (%)		175 (81.8)	210 (86.1)	0.211
Stage [no. patients (%)]	CIS	2 (0.9)	1 (0.4)	
	Localized	83 (37.9)	50 (20.5)	
	Spread to regional lymph node	99 (45.2)	92 (37.7)	0.001
	Spread to adjacent tissues	35 (16.0)	95 (38.9)	
	Unknown	0 (0)	6 (2.5)	
Three-year survival rate		52.5%	42.2%	0.057
Follow-up rate		64.8%	99.2%	
Nonsurgery group				
Number of patients		687	601	
Mean age (years)		69.0	66.4	0.000
Number of males (%)		588 (86.6)	500 (83.2)	0.089
Stage [no. patients (%)]	CIS	8 (1.16)	1 (0.2)	
	Localized	136 (19.8)	82 (13.6)	
	Spread to regional lymph node	297 (43.2)	217 (36.1)	0.001
	Spread to adjacent tissues	246 (35.8)	257 (42.8)	
	Unknown	0 (0)	44 (7.3)	
Three-year survival rate		20.3%	11.3%	0.001
Follow-up rate		67.3%	99.8%	

Abbreviations: PCS = Patterns of Care Study; OCR = Osaka Cancer Registry; CIS = carcinoma *in situ*.

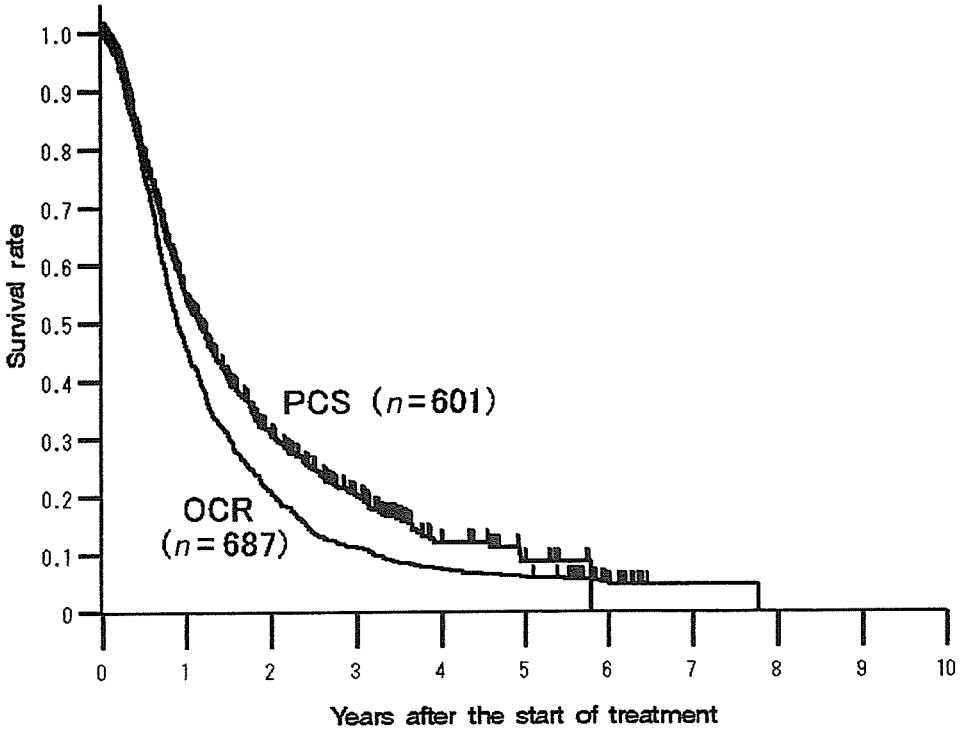

Fig. 2. Survival curves in nonsurgery groups in Patterns of Care and Osaka Cancer Registry studies.

surveyed very carefully by a radiation oncologist; therefore, the staging data in the PCS should be accurate. On the other hand, the OCR is based on registry activity, and the extraction of this study population from the entire body of OCR data was done after the registration of all data. Therefore, in the OCR registration process, patients' stages may be overestimated because they are based on passive data collection. The other possible reason is the way radiotherapy is used in Osaka Prefecture, where the frequency of radiotherapy use is higher than in other areas of Japan. The Japanese Cancer Registry groups reported on the rates of treatment obtained from 14 cancer registries in Japan. According to that report, the frequency of using radiotherapy for lung cancer, including small cell lung cancer, in Osaka Prefecture was 24.4%, higher than at any other cancer registry in Japan (14). For NSCLC patients in the OCR for the same period, the ratio of patients treated with radiation who were included in our study was 28.8%. It can therefore be concluded that patients in Osaka Prefecture are aggressively treated with radiation, even patients with advanced cancer. This difference accounts for the imbalance in stage distribution between the PCS and OCR.

As for combined treatment, the ratio of surgery use in the PCS was 4.7% higher than that in the OCR, but the OCR data show a 17.4% higher ratio of using chemotherapy. The difference could be due to the definition of combined treatment, especially for chemotherapy. In the OCR, information about treatment states what kind of treatment patients received, but whether the treatment was primary or adjuvant did not seem to be weighted in the data. For the PCS, radiation oncologists recorded only the primary use of chemotherapy. These results suggest that the sampling method of the PCS is adequate for gauging the basic treatment process for patients.

For both the surgery and nonsurgery groups, the 3-year survival rates were higher in the PCS than in the OCR. The reason for this difference is thought to be the tendency of patients in earlier stages to be more frequently entered in the PCS than in the OCR. For the nonsurgery group, the survival rate of the PCS patients was also higher than that of the OCR patients, and this difference was thought to be reflected in the surgery group. Furthermore, the follow-up time ratio was very different between the two databases. The follow-up rate of PCS was much lower than that of OCR. This study demonstrated the inferiority of follow-up rates in the PCS. Because the prognosis of the NSCLC patients is known to be very poor, many of the censored data would be classified into death cases if the follow-up rate were improved. The follow-up surveys of the OCR have been carried out thoroughly in three steps, because the OCR surveyed the registration of residents from the beginning of the study. The PCS is an ongoing study, and it is necessary to objectify the points and needs to make the follow-up surveys more thorough and complete. The reason the PCS and OCR were compared was to clarify how to further improve the PCS. The follow-up should be improved by referring to registers of inhabitants in local municipality offices and by referring to the registration records in regional cancer registries or hospital-based cancer registries. It is necessary to facilitate the utilization of these systems in Japan.

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CLINICAL INVESTIGATION **Lung**

PROCESS OF CARE AND PRELIMINARY OUTCOME IN LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS OF THE 1995–1997 PATTERNS OF CARE STUDY IN JAPAN

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Purpose: To evaluate the practice process using the national average (NA); to compare differences in the process of care by age group; and to provide a preliminary outcome data for limited-stage small-cell lung cancer in Japan.

Methods and Materials: The Patterns of Care Study conducted a nationwide survey of the care process for Stage I–III small-cell lung cancer in Japan. Patients were divided into three age groups: <65 years (younger group, n = 73); between 65 and 74 years (intermediate group, n = 81); and ≥75 years (elderly group, n = 20).

Results: The NA for the total dose was 49.0 Gy, and for use of photon energy ≥6 MV, chemotherapy, and prophylactic cranial irradiation was 77.3%, 93.2%, and 1.69%, respectively. Age stratification had no impact on the variables of radiotherapy (RT) such as total dose and field size. Only 37% of patients received chemotherapy and thoracic RT concurrently. The proportion of patients who received chemotherapy and RT concurrently was 44%, 27%, and 25% of the younger, intermediate, and elderly groups, respectively (p = 0.029). Etoposide and cisplatin were less frequently used in the elderly group (≥75 years old). Overall survival at 3 years for the entire group was 26%. The 3-year survival rate was 30% in the younger group, 28% in the intermediate group, and 9% in the elderly group. Variables found to have a significant impact on survival by multivariate analysis were the use of chemotherapy (p = 0.030), age (p = 0.032), and T stage (p = 0.042).

Conclusion: Calculated NAs showed that the results of clinical study had favorably penetrated into the practice process in Japan. The results demonstrated that patient age significantly influenced the process of chemotherapy such as the use of etoposide and cisplatin for limited-stage small-cell lung cancer in Japan. More concurrent chemotherapy and thoracic RT and the application of prophylactic cranial irradiation for complete responders need to be investigated in the future. © 2003 Elsevier Science Inc.

Patterns of Care Study, Small-cell lung cancer, Age, Chemotherapy, National average.

INTRODUCTION

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice processes for cancer patients during a specific period (1). The PCS should be the complementary study to prospective clinical trials in which oncologists search for new standards of care for cancer patients. In addition to documenting national practice patterns, the PCS is important in developing and spreading national guidelines for cancer treatment. This helps to promote more standardized care in the country.

In September 1998, the Japanese PCS started a nationwide survey for patients with lung cancer. The results of the previous study had already identified that processes in the nonacademic institutions were closely related to structural immaturity, especially in terms of equipment and personnel (2). However, we believe that the structure of radiation oncology is a domestic problem specific to each country. To allow intercomparisons with other countries, we focused on

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the influence of age on the care process for small-cell lung cancer (SCLC). The objectives of the present study were to evaluate the practice process using the national average (NA); to compare differences in the process of care by stratified age group; and to provide preliminary outcome data for limited-stage SCLC in Japan.

METHODS AND MATERIALS

Between September 1998 and March 2001, the PCS conducted a national survey of radiotherapy (RT) for patients with lung cancer in Japan. The Japanese PCS developed an original data format and performed an extramural audit survey of 78 of 556 institutions using stratified two-stage cluster sampling. The data collection method of the PCS consisted of two steps of random sampling. The first step was the classification of entire institutions into nationwide institution strata and the random selection of institutions from each stratum. The second step was the random selection of eligible patients from each sampled institution. The criteria of the institutional stratification have been detailed elsewhere (2). In brief, the PCS stratified Japanese institutions as follows: A1, academic institutions treating ≥300 patients annually; A2, <300 patients; B1, nonacademic institution treating ≥120 patients annually; and B2, <120 patients. The PCS collected specific information on 1088 patients with lung cancer treated with RT between 1995 and 1997. Eligible patients included those with 1997 International Union Against Cancer (UICC) Stage I–III SCLC, treated with RT between 1995 and 1997, with a Karnofsky performance status (KPS) >50 before the start of treatment and no evidence of other malignancies within the previous 5 years. The UICC staging system was used because the PCS comprehensively surveyed both patients with non–SCLC and those with SCLC. There were 179 Stage I–III SCLC patients, which constituted 16% of all lung cancer patients surveyed. Of those, 5 patients underwent initial surgical resection and adjuvant postoperative RT. Thus, in this study, the PCS analyzed the process and early outcome of the remaining 174 patients (139 men and 35 women; age range 37–88 years, median 65) treated without surgery. Stage I–III SCLC by the UICC system does not exactly match the definition of limited-stage SCLC by Mountain (3). However, no definition of this term has been universally accepted. The PCS survey of the RT charts revealed that the tumor of all 174 patients could be encompassed within an RT field. Thus, in the present study, all 174 patients were regarded as having limited-stage SCLC. Information about how these patients were staged was outside the scope of the audit, because the PCS survey format did not include items of detailed staging procedures.

The patients were divided into three age groups: <65 years (younger group, $n = 73$); between 65 and 74 years (intermediate group, $n = 81$); and ≥75 years (elderly group, $n = 20$). The rationales for this stratification were as follows: the median age was 65 years; and the eligibility requirements of clinical trials often exclude those ≥75 years.

To evaluate practice processes, NAs (4) from the sampling were calculated (see Appendix). The sample design allowed the estimation of the NAs for all patients who received thoracic RT during this period. The method that the PCS used to provide NAs has been described elsewhere (5, 6). The program to calculate the NAs using Statistical Analysis System, version 6.12 has been previously reported (6). The PCS surveyors consisted of 20 board-certified radiation oncologists from 10 academic institutions. For each institution, one radiation oncologist visited and surveyed the data by reviewing the patient charts. To validate the quality of the collected data, the PCS used the Internet mailing list among all the surveyors. An *in situ* real-time check and adjustment of the data input was available between each surveyor and the PCS committee. Statistical significance was tested using the chi-square test. Cases with unknown values were included when both the percentage and significance value were calculated. The initial survey form included the follow-up data of each patient. To update the individual patient follow-up data, the PCS conducted a second audit for each institution from July 2000.

Overall survival was assessed from the first day of RT and was estimated using the Kaplan-Meier product limit method. Log–rank statistics were used to identify important prognostic factors for survival. Multivariate analysis was conducted using the Cox proportional hazards model (7) to examine the effect of treatment processes and clinical factors on outcome.

RESULTS

NA for the care processes of SCLC in Japan

The NAs calculated for the process of care in Japan are listed in Table 1. The NA for patient age was 65.2 years and for the KPS of ≥80% was 69.9%. The NA for the use of chest CT in the workup was 96.1%. The NA for the total dose of RT was 49.0 Gy and for the dose prescription by isodose line was 26.7%. The NA for the use of photon energy ≥6 MV and spinal cord dose >50 Gy was 77.3% and 6.7%, respectively. The NA for the initial field size was 12.8 cm in width and 14.6 cm in length and for the field reduction during RT was 53.4%. The NAs for irradiation of the lymph node regions were as follows: ipsilateral mediastinum, 93.9%; contralateral mediastinum, 77.7%; contralateral hilus, 13.3%; and ipsilateral supraclavicular, 31.8%. The NA for the use of chemotherapy was 93.2% and for prophylactic cranial irradiation (PCI) was 1.69%.

Patient and tumor characteristics by age group

The patient and tumor characteristics by age group are shown in Table 2. A comparison of the three age groups failed to reveal differences in terms of demographic data, symptoms, or past medical history, other than cardiovascular disease. The distribution of cardiovascular disease differed significantly and was more frequently observed in the

Table 1. National averages of care processes for SCLC in Japan

Patient age	65.2
KPS ≥80 (%)	69.9
Chest CT used for workup (%)	96.1
Process of radiotherapy	
Dose prescription by isodose line (%)	26.7
Photon energy ≥6 MV (%)	77.3
Total dose (Gy)	49.0
Spinal cord >50 Gy (%)	6.7
Field size (cm) X/Y	12.8/14.6
Field included	
Ipsilateral mediastinal LNs (%)	93.9
Contralateral mediastinal LNs (%)	77.7
Contralateral hilar LNs (%)	13.3
Ipsilateral supraclavicular LNs (%)	31.8
Prophylactic cranial irradiation (%)	1.69
All fields treated/d (%)	76.1
Field reduced during course (%)	53.4
Chemotherapy received (%)	93.2

Abbreviations: SCLC = small-cell lung cancer; KPS = Karnofsky performance status; LNs = lymph nodes.

elderly group ($p = 0.031$). Patients in the elderly group tended to have a lower KPS. The proportion of patients with a KPS of ≥80 was ≥75% in the younger (<65 years) and intermediate (65–74 years) age groups and was only 45% in the elderly group (≥75 years). However, its distribution did not differ significantly among each group. No statistically significant difference was noted in either the distribution of clinical stage or the percentage of outpatients among each age group.

Treatment processes by age group

The treatment processes are detailed in Table 3. None of the variables of RT, such as total dose, photon energy, field arrangement, dose prescription method, or field size reduction during treatment, was influenced by age stratification.

Table 2. Patient and tumor characteristics by age group

	Age group (y)			
Characteristic	<65	65–74	≥75	*p*
Patients (n)	73	81	20	
Clinical stage (UICC 1997)				0.607
I	4	3	1	
IIA, IIB	3	6	0	
IIIA	24	23	10	
IIIB	39	46	9	
Unknown	3	3	0	
KPS ≥80 (%)	78	75	45	0.352
Symptom (%)				
Cough	51	63	50	0.378
Hemosputum	12	15	30	0.192
Dyspnea	27	26	10	0.424
Cardiovascular disease (%)	13	25	42	0.031
Diabetes mellitus (%)	4	9	5	0.292
Outpatient (%)	21	15	20	0.645

Abbreviations: UICC = International Union Against Cancer; KPS = Karnofsky performance status.

Seventy percent or more patients were treated with photon energies of ≥6 MV. The median initial field size in the elderly group was 12 cm in width and 12 cm in length, which was smaller than in the other age groups. However, this did not reach statistical significance. Similarly, slightly more elaborate treatment processes were observed in the younger group without significant differences. The dose was prescribed to the isodose line in 27%, 25%, and 20% of the younger, intermediate, and elderly groups, respectively. The corresponding figures for each age group were 52%, 51%, and 40% for field size reduction during treatment, 18%, 14%, and 10% for twice-daily RT, and 71%, 65%, and 55% for all field treatment daily.

The portal arrangement according to age group is shown in Fig. 1. The age stratification had no impact on the field arrangement. For ≥90% patients, the initial treatment port included the ipsilateral mediastinal lymph node area. The planning target volume covered the contralateral mediastinal lymph node region for approximately 75% of all patients irrespective of patient age. Contralateral hilus was irradiated for only 5% in the elderly group without translating into a statistically significant difference among the age groups. The ipsilateral supraclavicular lymph node region was irradiated in 22%, 30%, and 25% of the younger, intermediate, and elderly groups, respectively.

Of the 174 patients, 160 (92%) received combined chemotherapy and RT. For 37% of these patients, chemotherapy and thoracic RT were administered concurrently. For the patients who received chemotherapy, the most frequently used drugs were etoposide (91%) and cisplatin (69%). The process of chemotherapy according to age group is shown in Table 3 and Fig. 2. The elderly group received chemotherapy less frequently than the other age groups; the difference was of borderline significance ($p = 0.066$). Two key drugs, etoposide ($p = 0.017$) and cisplatin ($p = 0.001$), were less frequently used in the elderly group (≥75 years). In particular, cisplatin was used for only 19% of patients in the elderly group compared with >70% in the other age groups. The proportion of patients who received chemotherapy and RT concurrently was 44%, 27%, and 25% of the younger, intermediate, and elderly groups, respectively ($p = 0.029$). The number of chemotherapy cycles differed significantly by age group ($p = 0.001$).

Preliminary outcome analysis

The overall survival of the entire group is shown in Fig. 3. The overall survival at 3 years for the entire group was 26%; the actuarial follow-up ranged from 1.6 months to 5.8 years (median 10.4 months). The 3-year overall survival rate was 30%, 28%, and 9% for the younger, intermediate, and elderly groups, respectively. The processes and clinical factors found to be associated with improved survival on univariate analyses were Stage T1–T2 disease ($p = 0.0004$), use of chemotherapy ($p = 0.001$), and absence of cardiovascular disease ($p = 0.05$). The processes and clinical factors included in the Cox multivariate analysis were institution group, age group, cardiovascular disease, total

Table 3. Treatment processes by age group

Characteristic	Age group (y) <65	65–74	≥75	*p*
Median total dose (Gy)	50.0	50.0	50.4	0.926
Photon energy ≥6 MV (%)	75	75	70	0.630
Dose prescription by isodose line (%)	27	25	20	0.730
Twice-daily RT used (%)	18	14	10	0.662
All fields treated/d (%)	71	65	55	0.211
Median initial field size (cm)				
X	12.5	12.0	12.0	0.708
Y	14.0	14.0	12.0	0.165
Field size reduction during RT (%)	52	51	40	0.716
RT field included				
Ipsilateral mediastinal LNs (%)	95	91	90	0.710
Contralateral mediastinal LNs (%)	78	74	75	0.947
Contralateral hilar LNs (%)	18	16	5	0.667
Ipsilateral supraclavicular LNs (%)	22	30	25	0.711
Chemotherapy				
Received (%)	96	91	80	0.066
Concurrent with RT (%)	44	27	25	0.029
Etoposide (%)	96	97	75	0.017
Cisplatin (%)	77	73	19	0.001
Median cycles (*n*)	3	3	2	0.001

Abbreviations: RT = radiotherapy; LNs = lymph nodes.

dose, photon energy, field size, use of chemotherapy, T stage, N stage, and KPS (Table 4). Variables found to have a significant impact on survival were the use of chemotherapy ($p = 0.030$), age ($p = 0.032$), and T stage ($p = 0.042$).

DISCUSSION

Through this aggressive survey and data analyses, the PCS established the nationwide benchmark information on the current patterns of care for SCLC in Japan. Despite the

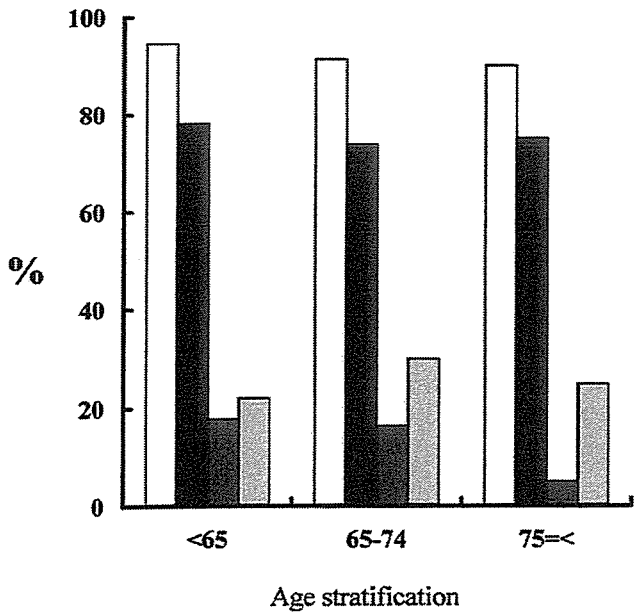

Fig. 1. Field arrangement according to stratified age group. No significant difference in portal arrangement could be seen among each age group. White bars, ipsilateral mediastinal lymph nodes; black bars, contralateral mediastinal lymph nodes; dark gray bars, contralateral hilar lymph nodes; light gray bars, ipsilateral supraclavicular lymph nodes. Differences not statistically significant.

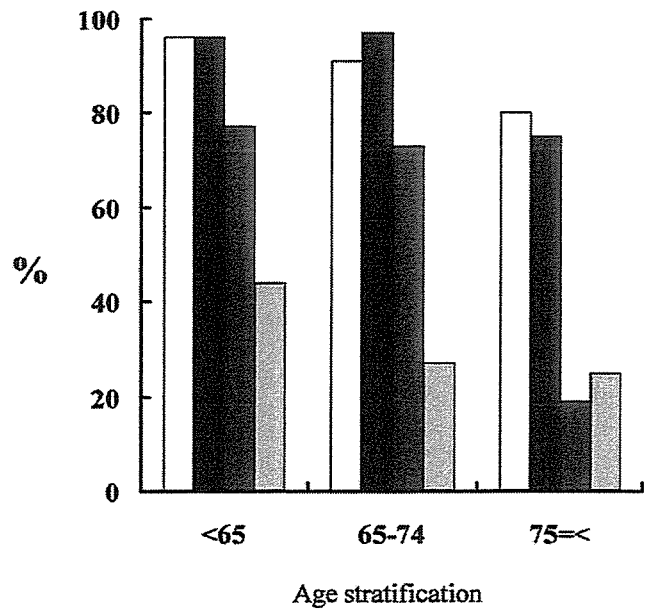

Fig. 2. Process of chemotherapy by stratified age group. Age had a significant impact on the process of chemotherapy. White bars, chemotherapy ($p = 0.066$); black bars, etoposide ($p = 0.017$); dark gray bars, cisplatin ($p = 0.001$); light gray bars, concurrent chemoradiation ($p = 0.029$).

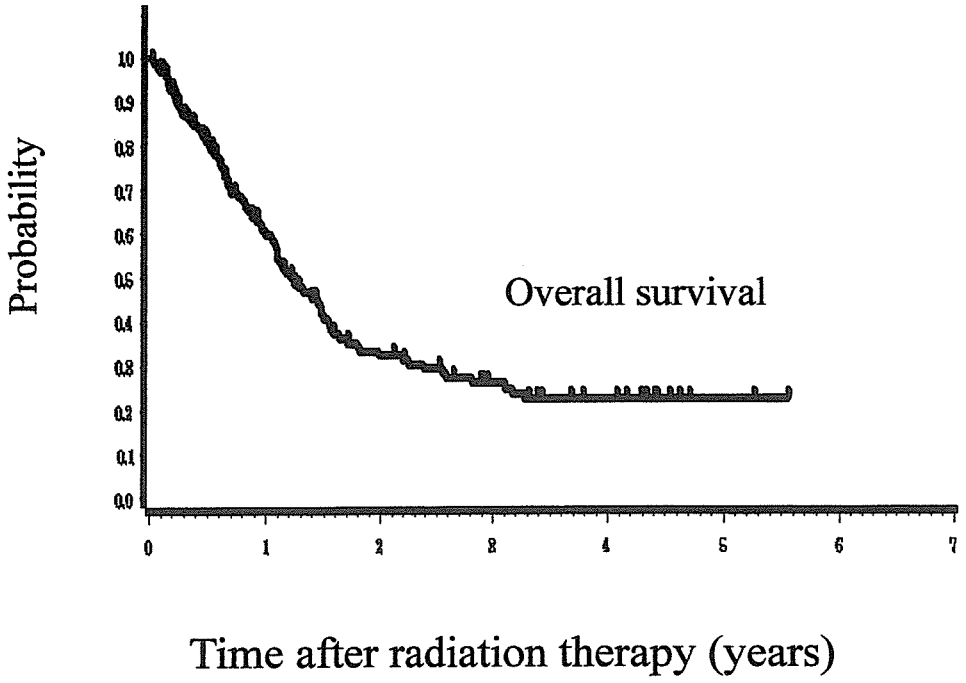

Fig. 3. Kaplan-Meier estimate of overall survival for 174 patients with Stage I–III SCLC surveyed in the 1995–1997 PCS in Japan.

lack of information about how the patients were staged, it appears that the results of this study reflect the national practice process for patients with limited-stage SCLC who received thoracic RT as a part of definitive treatment. On the basis of the results of the meta-analysis, RT was generally accepted as an essential component of standard management for limited-stage SCLC during 1995–1997 (8, 9). The NA for the use of chemotherapy was reasonably high. The most frequently used drugs were etoposide and cisplatin, and this combination was in accordance with the standard regimen at that time (10, 11). Thus, it seems that the results of clinical studies have favorably penetrated into the practice process for limited-stage SCLC during 1995–1997 in Japan. On the other hand, the lack of evidence as to the beneficial effect of PCI at that time might be reflected in its low NA. In addition, we consider that there are two profound reasons for this extremely low use of PCI in Japan.

Table 4. Multivariate analysis for survival

Variable	p	Risk ratio
Chemotherapy (yes)	0.030	0.503
Age (<75 y)	0.032	0.507
T stage (T1-2)	0.042	0.631
Karnofsky performance status (<80)	0.079	1.627
Field area (≥144 cm^2)	0.298	1.296
Institution (A1, A2)	0.411	0.833
Photon energy (≥6 MV)	0.459	0.825
Total dose (≥60 Gy)	0.753	0.923
Cardiovascular disease (yes)	0.778	1.577
N stage (N0–2)	0.788	0.926

According to the cancer statistics in Japan, RT was used for only 11.3% of all cancer patients in 1999 compared with medical treatment (27.5%) and surgical treatment (69.9%) (12). We guess that this low use of RT may reflect the practice process in Japan where many physicians are very cautious about a patient's radiation exposure even in cancer treatment. Accordingly, their patients are reluctant to receive RT even when it is beneficial. Another reason is that the structure of radiation oncology in Japan, especially in terms of personnel, is immature and still developing compared with that in the United States (13). As we have reported previously, the numbers of full-time equivalent radiation oncologists (devoting 40 h/wk to radiation oncology services) is extremely low in nonacademic institutions in Japan (2). For example, the median number of full-time equivalent radiation oncologists was 0.6 and 0.2 in B1 and B2 institutions, respectively. It can be speculated that these institutions could not offer RT properly. Because a recent meta-analysis showed a survival benefit of PCI in complete responders (14), it will be interesting to determine whether PCI has been accepted as a standard treatment in Japan. This will be clarified in the next PCS survey for patients who were treated between 1999 and 2001.

The previous PCS institution analyses had already confirmed the hypothesis that the institutional stratification might affect the process of care for lung cancer in Japan (2). For example, RT with suitable energies was more frequently done in academic institutions, and this reflected the greater flexibility of the external beam energy selection in those institutions. More than 40% of patients in nonacademic institutions treating

<120 patients annually received thoracic RT using a linear accelerator of 4 MV or a ^{60}Co machine. Institutional stratification had revealed that these institutions did not meet the basic level of equipment needed to treat patients with lung cancer. However, in the present study, age stratification had no impact on the process of RT, such as total dose, beam energy, or field size. Thus, combined with the results of the previous study, the PCS clearly demonstrated that the process of RT for SCLC in Japan was predominantly influenced by institution group rather than patient age.

On the other hand, as a result of the present study, the effect of age stratification on the practice process of chemotherapy has emerged. It appears that many physicians in Japan are tempted to alter the treatment strategy in a population with a supposed shorter life expectancy to prevent toxicities that might decrease the patient's general condition. Two key drugs are less frequently used for this group. It was also speculated that underlying cardiovascular disease precluded the use of cisplatin, which requires strict hydration. Because the eligibility criteria of most clinical trials excluded those ≥75 years mainly because of ethical reasons, information on the appropriate approach for this population is limited. A trial of concurrent chemoradiation for esophageal cancer conducted by the Radiation Therapy Oncology Group included those >80 years (15). However, the median patient age of that trial was <64 years and those aged ≥75 years constituted an extremely small proportion of the entire group. Thus, it appears that no evidence is available as to whether combined treatment can reasonably be applied to elderly patients. Although the beneficial effects of chemotherapy in this population have been reported in the treatment of non–SCLC (16, 17), controversy exists about the use of chemotherapy for the elderly group. The lack of evidence supporting the use of chemotherapy for the elderly have obscured whether the percentage of the patients who received chemotherapy in this group was high or low. Because it is very difficult to perform clinical studies that examine an aggressive experimental arm for the elderly, the role of the PCS in the establishment of more standardized care processes for this group is evolving. It was considered that the PCS should investigate the process of care for the elderly group in Japan.

In the present study, none of the processes of RT had an obvious impact on patient survival because of the possibly low rates of concurrent chemotherapy and RT. It seems that this can be explained by the concept that survival was dominated mainly by the use of chemotherapy in SCLC patients. Among medical oncologists, it is recognized that multidrug combination chemotherapy is the main treatment of patients with SCLC. However, the results of chemotherapy for SCLC have not sufficiently improved from the "state of the art" advocated in the 1980s (18).

During the past 20 years, survival prolongation in patients with limited-stage SCLC was mainly attained by clinical trials that studied some aspect of RT such as the addition of thoracic RT, a twice-daily RT technique, or PCI (8, 14, 19). Thus, the effect of the radiotherapeutic process on the outcome, including complications, should be carefully monitored in future PCS studies with an adequate follow-up.

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APPENDIX

Calculation of NAs

It was assumed that the entire RT facilities are divided into L strata and that there are N_h facilities in stratum h. The ith facility *(h, i)* belonging to stratum h has M_{hi} patients and patient *(h, i, k)* is the kth patient in facility *(h, i)*. Y_{hik} is the value for patients (h, i, k). If Y_{hik} is 1, this corresponds to "Yes" and if Y_{hik} is 0, this corresponds to "No." If calculation of the NA, θ, uses data for all patients, the calculation is represented by the following:

$$\theta = \frac{\sum_{h=1}^{L}\sum_{i=1}^{Nh}\sum_{k=1}^{Mhi} Y_{hik}}{\sum_{h=1}^{L}\sum_{i=1}^{Nh}\sum_{k=1}^{Mhi} X_{hik}} = \frac{\text{sum of } Y \text{ for all eligible patients}}{\text{number of all eligible patients}} \quad (1)$$

If patients *(h, i, k)* are included in the calculation, X_{hik} is 1; otherwise, X_{hik} is 0, and if X_{hik} is equal to 0, Y_{hik} is 0. This equation is similar to the simple method for calculating an arithmetic mean. If calculation of the NA uses randomly sampled data with adjustments of differences among institutional strata and individual facilities, the ratio estimator, $\bar{\theta}$, of θ is

$$\bar{\theta} = \frac{\sum_{h=1}^{L}\left(N_h/n_h \sum_{i=1}^{n_h} M_{hi}\,\bar{y}_{hi}\right)}{\sum_{h=1}^{L}\left(N_h/n_h \sum_{i=1}^{n_h} M_{hi}\,\bar{x}_{hi}\right)}$$

where n_h is the number of sampled institutions in stratum h, $\bar{y}_{hi}$, and $\bar{x}_{hi}$ are the means of y_{hik} and x_{hik} at all institutions and y_{hik} and x_{hik} represent the Y_{hik} and X_{hik} of all sampled patients.

2116 Risk of Radiation Pneumonitis Classified Via Dosimetric Parameters

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Purpose/Objective: To classify non-small cell lung cancer treatment plans according to the risk of grade 3, 4, or 5 pneumonitis complications.

Materials/Methods: One hundred sixty-six treatment plans were analyzed, including all patients with plan archives treated using 3-D treatment planning at Washington University between June 1991 and September 1998. There were 12 grade 3, 3 grade 4, and 4 grade 5 complications. The plans were processed, using software developed at Washington University, into a database, which contains the full treatment planning information, and which supports graphical, scripted, and interactive interrogation of the treatment plan characteristics. Heterogeneity corrected dose distributions were analyzed. For each plan two new anatomical structures were automatically generated: the normal lung volume, and the normal lung volume with the gross target volume (GTV) subtracted. Dosimetric parameters considered included: differential and cumulative dose-volume histogram parameters, in 5 Gy steps beginning at 5 Gy, mean dose, and a simple three-parameter normal tissue complication probability (NTCP) model. Pretreatment or concurrent chemotherapy was also considered. The NTCP model assumes that local physiological capacity decreases exponentially as a function of voxel dose. The overall pneumonitis complication probability is a z-shaped mathematical function of the mean residual lung capacity. Multivariable linear models were used with forward selection and backward elimination. Significance testing for goodness of fit, for either the overall multivariable linear models or the influence of individual explanatory variables, was performed using the F-test. Spearman's rank correlation coefficient (Rs) was also used for univariate significance testing.

Results: On univariate analysis, with the GTV removed from the analysis volume, including grades 3, 4, and 5, significant predictors ($p < 0.05$) were: V5, V10, V15, V20, V25, V30, V35, mean dose, and the NTCP model. Of those Vx parameters, V5 and V10 had the highest Rs. The rank of factors from most significant to least is: NTCP, V5, V10, and mean dose. The same results were obtained considering grades 4 and 5 only. A broad linear model was constructed which included chemotherapy, the NTCP model, the effect of mean dose, and differential dose histogram parameters from V5d, V10d, up to V45d, where each parameter is the fractional volume receiving dose between, say 5 Gy and 10 Gy (the next level). For grade 3, 4, and 5 complications, upon removal of the individual parameters, significant loss of correlation occurred (in order of importance) for: NTCP, mean dose, V20d, and V25d. When restricted to grades 4 and 5, significant factors included (in order of importance): V25d, NTCP, V35d, pretreatment chemotherapy, and mean dose. Simplified linear models were also constructed: for grades 3, 4, and 5, when only mean dose and NTCP were included, only the NTCP term was significant upon removal ($p < 0.00001$). For grades 4 and 5 only, pretreatment chemotherapy, mean dose, and the NTCP model were included in the simplified model. For the non-GTV analysis, only the NTCP model was significant upon removal. When the GTV was included in the analysis volume, both mean dose ($p = 0.002$) and the NTCP model ($p < 0.00001$) were significant. We hypothesize that pretreatment chemotherapy lost its predictive power in the simplified models because dosimetric factors mask its effect.

Conclusions: The risk of high and medium grade pneumonitis can be at least partially characterized using a combination of traditional dosimetric and treatment factors and mathematical models which are radiobiologically and physiologically motivated. Grade 3 or higher risk can be characterized as a linear function our NTCP model. However, multivariable linear models with more dosimetric and patient related parameters, including chemotherapy, performed marginally better. Inclusion or exclusion of the GTV from the analysis volume had only a small impact on the ability to model risk.

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2117 The Patterns of Care Study for Non-Small Cell Lung Cancer Patients Treated with Radiation Therapy in Japan: Comparison of the Process Between 1995-1997 Survey and 1999-2001 Survey

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Purpose/Objective: Radiation therapy (RT) is commonly used in the curative management of localized lung cancer. The goal of this study is to analyze the treatment process of patients with stage I-III non-small cell lung cancer (NSCLC) treated with RT in Japan. The purpose of the study presented here is to compare the results from 1995-1997 national survey and 1999-2001 national survey.

Materials/Methods: A Patterns of Care Study (PCS), a nationwide audit survey was conducted in 78 institutions out of 556 using two-staged cluster sampling and specific information was surveyed on 909 non-small cell lung cancer patients (median age, 68; range, 25-91) who received thoracic RT as part of definitive or adjuvant management in 1995 - 1997. Second survey has started in 2002 and data from 209 NSCLC patients (22 institutions) who were treated in 1999–2001 was analyzed.

Results: The characteristic of lung cancer patients has changed for several decades. The incidence of the elderly, adenocarcinoma in histology and stage I disease continue to increase from year to year 9). In PCS '99-'01, ninety-five (45.4%) patients were older than 70 years old. The relationship of age with treatment strategy showed that more elderly patients were among RT only group. There was a significantly higher rate of elderly (>70) in RT only group (86%) compared with other groups. Clinical Study was introduced in 11.5% and increased in PCS '99-'01 compared with PCS '95-'97 (0.3%). One hundred sixty-six patients (79.4%) completed planned treatment course. In PCS '99-'01, the most frequent treatment strategy was RT only (50.0%) followed by RT+OPE (30.6%) in patients with clinical stage I. In clinical stage II, there was a higher rate of RT+CTx (45.0% vs. 15.6%) and decreased rate of RT only (20.0% vs. 43.1%) in PCS '99-'01 compared with PCS '95-'97. Half of patients with clinical stage III were treated with RT+CTx. PCS '99-'01 demonstrated the increase of patients treated with RT+CTx+OPE (18.5%). One hundred twenty-nine patients (61.7%) received chemotherapy. While a significant difference in the rate of usage of platinum was apparent between RT+CTx and RT+CTx+OPE (86.6% vs.67.0%) in PCS '95-'97, chemotherapy including platinum is almost the same with RT+CTx and RT+CTx+OPE (90.5% and 91.1%) in PCS '99-'01. There was a higher rate of concurrent chemotherapy in PCS '99-'01 compared with PCS '95-'97 (61.2% vs. 46.8%).

There was some difference in usage of dose distribution configuration as the way of prescription (27.3% vs.17.1%) between PCS '99-'01 and PCS '95-'97. There was a significant difference in the rate of usage of higher energy in PCS '99-'01 from PCS '95-'97. X rays of 6MV or higher energy were used for 92.8% of the patients in PCS '99-'01. However, only 73.7% of the patients treated with higher energy X-rays in PCS '95-'97. The median spinal cord dose was 40Gy in all group. Only 6 patients (2.9%) received over 50Gy of spinal cord dose and the number was significantly decreased than PCS '95-'97 (12.0%).

Conclusions: In conclusion, the PCS of NSCLC is able to evaluate the patient characteristics, the strategy of the treatment, treatment process and outcome in patients with NSCLC treated with RT. Significant differences were noted in the equipment and treatment methods, such as frequency of use of chemotherapy administered for clinical stage II NSCLC between PCS '99-'01 and PCS '95-'97. These improvements in treatment process and equipments will reflect the quality of radiation therapy in the future practice and clinical trials.

Treatment Groups	PCS 95-97	PCS 99-01
Radiation Therapy alone (%)	308 (36.4)	56 (27.1)
RT+Chemotherapy (%)	336 (39.7)	95 (45.9)
RT+Surgery (%)	106 (12.5)	23 (11.1)
RT+Chemotherapy+Surgery (%)	96 (11.3)	33 (15.9)
Total (%)	846 (100)	207 (100)

2118 Patterns of Care Survey (PCS) in Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC) and Limited Small Cell Lung Cancer (LD-SCLC): How Well Does Current Practice Follow the Literature?

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Purpose/Objective: In LD-SCLC, combined modality therapy has emerged as the standard of practice in good performance status (PS) patients (pts). Pignons meta-analysis NEJM 1992; 327:1618-24) showed that combination chemotherapy and thoracic radiation (XRT) in LD-SCLC yielded an absolute 5.4% increase in 3-yr survival vs. chemotherapy alone. Concurrent chemoradiation upfront has generated the highest survival rates. (Murray JCO 1993; 11: 336-344; Jeremic JCO 1997; 15: 893-900; Takada JCO 2002; 20: 3054-60) In stage III NSCLC, six separate studies have shown therapeutic superiority for combination chemotherapy and XRT vs. RT alone (Dillman NEJM 1990; 323:940-945; Sause Chest 2000; 117:358-364; Schaake-Koning NEJM 1992; 326:524-530;Jeremic Cancer 1993; 71: 3732-3736), and recent literature suggests a therapeutic advantage for concurrent chemoradiation vs. chemotherapy → XRT (Curran ASCO 2000; 19: 484a; Furuse JCO 1999; 17: 2692-2699; Zatloukal ASCO 2002;A-1159). Data are less secure regarding the role of chemotherapy in stage I and II NSCLC.

Materials/Methods: A stratified two-step cluster sampling technique was used for data collection. 541 individuals diagnosed between 1998 and 1999 with lung cancer, either LD-SCLC or stages I, II, and III NSCLC were sampled from 58 institutions, which gives a weighted sample size (wss) of 42,335 patients. All pts received XRT and had KPS ≥60. We determined the percentage who received chemotherapy; the nature of chemotherapy and its timing with respect to XRT. SUDAAN statistical software was used to allow the incorporation of the design elements and weights that reflect the relative contribution of each institution and each patient in the analysis.

Results: Of 72 (wss=6,138) pts with LD-SCLC, 100% received XRT and 95% received chemotherapy (CT); 66% received concurrent (con) CT and XRT, of whom 52% also received CT pre XRT, and 45% received CT post XRT as well; 63% received sequential CT → XRT± con; and 38% received some CT after XRT. 52% received cisplatin (DDP), and 38% received carboplatin (CBDCA); 73% received VP-16, while 10% received paclitaxel. Of 469 pts (wss=36,197) with NSCLC, 52% received CT, including 30% with stage I disease, 48% with stage II NSCLC, 60% with stage III NSCLC, and 50% with unknown stage. 39% received sequential CT XRT± CT, of whom 49% received CT pre XRT only. 74% received con CT & XRT; and 27% received posterior CT, of whom 84% also received con CT/XRT. 4% received some CT in the pre-op setting and 9% in the post-op setting. 12% received DDP-based therapy, while only 13% and 7% received VP-16 or vincas respectively; 67% received CBDCA. 72% received taxanes, of whom 96% received paclitaxel. Gemcitabine was given to 3% of NSCLC patients.

Conclusions: Combined modality therapy is typically employed in the therapy of LD-SCLC and LA-NSCLC. The majority of those treated for SCLC receive concurrent CT/XRT, while nearly 3/4 of those treated with CT and XRT for LA-NSCLC received concurrent CT/XRT. Current practice generally matches evidence-based literature, although a significant % of practitioners substitute CBDCA for DDP in both venues and use paclitaxel in lieu of vincas or etoposide in NSCLC.

2119 Clinical Outcomes of Stereotactic Single High Dose Irradiation of Lung Tumors Under Respiratory Gating

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Purpose/Objective: To investigate the clinical response and the morbidities of a stereotactic single high-dose irradiation for lung tumors.

先端医療シリーズ29　脳神経外科

脳神経外科の最新医療

先端医療技術研究所

5. SRT（Stereotactic Radiotherapy）

5.1 はじめに

定位放射線照射（Stereotactic irradiation；STI）とは、厚生労働省がん研究助成金阿部班により以下のように定義されている。すなわちNarrow beamを用いて線量を集中的に照射させる技術のうち、①患者あるいはそれに連結された座標系において照射中心を固定精度内におさめるシステムであること、②定位型手術枠を用いた方法、または着脱式固定器具を用いた方法であること、③照射装置の照射中心精度が1mm以内であること、④治療中を通じて上記固定精度を保つこと、といった条件を満たす放射線治療とされている。通常の放射線治療に比較し、標的病変周囲の正常組織の線量を極力減少させつつ病巣に高線量を集中させる治療である。定位放射線照射は、ガンマナイフに代表される1回で照射する定位手術的照射（Stereotactic radiosurgery；SRS）と、分割照射する定位放射線治療（Stereotactic radiotherapy；SRT）に区別される。SRSの裏付けとなっているのはLars Leksellらの、治療体積が小さければ逆比例して耐容線量が上がり高線量1回投与が可能となる[1]という理論である。一方で、SRTは分割照射により治療可能比（＝正常組織の耐容線量/腫瘍の治癒線量）が高まるという、放射線生物学上の理論を背景としている。1回線量や照射回数などの治療スケジュールが腫瘍により理想的に設定可能であるが、精度がSRSより劣る可能性があり、さまざまな工夫が精度管理のためになされている。本稿では、SRTについて放射線生物学的特長と精度管理および臨床応用について述べる。

5.2 放射線生物学よりみた定位放射線治療

細胞死の主たる原因はDNAの二重鎖切断と考えられている。光子は物質を構成する原子と反応し高速電子を放出する。この高速二次電子がDNAの原子を直接電離したり励起して切断を起こす（直接作用）。二次電子は生体の水分子と反応し、反応活性の非常に高いラジカルを生成しDNAを損傷する（間接作用）。腫瘍細胞と正常細胞の両者で同様に障害されるDNAであるが、修復機構が正常細胞で機能するのに対し、腫瘍細胞では充分機能しないことが分割照射の利点の一つとされる。すなわち、1.5～3Gy程度の比較的低線量を照射した場合、生じたDNAのダメージを正常細胞は修復するが、腫瘍細胞は修復できず、死に至ることが期待され、分割照射が放射線治療では通常用いられている。腫瘍に大線量を照射する放射線治療としては、子宮頸癌における腔内照射や頭頸部癌に対する組織内照射のような小線源治療が良好な治療成績をあげている。しかし、近接するリスク臓器の照射線量増加により直腸炎や膀胱炎、下顎骨壊死などの副作用発症が増加することもよく知られており、放射線生物学的検討が行われてきた[2]。Linear-Quadratic model（LQ model）においては照射線量と生物学的効果は、一次的（linear）要素と二次的（quadratic）要素および回復により説明される。さらに、生物学的効果を比較する目的として使用されるbiological effective dose（BED）を用いることにより[3]、異なる線量・分割回数の治療方法の比較が可能である。分割照射の場合は照射間隔が1日以上であると完全回復と考えられるので、BED＝D（1＋d/(α＋β)）、D＝総線量、d＝1回線量と表現される。α/β値は個々の組織・臓器の障害に固有の値であり、実験的に多数報告されている。正常組織の急性反応のα/β値は大きく、急性反応は1回線量の大きさにはあまり依存しないとされる。一方、正常組織の急性反応のtarget cellsは分割照射中にも再生（repopulation）するため、治療期間の延長は急性反応を軽減する。急性反応は1週間当たりの合計線量がその反応の強弱を決定する。遅発性放射線反応のα/β値は小さく、遅発性反応の1回線量の大きさに対する感受性は急性反応に比較し高いとされる。中枢神経系では正常組織の早期反応や腫瘍に対する治療効果（early effect）についてはα/β値は10Gy前後とされ、遅発性反応（late effect）についてはα/β値は2Gy前後が用いられることが多い。SRSのような1回線量が10Gyを超える放射線治療において、このようなモデルの応用に関しては議論のあるところではあるが、他に確立されたモデルがないため、このモデルによりSRSとSRTの放射線生物学的検討がなされている。

茂松らによる検討では[4]、SRSにおける腫瘍辺縁での照射線量が20Gyであった場合、1回2Gyの標準分割照射に換算すると正常組織の早期反応や腫瘍に対する治療効果（early effect）についてはα/β＝10を用いると50Gy相当、遅発性反応（late effect）についてはα/β＝2を用いると110Gy相当となる。SRSでは

表7.5.1　Larsonらによる対象の形態と病理学的特徴よりみた治療方法の選択

Category	Pattern	特徴	代表的疾患	放射線治療
Category A	Late-responding target embedded within late-responding normal tissue	標的病変は正常組織に複雑に入り組んで存在	AVM	標的病変と正常組織が同様の線量で照射される
Category B	Late-responding target surrounded by late-responding normal tissue	標的病変と正常組織の境界が比較的明瞭	Meningioma	標的病変に集中した照射が可能
Category C	Early-responding target embedded within late-responding normal tissue	標的病変と正常組織の境界は不鮮明	Low grade astrocytoma	標的病変の辺縁では正常組織と同様の線量で照射される
Category D	Early-responding target surrounded by late-responding normal tissue	標的病変と正常組織の境界は比較的明瞭	Metastatic brain tumor	標的病変に集中した照射が可能

腫瘍の2～3mm外側では線量分布上15Gy程度の線量に低下するとしても約60Gy相当となり、この範囲に重要なリスク臓器となる神経組織などが近接すると問題となってくる。

茂松らは神経組織などリスク臓器の近接の有無により理想的なスケジュールを検討している[4]。すなわち、低リスク群では1回2Gyの標準分割照射で60Gy照射した場合のearly effectを考慮し、これを凌駕する照射スケジュールとして4分割以上の、6.9Gy×7回、6.1Gy×9回、5.1Gy×12回などを提示している。高リスク群では近接する正常組織の障害を回避するために照射線量の低減が図られるが、通常分割照射で50Gy程度の照射が行われているが、これを凌駕する照射スケジュールとして12分割以上の、3.7Gy×12回、3.1Gy×16回、2.9Gy×18回などを提示している。SRTにおける照射スケジュールは、そのmodelの確立と検証を通してさらに検討が必要な課題である。

TokuueらはSRT単独で治療し、1年以上の経過観察を行った転移性脳腫瘍64例、頭蓋底浸潤6例、原発性脳腫瘍10例の計80例を検討し、3例の有害反応を認めたと報告している[5]。2例は再々照射例であり、3例中2例は保存的治療で、1例は壊死除去術後に軽快していた。照射野径が大きい症例（4cm）および1回線量が多い症例（7.5Gy）で有害反応が出現していることを指摘している。現在われわれは通常6Gy×7回、腫瘍径が大きい場合や視神経や脳幹などリスク臓器に近接している場合4Gy×13回の治療スケジュールを用いている。このスケジュールによる転移性脳腫瘍の局所制御率は他の報告と同等の92%であり、急性期の副作用は認めていない。

分割照射において他に検討すべき問題点としては、放射線生物学的には腫瘍の再増殖や再酸素化という要素がある。低酸素細胞は放射線感受性が低く、分割照射により低酸素細胞が再酸素化されれば治療上は有利となるが、治療期間が数週間と延長すると再増殖も考慮する必要が生じてくる。

5.3　対象の形態と病理学的特徴よりみた治療方法の選択

Larsonらは定位放射線照射の対象となる病変を、その性質や形態により表7.5.1のように分類している[6]。Larsonらはglioblastomaをcategory Dに分類したがglioblastomaでは周囲の浮腫が広範に広がり、その中に腫瘍細胞が存在すると考えられ、Category Cに分類すべきという指摘がある。Category Aでは病変と正常組織が同様に照射されるがα/β値も正常組織と同様であり、Category Bでは分割回数増加によりBEDが低下するため、両者では分割照射の有用性はリスク臓器が近接する場合などに限られると考えられる。Category CおよびCategory Dでは病変のα/β値＝10であり分割照射によりBEDが上昇し、特にCategory Dでは照射線量が増大できることよりSRTの有用性が考えられている。

5.4　精度管理

STIでは治療システムの正確性（accuracy）と精度（preciseness）が問題であり、システムとしてQuality assurance（QA）が必要とされる[7]。すなわち、病巣の位置を三次元的に定めるlocalization、患者の位置を正確に設定するalignment、および治療計画と計画に一致した照射を行うdose deliveryである。

SRTの場合は定位フレームの使用が問題となり、侵襲的方法以外にさまざまに工夫された非侵襲的システムが開発されている。光学的ナビゲーションを応用し

たラジオカメラシステムもその一つである。フロリダ大学で開発された本システムは[8]、バイトプレート式ローカライズシステムと光学式ナビゲーションを組み合わせたシステムである。上顎に直接固定するバイトプレートを使用することにより、侵襲式ヘッドリングを使用した場合と同等の精度を得ている。SRSに比較しSRTでは治療期間を通じてのQAを必要とするため、重要な課題である。

治療装置の幾何学的精度の管理はSTI全体の重要な課題であるが、SRTでは、システムとしてのQAがより必要となり、治療期間を通じ一般の放射線治療に加え、SRTを行うこととなるため、精度管理システムの構築が必要であり時間と手間が問題となる。

5.5　血管性病変

脳内動静脈奇形（Arteriovenous malformation；AVM）の治療には手術や塞栓術とともに、STIが施行される。STIは手術の困難な部位でも比較的安全に治療できるという利点があり、完全閉塞率も2～3年で80～90%と高い[9~12]。しかし閉塞まで時間を要し、大きな病変の治療では出血や脳浮腫などの副作用が問題となる。閉塞率や副作用に関しては病変の大きさや線量が関与していると考えられている。Flickingerらによると351症例の治療後3～11年目の評価で血管造影上73%、MR上86%の閉塞率であったと報告している[9]。この報告では多変量解析により辺縁線量が閉塞に有意な因子として指摘され（$p < 0.0001$）、dose-response関係が示されている。副作用のリスクに関しては手術難易度・治療成績に基づいたSpetzler's grading systemがあり、大きさや部位（eloquent area）、流出静脈の経路により評価しており、STIにおいても参考とされている[13,14]。SRSによるAVM治療後の有害反応に関し、Flickingerらは Post-radiosurgery injury expression（PIE）scoreおよびSignificant Postradiosurgery Iinjury Expression（SPIE）scoreを発表している[15,16]。部位別に神経症状を伴ったMRIでの信号変化の発生頻度が異なることを指摘している（表7.5.2）。橋がもっとも危険であり中脳、基底核、視床のSRSによる脳壊死のリスクが高いことが示されている。治療方法を検討する際に部位により慎重な治療が必要である。SRTは分割照射により治療効果比が高まる可能性を期待し、SRSではリスクが高いと判断される症例など選択された症例に対し検討されている。青山らによると北海道大学附属病院の場合、①病変が大きい場合（2.5 cmあるいは10 ccを超える）、②視神経に近接している場合やeloquent areaにある場合、③標的病変が著しい不整形の場合に用いられている[17]。AVMの治療におけるSTIの評価は長期観察例の検討が現在進行中であり、今後より有効で副作用の少ない治療の確立のための努力が続けられている。

表7.5.2　Flickingerらによる AVM に対する SRS 治療例の location-risk score

部位	PIE score	SPIE score
Frontal	1	0.00
Temporal	2	1.89
Intraventricular	4	3.72
Parietal	2	4.83
Cerebellar	2	4.87
Corpus callosum	4	5.99
Occipital	3	6.04
Medulla	4	6.96
Thalamus	4	7.71
Basal ganglia	3	8.01
Pons / midbrain	4	10.00

PIE = Postradiosurgery Iinjury Expression score.
SPIE = Significant Postradiosurgery Iinjury Expression score

5.6　原発性脳腫瘍

原発性脳腫瘍において最も頻度の高い神経膠腫に関しては、STIの応用がさまざまな方法で試みられている[18~20]。悪性神経膠腫の再発形式の検討では、局所再発が多いことが指摘されており、小線源治療[21,22]やSTIによる追加照射が検討されている。STIは小線源治療や術中照射に比較し、標的体積に合わせた治療計画が可能であり線量分布の適正化においても自由度が高いと考えられる。さらにSRTは、放射線生物学的に治療可能比の向上が期待されるが、これは臨床試験により証明される必要がある[23]。追加照射が可能な症例は全身状態や腫瘍の大きさ、占拠部位などで選択された比較的予後良好群に属している可能性があり[24]、STIの意義を検討するためには充分に検討された前向き臨床試験による評価が必要である。Glioblastomaを対象にRadiation Therapy Oncology Group（RTOG）において施行されたchemoradiation（60 Gy/30Fr＋BCNU）±SRS（腫瘍径により15～24 Gy）の第Ⅲ相試験（RTOG9305）や、chemoradiation（50Gy/25Fr＋BCNU）＋SRT boost（腫瘍径により5または7 Gy×4）の第Ⅱ相試験（RTOG BR-0023）の治療成績の検討により悪性神経膠腫に対するSTIの応用について新たな知見が期待される。

髄膜腫はLarsonらの分類でcategory Bを代表する