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**CLINICAL INVESTIGATION** — **Radiation Oncology Practice**

# JAPANESE STRUCTURE SURVEY OF RADIATION ONCOLOGY IN 2005 BASED ON INSTITUTIONAL STRATIFICATION OF PATTERNS OF CARE STUDY

TERUKI TESHIMA, M.D.,* HODAKA NUMASAKI, M.S.,* HITOSHI SHIBUYA, M.D.,† MASAMICHI NISHIO, M.D.,‡ HIROSHI IKEDA, M.D.,§ HISAO ITO, M.D.,¶ KENJI SEKIGUCHI, M.D.,‖ NORIHIKO KAMIKONYA, M.D.,# MASAHIKO KOIZUMI, M.D.,** MASAO TAGO, M.D.,†† YASUSHI NAGATA, M.D.,‡‡ HIDEKAZU MASAKI, M.D.,§§ TETSUO NISHIMURA, M.D.,¶¶ SHOGO YAMADA, M.D.,‖‖ AND JAPANESE SOCIETY OF THERAPEUTIC RADIOLOGY AND ONCOLOGY DATABASE COMMITTEE

*Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Suita, Osaka, Japan; †Department of Radiology, Tokyo Dental and Medical University, Tokyo, Japan; ‡Department of Radiology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Hokkaido, Japan; §Division of Radiation Oncology, National Cancer Center, Tokyo, Japan; ¶Department of Radiology, Chiba University Graduate School of Medicine, Chiba, Japan; ‖Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan; #Department of Radiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; **Department of Radiological Technology, Fujita Health University School of Health Sciences, Nagoya, Aichi, Japan; ††Department of Radiology, University of Tokyo Hospital, Tokyo, Japan; ‡‡Department of Radiation Oncology and Image-Applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, Japan; §§Department of Radiology, National Center for Child Health and Development, Tokyo, Japan; ¶¶Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan; and ‖‖Tohoku University Hospital Cancer Center, Sendai, Japan

**Purpose:** To evaluate the structure of radiation oncology in Japan in terms of equipment, personnel, patient load, and geographic distribution to identify and improve any deficiencies.

**Methods and Materials:** A questionnaire-based national structure survey was conducted between March 2006 and February 2007 by the Japanese Society of Therapeutic Radiology and Oncology. These data were analyzed in terms of the institutional stratification of the Patterns of Care Study.

**Results:** The total numbers of new cancer patients and total cancer patients (new and repeat) treated with radiotherapy in 2005 were estimated at approximately 162,000 and 198,000, respectively. In actual use were 765 linear accelerators, 11 telecobalt machines, 48 GammaKnife machines, 64 $^{60}$Co remote-controlled after-loading systems, and 119 $^{192}$Ir remote-controlled after-loading systems. The linear accelerator systems used dual-energy function in 498 systems (65%), three-dimensional conformal radiotherapy in 462 (60%), and intensity-modulated radiotherapy in 170 (22%). There were 426 Japanese Society of Therapeutic Radiology and Oncology-certified radiation oncologists, 774 full-time equivalent radiation oncologists, 117 medical physicists, and 1,635 radiation therapists. Geographically, a significant variation was found in the use of radiotherapy, from 0.9 to 2.1 patients/1,000 population. The annual patient load/FTE radiation oncologist was 247, exceeding the Blue Book guidelines level. Patterns of Care Study stratification can clearly discriminate the maturity of structures according to their academic nature and caseload.

**Conclusions:** The Japanese structure has clearly improved during the past 15 years in terms of equipment and its use, although the shortage of manpower and variations in maturity disclosed by this Patterns of Care Study stratification remain problematic. These constitute the targets for nationwide improvement in quality assurance and quality control. 

Structure survey, Radiotherapy facility, Radiotherapy personnel, Radiotherapy equipment, Caseload.

Reprint requests to: Teruki Teshima, M.D., Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan. Tel: (+81) 6-6879-2570; Fax: (+81) 6-6879-2570; E-mail: teshima@sahs.med.osaka-u.ac.jp

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## INTRODUCTION

The medical care systems of the United States and Japan have very different backgrounds. In 1990, the Patterns of Care Study (PCS) conducted a survey of the 1989 structure of radiation oncology facilities for the entire census of facilities in the United States. The results of the survey, together with trends in the structure of specialization since 1974, were reported in detail by Owen *et al.* (1). In 1991, the Japanese Society of Therapeutic Radiation Oncology (JASTRO) conducted the first national survey of the structure of radiotherapy (RT) facilities in Japan based on their status in 1990, with the results reported by Tsunemoto (2). The first comparison of these two national structure surveys to illustrate the similarities and differences present in 1989–1990 was conducted by Teshima *et al.* (3) and reported in 1995. The resultant international exchange of information proved valuable for both countries, because each could improve their own structure of radiation oncology using those data.

The Japanese structure of radiation oncology has improved in terms of the greater number of cancer patients who are treated with RT, as well as the public awareness of the importance of RT, although problems still exist that should be solved. The JASTRO has conducted national structure surveys every 2 years since 1990 (4). In Japan, an anticancer law was enacted in 2006 in response to patients' urgent petitions to the government. This law strongly advocates the promotion of RT and increasing the number of radiation oncologists (ROs) and medical physicists. The findings of the international comparisons and the consecutive structural data gathered and published by the JASTRO have been useful in convincing the Japanese bureaucracy of the importance of RT. In this report, the recent structure of radiation oncology in Japan is presented, with reference to data obtained from previous international comparisons.

## METHODS AND MATERIALS

Between March 2006 and February 2007, the JASTRO conducted a questionnaire using a national structure survey of radiation oncology in 2005. The questionnaire included the number of treatment machines by type, number of personnel by category, and number of patients by type, site, and treatment modality. For variables measured over a period, data were requested for the calendar year 2005. The response rate was 712 (96.9%) of 735 of active facilities. The data from 511 institutions (69.5%) were registered in the International Directory of Radiotherapy Centres in Vienna, Austria in April 2007.

The PCS was introduced in Japan in 1996 (5–11). The PCS in the United States used structural stratification to analyze the national averages for the data in each survey item using two-stage cluster sampling. The Japanese PCS used similar methods. We stratified the RT facilities nationwide into four categories for the regular structure surveys. This stratification was based on academic conditions and the annual number of patients treated with RT in each institution, because the academic institutions require, and have access to, more resources for education and training and the annual caseload also constitutes essential information related to structure. For the present study, the following institutional stratification was used: A1, university hospitals/cancer centers treating ≥440 patients/y; A2, the same type of institutions treating ≤439 patients/y; B1, other national/public hospitals treating ≥130 patients/y; and B2, other national hospital/public hospitals treating ≤129 patients/y.

The Statistical Analysis Systems, version 8.02 (SAS Institute, Cary, NC), software program (12) was used for statistical analyses, and statistical significance was tested using the chi-square test, Student *t* test, or analysis of variance.

## RESULTS

*Current situation of radiation oncology in Japan*

Table 1 shows that the numbers of new patients and total patients (new plus repeat) requiring RT in 2005 were estimated at approximately 162,000 and 198,000, respectively. According to the PCS stratification of institutions, almost 40% of the patients were treated at academic institutions (categories A1 and A2), even though these academic institutions constituted only 18% of the 732 RT facilities nationwide.

The cancer incidence in Japan in 2005 was estimated at 660,578 (13) with approximately 25% of all newly diagnosed patients treated with RT. The number has increased steadily during the past 10 years and is predicted to increase further (4).

*Facility and equipment patterns*

Table 2 lists the RT equipment and related function. In actual use were 767 linear accelerators, 11 telecobalt machines, 48 Gamma Knife machines, 65 $^{60}$Co remote-controlled afterloading systems (RALSs), and 119 $^{192}$Ir RALSs. The linear accelerator system used dual-energy function in 498 systems

Table 1. PCS stratification of radiotherapy facilities in Japan

| Institution Category | Description | Facilities (*n*) | New patients (*n*) | Average new patients/facility* (*n*) | Total patients (new + repeat) (*n*) | Average total patients/facility* (*n*) |
|---|---|---|---|---|---|---|
| A1 | UH and CC (≥440 patients/y) | 66 | 45,866 | 694.9 | 54,885 | 831.6 |
| A2 | UH and CC (<440 patients/y) | 67 | 17,161 | 256.1 | 21,415 | 319.6 |
| B1 | Other (≥130 patients/y) | 290 | 71,627 | 247.0 | 88,757 | 306.1 |
| B2 | Other (<130 patients/y) | 289 | 21,664 | 75.0 | 26,116 | 90.4 |
| Total | | 712 | 156,318† | 219.5 | 191,173† | 268.5 |

*Abbreviations:* PCS = Patterns of Care Study; UH = university hospital; CC = cancer center hospital; Other = other national, city, or public hospital.

* $p < 0.0001$.

† Number of radiotherapy institutions was 735 in 2005, and number of new patients was estimated at approximately 162,000; corresponding number of total patients (new plus repeat) was 198, 000.

Table 2. Equipment, its function and patient load per equipment by PCS institutional stratification

| RT equipment and function | A1 ($n$ = 66) | | A2 ($n$ = 67) | | B1 ($n$ = 290) | | B2 ($n$ = 289) | | | Total ($n$ = 712) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $p$ | $n$ | % |
| Linear accelerator | 133 | | 85 | | 283 | | 264 | | — | 765 | |
| With dual energy function | 97 | 72.9* | 62 | 72.9* | 197 | 69.6* | 142 | 53.8* | <0.0001 | 498 | 65.1* |
| With 3D-CRT function (MLC width ≤1.0 cm) | 109 | 82.0* | 59 | 69.4* | 176 | 62.2* | 118 | 44.7* | <0.0001 | 462 | 60.4* |
| With IMRT function | 65 | 48.9* | 25 | 29.4* | 55 | 19.4* | 25 | 9.5* | <0.0001 | 170 | 22.2* |
| Annual patients/linear accelerator | 412.7† | | 243.8† | | 279.9† | | 93.4† | | <0.0001 | 234.6† | |
| Particle | 5 | | 0 | | 1 | | 1 | | — | 7 | |
| Tomotherapy | 0 | | 0 | | 0 | | 1 | | — | 1 | |
| Microtron | 8 | | 3 | | 9 | | 4 | | — | 24 | |
| Telecobalt (actual use) | 7 (5) | | 6 (1) | | 7 (1) | | 14 (4) | | — | 34 (11) | |
| Gamma Knife | 6 | | 3 | | 32 | | 7 | | 0.0004 | 48 | |
| $^{60}$Co RALS (actual use) | 8 (8) | 12.1‡ (12.1) | 13 (12) | 19.4‡ (17.9) | 41 (36) | 14.1‡ (12.4) | 12 (8) | 4.2‡ (2.8) | <0.0001 | 74 (64) | 10.4‡ (9.0) |
| $^{192}$Ir RALS (actual use) | 53 (52) | 80.3‡ (78.8) | 27 (24) | 38.8‡ (34.3) | 35 (35) | 12.1‡ (12.1) | 8 (8) | 2.8‡ (2.8) | <0.0001 | 123 (119) | 17.1‡ (16.6) |
| $^{137}$Cs RALS (actual use) | 0 (0) | | 0 (0) | | 2 (2) | | 0 (0) | | — | 2 (2) | |

*Abbreviations:* PCS = Patterns of Care Study; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; MLC = multileaf collimator; IMRT = intensity-modulated radiotherapy; RALS = remote-controlled after-loading system.

* Percentage calculated from number of systems using this function and total number of linear accelerator systems.

† Percentage calculated from number patients and number of institutions with linear accelerators; institutions without linear accelerators excluded from calculation.

‡ Percentage of institutions that have this equipment (≥2 pieces of equipment per institution).

(65%), three-dimensional conformal RT in 462 (60%), and intensity-modulated RT (IMRT) in 170 (22%). These functions were installed more frequently in the equipment of academic institutions than in that of nonacademic institutions ($p$ < 0.0001). The annual numbers of patients/linear accelerator were 413 for A1, 244 for A2, 280 for B1, and 93 for B2 institutions. The number of institutions with telecobalt machines in actual use showed a major decrease to 11. The Gamma-Knife machine was installed more frequently in B1 institutions. A significant replacement of $^{60}$Co RALS by $^{192}$Ir RALS was observed, especially in academic institutions. We had seven particle machines, three with carbon beam and five with proton beam RT. The total number of patients treated at the seven institutions was estimated at approximately 1,600 (1% of all new patients in Japan). Eleven advanced institutions were included in the A1 category and treated >800 patients annually. They were equipped with linear accelerators with dual-energy function (71% of the institutions), three-dimensional conformal RT function (89%) and IMRT function (70%), as well as with $^{192}$Ir-RALS (90%) and a computed tomography (CT) simulator (100%).

Table 3 lists the RT planning and other equipment. X-ray simulators were installed in 70% of all institutions, and CT simulators in 55%. A significant difference was found in the rate of CT simulator installation by institutional stratification, from 91% in A1 to 45% in B2 institutions ($p$ < 0.0001). Only a very few institutions used magnetic resonance imaging for RT, although computer use for RT recording was pervasive.

*Staffing patterns and patient loads*

Table 4 lists the staffing patterns and patients loads by institutional stratification. The total number of full-time equivalent (FTE) ROs in Japan was 774. The average number of FTE ROs was 4.41 for A1, 1.43 for A2, 0.89 for B1, and 0.45 for B2 institutions ($p$ < 0.0001). The patient load/FTE RO in Japan was 247, and the number for A1, A2, B1, and B2 institutions was 189, 224, 343, and 202, respectively ($p$ < 0.0001), with the patient load for B1 institutions by far the greatest. In Japan, 40% of the institutions providing RT had their own designated beds, and ROs must also take care of their inpatients. The percentage of distribution of institutions by patient load/FTE RO is shown in Fig. 1 and indicates that the largest number of facilities featured a patient/FTE staff level of 101–150, with 151–200 the second largest number. More than 60% of the institutions (438 of 712) had <1 FTE RO, as shown by the gray areas of the bars.

A similar trend for radiation technologists and their patient load by stratification of institutions was observed ($p$ < 0.0001). The percentage of distribution of institutions by patient load/radiation technologist is also shown in Fig. 2. The largest number of facilities had a patient/RT technologist level in the 81–100 range, with 101–120 the second largest number. There were 117 full-time (and 30 part-time) medical physicists and 257 full-time (and 13 part-time) RT quality assurance staff. In this survey, duplication reporting of these personnel numbers could not be checked because of a lack of

Table 3. Radiotherapy planning and other equipments by PCS institutional stratification

| RT planning and other equipment | A1 ($n$ = 66) | | A2 ($n$ = 67) | | B1 ($n$ = 290) | | B2 ($n$ = 289) | | $p$ | Total ($n$ = 712) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % | | $n$ | % |
| X-ray stimulator | 58 | 84.8* | 53 | 76.1* | 201 | 68.6* | 190 | 65.7* | 0.0130 | 502 | 69.7* |
| CT stimulator | 66 | 90.9* | 48 | 68.7* | 163 | 54.8* | 130 | 44.6* | <0.0001 | 407 | 55.3* |
| RTP computer (≥2) | 209 (190) | 100* (71.2) | 114 (82) | 94.0* (46.3) | 336 (101) | 95.9 (14.8) | 281 (50) | 88.6* (8.7) | 0.0005 (<0.0001) | 940 (146) | 93.1* (20.5) |
| MRI (≥2) | 164 (153) | 95.5* (78.8) | 134 (124) | 94.0* (79.1) | 470 (351) | 96.9 (55.9) | 344 (148) | 92.4* (24.6) | 0.1136 (<0.0001) | 1,112 (338) | 94.7* (47.5) |
| For RT only | 3 | 3.0* | 1 | 1.5* | 5 | 1.7* | 3 | 0.7* | | 12 | 1.4* |
| Computer use for RT recording | 63 | 95.5* | 62 | 92.5* | 263 | 90.7* | 238 | 82.4* | 0.0015 | 626 | 87.9* |

*Abbreviations:* CT = computed tomography; RTP = radiotherapy planning; MRI = magnetic resonance imaging; other abbreviations as in Table 2.
* Percentage of institutions that have equipment (≥2 pieces of equipment per institution).

individual identification on staffing data. Finally, there were 907 nurses and clerks.

*Distributions of primary sites, specific treatment and palliative treatment*

Table 5 lists the distribution of primary sites by institutional stratification. The most common disease site was the breast, followed by lung/bronchus/mediastinum and genitourinary. In Japan, the number of patients with prostate cancer undergoing RT was approximately 13,200 in 2005, but the number has been increasing most rapidly. The stratification of institutions indicated that more patients with lung cancer were treated at the nonacademic institutions (B1 and B2), and more patients with head-and-neck cancer were treated at academic institutions (A1 and A2; $p < 0.0001$).

Table 6 lists the distribution of use of specific treatment and the number of patients treated with these modalities by the PCS stratification of institutions. Brachytherapy, such as intracavitary RT, interstitial RT, and radioactive iodine therapy, for prostate cancer was used more frequently in academic institutions than in nonacademic institutions ($p < 0.0001$). Similar trends were observed for other specific treatments such as total body RT, intraoperative RT, stereotactic brain RT, stereotactic body RT, IMRT, thermoradiotherapy, and RT of the pterygium by $^{90}$Sr. In 2005, 4.6% of patients ($n$ = 755) were treated with IMRT at 33 institutions. This percentage was significantly lower than that of institutions using linear accelerators with IMRT function (22%; Table 2).

Table 7 lists the number of patients with any type of brain metastasis or bone metastasis treated with RT according to the same institutional stratification. B1 institutions treated more patients with brain metastasis (11% of all patients) than other types of institutions ($p < 0.0001$), and the use of RT for bone metastasis ranged from 11% for A1 to 19% for B2 ($p < 0.0001$). Overall, more patients were treated with RT at nonacademic type B2 institutions than at A1 or A2 institutions.

*Geographic patterns*

Figure 3 shows the geographic distributions of the annual number of patients (new plus repeat) per 1,000 population by 47 prefectures arranged in order of increasing number of JASTRO-certified physicians per 1,000,000 population (14). Significant differences were found in the use of RT, from 0.9 patients/1,000 population (Saitama and Okinawa) to 2.1 (Hokkaido). The average number of patients/1,000 population per quarter ranged from 1.37 to 1.57 ($p$ = 0.2796). A tendency was found for a greater number of JASTRO-certified physicians to be accompanied by an increased use of RT for cancer patients, although the correlation was not statistically significant. The use rate of RT in a given prefecture was not necessarily related to its population density in 2005, just as we observed in the 1990 data (3).

## DISCUSSION

In 1990, fewer facilities for RT were available and fewer patients were treated with RT in Japan than in the United States. However, the numbers for Japan improved

Table 4. Structure and personnel by PCS institutional stratification

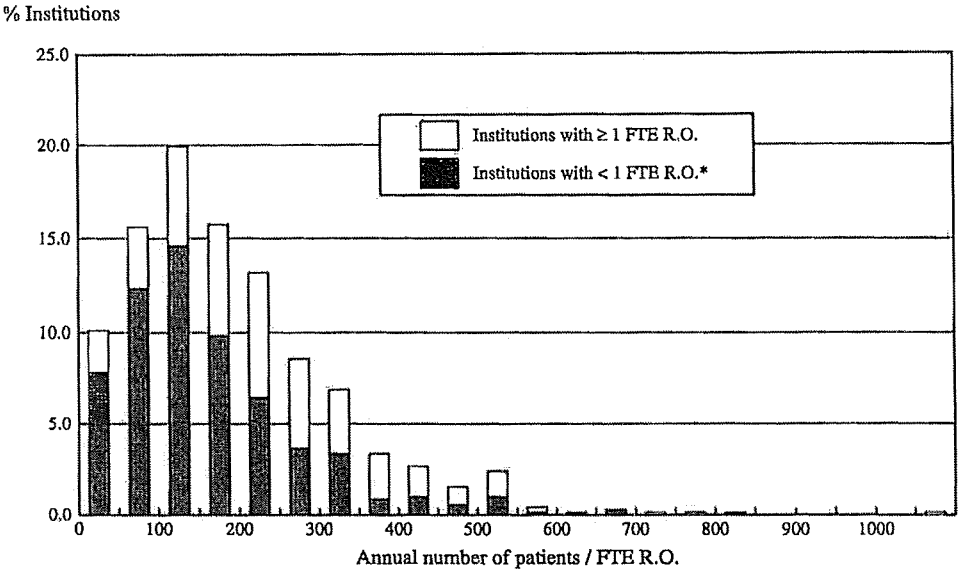
| | Structure and personnel | | | | | |
|---|---|---|---|---|---|---|
| | A1 ($n$ = 66) | A2 ($n$ = 67) | B1 ($n$ = 290) | B2 ($n$ = 289) | *p-value* | Total ($n$ = 712) |
| Institutions/total institutions (%) | 9.3 | 9.4 | 40.7 | 40.6 | | 100 |
| Institutions with RT bed ($n$) | 57 (86.4) | 35 (52.2) | 127 (43.8) | 68 (23.5) | | 287 (40.3) |
| Average RT beds/institution ($n$) | 14.0 | 4.8 | 3.4 | 1.0 | | 3.6 |
| JASTRO-certified RO (full time) | 181 | 62 | 139 | 44 | | 426 |
| Average JASTRO-certified RO/institution ($n$) | 2.7 | 0.9 | 0.5 | 0.2 | <0.0001 | 0.6 |
| Total (full-time and part-time) RO FTE* | 290.9 | 95.55 | 258.77 | 129.24 | | 774.46 |
| Average FTE ROs/institution | 4.41 | 1.43 | 0.89 | 0.45 | <0.0001 | 1.09 |
| Patient load/FTE RO | 188.7 | 224.1 | 343.0 | 202.1 | <0.0001 | 246.8 |
| Total RT* technologists | 388.6 | 176.3 | 637.7 | 431.9 | | 1634.5 |
| Average technologists/institution ($n$) | 5.9 | 2.6 | 2.2 | 1.5 | <0.0001 | 2.3 |
| Patient load/RT technologist | 141.2 | 121.5 | 139.2 | 60.5 | <0.0001 | 117.0 |
| Total nurses/assistants/clerks ($n$) | 202.2 | 92.4 | 390.55 | 221.8 | | 907 |
| Full-time medical physicists + part-time ($n$) | 51 + 10.1 | 8 + 7 | 39 + 7 | 19 + 6 | | 117 + 30.1 |
| Full-time RT QA staff + part-time | 81 + 0 | 31 + 7 | 102.5 + 3 | 42.3 + 3 | | 256.8 + 13 |

*Abbreviations:* JASTRO = Japanese Society of Therapeutic Radiation Oncology; RO = radiation oncologist; FTE = full-time equivalent (40 h/wk only for RT practice); QA = quality assurance; other abbreviations as in Table 2.

Data in parentheses are percentages.

significantly during the next 15 years, with respective increases by factors of 2 and 2.6 compared with those in 1990 (3). However, the use rate of RT for new cancer patients remained at 25%, less than one-half the ratio in the United States and European countries. The anticancer law was enacted in Japan to promote RT and education for ROs, as well as medical physicists or other staff members, from April 2006. For the implementation of this law, comparative data of the structure of radiation oncology in Japan and the United States, as well as relevant PCS data, proved helpful. Because the increase in the elderly population of developed countries is the greatest in Japan, RT is expected to play an increasingly important role.

Compared with 1990, the number of linear accelerator systems increased significantly by 2.3 times, and the percentage of systems using telecobalt decreased to 7%. Furthermore, the functions of linear accelerators, such as dual energy, three-dimensional conformal RT (multileaf collimator width <1 cm), and IMRT improved. The number of high-dose-rate RALS in use increased by 1.4 times and the use of




* Number of .FTEs for institutions with FTE<1 was calculated as FTE=1 to avoid overestimating pateint' load/R.O.

Fig. 1. Percentage of institutions by patient load/full-time equivalent (FTE) staff of radiation oncologists (RO) in Japan. White bars represent institutions with one or more FTE staff, and gray bars represent institutions with fewer than one FTE radiation oncologist. Each bar represents interval of 50 patients/FTE radiation oncologist.

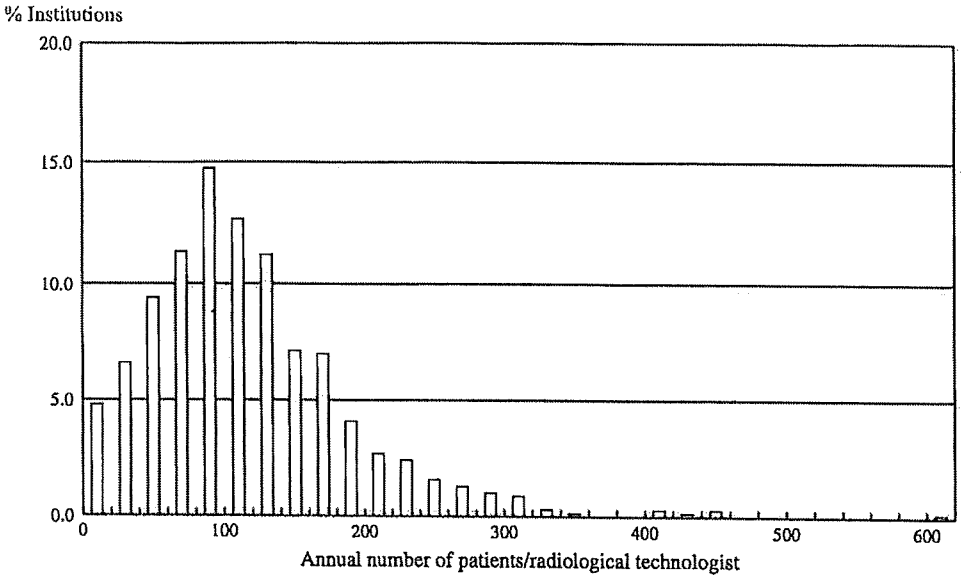



Fig. 2. Percentage of institutions by patient load/radiotherapy technologist in Japan. Each bar represents interval of 20 patients/full-time equivalent staff.

$^{60}$Co-RALS has largely been replaced by $^{192}$Ir-RALS. CT simulators were installed in 55% of institutions nationwide, and RT planning systems were used in 93%, for an increase in the number of RT planning systems of 4.87 times. The maturity of the functions of linear accelerator and greater possession rates of CT simulators and systems using $^{192}$Ir-RALS were closely related to the institutional stratification by PCS, which could therefore aid in the accurate discrimination of structural maturity and immaturity and the identification of structural targets to be improved. The Japanese PCS group published structural guidelines based on the PCS data (16), and we plan to use this structural data for a new PCS to revise the Japanese structural guidelines.

The staffing patterns in Japan also improved in terms of numbers. However, the institutions that had fewer than one FTE RO on their staff still accounted for >60% nationwide, and this rate did not change during the 15 years from 1990 to 2005. In Japan, most institutions still rely on part-time ROs. First, the number of cancer patients who require RT is increasing more rapidly than the number of ROs. Second, specialist fees for ROs in academic institutions are not recognized by the Japanese medical care insurance system, which is strictly controlled by the government. Most ROs must therefore work part-time at affiliated hospitals in the B1 and B2 groups to earn a living. Thus, to reduce the number of institutions that rely on part-time ROs and might encounter

Table 5. Primary sites of cancer treatment with RT in 2005 by PCS institutional stratification for new patients

| Primary site | A1 ($n$ = 65) | | A2 ($n$ = 67) | | B1 ($n$ = 285) | | B2 ($n$ = 284) | | Total ($n$ = 701) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $n$ | % |
| Cerebrospinal | 2,603 | 5.6 | 770 | 4.5 | 4,431 | 6.4 | 795 | 3.6 | 8,599 | 5.6 |
| Head and neck (including thyroid) | 6,318 | 13.7 | 2,372 | 13.9 | 6,033 | 8.7 | 1,650 | 7.5 | 16,373 | 10.6 |
| Esophagus | 3,164 | 6.9 | 1,171 | 6.9 | 4,426 | 6.4 | 1,452 | 6.6 | 10,213 | 6.6 |
| Lung, trachea, and mediastinum | 7,069 | 15.3 | 2,639 | 15.5 | 14,946 | 21.5 | 5,386 | 24.6 | 30,040 | 19.4 |
| Lung | 5,469 | 11.8 | 2,272 | 13.3 | 12,917 | 18.6 | 4,734 | 21.6 | 25,392 | 16.4 |
| Breast | 8,945 | 19.4 | 3,049 | 17.9 | 14,148 | 20.4 | 4,119 | 18.8 | 30,261 | 19.6 |
| Liver, biliary tract, pancreas | 1,936 | 4.2 | 713 | 4.2 | 2,742 | 3.9 | 964 | 4.4 | 6,355 | 4.1 |
| Gastric, small intestine, colorectal | 1,897 | 4.1 | 806 | 4.7 | 3,742 | 5.4 | 1,399 | 6.4 | 7,844 | 5.1 |
| Gynecologic | 3,253 | 7.0 | 1,156 | 6.8 | 3,405 | 4.9 | 855 | 3.9 | 8,669 | 5.6 |
| Urogenital | 5,544 | 12.0 | 2,043 | 12.0 | 8,068 | 11.6 | 2,905 | 13.3 | 18,560 | 12.0 |
| Prostate | 4,290 | 9.3 | 1,385 | 8.1 | 5,627 | 8.1 | 1,916 | 8.8 | 13,218 | 8.6 |
| Hematopoietic and lymphatic | 2,460 | 5.3 | 1,052 | 6.2 | 3,624 | 5.2 | 904 | 4.1 | 8,040 | 5.2 |
| Skin, bone, and soft tissue | 1,607 | 3.5 | 749 | 4.4 | 1,830 | 2.6 | 1,018 | 4.6 | 5,204 | 3.4 |
| Other (malignant) | 705 | 1.5 | 235 | 1.4 | 822 | 1.2 | 313 | 1.4 | 2,075 | 1.3 |
| Benign tumors | 664 | 1.4 | 268 | 1.6 | 1,289 | 1.9 | 135 | 0.6 | 2,356 | 1.5 |
| Pediatric <15 y (included in totals above) | 435 | 0.9 | 123 | 0.7 | 187 | 0.3 | 302 | 1.4 | 1,047 | 0.7 |
| Total | 46,165 | 100 | 17,023 | 100 | 69,506 | 100 | 21,895 | 100 | 154,589† | (100) |

Abbreviations as in Table 2.
*Number of total number of new patients different with these data, because no data on primary sites were reported by some institutions.

Table 6. Distribution of specific treatments and numbers of patients treated with these modalities by PCS stratification of institutions

| | A1 ($n$ = 66) | | A2 ($n$ = 67) | | B1 ($n$ = 290) | | B2 ($n$ = 289) | | | Total ($n$ = 712) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Specific therapy | $n$ | % | $n$ | % | $n$ | % | $n$ | % | $p$ | $n$ | % |
| Intracavitary RT ($n$) | | | | | | | | | <0.0001 | | |
| Treatment facilities | 61 | 92.4 | 37 | 55.2 | 71 | 24.5 | 12 | 4.2 | | 181 | 25.4 |
| Cases | 1,670 | | 527 | | 974 | | 75 | | | 3,246 | |
| Interstitial RT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 42 | 63.6 | 14 | 20.9 | 18 | 6.2 | 5 | 1.7 | | 79 | 11.1 |
| Cases | 1,818 | | 286 | | 638 | | 31 | | | 2,773 | |
| Radioactive iodine therapy for prostate cancer | | | | | | | | | <0.0001 | | |
| Treatment facilities | 25 | 37.9 | 6 | 9.0 | 7 | 2.4 | 1 | 0.3 | | 39 | 5.5 |
| Cases | 1,166 | | 152 | | 430 | | 17 | | | 1,765 | |
| Total body RT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 60 | 90.9 | 36 | 53.7 | 78 | 26.9 | 17 | 5.9 | | 191 | 26.8 |
| Cases | 706 | | 237 | | 687 | | 108 | | | 1,738 | |
| Intraoperative RT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 23 | 34.8 | 12 | 17.9 | 20 | 7.0 | 11 | 3.8 | | 66 | 9.3 |
| Cases | 212 | | 39 | | 111 | | 25 | | | 387 | |
| Stereotactic brain RT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 46 | 69.7 | 31 | 46.3 | 91 | 31.4 | 29 | 10.0 | | 197 | 27.7 |
| Cases | 1,680 | | 482 | | 8,513 | | 447 | | | 11,122 | |
| Stereotactic body RT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 31 | 50.0 | 14 | 20.9 | 36 | 12.4 | 11 | 3.8 | | 92 | 12.9 |
| Cases | 482 | | 263 | | 679 | | 234 | | | 1,658 | |
| IMRT | | | | | | | | | <0.0001 | | |
| Treatment facilities | 16 | 24.2 | 4 | 6.0 | 12 | 4.1 | 1 | 0.3 | | 33 | 4.6 |
| Cases | 426 | | 67 | | 212 | | 50 | | | 755 | |
| Thermoradiotherapy | | | | | | | | | 0.0004 | | |
| Treatment facilities | 10 | 15.2 | 4 | 6.0 | 15 | 5.2 | 7 | 2.4 | | 36 | 5.1 |
| Cases | 339 | | 27 | | 134 | | 81 | | | 581 | |

*Abbreviations:* PCS = Patterns of Care Study; RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

problems with their quality of care, a drastic reform of our current medical care systems is required. However, great care is needed to ensure that the long-term success of radiation oncology in Japan and patient benefits are well balanced with the costs. Even under the current conditions, however, the number of FTE ROs increased by 2.1 times compared with the number in 1990 (3). However, the patient load/FTE RO also increased by 1.4 times to 247 during the same period, perhaps reflecting the growing popularity of RT because of recent advances in technology and improvement in clinical results. This caseload ratio in Japan has already exceeded the limit of the Blue Book guidelines of 200 patients/RO (15, 16). The percentage of distribution of institutions by patient load/RO showed a slightly smaller distribution than that of the United States in 1989 (3). Therefore, Japanese radiation oncology seems to be catching up quickly with the western system despite limited resources. Furthermore, additional recruiting and education of ROs are now top priorities of the JASTRO.

The distribution of patient load/RT technologists showed that 13% of institutions met the narrow guideline range (100–120/RT technologist), and the rest were densely distributed around the peak. Compared with the distribution in the United States in 1989, >20% of institutions in Japan had a relatively low caseload of 10–60 because a large number of smaller B2-type institutions still accounted for nearly 40% of institutions exceeding the range of the guidelines. As for medical physicists, a similar analysis for patient load/FTE staff was difficult, because the number was still small, and they were working mainly in metropolitan areas. In Japan, radiation technologists have been acting as medical physicists, so that their education has been changed from 3 to 4 years

Table 7. Brain metastasis or bone metastasis patients treated with RT in 2005 by PCS institutional stratification

| | Patients | | | | | |
|---|---|---|---|---|---|---|
| Metastasis | A1 ($n$ = 66) | A2 ($n$ = 67) | B1 ($n$ = 290) | B2 ($n$ = 289) | $p$ | Total ($n$ = 712) |
| Brain | 2,565 (4.7) | 1,204 (5.6) | 9,774 (11.0) | 1,778 (6.8) | <0.0001 | 15,321 (8.0) |
| Bone | 6,243 (11.4) | 2,845 (13.3) | 13,331 (15.0) | 5,057 (19.4) | <0.0001 | 27,476 (14.4) |

Data presented as number of patients, with percentages in parentheses.

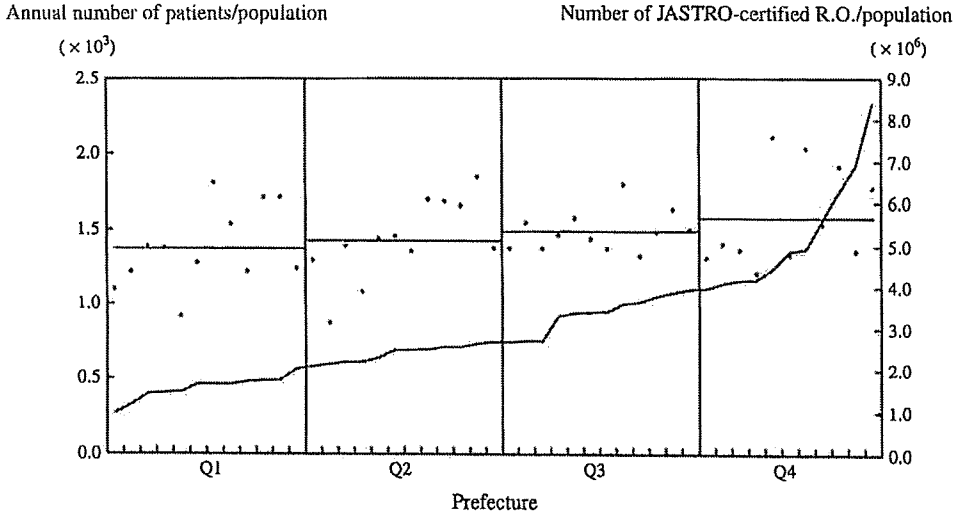



Fig. 3. Geographic distribution for 47 prefectures of annual number of patients (new plus repeat) per 1,000 population arranged in order of increasing number of Japanese Society of Therapeutic Radiation Oncology (JASTRO)-certified radiation oncologists (RO)/1,000,000 population by prefecture. Q1, 0–25%; Q2, 26–50%; Q3, 51–75%; and Q4, 76–100%. Horizontal bar shows average annual number of patients (new plus repeat) per 1,000 population of prefectures per quarter.

during the past decade and graduate and postgraduate courses have been introduced. Currently, those who have obtained a master's degree or radiation technologists with enough clinical experience can take the examination for qualification as a medical physicist, as can those with a master's degree in science or engineering, like those in the United States or Europe. In Japan, a unique education system for medical physicists might be developed because the anticancer law actively supports improvements in quality assurance/quality control specialization for RT. However, the validity of this education and training system remains unsatisfactory, because we are still in the trial-and-error stage.

The distribution of the primary site for RT showed that more lung cancer patients were treated in B1 or B2 nonacademic institutions and more head-and-neck cancer patients were treated in A1 or A2 academic institutions. These findings might be because more curative patients were referred to academic institutions and more palliative patients with lung cancer were treated in nonacademic institution in Japan. In addition, more patients with bone metastasis were treated in nonacademic institutions. The use of specific treatments and the number of patients treated with these modalities were significantly affected by institutional stratification, with more specific treatments performed at academic institutions. These findings indicate that significant differences in the patterns of care, as reflected in the structure, process, and, possibly, outcomes for cancer patients still exist in Japan. These differences point to opportunities for improvement. We, therefore, based the Japanese Blue Book guidelines on this stratification by the PCS data (16) and are now in preparing to revise them accordingly.

The geographic patterns demonstrated significant differences among the prefectures in the use of RT, ranging from 0.9 to 2.1 patients/1,000 population. Furthermore, the number of JASTRO-certified physicians/population might be associated with the use of RT, so that a shortage of ROs or medical physicists on a regional basis will remain a major concern in Japan. The JASTRO has been making every effort to recruit and educate ROs and medical physicists through public relations, training courses, involvement in the national examination for physicians, and seeking to increase the reimbursement by the government-controlled insurance program, and other actions.

## CONCLUSION

The Japanese structure of radiation oncology has clearly improved during the past 15 years in terms of equipment and its functions, although a shortage of manpower and differences in maturity by type of institution and caseload remain. Structural immaturity is an immediate target for improvement, and, for improvements in process and outcome, the PCS or National Cancer Database, which are currently operational and being closely examined, can be expected to play an important role in the future.

## REFERENCES

1. Owen JB, Coia LR, Hanks GE. Recent patterns of growth in radiation therapy facilities in the United States: A Patterns of Care Study report. *Int J Radiat Oncol Biol Phys* 1992;24: 983–986.
2. Tsunemoto H, for the Japanese Society of Therapeutic Radiology and Oncology (JASTRO). Present status of Japanese radiation oncology: National survey of structure in 1990 (in Japanese). Tokyo: Japanese Society of Therapeutic Radiology and Oncology, 1992.
3. Teshima T, Owen JB, Hanks GE, *et al.* A comparison of the structure of radiation oncology in the United States and Japan. *Int J Radiat Oncol Biol Phys* 1996;34:235–242.

4. Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. *Int J Radiat Oncol Biol Phys* 2005;62:1472–1476.
5. Tanisada K, Teshima T, Ikeda H, *et al.* A preliminary outcome analysis of the Patterns of Care Study in Japan for esophageal cancer patients with special reference to age: Non-surgery group. *Int J Radiat Oncol Biol Phys* 2000;46: 1223–1233.
6. Tanisada K, Teshima T, Ohno Y, *et al.* Patterns of Care Study quantitative evaluation of the quality of radiotherapy in Japan. *Cancer* 2002;95:164–171.
7. Uno T, Sumi M, Sawa Y, *et al.* Process of care and preliminary outcome in limited-stage small-cell lung cancer: Results of the 1995–1997 Patterns of Care Study in Japan. *Int J Radiat Oncol Biol Phys* 2003;55:629–632.
8. Gomi K, Oguchi M, Hirokawa Y, *et al.* Process and preliminary outcome of a Patterns-of-Care Study of esophageal cancer in Japan: Patients treated with surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:813–822.
9. Sugiyama H, Teshima T, Ohno Y, *et al.* The Patterns of Care Study and regional cancer registry for non–small-cell lung cancer in Japan. *Int J Radiat Oncol Biol Phys* 2003;56: 1005–1012.
10. Mitsumori M, Hiraoka M, Negoro Y, *et al.* The Patterns of Care Study for breast-conserving therapy in Japan: Analysis of process survey from 1995 to 1997. *Int J Radiat Oncol Biol Phys* 2005;62:1048–1054.
11. Teshima T, for the Japanese PCS Working Group. Patterns of Care Study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
12. SAS Institute Inc. SAS user's guide: statistics. Cary, NC: SAS Institute Inc.; 1985.
13. Oshima A, Kuroishi T, Tajima K, editors. Cancer statistics—2004. Tokyo: Shinohara Shuppan Shinsha; 2004. p. 207.
14. Statistics Bureau, Ministry of Internal Affairs and Communications. The 2005 population census, First basic complete tabulation. Available from: http://www.stat.go.jp/english/data/kokusei/2005/kihon1/00/hyodai.htm. Accessed May 17, 2007.
15. Parker RG, Bogardus CR, Hanks GE, *et al.* Radiation oncology in integrated cancer management: Report of the Inter-Society Council for Radiation Oncology. Merrifield, VA: American College of Radiology Publications, ISCRO; 1991.
16. Japanese PCS Working Group. Radiation oncology in multidisciplinary cancer therapy—Basic structure requirement for quality assurance of radiotherapy based on Patterns of Care Study in Japan, 2005. Self-publication supported by the Ministry of Health, Welfare and Labor in Japan.

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**CLINICAL INVESTIGATION** **Lung**

# STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTATIC LUNG TUMORS

YOSHIKI NORIHISA, M.D.,* YASUSHI NAGATA, M.D., PH.D.,* KENJI TAKAYAMA, M.D.,* YUKINORI MATSUO, M.D., PH.D.,* TAKASHI SAKAMOTO, M.D.,† MASATO SAKAMOTO, M.D.,‡ TAKASHI MIZOWAKI, M.D., PH.D.,* SHINSUKE YANO, B.S.,* AND MASAHIRO HIRAOKA, M.D., PH.D.*

*Department of Radiation Oncology and Image-Applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, Japan; †Department of Radiation Oncology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; and ‡Department of Radiology, Japanese Red Cross Society Wakayama Medical Center, Wakayama, Japan

**Purpose:** Since 1998, we have treated primary and oligometastatic lung tumors with stereotactic body radiotherapy (SBRT). The term "oligometastasis" is used to indicate a small number of metastases limited to an organ. We evaluated our clinical experience of SBRT for oligometastatic lung tumors.

**Methods and Materials:** A total of 34 patients with oligometastatic lung tumors were included in this study. The primary involved organs were the lung ($n = 15$), colorectum ($n = 9$), head and neck ($n = 5$), kidney ($n = 3$), breast ($n = 1$), and bone ($n = 1$). Five to seven, noncoplanar, static 6-MV photon beams were used to deliver 48 Gy ($n = 18$) or 60 Gy ($n = 16$) at the isocenter, with 12 Gy/fraction within 4–18 days (median, 12 days).

**Results:** The overall survival rate, local relapse-free rate, and progression-free rate at 2 years was 84.3%, 90.0%, and 34.8%, respectively. No local progression was observed in tumors irradiated with 60 Gy. SBRT-related pulmonary toxicities were observed in 4 (12%) Grade 2 cases and 1 (3%) Grade 3 case. Patients with a longer disease-free interval had a greater overall survival rate.

**Conclusion:** The clinical result of SBRT for oligometastatic lung tumors in our institute was comparable to that after surgical metastasectomy; thus, SBRT could be an effective treatment of pulmonary oligometastases. © 2008 Elsevier Inc.

**Stereotactic body radiotherapy, Metastatic lung tumor, Pulmonary metastases, Oligometastases.**

## INTRODUCTION

Stereotactic irradiation, stereotactic radiosurgery, and stereotactic radiotherapy are standard therapeutic techniques for intracranial tumors. With the introduction of three-dimensional localization techniques using a localizing frame of reference, hypofractionated irradiation using a stereotactic technique has been applied to extracranial tumors. Stereotactic body radiotherapy (SBRT) represents one of those treatments, and SBRT has been used in many institutes (1–9) mainly to irradiate lung or liver cancer.

Recently, patients with oligometastases, that is, a small number of metastatic lesions limited to an organ, have been considered candidates for curative treatment because long-term survival can be expected (10–13); therefore, surgical resection is the standard choice for patients with oligometastatic lung cancer. Since the effectiveness of SBRT for primary lung cancer was reported (5, 7, 14–17), awareness has been growing of SBRT as an effective option for curative treatment of lung tumors. In 1998, we began using SBRT for both primary and oligometastatic lung tumors. In this study, we retrospectively analyzed our experience with SBRT outcomes for oligometastatic lung tumors and reviewed the published data.

## METHODS AND MATERIALS

### *Patient and tumor characteristics*

The eligibility criteria of SBRT for oligometastatic lung tumor were as follows: *(1)* one or two pulmonary metastases, *(2)* tumor diameter ≤4 cm, *(3)* locally controlled primary tumor, and *(4)* no other metastatic sites. Of the patients treated between December 1998 and December 2004, 34 with oligometastatic lung tumors were included in this study. The primary involved organs were the lung ($n = 15$), colorectum ($n = 9$), head and neck ($n = 5$), kidney ($n = 3$), breast ($n = 1$), and bone ($n = 1$). Of these 34 patients, 25 were treated for

Reprint requests to: Yasushi Nagata, M.D., Ph.D., Department of Radiation Oncology and Image-Applied Therapy, Kyoto University Graduate School of Medicine, 54 Shogoin-Kawahara-Cho, Sakyo-Ku, Kyoto 606-8507, Japan. Tel: (+81) 75-751-3762; Fax: (+81) 75-751-3418; E-mail: nag@kuhp.kyoto-u.ac.jp

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a single pulmonary nodule and 9 for two lesions. The histologic diagnosis of the primary disease was adenocarcinoma in 22, squamous cell carcinoma in 5, renal cell carcinoma in 3, adenoid cystic carcinoma in 2, pleomorphic carcinoma in 1, and osteosarcoma in 1 patient. Lung metastases were diagnosed clinically according to repeated thoracic computed tomography (CT) findings. Most patients had previously undergone surgical resection and chemotherapy for their primary cancer. Adjuvant oral chemotherapy regimens after SBRT were allowed. The patient characteristics are given in Table 1.

*SBRT procedure*

We used a combined X-ray and CT simulator—an integrated system using the same couch for the X-ray and CT simulators (Shimadzu, Kyoto, Japan). The patients were fixed in the stereotactic body frame (ELEKTA AB, Stockholm, Sweden) while CT scanning was performed with a slow scan time (4 s/slice).

Three-dimensional RT planning was performed using a treatment-planning machine (CADPLAN, version 3.1, and Eclipse, version 7.1, Varian Medical Systems, Palo Alto, CA). The internal target volume (ITV) was delineated on the CT images, considering the tumor motion assessed by X-ray fluoroscopy, and then the essential margins—planning target volume (PTV) margin and leaf margins—were added to the ITV (18, 19). We added 5 mm to the ITV for the PTV margin and another 5 mm from the contour of the PTV to the edge of the multileaf collimator for penumbra; thus, typically, a 10-mm margin was used between the contour of the ITV and the edge of the multileaf collimator. We used five to seven noncoplanar, static 6-MV photon beams and irradiated 12 Gy in each fraction at the isocenter. The patients received four or five fractions; therefore, the total dose was 48 Gy or 60 Gy at the isocenter within 4–18 days (median, 12 days).

Because we experienced several local failures with 48 Gy, the prescribed dose was escalated to 60 Gy from January 2001. However, the dose for metastases from primary lung cancer was maintained at 48 Gy because of difficulties in distinguishing a second primary lung cancer from a metastatic lesion and because the 5-year local relapse-free rate of 95% using this dose (16) was satisfactory. Also, the general pulmonary function was better in patients with metastatic lung cancer than in those with primary lung cancer. With the exception of patients with poor pulmonary function, a total dose of 60 Gy was prescribed to patients with a primary cancer other than lung cancer.

Table 1. Patient characteristics

| Characteristic | Value |
|---|---|
| Patients (*n*) | 34 |
| Gender (*n*) | |
| Male | 22 |
| Female | 12 |
| Age (y) | |
| Range | 30–80 |
| Median | 71 |
| Performance status | |
| 0 | 23 |
| 1 | 9 |
| 2 | 2 |
| 3–5 | 0 |
| Primary tumor | |
| Lung | 15 |
| Colorectum | 9 |
| Head and neck | 5 |
| Kidney (renal cell carcinoma) | 3 |
| Bone (osteosarcoma) | 1 |
| Breast | 1 |

*Evaluation*

The local response was assessed using the Response Evaluation Criteria in Solid Tumors and categorized into four types: *(1)* the disappearance of all target lesions (complete response), *(2)* at least a 30% decrease in the sum of the longest diameter of the target lesions (partial response), *(3)* a response ranging from a 30% decrease to a 20% increase in the sum of the longest diameter of the target lesions (stable disease), and *(4)* a ≥20% increase in the sum of the longest diameter of the target lesions (progressive disease). Because of the presence of consolidation with unclear margins around the tumor (20), it can be difficult to distinguish between tumor regrowth and radiation-induced injury; such cases were categorized as stable disease until apparent tumor regrowth was detected by careful and appropriate clinical observation for several months.

Survival was calculated from the first day of RT to the last day of follow-up. For overall survival, lost patients with clinically progressive disease and those with the terminal stage of disease were censored as dead. Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 3.

Statistical calculations were performed using Prism, version 4, software (GraphPad Software, San Diego, CA). The survival rates were analyzed using the Kaplan-Meier method, and differences in their distributions were evaluated using the log–rank test.

## RESULTS

The study population comprised 22 men and 12 women, with median age of 71 years (range, 30–80 years). Of these 34 patients, 17 received 48 Gy in four fractions and 16 received 60 Gy in five fractions. One patient received 48 Gy in five fractions because of poor pulmonary function that necessitated a reduction in the fractional dose. The overall treatment time was 4–14 days (median, 12 days), except for

Table 2. Treatment results

| Variable | Value |
|---|---|
| Tumor total (*n*) | 43 |
| Tumor diameter (*n*) | |
| <15 mm | 17 |
| ≥15 but ≤30 mm | 22 |
| >30 mm | 4 |
| Prescribed dose (Gy) | |
| 48 | 18 |
| 60 | 16 |
| Overall treatment time (d) | |
| Range | 4–18 |
| Median | 12 |
| Follow-up period (mo) | |
| Range | 10–80 |
| Median | 27 |

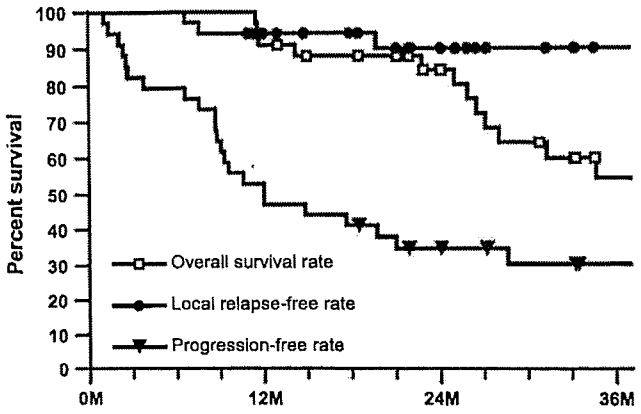


Fig. 1. Overall survival, local relapse-free survival, and progression-free survival rates after stereotactic body radiotherapy for oligometastatic lung cancer.

1 patient, for whom it was 18 days. The median follow-up period was 27 months (range, 10–80 months; Table 2).

*Response*

The overall survival rate, local relapse-free rate, and progression-free rate at 2 years was 84.3%, 90.0%, and 34.8%, respectively (Fig. 1). The numbers of patients with a complete response, partial response, stable disease, and progressive disease was 5, 8, 18, and 3, respectively. No statistically significant difference was found between those receiving 60 Gy and those receiving 48 Gy in terms of overall survival ($p$ = 0.192; Fig. 2a); however, a marginally significant difference was observed between those receiving 60 Gy and 48 Gy in local progression-free survival ($p$ = 0.078; Fig. 2b). No local progression was observed in tumors irradiated to 60 Gy, but three had local progression at 48 Gy. No differences were found in overall survival between patients with metastases from lung cancer and those with metastases from other cancers ($p$ = 0.75).

*Patterns of failure*

Disease progression was observed in 23 patients (Table 3). Regrowth of the target lesions of SBRT was observed in 3 patients and recurrence of the primary lesion in 2. New metastatic lesions were observed in 19 patients. New intrapulmonary metastases were observed in 9 patients, and mediastinal or hilar regional lymph nodal metastases developed in 6. Distant metastases were observed in 3 patients: the adrenal gland in 2 and the liver in 1. One patient was diagnosed with progressive disease because of elevations of carcinoembryonic antigen and underwent chemotherapy.

*Toxicity*

The adverse events resulting from SBRT were classified using the Common Terminology Criteria for Adverse Events, version 3 (Table 4). Pulmonary toxicity was observed as cough, hemosputum, dyspnea, pleural effusion, and radiographic changes and was Grade 1 in 23 patients (68%) and Grade 2 in 4 (12%). One patient required oxygen

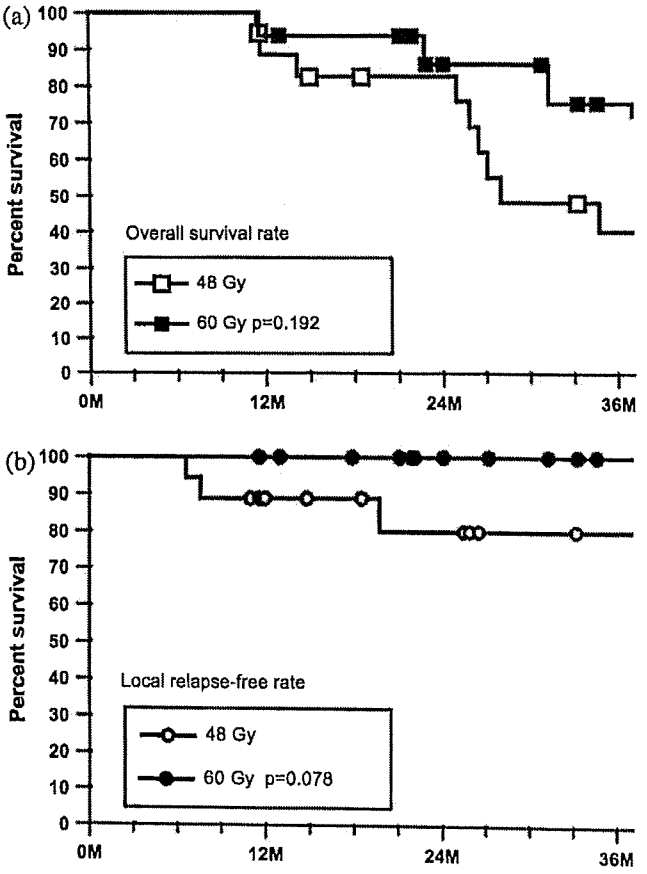


Fig. 2. (a) Overall survival rates of patients treated with 48 Gy and 60 Gy. (b) Local relapse-free rates of patients treated with 48 Gy and 60 Gy. Difference was marginally significant ($p$ = 0.078).

supplementation for bacterial pneumonia 18 months after SBRT and was considered to have Grade 3 pulmonary toxicity. The symptoms of most patients were mild and did not interfere with their activities of daily living. Grade 1 skin toxicity with faint erythema or pigmentation with or without symptoms was observed in 6 patients (17%). One patient had a skin ulcer at the site of the reirradiated field, contralateral to the site of SBRT, and was cured with conservative treatment. Musculoskeletal adverse events were

Table 3. Patterns of disease progression

| Pattern | *n* |
|---|---|
| New pulmonary metastasis | 9 |
| Regional lymph node metastasis | 6 |
| Local regrowth of target lesion of SBRT | 3 |
| Recurrence of primary lesion | 2 |
| Adrenal gland metastasis | 2 |
| Liver metastasis | 1 |
| Tumor marker elevation without any apparent recurrence | 1 |

*Abbreviation:* SBRT = stereotactic body radiotherapy.

Of 34 patients, disease progression observed in 23 patients; 1 patient had regrowth at site of SBRT and liver metastasis simultaneously.

Table 4. Toxicity

| Toxicity | Grade 0 | 1 | 2 | 3 |
|---|---|---|---|---|
| Pulmonary | 6 | 23 | 4 | 1 |
| Skin | 27 | 6 | 1 | 0 |
| Pain | 27 | 6 | 0 | 0 |
| Musculoskeletal | 32 | 2 | 0 | 0 |
| Cardiac general (pericardial effusion) | 32 | 2 | 0 | 0 |
| Hepatobiliary | 33 | 1 | 0 | 0 |

Total number of patients was 34.

observed in 2 patients (6%): bone fracture of the rib and musculitis of the chest wall. With these dermatologic or musculoskeletal complications of the thoracic wall, mild pain was observed in 6 patients (17%). Grade 1 pericardial effusion and temporal liver dysfunction were observed in 1 patient (3%) each. Most adverse events remained at Grade 1. No adverse effects of the spinal cord, great vessels, or esophagus were observed.

*Prognostic factors*

We also analyzed the survival differences stratified by the disease-free interval (DFI), previous chemotherapy, previous thoracic surgery, performance status, nodule size (sum of longer diameters), and number of targets. Except for DFI, no significant differences were observed. We stratified patients into three groups according to the DFI; <1 year, >1 year but <3 years, and >3 years (Fig. 3). Patients with DFI >3 years had significantly greater overall survival ($p$ = 0.02) among the three groups. However, other factors showed negative results, which might suggest a limitation of this small group study.

## DISCUSSION

Our clinical standard dose fractionation of SBRT for primary lung cancer was 48 Gy in four fractions. For metastatic lung cancer, we escalated the dose to 60 Gy because three local failures occurred with the 48-Gy dose. At last follow-up, 60 Gy appears to have been well tolerated by the patients with lung metastases. No local progression occurred with the 60-Gy dose. The difference between 48 and 60 Gy was not statistically significant in the survival rate, but was marginally significant ($p$ = 0.078) in the local progression rate. The incidence of Grade 1 and 2 pulmonary toxicity was comparable between the two doses, with 13 (72%) and 2 (11%) at 48 Gy and 10 (63%) and 2 (13%) at 60 Gy, respectively. Dose escalation from 48 to 60 Gy increased the local control rate without increasing the incidence or severity of pulmonary toxicity.

Several reports have been published regarding the outcomes of SBRT for primary or metastatic lung tumors. Table 5 lists the survival outcomes after SBRT for pulmonary metastases in these reports. Onimaru *et al.* (8) and Wulf

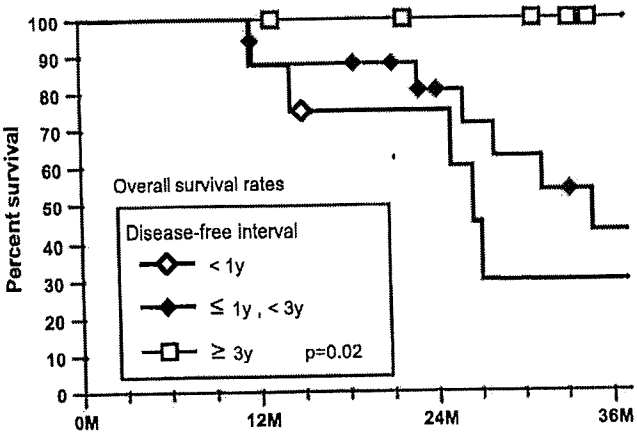


Fig. 3. Overall survival rates stratified by disease-free interval ($p$ = 0.02).

(14) reported overall survival rates of 49% and 33% at 2 years. Lee *et al.* (7) did not report the actuarial 2-year survival rate, although we calculated the crude survival rate to be 68% from data in their summary table. In the present study, it was 84%. The biologically effective dose, assuming the $\alpha/\beta$ ratio to be 10 ($BED_{10}$), in the present study was 105.6 Gy and 132.0 Gy for 48 Gy in four fractions and 60 Gy in five fractions, respectively. Onishi *et al.* (15) concluded that a $BED_{10}$ of >100 Gy at the isocenter is preferable for the treatment of primary lung cancer to achieve a better overall survival rate. The $BED_{10}$ of SBRT for pulmonary metastases ranged from 70 to 162 Gy, and the survival rates at 2 years ranged from 33% to 84% (Table 5).

An important aspect when discussing these results is the difference in treatment planning. One is the dose prescription point. We prescribed the dose to the isocenter. In contrast, some institutes prescribed to the margin of the PTV. Second is the PTV margin. The PTV margin differs depending on the setup accuracy at each institution. Third is the PTV contour. Contouring of the PTVs would reflect a difference in CT scanning: CT scanning with free breathing vs. breath holding and slow vs. fast scan times. Fourth is the dose calculation algorithm, including the inhomogeneity correction. Differences in the dose calculation algorithm would affect the marginal dose, particularly in treatment planning for lung tumors. Thus, we prescribed the dose to the isocenter to avoid unintended dose variations. Recently, more accurate dose calculation has become common, and adoption of a prescription with respect to the PTV is also worth considering, if a standard method has been established.

Surgical pulmonary metastasectomy has been recognized as a potentially curative treatment, particularly for patients without other metastases. Our published data review revealed that the 5-year survival rate for these patients was 26–40% (21–30) (Table 6). According to the International Registry of Lung Metastases, with >5,000 cases, surgical resection for metastatic lung tumor can result in long-term survival (21). In the International Registry of Lung

Table 5. SBRT for pulmonary metastases

| Investigator | Primary tumor (*n*) | Patients (*n*) | Prescription | $BED_{10}$ @ IC | Target | 2-y Survival rate (%) |
|---|---|---|---|---|---|---|
| Lee *et al.* (7), 2003 | Lung 5, liver 3, esophagus 2, trachea 2 | 19 | 30 Gy/3 Fr to 40 Gy/4 Fr | | CTV: GTV + 5 mm | 68* |
| | | 12 | 30 Gy/3 Fr (median 90% @ PTV margin) | 70† | PTV: CTV + 5–10 mm | |
| | | 7 | 40 Gy/4 Fr (median 90% @ PTV margin) | 94† | | |
| Onimaru *et al.* (8), 2003 | Lung 6, kidney 6, breast 2 | 20 | 48 Gy/8 Fr to 60 Gy/8 Fr | | ITV | 49 |
| | | 15 | 48 Gy/8 Fr @ IC | 76.8 | PTV: ITV + 5–10 mm | |
| | | 5 | 60 Gy/8 Fr @ IC | 105.0 | | |
| Wulf *et al.* (14), 2004 | Lung 23, breast 5, colorectum 4, kidney 4, sarcoma 4 | 51 | 26 Gy/1 Fr to 37.5 Gy/3 Fr | | CTV: GTV + 2–3 mm | 33 |
| | | 25 | 26 Gy/1 Fr (80% @ PTV margin) | 138† | PTV: CTV+ 5–10 mm | |
| | | 12 | 30 Gy/3 Fr (100% @ PTV margin, 150% @ IC) | 112.5 | | |
| | | 5 | 36 Gy/3 Fr (100% @ PTV margin, 150% @ IC) | 151.2 | | |
| | | 9 | 37.5 Gy/3 Fr (100% @ PTV margin, 150% @ IC) | 161.7 | | |
| Present study | Lung 15, colorectum 9, head and neck 5, kidney 3 | 34 | 48 Gy/4 Fr to 60 Gy/5 Fr | | ITV | 84 |
| | | 18 | 48 Gy/4 Fr @ IC | 105.6 | PTV: ITV + 5 mm | |
| | | 16 | 60 Gy/5 Fr @ IC | 132.0 | | |

*Abbreviations:* SBRT = stereotactic body radiotherapy; $BED_{10}$ = biologically effective dose ($\alpha/\beta = 10$); IC = isocenter; Fr = fractions; CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume; ITV = internal target volume.

* Calculated from patient summary table.

† Estimations according to their marginal doses.

Metastases study, with the exclusion of the apparently favorable tumors (*i.e.*, germ cell and Wilms tumors), the survival outcome at 2 years was approximately 70%. In our study, the overall survival rate at 2 years was 84%. Thus, SBRT appears to have the potential to cure, similar to that of surgical metastasectomy.

Table 6. Results of metastasectomy

| Investigator | Year | Primary cancer | Patients (n) | 5-y Survival rate (%) |
|---|---|---|---|---|
| IRLM (21) | 1997 | Various | 4,572 | 36 |
| | | Epithelial tumor | 1,984 | |
| | | Sarcoma | 1,917 | |
| | | Germ cell tumor | 318 | |
| | | Melanoma | 282 | |
| | | Other | 70 | |
| van Rens *et al.* (23) | 2001 | Lung | 121 | 26 |
| Saito *et al.* (25) (KCOG) | 2002 | Colorectum | 165 | 40 |
| Pfannschmidt *et al.* (27) | 2003 | Colorectum | 167 | 32 |

*Abbreviations:* IRLM = International Registry of Lung Metastases; KCOG = Kansai Clinical Oncology Group.

The International Registry of Lung Metastases also analyzed prognostic factors. They found that a DFI of ≥36 months, a single metastasis, and germ cell or Wilms tumor as the primary tumor were factors resulting in a good prognosis. In our study, a longer DFI of >3 years was also a good prognostic factor. They also showed that the difference in relative risk was not substantial for those with common epithelial cancers such as those of the bowel, breast, head and neck, and kidney. In our study, no significant difference was found in overall survival between those with metastases from lung cancer and those with metastases from other sites. For selected patients with pulmonary oligometastases, survival after SBRT might not be affected by the primary disease.

## CONCLUSION

The optimal regimen of SBRT for pulmonary metastasis has not yet been determined: 60 Gy was well tolerable and was superior to 48 Gy for local control at 2 years. SBRT for oligometastatic lung tumors was comparable to surgical metastasectomy with regard to the 2-year overall survival rate. SBRT could be an effective treatment for oligometastatic lung tumors.

## REFERENCES


1. Uematsu M, Shioda A, Tahara K, *et al.* Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: A preliminary experience. *Cancer* 1998;82: 1062–1070.
2. Nakagawa K, Aoki Y, Tago M, *et al.* Megavoltage CT-assisted stereotactic radiosurgery for thoracic tumors: Original research in the treatment of thoracic neoplasms. *Int J Radiat Oncol Biol Phys* 2000;48:449–457.
3. Wulf J, Hadinger U, Oppitz U, *et al.* Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000;57:225–236.
4. Hara R, Itami J, Kondo T, *et al.* Stereotactic single high dose irradiation of lung tumors under respiratory gating. *Radiother Oncol* 2002;63:159–163.
5. Nagata Y, Negoro Y, Aoki T, *et al.* Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041–1046.
6. Hof H, Herfarth KK, Munter M, *et al.* Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2003;56:335–341.
7. Lee SW, Choi EK, Park HJ, *et al.* Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung. *Lung Cancer* 2003;40:309–315.
8. Onimaru R, Shirato H, Shimizu S, *et al.* Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003;56:126–135.
9. Onishi H, Kuriyama K, Komiyama T, *et al.* A new irradiation system for lung cancer combining linear accelerator, computed tomography, patient self-breath-holding, and patient-directed beam-control without respiratory monitoring devices. *Int J Radiat Oncol Biol Phys* 2003;56:14–20.
10. Singh D, Yi WS, Brasacchio RA, *et al.* Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys* 2004;58:3–10.
11. Kavanagh BD, McGarry RC, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. *Semin Radiat Oncol* 2006;16:77–84.
12. Yang JC, Abad J, Sherry R. Treatment of oligometastases after successful immunotherapy. *Semin Radiat Oncol* 2006;16: 131–135.
13. Rubin P, Brasacchio R, Katz A. Solitary metastases: Illusion versus reality. *Semin Radiat Oncol* 2006;16:120–130.
14. Wulf J, Haedinger U, Oppitz U, *et al.* Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: A noninvasive treatment approach in medically inoperable patients. *Int J Radiat Oncol Biol Phys* 2004;60:186–196.
15. Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623–1631.
16. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63: 1427–1431.
17. Zimmermann FB, Geinitz H, Schill S, *et al.* Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. *Lung Cancer* 2005;48:107–114.
18. Negoro Y, Nagata Y, Aoki T, *et al.* The effectiveness of an immobilization device in conformal radiotherapy for lung tumor: Reduction of respiratory tumor movement and evaluation of the daily setup accuracy. *Int J Radiat Oncol Biol Phys* 2001; 50:889–898.
19. Takayama K, Nagata Y, Negoro Y, *et al.* Treatment planning of stereotactic radiotherapy for solitary lung tumor. *Int J Radiat Oncol Biol Phys* 2005;61:1565–1571.
20. Aoki T, Nagata Y, Negoro Y, *et al.* Evaluation of lung injury after three-dimensional conformal stereotactic radiation therapy for solitary lung tumors: CT appearance. *Radiology* 2004;230: 101–108.
21. The International Registry of Lung Metastases. Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37–49.
22. Asaph JW, Keppel JF, Handy JR Jr., *et al.* Surgery for second lung cancers. *Chest* 2000;118:1621–1625.
23. van Rens MT, Zanen P, de la Riviere AB, *et al.* Survival after resection of metachronous non-small cell lung cancer in 127 patients. *Ann Thorac Surg* 2001;71:309–313.
24. Sakamoto T, Tsubota N, Iwanaga K, *et al.* Pulmonary resection for metastases from colorectal cancer. *Chest* 2001;119: 1069–1072.
25. Saito Y, Omiya H, Kohno K, *et al.* Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 2002;124: 1007–1013.
26. Rena O, Casadio C, Viano F, *et al.* Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis: Twenty-year experience. *Eur J Cardiothorac Surg* 2002; 21:906–912.
27. Pfannschmidt J, Muley T, Hoffmann H, *et al.* Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: experiences in 167 patients. *J Thorac Cardiovasc Surg* 2003;126:732–739.
28. Inoue M, Ohta M, Iuchi K, *et al.* Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2004;78:238–244.
29. Monteiro A, Arce N, Bernardo J, *et al.* Surgical resection of lung metastases from epithelial tumors. *Ann Thorac Surg* 2004;77:431–437.
30. Kondo H, Okumura T, Ohde Y, *et al.* Surgical treatment for metastatic malignancies—Pulmonary metastasis: Indications and outcomes. *Int J Clin Oncol* 2005;10:81–85.

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# Time-dependent cell disintegration kinetics in lung tumors after irradiation

**Alexei V Chvetsov[1], Jatinder J Palta[1] and Yasushi Nagata[2]**

[1] Department of Radiation Oncology, University of Florida, Gainesville, FL, USA
[2] Department of Therapeutic Radiology and Oncology, Kyoto University, Kyoto, Japan

E-mail: chvetsov@ufl.edu

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**Abstract**

We study the time-dependent disintegration kinetics of tumor cells that did not survive radiotherapy treatment. To evaluate the cell disintegration rate after irradiation, we studied the volume changes of solitary lung tumors after stereotactic radiotherapy. The analysis is performed using two approximations: (1) tumor volume is a linear function of the total cell number in the tumor and (2) the cell disintegration rate is governed by the exponential decay with constant risk, which is defined by the initial cell number and a half-life $T_{1/2}$. The half-life $T_{1/2}$ is determined using the least-squares fit to the clinical data on lung tumor size variation with time after stereotactic radiotherapy. We show that the tumor volume variation after stereotactic radiotherapy of solitary lung tumors can be approximated by an exponential function. A small constant component in the volume variation does not change with time; however, this component may be the residual irregular density due to radiation fibrosis and was, therefore, subtracted from the total volume variation in our computations. Using computerized fitting of the exponent function to the clinical data for selected patients, we have determined that the average half-life $T_{1/2}$ of cell disintegration is 28.2 days for squamous cell carcinoma and 72.4 days for adenocarcinoma. This model is needed for simulating the tumor volume variation during radiotherapy, which may be important for time-dependent treatment planning of proton therapy that is sensitive to density variations.

## 1. Introduction

The goal of this paper is to show that the time-dependent disintegration of tumor cells which do not survive radiotherapy can be described using a simple analytical function. These cells are supposed to be lethally damaged by radiation with the probability described, for instance, by the LQ-model; however, they exist in some intact form and contribute to the tumor volume

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even though they are not able to proliferate (Fowler 1989, Hall and Giaccia 2006). We assume that these cells disintegrate at the first or subsequent division and their debris is removed from the tumor. This mechanism called mitotic death is a common form of cell death after irradiation; however, the probability of other disintegration mechanisms like apoptosis can also be included in our model (Hall and Giaccia 2006). The time-dependent kinetics which we apply to the population of lethally damaged cell has also been successfully used for the population of neurons with inherited degenerations (Clarke *et al* 2000). The neuron population with inherited degenerations is very similar to the lethally damaged tumor cells because they do not proliferate and their death initiated by a random event. For the analysis of this time-dependent cell kinetics, we utilized a clinical study on the volumetric changes of solitary lung tumors after stereotactic body radiotherapy (Aoki *et al* 2004).

The disintegration model of lethally damaged cells can be used in more complicated models which describe complete tumor cell kinetics during radiation therapy. This kinetics which includes both living and lethally damaged cells is implemented, for instance, in the computer models developed by Borkenstein *et al* (2004) and Dionysiou *et al* (2004). Potentially, these models can predict tumor volume during fractionated radiotherapy which can be important for time-dependent treatment planning because the tumor volume variation causes density variations which, in turn, can affect the prescribed dose distributions. During the last few years, several clinical studies have been published on tumor volume variation *in vivo* during fractionated radiotherapy. The data in these studies have been obtained using integrated 3D imaging techniques such as CT/linear accelerator system or tomotherapy (Barker *et al* 2004, Kupelian *et al* 2005, Siker *et al* 2006). Similar studies on tumor volume variation have been done using conventional CT scanners for treatment modalities where the integrated 3D imaging was not available, for instance proton therapy (Bucci *et al* 2007). The acquired data indicate that the physiological geometry changes in tumors and normal tissues between dose fractions can affect the dose distributions during fractionated radiotherapy, with an apparent maximum effect for lung and head and neck cancers. The research on tumor volume variation is important for intensity-modulated radiation therapy (IMRT), which provides sharp dose fall-off around the tumor (Mohan *et al* 2005). Emergent proton therapy is even more sensitive to the physiological changes because of the limited range of proton beams (Engelsman and Kooy 2005, Bucci *et al* 2007).

New models for tumor volume variation have been developed which can describe anatomical changes during fractionated radiotherapy (Seibert *et al* 2007, Chao *et al* 2007). These models are based on deformable image registration techniques or database analysis; however, they do not utilize the underlying radiobiological mechanisms. Therefore, these models cannot explain many phenomena which have been observed in tumor volume variation measurements. They lack predictive power because they do not utilize radiobiological principles. We believe that radiobiological models are necessary to explain these observed phenomena and predict tumor shrinkage based on radiobiological principles.

In the radiobiological modeling for radiotherapy treatment planning research has been primarily dedicated to developing effective dose fractionation schedules, models for tumor control probability (TCP) and normal tissue complication probability (NTCP) (Moiseenko *et al* 2005, Stewart and Li 2007). Less attention has been paid to the models for volume and mass variations during radiotherapy because it was likely not assumed that these changes could significantly affect the dose distributions and treatment outcomes. The cell loss mechanisms have been studied for growing tumors to explain the difference between the potential doubling time and volume doubling time (Fowler 1991); however, the problems of quantitative evaluation of dosimetry due to volume and mass variation in treatment planning have not been addressed. Circumstances have changed recently with the invention and widespread use

of effective imaging technologies which allow monitoring of human tumors *in vivo* (Barker *et al* 2004, Kupelian *et al* 2005, Siker *et al* 2006). Volumetric radiobiological tumor response to irradiation with X-rays has been studied in animal experiments (Tannock and Howes 1973, Bernheim *et al* 1977, Spang-Thomsen *et al* 1981). The obtained data have been important for understanding the radiobiological mechanisms responsible for tumor regression; however, they cannot be applied directly to the human tumors irradiated *in vivo*. The data required for *in vivo* verification of tumor volume modeling are available now due to 3D integrated imaging technologies for monitoring the tumor volume variation during radiotherapy treatment.

In this paper, we propose a simple radiobiological model for cell disintegration kinetics after radiation damage. We believe that this model can motivate further development of the computationally efficient and practical models that describe cell kinetics and tumor-volume changes during radiotherapy. These models can potentially be used to improve time-dependent treatment planning.

## 2. Methods

### 2.1. *Cell survival, death and disintegration*

Irradiation of the tumor cell population with dose D causes the death of a fraction of cells. The survival process of living cells can be described using the linear-quadratic (LQ) model which is given by

$$S = \exp(-\alpha D - \beta D^2), \tag{1}$$

where $\alpha$ and $\beta$ are the parameters of the survival model (Fowler 1989, Hall and Giaccia 2006). The survival curve $S$ defines the relative number of cells which survive; therefore, the relative number of cells which are lethally damaged by radiation is given by $1-S$. Usually, the number of surviving clonogens is studied in treatment planning because they finally define the TCP. In this paper, we study the clonogens which did not survive irradiation because we believe that the kinetics of these clonogens defines the tumor volume variation during radiotherapy. The clonogens which are lethally damaged by radiation do not disappear instantly. They contribute to the tumor volume for a period of time until they disintegrate and their debris is removed from the tumor. This kinetics of cell loss can help us to evaluate the time-dependent tumor volume variation which, in turn, can affect the dose distributions.

It is difficult to derive the cell disintegration kinetics using the data on tumor-volume variation during radiotherapy because the tumor volume is defined by the kinetics of proliferating and damaged cells. However, after radiotherapy, we can assume that the entire cell population did not survive irradiation and is lethally damaged; therefore, we have only one cell subpopulation which is much easier to model. The clinical data on the tumor-volume variation after radiotherapy are available, for instance, for solitary lung tumors treated with stereotactic body radiotherapy (Aoki *et al* 2004).

### 2.2. *Cell disintegration model*

It is usually assumed that a cell damaged by radiation disintegrates at the first or a subsequent division after radiation damage at the dose levels used in therapy. During the time from radiation damage to disintegration, the damaged cells contribute to the tumor volume even though they are not able to proliferate. We assume that the cell disintegration rate is proportional to the number of intact damaged cells; therefore, we can write the following

differential equation for the time-dependent number of damaged cells:

$$\frac{dN(t)}{dt} = -\mu(t)N(t). \tag{2}$$

We further introduce an approximation of constant disintegration risk which assumes that the disintegration constant is time independent $\mu(t) = \mu_0$. Equation (2) with $\mu(t) = \mu_0$ has an analytical exponential decay solution which is given by

$$N(t) = N(t_0)\exp(-\mu_0 t), \tag{3}$$

where $N(t_0)$ is the number of dead intact cells at the initial time $t_0$. This approach is similar to the mathematical formalism used by Clarke *et al* (2000) to describe the time-dependent kinetics of cell death in inherited neuronal degenerations.

Similar to the formula for radioactive decay, we introduce a parameter called half-life for the biological decay of the damaged cell population. The half-life is defined as the time required for the number of damaged cells to decay to half of their initial value. The half-life of the damaged cell population is related to the decay constant $\mu_0$ as

$$T_{1/2} = \frac{\ln 2}{\mu_0}. \tag{4}$$

The key problem for practical applications of this approach is to evaluate the half-life of the population of damaged cells. We have already mentioned that damaged cells disintegrate at the first attempted division; therefore, the disintegration rate may be associated with the proliferation rate because both parameters are related to the cell cycle. It is convenient to assume that the half-life $T_{1/2}$ is linearly related to the potential doubling time $T_{pot}$ as

$$T_{1/2} = bT_{pot}, \qquad b > \ln 2. \tag{5}$$

If we take into account that the cell disintegration happens at the first or subsequent division, we can further establish that $T_{1/2} > \ln 2T_{pot}$, which allows for the parameter $b > \ln 2$. We have utilized here the relationship $T_{1/2} = \ln 2T_a$ between the half-life $T_{1/2}$ and the mean life $T_a$. Obviously, we have $T_a = T_{pot}$ if all damaged cells would disintegrate at the first division. For more detailed evaluation of the half-life $T_{1/2}$, we have to study the variation with time of a large population of damaged cells *in vivo*. The large population of damaged cells can be found, for instance, at the end of radiotherapy treatment where the entire population of cancer cells is assumed to have not survived irradiation.

### 2.3. *Tumor volume simulation*

One of the possible ways to study the kinetics of cell disintegration is to evaluate the tumor volume after radiotherapy because we can assume that the entire tumor cell population did not survive radiotherapy. This is a relatively simple mathematical problem because we have to evaluate only one cell subpopulation damaged by radiation and unable to proliferate. However, to evaluate the kinetics of cell disintegration based on the volumetric measurements, we have to assume a linear relationship between the tumor volume $V(t)$ and the cell number $N(t)$:

$$V(t) = vN(t), \tag{6}$$

where $v$ is a constant which includes the cell volume and the volume of the related intercellular space. Experiments with animal irradiation indicate that the mean cell concentration in tumors can be a function of delivered radiation dose and time. Therefore, the gross changes in the tumor volume after irradiation are not always a reliable indicator of microscopic changes in the cell number. However, the experimental data of Tannock and Howes indicate that the mean cell concentration returns to the near-normal values after a limited time between 1 and 7 days

(Tannock and Howes 1973). For instance, Tannock and Howes have measured a 75% reduction in the mean cell concentration after 6 Gy with 1 day of recovery time and a 50% reduction in the mean cell concentration after 30 Gy with 7 days of recovery time. Therefore, we believe that the linear relationship between the cell number and the tumor volume is a reasonable approximation for tumor volume simulation in the clinical study analyzed in this paper. In this clinical study, tumors have been monitored during several months after radiotherapy.

## 3. Results

### *3.1. Clinical data analysis*

To validate the exponential model and determine decay parameters, we used the clinical data on tumor size variation after stereotactic body radiotherapy published by Aoki *et al* (2004). This clinical study includes analysis of shrinkage of solitary lung tumors in 31 patients after administering a total dose of 48 Gy in four fractions using conformal stereotactic radiation therapy. Taking into account the survival fraction given by equation (1), we can assume that the entire cell population tumors did not survive the radiotherapy for the majority of patients at this dose; therefore, the tumor volume variation after radiotherapy should be defined by the disintegration and removal of damaged cells which are not able to proliferate. This is probably true for most of the patients because tumor control was not obtained in only two cases.

The tumor size variation with time was determined by taking CT images after radiotherapy. The relative variation of tumor size as a function of time is shown in figure 1(a) for three representative cases. Additionally, we show in figure 1(a) an exponent function with $T_{1/2} = 21$ days. We see that the exponent function approximates the general trend in tumor size variation with time. However, the difference is that the exponent function approaches zero and the tumor volume variation approaches some constant value.

We note that the tumor size in the clinical study has been measured using the largest transversal cross section A of the tumor. To evaluate the tumor volume variation, we computed the relative change of value $AA^{1/2}$ which presents the relative volumetric change under the assumption of uniform tumor shrinkage. The relative change of the value $AA^{1/2}$ is shown in figure 1(b). We see that the constant component was reduced when the data have been recalculated to the volumetric tumor change. This small constant component in the volume variation does not change with time; therefore, this component may be due to residual irregular density as radiation fibrosis and was, therefore, subtracted from volume variation in our computations.

### *3.2. Evaluation of half-life and average life*

To determine the half-life $T_{1/2}$ of exponential decay, we performed a computerized fitting of the exponent function to the clinical data for seven adenocarcinoma and seven squamous cell carcinoma (SCC) patients. The clinical study of Aoki *et al* includes 15 adenocarcinoma cases, 9 SCC cases, 4 metastasis cases, 2 unknown cases and 1 small cell carcinoma case. We have separated the adenocarcinoma and SCC cases and excluded all other cases. The tumor shrinkage was observed in all adenocarcinoma and SCC patients; however, not all of them had enough tumor size measurements to perform a reasonable fitting. Therefore, the patients for the fitting have been selected based on the number and density of tumor measurements available for each case. One of our selection criteria was the availability of at least three tumor measurements for each patient and at least one tumor measurement within the first 4 months after treatment.