ORIGINAL ARTICLE

Radiation Medicine: Vol. 22 No. 4, 233–238 p.p., 2004

Effects of Density Changes in the Chest on Lung Stereotactic Radiotherapy

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To experimentally and theoretically evaluate dose distribution during lung stereotactic radiotherapy, we investigated the relative electron densities in lung and tumor tissues using X-ray computed tomography images obtained from 30 patients in three breathing states: free breathing, inspiration breath-hold, and expiration breath-hold. We also calculated dose distribution using Monte Carlo simulation for lung tissue with two relative electron densities. The effect of changes in relative electron density on dose distribution in lung tissue was evaluated using calculated differential and integral dose volume histograms. The relative electron density of lung tissue was 0.22 in free breathing, 0.23 in shallow expiration, and 0.17 in shallow inspiration, and there was a tendency for relative electron density to decrease with age. The relative electron density of tumor tissue was approximately 0.9, with little variation due to differences in breathing state. As the relative electron density of lung tissue decreases, the low-dose region expands and leads to changes in the marginal dose.

Key words: lung stereotactic radiotherapy, relative electron density, dose distribution

Introduction

Lung stereotactic radiotherapy in early-stage lung cancer has been performed under various breathing states such as free breathing, inspiration breath-hold, and expiration breath-hold, depending on the facility.[1-3] The dose calculations are made based upon patient-specific physical information obtained from X-ray computed tomography (CT). In the dose calculation for lung stereotactic radiotherapy, however, the lack of lateral electron equilibrium due to the small radiation field, the presence of inhomogeneous tissue within the chest,[4] and mistaken information on patient-specific density caused by breathing stage may cause physicians to choose an insufficient planning target volume (PTV) setting and inaccurate dose distribution using a CT-based treatment planning system.

CT scans for positioning lung stereotactic radiotherapy are obtained during free breathing, inspiration breath-hold, and expiration breath-hold states. CT scans obtained during free breathing have a long scan time and are assumed to show the mean position of the lung tumor.[5] While the PTV is somewhat larger because of respiratory movement of the lung tumor, there are advantages including short-time irradiation and the lack of need for continuous verification monitoring of tumor position. However, CT imaging gated to a particular breathing phase, such as gated irradiation or tracking irradiation,[1,6] has a number of limitations.

Treatment planning for lung stereotactic radiotherapy is generally done using three-dimensional treatment planning systems with computer-friendly algorithms. However, the calculated dose distributions are probably least accurate near areas with steep density gradients owing to film measurement and the Monte Carlo simulation for the chest phantom.[4,7]

To accurately evaluate dose distribution, it is

Received December 25, 2003; revision accepted February 6, 2004.

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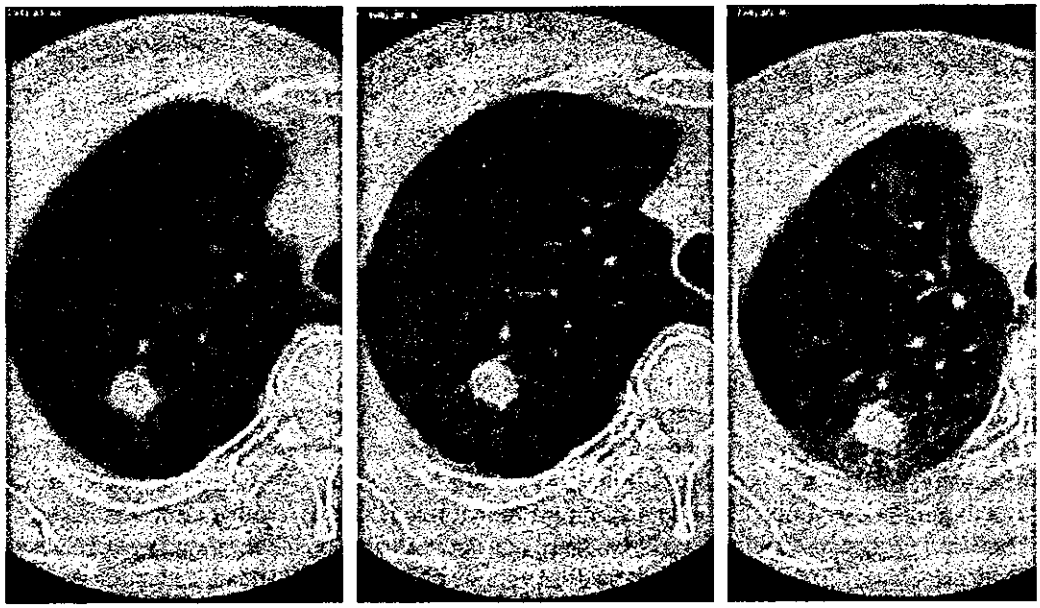

Fig. 1. CT scans in three breathing states (from left, CT scans obtained during free breathing, inspiration breath-hold, and expiration breath-hold).

necessary to ascertain the relative electron density obtained from the CT data of organs and tissues in the chest. In this study, we investigated the relative electron densities of lung tissue and tumor in the chest from CT images obtained in three breathing states for patients undergoing lung stereotactic radiotherapy. In addition, we calculated the effects of relative electron density on dose distribution using Monte Carlo simulation.

METHODS

Acquisition of CT images

The subjects consisted of 30 patients with a diagnosis of lung cancer (23 men and 7 women; mean age, 70 y) scheduled to undergo lung stereotactic radiotherapy. The patients were immobilized using a body immobilization system (Stereotactic Body Frame; Elekta Inc., GA, USA) on the flat table of a CT system (Xvigor; Toshiba Medical Systems Co., Ltd., Tokyo, Japan).

CT scans were acquired after training patients in breathing techniques at the time of treatment, by step-and-shoot scans during free breathing, and by helical scans during resting inspiration breath-hold and expiration breath-hold. The slice thicknesses and scan times were 5 mm and 4 sec/rotation for step-and-shoot scans and 3 mm and 1 sec/rotation for helical scans, and the table pitch was 1.0. Figure 1 shows the CT images obtained in each breathing phase. Because of the slow scan time during free breathing, the image edges of lung and tumor tissues on CT images appear indistinct. With a fast scan time under breath-hold conditions, the image edge is sharp but the lung tissue varies in size according to the breathing state.

Calibration of CT numbers

With the CT number (in Hounsfield Units, HU) of the linear attenuation coefficient of water defined as 0, the CT number of medium m (CT_m) is related to the linear attenuation coefficient of the medium consisting of the voxels in CT image by the following equation,[8,9]

$$CT_m=\kappa(\mu_m-\mu_w)/\mu_w=\kappa(\mu_m/\mu_w-1) \quad \cdots\cdots(1)$$

where μ_m is the linear attenuation coefficient of m in the pixel under analysis, μ_w is the linear attenuation coefficient of water, and κ is the constant that determines the scale factor for the range of CT number.[8] Because the CT number is obtained in the diagnostic X-ray energy region, the photoelectric effect cannot be ignored. The Compton effect is dominant in the X-ray energy region in radiotherapy, and it must be converted to electron density, ρ_e. Equation (1) is expressed as

$$CT_m=\kappa(\rho_e^m/\rho_e^w-1) \quad \cdots\cdots(2)$$

where ρ_e^m/ρ_e^w is the electron density relative to water. Therefore, ρ_e^m/ρ_e^w is used in treatment planning.

In order to establish the relationship between CT number and electron density, we obtained CT images of the electron density of a CT phantom (RMI 467,

GAMMEX rmi, Middleton, WI, USA) with electron densities corresponding to various tissues of the body. The CT phantoms included lung tissue (relative electron density 0.273-0.439), mammary gland (0.930), water (1.000), and bone (1.111-1.693). CT scans were performed with the measurement substance arranged so as to minimize artifacts.

Measurement of CT numbers

Image data were stored on a personal computer (VAIO PCG-FX33G/BP, SONY, Tokyo, Japan) via DICOM-protocol transfer from the CT system. The lung tissue and tumor on the CT images was selected as the region of interest, and the size (volume), location, and CT numbers were measured using OSIRIS imaging software.[10] The entire lung tissue was averaged because the X-ray beam for lung stereotactic radiotherapy covers the entire lung. We also established the relationship between CT number and relative electron density using the CT image of the CT phantom. The relative electron densities of the lung tissue and tumor were evaluated in each breathing state.

Monte Carlo simulation

The effect of changes in the relative electron density of the lung tissue on dose distribution was calculated using a user-coded EGS4 Monte Carlo code system.[11,12] This code enables deposit energy sampling of the same model as the CT image.

For irradiation, we adopted a clinically used method for stereotactic radiotherapy of solitary lung cancer: three non-coplanar arcs (–20, 0, +20° bed rotation; 180° gantry rotation on the lesion side) with an irradiation field of 3 cm in diameter for a tumor of 2 cm in diameter. The chest model used in this simulation was based on Cristy's ellipse human-body mathematical phantom of an adult male chest,[13] and was composed of soft tissue, lung tumor, and lung tissue (Fig. 2). The density of the soft tissue and lung tumor was 1.0 g/cm^3, and that of the lung tissue varied between 0.3 and 0.15 g/cm^3. The absorbed dose was calculated in a voxel of 2 mm in size. For incident photons, a 6 MV photon energy spectrum calculated by Mohan[14] was used, a history of 100 million (10 batches) was generated, and the radiation source and beam shape were assumed to be a point source and fan-line beam, respectively. The mass-stopping powers and density-correction factors were determined according to ICRU Report 37,[15] and cross-section data were prepared using a PEGS preprocessor of the EGS4 code system.

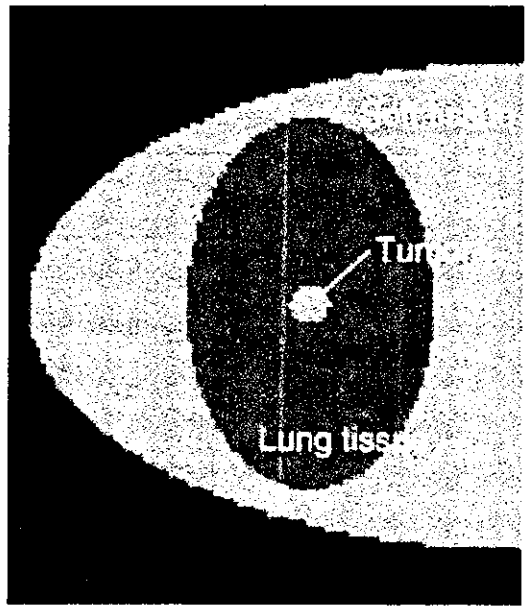

Fig. 2. Chest model in a Monte Carlo simulation. Water with density of 1.0 g/cm^3 is used as a material for soft tissue and tumor, and water with density of 0.3 g/cm^3 is used as a material for lung tissue.

Results

The relationship between CT number and relative electron density was a diphasic linear relationship, the two phases being delineated at a CT number of 100. Since the CT number in the chest is typically not greater than 100 except for bone, it could be expressed using the following equation,

$$\rho_e^m/\rho_e^w=\frac{CT_m}{974}+1 \quad \cdots\cdots(3)$$

Table 1 presents data for the relative electron density of the lung field in 30 patients with a mean age of 70 years who underwent lung stereotactic radiotherapy. The relative electron density was 0.22, 0.17, and 0.23 for free breathing, shallow inspiration, and shallow expiration, respectively, and that of the tumor was approximately 0.9 in each breathing phase. For the relative electron density of the lung tissue, we found that free breathing produced about the same values as for expiration, and the relative electron density varied with the breathing phase. Figure 3 shows the relationship between age and relative electron density of the lung tissue. The straight line is produced from a linear least squares fit through all data points. The data demonstrate that relative electron density decreases with age.

Figure 4 shows the differential and integral dose volume histograms (DVH), expressed with the isocenter dose defined as 100, calculated by a Monte Carlo

Table 1. Relative electron density (mean±S.D.) of lung tissue and tumor in three breathing states

	Free breathing	Shallow inspiration	Shallow expiration
Lung tissue	0.22±0.08	0.17±0.05	0.23±0.08
Tumor	0.87±0.11	0.91±0.08	0.92±0.09

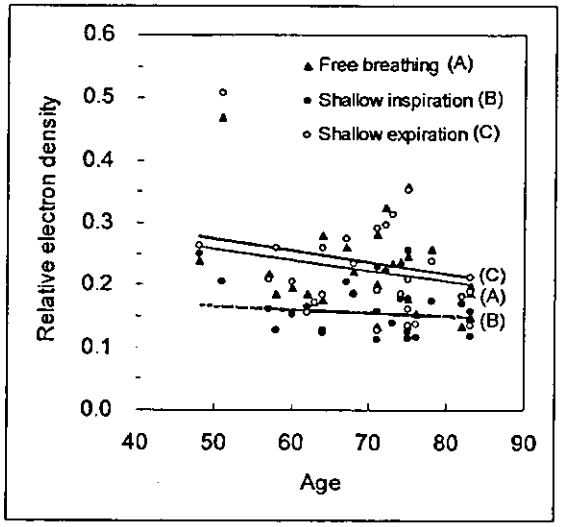

Fig. 3. Age and relative electron density of the lung tissue in 30 patients undergoing lung stereotactic radiotherapy.

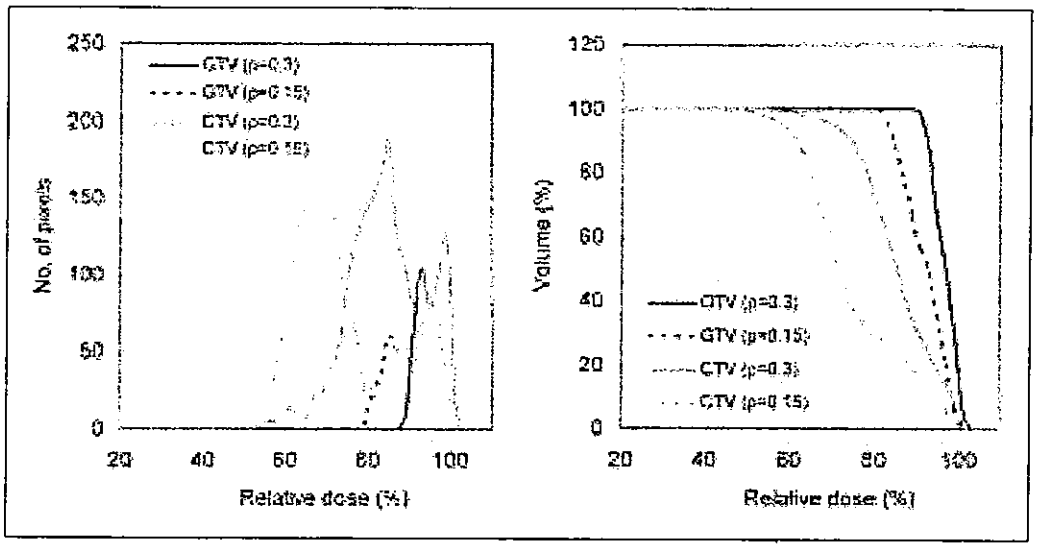

Fig. 4. Differential DVH and integral DVH calculated from a Monte Carlo simulation.

simulation. The gross target volume (GTV) is the tumor, and the clinical target volume (CTV) is a 3 cm diameter plus a 0.5 cm margin around the GTV. Numerals enclosed in parentheses in the figure represent the density of the lung tissue and are equal to the relative electron densities. In both the differential DVH and integral DVH, the relative electron density decreased and shifted leftward. Additionally, when the relative electron density of the lung tissue was altered to 0.3 and 0.15, D95 (the dose to 95% of the volume) within the CTV was 69.6

and 57.4, respectively.

Discussion

Analysis of the relative electron density of the lung tissue in three breathing states showed that the relative electron density varied according to breathing state. The volume of lung tissue increased by approximately 1% in free breathing and by about 12% in shallow inspiration relative to shallow expiration. It is indicated that the increase in lung volume due to breathing is a factor of change in density for the particular breathing state. The finding that the relative electron density for free breathing and shallow expiration were almost the same suggests that breathing is restricted by body frame and that the expiratory phase accounts for a greater proportion of the breathing cycle. Ohara *et al.*[1] improved the dose distribution of respiratory movement by synchronizing irradiation with the expiration phase, in which the respiratory movement of the tumor was small.

With regard to the density of the lung tissue, Rosenblum *et al.*[16] reported mean values of 0.27 g/cm^3 in quiet breathing and 0.20 g/cm^3 in inspiration breath-hold for subjects over the age of 10. Van Dyk *et al.*[17] proposed a linear approximation formula based on age for breathing at normal, full inspiration, and full expiration. The reported densities at 70 years of age were 0.22 g/cm^3, 0.16 g/cm^3, and 0.24 g/cm^3, respectively. They also demonstrated that density decreases with age. Tachibana *et al.*[18] reexamined this study, and reported densities at 70 years of age of 0.22, 0.17, and 0.23 g/cm^3, respectively. These results are largely consistent with our results, including the age-based approximation formula. The mean density of the lung tissue might be almost unchanged in the shallow breathing phase, independent of race and physical constitution. Most commercially available lung tissue phantoms typically have densities in the range 0.26-0.32 g/cm^3 because ICRU recommends 0.26 g/cm^3 as a density of the lung.[19] Accordingly, the dose in lung tissue may be overestimated when a phantom of a higher density is used for dosimetry of the lung tissue. However, change in the density of the lung tissue caused by gravity-dependent opacity was not considered in this study. An adequate patient position (supine, prone, sitting) for lung stereotactic radiotherapy can be obtained by examining this phenomenon.

It is thought that the DVH curve shifted leftward owing to a reduction in the number of recoil electrons generated per unit volume as the recoil electron range lengthens with a decrease in density. The same phenomenon also applies to the recoil electrons generated from the tumor. The density of the lung tissue in the surrounding GTV changes with breathing state, though GTV is assumed to be homogeneous. Accordingly, it was shown that D95 within the CTV changes greatly depending on density. It will be necessary to examine variation in the clinical data in the future because D95 also depends on the energy and path length of the X-ray beam. In stereotactic radiotherapy, prescription dose is frequently determined by the marginal dose. Additionally, it has been reported that the dose delivered to the lung contributes to radiation pneumonitis.[20] Moreover, the dose distributions calculated with treatment planning systems are probably the least accurate near areas of steep density gradient, and a target boundary may be the most likely site of recurrence. In this study, we demonstrated the need to determine the size of the margin in the breathing state.

Acknowledgement

This research was funded in part by grants from Core Research for Evolutional Science and Technology, Japan Science and Technology Agency.

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Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 4, pp. 1117–1122, 2005
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0360-3016/05/$-see front matter

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doi:10.1016/j.ijrobp.2004.07.692

CLINICAL INVESTIGATION **Lung**

A PHASE II STUDY OF HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) AFTER INDUCTION CISPLATIN (CDDP) AND VINORELBINE (VNR) FOR STAGE III NON–SMALL-CELL LUNG CANCER (NSCLC)

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Purpose: The purpose was to assess the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HART) after induction chemotherapy for Stage III non–small-cell lung cancer.

Methods and Materials: Treatment consisted of 2 cycles of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART, 3 times a day (1.5, 1.8, 1.5 Gy, 4-h interval) for a total dose of 57.6 Gy.

Results: Thirty patients were eligible. Their median age was 64 years (range, 46–73 years), 24 were male, 6 were female, 8 had performance status (PS) 0, 22 had PS 1, 9 had Stage IIIA, and 21 had Stage IIIB. All but 1 patient completed the treatment. Common grade ≥3 toxicities during the treatment included neutropenia, 25; infection, 5; esophagitis, 5; and radiation pneumonitis, 3. The overall response rate was 83%. The median survival was 24 months (95% confidence interval [CI], 13–34 months), and the 2-year overall survival was 50% (95% CI, 32–68%). The median progression-free survival was 10 months (95% CI, 8–20 months).

Conclusion: Hyperfractionated accelerated radiotherapy after induction of cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is needed. © 2005 Elsevier Inc.

Non–small-cell lung cancer, Hyperfractionated accelerated radiation therapy, Chemoradiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2001, approximately 55,000 patients died of lung and bronchus cancer (1). Surgery is the standard of care for patients with Stage I–II non–small-cell lung cancer (NSCLC), but a combination of chemotherapy and thoracic radiotherapy with or without surgery is indicated for the majority of patients with Stage III disease. Cisplatin (CDDP) based chemotherapy with conventional radiotherapy improved survival compared to conventional radiotherapy alone (2–6) and was the standard of care in the 1990s. Recently, concurrent chemoradiotherapy has been revealed to be superior to sequential chemoradiotherapy (7, 8), but it is difficult to give full-dose chemotherapy using newer cytotoxic agents concurrently with radiotherapy, and the optimal combination has not yet been clarified. In the meantime, continuous hyperfractionated accelerated radiotherapy (CHART) with 3 daily fractions to intensify the local effect of radiotherapy has been found to be superior to conventional radiotherapy (9). The survival benefit of CHART was encouraging, but the protocol including treatments on weekends and 6-h intervals between fractions had some difficulties in practicality. Mehta *et al.* introduced hyperfractionated accelerated radiotherapy (HART) (modified CHART) with 3 daily fractions and 4-h interfraction intervals with weekend breaks and also showed promising results similar to those using sequential chemoradiotherapy (10). After these results, we started a Phase II trial to evaluate the feasibility and efficacy of induction chemotherapy with HART for patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven NSCLC with clinical tumor-node-metastasis system Stage III, and pathologic N2 was also required for Stage

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This study was presented in part at the 38th Annual Meeting of ASCO in Orlando, Florida, May 18–21, 2002.

Acknowledgment—We thank Mrs. Fumiko Ko for her contribution to data management.

Received Mar 29, 2004, and in revised form Jul 9, 2004. Accepted for publication Jul 13, 2004.

IIIA; age, 20 to 74 years; performance status (PS) (based on Eastern Cooperative Oncology Group [ECOG] scale) 0 to 1; measurable disease; adequate hematologic (WBC count ≥4,000/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9.5 g/dL), hepatic (AST and ALT level ≤2 times the upper limit of normal and total bilirubin level ≤ the upper limit of normal), and renal (creatinine ≤1.2 mg/dL and creatinine clearance ≥60 mL/min) functions; PaO_2 ≥70 torr; no pleural and pericardial effusion; radiation field encompassed one-half or less of the ipsilateral lung; and no serious comorbidity. All patients signed written informed consent in accordance with our institutional review board.

Pretreatment evaluation included history and physical examination; serum chemistries (lactate dehydrogenase, alkaline phosphatase, AST, ALT, bilirubin, albumin, creatinine, and calcium); chest radiograph; CT scan of the chest; ultrasound of the abdomen; MRI or CT scan of the brain; and bone scintigraphy.

Treatment details

The treatment consisted of 2 cycles of CDDP 80 mg/m^2 on Day 1 and vinorelbine (VNR) 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART; 3 times a day with minimal interval of 4 hours for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks.

Radiation therapy was started after the patient recovered from the toxicity of chemotherapy and was delivered with megavoltage equipment. Lung heterogeneity corrections were not used. The first and third fraction of each day consisted of anterior-posterior opposed fields that encompassed the primary tumor, the metastatic lymph nodes, and the regional lymph nodes with a 1.5 to 2-cm margin. The fraction size was 1.5 Gy. Regional nodes excluding the contralateral hilar and supraclavicular nodes were included in these fractions. However, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The second fraction of each day consisted of bilateral oblique fields that encompassed the primary tumor and the metastatic lymph nodes with a 1.5 to 2-cm margin; the fraction size was 1.8 Gy. Attempts were made to design the field of the second fraction to minimize the irradiated volume of the esophagus without compromising the margin around the tumor or spinal cord.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 2 months for the first year, every 3 months for the second year, and every 6 months thereafter: physical examination, toxicity assessment, and chest radiograph. CT scan of the chest was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. Restaging at 6 months after the treatment was also performed with ultrasound of the abdomen, MRI or CT scan of the brain, and bone scintigraphy.

Response assessment

Complete response (CR) was defined as complete disappearance of all measurable and assessable lesions for ≥4 weeks, partial response (PR) was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions for ≥4 weeks, and progressive disease (PD) was defined as an increase of 25% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion. Stable disease was defined as the remainder of evaluable patients without CR, PR, or PD.

Pattern of failure

Patterns of failure were defined as first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

A Simon's two-stage optimal design was used for this study with the assumption that a protocol compliance rate of less than 60% would not be feasible, and protocol compliance rate of 80% or greater with α error of 0.10 and β error of 0.10 would warrant further investigation of this regimen. In the first stage, 11 assessable patients were entered. If fewer than 7 patients completed the treatment, accrual would be stopped with the conclusion that the regimen was not feasible for further investigation. If 7 or more patients completed the treatment, an additional 27 patients would be accrued in the second study. According to this design, this study would be determined to be feasible and be proceeded to a multicenter Phase II study if 27 patients completed the treatment. The actuarial median survival time and 2-year survival were estimated by the Kaplan–Meier method (11).

RESULTS

Patient population

Between July 1999 and March 2001, 30 patients were enrolled in the study. The accrual was stopped, because 29 of 30 patients completed the treatment, and conclusions could be drawn at that time. The patients' median age was 64 years (range, 46–73 years), 24 were male, and 6 were female. The patient and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity

All patients completed 2 cycles of induction chemotherapy. Six of 30 patients required dose modification, and 13 patients had treatment delay. The median time to start of HART from start of chemotherapy was 49 days (range, 41–62 days). Twenty-nine of 30 patients completed HART, and the median overall treatment time of HART was 17 days (range, 16–22 days). In total, 29 of 30 patients (97%; 95% confidence interval [CI], 83–100%) completed this combined treatment.

The toxicity profile of the treatment is shown in Tables 2 and 3. Common Grade 3 or greater acute toxicities were neutropenia, 25 (83%); infection, 5 (17%); esophagitis, 5 (17%); and radiation pneumonitis, 3 (19%). There were 2 cases of treatment-related death due to radiation pneumonitis. As of the date of this analysis, 2 cases with Grade

Table 1. Patient and tumor characteristics

Number of patients	30
Age	
Median	64
Range	46–73
Gender	
Male	24
Female	6
Performance status	
0	8
1	22
Weight loss	
<5%	25
≥5%	5
Tumor and lymph nodes	
T1N2	3
T1N3	1
T2N2	5
T2N3	5
T3N2	1
T4N0	1
T4N1	4
T4N2	9
T4N3	1
Stage	
IIIA	9
IIIB	21
Histology	
Squamous	13
Nonsquamous	17

3 s.c. tissue fibrosis and 1 case with spontaneous rib fracture were observed as late toxicities.

Response and survival

Of 30 patients, 2 achieved CR, and 23 achieved PR with a response rate of 83% (95% CI, 65–94%). Five patients remained in a stable disease state, and there were no PD patients. With a median follow-up period of 40 months for surviving patients, the median survival and the 2-year and 3-year survivals (Fig. 1) were 24 months (95% CI, 13–34 months), 50% (95% CI, 32–68%), and 32% (95% CI, 15–49%), respectively. The median progression-free survival and the 1-year progression-free survival (Fig. 2) were 10 months (95% CI, 8–20 months) and 47% (95% CI, 29–65%), respectively.

Pattern of failure

At the time of this analysis, 22 of 30 patients (73%) showed tumor progression, 2 patients (7%) had died as a result of treatment, and 6 patients (20%) were alive without disease progression. The patterns of first failure were as follows: local/regional only, 13 (43%); local/regional and distant, 4 (13%); distant only, 5 (17%).

DISCUSSION

In the 1970s, treatment of locally advanced NSCLC was by conventional radiotherapy alone. In the 1980s, sequential chemotherapy and conventional radiotherapy were revealed to be superior to conventional radiotherapy alone. In the 1990s, optimal sequences of chemoradiotherapy and radiation fractionation were investigated. The West Japan Lung Cancer Group compared sequential vs. concurrent radiotherapy with induction CDDP, vindesine, and mitomycin (7). In an RTOG 9410 trial, induction CDDP and vinblastine plus sequential standard radiotherapy, CDDP and vinblastine plus concurrent standard radiotherapy, and CDDP and etoposide plus concurrent twice-daily hyperfractionated radiotherapy were compared (8). Both trials showed similar results; concurrent chemoradiotherapy was superior to the sequential approach and achieved 5-year survivals for concurrent and sequential approach of approximately 20% and 10%, respectively. However, twice-daily hyperfractionated radiotherapy, which seemed to be promising in a preceding RTOG 9015 trial (12), failed to show a survival advantage over standard once-daily radiotherapy, and concurrent chemotherapy and once-daily radiotherapy is the standard of care today. Recently, a Czech randomized Phase II trial (13) suggested a similar advantage of the concurrent approach using CDDP and VNR, a newer cytotoxic agent. However, there remains some argument that newer cytotoxic agents cannot be delivered as full-dose chemotherapy with concurrent radiotherapy, and the survival advantage of newer cytotoxic agents over old ones has not yet been demonstrated in Stage III NSCLC patients. The optimal schedule and fractionation of thoracic radiotherapy in combination with chemotherapy also remains to be determined.

Table 2. Hematologic toxicities (n = 30)*

	Grade					
	0	1	2	3	4	≥Grade 3 (%)
Leukopenia	1	3	8	16	2	18 (60)
Neutropenia	3	0	2	6	19	25 (83)
Thrombocytopenia	20	7	1	2	0	2 (7)
Anemia	1	10	16	3	0	3 (10)

* National Cancer Institute–Common Toxicity Criteria version 2.

Another promising regimen was altered fractionation of radiotherapy such as CHART or HART, 3 times a day with a fraction interval of 4 to 6 hours over 2.5 weeks or less. CHART was developed at Mount Vernon Hospital, United Kingdom, in the 1980s. It was designed to combine both a shortening of the overall treatment time of radiotherapy, which is analogous to the concept of dose intensification of cytotoxic chemotherapy, and a reduction in dose per fraction. The rationale was to overcome accelerated repopulation of the tumor during the course of radiotherapy, which may lead to local failure, and to reduce normal tissue toxicities that depend on the dose per fraction. After the results of a randomized trial that showed survival benefits of CHART over conventional

Table 3. Nonhematologic toxicities (n = 30)*

	Grade						
	0	1	2	3	4	5	≥Grade 3 (%)
Acute toxicity							
Nausea	7	16	4	3	0	0	3 (10)
Vomiting	23	3	4	0	0	0	0
Infection	20	3	2	5	0	0	5 (17)
Esophagitis	1	11	13	4	1	0	5 (17)
Pneumonitis	18	4	5	1	0	2	3 (10)
Late radiation morbidity†							
Esophagus	26	1	0	0	0	0	0
Heart	26	0	1	0	0	0	0
Lung	9	13	5	0	0	0	0
Subcutaneous tissue	17	6	2	2	0	0	2 (7)
Bone	26	0	0	0	1	0	1 (3)

* National Cancer Institute–Common Toxicity Criteria version 2.
† Three patients died within 90 days of the beginning of radiotherapy.

radiotherapy (9), the Department of Health in the United Kingdom recommended CHART as the radiotherapy schedule of choice in inoperable NSCLC, and a CHART implementation group was formed to facilitate its introduction throughout the United Kingdom (14). There were difficulties in changing departmental working hours and a lack of sufficient financial support in UK hospitals to introduce CHART into routine practice (15), although it was suggested that CHART gave more benefit than any sequential combination of conventional radiotherapy and chemotherapy with minimally increased toxicity. To make the accelerated regimen more widely applicable, Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less (CHARTWEL) and HART were introduced and were found to be as effective as CHART. Both CHARTWEL and HART showed improved survival over conventional radiotherapy, but the local tumor control was still unsatisfactory. Radiation dose escalation and use of chemotherapy combined with CHARTWEL/HART were also investigated to improve the local control and survival. Saunders *et al.* (16) reported on CHARTWEL combined with induction chemotherapy (17). In that study, 113 patients were enrolled, and dose escalation from 54 Gy to 60 Gy with or without chemotherapy was successfully achieved. Locoregional control at 2 years was 37% and 55% for CHARTWEL 54 Gy and 60 Gy alone, respectively, compared with 72% in those treated with 60 Gy and induction chemotherapy. These results suggested that chemotherapy improved locoregional control, but unfortunately they failed to show a statistically significant survival advantage, because of the relatively small number of patients and imbalanced tumor characteristics enrolled in each arm. The advantage of dose-escalated CHARTWEL against conventional radiotherapy is currently being investigated in a German Phase

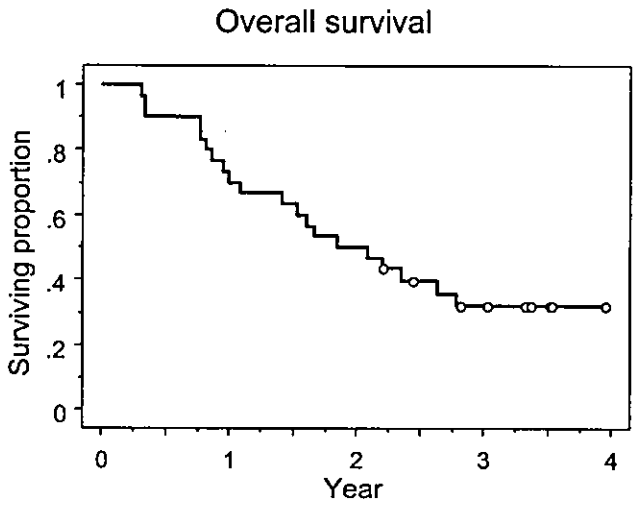

Fig. 1. Overall survival for all patients enrolled in this study.

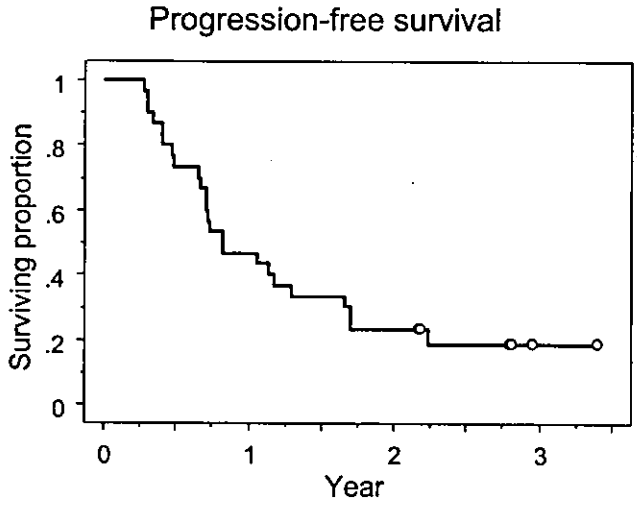

Fig. 2. Progression-free survival for all patients enrolled in this study.

III trial (18). Belani *et al.* reported the results of a randomized Phase III trial (19) that compared conventional radiotherapy with HART after induction chemotherapy (ECOG 2597). This study randomized 119 patients and unfortunately was closed because of slow accrual, but the results were provocative: The median survival time and the 2-year survivals for conventional radiotherapy and HART were 13.7 months and 33% vs. 22.2 months and 48%, respectively. These results seemed to be reliable despite the modest number of patients, because the median survival time of 13.7 months for the conventional radiotherapy arm was similar to that of a sequential chemoradiotherapy trial (2). The optimum chemotherapy regimen in combination with radiotherapy has not yet been determined, and we used a CDDP/VNR regimen instead of the carboplatin/paclitaxel regimen used in the ECOG 2597 trial. Both regimens are standards for advanced-stage NSCLC (20, 21). The compliance and toxicity profiles of chemotherapy in our study were acceptable, the incidence of esophagitis after HART was less than we expected, and the survival figure was nearly identical to that of the ECOG 2597 trial. This suggests that HART after induction CDDP/VNR or carboplatin/paclitaxel can achieve reproducible and promising results.

The pattern of failure in our study showed that local failure was still high (17 of 30, 57%) compared with distant metastasis (9 of 30, 30%), and further improvement of local control is needed. Future directions may include further dose intensification of radiotherapy and introduction of molecular-targeted agents. Recent innovation of information technology has made it possible to use sophisticated three-dimensional conformal radiotherapy (3DCRT). This can deliver intensified radiation doses to the tumor while minimizing the doses to the normal tissues that prevented further dose escalation using conventional two-dimensional radiotherapy. There have been several reports evaluating dose-intensified 3DCRT (22–25), and the technique is now under investigation in combination with cytotoxic chemotherapy in the Radiation Therapy Oncology Group trial (RTOG L-0117). Currently, molecular-targeted agents are being investigated most enthusiastically in Phase II and Phase III trials (26–29). It will be determined in the near future whether or not the combination of these agents has a survival impact. However, the optimal combination of these agents, newer cytotoxic agents, radiation fractionation, and 3DCRT will still need to be determined. Further investigation employing dose-intensified radiotherapy will be necessary to make a great leap in the treatment of locally advanced NSCLC.

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臨床：内科サイドからみた肺癌診療の最近の話題

肺癌治療における放射線治療の位置づけ

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はじめに

我が国における悪性腫瘍による死亡率のうち肺癌は男性で第一位，女性では胃癌についで第二位を占め，2001年には約55,000人が肺癌で死亡している[1]．Ⅰ～Ⅱ期非小細胞肺癌に対しては手術が標準治療であるが，2004年春には先端的放射線治療の一つである体幹部定位放射線治療が保険適応となり，手術不能な患者では従来の放射線治療を上回る治療成績が，また一部の手術拒否の患者では手術に匹敵し得る治療成績が期待されている．

Ⅲ期非小細胞肺癌に対しては化学療法と放射線治療の併用，あるいは臨床試験として化学療法，放射線治療および手術の併用が行われている．シスプラチンを中心とする化学療法と放射線治療の併用は放射線単独治療より良好な生存率を示したことから，1990年代より化学療法と放射線治療の併用が標準治療となっている[2~6]．最近では化学療法と放射線治療の同時併用が逐次併用よりも治療成績が良好であることが示されたが[7,8]，同時併用において新規抗癌剤を含む化学療法を用いる場合には通常用量を投与することが困難なことも判明し，至適併用方法は確立されていない．最近では分子標的薬剤の登場に伴いさらなる治療成績の向上が期待される一方で，放射線治療，化学療法との至適併用方法については模索が始まったばかりである．また，急速な社会の高齢化に伴い，化学療法の適応が困難な高齢者も増加しており，高齢者に対する分子標的薬の導入も期待されている．

限局型小細胞肺癌においては，Ⅰ期の手術適応例を除いて，化学療法と放射線治療の併用が標準治療であり，腫瘍縮小効果が良好な場合には予防的全脳照射注）も行われる．現在は標準治療であるシスプラチン，エトポシドと放射線治療の同時併用に新規抗癌剤を導入する試みがおもに行われている．

本稿では，Ⅰ期およびⅢ期非小細胞肺癌における放射線治療の現状および今後の方向性について述べる．

注）予防的全脳照射：
小細胞肺癌において，初期治療で良好な成績が得られた場合，全脳に放射線を照射することにより，脳転移率を下げるのみならず，生存率も向上させることが報告され，推奨されている．

I期非小細胞肺癌に対する定位放射線治療

I期非小細胞肺癌に対する標準治療は上述のように手術であるが，術後の肺機能が十分でないと予測される場合や，肺線維症やCOPDの肺合併症，あるいは心血管系合併症等の合併基礎疾患のために手術が不能な場合には，従来から放射線治療がなされてきた．従来の放射線治療による5年生存率は6～27%と報告され，手術例に比して不良である．これは主として手術不能例に対する治療成績であり，手術との単純な比較はできないものの，遠隔転移の有無を加味しない局所再発の頻度は36～70%と報告されており，局所再発のみが30%程度である手術と比較して明らかに不良である[9~13]．そのため，局所制御効果の向上を意図した新しい放射線治療技術として，3次元照射計画を用いて病巣へ放射線を集中することが可能な定位放射線治療が期待されている．

定位放射線治療が最初に臨床応用されたのは1960年代，脳腫瘍に対してであったが，患者固定法の改良等により，1990年代後半から体幹部腫瘍，とくに肺癌，肝臓癌に対して精力的に応用されてきた．肺癌に対する体幹部定位放射線治療の前向き研究は限られているが，国内の245例を対象とした調査研究がある[4]．観察期間は短いものの3年生存率は63%(手術不能例：50%，手術可能例：80%)，85%の症例で局所増悪/再発を認めておらず，高い有効性が示唆されている(図1)．

2003年現在，体幹部定位放射線治療を施行された肺癌患者は国内でも300例を超え，増加傾向にある．1999年より高度先進医療として一部施設で実施されてきたが，2004年4月には保険収載され，今後さらに普及することが予想される．しかし，これまでのエビデンスは日常診療の調査研究もしくは単施設の研究によるものに限られているため，日本臨床腫瘍研究グループ(JCOG)の放射線治療グループにおいて前向きの多施設共同研究が計画されている．この臨床試験により体幹部放射線治療の有効性と安全性が確認されると，標準手術不能例に対しては従来の放射線治療よりも優れた治療法が確立されることになり，また標準手術可能例に対しては低侵襲治療として，将来外科的切除にとって替わるかも知れない有望な標準治療の候補となり，その結果が待たれる．

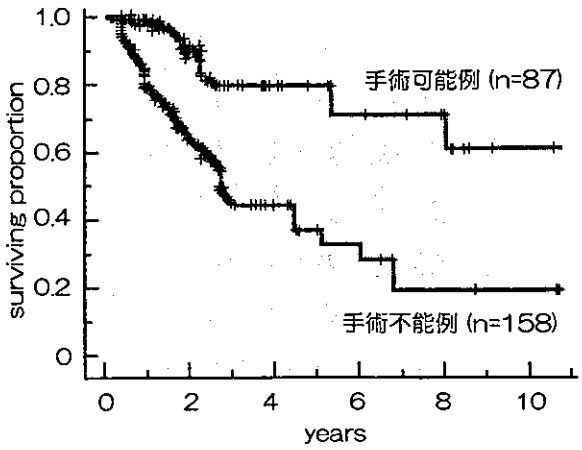

図1. I期非小細胞肺癌に対する定位放射線治療の治療成績

手術不能例と手術可能例の治療成績．従来の放射線治療を上回る治療成績が期待されている．

III期非小細胞肺癌における放射線治療

1970年代の局所進行非小細胞肺癌の治療は放射線単独治療が標準であった．1980年代には，逐次併用化学放射線療法が放射線単独治療よりも治療成績が良いことが明らかとなった．1990年代には，化学放射線療法の至適併用時期および放射線治療の分割法が研究されてきた．西日本肺癌グループでは，シスプラチン，ビンデシン，マイトマイシンと放射線治療56 Gyの逐次併用と同時併用を比較した[7]．米国Radiation Therapy Oncology Group(RTOG)94-10 trialではシスプラチン，ビンブラスチンと放射

線治療の逐次併用群，同時併用群，シスプラチン，エトポシドと同時併用過分割放射線治療群の3者を比較した[8]．この二つの臨床試験の結果は，ともに同時併用化学放射線療法の治療成績が逐次併用よりも良好であった．また先行する第Ⅱ相試験(RTOG 90-15)で有望視された1日2回照射の過分割照射[15]は，1日1回の通常分割照射より治療成績が良好であることが証明されず，現在では通常分割照射を用いた同時併用化学放射線療法が標準治療となっている．また，チェコで行われたシスプラチン，新規抗癌剤の酒石酸ビノレルビンと放射線治療の逐次併用と同時併用のランダム化第Ⅱ相試験では，同時併用の優越性を示唆する結果も示されているが[16]，新規抗癌剤併用においては通常量の投与が困難なため，新規抗癌剤により治療成績が向上するか否かは現在のところ不明である．

通常分割照射を用いた同時併用化学放射線療法以外に期待できる治療法としてContinuous Hyperfractionated Accelerated Radiation Therapy(CHART)やHyperfractionated Accelerated Radiation Therapy(HART)といった加速過分割照射がある[17,18]．これらは4～6時間間隔で1日に3回，2～3週間の総治療期間で治療を行うものである．CHARTは1980年代にイギリスで発案されたもので，治療期間の短縮による治療強度の上昇により，局所非制御の原因とされる腫瘍細胞の加速再増殖の克服を狙うとともに，1回線量を低下させることにより，正常組織に対する毒性の軽減を意図した治療法である．CHARTと通常分割照射を比較したランダム化第Ⅲ相試験の結果，CHARTの優越性が示されたものの[17]，局所制御は十分ではなく，Saundersらは，週末には治療を行わないCHART Week-End Less(CHARTWEL)を用いて放射線治療の線量増加と化学療法の併用を検討した[19,20]．その結果，CHARTWEL単独における線量増加および化学療法の併用によりそれぞれ局所制御が向上することが示された．

Belaniらは，導入化学療法後の通常分割放射線治療とCHART変法であるHARTとを比較したランダム化第Ⅲ相試験(ECOG 2597)の結果を報告した[21]．この試験では患者登録が十分に進まなかったため119例で登録が終了となったものの，HARTの有用性を示唆する結果が得られている．

最近では分子標的薬が最も精力的に研究されており[22～25]，近い将来にはこれらが生存に寄与するか否かが明らかになると思われるが，分子標的薬，新規抗癌剤，放射線治療の分割法などの至適併用方法については依然検討課題として残っている．それぞれの効果を最大限に生かすために，治療強度を高めた放射線治療を組入れた集学的治療の研究は重要であり，治療成績のbreak throughに繋がることを期待したい．

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放射線治療の品質管理・品質保証

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放射線治療において品質管理・品質保証（QC・QA）は欠かせないものである。しかしながらここ数年続けて「過剰照射事故」が報道されているように，医療現場ではQC・QAを行う体制が必ずしも整っていない現状がある。放射線治療の技術進歩はめざましく，三次元放射線治療（3D-CRT），強度変調放射線治療（IMRT），粒子線治療などの先端医療の普及，治療成績の向上のためにも，早急なQC・QA体制の確立が必要である。

Ⅰ．品質管理・品質保証の必要性

身体侵襲が少なく形態・機能温存を図れること，社会の高齢化とquality of lifeの視点などにより放射線治療を受ける患者数は増加の一途を辿っている。日本放射線腫瘍学会が行った構造調査結果によると1990年から1999年の10年間で放射線治療件数は約40%の増加がみられ，特にここ数年間の増加傾向は顕著である。

放射線治療の実施過程は複雑である。治療に先立つ計画の段階においては，放射線を照射する部位（標的体積という），方法，線量の決定およびモニターユニット値という放射線照射量の算出など多くの過程が存在する。また標的体積の決定一つを取ってみても，病巣進展範囲の認識や手術におけるリンパ節隔清に相当する予防照射領域の設定には治療計画者によりばらつきが生じうるところである。そのため放射線治療の実施にあたっては，その一連の過程に対する品質管理（quality control：QC）および品質保証（quality assurance：QA）の概念が必要となる[1]。もちろん誤って使用すれば死亡にもつながる障害を引き起こす可能性があり，放射線の照射装置そのものの精度管理も欠かせないものである。しかしながら，ここ数年たてつづけに「過剰照射事故」が報道されているように，医療現場ではこれらの精度管理を行う体制が整っていない状況が少なからず存在しており，その体制の早急な確立が必要である。

また，一般診療，臨床試験を問わず，異なる施設間での治療内容の差，施設間較差を解消する観点においても品質管理，品質保証活動は重要な役割を担っている。臨床試験における一つの悪い例として米国Southwest Oncology Group（SWOG）で過去に行われたホジキン病に対する臨床試験をあげる。この臨床試験では登録された症例のうち，36%の症例で放射線治療の

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プロトコール規定の逸脱が認められた。その結果プロトコールの規定を遵守していた症例では10%であった再発率が逸脱例では44%にも及んだことが報告がされている[3]。その他にもプロトコール規定の逸脱により治療成績が低下する複数の報告がある[3]。臨床試験が一般診療に適用可能な科学的結果を出すためには，異なる施設間において治療内容を比較することが可能でかつその較差が最小化されている必要があり，放射線治療における技術面を含めた治療の標準化は欠かせないものである。もちろん患者の安全を確保する，すなわち毒性の増強や効果の低減を防止する観点からも必須といえる。

Ⅱ．国外における品質管理・品質保証活動

米国においては放射線治療のQC・QAプログラムが確立されている。歴史的には1969年にNational Cancer Institute (NCI) の補助金を受けRadiological Physics Center (RPC) が活動を始めた[4]。その役割は多施設共同臨床試験に参加している施設の間で技術的に大きな乖離がないこと，適切なQCシステムにより施設間で比較可能な放射線治療が行われていることを第三者的に保証することである。RPCでは主として物理的な精度管理，すなわち施設間の線量のばらつきを解消するため，郵送可能な線量計を用いたoff-site auditによるスクリーニングや施設訪問による線量測定，施設のQC・QAプログラムの確認といったon-site auditを全米に約1,800存在する放射線治療施設のうち，NCIスポンサーの臨床試験に参加する全施設を含め，約1,350の施設を対象に実施している。このような活動は米国に限ったものではなく，International Atomic Energy Agency (IAEA)[5, 6]では主として発展途上国の115カ国，約1,200施設を対象として，European Society for Therapeutic Radiology and Oncology (ESTRO)[7]ではEU諸国の約450施設を対象として同様のQC・QAプログラムを実施している。これらにより全世界の約60%の施設がauditを受けていることになる。これらのプログラムに参加している施設においては，投与される放射線線量の誤差が5%以内であることが保証されている。放射線治療においては各過程にそれぞれ誤差が存在しその積み重ねがあるため，「5%以内の誤差」が精度管理を十分に行っていると判断される基準とされている。米国においてはRPCによるauditを受けていることが臨床試験に参加するための必須条件ともなっている。

物理的QC・QAプログラムとは別に，いわゆる照射野の設定方法など治療内容の臨床的QC・QAプログラムは主として臨床試験を通して実施されてきた。ここで臨床試験における放射線治療のQC・QA活動の草分け的存在であるQuality Assurance Review Center (QARC) による活動の歴史を紹介する[4]。QARCは多施設共同研究グループであるAcute Leukemia Group B (ALGB) の放射線治療委員会により1972年に設立された組織である。当時，臨床試験実施計画における放射線治療の項目は臨床腫瘍医にとって，同時に放射線腫瘍医にとってもいわばブラックボックスであった。臨床試験実施計画書には放射線治療の詳細については記載されておらず，実際に患者がどのような放射線治療を受けたかについてほとんど知られることはなかった。また実際に行われた治療内容を評価しようにも利用できる放射線治療の情報は20%にも至らなかった。そのため，ALGBの放射線治療委員会は，放射線治療の研究プログラムの策定のみならず，臨床試験に参加しているすべての施設研究者が確立されたガイドラインに従って均一な放射線治療が行えるように放射線治療手順を明確に規定することから着手した。同時に治療の適切さを評価するため，放射線治療に関わる資料を系統的かつ適切な時期に収集するシステムを確立した。これにより評価できる放射線治療の情報は2年間で30%未満から70%以上に上昇し5年間では90%以上となったが，これらの情報が集積されることにより多施設共同研究においては治療の均一性が達成されていないことも同時に明らかとなった。この結果を受けて放射線治療委員会では「プロトコール実施における問題点と落とし穴」と題した教育プログラムを定期的に実施し，それによりその後のプロトコール規定の遵守率は3年間で40%から70%へと改善，その後も堅調に上昇が認められた。

このような放射線治療の質の改善がきっかけとなり他の多施設共同研究グループにおいても同様のQC・

QAプログラムが実施されるようになり，同様の改善が示された[9,10]。その一方で，それぞれの多施設共同研究グループから，QC・QAプログラムを標準化し，同一の組織，均一な手順で実施する要求が高まり，1980年にQARCが正式に設立された。またその活動内容からQARCは多施設研究グループと独立してNCIから資金援助を受けている。欧州においてもEuropean Organisation for Research and Treatment of Cancer (EORTC)[11]で同様のプログラムが実施されており，放射線治療のQC・QAを行うことはglobal standardとして認識されている。2002年には米国内に5つあった放射線治療のQA組織：Image-Guided Therapy Center (ITC), Resource Center for Emerging Technology (RCET), RPC, Radiation Therapy Oncology Group (RTOG), QARCを統括する組織としてAdvanced Technology Consortium (ATC)が設立され，QC・QA手順の標準化，効率化がはかられている[12~15]。また同時に米国内のみならずNational Cancer Institute Canada (NCIC), EORTC, 日本臨床腫瘍研究グループ(Japan Clinical Oncology Group；JCOG)との間でも標準化のための共同プロジェクトが開始されている。

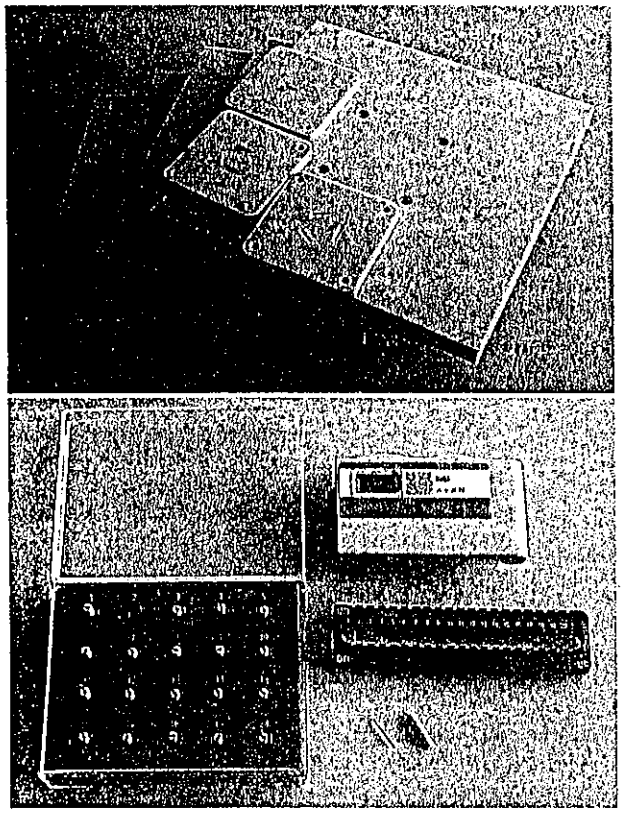

図1　ガラス線量計を用いた郵送調査
郵送調査で使用している固体ファントム（上段）とガラス線量計セット（下段）。
下段右上は大きさを比較するためにおかれたフィルムバッジケース（7×4 cm）。

Ⅲ．国内の状況

わが国においては，「線量計の校正」活動により各施設の線量計の精度は管理されてきたが，実際の治療装置等の線量管理を行なう物理的QC・QAおよび臨床的な照射野の設定等に関する臨床的QC・QAは，最近まで全国規模で体系的なQC・QA活動のシステム構築はなされてこなかった。日本放射線腫瘍学会(JASTRO)からQC・QAに関するガイドラインが出されてはいるものの，実際に各施設でどのようなQC・QA活動がなされているかの実態は明らかとはいえない。そのためわが国の放射線治療の質あるいは臨床試験の質は未だにブラックボックスで国際的に信頼性を得ることが出来ていないとともに，前述のようにここ数年間連続して過剰照射事故が判明するといった深刻な状況にある。「最近事故が増えた」のではなく，今まで知られていなかった事故の存在が「最近明らかになった」のであり，報告されていない事故も少なからず存在すると考えられる。これらの事故を防止することにもつながる物理的QC・QAについては厚生労働科学研究費補助金による研究班が米国RPCで実施されている手法に準じ，ガラス素子線量計の郵送によるoff-site audit（図1）および施設訪問によるon-site auditを2002年より開始した。研究班を基盤とした活動であり，自ずとマンパワーに限りがあり対象施設数は限られたが，その中でも各施設間で放射線照射線量のばらつきが許容範囲を超えて存在することが判明している。これには放射線治療を行なう上で物理的QC・QAに責任をもつ物理士の不足，急速な技術発展に伴い，すでに体制の充実した欧米とは対照的に，日本ではマンパワーおよび施設的条件が十分に整っていない中で技術導入が進められていることが背景にある。この研究班におけるaudit活動により照射線量の