

Design, development of water tank-type lung phantom and dosimetric verification in institutions participating in a phase I study of stereotactic body radiation therapy in patients with T2N0M0 non-small cell lung cancer: Japan Clinical Oncology Group trial (JCOG0702)

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(Received 3 June 2013; revised 31 August 2013; accepted 24 October 2013)

A domestic multicenter phase I study of stereotactic body radiotherapy (SBRT) for T2N0M0 non-small cell lung cancer in inoperable patients or elderly patients who refused surgery was initiated as the Japan Clinical Oncology Group trial (JCOG0702) in Japan. Prior to the clinical study, the accuracy of dose calculation in radiation treatment-planning systems was surveyed in participating institutions, and differences in the irradiating dose between the institutions were investigated. We developed a water tank-type lung phantom appropriate for verification of the exposure dose in lung SBRT. Using this water tank-type lung phantom, the dose calculated in the radiation treatment-planning system and the measured dose using a free air ionization chamber and dosimetric film were compared in a visiting survey of the seven institutions participating in the clinical study. In all participating institutions, differences between the calculated and the measured dose in the irradiation plan were as follows: the accuracy of the absolute dose in the center of the simulated tumor measured using a free air ionization chamber was within 2%, the mean gamma value was ≤ 0.47 on gamma analysis following the local dose criteria, and the pass rate was $>87\%$ for 3%/3 mm from measurement of dose distribution with dosimetric film. These findings confirmed the accuracy of delivery doses in the institutions participating in the clinical study, so that a study with integration of the institutions could be initiated.

Keywords: visiting dose verification; water tank-type lung phantom; lung SBRT clinical trial; JCOG0702

INTRODUCTION

The progression of techniques for accurately identifying tumor locations and reliably irradiating tumors in the 1990s culminated in stereotactic body radiotherapy for the lung (lung SBRT) [1, 2]. In lung SBRT, high-dose irradiation is delivered in 4–10 fractions at 5–12 Gy per day for a 2-week or shorter period, and tumors are irradiated with a biological equivalent dose (BED) of 80 Gy ($\alpha/\beta = 10$) or higher. Lung SBRT is performed employing multiport irradiation or arc irradiation using a multileaf collimator (MLC). Studies on lung SBRT are actively performed in Japan and other countries, and markedly favorable clinical outcomes have been achieved [3–11]. This therapy has been supported by National Health Insurance since 2004 in Japan, and the numbers of institutions performing this (and the numbers of treated patients) have been rapidly increasing [12].

In 2003, we initiated a multicenter phase II trial of SBRT for T1N0M0 non-small cell lung cancer (JCOG0403) as a study conducted by the Japan Clinical Oncology Group trial (JCOG) [13–17]. Prior to the clinical trial, we verified the accuracy of the calculated dose by the radiation treatment-planning system (RTPS) in the participating institutions. For the verification of the dose, a visiting survey of 16 institutions was performed using a solid lung phantom. After computed tomography (CT) imaging of the solid lung phantom, treatment planning and dose calculation were undertaken, and the difference between the calculated dose and measured dose at the center of a simulated tumor were evaluated using dosimetric EDR2 film (Kodak Inc., NY, America) in each institution. Based on the findings obtained during the visiting survey, the absolute dose at the center of the tumors investigated in the participating institutions had high-level consistency with only a 2% difference from the result obtained by using the non-model-based dose calculation algorithm with heterogeneity correction in the RTPS [18]. Based on the results of the visiting survey of institutions participating in JCOG0403 and retrospective analysis of the dose distributions determined by dose calculation algorithms using clinical CT images [16], the multicenter phase I trial of SBRT for T2N0M0 non-small cell lung cancer in inoperable patients and elderly patients who refused surgery (JCOG0702) was initiated in 2008, adopting the D95 prescribed dose and the model-based dose calculation algorithm with heterogeneity correction in the RTPS.

In this study, the method used for the previous institution-visiting survey using a solid lung phantom and dosimetric EDR2 film was reviewed, a survey method appropriate for the JCOG0702 multicenter trial was developed, and this method was used to verify the consistency of the dose between the institutions participating in JCOG0702.

MATERIALS AND METHODS

Water tank-type lung phantom designed for dosimetric verification of lung SBRT

In the visiting survey of institutions participating in the JCOG0403 multicenter clinical trial, the accuracy of dose calculation was verified using a simulated solid lung phantom and dosimetric EDR2 film. However, no simple phantom that was easy to handle was available for accurate and comprehensive measurement of the point dose and dose distribution in many planes in the simulated tumor and lung field.

Thus, we developed a water tank-type heterogeneous lung phantom (Taisei Medical Inc., Osaka/Keen Medical Physics Co. Ltd, Tokyo, Japan). This phantom is comprised of a water tank made of a thin polymethyl methacrylate (PMMA) plate and a lung field made of cork, and a 3 cm φ spherical simulated tumor for T2 lung tumor size < 4 cm was buried in the lung field. It is possible to locate the simulated tumor at a specific position in the lung field. Mediastinum insertion is also possible.

Figure 1 shows pictures of the prepared water tank-type lung phantom. The phantom simulated the unilateral lung. It measured 23 \times 20 cm in the axial plane, and a rounding processing was applied to the corners to form 6 and 3 cm radii on the lateral and medial sides of the phantom, respectively. The length of the phantom in the longitudinal direction is 25 cm, and it was designed so that non-coplanar irradiation is applicable. The thickness of the PMMA-made region, through which beams pass, was 3 mm. The simulated tumor had a 3 cm φ spherical shape and was made of Tough Water material (Kyoto Kagaku Co. Ltd, Kyoto, Japan). The absolute dose can be measured by placing a 3D PinPoint free-air ionization chamber (PTW GmbH, Freiburg, Germany) in the center of the simulated tumor. The simulated lung field has a volume of 10 \times 15 (axial plane) \times 25 (longitudinal direction) cm³, and it is comprised of 2 cm thick cork plates with



Fig. 1. Pictures of the water tank-type lung phantom (left: arrangement for the right lung, right: arrangement for the left lung including the simulated mediastinum).

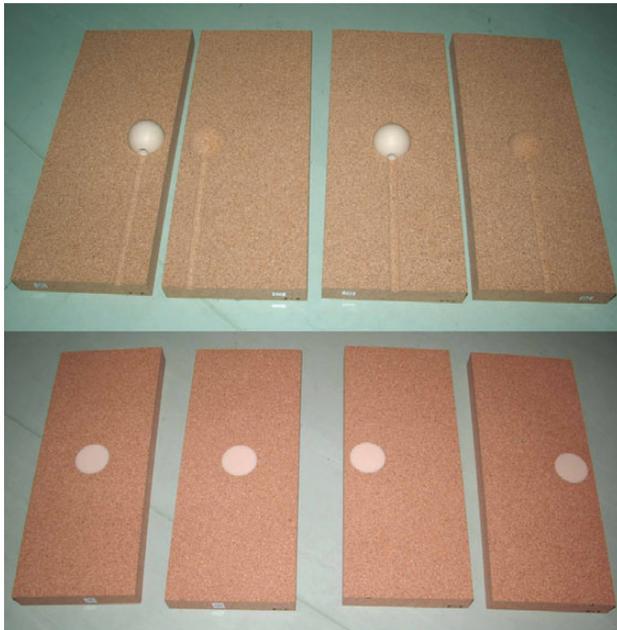


Fig. 2. 3 cm ϕ spherical simulated tumors buried in cork plates (upper row: simulated tumors for free-air ionization chamber, lower row: those for dosimetric film).

various rectangular shapes. Dose distribution measurement using dosimetric measurement film is possible in any plane, including that containing the center of the simulated tumor, using a combination of the cork plates. The simulated mediastinum is a Tough Water material, 25 cm high column with a 4 cm radius and 90 degree fan-shaped bottom. Figure 2 shows pictures of simulated tumors buried in simulated lung fields for dose measurement using a free-air ionization chamber in which film for dose distribution measurement can be placed in the central plane of the simulated tumor. This phantom is suitable for surveys of visiting institutions using the postal service because it is very light after draining out the water.

Verification of absolute dose and dose distribution calculated using the RTPS

The visiting survey of the seven institutions participating in the domestic clinical trial was performed, in which the absolute dose and dose distribution calculated in the RTPS and the measured values were verified and compared. Two sets of the water tank-type lung phantom, dosimetric measurement film: gafchromic EBT film (ISP Inc., NJ, USA), 3D PinPoint free-air ionization chamber, and electrometer: UNIDOS (PTW GmbH, Freiburg, Germany) were sent using the postal service to the institution to be investigated prior to the visit (Fig. 3). Since three of the seven institutions were also surveyed for the renewal or addition of a linear accelerator to be used in the clinical trial, dosimetric verification of 10 radiotherapy systems were performed. Six types of linear accelerator were

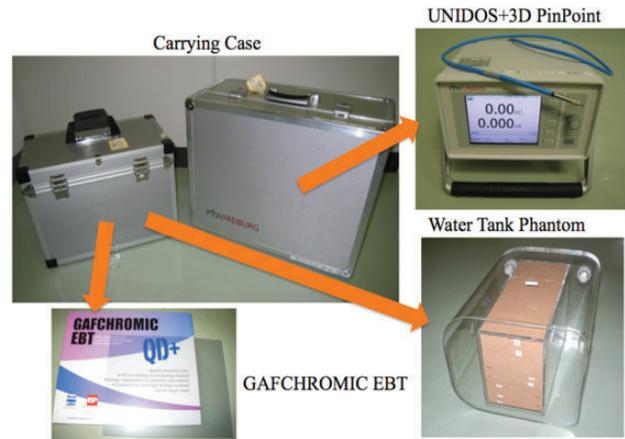


Fig. 3. Pictures of the device set for visiting survey.

surveyed: CLINAC iX and CLINAC 21EX of Varian, Novaris of BrainLab, ONCOR of Siemens, LINAC of Mitsubishi Electric, and Vero of Mitsubishi Heavy Industries. Three types of RTPSs were used: XiO of Elekta, Eclips of Varian, and iPlan of BrainLab. The X-ray energy was 4 MV in one institution and 6 MV in the others. This is summarized in Table 1.

Figure 4 shows CT operation of the water tank-type lung phantom using a CT device possessed by the institution (left). The location of the simulated tumor was changed (three sites), and three sets of CT images were acquired with 2- or 3-mm thickness slices in the area around the tumor and non-helical or helical scan. In each of the three sets of CT images, treatment planning and dose calculation were performed using RTPSs possessed by the institution (center of the lung field: Plan 1, vicinity of the chest wall: Plan 2, and vicinity of the mediastinum: Plan 3). The volume of the simulated tumor with a 3D auto 5-mm margin was regarded as the planning target volume (PTV). Regarding the MLC margin, the center of the leaf width was set at 5 mm from the circumscribed PTV. Plans 1 and 2 were designed so that the center of the simulated tumor was irradiated from three ports (20° , 260° and 315°) at 2 Gy per angle, with a total of 6 Gy. In Plan 3, the number and angle of irradiation ports were set following the lung SBRT procedure at each institution, setting the dose at the simulated tumor center at 12 Gy. In Plan 3, a treatment plan of five arc irradiations (4 non-coplanar and one coplanar irradiation) was performed in one institution. Fixed six or eight multi-port irradiations including non-coplanar irradiations were employed in the other institutions. Absolute dose and dose distribution were calculated using dose calculation algorithms with heterogeneity correction and a grid size of 2–3 mm by the superposition/convolution, AAA, and Monte Carlo (MC) methods in XiO, Eclips and iPlan, respectively.

Beams defined in the three plans were irradiated to the water tank-type lung phantom. The absolute dose at the simulated tumor center was measured using a 3D PinPoint

free-air ionization chamber (Fig. 4, right). In addition, the MU values calculated in the three plans were converted to adjust to 2 Gy for film dosimetry. Gafchromic EBT film was set in the cross section containing the center of the simulated tumor, and the dose distribution in the coronal plane was measured in each plan. Dose distribution measurement in the axial plane was only performed in Plan 3. To prepare a characteristic curve of the density of gafchromic EBT film against the exposure dose, gafchromic EBT film was irradiated with 4- or 6-MV X-rays of every 25-MU step from 0–350 MU in an irradiated condition of 10-cm field size and 10-cm depth in water equivalent. Irradiated film data were imported using a transmission scanner ES-1000G (Epson Co. Ltd, Nagano, Japan), and dose distribution analysis was performed using the film dosimetry analysis software DD system (R-TEC Inc., Tokyo, Japan) at the National Cancer Center.

RESULTS

Evaluation of absolute dose at center position of simulated tumor in lung phantom

Figure 5 shows the differences between the measured and calculated doses at the center of the simulated tumor in the water tank-type lung phantom. The differences by irradiation plan (upper graph) and port (lower graph) are shown. The differences between the measured and calculated doses in the 30 irradiation plans (three plans for 10 radiotherapy systems) in the clinical trial-participating institutions were within 2%, and those of 131 ports in all plans were within 4%. The mean differences by irradiation plan and port in the clinical trial-participating institutions were $-1 (\pm 1)\%$, respectively. The differences in the absolute dose for each linear accelerator to be used in the clinical trial in the institutions are summarized in Table 1. Figure 6 shows the water-equivalent path lengths of the physical lengths between the lung phantom surface and center of the tumor at each irradiation angle in Plans 1 and 2 calculated by the RTPS and those calculated from the phantom shape and materials. The differences between the two calculated water-equivalent path lengths were <2 mm.

Evaluation of dose distribution on coronal and axial planes crossing at the center of simulated tumor in lung phantom

Figure 7 shows the exposure dose of X-ray irradiation and density of the gafchromic EBT film in each institution. The film density of 4-MV X-rays relative to the exposure dose was slightly higher than that of 6-MV X-rays, showing dependency on X-ray energy. Figure 8 shows an example of the dose distribution measured using gafchromic EBT film and calculated in RTPS. Gafchromic EBT film for dose distribution measurement can only be set in the lung field in the

Table 1. Differences in the absolute dose by linear accelerator and RTPS for the clinical trial at each institution and summary of gamma analysis results

Institutions	Linear Accelerator (LINAC)			RTP system			Difference of absolute dose ((RTP dose) – (Chamber dose)) / (Chamber dose) [%]			Gamma Index (3 mm/3%, dose > 20%) Gamma value Pass rate [%]	
	company	type	energy [MV]	company	type	calculation algorithm	Plan 1	Plan 2	Plan 3	mean (SD)	mean (SD)
A	Mitsubishi Electric Siemens	LINAC ONCOR	6 6	Elekta	XiO	Superposition	-1 0	-2 -1	-1 1	0.47 (0.07) 0.41 (0.02)	87 (7) 94 (3)
B	Mitsubishi Electric	LINAC	6	Elekta	XiO	Superposition	-1	-1	1	0.37 (0.07)	96 (2)
C	Mitsubishi Electric Varian	LINAC CLINAC iX	4 4	Elekta	XiO	Superposition	1 2	0 1	0 1	0.43 (0.01) 0.44 (0.04)	90 (2) 92 (5)
D	Varian	CLINAC iX	6	Varian	Eclips	AAA	1	1	1	0.31 (0.04)	99 (1)
E	Varian	CLINAC 21EX	6	Varian	Eclips	AAA	1	0	1	0.41 (0.04)	97 (1)
F	BrainLab Mitsubishi Heavy Industries	Novaris Vero	6 6	BrainLab	iPlan	MC	2	0	2	0.39 (0.04)	95 (4)
G	Mitsubishi Electric	LINAC	6	Elekta	XiO	Superposition	-1	-1	-1	0.31 (0.04)	99 (1)
							-1	-1	-1	0.46 (0.02)	89 (3)



Fig. 4. CT operation of the water tank-type lung phantom (left) and dosimetry (right).

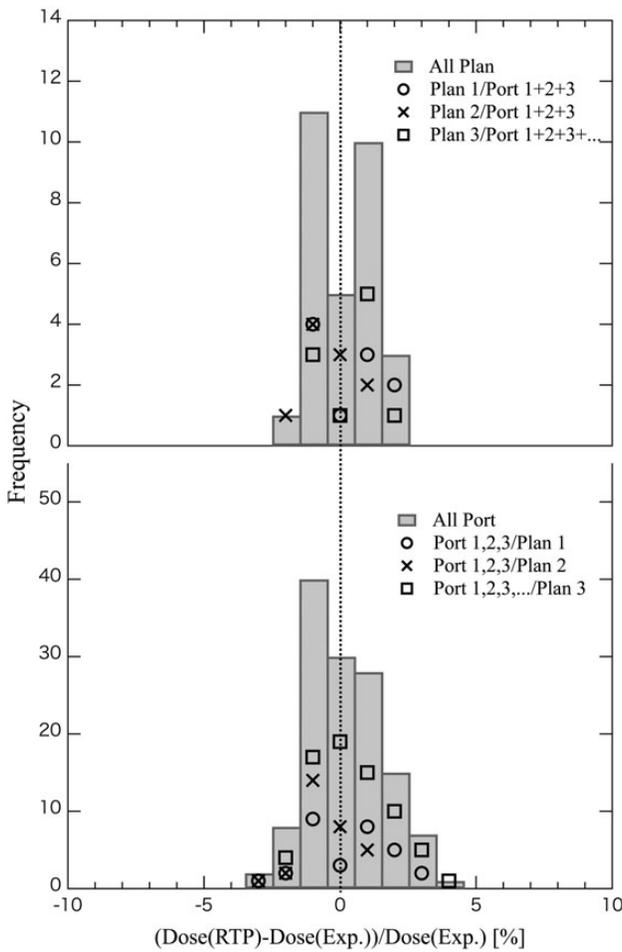


Fig. 5. Differences between the measured and planned doses at the center of the simulated tumor in the water tank-type lung phantom. Differences in the dose by irradiation plan (upper graph) and by irradiation port (lower graph) are shown.

water tank-type lung phantom, and this condition should be considered in setting the dose range for evaluation of the dose distribution measurement. We compared the calculated dose distribution with that measured using gafchromic EBT

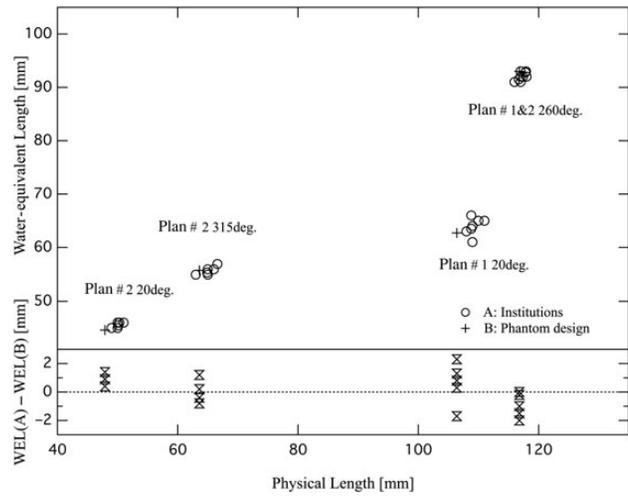


Fig. 6. Water-equivalent path lengths of physical lengths from the lung phantom surface to the center of the tumor at each irradiation angle in Irradiation Plans 1 and 2. The lengths calculated by the RTPS and those calculated from the materials of the phantom are shown in the upper region, and differences between the calculated lengths are shown in the lower region.

film, and performed gamma analysis in a dose range >20%. The dose distribution was normalized at the center of the simulated tumor consistent with the isocenter. Figure 9 shows the gamma analysis results comparing the local dose criteria of the dose distribution calculated using the RTPS in each plan with that measured in gafchromic EBT film at each institution. The mean gamma value was <0.47, and the pass rate was >87% for 3%/3 mm. Table 1 summarizes the results of gamma analysis by the linear accelerator for the clinical trial at the institutions.

DISCUSSION

A water tank-type lung phantom was developed for use in a visiting survey to determine uniformity of dosimetry of the treatment plans between the participating institutions prior to

the JCOG0702 phase I study. JCOG0702 is an investigation into the use of SBRT for T2N0M0 non-small cell lung cancer in inoperable patients and elderly patients who refuse surgery. There have been several reports of development of a solid phantom and a water tank-type phantom for dose verification using a thermoluminescent dosimeter (TLD) and dosimetric film [19–21]. The main unit of these phantoms was large, the interior was not transparent because of being made

of gray polyvinyl chloride, dose distribution measurement using dosimetric film in a specific plane in the lung field was difficult, and absolute dose measurement using an air chamber was not applicable. Moreover, the system was not prepared to measure the absolute dose on the plane of dose distribution measurement. In contrast, in the water tank-type lung phantom developed by us, it is possible to measure the absolute dose and dose distribution using a free-air ionization chamber set in the center of the simulated tumor, and dosimetric film set in the tumor-containing lung field on the coronal and axial planes at a site corresponding to a specific location in the simulated tumor. Measurement of the absolute dose on the plane of measured dose distribution is possible. Since the main body of this phantom is light, it is suitable for visiting surveys of dose verification at multiple institutions, sending it by the postal service. The PMMA-made main body of the phantom is colorless and transparent, and it is easy to confirm whether the free-air ionization chamber or dosimetric film has been placed at the correct position. The relative electron density of the PMMA material calculated from the CT value of kV X-ray energy was about 5% lower than that of water, but a water-equivalent path of therapeutic MV X-ray energy shows slightly higher relative electron density than that of water. In dose calculation in the RTPS, therapeutic X-rays pass the 3 mm thick PMMA-made region of the main body of the phantom, but their influence on reducing the accuracy of dose calculation will be negligible. Since the phantom body is made of thin PMMA, the phantom shape may be slightly altered according to the weight and temperature of water added, and this effect may have been observed in the result for the 20° irradiation angle shown in

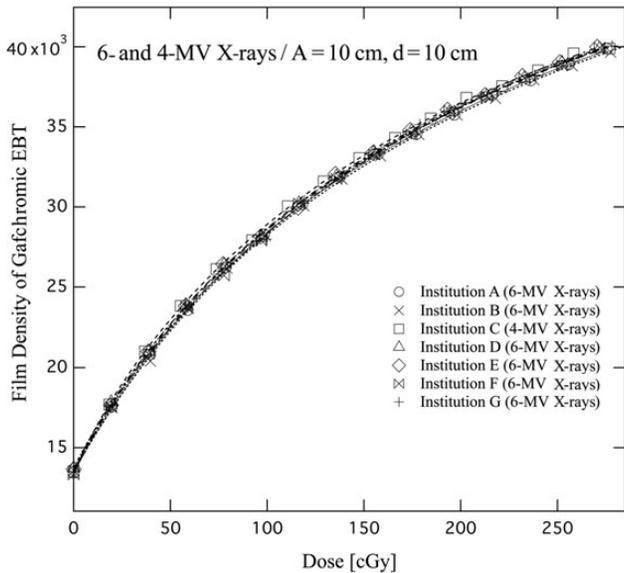


Fig. 7. Exposure dose of therapeutic X-ray irradiation and density of gafchromic EBT film at each institution.

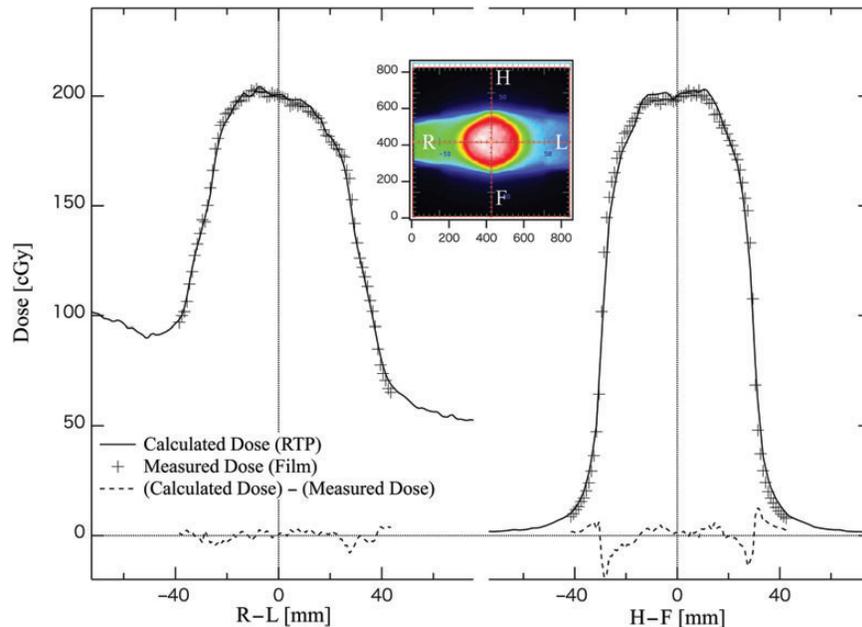


Fig. 8. Example of the dose distribution measured using gafchromic EBT film and calculated in RTPS.

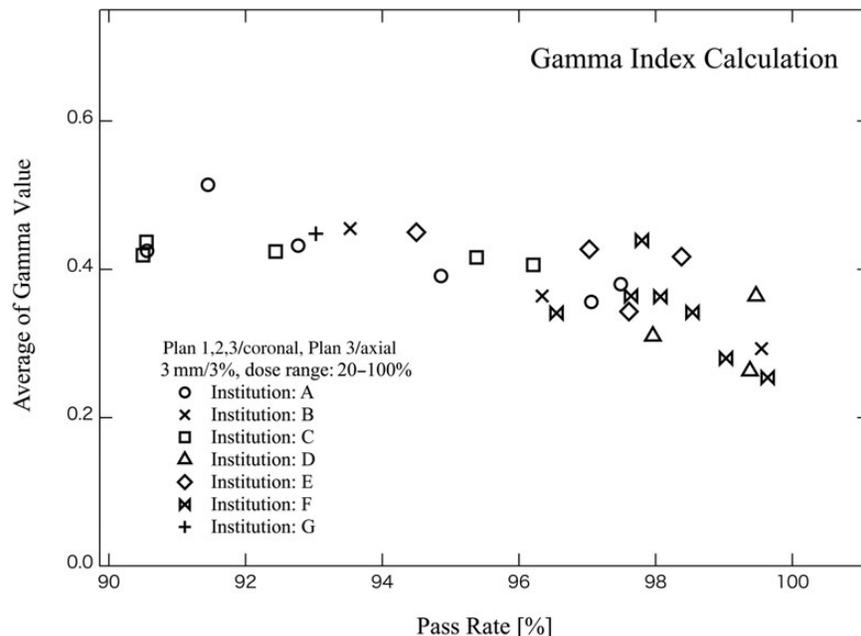


Fig. 9. Results of gamma analyses of dose distribution calculated by the RTPS and that measured using EBT film in each plan at each institution.

Fig. 6: the physical length from the phantom surface to the center of the simulated tumor and water-equivalent path length were slightly longer than the design value of the phantom at all institutions. This difference in the length was <2 mm. For example, considering the percentage depth dose shape for 6-MV X-rays, the 2-mm difference in a deep region corresponds to a difference of $<1\%$ of the dose. Since the thin PMMA-made phantom is easily broken, caution is necessary for handling it after the addition of water.

A visiting survey of the seven institutions participating in the JCOG0702 multicenter clinical trial was performed for dosimetric verification of 10 linear accelerators and seven RTPSs using the developed water tank-type lung phantom. Since the diameter of the simulated tumor was small (3 cm), the dose distribution near the center of the simulated tumor tended to show a convex pattern, generating an $\sim 1\%/1$ mm dose error in the accuracy of tumor location. In this dosimetric verification, the accuracy of tumor location based on laser in the treatment room may have been <1 mm. In a total of 30 irradiation treatment plans at seven institutions, the differences between the calculated dose at the center of the simulated tumor and the measured dose using a free-air ionization chamber were $<2\%$, indicating a high level of consistency. On evaluation of the dose distribution, the pass rate was $>87\%$ for 3%/3 mm on gamma analysis of the dose distribution calculated by the RTPS with respect to that measured using dosimetric film. An inconsistent dose distribution was observed near the surface of the PTV, which was located in the lung field near the tumor (Fig. 8). The calculation

accuracy will tend to decrease in the boundary region between low- and high-density substances using any dose calculation algorithm. Based on the results of verification of the absolute dose and the dose distribution in the simulated tumor, the dose given by the model-based dose calculation algorithm with heterogeneity correction carried out in the RTPS of the institutions was remarkably consistent between the institutions. Therefore, it was concluded that the multicenter phase I trial of the use of SBRT for T2N0M0 non-small cell lung cancer in inoperable patients and elderly patients who refuse surgery (JCOG0702) could be performed with accurate delivery doses.

In lung SBRT, therapeutic X-rays are used for irradiation under respiratory control or with gating for moving of the tumor with breathing, and the irradiation margin is set according to the accuracy of the irradiation method. Respiratory tumor motion was not considered in this dose verification. To increase the accuracy of dose verification using this light water tank-type lung phantom, it will be necessary to verify the dose effect of movement by placing the phantom on a stage moving with respiration.

ACKNOWLEDGEMENTS

We would like to thank the medical physicists and the staff of the institutions who helped us during the visiting survey. We would also like to thank the members of the JCOG Radiation Therapy Study Group for suggestions.

FUNDING

This study was supported by Grants-in-Aid No. H20-020 of Health and Labor Sciences Research Grants, and by Grants-in-Aid No. 23-A-21, 25-B-4 of the National Cancer Center Research and Development Fund in Japan.

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