principal investigator (S.I.), and also by an independent radiation oncologist (N.S.) after patient accrual. RT QA for prophylactic cranial irradiation was not performed. After the review of the initial RT plan, the RT principal investigator sent each institution a letter reporting whether they had complied with the treatment protocol as well as an inquiry about QA documentation when necessary (Figure 2). Progress remarks and problems were reported at periodical meetings for investigators.

To assess protocol compliance for RT, the following parameters were reviewed: the dose and field border placement for PTV (adequacy of margins for GTV and ENI), doses to organs at risk, such as the spinal cord and the normal lung, overall treatment time, interfraction interval, and dose calculation without heterogeneity correction. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable (I/NE). The criteria were set for each parameter as follows. For the dose and field coverage of GTV, VU was defined as a dose less than 40.5 Gy, more than 49.5 Gy, or the distance between the field edge of the blocks or multileaf collimators and the rim of GTV less than 1 cm or more than 3.5 cm. For the dose and field coverage of ENI, a dose less than 27 Gy, more than 36 Gy or inclusion of the contralateral hilum was judged as VU. If hererogeneity correction was used for dose calculation and the recalculated uncorrected dose deviated more than 10%, it was judged as VU. Other criteria for the QA assessment are listed in Table 1. These criteria were arbitrary rather than based on the literature. We set these criteria based on the patterns of practice in Japan at the start of this trial. After parameter compliance was assessed, overall RT compliance was determined as PPoverall, no DA or VU in any parameter; VUoverall, at least one VU in any parameter; or DAoverall, neither PP nor VU. The proportion of 2-D X-ray simulation vs. 3-D CT simulation was analyzed, and a comparison was also made between compliance in the first half vs. the second.

Results

From September 2002 to September 2006, 283 cases were accrued. Of these, 204 (72%) were fully evaluable, excluding 79 cases (Table 2). Partially evaluable cases were included to evaluate each item.

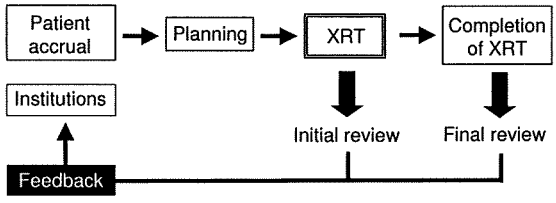

Figure 2
Flow of QA review. After the QA review, feedback was given to the institutions. Treatment planning was modified when possible.

Among 258 patients evaluable for the treatment planning method, conventional 2-D X-ray simulation was performed in 62 (24%) patients, while 196 (76%) had 3-D CT simulation. Of 35 participating institutions, 24 institutions had introduced 3-D CT simulation, 6 used only 2-D X-ray simulation, and 5 used both.

RT compliance for each parameter is listed in Table 3. There were 18 VU in GTV (8% of 238 evaluated), of which, 14 (78%) had insufficient lateral margins, while 3 (17%) and 2 (11%) had insufficient caudal and cranial margins, respectively (one case, both lateral and caudal margins). There was no VU in the GTV dose. With regard to ENI, 4 VU and 23 DA (2% and 9% of 243 evaluated, respectively) were observed. Of these 4 VU, a total dose of 45 Gy instead of 30 Gy was given in 3, and the contralateral hilum was irradiated in one case. Of these 23 DA, 17 had larger field placement than required in the protocol, such as the inclusion of uninvolved supraclavicular fossa, upper mediastinum, or subaortic/paraaortic lymph node area, etc, whereas 3 had insufficient margins. Three had both larger field placement and insufficient margins. No VU was found in overall treatment time, interfraction interval and dose calculation, while some VU were observed in organs at risk (1 VU in the lung and 5 VU in the spinal cord). Overall RT compliance (PP + DA) was 92% (187 of 204 fully evaluable).

In regard to the 35 participating institutions, 17 (49%) had no VU. In 18 institutions with VU, 15 (83%) had only one VU and 3 (17%) had 2 or more VU. Sixteen institutions (89%) had VU in their first 3 cases.

Comparison between the former and latter halves of the accrued cases (141 and 142 cases, respectively) revealed that the number of VU and DA had decreased: for GTV, the number of VU was 13 in the early period (9%; 95% CI, 5%–15%), while 5 in the late period (4%; 95% CI, 1%–8%). In regard to ENI, DA decreased from 20 (14%; 95% CI, 9%–21%) to 3 (2%; 95% CI, 0.4%–6%), respectively.

Discussion

In clinical trials, patients must receive optimal treatment. Since the 1980s, a number of reports have focused on the relationship between RT compliance and treatment outcomes in various types of malignancy [1-5]. These results suggested that failure to adhere to RT protocol guidelines compromises survival. Overall compliance of 92% in the current trial seemed acceptable to provide reliable results. More than half of the participating institutions did not have VU, and even with VU, the majority had only one VU; however, there is room for improving compliance in

Table 1: Criteria for QA scores

	PP	DA	VU
GTV			
distance to field borders	1 – 3.5 cm	NA	< 1 cm or > 3.5 cm
prescribed dose	45 Gy	Neither PP nor VU	< 40.5 Gy or > 49.5 Gy
ENI			
distance to field borders	1 – 3.5 cm	Neither PP nor VU	contralateral hilum included
prescribed dose	27 – 36 Gy	NA	< 27 Gy or > 36 Gy
Overall treatment time	21 – 42 days	NA	> 42 days
Interfraction interval	≥ 5.5 hrs	4 – 5.5 hrs or <4 hrs (once)	< 4 hrs more than once
Organs at risk			
Spinal cord	≤ 36 Gy	Neither PP nor VU	> 39 Gy
Lung	≤ 1/2 ipsilateral hemithorax (≤ 2/3, upper lobe tumor) or V_{20} ≤ 35%	Neither PP nor VU	> 1/2 ipsilateral hemithorax (> 2/3, upper lobe tumor) or V_{20} > 40%
Heterogeneity correction	No	Yes (≤ 10% total dose difference)	Yes (> 10% total dose difference)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable; GTV, gross tumor volume; ENI, elective nodal irradiaton; NA, not applicable; hrs, hours; V_{20}, percentage of the total lung minus PTV receiving ≥ 20 Gy.

future trials incorporating RT. GTV and ENI violations and/or deviations were more frequent in the early period. In addition, among institutions with VU, the majority had VU in the first 3 cases. This may be because the institutions received feedback on how to better comply with the treatment protocol by the RT principal investigator, which enabled participants to follow the protocol guidelines in their later cases.

In the current study, more suboptimal treatments were observed in field placement than in the dose for tumors or risk organs. A similar trend was reported in other studies [7,8]. The majority of VU consisted of smaller lateral margins. The reason may have been a discrepancy between the protocol guidelines and their daily practices. The physicians tended to reduce lateral margins rather than craniospinal margins for fear of radiation pneumonitis. The varied ENI coverage also suggested a discrepancy. In this trial, a dry-run procedure was not attempted and therefore the radiation oncologists in each institution might not have been familiar with the protocol guidelines in the initial period of this trial. Wallner et al. [4] speculated the influence of clinical trial experience by reviewing a large number of cases in RTOG studies for lung and head and neck cancer. They reported that adequate primary and lymph node margins and dose prescriptions had progressively improved over the years, suggesting long-lasting learning experiences in clinical trials. As the need for immediate monitoring was described by Schaake-Koning et al. [9] from a quality control study in the EORTC lung cancer trial, some early interventions, such as a dry-run and immediate feedback before the start of treatment, will be more effective to improve compliance in clinical trials involving RT.

Table 2: Number of evaluable cases and overall RT compliance

	number	(%)
Total	283	
Data insufficient/partially evaluable	62	
Off-protocol	12	
Ineligible	5	
Fully evaluable	204	(100)
PPoverall	158	(77)
DAoverall	29	(14)
VUoverall	17	(8)
Compliance (PPoverall+DAoverall)	187	(92)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable

There were several limitations of our study. We did not perform 3-D volumetric data analyses due to technical limitations. Other factors, such as inter-observer contouring variations, 2-D vs. 3-D planning, may have had a much greater impact on the outcome of this trial than protocol compliance. The transition from 2-D to 3-D treatment planning is now almost complete in Japan, and more precise QA analyses using digital data, exported from treatment planning systems with the DICOM-RT format, have been introduced in recent JCOG 3-D RT trials.

In addition, all described QA activities focused on the medical aspects and treatment planning. Another important aspect is dosimetric QA. It is well known from the reports and scientific publications of the WHO/IAEA network [10], the ESTRO-EQUAL network in Europe [11] and the NCI network in the US [12] that external dosimetric audits are a powerful tool to avoid systematic errors. Dosimetric audits are generally recommended as integral parts of QA activities for clinical trials. In Japan, dosimetric audits were introduced in 2003, and were therefore not available at the beginning of this trial, and have been implemented in recent JCOG radiotherapy trials [13]. We

Table 3: RT compliance for each parameter

	Evaluable cases	PP	(%)	DA	(%)	VU	(%)
GTV	**238**	**220**	(92)	**NA**		**18**	(8)
ENI	**243**	**216**	(89)	**23**	(9)	**4**	(2)
Overall treatment time	**227**	**227**	(100)	**NA**		**0**	(0)
Interfraction interval	**205**	**195**	(95)	**10**	(5)	**0**	(0)
Organs at risk							
Spinal cord	**236**	**231**	(98)	**0**	(0)	**5**	(2)
Lung	**246**	**245**	(100)	**0**	(0)	**1**	(0.4)
Heterogeneity correction	**244**	**228**	(93)	**16**	(7)	**0**	(0)

Abbreviations: PP, per protocol; DA, deviation acceptable; VU, violation unacceptable; GTV, gross tumor volume; ENI, elective nodal irradiaton; NA, not applicable.

also believe that these activities will have run-on effects in routine practice and lead to higher quality cancer care.

Conclusion

In conclusion, the results of the RT QA assessment of JCOG 0202 seemed to be acceptable, providing scientifically reliable results. The time trend toward improved compliance in this trial showed the importance of introducing an RT QA program. A dry-run procedure and intensive feedback to participating institutions are being implemented to further improve JCOG trials.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NS performed the QA evaluation. SI was in charge of the QA program and performed the QA evaluation. KH participated in the design of the QA program and helped to draft the manuscript. KK, and YN and TT conceived the study and helped to draft the manuscript.

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CLINICAL INVESTIGATION

VARIATIONS IN TARGET VOLUME DEFINITION FOR POSTOPERATIVE RADIOTHERAPY IN STAGE III NON–SMALL-CELL LUNG CANCER: ANALYSIS OF AN INTERNATIONAL CONTOURING STUDY

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Purpose: Postoperative radiotherapy (PORT) in patients with completely resected non–small-cell lung cancer with mediastinal involvement is controversial because of the failure of earlier trials to demonstrate a survival benefit. Improved techniques may reduce toxicity, but the treatment fields used in routine practice have not been well studied. We studied routine target volumes used by international experts and evaluated the impact of a contouring protocol developed for a new prospective study, the Lung Adjuvant Radiotherapy Trial (Lung ART).

Methods and Materials: Seventeen thoracic radiation oncologists were invited to contour their routine clinical target volumes (CTV) for 2 representative patients using a validated CD-ROM–based contouring program. Subsequently, the Lung ART study protocol was provided, and both cases were contoured again. Variations in target volumes and their dosimetric impact were analyzed.

Results: Routine CTVs were received for each case from 10 clinicians, whereas six provided both routine and protocol CTVs for each case. Routine CTVs varied up to threefold between clinicians, but use of the Lung ART protocol significantly decreased variations. Routine CTVs in a postlobectomy patient resulted in V_{20} values ranging from 12.7% to 54.0%, and Lung ART protocol CTVs resulted in values of 20.6% to 29.2%. Similar results were seen for other toxicity parameters and in the postpneumectomy patient. With the exception of upper paratracheal nodes, protocol contouring improved coverage of the required nodal stations.

Conclusion: Even among experts, significant interclinician variations are observed in PORT fields. Inasmuch as contouring variations can confound the interpretation of PORT results, mandatory quality assurance procedures have been incorporated into the current Lung ART study. © 2009 Elsevier Inc.

Non–small-cell lung cancer, Resection, Postoperative radiotherapy, Target volumes, Interobserver variability.

INTRODUCTION

The role of postoperative radiotherapy (PORT) in patients with completely resected non–small-cell lung cancer is still controversial. Despite increasing local control rates (1–3), a large meta-analysis has shown a detrimental impact of PORT on overall survival, particularly in patients with no mediastinal involvement (4). However, the meta-analysis has been criticized because the studies included may have led to higher morbidity and mortality rates resulting from the use of two-dimensional radiotherapy techniques, high doses and fraction sizes, and large-field radiotherapy that incorporated the entire mediastinum using suboptimal radiotherapy techniques and lacking modern verification procedures or trial quality assurance (QA) (5–7).

Recently, data from the Surveillance, Epidemiology, and End Results (SEER) database and an unplanned subgroup analysis of a Phase III trial suggested that PORT using more recent techniques may improve survival in patients with resected N2 disease (8, 9). This has renewed interest in evaluating PORT in this patient category. A new international Phase

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III trial, the Lung Adjuvant Radiotherapy Trial (Lung ART), has been activated to compare PORT with no PORT in patients with completely resected N2 disease, irrespective of the use of chemotherapy (10). However, the cornerstone of radiotherapy is the use of consistent and reproducible target definitions, and current literature suggested that many groups were using target volumes defined in the era of two-dimensional radiotherapy (7, 11). In addition, large interobserver variations in target volumes have been observed in patients presenting with lung tumors that were visible on CT or positron emission tomography (PET)—CT scans (12–15). It is conceivable that the lack of identifiable tumor after a radical resection may potentially result in even greater variations. In the Lung ART study, the use of conformal radiotherapy is mandatory, and the target volumes are tailored based on both radiologic and surgical findings. As a prelude to Lung ART, the present study was designed to identify potential variations in target definitions in an international setting. In addition, the ability of the Lung ART protocol to reduce the potential variations in defining clinical target volumes (CTVs) was studied.

METHODS AND MATERIALS

Study design

Seventeen radiation oncologists in Europe, Asia, Australasia and North America who were considered to be experts in the treatment of lung cancer were invited to participate in this study. Radiation oncologists who were invited to participate had to be members of the International Association for the Study of Lung Cancer and to be also actively involved in research in radiotherapy for lung cancer. All were attached to academic centers, had experience in treating patients with postoperative radiotherapy, and had access to CT-based treatment planning for this purpose. Each participating expert was asked to contour his/her current routine CTV for 2 patients eligible for PORT. For contouring purposes, a CD-ROM–based validated contouring program was provided (16), which contained complete CT datasets (slice thickness 2.5 mm) of both patients and a tutorial regarding use of the contouring program in PowerPoint format (MS Office). In addition, relevant patient details were provided in the first mailing. The CTVs were contoured using standardized window level settings and saved to the CD-ROM, which was then mailed to the study coordinator. Subsequently, details of the contouring protocol for Lung ART were mailed to experts approximately 2 weeks after response to the initial mailing, to derive a second set of contours (protocol CTV) of the same 2 patients. Contours from each observer were copied (made anonymous) to a template CT dataset of the corresponding patient (Fig. 1).

Patient 1 (post-lobectomy). The first patient had undergone a radical right upper lobectomy with a mediastinal lymph node dissection for a stage $pT_2N_2M_0$ tumor. Histology revealed a 3-cm adenocarcinoma with extension to the visceral pleura. Hilar nodes showed no metastases, but two out of seven explored ipsilateral mediastinal nodes (stations 4 and 7 right) showed tumor deposits (17) (Fig. 2). Adjuvant treatment consisted of administration of four cycles of systemic chemotherapy, after which the patient was referred for PORT.

Patient 2 (post-pneumonectomy). The second patient had received induction chemotherapy (three cycles of a platinum-based combination) for a 5-cm nodule in the right upper lobe extending to the visceral pleura, with both ipsilateral hilar and subcarinal nodal disease. As response evaluation revealed a partial response of the tumor and no hilar abnormalities, a right pneumonectomy and mediastinal dissection was performed. Nine lymph nodes were explored: three intrapulmonary and hilar nodes, two subcarinal nodes (station 7), and four paratracheal nodes (2 station 4R and 2 station 2R). Histology revealed a poorly differentiated large-cell carcinoma measuring 4 cm in diameter with 50% necrosis. Metastases were found in a subcarinal node and a right paratracheal node (station 4R). All resection margins were free of tumor, and the patient was referred for PORT for a stage $pT_2N_2M_0$ tumor.

Lung ART contouring protocol (Appendix A). The CTV includes the bronchial stump, the ipsilateral hilar node region, and any possible extension to the mediastinal pleura adjacent to the resected tumor bed. In addition, the mediastinal CTV is to include all the lymph nodes that lie between two noncontiguous nodal stations that have contained metastases at any stage. Based on the surgical literature, subcarinal (LN7) and ipsilateral paratracheal nodes (LN4) are always included in the CTV (Fig. 2). In the case of leftsided tumors, the subaortic and para-aortic nodes (LN 5 and 6) should be included in the CTV (Fig. 2). When metastases are identified in a nodal station, the next nodal station superior to it is included in the CTV, as is the nodal station immediately inferior to the lower involved mediastinal node. However, in some cases the volumes delineated for the CTV could become too large. For instance, in the case of LN7 involvement, LN8 should theoretically be included so that the lower limit will be at the gastroesophageal junction. Therefore, it was decided to define the boundaries more clearly in a table (Appendix B).

Analysis of clinical target volumes

Volumes of the routine and protocol contoured targets of each observer were determined, using a tracing tool in ImageJ (http://rsb.info.nih.gov/ij/). The outlines of all axial two-dimensional contours were traced, and the number of encompassed internal pixels (pixel-size 0.87*0.87 mm) and the number of contoured slices (slice thickness 2.5 mm) were calculated. In addition, both length in three orthogonal directions and center-of-mass (COM) coordinates of each CTV were determined. To determine the coverage of nodal stations to be included in the CTV, a gold standard for mediastinal nodal regions was generated by two clinicians (F.S. and S.S.) at the VU University Medical Center for both patients according to the definitions by Chapet *et al.* (18) using Eclipse v8.1 software (Varian Med. Systems, Palo Alto, CA).

Dosimetric analysis

To evaluate the influence of contouring variation on dose–volume histogram (DVH) statistics before and after use of the protocol, a dosimetric analysis was performed based on both the smallest and the largest target volume. Planning target volumes (PTVs) were generated by expanding CTVs with a margin of at least 5 mm in the mediolateral and dorsoventral directions and of 10 mm in the craniocaudal direction to account for tumor motion and variations in patient setup. A routine conformal treatment plan consisting of five fields using 6- to 15-mV photons was designed in Eclipse v8.1, based on a gold standard CTV contoured by the principal investigator (S.S.). The Lung ART protocol prescribed a dose of 54 Gy in daily fractions of 2.0 Gy. This plan was then projected on each PTV (smallest and largest routine and protocol PTV) and adjusted such that the 95% isodose volume tightly conformed the PTV while respecting dose constraints to organs at risk according to International Commission on Radiation Units and Measurements objectives (19). Specifically, it was aimed to limit the percentage volume of lung tissue outside the PTV planned to receive 20 Gy to 35% ($V_{20} \leq 35\%$) and the maximum spinal cord dose to 50 Gy. The DVHs were calculated to evaluate variability in toxicity

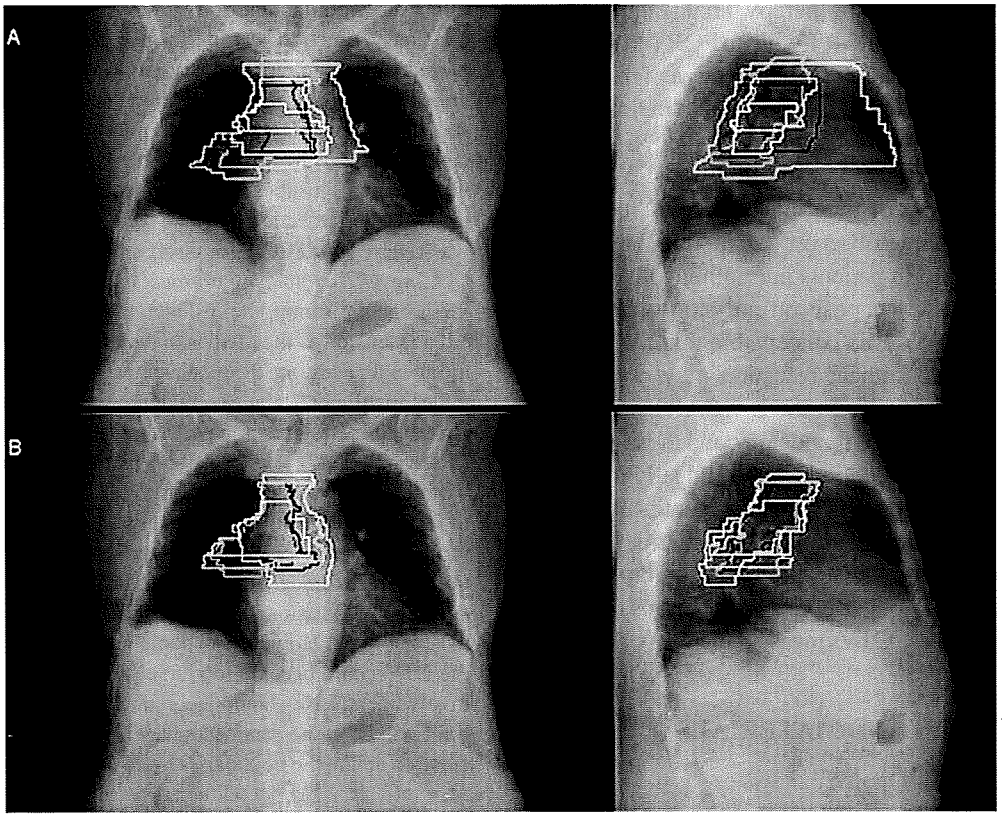

Fig. 1. Routine clinical target volumes (CTVs) (upper panel) and protocol CTVs (lower panel) from six observers projected on a digital reconstruction of a computed tomography dataset from the postlobectomy patient.

profile, and the following parameters were assessed: mean lung dose, total lung volume minus PTV receiving either ≥20 Gy (V_{20}) or ≥5 Gy (V_5), total cardiac volume percentage receiving ≥45 Gy (V_{45}), maximum spinal cord dose, and esophageal length receiving ≥45 Gy.

Statistical analysis

The variance between routine and protocol CTVs of different observers was assessed by constructing a mixed-effects model for each endpoint (*i.e.*, volume, length, or COM position). Contouring procedure and patient identifier were taken as fixed effects, whereas the observer identifier was taken as the random grouping variable. Significance was reported at levels 0.05 and 0.007, with the latter being the adjusted value for multiple testing using the Bonferroni method. Differences in nodal coverage between routine and protocol CTVs were evaluated using an F test in Excel (Microsoft Office 2003).

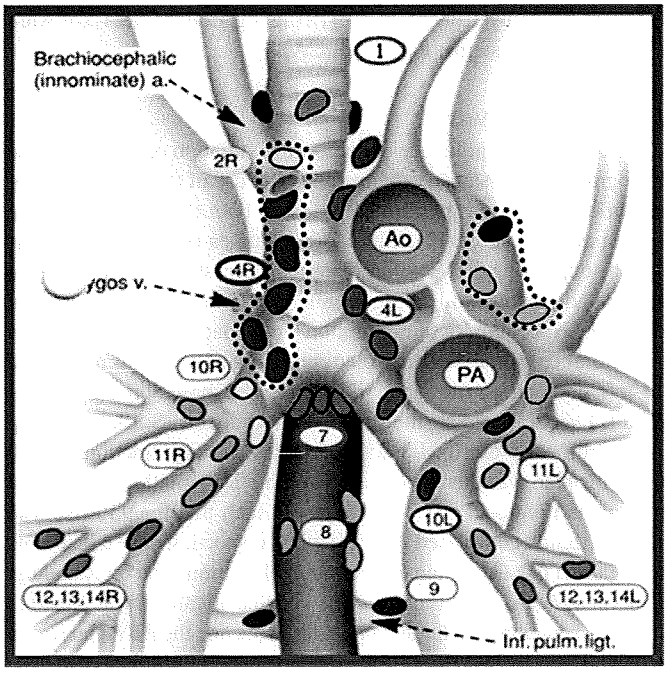

Fig. 2. Nodal staging system (Mountain-Dresler).

RESULTS

Number of datasets received

For each case, a total of 10 clinicians generated routine clinical target volumes (CTV); they included the principal investigator, who had knowledge of the protocol. Both routine and protocol CTV's for both patients were available from six expert observers. One participating clinician returned only a protocol CTV for both cases because the center did not perform routine PORT.

Analysis of clinical target volumes

Regarding experts who returned routine and protocol datasets, for the postlobectomy patient, the median routine CTV was 90.2 cc (range, 36.2–678.4 cc), and the median corresponding protocol CTV was 91.3 cc (range, 60.0–112.4 cc). For the postpneumectomy patient, the median routine CTV was 115.5 cc (range, 48.5–712.1 cc), and the median corresponding protocol CTV was 93.3 cc (range, 78.3–125.3). Regarding all experts, routine CTVs varied up to threefold between clinicians, but this variance was significantly reduced

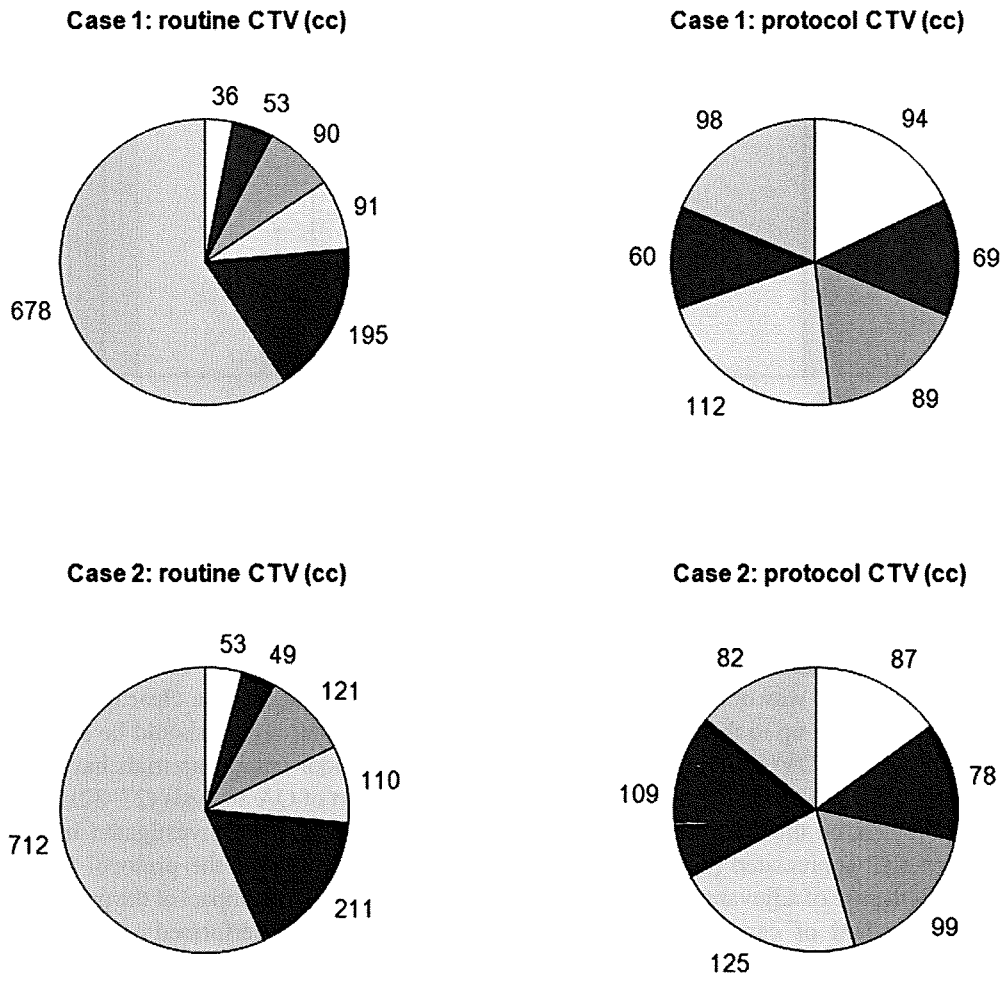

Fig. 3. Routine vs. protocol clinical target volumes (CTVs) (cc) from six observers for the postlobectomy patient (upper panel) and the postpneumectomy patient (lower panel).

for both cases when clinicians used the Lung ART protocol ($p < 0.007$) (Fig. 3). In addition, both the variance in cranial-caudal COM positions ($p < 0.007$) and contoured target lengths along the cranial-caudal Z axis were significantly reduced ($p < 0.05$) using the protocol. All results maintained significance when data of the observer with the most deviating CTV were excluded from analysis.

In both patients, the Lung ART protocol required the CTV to include nodal stations 2 right (LN2R), 4 right (LN4R), 7 (LN7), and ipsilateral hilus. Median coverage of LN4R and LN7 by routine CTVs were 82% (range, 44–97%) and 94% (range, 20–100%), respectively, for the postlobectomy patient. Use of the protocol resulted in an increased median coverage of LN4R ($p < 0.05$) (Fig. 4). Although median coverage did not significantly improve in LN7, the range between observers was much smaller with the protocol (73–100%) compared with routine (20–100%) contoured CTVs (Fig. 4). Similar results were seen in the postpneumectomy patient (Fig. 4). Median coverage of LN2R by routine CTVs was poor in both cases, with values of 0% (range, 0–47%) and 38% (range, 0–62%) in the postlobectomy and postpneumectomy patients, respectively. The results did not significantly improve using the protocol (Fig. 4).

Dosimetric analysis

The difference in 95% isodose volume between the smallest and the largest CTV was reduced from 1,802 cc to 216 cc in the postlobectomy patient and from 1,342 cc to 53 cc in the postpneumectomy patient. Variations in routine CTVs led to important differences in the risk of radiation-induced toxicity; *i.e.*, the V_{20} ranged from 12.7% to 54% in the postlobectomy patient, whereas corresponding values in the postpneumectomy patient ranged from 1.5% to 20.6% (Table 1). Similarly, large variations between experts were observed in mean lung dose, lung V_5, and cardiac V_{45} in both cases. When the protocol was used, differences between observers were significantly reduced, resulting in a more consistent toxicity profile (Table 1). The differences in both spinal cord doses and esophageal length receiving > 45 Gy between routine and protocol CTVs were not as striking as seen with the other parameters.

DISCUSSION

Studies planned to evaluate PORT should use not only modern radiotherapy techniques but also consistent target volume definition. The latter is particularly relevant because the lack of standardized protocol definitions in the past may

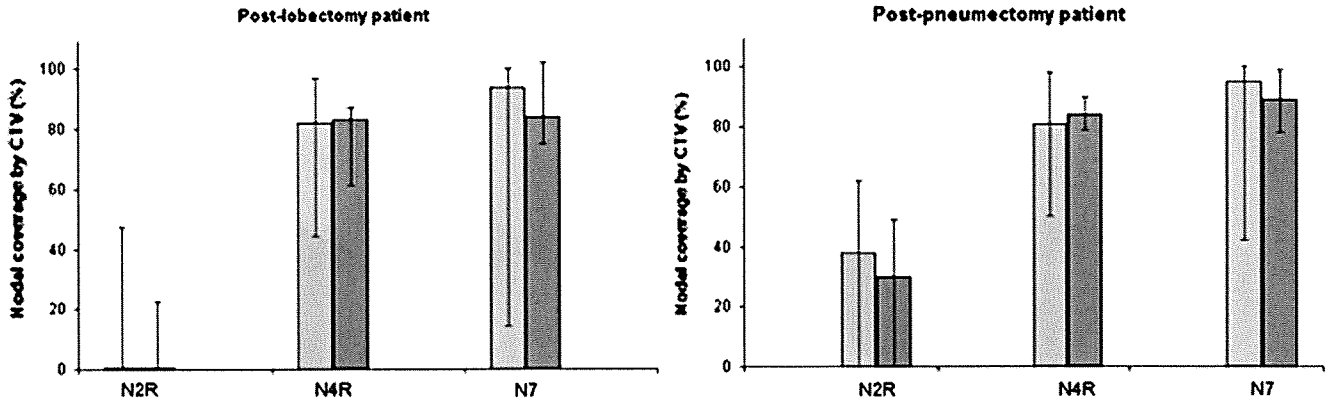

Fig. 4. Nodal coverage (%) by routine and protocol clinical target volumes in the postlobectomy patient (left) and the postpneumectomy patient (right).

have contributed to inconclusive results (10, 20); i.e., the total dose was often not standardized and excessively high (5), with variable field sizes influencing both local recurrence rates and radiotherapy-induced mortality (6). The results of the present study show that even among thoracic radiation oncology experts, large variability was observed in routine target definition for PORT, and the up to threefold variation resulted in important differences in DVH parameters. The potential influence of pulmonary and cardiac toxicity, arising from unnecessarily large fields, on the risk of radiotherapy-induced mortality is now well appreciated (6). Similar concerns are experienced with the use of adjuvant chemotherapy, which is presently the standard of care in patients with non–small-cell lung cancer and resected N1 and N2 disease (21). Follow-up after more than 5 years after adjuvant chemotherapy revealed an increase in mortality (22), a development that highlights the potential for long-term hazards after any adjuvant therapy for such patients.

Before the commencement of the Lung ART trial, protocol target volumes were developed by the Lung ART writing committee based on patterns of local recurrence after surgery (23, 24), lymphatic pathways, and results of the omission of elective nodal irradiation (25, 26). The present study revealed that use of the Lung ART protocol resulted in a large degree of consensus between clinicians. However, residual interobserver variability may still exist as a result of misinterpretation, lack of clear formulation, or ignorance of the protocol. This is supported by the finding that use of the protocol did not improve coverage of the upper para-aortal nodes (LN2R). Consequently, a clear definition of the boundaries of this particular region should be specified in the protocol.

Recent major intergroup trials have also included dummy runs as a part of QA analysis (27–32), but these studies differ from ours in that we investigated interobserver variability both before and after the protocol was provided, allowing for evaluation of the impact of the protocol. In addition, earlier dummy runs were performed using hard copies, whereas we used a CD-ROM–based contouring program containing complete CT datasets that can be run automatically on each Windows-based computer. Our previous study validating this CD-ROM tool has established a more realistic assessment of clinical variations than with hard copies, and it was shown that most clinicians were able to complete the exercise (16).

One limitation of our study is that none of the invited experts from North America finally participated in this study. Furthermore, experts were arbitrarily identified from members of International Association for the Study of Lung Cancer and European Organisation for Research and

Table 1. Variability in planning parameters between the smallest and largest target volumes

	Postlobectomy patient				Postpneumectomy patient			
	Routine		Protocol		Routine		Protocol	
	Range	Difference	Range	Difference	Range	Difference	Range	Difference
Planning target volume (cc)	148–1,342	(1,194)	297–382	(85)	187–1,262	(1,075)	275–308	(33)
95% Isodose volume (cc)	300–2102	(1,802)	518–734	(216)	446–1,788	(1,342)	556–609	(53)
Lung								
Mean lung dose (Gy)	8.0–26.1	(18.1)	11.6–15.3	(3.7)	3.4–13.4	(10.0)	4.0–4.1	(0.1)
V_{20} (%)	12.7–54.0	(41.3)	20.6–29.2	(8.6)	1.5–20.6	(19.1)	2.1–2.9	(0.8)
V_5 (%)	34.7–79.5	(44.8)	52.2–63.1	(10.9)	31.6–59.3	(27.7)	30.4–35.7	(5.3)
Heart								
V_{45} (%)	0–20.5	(20.5)	1.6–5.1	(3.5)	4.3–37.0	(32.7)	7.1–10.0	(2.9)
Spinal cord								
D_{max}	45.3–49.5	(4.2)	47.8–50.0	(2.2)	50.0–51.0	(1.0)	44.8–48.7	(3.9)
Esophagus								
Length receiving 45 Gy (cm)	4.5–11.5	(7.0)	6.8–9.5	(2.8)	5.8–12.0	(6.3)	7.5–10.8	(3.3)

Treatment of Cancer who were active in lung cancer and who were known to the study group. In addition, the participating experts themselves did not perform treatment planning; therefore, interinstitution variability in dose statistics could not be assessed. Instead, dosimetric impact of contouring variability was evaluated by designing a standard plan in our own institution, although we believe that this was of minor influence, as contouring variation seems to be the largest source of systemic errors in lung cancer (33). Furthermore, the results are based on a routine conformal plan consisting of five fields, whereas the use of three fields (which is allowed in the protocol) may have resulted in a more forgiving situation, leading to less striking differences between routine and protocol target volumes. In addition, this study did not account for interobserver variability with respect to shape of the contours, which has been reported to be imprecise between observers (34). Other factors besides the Lung ART protocol could have contributed to the reduction in contouring variability over a period of time, including test–retest reliability. We were unable to study the latter because the logistic difficulties involved in obtaining the full cooperation of all the invited experts were considerable.

This dummy run test was part of the first phase of an external QA program, and the results were sent to the QA team for protocol validation. The magnitude of the observed differences led to a decision to invest in a web-based dummy run for the Lung ART trial. This ongoing study will address the above issues in a more representative population of thoracic radiation oncologists. The next step will include collection of the plans and its verification images for the first patient from each participating center. Subsequently, 15% of the plans will be collected by the QA team to ensure protocol adherence in centers where plans of the first patients were adequate, whereas plans of the patients included in the RT arm will be considered for revision in centers where plans were not adherent to the protocol.

CONCLUSIONS

The large interobserver variation in target definition seen among experts is a confounding factor in clinical outcomes of multicenter clinical trials, emphasizing the need for standardization. A protocol defining target definitions was shown to serve this purpose and is therefore incorporated in the QA program of the Lung ART.

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APPENDIX A: CONFORMATIONAL POSTOPERATIVE RADIOTHERAPY

According to randomization, patients will receive or not receive postoperative radiotherapy (PORT). We recommend that patients randomized in the treatment arm start PORT as soon as possible after randomization. No concomitant chemotherapy is allowed. At least 10 days' interval between the last day of chemotherapy and PORT is requested. This interval may be extended in case radiosensitizing drugs such as gemcitabine have been used, or when the patient does not have full haematologic recovery from the chemotherapy.

Radiotherapy technique

High-energy photons (≥6 MV) should be used. The planned dose to the International Commission on Radiation Units and Measurements reference point is 54 Gy in 27 fractions of 2.0 Gy. The radiotherapy will be given once each day, 5 days per week. The use of conformal techniques is mandatory. A planning computed tomography (CT) scan in treatment position should be used, with a maximal slide thickness of 5 mm for the whole thorax. The use of intravenous contrast is recommended. All target volumes as well as the critical organs should be delineated on this CT scan. Dose–volume histograms (DVH) of all target volumes—resected clinical tumor volume (rCTV), clinical target volume (CTV), and planning target volume (PTV)—and of all critical organs (lungs, cardiac volume, and spine, with or without esophagus) as described in the following section are required. All patients should be treated with a minimum of three fields. All fields should be treated daily.

Definition of volumes

rCTV in the mediastinum. This corresponds to lymph nodes involved according to the pathologic report of the lymph node exploration. The bronchial stump, the homolateral hilar node region, and the eventual extension to mediastinal pleura facing the resected tumor bed completely resected will always be included in the rCTV.

CTV in the mediastinum. In the CTV will be included the rCTV plus a margin corresponding to the upper and lower lymph node station to the involved lymph node area. All the lymph nodes that lie between two noncontiguous node stations that are involved will be included in the CTV. Because of the frequent involvement of subcarinal (LN7) and paratracheal nodes (LN4) on surgical series, these stations will also be systematically included in the CTV.

In the case of a leftsided tumor, the subaortic and the paraaortic nodes (LN 5 and 6) should also be included in the CTV because they are very often involved (as shown in Appendix B). The homolateral supraclavicular region will not be included systematically in the CTV.

PTV. Owing to organ movements and to setup uncertainties, an additional margin of at least 0.5 cm (lateral, anterior, and posterior) and 1 cm (superior and inferior) is recommended. The margins may be individualized according to 4D-CT scan data and/or measurements of the daily setup error. For patients who have had a positron emission tomography (PET)—CT scan before treatment, all data will be collected concerning positive nodes. However, only surgical positive nodes will be included in the rCTV.

APPENDIX B

Surgically involved mediastinal nodes	LN stations to be included in the CTV
1–2R	1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
1–2L	1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
3 (Right -sided tumor)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
3 (Left-sided tumor)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
4R	2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
4L	2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
5	2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*
6	2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
7 (Right-sided tumor)	4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
7 (Left-sided tumor)	4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
8 (Right-sided tumor)	4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction
8 (Left-sided tumor)	4L, 5, 6, 7 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction

Abbreviations: LN = lymph node; CTV = clinical target volume.
* Unless other nodes are involved.

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9. 放射線治療の品質管理

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key words radiation therapy, quality control, quality assurance, external audit, advanced technology

動 向

身体侵襲が少なく形態・機能温存をはかれること，社会の高齢化とQuality of Lifeの視点などにより放射線治療を必要とする患者数が増加している．また，わが国では諸外国に比べがん治療における放射線治療の施行割合が低いが，2007年に策定されたがん対策基本計画では放射線治療の推進・普及が謳われており，今後ますますその需要が高まるものと思われる．

放射線治療の実施過程は複雑かつ多岐にわたる．1）患者の評価，2）放射線治療の適応の判断，3）放射線治療プロトコールの選択，4）放射線治療のための患者体位の決定および患者固定具の作成，5）コンピュータを用いたバーチャルシミュレーション：治療計画のための画像撮影，腫瘍および正常組織の輪郭取得，6）照射方法の決定，放射線線量の評価，7）治療計画コンピュータから治療装置へ治療計画情報の転送，8）治療室での患者位置決め，9）照射，10）治療内容の照合など，各段階において不確実性が存在し，エラーが生じる危険性を孕んでいる（図1）．たとえば，バーチャルシミュレーションでは，腫瘍の進展範囲の判断には施術者間の無視できないばらつきが存在することがいわれており[1,2]，また，放射線線量の評価においても施設間較差が存在する危険性が指摘されている[3]．誤って使用すれば死亡にもつながる障害を引き起こす危険もあり，放射線治療の実施にあたっては，その一連の過程に対して品質管理 quality control（QC）および品質保証 quality assurance（QA）を行うことにより治療の質を保つことが必須となる[4]．さらに治療の実施に先立ち放射線照射装置（リニアック）そのもののQC/QAも欠くことができない．

また，不適切な治療により治療成績が低下することは想像に難くないが，臨床試験においてもプロトコール規定の逸脱により治療成績が低下するとの報告が複数ある[5,6]．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・均てん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下を防止する観点からも必須といえる．

一方で，近年のinformation technology（IT）技術の進歩により，放射線治療も従来の二次元的なものから三次元/四次元放射線治療（3D/4D-CRT），定位放射線治療（SRT），強度変調放射線

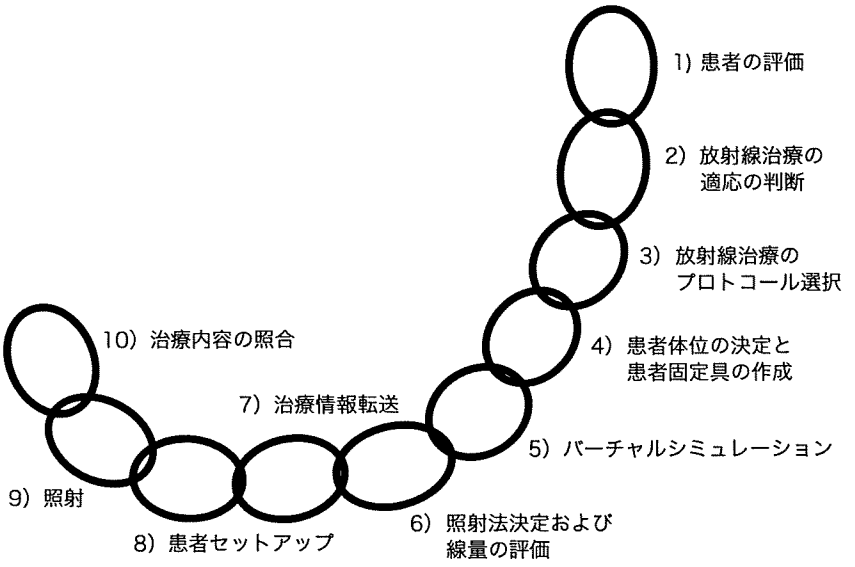

図1　放射線治療のプロセス

放射線治療のプロセスは連鎖状であり，各ステップの一つでもエラーが生じると鎖が切れ事故につながる危険がある．

治療（IMRT）などへと急速に高度化が進んでいる．これらの先進的技術を安全に臨床導入するためにも各技術に応じた適切なQC/QAプログラムの実施が求められている．

A. 国外におけるQC/QA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．1969年にNational Cancer Institute（NCI）の補助金を受けて設立されたRadiological Physics Center（RPC）が物理技術的QC/QAに関する代表的な組織であり，郵送可能な線量計を用いたoff-site auditによる線量モニタリングや，施設訪問による線量測定およびQC/QAプログラムの確認といったon-site auditを全米に約2100存在する放射線治療施設のうち約1500の施設を対象に実施している．さらにはNCIにより臨床試験に参加するためにはRPCによるauditを受けることが必須とされている[7]．最近では，放射線治療技術の高度化に伴い，3D-CRT，SRT，IMRTなどの臨床試験の参加施設，参加医師などにこれらを正しく使用できる知識と経験があること，およびその治療精度を保証するための事前承認制度が導入されている[8]．治療精度の評価においてはRPCで作成された人体腫瘍模擬ファントム（以下RPCファントム：図2）を使用して治療計画を立て，治療

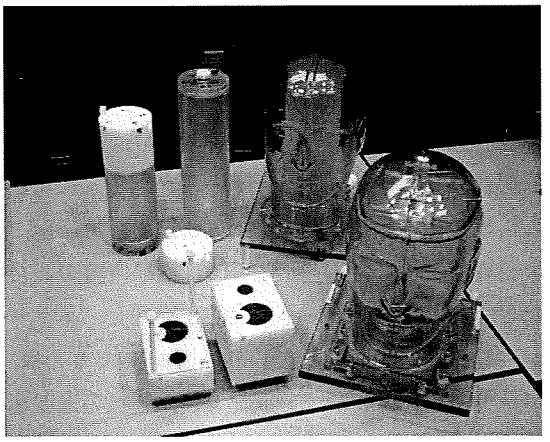

図2　RPCファントム

頭部用（奥）および頭頸部用（手前）

表1　RPCファントムによる治療精度の評価結果[9)]

ファントム	頭頸部	前立腺	胸部	肝臓
照射回数/のべ施設数	250（100%）	64（100%）	24（100%）	4（100%）
許容範囲内	179（ 72%）	55（ 86%）	17（ 71%）	3（ 75%）
許容範囲外	71（ 28%）	9（ 14%）	7（ 29%）	1（ 25%）
開始年	2001	2004	2004	2005

計画装置で計算された放射線の線量分布と実際に投与された線量を比較している．頭頸部がんに対するIMRTの評価では，約30%の施設で一定の基準をクリアできなかったとの結果があるが（表1），これらを通して放射線治療計画装置へのデータ入力の誤り，線量分布計算精度の確認不足，治療計画装置の誤用，治療用寝台の位置表示や患者位置決めエラー，治療計画ソフトのエラーなどが発見され，それぞれの修正が可能であった．同時にこれら事前承認制度が導入された臨床試験においては，導入されていない臨床試験に比べてプロトコール規定からの逸脱・違反割合が少ないことも報告されており，このような事前承認制度は質の確保にきわめて有効である[9)]．

物理技術的QC/QAプログラムとは別に，放射線を照射する標的となる腫瘍の体積やいわゆる照射野の設定方法など治療内容に関する臨床的QC/QAプログラムがあり，こちらも主として臨床試験を通して実施されてきた．Quality Assurance Review Center（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年に設立された臨床試験の放射線治療QC/QA活動を実施している米国最古の組織である[10)]．その後，他の多施設共同研究グループにおいて複数のQA組織によりQC/QAプログラムが実施されるようになり，放射線治療の質の改善が示された[11,12)]．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[13)]．

欧州においてもEuropean Organisation for Research and Treatment of Cancer（EORTC）で同様のプログラムが導入されており[14)]，放射線治療のQC/QAを行うことはglobal standardと認識されているのみならず，教育的観点ならびに均てん化の面からも重要である．現在ではATCと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実施されている[15)]．

B. 国内の状況

わが国においては，従来より「治療用線量計の校正」活動により各施設の線量測定機器の精度は管理されてきたが，リニアックなどの治療装置の線量管理を行う物理技術的QC/QAおよび放射線治療の内容に関する臨床的QC/QAを全国規模で体系的に実施するシステムは近年まで構築されていなかった．物理技術的QC/QAについては2002年より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を試験的に実施し[16)]，2007年11月にはoff-site audit事

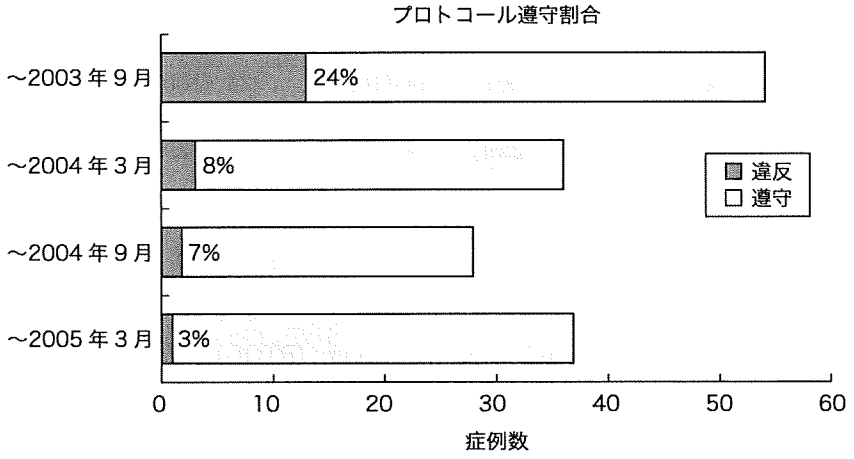

図3　臨床試験におけるプロトコール放射線治療規定遵守割合の変化
開始当初は違反割合が高かったが，その後急速に遵守割合の改善がみられた．

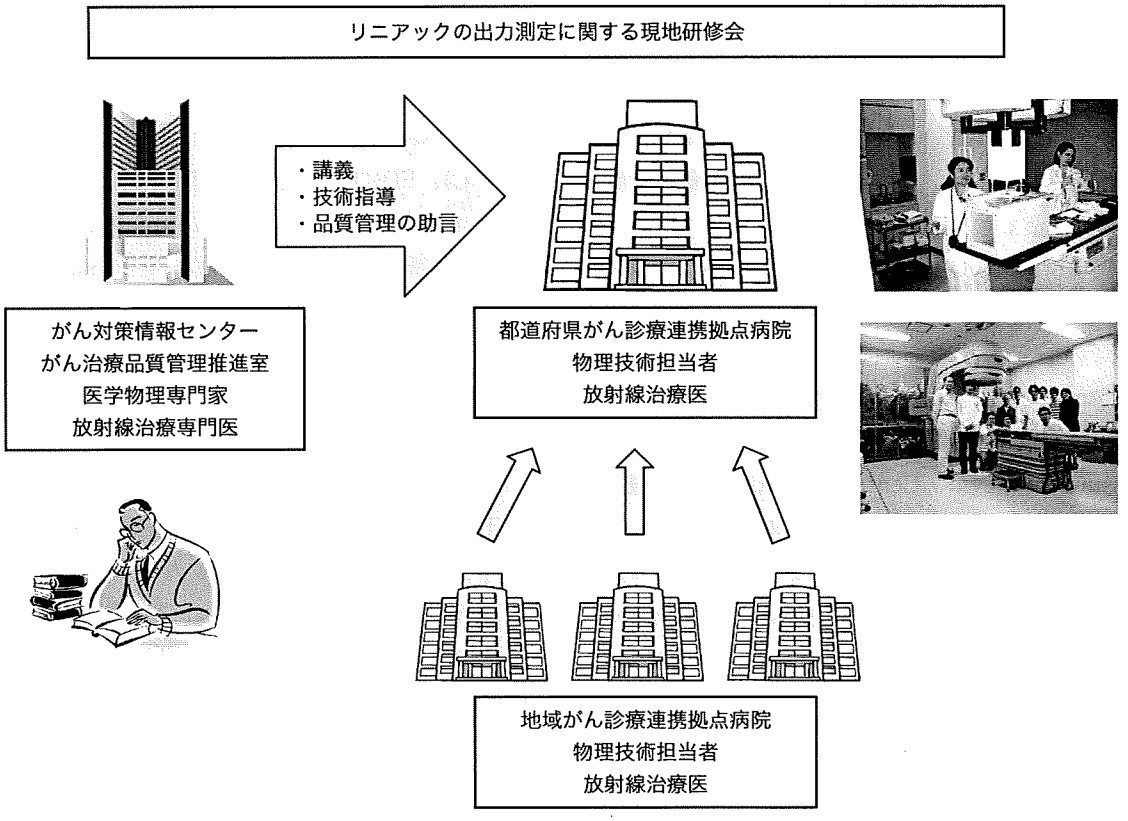

図4a)　がん診療連携拠点病院に対する研修会の開催

業が全国の放射線治療施設を対象に開始された．

一方，臨床的QC/QAに関しては1999年にJCOGがALGB同様に放射線治療委員会を立ち上げた．2001年には一つのランダム化比較試験において放射線治療のプロトコール規定の遵守率はわずか40%であることが判明し，わが国においても臨床試験において積極的にQC/QAプログラムを導入することの重要性が認識された[17]．2002年以降のJCOG臨床試験ではQC/QAプログラムが導入されており[18]，短期間のうちにプロトコール規定の遵守率が飛躍的に向上している(図3)．2004年には臨床試験のQC/QA活動を支援する特定非営利活動法人放射線治療支援センターが設立，また2006年には国立がんセンターがん対策情報センターにがん治療品質管理推進室が設置され[19]，がん診療連携拠点病院および臨

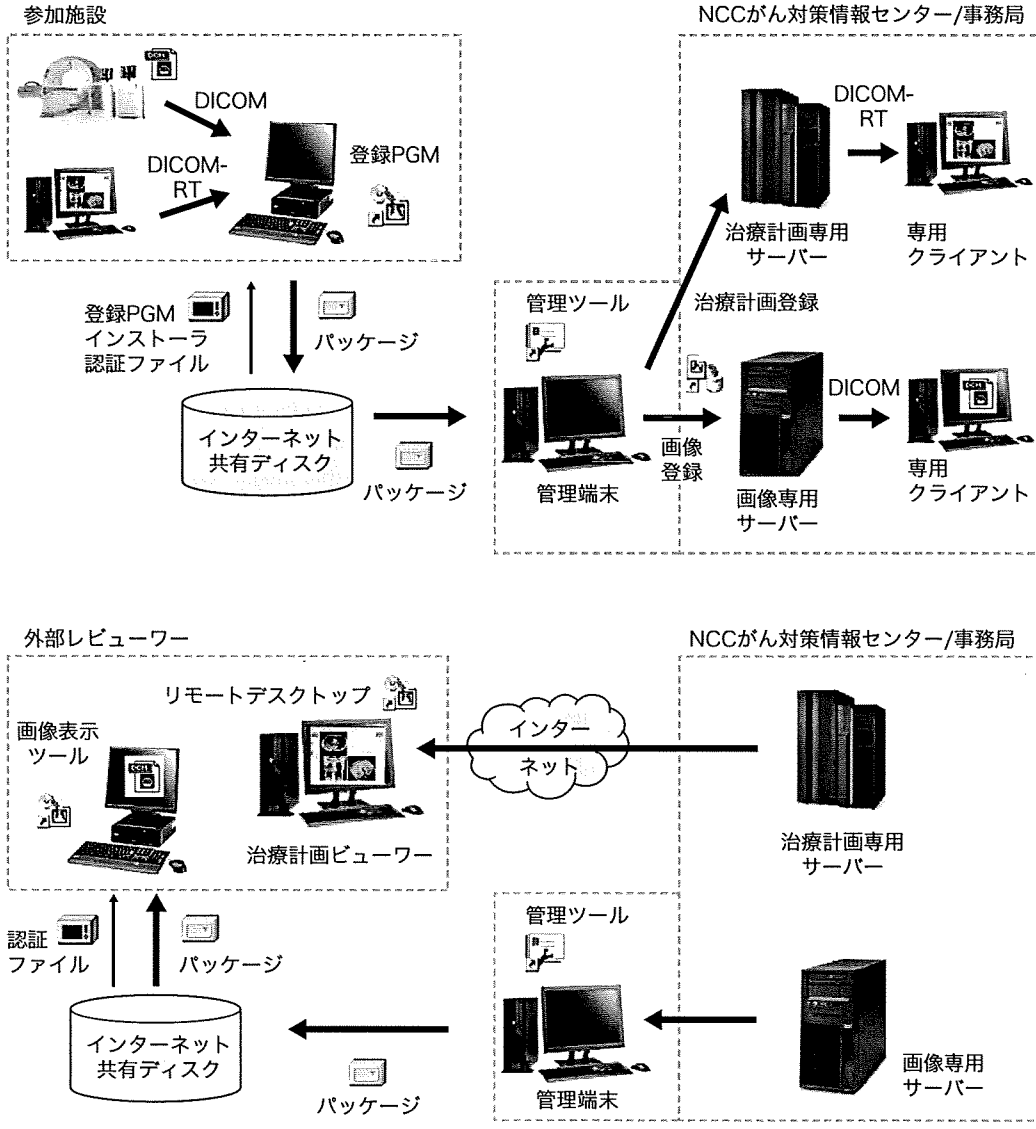

図4b)　放射線治療計画遠隔評価システム

床試験参加施設を中心に物理技術的QC/QAおよび臨床的QC/QAを支援する体制が整備されつつある（図4a，b）.

C. 今後の展望

近年の技術革新による先進的放射線治療の導入により，従来のQC/QAガイドラインでは一部不完全あるいは時代遅れとなっている．特に肺癌の呼吸による腫瘍の移動を考慮した四次元放射線治療のような画像誘導による放射線治療計画および治療，あるいはコンピュータ制御による治療の実施に当たっては，新たなQC/QAガイドラインの作成が急務となっている．主なポイントをあげると，1）IMRTおよび画像誘導による放射線治療計画がコミュニティーに浸透するスピードに比べ，それらのQC/QAガイドラインの作成は遙かに遅れており，医学物理士および放射線腫瘍医は治療の質と安全性を確保するための明確な方針を打ち出せていない状況となっている．先述のRPCファントムを用いた治療精度の評価において少なからず精度を保てていない施設が存在したことは，わが国に比し人的資源が豊富といわれる米国においてすらIMRTの質が思いのほか保たれていないことを示唆しており，深刻な医療事故のリスクが高まっている．2）包括的なQC/QAガイドラインのタイムリーな更新ができるよう，関連学会は体制整備を急ぐ必要がある．3）各施設においては，確率が低い医療事故を予防し限られたQC/QA資源を効率的に利用するためには，産業技術分野の手法に準じプロセスを重視したQC/QAプログラムを作成するなど，新たなパラダイムが必要である．

これらを踏まえて，International Atomic Energy Agency（IAEA）による国際シンポジウム[20] “Quality Assurance and New Techniques in Radiation Medicine” や，米国放射線腫瘍学会によるシンポジウム[21] “Quality Assurance of Radiation Therapy and the Challenges of Advanced Technologies” などが相次いで開催され，対応策の検討が行われている．また，World Health Organization（WHO）でも，“World Alliance for Patient Safety” というプロジェクトチームが作られ，これまでの放射線治療事故事例の分析とともにリスクの高いプロセスを明らかにし，より効率的に患者の安全確保をはかる方策，たとえば，1）治療計画プロトコールチェックリスト，2）放射線治療機器のQC/QAプログラム，3）ピアレビューによる第三者評価の導入など，ガイドラインの作成が進められている．今後これらの活動が実を結び，先進的放射線治療技術が安全かつ効果的に導入され，がんの治療成績の向上に寄与することを期待したい．

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PHYSICS CONTRIBUTION

EVALUATION OF THE EFFECTIVENESS OF THE STEREOTACTIC BODY FRAME IN REDUCING RESPIRATORY INTRAFRACTIONAL ORGAN MOTION USING THE REAL-TIME TUMOR-TRACKING RADIOTHERAPY SYSTEM

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Purpose: To evaluate the effectiveness of the stereotactic body frame (SBF), with or without a diaphragm press or a breathing cycle monitoring device (Abches), in controlling the range of lung tumor motion, by tracking the real-time position of fiducial markers.

Methods and Materials: The trajectories of gold markers in the lung were tracked with the real-time tumor-tracking radiotherapy system. The SBF was used for patient immobilization and the diaphragm press and Abches were used to actively control breathing and for self-controlled respiration, respectively. Tracking was performed in five setups, with and without immobilization and respiration control. The results were evaluated using the effective range, which was defined as the range that includes 95% of all the recorded marker positions in each setup.

Results: The SBF, with or without a diaphragm press or Abches, did not yield effective ranges of marker motion which were significantly different from setups that did not use these materials. The differences in the effective marker ranges in the upper lobes for all the patient setups were less than 1mm. Larger effective ranges were obtained for the markers in the middle or lower lobes.

Conclusion: The effectiveness of controlling respiratory-induced organ motion by using the SBF+diaphragm press or SBF + Abches patient setups were highly dependent on the individual patient reaction to the use of these materials and the location of the markers. They may be considered for lung tumors in the lower lobes, but are not necessary for tumors in the upper lobes. © 2009 Elsevier Inc.

Organ motion, Body frame, Real-time tracking, Effective range.

INTRODUCTION

The risk of radiation-induced lung complications may be minimized if intrafractional tumor motion caused by respiration during irradiation can be accurately accounted for. Various approaches to the management of respiratory motion in radiation therapy are comprehensively discussed in the AAPM Report 91 (1). These include the accurate tracking of organ and tumor motion during treatment and methods by which the motion may be restricted or dampened.

Motion tracking may be accomplished by taking two sets of fluoroscopic images of the tumor itself, other anatomical structures, or fiducial markers placed near the tumor (2–4). Ideally, the function of real-time tracking is to determine the full range of tumor motion, as well as its trajectory during treatment from these fluoroscopic images taken at high frequency. At present, this is only possible in a few centers that have facilities dedicated for this purpose, such as the real-time tumor-tracking radiation therapy system developed at Hokkaido University Hospital (5, 6).

Restriction of respiration, on the other hand, can be achieved by using patient immobilization and by applying abdominal pressure. In extracranial stereotactic irradiation, Lax *et al.* (7), Herfarth *et al.* (8), and Negoro *et al.* (9) have reported the effectiveness of an abdominal press in reducing respiratory-induced tumor movement in stereotactic conformal radiation therapy of body tumors. Alternatively, an air-injected blanket has also been suggested for abdomen

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Conflict of interest: This study was conducted in cooperation with Elekta Oncology Systems, Japan.

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