ELSEVIER

Radiotherapy and Oncology 70 (2004) 45–48

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Technical note

Measurement of beam-axis displacement from the isocenter during three-dimensional conformal radiosurgery with a micro-multileaf collimator

Etsuo Kunieda[a,*], Osamu Kawaguchi[a], Hidetoshi Saitoh[a,b], Tatsuya Fujisaki[a,c], Atsuya Takeda[a], Takatsugu Kawase[a], Hossain M. Deloar[a,d], Naoyuki Shigematsu[a], Atsushi Kubo[a]

[a]*Department of Radiology and Neurosurgery, Keio University, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan*
[b]*Department of Radiologic Sciences, Tokyo Metropolitan University of Health Sciences, Tokyo, Japan*
[c]*Department of Radiological Sciences, Ibaraki Prefectural University of Health Sciences, Ibaraki, Japan*
[d]*Japan Science and Technology Agency, Japan*

Received 20 March 2003; received in revised form 7 November 2003; accepted 17 November 2003

Abstract

We describe the displacement of the beam-axis from the planning isocenter in clinical situations during three-dimensional conformal radiosurgery using an Acculeaf bi-directional micro-multileaf collimator. The displacements were recorded for 64 ports using a video imaging system and a stereotactic arc. The mean displacement was 0.41 ± 0.25 mm.

Keywords: Accuracy; Linear accelerator; Radiosurgery; Beam's eye monitor

1. Introduction

Recently, micro-multileaf collimators (MMLC) have been used for radiosurgery or precise three-dimensional (3D) conformal radiotherapy [2,4,5,8,9]. Nevertheless, the majority of medical linear accelerators (linacs) currently in operation are not designed to be used with heavy auxiliary MMLC hardware. Moreover, as a result of the patient's head and the couch interfering with placement of the film, verification of each actual treatment port is very difficult or practically impossible to carry out during 3D-conformal radiotherapy or radiosurgery. Most of the previously reported measurements were not carried out during treatment, but instead, were taken in phantom studies [3,6,7].

We report a method to evaluate the degree of error during MMLC-based radiosurgery and indicate the displacement of the beam-axis from the planning isocenter during this procedure in clinical situations.

2. Materials and methods

A 6-MV linac (ML15MV: Mitsubishi Electric Corp. Tokyo, Japan) was used to produce the X-ray beam. This machine has been used for the last 8 years for radiosurgery in addition to daily conventional irradiation. During radiosurgery or stereotactic radiotherapy with this linac, a computer-controlled MMLC module (AccuLeaf: Alayna Enterprises Corporation, Paris, France) was mounted on the linac gantry-head. Forty-eight pairs of MMLC leaves, driven by individual motors, are composed of two levels with the direction of the two levels of leaves being perpendicular to each other. The effective leaf thickness of the inner 14 pairs is 2.6 mm, while the thickness of the outer pairs is 5.3 mm at the isocenter [1]. The outer dimensions of the MMLC are 540 mm in diameter and 135 mm in height with a weight of 28 kg (Fig. 1).

For the purpose of target positioning, we have been using a small charge-coupled device (CCD) video camera mounted in the gantry head where the source of the light field is placed (beam's eye monitor). Details were described elsewhere [6]. During each treatment or QA procedure, a stereotactic arc is mounted on the base frame in such a way that the center of the arc can be matched with the intended target point (i.e. the planning isocenter). A target pointer, consisting of a convex lens and a bull's eye, can slide along the arc with its axis perpendicular to the arc. If we observe the bull's eye through the lens from the video camera, the lens forms a virtual image of the bull's eye ('virtual target') at the position of the arc center (planning isocenter), even

* Corresponding author.

0167-8140/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2003.11.008

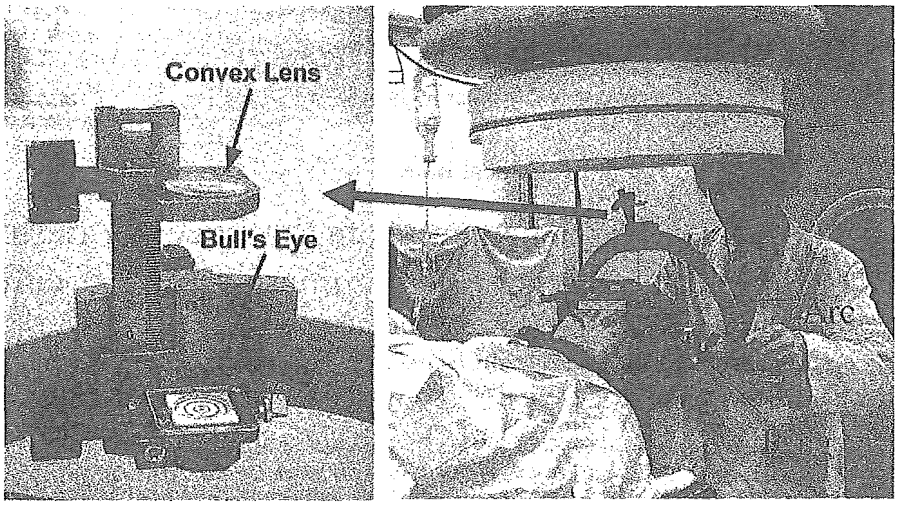


Fig. 1. The micro-multileaf collimator (MMLC) module and the stereotactic arc device (right). Mounted on the arc is a target pointer, consisting of a convex lens and a bull's eye (left).

though the actual position of the bull's eye is far away from the center. Since the virtual target is 'located' at the center of the arc, the position is stable as long as we observe the image of the bull's eye through the lens.

Although this mechanism was developed originally for target positioning during circular collimator-based radiosurgery, we integrated it using in-house software for quantitative analysis of beam displacement. The calibration for determining the center of the beam's eye image was also carried out for the measurement each time prior to treatment of a patient. To indicate actual distances at the isocenter, concentric circles were prepared on the bull's eye of the target indicator so that each circle represented displacement in millimeters. That is, the virtual image of the concentric circles was located at the isocenter, with the diameter of the innermost circle being 1 mm. The distances in the beam's eye image and actual shifts from the isocenter were compared and verified by application of conversion software.

A tungsten ball of 4 mm diameter was used to confirm the agreement between the beam's eye monitor and the irradiation field. The ball was first placed near the isocenter of the linac using wall-mounted laser beams. It was not necessary to position the ball precisely at the true 'isocenter' of the machine. Instead it was positioned at a temporarily defined 'isocenter' that was eventually corrected by the iterative procedure described below. The ball was used only for calibration purposes for the monitor system and not used directly for target positioning.

The tungsten ball fixed at the temporary isocenter was observed through the beam's eye monitor at gantry angles of both 0 and 180°. The position of the ball in both beam's eye images was measured on the computer screen. If both positions were the same, the ball was considered to be at the isocenter, or at least at an isocentric point in the plane of gantry rotation. Alternatively, if the position of the center of the ball was different in both images, then the midpoint was defined as the second temporary isocenter. The third or fourth temporary isocenter was decided by the same procedure, until the position of the ball was stabilized. The position of the ball at the isocenter was finally confirmed with continuous observation of the beam's eye monitor during 360° rotation of the gantry.

With the above procedure, only the position of the ball in the plane of gantry rotation was aligned with the isocenter. Therefore, similar adjustments were carried out using the collimator rotation mechanism of the linac gantry-head. This calibration procedure was completed with real-time monitoring of the beam's eye image displayed on the computer screen, thereby eliminating the need to leave the treatment room to avoid X-ray exposure. This adjustment of the isocenter could be carried out within 5 min. Finally, after defining the 'isocenter', alignment of both the axis of the X-ray beam and the beam's eye monitor was confirmed using X-ray film exposure of the tungsten ball. The 'center' of the beam's eye image was also confirmed from the position of the center of the tungsten ball in the image, with the 'center' being used for subsequent measurements of beam-axis displacement.

2.1. Measurement of beam-axis displacement

During the treatment, before each fixed-beam irradiation, the position of the virtual target was observed and recorded. Five consecutive radiosurgery cases involving a total of 64 irradiation fields were analyzed for this study. The patients' heads were fixed in a Leksell stereotactic frame with screws. After the couch and gantry settings had been established for each field of irradiation, the stereotactic arc was rotated, and

the target indicator was moved along the arc so that the virtual image of the bull's eye could be seen through the lens. The image of the beam's eye monitor was then recorded. For reference, images were also recorded at a couch angle of zero, with a gantry angle of 0, ±90°, and at couch angles of −45, +45, and +90° with a gantry angle of 0. The distances from the 'center' of the beam's eye image to the position of the bull's eye were then measured.

According to our protocol, when the error was greater than 0.7 mm, the position of the patient was corrected with a horizontal movement of the couch. Nevertheless, the data of the displacement that we used for further analysis were those obtained before this correction.

The stereotactic arc with the target indicator was kept on the frame during the treatment but not left in the radiation field with the arc being rotated and usually kept in the most downward position during irradiation. Less than 1 min was required to measure the displacement for each beam.

3. Results

The displacements of the beam-axis from the center of the arc are shown in Fig. 2. The mean displacement (±SD) was 0.41 ± 0.25 (range 0–0.99) mm for all measurements. For 25 measurements, when the couch angle was zero, the mean displacement was 0.16 ± 0.12 (0–0.44) mm (Fig. 2a), whereas for 39 measurements with non-zero couch angles, the displacement was 0.56 ± 0.24 (0.14–0.99) mm. Among non-zero couch angles, for absolute couch angles greater than 40° (33 measurements) and ≤40° (six measurements), the displacements were 0.61 ± 0.24 (0.14–0.85) mm and 0.32 ± 0.09 (0.22–0.50) mm, respectively.

To clarify the contribution of gantry rotation to the displacements, 25 measurements with the couch angle position at 0° were used. The contributions of the displacement attributable to gantry rotation were then examined (Fig. 2b). In this subset of measurements, the displacements were 0.09 ± 0.04 (0–0.14) mm when the gantry head was in upper positions (i.e. from −50 to 50°: 13 measurements), and 0.26 ± 0.11 (0.12–0.44) mm when the gantry head was at lateral positions (at an angle greater than 50° from the top on either side: 12 measurements). The maximum displacement for couch angle 0 was 0.44 mm and found at gantry angle of 114° (clockwise rotation). For six measurements with both couch and gantry angles equal to zero, the displacement was 0.07 ± 0.06 (0–0.14) mm. The displacements were greater than 0.7 mm in 12 of the 64.

4. Discussion

Although our positioning mechanism was developed primarily for target positioning in radiosurgery [6], we employed it to verify the isocentric accuracy of each beam

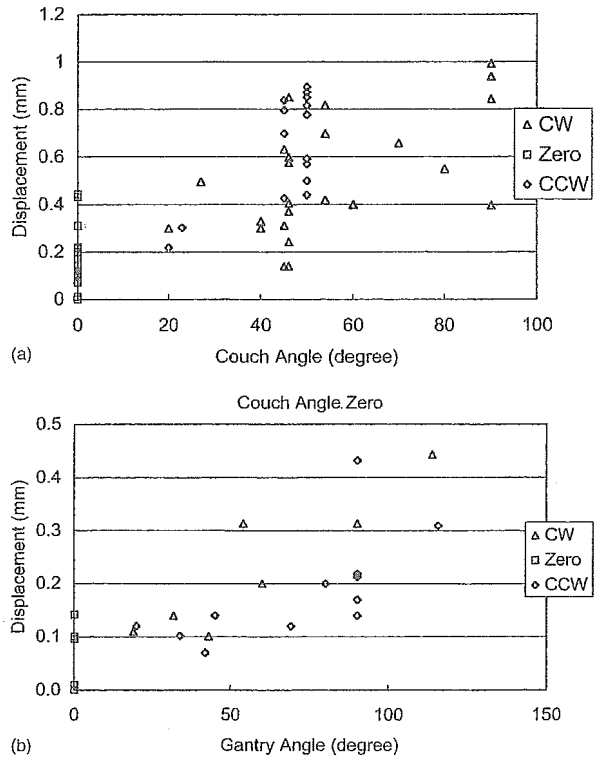


Fig. 2. (a) Couch angle (absolute value) and the displacements of the beam-axis from the planning isocenter. CW, clockwise rotation of the couch; CCW, counter-clockwise rotation; Zero, couch angle of zero. (b) Gantry angle (absolute value) and the displacements of the beam-axis from the planning isocenter for 25 measurements performed at the couch angle of zero. CW, clockwise rotation of the gantry; CCW, counter-clockwise rotation; Zero, gantry angle of zero.

during fixed-beam radiosurgery with an MMLC. The major advantages of using this mechanism for verification are as follows.

1. The verification of geometric accuracy can be obtained even when the patient's head is placed at the isocenter.
2. The verification is available while the gantry and couch are in a rotated position.
3. Correction of the patient's position can be carried out immediately by referring to the real-time images, without the need for X-ray exposures.

In reality, there are many factors that affect beam-axis deviation from the intended target. Even after positioning of the patient's head is completed, some degree of misalignment of the planning isocenter and the beam-axis may occur, as a result of unintended stress to the patient's head or mechanical error of the machine.

Our measurements indicated more than 0.7 mm shift of the planning isocenter from the mechanical isocenter in 12 out of 64 ports, and we corrected the displacement for each fixed-port irradiation. These shifts were larger than values

we obtained in our previous study [6] and also those reported in other phantom studies [3,7]. This discrepancy could be due to the fact that our current measurements were carried out during treatment while using an additional MMLC collimator. The displacements were large when the angle of rotation of the couch was non-zero. This is possibly as a consequence of wobbling and excursion of the couch rotation-axis from the 'true' isocenter, and this deviation is often difficult to correct once the machine has been installed. When arc irradiations are employed for radiosurgery or when port-by-port correction is not available, the horizontal position of the couch should be moved and corrected at each rotational angle to avoid the inaccuracy caused by rotation of the couch. From our data and other investigations, displacement of the beam-axis from the 'isocenter' depends on the gantry rotational angle [3,7]. This displacement can be explained by gravitational bending of the gantry head due to its weight, and in order to minimize this effect the range of gantry rotation should be limited. We recommend aligning the beam-axis to the mechanical isocenter for each port, or at least at each couch rotation, when a high degree of accuracy is required for each beam delivery.

References

[1] Bucciolini M, Russo S, Banci Buonamici F, Pini S, Silli P. Dosimetric characterization of a bi-directional micromultileaf collimator for stereotactic applications. Med Phys 2002;29:1456–63.
[2] Cosgrove VP, Jahn U, Pfaender M, Bauer S, Budach V, Wurm RE. Commissioning of a micro multi-leaf collimator and planning system for stereotactic radiosurgery. Radiother Oncol 1999;50:325–36.
[3] Gibbs FJ, Buechler D, Leavitt DD, Moeller JH. Measurement of mechanical accuracy of isocenter in conventional linear-accelerator-based radiosurgery. Int J Radiat Oncol Biol Phys 1993;25:117–22.
[4] Grebe G, Pfaender M, Roll M, Luedemann L, Wurm RE. Dynamic arc radiosurgery and radiotherapy: commissioning and verification of dose distributions. Int J Radiat Oncol Biol Phys 2001;49:1451–60.
[5] Kubo HD, Pappas CT, Wilder RB. A comparison of arc-based and static mini-multileaf collimator-based radiosurgery treatment plans. Radiother Oncol 1997;45:89–93.
[6] Kunieda E, Kitamura M, Kawaguchi O, et al. New system for linear accelerator radiosurgery with a gantry-mounted video camera. Int J Radiat Oncol Biol Phys 1998;40:739–46.
[7] Lutz W, Winston KR, Maleki N. A system for stereotactic radiosurgery with a linear accelerator. Int J Radiat Oncol Biol Phys 1988;14:373–81.
[8] Schlegel W, Pastyr O, Bortfeld T, et al. Computer systems and mechanical tools for stereotactically guided conformation therapy with linear accelerators. Int J Radiat Oncol Biol Phys 1992;24:781–7.
[9] Shiu AS, Kooy HM, Ewton JR, et al. Comparison of miniature multileaf collimation (MMLC) with circular collimation for stereotactic treatment. Int J Radiat Oncol Biol Phys 1997;37:679–88.

Radiation Injury After Hypofractionated Stereotactic Radiotherapy for Peripheral Small Lung Tumors: Serial Changes on CT

Toshiaki Takeda[1]
Atsuya Takeda[1]
Etsuo Kunieda[1,2]
Akitoshi Ishizaka[3]
Kazuhiko Takemasa[1]
Kyoko Shimada[1]
Seika Yamamoto[1]
Naoyuki Shigematsu[2]
Osamu Kawaguchi[2]
Jun-ichi Fukada[1,2]
Toshio Ohashi[2]
Sachio Kuribayashi[2]
Atsushi Kubo[2]

OBJECTIVE. We studied the serial changes and CT manifestations of pulmonary radiation injury after hypofractionated stereotactic radiation therapy for peripheral small lung tumors.

SUBJECTS AND METHODS. Hypofractionated stereotactic radiation therapy was applied to 20 patients with proven primary ($n = 11$) or metastatic ($n = 9$) lung cancer, for a total of 22 lesions of 3 cm or less in diameter located within 3 cm from the parietal pleural surface. Follow-up CT was scheduled at 1 and 3 months, and every 3 months thereafter.

RESULTS. Ground-glass opacities were observed around four (18%) of 22 lesions at 3–6 months. The opacities nearly corresponded to the planned target volume, but half of them were unevenly distributed. Ground-glass opacities gradually disappeared or evolved into dense consolidation while shrinking. Dense consolidations developed in 16 (73%) of 22 lesions, including seven in the center of the planned target volume and nine in the periphery of the planned target volume. Dense consolidations moved in six of these 16 lesions and gradually shrank, becoming fixed as solid or linear opacities approximately 12 months later.

CONCLUSION. The pulmonary opacities observed after hypofractionated stereotactic radiation therapy for peripheral small lung tumors may not precisely correspond to the planned target volume (unlike those with conventional radiation therapy) and may change in shape and location dynamically during the first year. Knowledge of these findings is necessary to avoid misunderstandings concerning tumor regrowth or new tumors.

Currently, surgery is the treatment of choice in the early stages of lung cancer. Although conventional radiation therapy may be selected as a less invasive intervention in elderly patients and in those with inoperable disease, the rate of local control of malignancy after radiation therapy is approximately 30%, which is lower than for surgical resection [1]. Stereotactic irradiation can deliver high radiation doses to localized lesions with great accuracy, allowing a strong antitumoral effect while lessening radiation injury to normal tissues [2]; it has been applied to the treatment of small intracranial tumors with excellent results [2]. More recently, hypofractionated stereotactic radiotherapy has been applied to the treatment of extracranial malignant tumors, with preliminary studies reporting greater than 90% control rates for small localized lung tumors [3–5].

In this study, we applied hypofractionated stereotactic radiotherapy to the treatment of small lung tumors and observed the various radiologic patterns of change after irradiation. As indicated by previous reports [6, 7], radiation injuries caused by conventional coplanar radiotherapy show distinct linear margins on CT that correspond to the margins of the irradiation field. However, because hypofractionated stereotactic radiotherapy is delivered in a 3D spherical volume with a steep gradient between the periphery of the planned target volume and normal adjacent tissue, the shape of the radiation injury should be considered three-dimensionally. Hypofractionated high-dose irradiation, with highly concentrated narrow beams that target small volumes, is associated with markedly different dose distributions and biologic effects on tissues from those described for coplanar conventional radiotherapy. The aim of this study was to describe the CT characteristics of radiation injury after hypofractionated stereotactic radiotherapy for small lung malignancies.

Subjects and Methods

The patient population consisted of 17 men and three women (age range, 56–89 years; median, 72.6

Received June 16, 2003; accepted after revision November 10, 2003.

[1]Department of Radiology, Tokyo Metropolitan Hiro-o General Hospital, 2-34-10 Ebisu, Shibuya-ku, Tokyo 150-0013, Japan. Address correspondence to T. Takeda (t-takeda@hiroo-hospital.metro.tokyo.jp).

[2]Department of Radiology, School of Medicine, Keio University, 35 Shinanomachi, Shinkuku-ku, Tokyo 160-8582, Japan.

[3]Department of Medicine, School of Medicine, Keio University, Tokyo 160-8582, Japan.

AJR 2004;182:1123–1128

0361–803X/04/1825–1123

years) who were treated with hypofractionated stereotactic radiotherapy at our institutions between January 1998 and November 2002. For most patients, surgery was not indicated because of patient age, the presence of multiple lesions, or poor pulmonary function. Five patients preferred hypofractionated stereotactic radiotherapy treatment even though surgery was possible. The study protocol was approved by the institutional review boards of the institutions, and written informed consent was obtained from each participant before hypofractionated stereotactic radiotherapy was performed.

Primary lung cancer was pathologically proven in 11 patients (11 lesions), and metastases from other primary cancers were diagnosed clinically in nine patients (11 lesions). Hypofractionated stereotactic radiotherapy was generally considered if the tumor was 3 cm or smaller in diameter, if it was 3 cm or less from the parietal pleural surface, if craniocaudal breathing-associated motion of the lesion was 1 cm or less, and if three or fewer lesions were present at the start of treatment. Because the risk of atelectasis and reduction of pulmonary function caused by the collapse of large bronchi was unknown, potential lesions for treatment were limited to peripheral lesions 3 cm or less from the parietal pleural surface so that the planned target volume would not contain lobar bronchi. Tumor pathology and mean tumor volumes are listed in Table 1.

Pretreatment Evaluation and Radiation Treatment

The planned target volume was determined using CT (Xvision, Toshiba) performed on patients who were breathing at rest. Serial 2-mm-thick scans were obtained in 2-mm increments at 4–8 sec per slice. Longer scanning periods were used to define the tumor trajectory associated with breathing. The planned target volume consisted of the imaged volume, defined as the gross tumor volume plus an internal margin, plus a 5- to 10-mm setup margin.

Tumor volumes (V) were calculated according to the following formula:

$$V = 4/3\,\pi \times R_1 \times R_2 \times R_3,$$

where R_1 (half the maximum diameter), R_2 (half the diameter perpendicular to R_1), and R_3 (half the maximum diameter in the craniocaudal direction) were obtained with calipers on CT. When the tumor margin was ill defined, the outermost circumference was used. The diameter in the craniocaudal direction was defined as the product of the thickness and the number of slices from the top to the bottom of the lesion. Estimated tumor volumes ranged from 0.5 to 45.5 cm^3 (mean, 9.5 cm^3).

Treatments were planned using a radiation treatment planning system (FOCUS version 2.7.0, Computerized Medical Systems). Volumes to be treated were set so that the planned target volume received an 80% isodose of the maximum dose, with 80% isodose defined as the therapeutic dose (Figs. 1A, 2A, and 3A). The shape of the field was adjusted dynamically according to the tumor shape using a multileaf collimator.

The irradiation dose generally consisted of 50 Gy in five fractions administered over 5–7 days. Seventeen lesions in 15 patients were treated using this dose regimen. When a tumor was adjacent to critical organs (e.g., spinal cord or esophagus), the fractionated dose was reduced to 5–7 Gy and the total dose was limited to 40–50 Gy.

Radiologic Follow-Up

Patients were interviewed monthly to determine the presence or absence of symptoms and for chest roentgenographic examination.

TABLE 1 CT Manifestations of Radiation Pneumonitis

Lesion Characteristics			Ground-Glass Opacity		Dense Consolidation					Bronchiectasis
No.	Pathology	Volume (cm^3)[a]	Time of Appearance (mo)	Distribution	Time of Appearance (mo)[c]	Location[b]	Shrinkage (mo)[c]	Movement	Fixation (mo)[c]	Time of Appearance (mo)
1	Metastasis	0.5	—		4	Center	8	Hilum	11	8
2	Metastasis	4.7	—		8	Center	11	Pleura	—	4
3	Metastasis	25.6	—		3	Periphery	9	Hilum	12	6
4	Metastasis	6.3	—		6	Center	9	Hilum	12	6
5	Squamous cell carcinoma	15.1	—		5	Center	—	—	—	—
6	Adenocarcinoma	—	—		—		—	—	—	—
7	Metastasis	1.1	6	Even	—		—	—	—	—
8	Squamous cell carcinoma	12.7	4–6	Even	6	Center	9	Hilum	12	6
9	Metastasis	3.6	4–6	Uneven	6	Center	9	—	—	6
10	Adenocarcinoma	10.3	—		3	Periphery	—	Hilum	—	6
11	Squamous cell carcinoma	11.2	—		3	Periphery	—	—	—	3
12	Adenocarcinoma	26.6	—		—		—	—	—	—
13	Metastasis	3.1	—		5	Periphery	—	—	9	—
14	Metastasis	8.2	—		4	Center	—	—	—	4
15	Metastasis	0.9	—		3	Periphery	6	—	6	5
16	Metastasis	0.5	—		—		—	—	—	—
17	Squamous cell carcinoma	—	—		—		—	—	—	—
18	Adenocarcinoma	2.8	—		6	Periphery	—	—	—	—
19	Adenocarcinoma	7.9	—		3	Periphery	—	—	—	—
20	Adenocarcinoma	0.7	—		3	Periphery	—	—	—	—
21	Metastasis	2.0	3	Uneven	4	Periphery	—	—	—	—
22	Squamous cell carcinoma	45.5	—		—		—	—	—	—

Note.—Dash (—) indicates changes were not observed.

[a]Estimated. Volumes of lesions 6 and 17 were not calculated because they were postoperative residual tumors already enclosed in scars.

[b]Center of planned target volume or periphery of planned target volume.

[c]First observed after therapy.

Lesion characteristics were periodically examined on CT (Xvigor or Xvision, Toshiba) even in the absence of clinical symptoms at follow-up visits approximately 1 and 3 months after treatment, and in principle every 3 months thereafter. The interval of CT varied slightly depending on each patient's clinical status. If dubious opacities were seen on periodic radiography, additional CT was performed between the scheduled examinations. Single-slice helical CT of the entire lung without contrast material was performed using scanning parameters of slice thickness, 10 mm; pitch, 1; tube voltage, 120 kV; tube current, 200 mA; and 0.75 sec per slice. Images focused on tumors and associated pneumonitis were obtained by helical scanning with slice thickness, 2 mm; pitch, 1; tube voltage, 120 kV; tube current, 250 mA; and 0.75 sec per slice. High-resolution CT was reconstructed using a high-spatial-resolution algorithm. Of 100 total CT series, high-resolution CT scans were obtained concurrently in 61 studies. An average of 4.5 CT series per lesion were performed, including an average of 2.8 high-resolution CT series. The mean follow-up period after high-resolution CT was 17.6 months (range, 4.5–51.6 months). No patients received chemotherapy.

Interpretation of CT Findings

The time of appearance of ground-glass opacities or dense consolidations (with respect to completion of radiation therapy), location of appearance (center or periphery of the planned target volume), serial changes (changes in density, size, and location), and time of appearance of bronchiectasis were systematically recorded. CT images were independently interpreted by four diagnostic radiologists who were familiar with the clinical diagnosis and the development of lung tumors. CT characteristics were determined on the basis of a consensus among at least three of the four examiners.

Results

Demographic characteristics of the lesions and characteristics of the radiation injuries are detailed in Table 1.

After hypofractionated stereotactic radiotherapy, ground-glass opacities and dense consolidations were observed as initial lung CT findings at 3–4 months. Thereafter, the ground-glass opacities either disappeared or evolved into dense consolidations. Dense consolidations that were seen initially gradually shrank to become solid or linear opacities con-

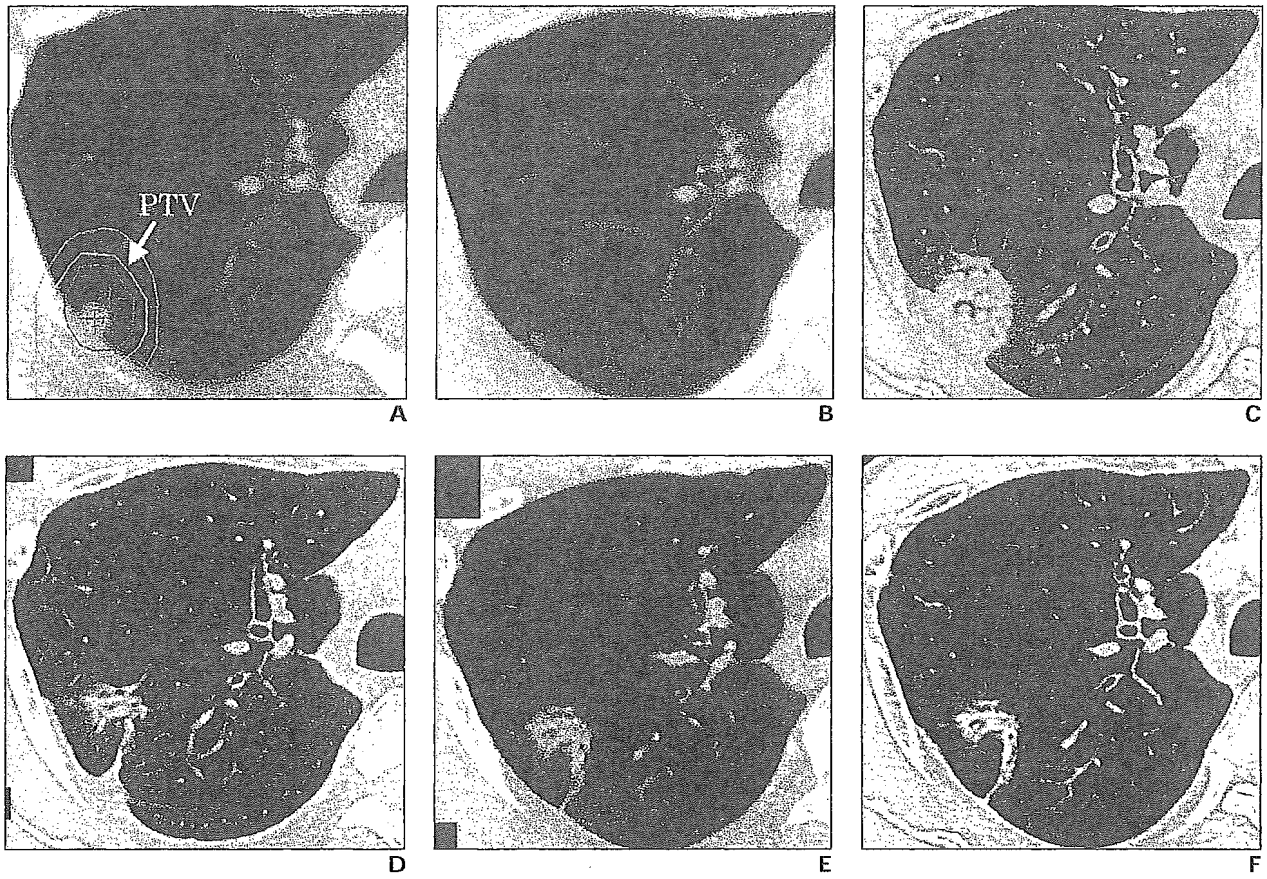


Fig. 1.—59-year-old man with lung metastasis from rectal carcinoma. Typical characteristics of radiation pneumonitis and fibrosis after hypofractionated stereotactic radiotherapy are seen on serial lung CT scans after irradiation.
A, Axial unenhanced CT scan obtained before treatment shows tumor in right upper lobe. PTV = planned target volume.
B, CT scan at 1 month after irradiation shows decrease in tumor size.
C, CT scan at 4 months reveals appearance of dense consolidation and its surrounding ground-glass opacity.
D, CT scan at 8 months shows shrinkage of dense consolidation and its movement toward hilum.
E, CT scan at 11 months shows presence of dilated bronchi within opacity.
F, CT scan at 22 months shows fixation of opacity. Subsequent CT characteristics remained unchanged.

sistent with lesion fixation (Figs. 1–3). No ground-glass opacities or dense consolidations were observed at sites remote from the planned target volume.

Ground-glass opacities appeared on CT scans in four (18%) of 22 lesions at 3–6 months after completion of radiation therapy. They all corresponded closely to the planned target volume. In two instances, the ground-glass opacities were evenly distributed in the planned target volume (Figs. 1C and 3C), and in the other two instances the opacities remained unevenly distributed at 4 months, thereafter evolving into dense consolidations consistent with the planned target volume.

Dense consolidations appeared in 16 (73%) of 22 lesions on CT scans obtained at 3- to 8-months' follow-up. Of these, seven exhibited dense peritumoral consolidations corresponding to the planned target volume (Figs. 1C and 2D), and the remaining nine showed consolidation limited to the margin of the planned target volume, a short distance from the isocenter (Figs. 3C and 3D). Although dense consolidations shrank in seven (44%) of these 16 lesions, the consolidations did not disappear completely but persisted as solid or linear opacities (Figs. 1F, 2E, and 3F). This shrinkage occurred within 6–11 months after radiotherapy. In six of 10 lesions followed up for at least 12 months, the pulmonary opacities became fixed on CT scans, consistent with the development of fibrosis. Movement of the opacity was observed in six (37.5%) of the 16 densely consolidated lesions. This movement was detected simultaneously with shrinkage in five of the six lesions, with movement toward the hilum in five (Figs. 1 and 2A–2D), and with movement away from the hilum in one.

Bronchiectasis was present in 10 (45.5%) of 22 lesions and developed almost contemporaneously with dense consolidations that contained dilated or thickened bronchi. Bronchial thickening and lumen irregularities caused by traction (i.e., traction bronchiectasis) became apparent along with movement of the opacities (Figs. 2D and 3E).

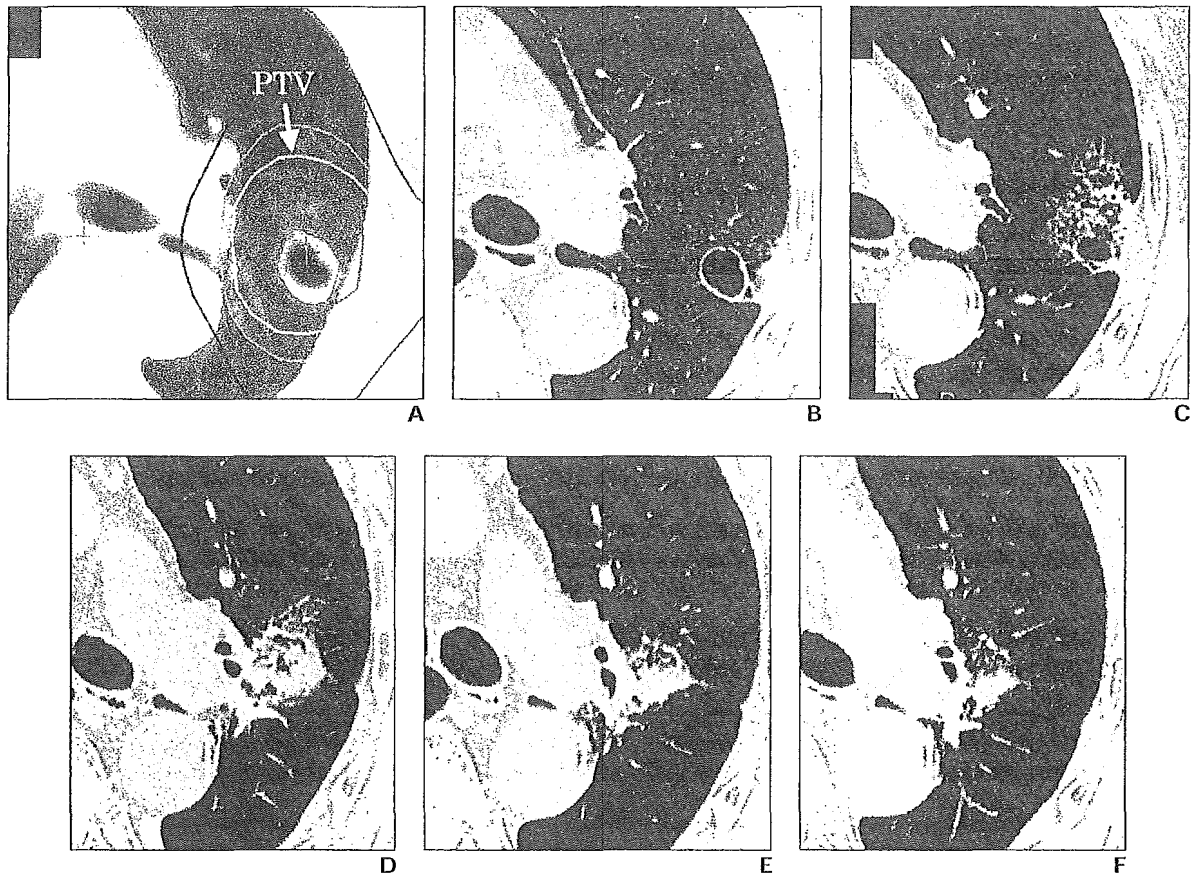


Fig. 2.—85-year-old man with squamous cell cancer.
A, Axial unenhanced CT scan obtained before treatment shows cavitated tumor in left upper lobe. PTV = planned target volume.
B, CT scan at 1 month after irradiation shows almost no change.
C, CT scan at 4 months shows presence of ground-glass opacity distributed in planned target volume.
D, CT scan at 6 months shows conversion of ground-glass opacity to dense consolidation and shift toward hilum. Tumor has almost disappeared.
E, CT scan at 10 months shows shrinkage of opacity and further movement toward hilum.
F, CT scan at 12 months shows further decrease in size. Subsequently, opacity remained unchanged.

Discussion

Hypofractionated stereotactic radiotherapy, a new treatment method for small lung malignancies, differs considerably from conventional coplanar radiation therapy because it consists of delivering a single high dose of radiation with hypofractionation to small irradiation fields. Although hypofractionated stereotactic radiotherapy is expected to be highly effective in the control of localized lesions, its acceptance and indications will expand only if its use is not complicated by high rates of adverse reactions. Therefore, before considering increased radiation doses in the hope of achieving improved local therapeutic effects, a thorough clinical and radiologic evaluation of pulmonary parenchymal injuries caused by irradiation is needed to verify that hypofractionated stereotactic radiotherapy is a safe and effective treatment for small lung malignancies.

Classic radiation pneumonitis induced by conventional radiation therapy is characterized by a linear margin demarcating the treatment port and is uncommon with exposures of less than 30 Gy but inevitable for exposures greater than 40 Gy [8]. However, the reported incidence of clinical manifestations associated with radiation pneumonitis is 7–8%, and the symptoms are usually mild, despite imaging findings that may appear more prominent [9, 10]. In our study, only three patients reported a mild cough associated with radiation injury, and all were successfully treated with simple therapy. In contrast, sporadic radiation pneumonitis is an immune-mediated process resulting in lymphocytic alveolitis that leads to a response remote from the localized pulmonary irradiation and that is usually associated with severe symptoms and high mortality in the absence of a "threshold" dose [11]. Classic radiation pneumonitis can be classified as either early (1–3 months after irradiation) or late (3–6 months after irradiation), depending on the time of appearance of the pulmonary reaction to the radiation. In our study, hypofractionated stereotactic radiotherapy-induced lung injuries did not systematically develop in the center of treated volumes, but often began at the periphery. However, injuries eventually conformed to and remained in the planned target

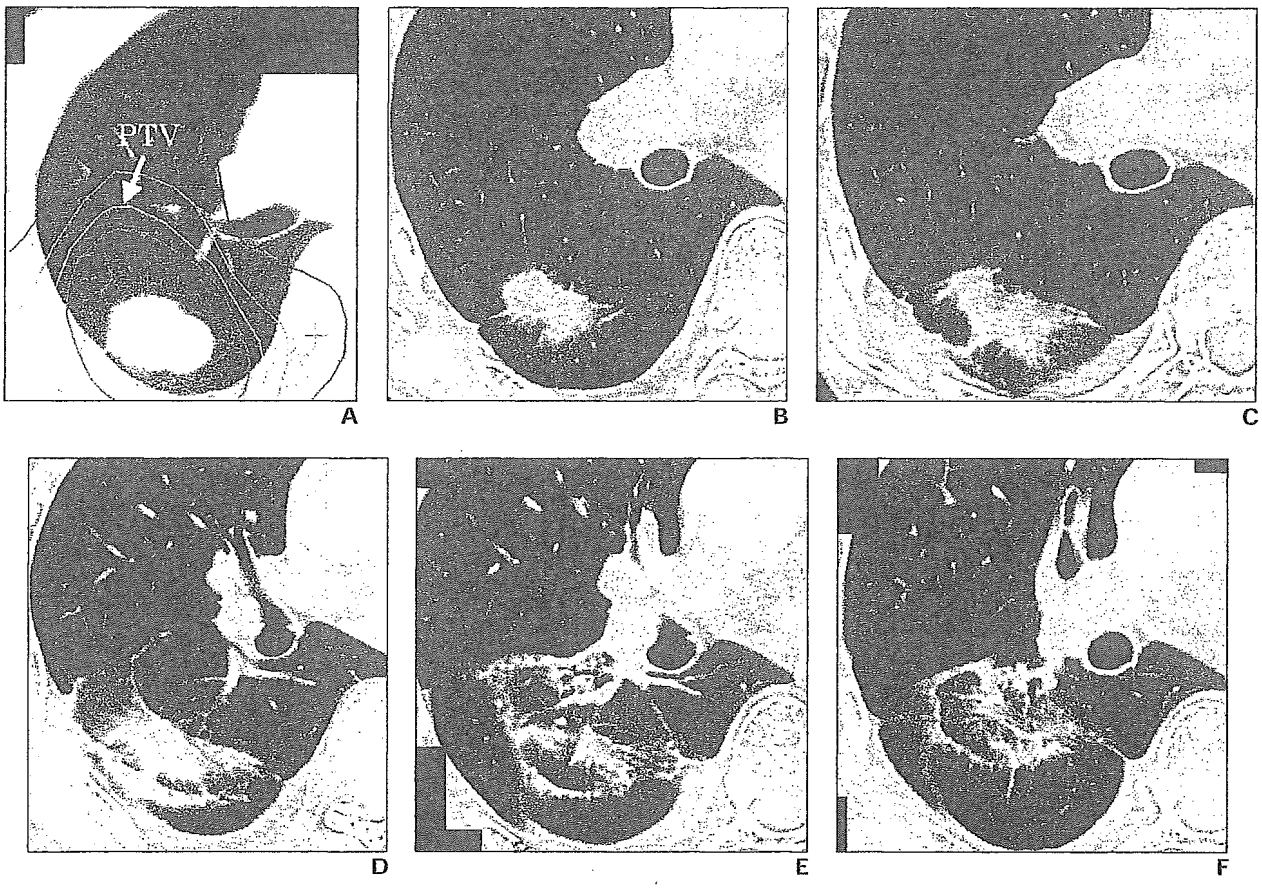


Fig. 3.—70-year-old man with lung metastasis of oropharyngeal carcinoma.
A, Axial unenhanced CT scan obtained before treatment shows metastatic tumor in right lower lobe. PTV = planned target volume.
B, CT scan at 1 month after irradiation shows decrease in tumor size.
C, CT scan at 3 months reveals appearance of dense consolidation in subpleural space of planned target volume.
D, CT scan at 6 months shows increase in size of dense consolidation and onset of movement. Center of tumor is now located more cranially.
E, CT scan at 9 months shows decrease in tumor size, thinning of dense consolidation, and movement of lesion toward hilum.
F, CT scan at 12 months shows presence of linear opacity surrounding tumor and fixation of lesion.

volume. These findings suggested that a threshold dose was required to develop pneumonitis, and that hypofractionated stereotactic radiotherapy-induced lung injuries were classifiable as classic radiation pneumonitis.

Evolution from ground-glass opacity to dense consolidation to fibrosis was observed on CT in a relatively small subset of our patients. In contrast, in a study of 3D conformal radiation therapy, Koenig et al. [12] observed the development of ground-glass opacity around tumors on CT scans at 3 months after radiation therapy in 19 of 19 patients treated with total doses between 69.6 and 90.3 Gy in 33–58 fractions. Three-dimensional conformal radiation therapy used in that study differs considerably from the hypofractionated stereotactic radiotherapy used in our study, particularly from the standpoint of the single dose. The incidence and severity of radiation pneumonitis can depend on the extent of irradiation, the total dose, and the number of fractions, and may also be influenced by concurrent chemotherapy [9]. Thus, the differences between the two studies with regard to CT patterns are probably attributable to researchers for the previous study using a higher radiation dose delivered as a single fraction. Therefore, we hypothesize that on CT, early or mild radiation injuries appear as ground-glass opacities, whereas severe radiation injuries appear as dense consolidations.

Movement of dense consolidations often occurred. Movement toward the hilum was seen in all but one case. Because shrinkage of the opacity and traction bronchiectasis were usually seen concurrently, the mechanism of these phenomena seems attributable to fibrosis. Therefore, we think that the apparent movement of the opacity is largely attributable to the deformity of the lung caused by fibrosis. Takahashi et al. [13] observed that the ground-glass opacities corresponded to thickened interlobular walls because of fibroblastic cells and collagen fibers in a pig model of radiation pneumonitis.

Takahashi et al. [13] also found that the ground-glass opacities were not evenly distributed but at pathology were predominant near the interstitium. In a dog model, the same radiation dose caused a more severe reaction when delivered to the periphery of the right lower lobe than to the right hilum [14]. These findings indicate that variable local sensitivity to radiation, depending on the amount of interstitium, causes nonuniform distribution of ground-glass opacities and dense consolidations.

We acknowledge several limitations in our study. Although we differentiated radiation injury patterns as ground-glass opacity, dense consolidation, and fibrosis, we had no pathologic proof. As with other studies examining radiation pneumonitis, we found it difficult to obtain specimens from otherwise asymptomatic patients. Another limitation was the relatively small number of patients in our study. Although it is fortunate that only a few patients complained of mild cough and recovered without resorting to steroids or hospital admission, the number of patients was too small to allow analysis of the relationship among symptomatic pneumonitis, patient background factors, and radiation treatment.

In assessing radiologic findings, residual tumor regrowth, lymphatic spread, and infection should be differentiated from radiation pneumonitis. Local recurrences especially are sometimes difficult to diagnose in the early phase because they are often asymptomatic, as is radiation pneumonitis. Four cases recurred after hypofractionated stereotactic radiotherapy, of which two had no radiation pneumonitis–induced opacities and one had minimal ground-glass opacity. In these three cases, the initial radiation effect was minimal or could not be evaluated and tumors gradually enlarged without a dramatic change in shape. Therefore, regrowth of the tumors was readily diagnosed. In the last case, the tumor had almost disappeared shortly after hypofractionated stereotactic radiotherapy. Dense consolidation surrounding the initial tumor appeared 6 months later, followed by overtly solid tumor on its periphery. Needle biopsy confirmed the presence of adenocarcinoma. We suppose that this may be a typical case of recurrence after hypofractionated stereotactic radiotherapy. However, we have experienced too few cases to draw a clear-cut distinction between recurrence and radiation pneumonitis. It is important to be especially careful during the early assessment of radiation pneumonitis on CT because the CT pattern evolves serially, and pulmonary opacity can move. We should be aware that the CT appearance reflects only one phase of the spectrum.

In conclusion, a size decrease in small lung tumors was generally observable on CT scans 1–3 months after completion of irradiation by hypofractionated stereotactic radiotherapy. This decrease in tumor size was accompanied by reduced areas of dense consolidation and surrounding ground-glass opacity at 3–6 months. Although ground-glass opacities generally resolved, the dense consolidations assumed typical CT patterns, including movement toward the hilum, shrinkage, and fixation at approximately 1 year after treatment. The incidence of ground-glass opacities was relatively low, and neither ground-glass opacities nor dense consolidations coincided exactly with dose distribution, occasionally developing away from the isocenter or remaining heterogeneous. Dynamic changes in ground-glass opacities and dense consolidations were observed over time. Our results indicate that assessment of lesions should be done with knowledge of these changes of radiation pneumonitis on CT during the first year after treatment, before fixation, to avoid misunderstandings about CT findings resembling tumor regrowth or the appearance of new lesions.

References

1. Sibley GS. Radiotherapy for patients with medically inoperable stage I nonsmall cell lung carcinoma: smaller volumes and higher doses—a review. *Cancer* 1998;82:433–438
2. Wasserman TH, Rich KM, Drzymala RE, Simpson JR. Stereotactic irradiation. In: Perez CA, Brady LW, eds. *Principles and practice of radiation oncology*, 3rd ed. Philadelphia, PA: Lippincott-Raven, 1998:387–404
3. Fukumoto S, Shirato H, Shimizu S, et al. Small-volume image-guided radiotherapy using hypofractionated, coplanar, and noncoplanar multiple fields for patients with inoperable stage I nonsmall cell lung carcinomas. *Cancer* 2002;95:1546–1553
4. Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. *Cancer* 1998;82:1062–1070.
5. Nagata Y, Negoro Y, Aoki T, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041–1046
6. Libshitz HI, Shuman LS. Radiation-induced pulmonary change: CT findings. *J Comput Assist Tomogr* 1984;8:15–19
7. Forrest LJ, Mahler PA, Vail DM, Mackie TR, Ladd WM, Kinsella TJ. Computed tomographic evaluation of radiation pneumonitis in a canine model. *Radiat Oncol Investig* 1998;6:128–134
8. Libshitz HI, Southard ME. Complications of radiation therapy: the thorax. *Semin Roentgenol* 1974;9:41–49
9. Movsas B, Raffin TA, Epstein AH, Link CJ Jr. Pulmonary radiation injury. *Chest* 1997;111:1061–1076
10. Roach M III, Gandara DR, Yuo HS, et al. Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. *J Clin Oncol* 1995;13:2606–2612
11. Morgan GW, Breit SN. Radiation and the lung: a reevaluation of the mechanisms mediating pulmonary injury. *Int J Radiat Oncol Biol Phys* 1995;31:361–369
12. Koenig TR, Munden RF, Erasmus JJ, et al. Radiation injury of the lung after three-dimensional conformal radiation therapy. *AJR* 2002;178:1383–1388
13. Takahashi M, Balazs G, Pipman Y, et al. Radiation-induced lung injury using a pig model: evaluation by high-resolution computed tomography. *Invest Radiol* 1995;30:79–86
14. Stenton CG, Boland J. Experimental radiation pneumonitis: radiographic and pathologic correlation. *Cancer* 1967;20:2170–2183

特集

化学放射線療法の現況ならびに対象症例の選択
(第41回日本癌治療学会総会より)

非小細胞肺癌の化学放射線療法

唐澤克之[*1]　家城隆次[*2]

Chemoradiotherapy for Locally-Advanced Non-Small Cell Lung Cancer: Karasawa K[*1] and Ieki R[*2] ([*1]Dept of Radiology, [*2]Dept of Respiratory Medicine, Tokyo Metropolitan Komagome Hospital)

The incidence and mortality of non-small cell lung cancer (NSCLC) have been increasing very rapidly in Japan. Certain measures have to be taken to solve this serious problem. The standard treatment of locally-advanced NSCLC has become the concurrent use of Cisplatinum (CDDP) based chemotherapy and radiotherapy. The results have gradually been improving but still unsatisfactory ones (5-year survival rates of about 10–20%). To raise the therapeutic ratio, we have been giving CDDP intraarterially through bronchial artery instead of intravenous injection combined with radiotherapy. The 5-year local control rate and survival rate of 42 so-treated cases between 1996 and 2001 were 57% and 40%, respectively, with no severe esophageal toxicity. The history of randomized controlled trials mainly conducted by Radiation Therapy Oncology Group was discussed and our methods and preliminary results were introduced.

Key words: Non-small cell lung cancer, Chemoradiotherapy, Bronchial artery, Arterial infusion chemotherapy, RTOG
Jpn J Cancer Clin **50**(2): 125～131, 2004

はじめに

わが国における肺癌の罹患率および死亡率は近年も年々上昇傾向にあり，禁煙等も含めてその死亡数の減少が課題となっている．肺癌のうちの8割を占めるのが非小細胞肺癌であり，また非小細胞癌のうちの大多数がⅢ，Ⅳ期であり，これらの治療成績の向上が肺癌の死亡率の低下に大きく貢献すると考えられている．

非小細胞肺癌の病期別の治療成績（5年生存率）はおのおのⅠA期が61%，ⅠB期が38%，ⅡA期が34%，ⅡB期が24%，ⅢA期が13%，ⅢB期が5%，Ⅳ期が1%（いずれも臨床病期）と，ほとんどの病期で満足のいかない治療成績である[1]．

その原因としては，局所再発および遠隔転移のいずれも高頻度に出現することが主たるものと考えられている．特に局所進行期（Ⅲ期）においては手術よりも化学放射線療法のウエイトが多くを占めるようになり，両モダリティをいかにうまく組み合わせて最善の効果を出すことが探究され，少しずつではあるが，治療成績は改善する傾向にある．しかし，依然として満足する結果ではないのは，その強度が不足しているためと考えられる．これまでの研究の結果，放射線治療の線量は60 Gy以上が望ましく，また単独では過分割照射が望ましいということがわかった．また放射線治療単独よりも，化学療法との併用のほうが，よりよい成績が挙げられることがわかり，さらに併用も同時併用したほうがより良い成績を挙げられることがわかってきた．この段階でもまだ大半の症例は治癒したとはいえず，さらなる治療効果の改善のためには，何かさらなる工夫が必要である．

本稿では，アメリカのRadiation Therapy Oncology Group（RTOG）における非小細胞肺癌の

*1 東京都立駒込病院放射線科
*2 東京都立駒込病院呼吸器内科

臨床試験の変遷および現時点での問題点と，われわれが行っている治療法（CDDP動注＋放射線治療）[2]の紹介を行う．

1. RTOGの肺癌に関する臨床試験

RTOGはアメリカおよびカナダの約250施設からなり，放射線治療を主体とした臨床試験を行う多施設研究グループであり，これまで約30年の歴史を持ち，数多くの臨床試験を行っている[3]．

RTOGの肺癌のプロトコールはRTOG73-01が最初のものであった．その臨床試験は総線量と分割方法を決定するもので，Ⅲ期の非燕麦細胞癌，Karnofsky Performance Status（KPS）が40以上，年齢80歳以下を対象として，4,000 cGyのスプリットコース（アーム1），4,000 cGyの連続照射（アーム2），5,000 cGyの連続照射（アーム3），6,000 cGyの連続照射（アーム4）という4つのレジメンで生存期間の比較を行った．その結果は（生存期間の中央値で比較すると，アーム1が36.8週，アーム2が45.5週，アーム3が41.0週，アーム4が47.2週であった）6,000 cGy/6 wのアームがわずかにすぐれている結果（生存率および局所制御率において）が示されたが，5年生存率は5%であった[4]．

続いて行われたRTOG83-01のプロトコールでは過分割照射の至適線量を求めるランダム化比較試験（RCT）を行った．手術不能のⅡ期以上で遠隔転移のない非小細胞癌，KPS70以上，年齢19歳以上，体重減少6%以内の症例で，60 Gy/50 fr（アーム1），64.8 Gy/54 fr（アーム2），69.6 Gy/58 fr（アーム3），74.4 Gy/62 fr（アーム4），79.2 Gy/66 fr（アーム5）の5つのアームで生存期間を比較した．その結果として生存期間の中央値が，アーム1が10.0カ月，アーム2が7.8カ月，アーム3が13.0カ月，アーム4が12.0カ月，アーム5が10.7カ月であった．アーム1からアーム3までは線量の増加により生存期間の延長がみられたが，アーム4とアーム5は反対に線量の増加により，かえって生存期間が短縮したというものであった．よって69.6 Gy/58 fr以上の線量を投与しても成績は向上しないことがわかった．その原因は主に有害事象の増加にあるとされた．また全身状態が良好な患者群が良好な成績をあげることもわかった[5]．

引き続いて行われたRTOG88-08では初めて抗癌剤との併用が行われた．すなわち，この試験は，手術不能のⅡ期，Ⅲ期の非小細胞癌，KPS70以上，年齢19歳以上，体重減少5%以内の症例で，60 Gy/30 frの標準アーム（アーム1）に対し，シスプラチン（CDDP）とビンブラスチンを誘導化学療法として加えたのちに，60 Gy/30 frの放射線治療を行うアーム（アーム2）と，RTOG83-01で最も良い治療成績をあげた69.6 Gy/58 frのアーム（アーム3）を比較する第Ⅲ相試験であった．その結果として生存期間の中央値は，アーム1が11.4カ月，アーム2が13.8カ月，アーム3が11.4カ月であった．化学療法を併用したアームが最もよい治療成績（$p=0.03$）をあげた．そのため，以後の治療には抗癌剤の併用が望ましい治療法となった[6]．

引き続いて行われたRTOG94-10は放射線治療を化学療法と同時に（concurrent）行うか，化学療法に引き続いて（sequential）行うかの優劣を比較するRCTであった．すなわち，手術不能のⅡ期以上で遠隔転移のない非小細胞癌，KPS70以上，年齢19歳以上，体重減少5%以内の症例で，2コースのCDDPとビンブラスチンによる化学療法に60 Gy/6週の放射線治療を第50日から（sequential）併用するアーム（アーム1）と第1日から（concurrent）併用するアーム（アーム2），およびCDDPとVP-16による化学療法と69.6 Gy/58 frの過分割照射を第1日から（concurrent-BID）併用するアーム（アーム3）とを比較するものであった．その結果として生存期間の中央値はアーム1が14.6カ月，アーム2が17.0カ月，アーム3が16.0カ月であり，通常分割法（1日一回照射法）で同時に化学療法と併用するアーム（アーム2）の治療成績が優れていた．アーム1においては抗腫瘍効果が十分でなく，アーム3では有害事象が目立っているということが治療成績が劣っている原因と考えられた．有害事象としては，食道炎が治療を制限する有害事象であった[7]．

表1　主なランダム化比較試験

報告者	N	化学療法	RT (Gy)	MST (mo)		2-y 2生率(%)		5-y 5生率(%)		P
				RT	Ch/RT	RT	Ch/RT	RT	Ch/RT	
Schaake-Koning, et al	210	P 連日	55	12	12	13	26	*2*	*10*	0.009
Trovo, et al	146	P 連日	45	10	10	14	14	—	—	NS
Jeremic, et al	135	CbE 連日	69.6 HF	14	22	26	43	*9*	*23*	0.02
Schaake-Koning, et al	206	P 毎週	55	12	13	13	19	*2*	*10*	NS
Jeremic, et al	113	CbE 毎週	64.8HF	8	18	25	35	5	21	0.003
Jeremic, et al	117	CbE 隔週	64.8HF	8	13	25	27	5	16	NS
Blanke, et al	215	P 3週毎	60–65	10	11	13	18	2	5	NS
Average				11	14	18	26	4	14	

イタリック体は4年　　P：CDDP　Cb：CBDCA　E：Vp-16　HF：過分割照射
文献9より改変

さらに同臨床試験の70歳以上の高齢者での成績では，上記の傾向がさらにみられ，生存期間の中央値はアーム1が10.8カ月，アーム2が22.4カ月，アーム3が16.4カ月と，アーム2の優位性がさらに際立っていた．また3度以上の食道の有害事象は，アーム1が0%，アーム2が33%，アーム3では60%と，局所効果を高めるべく施行された過分割照射法はかえって有害事象のために，治療成績の向上には結びつかなかった[8]．

上記のような経緯で現在の手術不能非小細胞肺癌で，全身状態が良好な場合の標準治療は化学放射線療法となってきている．併用時期については同時併用のメリットを示す報告が多いが，比較試験ではいずれも同時併用群で食道炎，骨髄抑制などの有害事象が多く，同時併用を一般的治療法として評価されているとはいえない．そして，今までに行われているその他の数多くの臨床試験から，現在の標準はCDDPをキードラッグとした多剤併用化学放射線療法とされている．

表1はCDDPを使用した主な同時化学放射線療法のRCTの治療成績である[9]．生存期間の中央値は10～22カ月，平均14カ月，2年生存率は14～43%，平均26%，5年生存率は5～23%，平均14%である．いずれも放射線治療単独よりも有意に予後を改善している．問題はこれだけ投与量および投与方法，投与のタイミングを工夫しても，大多数の症例は治癒して長期生存していない点である．放射線の投与方法，投与量はもうすでに研究が進んでおり，これ以上の線量投与は有害事象の発生確率を上げるほうに働くと考えられている．また薬剤については，これからCDDPと新規抗癌剤との組み合わせ，またCDDP以外の薬剤のキードラッグとしての使用，さらに分子標的治療薬との併用などが控えているが，どれもただちにエポックメーキングな治療成績はあげられる可能性は高くないと考えられている．

さらに問題点としては，特にわが国においては，その超高齢化現象によって，高齢者肺癌の実数および割合が爆発的に増加するであろうという予測があることである[10]．すなわち，そのような症例群には，標準的な化学放射線療法は有害事象のため用い難い可能性が高い．

2. CDDPの気管支動脈動注の試み

そのような背景のもと，われわれは1996年から放射線治療にCDDPの気管支動脈動注（Bronchial arterial infusion (BAI)）を同時併用することによる化学放射線療法のプロトコールを始めた．そのプロトコールを表2に示す．表2のように放射線治療と同時併用する形で，原則的に2コースのBAIを施行する．投与するCDDPの量は80 mg/m^{2}であるが，腎機能低下例にはその機能に応じてCDDPの量を減じる．

図1は気管支動脈造影像である．図にあるように造影により原発腫瘍だけでなく，縦隔リンパ節も同様に造影されている．われわれは気管支動脈だけでなく，肋間動脈，鎖骨下動脈などできる

表2　BAIのプロトコール

適格規準
組織学的に非小細胞肺癌が示された症例
PS 0-3
胸部照射（TRT）と化学放射線療法に耐えうる症例
スケジュール
TRT xxxxx xxxxx xxxxx xxxxx xxxxx xxxxx (xxxxx) (2 Gy/f)
BAI　X　X　(X)
CDDP (80 mg/m²)

だけ多くの支配動脈を発見し，造影の程度に応じてCDDPを投与することとしている．

患者の背景因子は次の通りである．1996～2001年までに根治線量（50 Gy以上）の放射線治療が行えた42例のⅢ期非小細胞癌を対象とした．年齢は43～85歳，平均72.6歳，男性33例，女性9例，PSは0-1が36例，2が4例，3が2例．組織学的には扁平上皮癌が28例，腺癌が11例，大細胞癌が1例，その他が2例であった．ⅢA期が10例，ⅢB期が32例であった．

放射線の線量は50.4～73.2 Gy，平均63.5 Gy，分割回数は28～60回，平均37.0回，全治療期間は32～86日，平均49.4日，照射野の大きさは，横が5～20 cm，平均12.1 cm，縦が5～20 cm，平均12.8 cmであった．9例（21%）で一回線量1.2 Gy, 1日2回の過分割照射を行った．また7例に導入化学療法を，3例に同時併用化学療法を併用した．BAIの回数は1～3回，平均1.7回，1回のBAI当たりのCDDP使用量は50～130 mg，平均113 mg, CDDPの総投与量は50～360 mg，平均195 mgであった．

図2に局所非再発率曲線を示す．2年局所非再発率は66%，5年局所非再発率は57%であった．図3に生存率曲線を示す．生存期間の中央値，1, 2, 5年生存率はおのおの33カ月，73, 54, 40%であった．

図4に典型的な症例を示す．症例は70歳，男性，T3N0M0，ⅢB期の症例である．60 Gy/30分割/47日の放射線と2コースのBAIを施行した．腫瘍は完全に消失し，4年後のCTにても局所制御を維持している．5年以上無再発である．

急性期の有害事象は，Grade 3の白血球減少が6例（14%），Grade 3の血小板減少が1例（2%），Grade 3の肺炎が2例（5%）出現した．しかしながら，Grade 3以上の食道炎は1例も発生がなかった．またBAI手技中の合併症の発生はなかった．

3. 考　察

数多くの部位の腫瘍で局所制御の向上が治療成績（生存率）の向上につながると報告されている[11,12]．非小細胞肺癌においてもこの考えは通じると考えられる．われわれの方法によれば，5年局所非再発率は57%と過半数の症例は局所制御を得られる．それは高い濃度のCDDPが直接的に腫瘍に到達されることによると考えられ，経静脈投与による方法よりは簡便に抗癌剤のdose intensityが高められることが期待される．また，われわれの症例の平均年齢が72.6歳と高齢者を多く含むのにもかかわらず，有害事象の発生を低く抑えられているのは，全身に回る抗癌剤の濃度を低く抑えることができているためと考えられる．

この点に関しては，多くの研究者が不安に感じている，全身に回る抗癌剤の濃度が減るので，微小遠隔転移の制御は難しいのでは，という考え方もある．なるほど，Ⅲ期非小細胞肺癌の死因の最大のものは遠隔転移であるかもしれないが，局所制御が得られなければ，いずれ遠隔転移が生じることもあることから，現在までの観察では局所制御のメリットが遠隔転移の出現によるデメリットを上回っているということができる．

これまでの臨床試験の結果からいえることは，抗癌剤と放射線の組み合わせ，および初回治療以降の維持化学療法により，2年生存率は50%付近まで向上できることがわかってきた．しかしながら，5年生存率は依然として10～20%前後とほとんどの症例で治癒が得られていないことが示唆される．われわれの生存率は2年で54%であるが，5年でも40%と，その間にあまり低下していないことが特徴である．

さらに本療法の特長は，有害事象（特に食道炎）が少ないことである．数多くの非小細胞肺癌の化学放射線療法の臨床試験で制限因子となっている

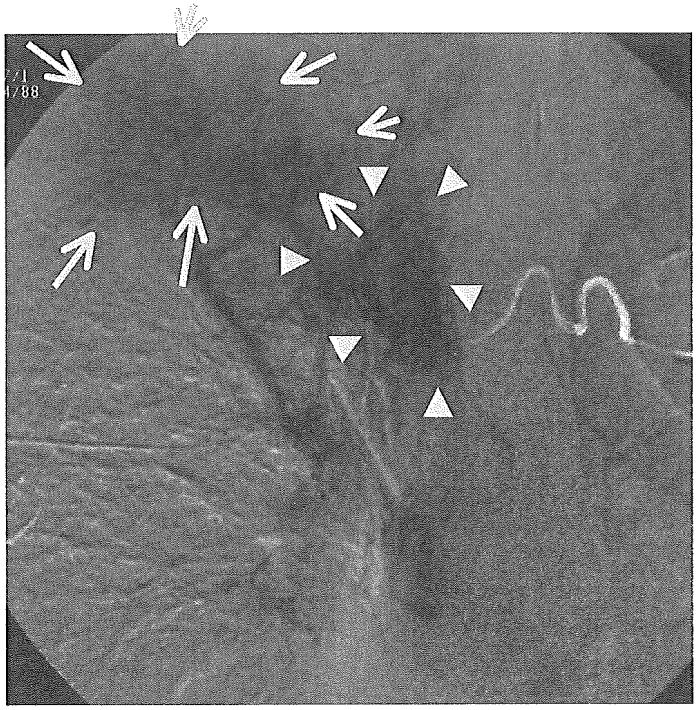


図1　典型的な気管支動脈造影像
原発巣（矢印）と縦隔リンパ節（矢頭）が同様に造影され，薬剤の到達が示唆される．

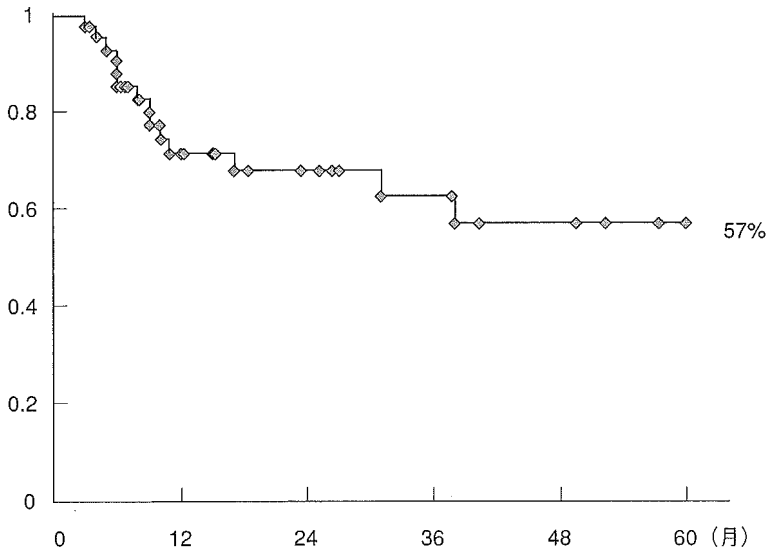


図2　局所非再発率曲線

有害事象は食道炎であることから，この治療法ではまだ線量もしくは薬剤量の増加は可能である．そして，さらなる特長としては今回の症例には，再発までは維持療法などの抗癌剤を使用しておらず，また90%以上の症例で放射線治療中に併用した抗癌剤はCDDPのみであるので，この治療法はきわめてcost-effectiveということと，放射線治療終了後は通常の化学療法のように繰り返し

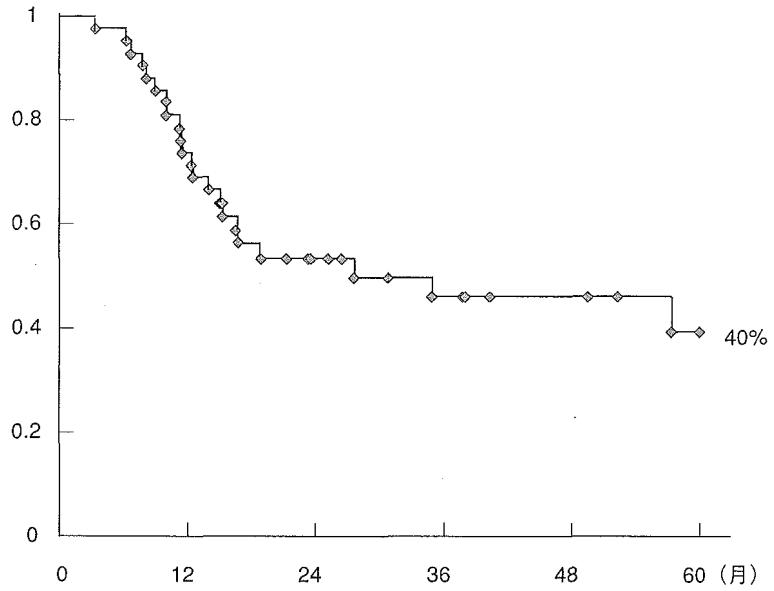
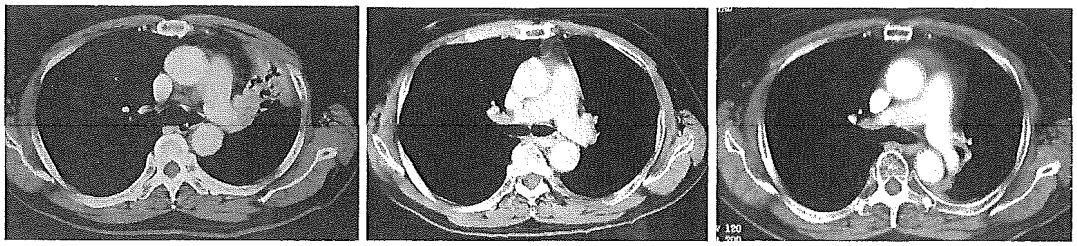


図3　全生存率曲線



治療前　　治療後　　治療4年後

図4　典型的に奏効した症例のCT

治療のために入院や通院治療を必要とせず，患者のQOLを良好に保つことができる．

BAIの手技については，一般にSeldinger法を用いて血管の確保まで1～2時間，薬液投与に1時間程度の時間で可能であり，ルーチンワークとして十分可能である．

最近は局所制御困難な局所進行頭頸部癌に対しても，CDDPの動注化学療法が行われ効果を得ている[13]．局所制御を得て，長期生存につなげるという方法は，今後非小細胞肺癌においても試みられても不思議ではないことと考えられる．現在われわれは，本法を用いた多施設共同試験を企画している．

まとめ

まとめとして，非小細胞肺癌の死亡率が上昇する中，局所進行非小細胞肺癌で全身状態の良好な70歳以下の患者に対する化学放射線療法が理想的な治療となってきている．しかし治療関連死が少なくないことや，その長期成績も依然として満足のできるものではない．われわれの方法（CDDPの気管支動脈動注同時併用の放射線療法）は食道などへの有害事象も軽微で，局所制御に優れ，長期生存割合も好ましく，今後高齢者肺癌の爆発的増加が予測される中，その有用性が示唆される．

文　献

1) Montain CF: Revisions in the international system for staging lung cancer. *Chest* **111**: 1710–1717, 1997
2) Karasawa K, Niibe Y, Igaki R, et al: Radiotherapy combined with concurrent use of bronchial arterial infusion of CDDP for the treatment of stage Ⅲ non-small cell lung cancer. *Proc 38th Am Soc Clin Oncol*: 315a, 2002
3) RTOG Homepage: http://www.rtog.org/
4) Perez CA, Stanle YK, Rubin P, Kramer S, Brady L, Perez-Tamayo R, Brown GS, Concannon J, Rotman M, Seydel HG: A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary Report by the Radiation Therapy Oncology Group. *Cancer* **45**(11): 2744–2753, 1980
5) Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF: A randomized phase Ⅰ/Ⅱ trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage Ⅲ non-small-cell lung carcinoma: Report of Radiation Therapy Oncology Group 83–11. *J Clin Oncol* **8**(9): 1543–1555, 1990
6) Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT, et al: Radiation Therapy Oncology Group (RTOG) 88–08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase Ⅲ trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* **87**(3): 198–205, 1995
7) Komaki R, Seiferheld W, Curran W, et al: Sequential vs. concurrent chemotherapy and radiation therapy for inoperable non-small cell lung cancer (NSCLC): Analysis of failures in a phase Ⅲ study (RTOG 9410). *Int J Radiat Oncol Biol Phys* **48**(2 Suppl): S113, 2000
8) Langer CJ, Hsu C, Curran WJ, et al: Elderly patients (pts) with locally advanced non-small cell lung cancer (LA-NSCLC) benefit from combined modality therapy: secondary analysis of Radiation Therapy Oncology Group (RTOG) 94–10. *Proc 38th Am Soc Clin Oncol*: 299a, 2002
9) Hersing TA, Halle JS, Socinski MA: Chemoradiotherapy for stage ⅢA, B non-small cell lung cancer. In Detterbeck FC, Rivera MP, Socinski MA, et al: Eds. Diagnosis and treatment of lung cancer. An evidence-based guide for practicing clinician 291–303, 2001, W. B. Saunders Company, Philadelphia
10) 国頭英夫：肺癌，2010年までの標準治療を提示する．*Medical Practice* **19**(1): 5–6, 2002
11) Perez CA, Bauer M, Edelstein S, Gillespie BW, Birch R: Impact of tumor control on survival in carcinoma of the lung treated with irradiation. *Int J Radiat Oncol Biol Phys* **12**(4): 539–547, 1986
12) Suit HD: Local control and patient survival. *Int J Radiat Oncol Biol Phys* **23**(3): 653–660, 1992
13) Ahmed KA, Robbins KT, Wong F, Salazar JE: Efficacy of concomitant chemoradiation and surgical salvage for N3 nodal disease associated with upper aerodigestive tract carcinoma. *Laryngoscope* **110**(11): 1789–1793, 2000

肺定位放射線治療におけるQAについて

国立がんセンター東病院　放射線部
物理専門官
西尾　禎治

〒277-8577　千葉県柏市柏の葉６－５－１
Tel：04-7133-1111
E-mail：tnishio@east.ncc.go.jp

1.　はじめに

現在の日本で、死因の第１位は悪性新生物であり、２００３年の報告書[1]によれば、全死亡数３００,６５８人の内、３１.０％がそれに該当する。悪性新生物の部位別死亡率では、気管支及び肺がんが１８.２９％、胃がんが１２.６２％である。胃がんによる死亡率は年々減少傾向にあり、その反面、肺がんは増加傾向にある。また、近年のCT診断装置の技術発展[2]に伴い、早期肺がんの症例数が非常に増加してきている[3]。

近年、光子線を利用した放射線治療において、定位放射線治療及びIMRTなど腫瘍に対して線量集中性を高めることが可能である高精度放射線治療の進歩が急速に進んでいる[4-7]。特に体幹部定位放射線治療は、我が国で開発された新しい放射線治療技術である。しかし、一方で、高精度放射線治療だからと言ってその品質保証・管理を怠ると質の高い放射線治療を患者に提供出来なくなってしまう。我々が患者へ提供する放射線治療の精度は、臨床を行う施設側で、その品質保証・管理が十分に行われているか否かによって大きく左右されるであろう。

高精度放射線治療の中で、今年４月より、直線加速器による体幹部定位放射線治療が保険収載された。その点数は６３,０００点であり、脳の直線加速器による定位放射線治療と同じ点数である。また、厚生労働省出版の医科点数表解釈に、放射線治療に関する機器の精度管理を専ら担当する者がその条件の一つとして記載され、その担当者の一例としてだが医学物理士と言った職種名が初めて保険点数加算に関わる形で登場した。

保険適応の体幹部定位放射線治療を実施できる施設基準としては、以下の条件が挙げられている。

- 放射線治療を専ら担当する常勤医師が配置されていること
- 当該治療を行うために、十分な機器、施設を有していること

また、保険適応の体幹部定位放射線治療を行うための従事スタッフとしては、以下の条件が挙げられている。

- 放射線治療を専ら担当する常勤医師（ライナックまたはマイクロトロンを利用した治療経験が５年以上）が１名以上いること
- 放射線治療を専ら担当する診療放射線技師（ライナックまたはマイクロトロンを利用した

治療経験が５年以上）が１名以上いること

- 放射線治療に関する機器精度管理を専ら担当する者（診療放射線技師、医学物理士など）

尚、上記、機器精度管理を専ら担当する者に関しては、放射線治療を専ら担当する診療放射線技師とは異なる者でなければならないとある。

原発病巣の直径が 5cm 以内で転移病巣の無い原発性肺癌または原発性肝癌、および３個以内で他病巣のない転移性肺癌または転移性肝癌、および脊髄動静脈奇形に対して行った場合にのみ算定し、数か月間の一連の治療過程に複数回の治療を行った場合であっても、所定点数は１回のみ算定するとの記載がある。また、定位型手術枠又はこれと同等の固定精度を持つ固定装置を取り付ける際等の麻酔、位置決め等に係る画像診断、検査、放射線治療管理等の当該治療に伴う一連の費用は所定点数に含まれ、別に算定できないとの記載もある。

現在、日本国内では６００施設とも言われる多くの施設で何らかの放射線治療が行われているとの調査結果がある。その中で体幹部定位放射線治療を行っている施設は僅か４０施設ほどである。

近年、放射線治療関連の医療事故が頻発しており、その問題はマスコミでも多く取り上げられている。その中で放射線治療の品質保証（Quality Assurance）[8、9]のあり方が強く問題視されている。しかし、体幹部定位放射線治療を含む放射線治療の技術は飛躍的に進歩しているが、その治療技術の QA は確立したものとはなっていない。更に、放射線治療の QA は非常に幅広い領域に及んでいるため、技術の進歩に使用者側が追い付いていけない現象が起こっている。

今回、医学物理士は高品質の体幹部定位放射線治療を患者に提供するために必要である、と言った、臨床現場スタッフ、特に医師側からの強い要望があったからこそ、保険点数に関わる形でその職種名が記載される運びとなった。我々医学物理士は、この要求に対して責任を持って応えなければならない立場にあることを忘れてはならない。各施設の治療運用において、実現可能なレベルで自ら品質（Quality）を定め、それを保証（Assurance）することが出来るような人材であることが要求されている。

2. 体幹部定位放射線治療とは

医科点数表解釈の注釈にも記載されているように、体幹部定位照射治療とは、直線加速器（マイクロトロンを含む）により極小照射野で線量を集中的に照射する治療法であり、

- 放射線照射中心位置精度が高い：照射中心精度は 2mm 以内
- 患者固定精度が高い：呼吸同期を加味しない固定精度で 5mm 以内
- 患者の呼吸に伴う臓器移動を何らかの方法で加味または制御する

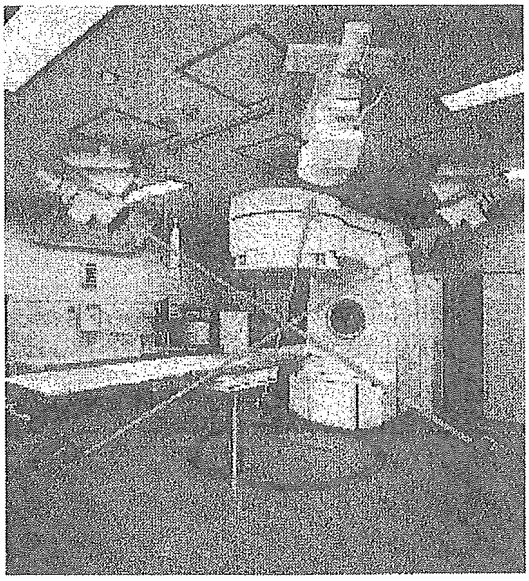


図１：動体追跡装置。

の技術的条件の基で定義される放射線治療である。これらの条件を満たすことで、時間的に動きが

ある腫瘍に対し、高い一回照射線量を正確に照射することが可能となる。そして、患者の固定位置精度を向上させる専用ボディフレーム、照射装置一体型 CT など、それに加えて呼吸による臓器移動を抑制する装置や呼吸同期装置、動体追跡装置[10-15]（図１参照）などを利用することで、腫瘍への正確な照射を実現させる。また、現在、体幹部定位照射治療の対象臓器は肺及び肝臓であるが、実際に行われている治療のほとんどは肺体幹部定位放射線治療であると言ってもよい。

また、体幹部定位放射線治療を行う上では、以下のような、必要機器・設備、機器精度管理の最低基準がある。患者位置固定精度が高いことが定位放射線治療の特徴の一つでもあるので、各メーカが販売している専用ボディフレームの一例も列挙した。

体幹部定位放射線治療は、現在のところ早期肺癌の治療にもっとも期待されている放射線治療の一つである。直径 3cm 程度以下の肺癌に対しては、手術不能な患者にも、副作用なく手術と同程度の治療成績が得られることがほぼ認められている状況にある[3]。

体幹部定位放射線治療の典型的な照射線量及び分割回数は、5-12Gy の高い１回線量で４回から１０回の短い分割回数で治療を行う。一般の放射線治療では１回 2Gy で３０回ほどの分割照射を行うので、体幹部定位放射線による治療期間は短くて済む。照射方法は多門照射やアーク照射を利用して行われ、国内の１０施設ほどの治療利用実績データからだと、多門では平均７門照射、アークでは平均３アークで照射が行われている。また、M.L.C.を利用して、腫瘍の形状に沿った照射野形成を行って照射する場合がほとんどである。尚、利用される照射野のサイズは小さい。１回の治療に要する時間は１時間ほどで、照射室内での患者位置決め作業に、その大半の時間が費やされる。

必要機器・設備

- 直線加速器（マイクロトロン含む）
- 治療計画用 CT 装置
- ３次元治療計画装置
- 患者位置及び固定精度を向上させる物及び手法
- 呼吸に伴う臓器変動を制御する物及び手法
- 微小電離箱線量計及び半導体検出器など絶対線量を測定出来る物
- 水ファントム、水等価固体ファントム

患者位置固定具の例

名称	メーカ
BodyFix	ユーロメディック
BodyFIX	村中医療機器
ESFORM ボディサポート（図２参照）	エンジニアリングシステム
Interloc	東洋メディック
Moldcare	アルケア
Stereotactic Body Frame	エレクタ
Vac-Fix 真空固定具	ハンドシェイク
VAC・LOK	東洋メディック