washed with H_2O (5 mL). The trapped FRP-170 was then eluted from the cartridge by the following three eluents, each of which was 2 mL in total quantity and contained 0.1 mL AcOH: Eluent 1, MeCN/AcOH/H_2O; Eluent 2, 1 mL MeCN/AcOH/H_2O + 1 mL H_2O; Eluent 3, MeCN/AcOH + H_2O. The efficiency was determined by HPLC analysis of FRP-170.

2.4. Automated radiosynthesis

The automated procedure was realized by a commercial automated module (F121, Sumitomo Heavy Industries). Fig. 2 shows a schematic flow diagram of the module after modification according to the optimization described above. Since all liquids were transferred by He pressure (+0.15 MPa) and azeotropic evaporation was carried out under He flow, the whole procedure from the first step of passing [^{18}F]F^- through a Sep-Pak Accell QMA to the step of transferring the eluate to the reservoir for the HPLC injector was automatically controlled by sensing the change in the He flow (Iwata et al., 1990). As shown in Fig. 3, rapid increases in He flow, usually corresponding to a sort of "peak" on a recorder, can be seen whenever an evaporation step was completed or the content of a reservoir has been totally transferred.

3. Results and discussion

The usefulness of on-column hydrolysis was demonstrated for the first time in the preparation of [^{18}F]FDG, where the tetraacetylated [^{18}F]FDG after [^{18}F]fluorination was first retained in a Sep-Pak tC18 cartridge and then hydrolyzed by alkali in the same cartridge (Lemaire et al., 2002). Since many radiosyntheses of ^{18}F-labeled compounds comprise sequential steps of [^{18}F]fluorination and isolation by solid-phase extraction before deprotection, on-column hydrolysis is expected to have versatile utility in PET radiochemistry.

One of the advantages of on-column hydrolysis is the simplified procedure. In the manual preparation described previously (Wada et al., 2000), the [^{18}F]fluorinated intermediate **2** was eluted from the C18 cartridge with MeCN (4 mL) and the eluate was concentrated under reduced pressure and treated by a NaOH solution for hydrolysis. This procedure also required another concentration procedure before HPLC separation necessitating three reaction vessels in total. As a consequence, the present on-column hydrolysis helps simplify the synthetic procedure to a great extent.

Fig. 4 shows that the conventional hydrolysis in homogeneous solutions carried out for comparison proceeded efficiently at room temperature even in dilute concentrations (0.05–0.1 M). In contrast, much higher concentrations were needed for the on-column hydrolysis to achieve comparable results. This discrepancy between on-column and solution hydrolyses is something also observed in the preparation of [^{18}F]FDG (Lemaire et al., 2002), and it can be attributed to differences in kinetics between homogeneous and heterogeneous phases. With a gradual increase in NaOH concentration, the on-column hydrolysis became more and more efficient. The use of higher NaOH concentration, however, should be avoided because it might decompose [^{18}F]FRP-170 as seen in the homogeneous

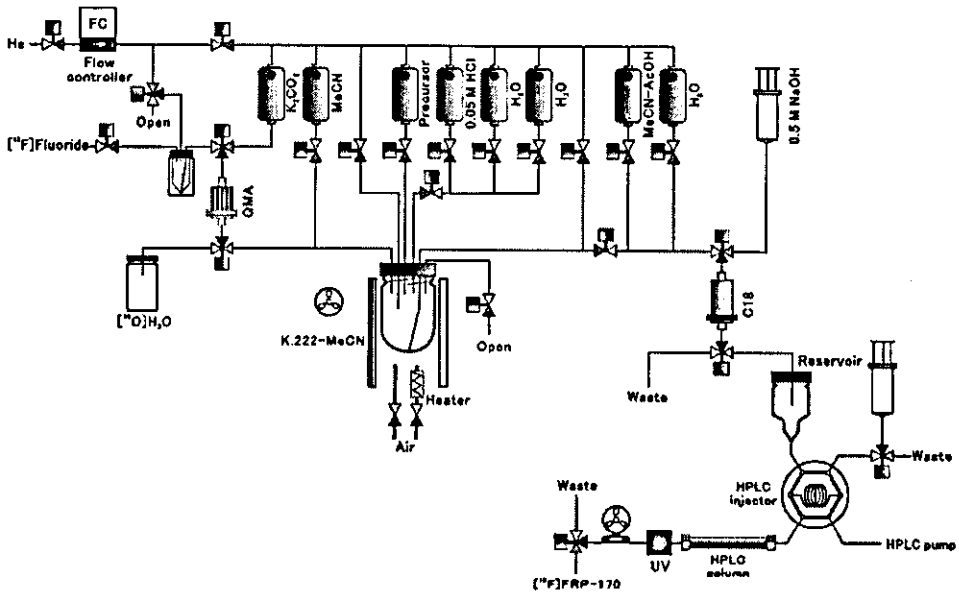


Fig. 2. Schematic diagram of the automated system.

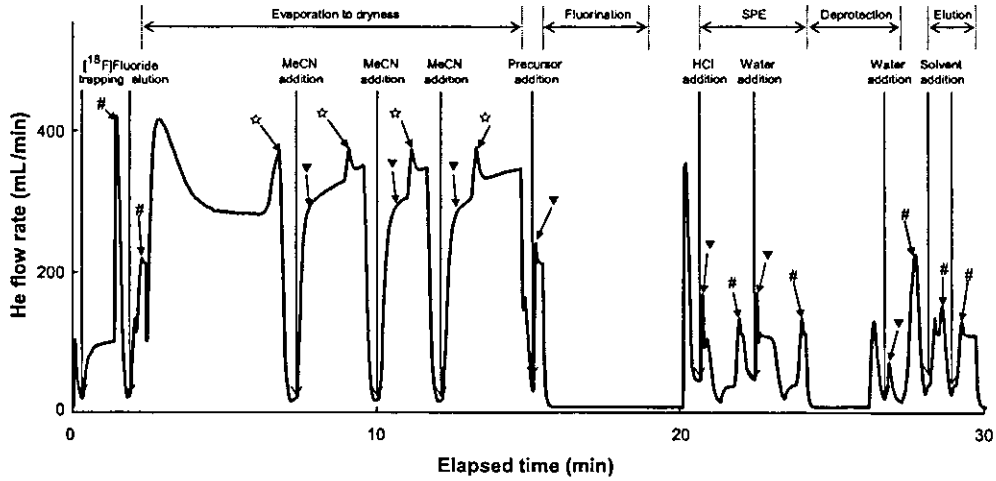


Fig. 3. He flow change during the automated preparation: (☆) completion of evaporation; (▼) completion of addition; and (#) completion of passage.

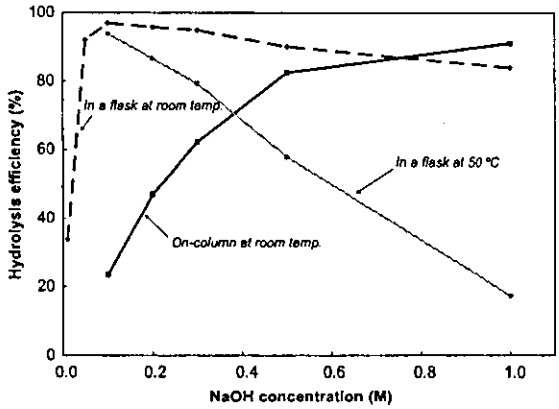


Fig. 4. Hydrolysis efficiency vs. the NaOH concentration. Reaction time 3 min.

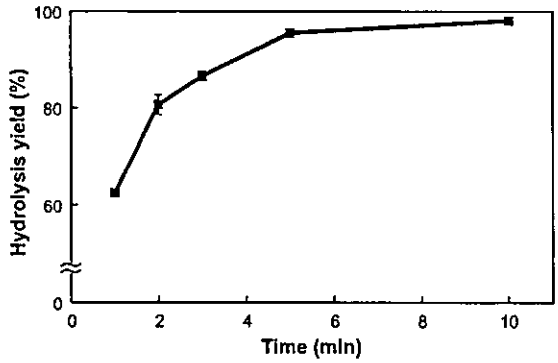


Fig. 5. Yield vs. time for hydrolysis of protected [^{18}F]FRP-170 with 0.5 M NaOH.

solution and also require an increased amount of AcOH in the SPE eluent. Thus, a 0.5 M concentration of NaOH was determined to be a practical compromise as it provided a satisfactorily high conversion rate for the hydrolysis step. At this concentration the time dependence was measured. As shown in Fig. 5, this process was rapid and nearly 90% conversion was obtained within 3 min.

Although most of the NaOH loaded on the cartridge was removed by rinsing with H_2O, the following elution for product **3** was sometimes observed to afford an alkaline solution, probably due to a small quantity of NaOH remaining in the valve dead space. Therefore, in order to protect an expensive HPLC column from being damaged by alkali, AcOH (0.1 mL) was always added to the eluent. This choice was preferred to the use of a disposable cation-exchange resin cartridge for neutralization, because of the obvious simplification in the setup.

One of the most troublesome steps when it comes to switching a system from manual to automated is the preparation of the crude reaction mixture for injection into a preparative-HPLC column. In order to simplify this operation we decided to replace the manual procedure of solvent replacement/concentration by a more easily automatable direct injection of the eluent from the Sep-Pak C18 cartridge.

In general, HPLC separation is strongly affected by volume and polarity of the solution dissolving a sample. This can be clearly seen in the separation of [^{18}F]FRP-170 from a more strongly retained cold impurity (Fig. 6). A satisfactory separation was obtained only when the MeCN content was decreased to less than 15%. However, as shown in Fig. 7, it was found that only less than 20% of the retained [^{18}F]FRP-170 was eluted

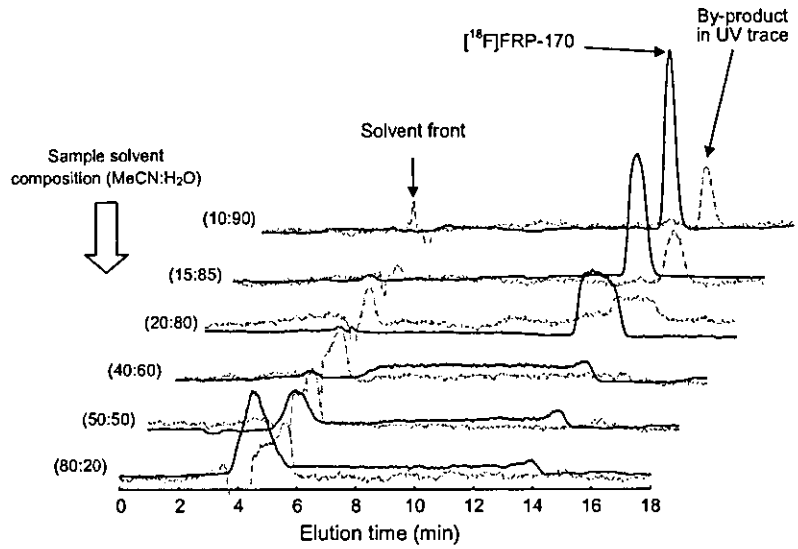


Fig. 6. Effect of the solvent system on the HPLC separation of [^{18}F]FRP-170.

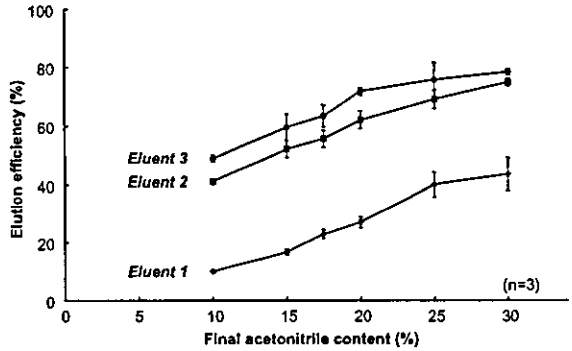


Fig. 7. Effect of the solvent system on the elution efficiency of FRP-170 from a C18 cartridge.

from the Sep-Pak with this solvent system (Eluent 1). Thus, an increase in MeCN content spoiled the separation, whereas a decrease lowered the elution efficiency.

This conflicting requirement was settled with the other two eluents (Eluent 2 and 3). In fact, in Eluent 2 the doubled concentration of MeCN was found to improve the elution, markedly. An even better result was achieved with Eluent 3, where the cartridge was eluted with MeCN/AcOH followed by H_2O. In this last case, 60% of the retained [^{18}F]FRP-170 could be eluted with MeCN (0.35 mL)/AcOH (0.1 mL) followed by H_2O (1.55 mL).

[^{18}F]FRP-170 was obtained in the overall radiochemical yield of around 20–30% (decay-corrected) within 60 min. The preparation was considerably improved for yield and synthesis time compared with those by the manual method (about 10% in 90 min), mainly due to the on-column hydrolysis and simplified elution procedure. The present approach to deprotection and purification is versatile and can be easily adopted satisfactorily in similar radiosyntheses.

Acknowledgments

The authors are grateful to POLA Chemical Industries Inc. for the gifts of RP-170 and FRP-170. Dr. C. Pascali (National Cancer Institute, Milan) is greatly acknowledged for helpful and critical discussion.

References

Dolbier Jr., W., Li, A.-R., Koch, C.J., Shiue, C.-Y., Kachur, A.V., 2001. [^{18}F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure. Appl. Radiat. Isot. 54, 73–80.

Iwata, R., Yamazaki, S., Ido, T., 1990. Intelligent control of liquid transfer for the automated synthesis of positron emitting radiopharmaceuticals. Appl. Radiat. Isot. 41, 509–511.

Jerabek, P.A., Patrick, T.B., Kilbourn, M.R., Dischino, D.D., Welch, M.J., 1986. Synthesis and distribution of ^{18}F-labeled fluoronitroimidazoles: potential in vivo markers of hypoxic tissue. Appl. Radiat. Isot. 37, 599–605.

Kaneta, T., Takai, Y., Kagaya, Y., Yamane, Y., Wada, H., Yuki, M., Iwata, R., Tsujitani, M., Takahashi, S., Yamada, S., 2002. Imaging of ischemic but viable myocardium using a new ^{18}F-labeled 2-nitroimidazole analog, ^{18}F-FRP170. J. Nucl. Med. 43, 109–116.

Lemaire, C., Damhaut, Ph., Lauricella, B., Mosdzianowski, C., Morelle, J-L., Plenevaux, A., Brihaye, C., Luxen, A., 2002. Fast [^{18}F]FDG synthesis by alkaline hydrolysis on a low polarity solid phase support. J. Labelled Compd. Radiopharm. 45, 435–447.

Murayama, C., Suzuki, A., Suzuki, T., Miyata, Y., Sakaguchi, M., Tanabe, Y., Tanaka, N., Mori, T., 1989. Radiosensitization by a new nucleoside analogue: 1-[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl-2-nitroimidazole (RP-170). Int. J. Radiat. Oncol. Biol. Phys. 17, 575–581.

Nunn, A., Linder, K., Strauss, H.W., 1995. Nitroimidazoles and imaging hypoxia. Eur. J. Nucl. Med. 22, 265–280.

Tewson, T.J., 1997. Synthesis of [^{18}F]fluoroetanidazole: a potential new tracer for imaging hypoxia. Nucl. Med. Biol. 24, 755–760.

Wada, H., Iwata, R., Ido, T., Takai, Y., 2000. Synthesis of 1-[2-[^{18}F]fluoro-2-(hydroxymethyl)-ethoxy]methyl-2-nitroimidazole ([^{18}F]FENI), a potential agent for imaging hypoxic tissues by PET. J. Labelled Compd. Radiopharm. 43, 785–793.

Yang, D.J., Wallace, Cherif, S.A., Gretzer, M.B., Kim, E.E., Podoloff, D.A., 1995. Development of F-18-labeled fluoroerythronitroimidazole as a PET agent for imaging tumor hypoxia. Radiology 194, 795–800.

Int J Clin Oncol (2005) 10:26–29
DOI 10.1007/s10147-004-0446-9

ORIGINAL ARTICLE

Yoshihiro Ogawa · Kenji Nemoto · Yoshihisa Kakuto
Hiromasa Seiji · Kazuya Sasaki · Chiaki Takahashi
Yoshihiro Takai · Shogo Yamada

Construction of a remote radiotherapy planning system

Received: October 17, 2003 / Accepted: September 1, 2004

Abstract
Background. We constructed a remote radiotherapy planning system, and we examined the usefulness of and faults in our system in this study.
Methods. Two identical radiotherapy planning systems, one installed at our institution and the other installed at an affiliated hospital, were used for radiotherapy planning. The two systems were connected by a wide area network (WAN), using a leased line. Beam data for the linear accelerator at the affiliated hospital were installed in the two systems. During the period from December 2001 to December 2002, 43 remote radiotherapy plans were made using this system.
Results. Data were transmitted using a file transfer protocol (FTP) software program. The 43 radiotherapy plans examined in this study consisted of 13 ordinary radiotherapy plans, 28 radiotherapy plans sent to provide assistance for medical residents, and 2 radiotherapy plans for emergency cases. There were ten minor planning changes made in radiotherapy plans sent to provide assistance for medical residents.
Conclusion. Our remote radiotherapy planning system based on WAN using a leased line is useful for remote radiotherapy, with advantages for both radiation oncologists and medical residents.

Key words Radiotherapy · Remote planning · WAN · Oncologist

Y. Ogawa (✉) · K. Nemoto · C. Takahashi · Y. Takai · S. Yamada
Department of Radiation Oncology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
Tel. +81-22-717-7312; Fax +81-22-717-7316
e-mail: ogaway@rad.med.tohoku.ac.jp

Y. Kakuto
Department of Radiology, Miyagi Cancer Center, Natori, Japan

H. Seiji · K. Sasaki
Department of Radiology, Furukawa City Hospital, Furukawa, Japan

Introduction

There has been an increase in recent years in the number of patients undergoing radiotherapy.[1] In Japan, more than 700 institutions now have linear accelerators,[2] but there are only about 400 board-certified radiation oncologists.[3] Radiation oncologists in Japan must therefore work long hours, and many radiation oncologists perform extra duties at other institutions. The establishment of an effective remote radiotherapy planning system is therefore needed to reduce the workload of oncologists in Japan. Remote radiotherapy planning systems have already been established in many countries.[4–7] Data transmission in many of these systems is via telephone lines, using an integrated service digital network (ISDN).[8,9] We constructed a remote radiotherapy planning system, based on a wide area network (WAN), using a leased line. We report here the usefulness of and the faults in our system.

Subjects, materials, and methods

Systems

Two identical radiotherapy planning systems, one installed at our institution and the other installed at an affiliated hospital 50km distant from our institution, were used for radiotherapy planning. The two systems were connected by WAN, using a leased line. The leased line was a fiber-channel, and the network protocol was Transmission Control Protocol/Internet Protocol (TCP/IP; Fig. 1). The network speed was initially set at 128Kbps and was increased to 1.5Mbps after 1 year. Beam data for the linear accelerator in the affiliated hospital were installed in the two systems.

Radiotherapy planning

The physical condition and clinical data of patients who are to undergo radiotherapy for the first time are checked by a

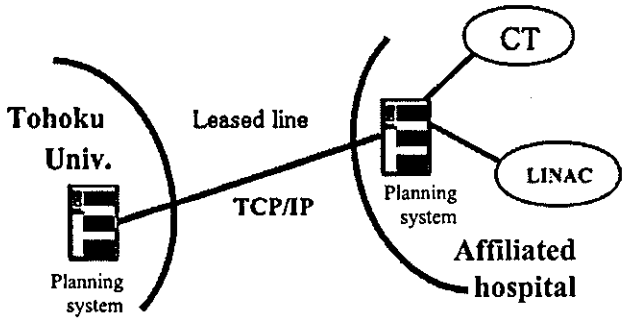


Fig. 1. Remote radiotherapy planning system. Two identical radiotherapy planning systems were connected by a wide area network (WAN), using a leased line. The network protocol was Transmission Control Protocol/Internet Protocol (TCP/IP). *CT*, computed tomography; *LINAC*, linear accelerator

doctor at an affiliated hospital, not by a radiation oncologist. For planning purposes, a computed tomography (CT) scan is performed, and images of slices are sent to the remote radiotherapy planning system. These data are then sent to the planning system at our institution, by using a file transfer protocol (FTP) software program. This enables us to perform radiotherapy planning for the patients at affiliated hospitals. After completion of the patient's treatment plan, the data are returned, using the FTP software program, and the radiotherapy is then started at the affiliated hospital.

Evaluation of the usefulness of the system

During the period from December 2001 to December 2002, 200 patients underwent radiotherapy for the first time at Furukawa City Hospital (the affiliated hospital). A total of 304 new plans were made for radiotherapy, and 43 of these plans were made using the planning system installed at our institution. We evaluated these 43 plans to determine the usefulness of our remote radiotherapy planning system. For this purpose, the 43 radiotherapy plans were classified according to: (1) the reason for sending the plan (ordinary remote radiotherapy plan, radiotherapy plan for an emergency case, or radiotherapy plan to provide assistance for a medical resident) and (2) changes in planning (no changes made in planning, minor changes made in planning, or major changes made in planning).

Results

At the initially set network speed of 128 Kbps, it took about 1 min to send data for 1 CT slice. Because about 30 CT slices are usually needed for radiotherapy planning, the total data transmission time required for radiotherapy planning for one patient was about 30 min. The transmission time of the data for a radiotherapy plan was about 1 min. Transmission of data was performed by using an FTP software program. In June 2002, the network speed was increased to 1.5 Mbps, and this increase in network speed resulted in a significant shortening of data transmission time. Transmission of CT data now takes only about 3 to 5 min.

Of the 43 remote radiotherapy plans examined in this study, 13 were ordinary remote radiotherapy plans, 28 were sent to provide assistance for medical residents, and 2 were radiotherapy plans for emergency cases (Table 1). There were no major planning changes, but ten minor planning changes were made in radiotherapy plans sent to provide assistance for medical residents (Table 2).

Table 1. Reasons for remote radiotherapy plans and body sites requiring radiotherapy

Site	Total	Ordinary	Emergency	Assistance
Prostate	14	5	1	8
Lymphoma	6	2	0	4
Esophagus	5	0	0	5
Lung	5	1	0	4
Uterine cervix	4	0	0	4
Head and neck	4	2	0	2
Others	5	3	1	1
Total	43	13	2	28

Ordinary, ordinary remote radiotherapy plan; Emergency, radiotherapy plan for emergency case; Assistance, radiotherapy plan to provide assistance for a medical resident

Table 2. Changes made in remote planning to provide assistance for medical residents

Site	C1	C2	C3	Total
Prostate	7	1	0	8
Lymphoma	2	2	0	4
Esophagus	4	1	0	5
Lung	1	3	0	4
Uterine cervix	3	1	0	4
Head and neck	1	1	0	2
Others	0	1	0	1
Total	18	10	0	28

C1, no changes made in planning; C2, minor changes made in planning; C3, major changes made in planning

Discussion

Much progress has been made in recent years in the development of various aspects of telemedicine, particularly in the fields of pathological and radiological diagnoses. There have been few reports, however, on the use of telemedicine in the field of radiation oncology. Teslow et al.[4] reported the effectiveness of a teleradiology case-conference system for radiation therapy. Their system included all radiological data, CT, i.e., magnetic resonance imaging (MRI), and radio-isotope imaging (RI) data. They used an ISDN bridge for the connection between two places, and the network speed was 64 Kbps. Smith et al.[5] presented the network architecture for developing a radiotherapy image network. Olsen et al.[6] described a telemedicine system for radiation

Table 3. Telemedicine requirements according to the classification of Olsen et al.[6]

	Video conference	Image display (wide screen)	Database replication, on request	"Real-time" remote operations
Level 1	+	+	–	–
Level 2	+	+	+	–
Level 3	+	+	+	+

therapy. They divided telemedicine requirements and applications into three levels. These levels are shown in Table 3. Our remote radiation planning system, which provides real-time remote planning, may belong to level 3 of the classification of Olsen et al.[6] However, the design of our system is very simple, i.e., two workstations connected by a WAN. Our system is only for radiation therapy planning, and other fields, such as pathology or radiation diagnosis, are not connected to our WAN. Therefore, our system does not strictly fulfill the criteria for level 3 in the classification of Olsen et al.[6] The advantage of our system is that data from a remote place can be corrected by the connection of two workstations in which the same beam data have been installed. Hirota et al.[10] reported a telemedicine system for three-dimensional (3D)-radiotherapy treatment planning. In their system, data were transmitted between two institutions, but data transmission was performed using floppy disks. Seung et al.[7] reported an ISDN-based international telecommunication system for radiotherapy. Their system also included an image server, and the network speed was 64 Kbps. The incorporation of an image server, though convenient for sending clinical data, makes the system complicated. For this reason, we did not incorporate an image server in our radiotherapy planning system.

Our radiotherapy planning system is operated on a UNIX system, and a UNIX system is designed with a network. It is easy to connect two workstations by WAN and to exchange data using an FTP software program. We connected two workstations by WAN, using a leased line. The network speed was initially set at 128 Kbps and was increased to 1.5 Mbps after 1 year. The time required to transmit data for images of 30 CT slices is about 3 min, and the transmission of radiotherapy plan data is instantaneous.

Ten of the 43 radiotherapy plans examined in the present study required minor changes. These changes were made for medical residents. A remote radiotherapy planning system is therefore beneficial for both the training of medical residents and for doctors in remote locations.

Although the design of our remote radiotherapy planning system is simple, construction of the system was expensive, due to the requirement of two workstations and a leased line. A system in which one workstation and one personal computer are connected as a server and a client is now being developed to reduce the cost of construction of a remote radiotherapy planning system. The advantage of a leased line is that there is no interference from data transmission through other networks. Much progress has been made recently in network communications, due to the increase in the number of Internet users. Progress is also being made in the development of technology for the establishment of virtual local area network (VLAN), a network on the Internet for which there is no interference from data transmission through other networks. The establishment of a VLAN would make it possible to connect two machines through the Internet without the requirement of a leased line. In our system, an FTP software program is used for data transmission. Because this system is connected by a leased line, other software programs for communication, such as TV conferences, Internet Protocol (IP) phones, messenger systems, and remote consoles, are being developed. All of these software programs can be operated on a UNIX system.

The establishment of a remote radiotherapy planning system enables radiotherapy planning to be performed at an affiliated hospital. However, the patient's condition and effects of radiation can only be determined by examination of the patient. It is therefore necessary for the relevant medical practitioner to go to the affiliated hospital and examine patients at least once a week.

Conclusions

We have constructed a remote radiotherapy planning system, based on WAN, using a leased line, and the results of this study show that this system is useful for remote radiotherapy, with advantages for both radiation oncologists and medical residents.

References

1. Sikora K (2002) The impact of future technology on cancer care. Clin Med 2:560–568
2. JASTRO Database Committee (2001) Present status of radiotherapy in Japan. The regular structure survey in 1999. J Jpn Soc Ther Radiol Oncol 13:227–235
3. JASTRO (Japanese Society for Therapeutic Radiology and Oncology) (2004) Members Directory. 176–177
4. Teslow TN, Gilbert RA, Grant WH III, et al. (1995). A teleradiology case conference system. J Telemed Telecare 1:95–99
5. Smith CL, Chu WK, Enke C (1998) A review of digital image networking technologies for radiation oncology treatment planning. Med Dosim 23:271–277
6. Olsen DR, Bruland OS, Davis BJ (2000) Telemedicine in radiotherapy treatment planning: requirements and applications. Radiother Oncol 54:255–259
7. Seung JH, Shirato H, Hashimoto S, et al. (2000) An integrated service digital network (ISDN)-based international telecommunication between Samsung Medical Center and Hokkaido

University using telecommunication helped radiotherapy planning and information system (THERAPIS). Radiother Oncol 56:121–123
8. Hashimoto S, Shirato H, Kaneko K, et al. (2001) Clinical efficacy of telemedicine in emergency radiotherapy for malignant spinal cord compression. J Digit Imaging 14:124–130
9. Engelmann U, Schroter A, Baur U, et al. (1997) Experiences with the German teleradiology system MEDICUS. Comput Methods Programs Biomed 54:131–139
10. Hirota S, Tsujino K, Kimura K, et al. (2000) Evaluation of isocenter reproducibility in telemedicine of 3D-radiotherapy treatment planning. J Jpn Soc Ther Radiol Oncol 12:259–266

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 4, pp. 1307–1313, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.07.718

PHYSICS CONTRIBUTION

REPRODUCIBILITY OF ORGAN POSITION USING VOLUNTARY BREATH-HOLD METHOD WITH SPIROMETER FOR EXTRACRANIAL STEREOTACTIC RADIOTHERAPY

TOMOKI KIMURA, M.D.,* YUTAKA HIROKAWA, M.D., PH.D.,* YUJI MURAKAMI, M.D.,* MASATSUGU TSUJIMURA, R.T.T.,† TATEO NAKASHIMA, R.T.T.,† YOSHIMI OHNO, R.T.T.,† MASAHIRO KENJO, M.D.,* YUKO KANEYASU, M.D., PH.D.,* KOICHI WADASAKI, M.D., PH.D.,* AND KATSUHIDE ITO, M.D., PH.D.*

*Department of Radiology, Hiroshima University Graduate School of Medicine, Hiroshima, Japan; and †Department of Radiology, Hiroshima University Hospital, Hiroshima, Japan

Purpose: To evaluate in healthy volunteers the reproducibility of organ position using a voluntary breath-hold method with a spirometer and the feasibility of this method for extracranial stereotactic radiotherapy in a clinical setting.

Methods and Materials: For this study, 5 healthy volunteers were enrolled. After training sessions, they held their breath at the end-inspiration and the end-expiration phase under spirometer-based monitoring. Computed tomography (CT) scans were performed twice at each respiratory phase, with a 10-min interval, on 2 separate days. The total number of CT scans was four at each respiratory phase. After CT volume data were transferred to a three-dimensional treatment-planning system, digitally reconstructed radiographs (DRRs) were calculated for anterior–posterior and left–right beams. Verification was performed with DRRs relative to the diaphragm position, bony landmarks, and the isocenter in each healthy volunteer at each respiratory phase. To evaluate intrafraction reproducibility, we measured the distance between diaphragm position and bony landmarks. To evaluate interfraction reproducibility, we measured the distance between diaphragm position and the isocenter. Reproducibility and setup error were defined as the average value of the differences between each DRR with regard to the first DRR.

Results: Intrafraction reproducibility of the caudal–cranial direction was 4.0 ± 3.5 mm at the end-inspiration phase and 2.2 ± 2.0 mm at the end-expiration phase. Interfraction reproducibility of the caudal–cranial direction was 5.1 ± 4.8 mm at the end-inspiration phase and 2.1 ± 1.8 mm at the end-expiration phase. The end-expiration phase was more stable than the end-inspiration phase.

Conclusions: The voluntary breath-hold method with a spirometer is feasible, with relatively good reproducibility. We are encouraged about the use of this technique clinically for extracranial stereotactic radiotherapy.

Spirometer, Breath-hold, Reproducibility, End-inspiration, End-expiration.

INTRODUCTION

Extracranial stereotactic radiotherapy (ESRT) for lung or liver tumors has been widely performed and has been shown to be a highly effective treatment (1–3). With delivery of a single high dose in ESRT, large irradiated volumes of lung or liver due to large internal margins under free breathing might result in fetal pneumonitis or liver dysfunction. It is important to compensate for breathing motion to reduce pulmonary or liver complications by some method. There are several methods for coordinating respiratory motion, including, for example, active breathing control or coordination (ABC) (4), real-time tumor-tracking systems (5), respiratory gating systems (6–8), abdominal pressure (9), and the voluntary deep inspiration breath-hold (DIBH) technique (10, 11).

Breath-hold methods, such as ABC and DIBH, might be especially demanding, and therefore less feasible, in elderly patients or those with pulmonary dysfunction. To improve feasibility, we developed a voluntary breath-hold method using spirometer-based monitoring to reduce respiratory motion, whereby patients can hold their breath within their comfortable respiratory phase. We consider this method to have higher feasibility for elderly patients or patients with pulmonary dysfunction.

For clinical application, we performed a study to confirm

Reprint requests to: Tomoki Kimura, M.D., Department of Radiology, Hiroshima University Graduate School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Tel: (+81) 82-257-5257; Fax: (+81) 82-257-5259; E-mail: tkkimura@hiroshima-u.ac.jp

This work was presented in part at the 45th Annual Meeting of the American Society for Therapeutic Radiation and Oncology (ASTRO), October 19–23, 2003, Salt Lake City, UT.

Received Jan 12, 2003, and in revised form Jul 7, 2004. Accepted for publication Jul 13, 2004.

the feasibility and reproducibility of this method, using healthy volunteers. The purpose of this study was to evaluate the intrafraction and interfraction reproducibility of organ position with a spirometer and the feasibility of this method for ESRT in a clinical setting.

METHODS AND MATERIALS

Spirometer-based monitoring

For respiratory phase and breath-hold monitoring, healthy volunteers breathed through a mouthpiece connected to a gas-monitoring sensor (sensor-D-light, Datex-Ohmeda, Helsinki, Finland). The other end of the gas-monitoring sensor was attached to a three-way connector, and 5 L/min of oxygen was inhaled through one tube of the three-way connector to assist the breath hold. A nose clip was used to prevent nasal breathing and to ensure that volunteers breathed through the mouthpiece (Fig. 1). We used a commercially available spirometer (Ultima, Datex-Ohmeda), which is usually used in anesthesia management. This spirometer displays a flow–time curve, which shows the state of inspiration, expiration, and breath-hold (Fig. 2).

Training

For this study, 5 healthy volunteers were enrolled. To inform them of the procedure, we gave them training sessions before the CT scans. They held their breath at the end-inspiration and the end-expiration phase, which they felt to be comfortable, under spirometer-based monitoring, and we instructed them to keep a stable tidal volume at each respiratory phase. The reproducibility of the maneuver as determined by the spirometry level was carefully monitored, and the volunteers repeated this maneuver three to four times until they became familiarized.

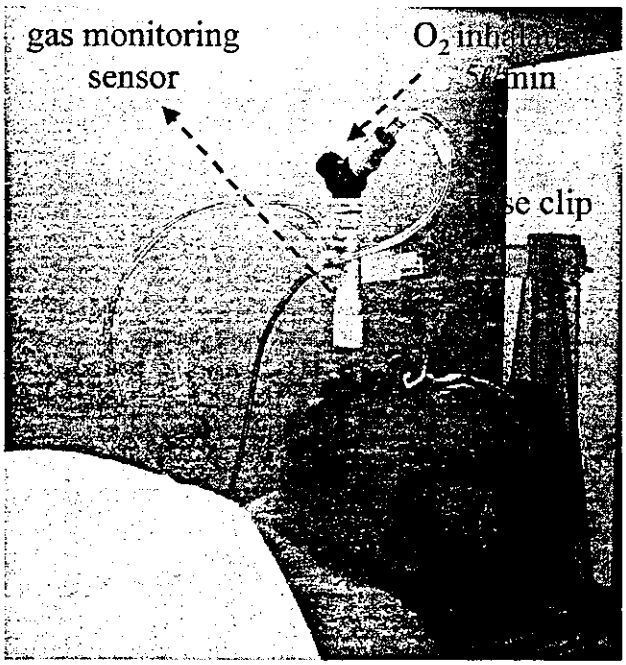


Fig. 1. A healthy volunteer breathes through a mouthpiece connected to a gas-monitoring sensor. A nose clip is used to prevent nasal breathing and ensure that the volunteer breathes through the mouthpiece.

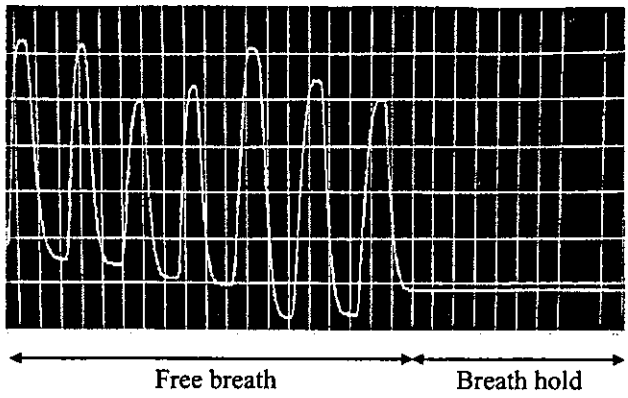


Fig. 2. Representation of spirometry tracings. It is possible for this spirometer to display only a flow–time curve, which can show the state of inspiration, expiration, and breath-hold.

Simulation

For the simulation, each volunteer was placed in the supine position on the X-ray simulator (Ximatron; Varian, Palo Alto, CA). To set up the volunteers in the same position, the isocenter was set on the lower end of the ensiform process at the center of body thickness. First, to measure the diaphragmatic motion from the end-inspiration phase to the end-expiration phase in the cranial–caudal (CC) direction, the volunteers breathed freely under X-ray fluoroscopy (Fig 3). Second, the volunteers held the mouthpiece and held their breath as in the training sessions under

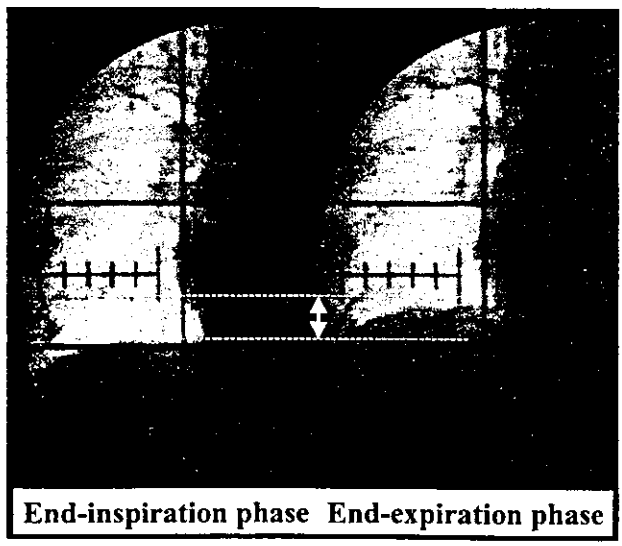


Fig. 3. Diaphragm motion distance under free breathing. To measure the diaphragmatic motion from the end-inspiration phase to the end-expiration phase in the CC direction, the volunteers breathed freely under X-ray fluoroscopy.

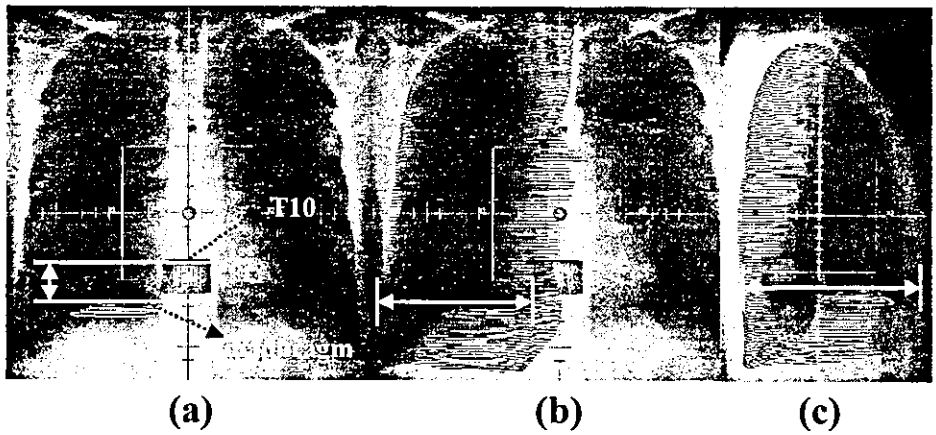


Fig. 4. Evaluation method for intrafraction reproducibility. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC distance between T10 and the diaphragm, LR distance between T10 and the thoracic wall at the diaphragmatic level, and AP distance of the right lung at the diaphragmatic level.

X-ray fluoroscopy. We verified the reproducibility of the diaphragm level in the CC direction obtained at each respiratory phase.

CT scan procedure

Participants enrolled in this study were all healthy volunteers. Informed consent, outlining the risk of low-dose radiation exposure, was gained from all. To avoid unnecessary radiation exposure, CT scans were performed with low voltage and current. Each volunteer was set up on the CT scanner (Lightspeed QX/I; GE Yokogawa Medical System, Tokyo, Japan) at the isocenter. Computed tomography scans were performed four times at each respiratory phase. Slice thickness and interval were each 2.5 mm. Scans were performed twice at each respiratory phase with a 10-min interval on 2 separate days. We ran through the setup process every time before each CT scan was performed. Computed tomography volume data were transferred to a three-dimensional (3D) treatment-planning system (Pinnacle^3 version 6.0; ADAC, Milipitas, CA), and digitally reconstructed radiographs (DRRs) were calculated for anterior–posterior (AP) and left–right (LR) beams.

Verification and data analysis

Verification was performed with DRRs relative to bony landmarks, the diaphragm, and the isocenter. The reasons for using DRRs for verification were as follows: (*1*) because we also use DRRs and lineacgraphys (LG) for verification clinically, (*2*) to evaluate systematic error of CT and the 3D treatment-planning system, and (*3*) because bony landmarks are often unclear on radiographic simulations, especially on the lateral view; thus DRRs, which reflect marked bony landmarks on CT, would be more correct. To evaluate intrafraction reproducibility, we measured lung volume, CC distance between T10 and the diaphragm, LR distance between T10 and the thoracic wall at the diaphragmatic level, and AP distance of the right lung at the diaphragmatic level (Fig. 4). Lung volume was calculated automatically by the 3D treatment-planning system (the threshold of CT value was between 700 Hounsfield units [HU] and 4096 HU).

To evaluate interfraction reproducibility, we measured CC distance between the isocenter and the diaphragm, LR distance between the isocenter and the thoracic wall, and AP distance of the right lung at the isocenter level (Fig. 5). To evaluate setup error, we measured CC, LR, and AP distances between the isocenter and T10 (Fig. 6). Reproducibility and setup error were defined as the average value of the differences between each DRR with regard to the first DRR.

From these data, geometric uncertainties were determined. Geometric uncertainties in radiotherapy consist of internal organ movement and external setup deviations. Both deviations consist of a systematic component (i.e., the same for each fraction of the treatment) and a random component (i.e., varying from day to day) (12, 13). The overall deviations of internal organ motion and setup were calculated by standard deviations (SDs) of the mean differences between first scan DRR and each subsequent DRR, averaged over all the volunteers. The systematic deviations were calculated by determining the spread (1 SD) in the individual means of the differences between the first DRR and each subsequent DRR. The random deviations were calculated by the spread (1 SD) of these differences around the corresponding mean in each volunteer and subsequent calculation of the average of these SDs for the whole group (14).

Statistical significance in the differences was determined with the Student t test. Statistical significance was established at the level of $p < 0.05$.

RESULTS

Diaphragm motion under free breathing

The diaphragm motion distance in the CC direction from end-inspiration to end-expiration ranged from 10 mm to 22.6 mm, with an average of 15.8 ± 5.6 mm (mean and overall SD).

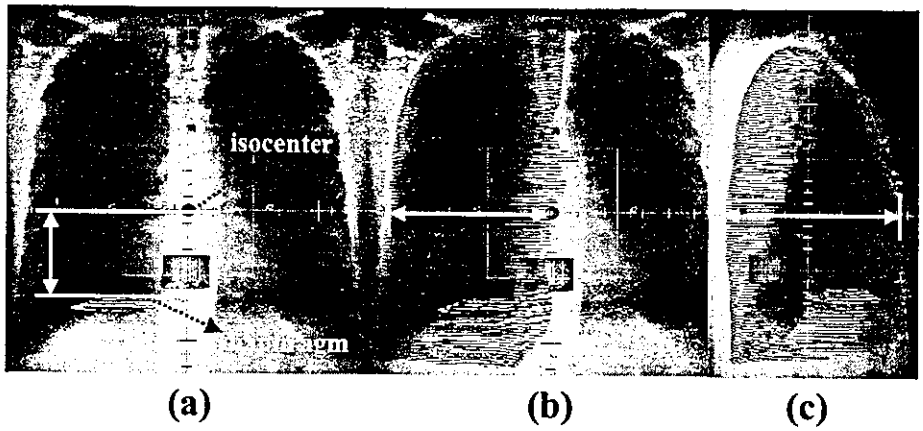


Fig. 5. Evaluation method for interfraction reproducibility. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC distance between the isocenter and the diaphragm, LR distance between the isocenter and the thoracic wall, and AP distance of the right lung at the isocenter level.

Intrafraction reproducibility

Intrafraction reproducibility of the lung volume was 6.4% ± 4.3% at the end-inspiration phase and 3.6% ± 2.5% at the end-expiration phase. Between each breath-holding phase, there was no significant difference (p = 0.342).

Intrafraction reproducibility of the CC, LR, and AP directions was 4.0 ± 3.5 mm, 2.3 ± 2.2 mm, and 2.3 ± 2.1 mm at the end-inspiration phase and 2.2 ± 2.0 mm, 1.4 ± 1.3 mm, and 2.0 ± 1.1 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was no significant difference in all directions (p = 0.297, 0.227, and 0.686 in CC, LR, and AP directions, respectively).

Interfraction reproducibility

Interfraction reproducibility of the CC, LR, and AP directions was 5.1 ± 4.8 mm, 2.9 ± 2.2 mm, and 3.0 ± 3.2 mm at the end-inspiration phase and 2.1 ± 1.8 mm, 1.1 ± 0.8 mm, and 1.9 ± 1.6 mm at the end-expiration phase, respectively. Between each breath-holding phase, interfraction reproducibility at the end-expiration phase was better than that at the end-inspiration phase. There was no significant difference in the CC and AP directions (p = 0.181 and 0.423, respectively) but a significant difference in the LR direction (p = 0.046).

Setup error

Setup error of the CC, LR, and AP directions was 2.8 ± 2.3 mm, 2.9 ± 2.2 mm, and 2.9 ± 2.9 mm at the end-inspiration phase and 2.2 ± 1.7 mm, 1.4 ± 1.1 mm, and 1.4 ± 0.9 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was no significant difference (p = 0.352, 0.382, and 0.109 in the CC, LR, and AP directions, respectively).

Table 1 shows a summary of the results. In all directions, especially in the CC direction, the reproducibility and setup were relatively better at the end-expiration phase than at the end-inspiration phase. Between the breath-holding phase and free breathing, there was a significant reduction of diaphragm motion in the CC direction (p = 0.0015) (Fig. 7).

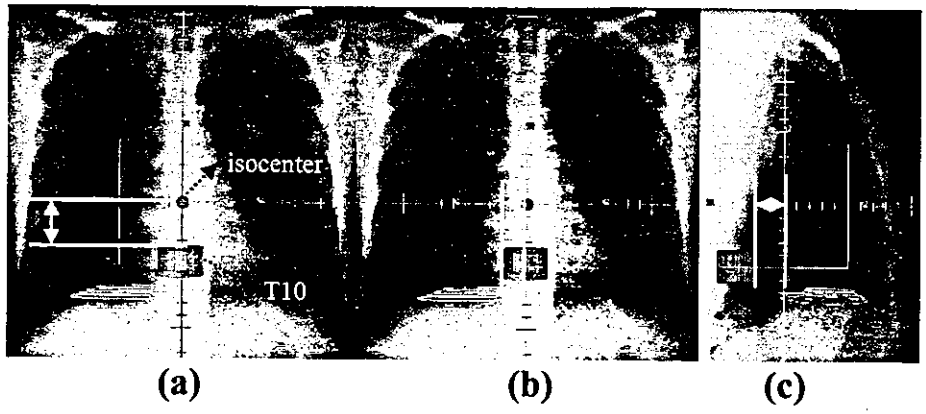


Fig. 6. Evaluation method for setup error. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC, LR, and AP distance between the isocenter and T10.

Table 1. Summary of results

		Inspiration	Expiration	*p* value
Intrafraction (mm)	CC	4.0 ± 3.5	2.2 ± 2.0	0.3
	LR	2.3 ± 2.2	1.4 ± 1.3	0.23
	AP	2.3 ± 2.1	2.0 ± 1.1	0.69
Interfraction (mm)	CC	5.1 ± 4.8	2.1 ± 1.8	0.18
	LR	2.9 ± 2.2	1.1 ± 0.8	0.046
	AP	3.0 ± 3.2	1.9 ± 1.6	0.42
Setup (mm)	CC	2.8 ± 2.3	2.2 ± 1.7	0.35
	LR	2.9 ± 2.2	1.4 ± 1.1	0.38
	AP	2.9 ± 2.9	1.4 ± 0.9	0.11

Abbreviations: CC = cranial–caudal; LR = left–right; AP = anterior–posterior.

Geometric uncertainties

Table 2 shows the results of geometric uncertainties. Systematic deviations of intrafraction in the CC, LR, and AP directions were 3.3 mm, 1.4 mm, and 1.6 mm at the end-inspiration phase and 1.4 mm, 0.8 mm, and 0.7 mm at the end-expiration phase, respectively. Systematic deviations of setup in the CC, LR, and AP directions were 1.5 mm, 2.1 mm, and 1.7 mm at the end-inspiration phase and 0.6 mm, 0.7 mm, and 0.8 mm at the end-expiration phase, respectively. Random deviations of intrafraction in the CC, LR, and AP directions were 1.9 mm, 1.6 mm, and 1.5 mm at the end-inspiration phase and 1.6 mm, 1.2 mm, and 1.1 mm at the end-expiration phase, respectively. Random deviations of setup in the CC, LR, and AP directions were 2.0 mm, 1.2 mm, and 2.2 mm at the end-inspiration phase and 1.8 mm, 1.0 mm, and 0.5 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was significant difference in systematic deviations of setup (p = 0.0045).

DISCUSSION

The breath-hold method is one of the methods used to coordinate respiratory motion. Several approaches have been used in the breath-hold method. One is the ABC method, which temporarily immobilizes the patient's breathing. Wong *et al.* (4) reported on an ABC apparatus

Table 2. Geometric uncertainties

		Inspiration		Expiration	
		Σ	σ	Σ	σ
Intrafraction (mm)	CC	3.3	1.9	1.4	1.6
	LR	1.4	1.6	0.8	1.2
	AP	1.6	1.5	0.7	1.1
Setup (mm)	CC	1.5	2	0.6	1.8
	LR	2.1	1.2	0.7	1
	AP	1.7	2.2	0.8	0.5

Abbreviations: Σ = systematic deviations; σ = random deviations. Other abbreviations as in Table 1.

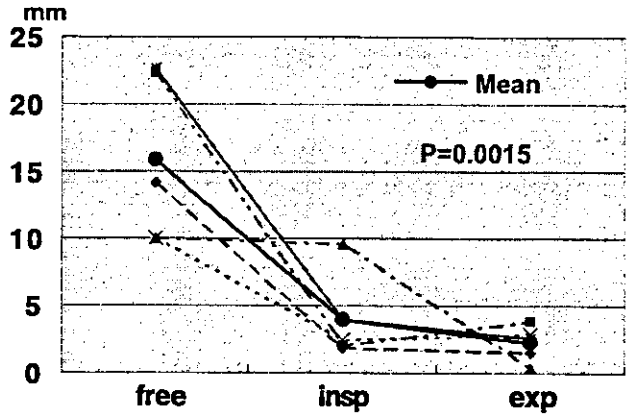


Fig. 7. Reduction of diaphragm movement with the breath-hold method using a spirometer. Between the breath-holding phase and free breathing, there was significant reduction of the diaphragm motion in the cranial-caudal direction (p = 0.0015). Insp = inspiration; Exp = expiration.

constructed of two pairs of flow-monitoring and scissor valves, one each to control the inspiration and expiration paths to the patients; the operator closes both valves to immobilize breathing motion. From the analyses of positioning radiographs, the average intrafraction and interfraction CC reproducibility of the diaphragm relative to the bony landmarks with ABC was 2.5 mm and 4.4 mm, respectively (15). The reproducibility of ABC is good, but the apparatus is relatively expensive and rather demanding of patients. The second breath-hold method is the DIBH technique with a commercially available spirometer. The DIBH technique is able to displace normal lung or heart out of the high-dose treatment field. Rosenzweig *et al.* (10) showed that calculated normal tissue complication probability (NTCP) of the lung for 7 lung cancer patients decreased with the DIBH technique as compared with free breathing at their prescribed dose. Sixel *et al.* (16) showed that the DIBH technique during tangential breast irradiation has the potential to significantly decrease irradiated cardiac volume for suitably selected patients. Another benefit is relatively good reproducibility: Hanley *et al.* (17) analyzed data from 5 lung cancer patients with the DIBH technique and found that intrafraction and interfraction reproducibility was 1.0 ± 0.9 mm and 2.5 ± 1.6 mm, respectively, as determined from the diaphragm position. However, Mah *et al.* (18) reported that a disadvantage of the DIBH technique is patient compliance, because only approximately half of the lung cancer patients they evaluated could perform this method. The third method is the self-breath-hold method without respiratory monitoring devices. Onishi *et al.* (11) demonstrated that the reproducibility of tumor position during 20 lung cancer patients' self-estimated breath-holding at the inspiration phase was 2.2 mm in the CC direction, 1.4 mm in the AP direction, and 1.3 mm in the LR direction. They concluded that they were able to obtain good reproducibility with this technique in combination with a linear accelerator

and without respiratory monitoring devices. However, in some institutions, including ours, where clinicians depend on conventional LG without the fusion of CT and a Linac (FOCAL) unit (1) or an electronic portal imaging device (EPID) for verification, it could not be verified whether patients held their breath during treatment appropriately. We therefore think it would be better to monitor respiratory motion with some kind of method in these institutions.

In our study, we developed a voluntary breath-hold method using a commercially available spirometer. We think the advantage of this method will be feasibility to many patients and adaptability to many institutions. This study was preclinical and used healthy volunteers; however, they could hold their breath comfortably at the end-inspiration or the end-inspiration phase under inhalation of oxygen. Considering that most lung cancer patients are elderly and have respiratory dysfunctions, this method, which allows for holding the breath at the comfortable respiratory phase, would be more feasible than other breath-hold methods, in which breath-holding is mandatory, such as ABC or DIBH. Additionally, verification is performed by conventional LG and DRR in this method. therefore this method would be adaptable to institutions without an apparatus, such as a FOCAL unit or EPID, to monitor respiratory motion during treatment, with relatively lower cost.

Our study demonstrated the feasibility of this method, with relatively good reproducibility of the diaphragm position, which was better at the end-expiration phase than at the end-inspiration phase. Between the end-expiration phase and free breathing, diaphragm movement was significantly reduced to a range of 7.1–19 mm (mean, 13.4 mm) in the CC direction. There is discussion as to whether patients should hold their breath at the inspiration or the expiration phase, because an advantage and a disadvantage exist in each phase. The advantage of breath-holding at the inspiration phase, as with the DIBH technique, is described above. On the other hand, at the expiration phase, Balter *et al.* (19) reported that the reproducibility of the diaphragm position was better than that at the inspiration phase. They analyzed the ventilatory time courses of diaphragm movement for 15 patients, and the average patient's diaphragm remained within 25% of the range of ventilatory excursion from the average expiration position for 42% of the typical breathing cycle and within 25% of the range from the average inspiration position for 15% of the cycle. Reproducibility of the expiration position over multiple cycles was 0.9 mm, as opposed to 2.6 mm for inspiration. Planning target volume (PTV) in ESRT is smaller than that in conventional radiotherapy, thus there was no large difference of NTCP in ESRT. Considering the feasibility of this method, patients can select a more comfortable respiratory phase, the end-inspiration phase or the end-expiration phase. However, to secure the accuracy of reproducibility for ESRT, we considered it better to hold the breath at the end-expiration phase, if possible, for more sufficient reproducibility.

Although we did not use immobilization devices such as a stereotactic body frame in this study, mean setup error was also within 3 mm in all directions. It was also slightly better at the end-expiration phase than at the end-inspiration phase, because the motion of the thoracic walls, which are attached to the skin mark, was greater on inspiration than on expiration at setup. Regarding setup error, our results also demonstrated that the end-expiration phase was better.

We calculated geometric uncertainties from our results. Systematic deviations included setup error and organ motion on the CT scanner, delineation errors, and equipment calibration errors. Random deviations included target movement and day-to-day variation in the patient setup or equipment. Systematic deviations that occur during treatment execution are called preparation errors because these types of errors are caused by the preparation of the equipment (20). Stroom *et al.* (13) evaluated the effect of systematic and random deviations on target dose and demonstrated a clinical target volume (CTV)-to-PTV margin size that ensures at least a 95% dose to (on average) 99% of CTV, which seems to be equal to approximately $2\Sigma + 0.7\sigma$, where Σ and σ are combined systematic and random deviations for a prostate, cervix, lung cancer case. Herk *et al.* (20) also demonstrated that a CTV-to-PTV margin size must be approximately $2.5\Sigma + 0.7\sigma - 3$ mm to give 90% of patients at least 98% equivalent uniform dose. They concluded that systematic deviations have a much larger impact on target dose, thus it is most efficient to address systematic deviations first when working to improve the quality of radiotherapy. In our results, between the end-inspiration and the expiration phase, random deviations of intrafraction and setup did not have large difference in all directions, but systematic deviations of intrafraction and setup at the end-inspiration phase tended to be worse than those at the end-expiration phase in all directions. Systematic deviations of setup especially had significant difference between these phases ($p = 0.045$). Large CTV-to-PTV margin size is therefore necessary at the end-inspiration phase. We also recommend holding the breath at the end-expiration phase in radiotherapies in which the accuracy of reproducibility from the analysis of geometric uncertainties is needed, like ESRT.

Because we used healthy volunteers in this study, we evaluated the reproducibility of the diaphragm position as a landmark. However, the correlation between the diaphragm and lung or liver tumor position is still unclear. Regarding liver tumors, Balter *et al.* (21) demonstrated that the range of ventilatory movement of different locations of coils within the liver is predicted by diaphragm position and suggested that the diaphragm is an acceptable anatomic landmark for radiographic estimation of liver movement in AP projections for most patients. Regarding lung tumors, Seppenwoolde *et al.* (22) demonstrated that the trajectory of the tumor during inhalation is different from the trajectory during exhalation (i.e., hysteresis) by analyzing 3D motion of lung tumors during radiotherapy, using the real-time tumor tracking system. They also suggested that when hysteresis in tumor motion is caused by the dynamic properties of lung tissue, breath-hold scans will not give a representative position of the tumor. According to the complexity of tumor motion from this analysis, we should take into consideration that diaphragm position does not necessarily re-

flect lung tumor position directly, especially tumors in the lower lobe, and from now on evaluate not only the reproducibility of the diaphragm or other organ position but also that of tumor position in a clinical setting.

CONCLUSIONS

The voluntary breath-hold method using spirometer-based monitoring is feasible, with relatively good intrafraction and interfraction reproducibility, especially at the end-expiration phase in healthy volunteers. However, we need to improve interfraction reproducibility for more accurate organ positioning; therefore, daily film verification and repositioning will play a more important role in a clinical setting. We encourage the use of this technique clinically for ESRT and plan to demonstrate not only the reproducibility of organ position but also that of target immobilization in lung and liver tumor patients.

REFERENCES

1. Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small-cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
2. 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.
3. Hof H, Herfarth KK, Munter M, *et al.* Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2003;56:335–341.
4. Wong JW, Sharpe MB, Jaffray DA, *et al.* The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys* 1999;44:911–919.
5. Shirato H, Shimizu S, Kitamura K, *et al.* Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor. *Int J Radiat Oncol Biol Phys* 2000;48:435–442.
6. Ohara K, Okumura T, Akisada M, *et al.* Irradiation synchronized with respiration gate. *Int J Radiat Oncol Biol Phys* 1989;17:853–857.
7. Tada T, Minakuchi K, Fujioka T, *et al.* Lung cancer: Intermittent irradiation synchronized with respiratory motion—Results of a pilot study. *Radiology* 1998;207:779–783.
8. Minohara S, Kanai T, Endo M, *et al.* Respiratory gated irradiation system for heavy-ion radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:1097–1103.
9. Negoro Y, Nagata Y, Aoki T, *et al.* The effectiveness of an immobilization device in conformal radiotherapy for lung tumors: Reduction of respiratory tumor movement and evaluation of the daily setup accuracy. *Int J Radiat Oncol Biol Phys* 2001;50:889–898.
10. Rosenzweig KE, Hanley J, Mah D, *et al.* The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2000;48:81–87.
11. Onishi H, Kuriyama K, Komiyama T, *et al.* A new irradiation system for lung cancer combining linear accelerator, computed tomography, patient self-breath-holding, and patient-directed beam-control without respiratory monitoring devices. *Int J Radiat Oncol Biol Phys* 2003;56:14–20.
12. Bijhold J, Lebesque JV, Hart AAM, *et al.* Maximizing setup accuracy using portal images as applied to a conformal boost technique for prostatic cancer. *Radiothear Oncol* 1992;24:261–271.
13. Stroom JC, Boer HCJ, Huizehga H, *et al.* Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. *Int J Radiat Oncol Biol Phys* 1999;43:905–919.
14. Samson MJ, Koste JRS, Boer HCJ, *et al.* An analysis of anatomic landmark mobility and setup deviations in radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* 1999;43:827–832.
15. Dawson LA, Brock KK, Kazanjian S, *et al.* The reproducibility of organ position using active breathing control (ABC) during liver radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;51:1410–1421.
16. Sixel KE, Aznar MC, Ung YC. Deep inspiration breath hold to reduce irradiated heart volume in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2001;49:199–204.
17. Hanley J, Debois MM, Mah D, *et al.* Deep inspiration breath-hold technique for lung tumors: The potential value of target immobilization and reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys* 1999;45:603–611.
18. Mah D, Hanley J, Rosenzweig KE, *et al.* Technical aspects of the deep inspiration breath-hold technique in the treatment of thoracic cancer. *Int J Radiat Oncol Biol Phys* 2000;48:1175–1185.
19. Balter JM, Lam KL, McGinn CJ, *et al.* Improvement of CT-based treatment-planning models of abdominal targets using static exhale imaging. *Int J Radiat Oncol Biol Phys* 1998;41:939–943.
20. Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. *Int J Radiat Oncol Biol Phys* 2002;52:1407–1422.
21. Balter JM, Dawson LA, Kazanjian S, *et al.* Determination of ventilatory liver movement via radiographic evaluation of diaphragm position. *Int J Radiat Oncol Biol Phys* 2001;51:267–270.
22. Seppenwoolde Y, Shirato H, Kitamura K, *et al.* Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–834.

体幹部腫瘍に対する定位放射線照射

木村　智樹・廣川　　裕・村上　祐司
権丈　雅浩・兼安　祐子・伊藤　勝陽

広島医学 Vol. 56 No. 6 2003 別冊

—図　説—

体幹部腫瘍に対する定位放射線照射

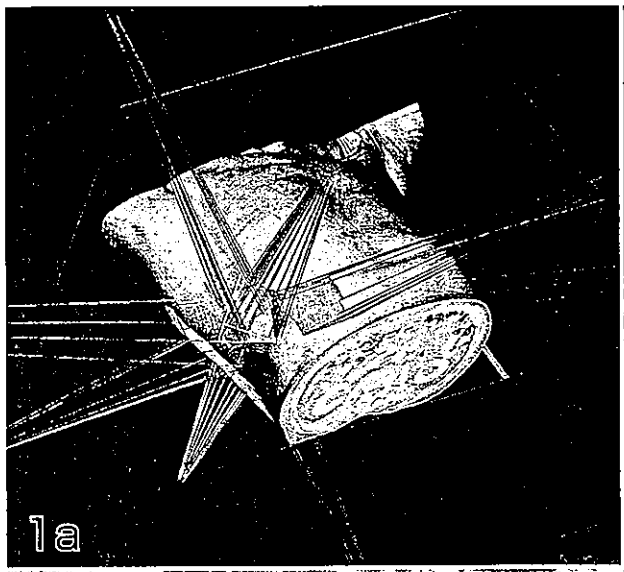
はじめに

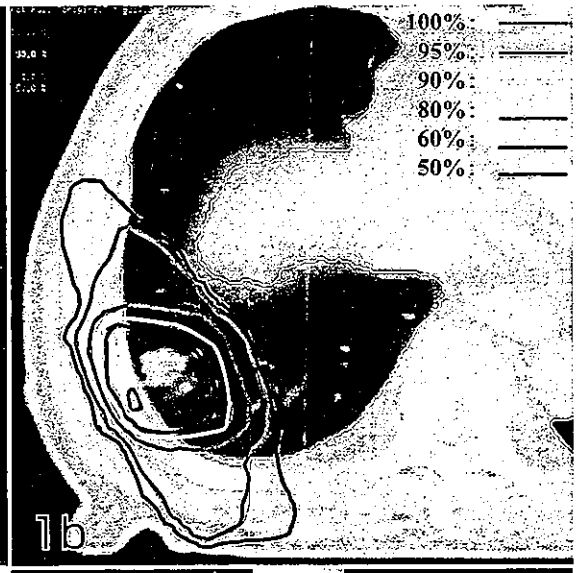
高齢化社会を迎え，癌治療の分野においても低侵襲的な治療法が求められる機会が増加している。このような現状で，局所に大線量を集中させることで，最小限の副作用で最大限の効果が期待できる定位放射線照射の適応は拡大しつつある。ガンマナイフをはじめとする頭蓋内病変に対する定位放射線照射は既に一般的であるが，肺癌や肝癌などの体幹部腫瘍に対してもいくつかの施設で定位放射線照射が施行されており，良好な成績が報告されている[1),2)]。当科でも，1999年6月より開始し，2003年5月までに，31例の肺腫瘍および3例の肝腫瘍に対して定位放射線照射を行ってきた。現在のところ肺腫瘍（術後断端再発例）の1例を除く全例で局所制御が得られている（観察期間1～35カ月：中央値11カ月）。また，最近では腫瘍の呼吸性移動を抑制する目的で，スパイロメータを用いた呼吸停止法[4)]を併用しており，これも併せて紹介する。

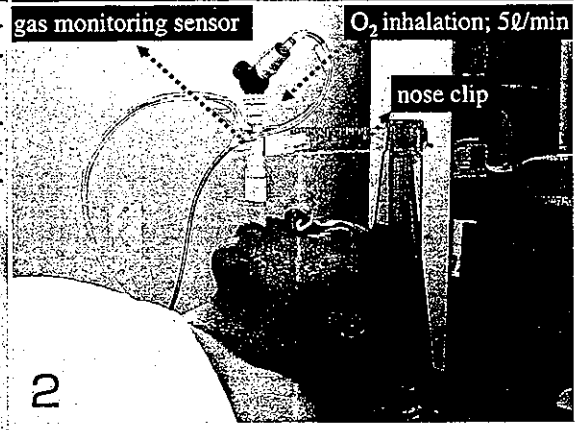
方　法

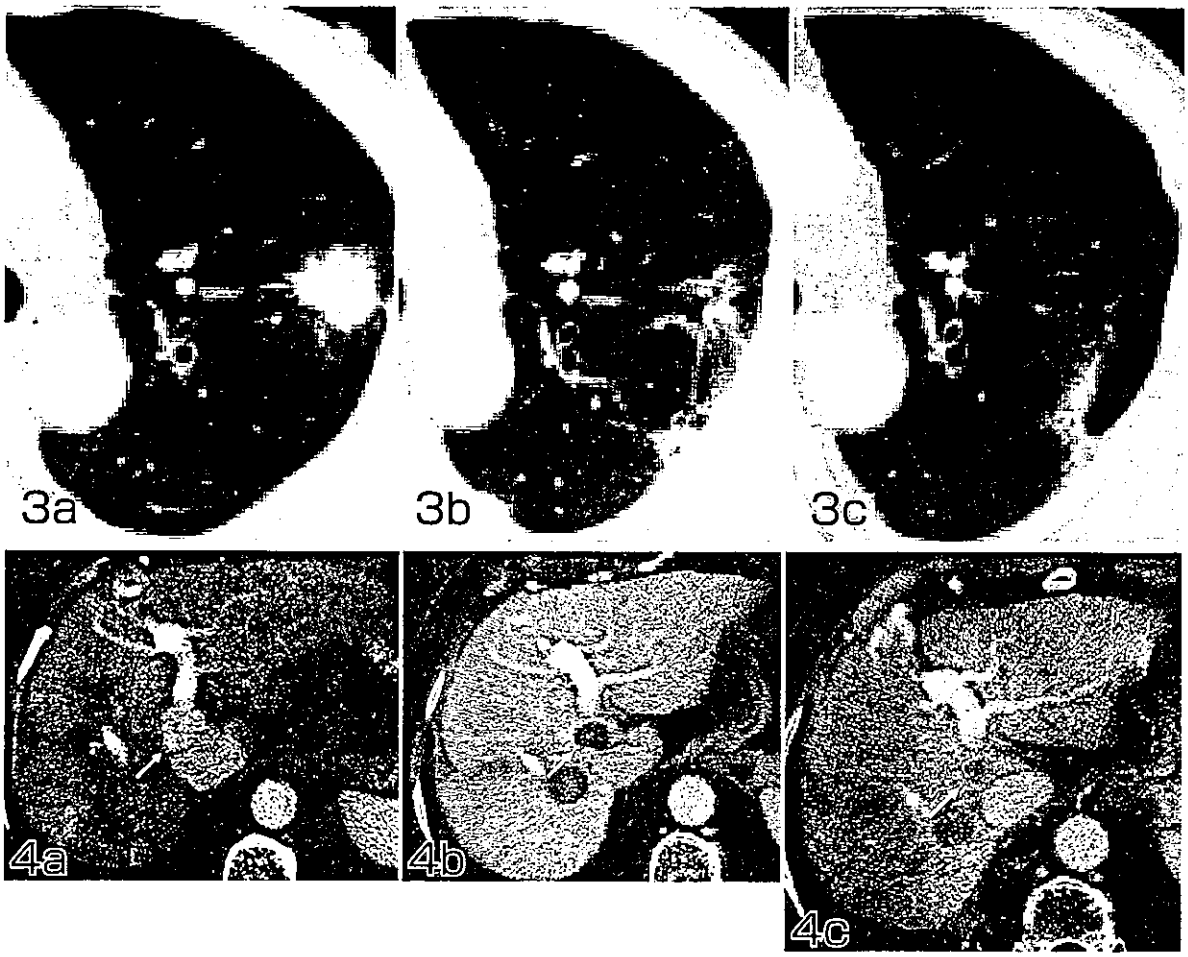
(1)　治療計画

治療計画装置（Pinnacle[3)]）を用いて，肉眼的腫瘍体積（GTV）に潜在的浸潤範囲，呼吸性移動およびセットアップの再現性を考慮した1～1.5 cmの安全域を付加した計画標的体積（PTV）に対して，多方向（non-coplanar）から8門の照射野を設定する（図1-a)。線量分布にてPTVが90％領域に含まれることを確認する（図1-b, c)。総線量は1999年の開始以来，線量増加と分割回数の減少を行い，現在60 Gy/8回である。毎回の照射前には正側のリニアックグラフィを撮影し，アイソセンタの位置の再現性を確認する。









(2)　スパイロメータを用いた呼吸停止法（正常ボランティア）

図 2 の如く，患者はマウスピースに接続したガスモニタリングセンサを介して呼吸を行い，原則として安静呼気時に呼吸停止を行う（1 回の呼吸停止時間は約 15 秒間）。照射中に呼吸停止されていることをスパイロメータにて監視する。正常ボランティアを用いた実験によると，呼気での呼吸停止による横隔膜の位置再現性は頭尾方面で約 3 mm であり，自由呼吸下での呼吸性移動（約 15 mm）と比較して明らかに呼吸性移動の抑制が可能となった。

症　例

症例 1：74 歳男性，肺扁平上皮癌，肺内転移（図 3）。a. 照射前：左上葉に 3 cm 大の腫瘍を認め 56 Gy/14 回の定位放射線照射を施行。b. 照射後 1 カ月：腫瘍は PR にまで縮小。c. 照射後 10 カ月：腫瘍は CR となり，照射野内に限局した Grade I の放射線肺炎を認める。

症例 2：69 歳女性，肝細胞癌，肝内転移（図 4）。a. 照射前：肝 S5 に下大静脈に接する腫瘍を認め（矢印），呼吸停止法を併用して 60 Gy/8 回の定位放射線照射を施行。b. 照射後 1 カ月：腫瘍内部は低吸収域（矢印）を呈した。c. 照射後 4 カ月：腫瘍（矢印）は縮小し，AFP も陰性化した。

文献　1) Uematsu M, Shioda A et al: Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. Int J Radiat Oncol Biol Phys 51: 666–670, 2001.
2) Nagata Y, Negoro Y 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 52: 1041–1046, 2002.
3) Shioyama Y, Tokutake K et al: Clinical evaluation of proton radiotherapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 56: 7–13, 2003.
4) Kimura T, Hirokawa Y et al: Reproducibility of organ position using spirometer during extracranial stereotactic radiotherapy: Int J Radiat Oncol Biol Phys 55: 539, 2003.

広島大学大学院医歯薬学総合研究科展開医科学専攻病態情報医科学講座（旧放射線医学講座）
木村　智樹・廣川　　裕・村上　祐司・権丈　雅浩・兼安　祐子・伊藤　勝陽

Lung Cancer (2004) 45, 45–55

ELSEVIER

LUNG CANCER

www.elsevier.com/locate/lungcan

Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner☆

Hiroshi Onishi[a,*], Kengo Kuriyama[a], Takafumi Komiyama[a], Shiho Tanaka[a], Naoki Sano[a], Kan Marino[a], Satoshi Ikenaga[a], Tsutomu Araki[a], Minoru Uematsu[b]

[a] *Department of Radiation Oncology, Yamanashi Medical University, 1110 Shimokato Tamaho-cho, Nakakoma-gun, Yamanashi 409-3898, Japan*
[b] *Department of Radiation Oncology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan*

Received 22 August 2003; received in revised form 30 December 2003; accepted 8 January 2004

KEYWORDS
Stereotactic radiotherapy;
Non-small cell lung cancer;
Stage I;
Breath-hold;
CT-guided

Summary We have developed a novel irradiation technique for lung cancer that combines a linear accelerator and CT scanner with patient-controlled breath-hold and radiation beam switching. We applied this technique to stereotactic three-dimensional (3D) conformal radiotherapy for stage I non-small cell lung cancer (NSCLC) and evaluated the primary therapeutic outcomes. A total of 35 patients with stage I (15 IA, 20 IB) primary NSCLC (20 adeno, 13 squamous cell, and 2 others) were treated with this technique. Patients ranged from 65 to 92 years old (median, 78 years). Twenty-three (66%) patients were medically inoperable due to mainly chronic pulmonary disease or high age. Three-dimensional treatment plans were made using 10 different non-coplanar dynamic arcs. The total dose of 60 Gy was delivered in 10 fractions (over 5–8 days) at the minimum dose point in the planning target volume (PTV) using a 6 MV X-ray. After adjusting the isocenter of the PTV to the planned position by a unit comprising CT and linear accelerator, irradiation was performed under patient-controlled breath-hold and radiation beam switching. All patients completed the treatment course without complaint. Complete response (CR) and partial response (PR) rates were 8/35

☆ Presented at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, 31 May–3 June 2003.

*Corresponding author. Tel.: +81-55-273-1111x4616; fax: +81-55-273-6744.
E-mail address: honishi@res.yamanashi-med.ac.jp (H. Onishi).

0169-5002/$ - see front matter
doi:10.1016/j.lungcan.2004.01.004

(23%) and 25/35 (71%), respectively. Pulmonary complications of National Cancer Institute-Common Toxicity Criteria grade >2 were noted in three (9%) patients. During follow-up (range, 6–30 months; median, 13 months), two (6%) patients developed local progression and five (14%) developed distant or regional lymph node metastases. Two-year overall survival rates for total patients and medically operable patients were 58 and 83%, respectively. In conclusion, this new irradiation technique, utilizing patient-controlled radiation beam switching under self-breath-hold after precise alignment of the isocenter, allows safe high-dose stereotactic radiotherapy with sufficient margins around the CTV and reduced treatment times. Based on the initial results, excellent local control with minimal complications is expected for stage I NSCLC.

1. Introduction

Lung cancer is the leading cause of mortality among males in Japan. Despite continued research into novel therapeutic strategies, 5-year survival rates for lung cancer remain at approximately 15% [1]. One of the main reasons for this disappointing survival rate is the relatively late diagnosis of lung cancer. However, lung cancers are increasingly being detected in the earlier stages, thanks to the routine use of computed tomography (CT). For early stage lung cancers, the cure rate is 29–72% if surgical resection of the tumor can be achieved [2]. Surgical resection may not be an option for lung cancer patients with tobacco-related illnesses, severe cardiovascular disease, or other medical conditions. Other patients refuse surgery for personal reasons. Historical 5-year survival rates for early stage lung cancer patients treated using conventional radiotherapy are 0–42% [3]. Recently, fractionated high-dose stereotactic radiotherapy (SRT) has been actively performed for early stage lung cancer [4–6]. In a landmark study by Uematsu, SRT was performed using a novel combination of CT scanner and linear accelerator (linac) [4,7]. This combined unit allowed visualization of the tumor at the time of radiotherapy, directing multiple non-coplanar beams of radiation to converge on the tumor with great accuracy. Such real-time CT-guided treatment provides precise targeting of the tumor and maximal sparing of normal lung tissues.

SRT has focused attention on the need to control tumor motion due to respiration using methods that prevent enlargement of the irradiated lung volume, such as respiratory gating, active breath control, or breath-holding. We developed a new irradiation technique comprising breath-hold and patient-controlled radiation beam switching with a moving CT scanner and linac unit (linac-CT) [8]. The current study aimed to apply this technique to SRT for stage I non-small cell lung cancer (NSCLC) and to evaluate the resultant primary clinical outcomes.

2. Material and methods

2.1. Eligibility criteria

All patients enrolled in this study satisfied the following eligibility criteria: (1) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdomen CT, bronchoscopy, bone scintigram, and brain magnetic resonance imaging; (2) histologically confirmed NSCLC; (3) tumor diameter <60 mm; (4) performance status according to World Health Organization guidelines ≤2; (5) demonstrated ability to maintain breath-hold for more than 10 s; (6) demonstrated ability to understand and perform self-breath-hold and radiation beam control. Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. This study was approved by the ethics committee of our institution.

2.2. Patient characteristics

Between July 2000 and October 2002, a total of 38 patients were identified as candidates for the irradiation procedure. However, three patients (8%) were excluded, as they could not suitably perform self-breath-holding and beam switching techniques. A summary of patient characteristics is provided in Table 1. A total of 35 patients were treated using this irradiation procedure. Fourteen patients displayed pulmonary emphysema or fibrosis before treatment. Twelve patients were considered medically operable, but had refused surgery or were advised to select SRT by medical oncologists. The remaining 23 patients were judged medically inoperable due to poor respiratory function, advanced age, or other chronic illness.

2.3. Treatment methods

Treatments were delivered using our newly developed unit, comprising a linear accelerator (linac)