Featured Articles

Development of Compact Proton Beam Therapy System for Moving Organs

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OVERVIEW: The use of particle beams in treating cancer, both in Japan and overseas, is growing in recognition of their ability to precisely target the dose of radiation on the cancerous tumor while minimizing the impact on surrounding organs. In particular, it is anticipated that particle therapy using scanning irradiation will become mainstream in the future. Having led the world in the commercialization of this form of treatment, Hitachi has also been working on the development of compact particle therapy systems that have been designed specifically to use this method. In 2009, as part of the "Advanced Radiation Therapy Project Real-time Tumor-tracking with Molecular Imaging Technique" funded by the FIRST Program as a national project launched in partnership with Hokkaido University, Hitachi jointly developed and commercialized a scanning irradiation technique that can track moving organs, and that incorporated a tumor-tracking radiotherapy system developed by Hokkaido University. Hitachi intends to utilize these new technical developments to help encourage the wider adoption of particle therapy.

INTRODUCTION

THE use of radiation in cancer therapies has become increasingly important in recent years as a form of treatment that can improve the patient's subsequent quality of life (QoL). Particle therapy, in particular, which uses protons or carbon ions accelerated to a high energy, is seen as having significant potential, in terms of treatment effectiveness and the minimizing of side effects, due to its ability to focus a high proportion of the dose on the cancerous tumor. Currently particle therapy is offered by a total of 53 different facilities around the world, with more than 120,000 patients having received treatment to date. With further 32 facilities currently under construction and 17 more planned, it is anticipated that the technology will continue to proliferate in the future(1). Hitachi develops its particle therapy systems by utilizing technology built up through the development and manufacture of particle accelerators for use in physics research(2). Based on its success in supplying a proton beam therapy system to the Proton Medical Research Center at the University of Tsukuba Hospital, which commenced operation in 2001(3), Hitachi received an order in 2002 for a proton beam therapy system from the University of Texas MD Anderson Cancer Center (MDACC), which became the first commercial facility in the world to commence therapy using proton beam spot scanning irradiation technology in 2008(4), (5). Spot scanning irradiation technology is able to further enhance the ability of particle therapy to precisely target the dose. Meanwhile, recognizing the need to reduce overall system size and cost to encourage the wider adoption of particle therapy, Hitachi has continued to work on ways of achieving this since completing the MDACC system.

As part of the "Advanced Radiation Therapy Project Real-time Tumor-tracking with Molecular Imaging Technique," which was selected as a national project in 2009 and funded by the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program), Hitachi worked in partnership to incorporate the tumor-tracking radiotherapy system being developed by Hokkaido University that can perform radiotherapy on moving tumors. Fig. 1 shows photographs of the treatment room and synchrotron (main accelerator) of the completed molecular tracking proton beam therapy system, and also of the facility in which it is housed. The Hitachi proton beam therapy system supplied to Hokkaido University was approved for manufacture and sale as a medical device under the Pharmaceutical

(a) Treatment room (b) Synchrotron (c) Proton Beam Therapy Center

Fig. 1—Proton Beam Therapy System at Hokkaido University Hospital Proton Beam Therapy Center.
(a) Treatment room equipped with rotating gantry. The irradiation field shaping mechanism (located under the table) enables the proton beam to be directed at the patient from any angle (360°). (b) The proton beam is accelerated by a synchrotron accelerator. (c) The Proton Beam Therapy Center is located next to Hokkaido University Hospital for easy access by patients.

Affairs Act in February 2014, and proton beam therapy based on the scanning irradiation method commenced in March of that year. Approval for manufacture and sale as a medical device under the Pharmaceutical Affairs Act was also obtained for a therapy system that combines the tumor-tracking and spot scanning irradiation techniques in August 2014.

This article describes the development of a compact proton beam therapy system specifically designed for spot scanning irradiation, and the current progress on developing techniques for the precise irradiation of tumors that are in motion (due to the patient's breathing, for example).

MAKING PROTON BEAM THERAPY SYSTEM SMALLER

To irradiate tumors located deep in the body, proton beam therapy accelerates protons to about 70% of the speed of light. Hitachi uses a synchrotron for this purpose, a form of circular accelerator. Recognizing that reducing the size of the synchrotron is essential to reducing the size of the overall proton beam therapy system, Hitachi embarked on development with the aim of creating a system designed specifically for scanning irradiation.

A proton beam therapy system consists of a synchrotron (main accelerator), a linear accelerator that acts as the injector for the synchrotron, a high-energy beam transport line that directs the high-energy protons to the treatment room, a rotating gantry that can aim the proton beam at the patient from any direction, and an irradiation nozzle that shapes the proton beam to match the shape of the patient's tumor (see Fig. 2).

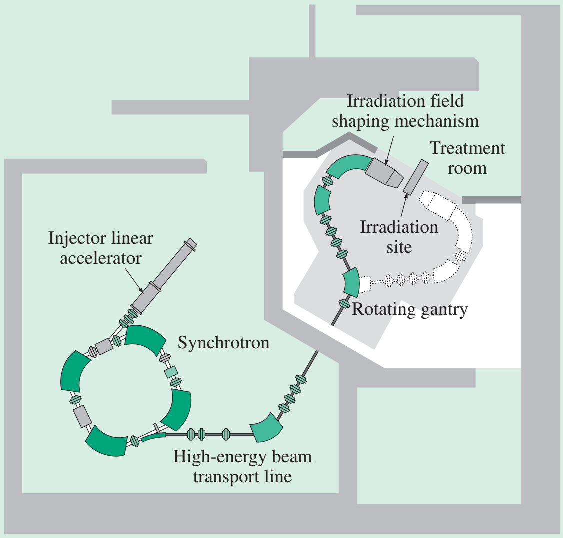


Fig. 2—Overall Structure of Proton Beam Therapy System.
Protons accelerated by the synchrotron are transported to the treatment room where the irradiation field shaping mechanism directs the beam at the tumor, shaping it to match the shape of the tumor.

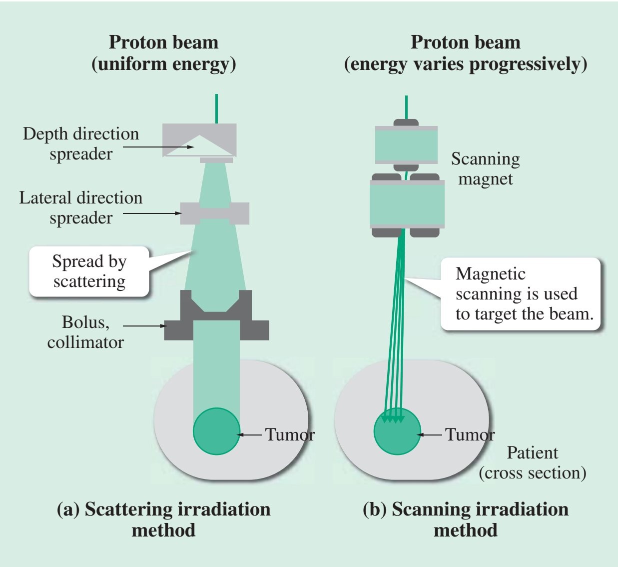


Fig. 3—Comparison of Systems for Shaping Irradiation Field.
Whereas the scattering irradiation method utilizes the energy loss that occurs as protons pass through a material to spread the proton beam in the depth direction and scattering to spread the beam in the lateral direction, in the scanning irradiation method, spreading the irradiation field over a three-dimensional region is performed entirely magnetically, resulting in low energy loss and high proton utilization.

Advantages of Spot Scanning Irradiation

Fig. 3 shows the designs of the systems that shape the irradiation field for radiotherapy using the previous scattering irradiation method and for the scanning irradiation method. In the case of the scattering irradiation method, the proton beam enters the irradiation field shaping mechanism with uniform energy. Here, the high dose rate region is enlarged using devices that spread the beam in the depth and lateral directions respectively, and the beam then passes through a beam-limiting collimator to match its cross-section to that of the tumor. Spreading the dose distribution in the lateral direction utilizes the principle whereby the proton beam scatters as it passes through a material, a process that is accompanied by a loss of energy. Because the collimator is used to block the unwanted part of this widened irradiation field, the proton utilization of this method is low. In contrast, spot scanning irradiation seeks to focus a narrow proton beam from the accelerator at the target without allowing its diameter to spread, and matches the dose distribution to the tumor shape by three-dimensional scanning of the irradiation site. The irradiation depth (in the direction of the proton beam) is adjusted by varying the energy to which protons are accelerated by the synchrotron, and two scanning magnets are used to magnetically scan the beam over the plane perpendicular to the beam direction. This results in a very high proton utilization, where close to 100% of the proton beam that enters the irradiation field shaping mechanism reaches the tumor. Consequently, the advantages of designing a system specifically for spot scanning irradiation are that there is minimal energy loss in the irradiation field shaping mechanism and high proton utilization. These were incorporated into the development of the compact accelerator system.

Development and Testing of Compact Accelerator System

The development of the compact accelerator system designed specifically for spot scanning irradiation took advantage of the minimal energy loss in the irradiation field shaping mechanism to down-rate the performance of the synchrotron (main accelerator) from the 250-MeV maximum energy of the previous system to 235 MeV. This reduced the required magnetic field performance of the various system components and the specifications of the power supply for the electromagnets used to produce the magnetic field. Similarly, Hitachi realized it could take advantage of the high proton utilization to reduce the intensity of the beam of accelerated protons extracted from each cycle of the synchrotron. Because utilization of these features gave Hitachi greater flexibility in the basic design of the synchrotron, Hitachi started out on the development with the idea of using a bare-minimum configuration, the end result of which was a basic layout that consisted of four linear sections linked by four 90° bending magnets (one linear section each for injection and acceleration and two for extraction). As a result, the new design has two fewer bending magnets than the six on the previous system. Similarly, whereas the previous synchrotron had 10 quadrupole magnets to provide adequate range for post-commissioning adjustment, the compact accelerator system has only four thanks to coupling a dispersion function to the magnetic fields generated at the end shapes of the bending magnets (see Fig. 4).

The three-dimensional magnetic field distributions at the ends of the bending magnets are particularly important for the new compact accelerator system. By obtaining precise estimates of the behavior of particles in the magnetic field from the bending magnet and utilizing this information in the magnetic pole design, Hitachi developed and implemented a simulation technique for particle trajectory tracking that could be used to verify the orbital stability of protons in the synchrotron based on the results of three-dimensional

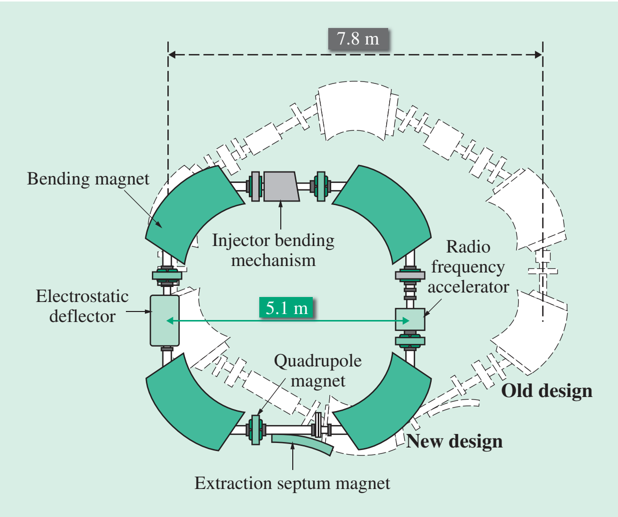


Fig. 4—Comparison of New and Old Synchrotron Designs.
By coupling the functions of the quadrupole magnets to the ends of the bending magnets, the new design has reduced the total number of main magnets (bending magnets and quadrupole magnets) to eight. This compares to 16 on the old design.

magnetic field analysis. This involved performing a three-dimensional magnetic field analysis over the range of the magnetic excitation field of the bending magnets to determine the magnetic field distribution in the region through which the protons pass and assessing the stability of the proton beam as the particles travel multiple times around the accelerator(6).

These developments were used for reference when performing on-site testing of accelerator performance. The testing started with the generation and acceleration of a proton beam from the linear accelerator that acts as the injector, and extended up to injection of the beam into the synchrotron, acceleration, and extraction. The fact that this process was completed in approximately one week demonstrates the usefulness of the simulation technique for particle trajectory tracking developed by Hitachi.

INCORPORATION OF TUMOR-TRACKING

A number of methods have been proposed for the radiotherapy of organs such as lungs and liver that move due to the patient's breathing and other movements. For the use of proton beam therapy to treat organs such as the lungs or liver, Hitachi supplied a respiration-synchronized irradiation technique in partnership with the Proton Medical Research Center at the University of Tsukuba Hospital(3). This uses a device for providing a respiration synchronization signal that detects the surface movement of the patient's body to obtain a respiration phase signal, and only outputs a gate signal when the movement reaches a predetermined phase. The proton beam is only output when this gate signal is on. The current development has involved combining Hitachi's spot scanning irradiation with tumor-tracking, a technique that has been developed by Hokkaido University to enable the radiotherapy of moving tumors(7). Tumor-tracking works by injecting a gold marker (1 to 2 mm in diameter) into the patient close to the tumor and obtaining X-ray images from two different directions at a rate of 30 frames per second to determine the location of the gold marker in the patient's body in three dimensions. The beam is then only output when the location of the marker is within a predefined range (see Fig. 5). The combination

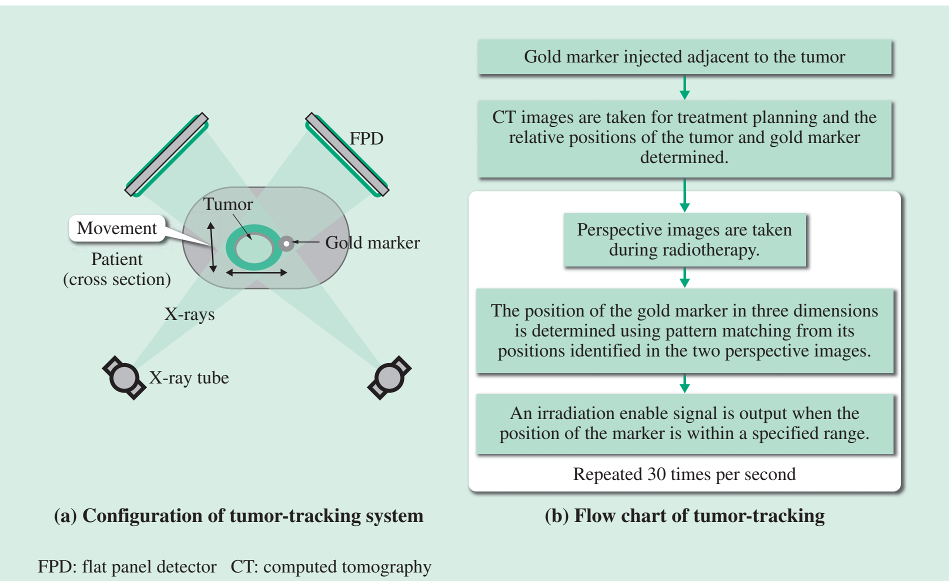


Fig. 5—Tumor-tracking.
(a) The system incorporates an X-ray imaging system that can obtain images of the patient from two different directions.
(b) A gold marker injected adjacent to the tumor is captured in the X-ray images and its position is determined in three dimensions using geometry based on its location above the detector (FPD). Because the position of the gold marker can be determined with high accuracy (within ±1 mm), it is possible to track the movement of the organ.

of tumor-tracking and spot scanning irradiation enables the movement of the tumor to be determined and ensures precise irradiation of moving organs.

Improvements in Accelerator Control

Hitachi has worked with a research team at Hokkaido University on the joint development of an accelerator operation control technique that improves irradiation efficiency on systems that combine tumor-tracking with spot scanning using a synchrotron accelerator. In this context, irradiation efficiency means the probability that the proton beam will be available when the signal from the tumor-tracking system specifies beam output. The operating practice that Hitachi adopted for the previous respiration-synchronized irradiation technique achieved efficient irradiation even if the respiration cycle varied by making the synchrotron operation cycle variable, switching operation to a standby mode after protons had been injected into the synchrotron and accelerated to the point where they were ready for extraction [see Fig. 6 (a)].

With tumor-tracking, on the other hand, a problem identified during discussions associated with the joint research was that, because the marker position can be determined 30 times a second, there is the potential for the irradiation enable signal to be turned on and off in short succession (33 ms), meaning that, if the previous operating practice is used, the proton beam will only be output for this very short time when irradiation is enabled, and the synchrotron accelerator will switch to deceleration. To prevent this, Hitachi has devised an operation and control technique that can maintain the quality of the delivered proton beam while still achieving a high irradiation efficiency. The technique utilizes a new delay gate during the control period after extraction starts that prevents the accelerator from switching to deceleration during short periods when the irradiation enable signal is off, but only after a fixed period of time has elapsed. This technique enables the synchrotron to be operated in such a way that multiple irradiation enable signals can occur within a single operation cycle [see Fig. 6 (b)].

The Hokkaido University research team has conducted testing of the irradiation enable gate signals for actual patients when using the previous tumor-tracking radiotherapy and found that the irradiation time that results from using this new control technique is about 20% shorter on average than for the previous method[8].

Testing Using Dose Distribution Calculation

By making enhancements to a dose analysis technique for scanning that has been the subject of ongoing development since commercializing spot scanning irradiation at MDACC, the dose distribution when using tumor-tracking in combination with spot scanning irradiation has been evaluated to verify the benefits. A target representing a tumor and consisting of a cube with 6-cm sides was placed in water used

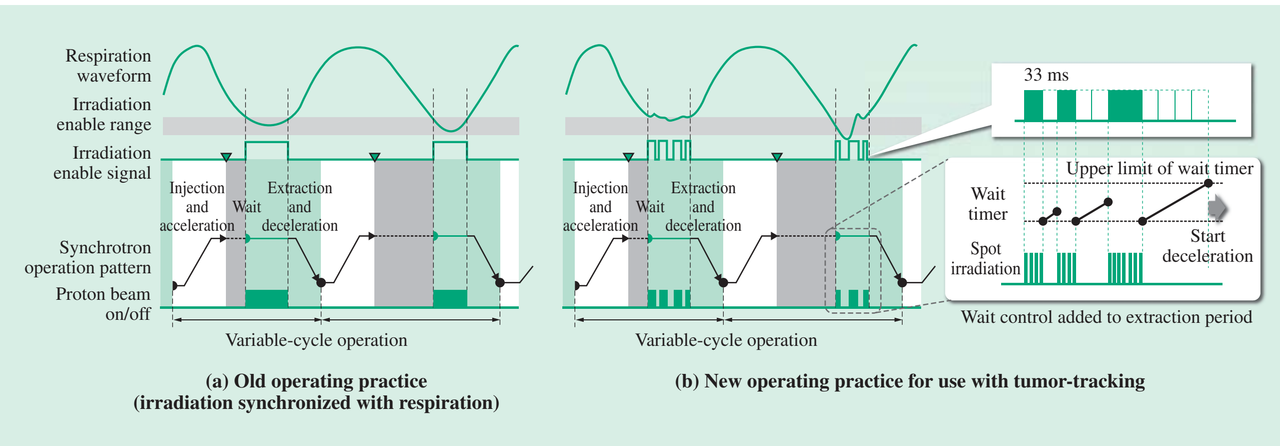


Fig. 6—Comparison of Old and New Synchrotron Operating Practices.
(a) The respiration-synchronized irradiation technique used in the past utilized the variable-cycle operation of the synchrotron to achieve highly efficient irradiation synchronized with the patient's breathing when the generated irradiation enable signal was comparatively long (less than 1 s). (b) Because the irradiation enable signal may be generated for periods as short as 33 ms (equivalent to determining of marker position 30 times per second) when combined with tumor-tracking, Hitachi improved irradiation efficiency by amending the operating practice to include standby control instead of decelerating immediately after the irradiation enable signal turns off, thereby enabling irradiation to occur multiple times during each operation cycle.

as a model of the human body and the irradiation conditions for delivering a uniform dose to the target were determined. Assuming that the movement of the target would follow a sine wave function raised to the fourth power with a peak-to-peak amplitude of 20 mm and a period of 3 s, the range of positions within that movement in which irradiation would be enabled was specified and a study was made of the relationship between the amplitude and the degree of uniformity of dose distribution within the target. Three directions of movement were specified: parallel to the preferred scanning direction for spot irradiation (primary direction), perpendicular to this direction (secondary direction), and the depth direction (direction of the proton beam) [see Fig. 7 (a)]. After first determining the dose distribution under each set of conditions, the dose uniformity was determined as follows based on the maximum and minimum doses in the target (D_{max} and D_{min}).

$$\text{Dose uniformity} = \frac{D_{max} - D_{min}}{D_{max} + D_{min}}$$

Using a 2-mm-wide irradiation enable range ensures a dose uniformity of within 3% of the intended value regardless of the direction of target movement [see Fig. 7 (b)].

To conduct testing under more realistic conditions, the Hokkaido University research team undertook a study using data from the respiratory movements of actual patients treated using the previous tumor-tracking radiotherapy technique or computed tomography (CT) data used for treatment planning. The study found that using tumor-tracking and spot scanning irradiation in combination resulted in precise irradiation of the tumor and identified the conditions for achieving this[(9), (10)].

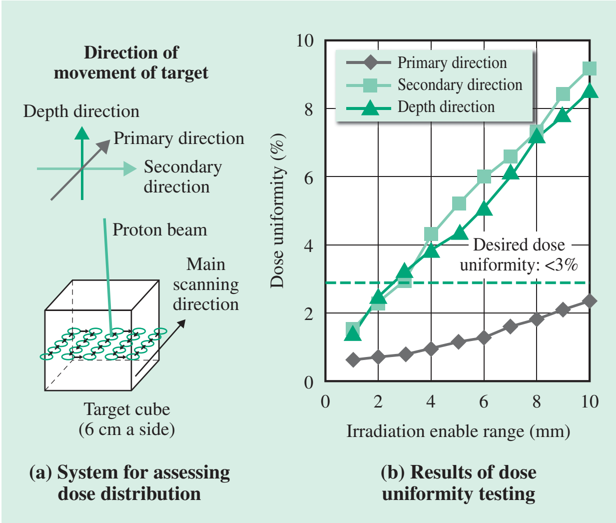


Fig. 7—Results of Dose Distribution Testing.
(a) The target cube was moved in a trajectory that mimicked respiration and the dose distribution determined. (b) Although performance differed depending on the scanning direction, the results indicate that the desired dose uniformity of 3% or less of the intended value can be achieved with an irradiation enable range of 2 mm.

The basic operation and dose distribution when using tumor-tracking and spot scanning irradiation in combination have already been determined, and work on testing the benefits of the control technique described above is ongoing.

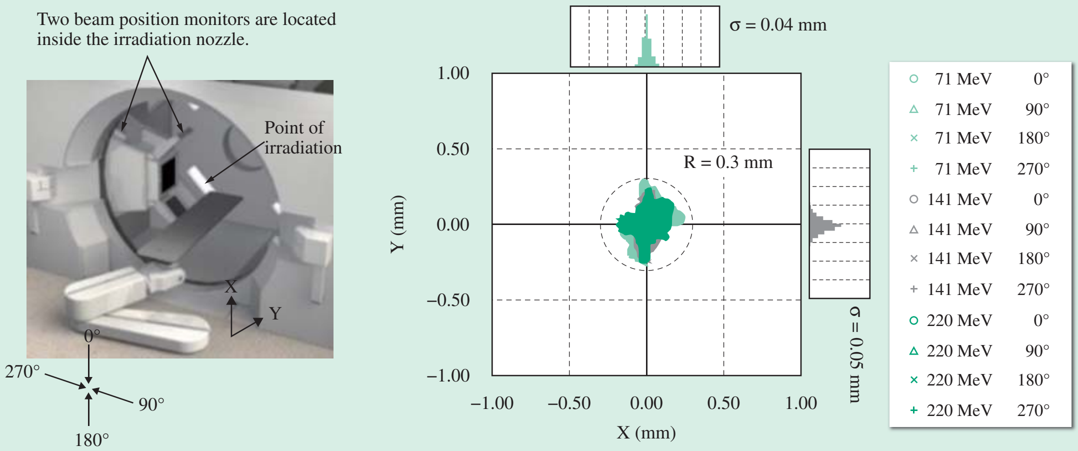
EVALUATION OF PROTON BEAM RADIOTHERAPY PERFORMANCE

Testing was conducted to determine the performance at the point of irradiation for a proton beam from the synchrotron that had traveled to the treatment room via a high-energy beam transport line. When the position of the proton beam at the point of irradiation in the treatment room [see Fig. 8 (a)] was determined using measurements from a position monitor located in the irradiation field shaping mechanism, the error was less than 0.3 mm and the variability was low (1σ = 0.05 mm), indicating that the irradiation position can be controlled accurately [see Fig. 8 (b)].

CONCLUSIONS

This article has described the development of a compact proton beam therapy system designed specifically for spot scanning irradiation, and the progress being made on developing techniques for the precise irradiation of moving tumors (due to the patient's breathing, for example).

The compact proton beam therapy system was developed by designing it specifically for spot scanning irradiation. The development included use of a simulation technique for particle trajectory tracking that could verify the orbital stability of protons in the synchrotron accelerator based on the results of three-dimensional magnetic field analysis. The synchrotron (main accelerator) in the new system has a circumference of only 18 m, compared to 23 m for the previous system, and also has fewer main magnets. Hitachi has also developed an irradiation method that combines spot scanning irradiation technology with the tumor-tracking technology developed by Hokkaido University to provide proton



(a) Measurement system **(b) Measured proton beam positional accuracy**

Fig. 8—Proton Beam Irradiation Performance Testing.
(a) To assess beam performance at the point of irradiation, the beam position was determined using measurements for each spot obtained by a beam position monitor located in the irradiation field shaping mechanism and the dose distribution was determined using a measurement device located at the point of irradiation. (b) The graph shows the results of testing from four different angles and at three typical energy levels, irradiating 2,000 spots each time.

beam therapy for tumors in organs that are moving (due to the patient's breathing, for example), and it has devised a synchrotron operating practice that improves irradiation efficiency.

In the future, Hitachi intends to contribute to the wider adoption of particle therapy by continuing with research and development aimed at building systems with smaller size and lower cost through the application of techniques developed through this research not only to particle beam therapy systems that use proton beams but also to those that use carbon ions.

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REFERENCES

(1) Particle Therapy Co-Operative Group (PTCOG), http://www.ptcog.ch/
(2) J. Hirota and K. Hiramoto, "System Design of Particle Accelerator," Hitachi Hyoron **79**, pp. 211–216 (Feb. 1997) in Japanese.
(3) K. Umegaki et al., "Development of Advanced Proton Beam Therapy System for Cancer Treatment," Hitachi Review **52**, pp. 196–201 (Dec. 2003).
(4) K. Matsuda et al., "World-first Proton Pencil Beam Scanning System with FDA Clearance," Hitachi Review **58**, pp. 225–232 (Oct. 2009).
(5) A. Smith et al., "The M. D. Anderson Proton Therapy System," Med Phys. **36**, 4068–4083 (2009).
(6) T. Aoki et al., "Estimate of Magnetic Field Dependence of Optics Properties of Synchrotron Bending Magnet for Particle Beam Therapy System," Proceedings of the 8th Annual Meeting of the Particle Accelerator Society of Japan, pp. 690–693 (Aug. 2011) in Japanese.
(7) H. Shirato et al., "Real-time Tumour-tracking Radiotherapy," THE LANCET **353** (9161), pp. 1331–1332 (1999).
(8) T. Matsuura et al., "On Reduction of Irradiation Time in Gated Spot-Scanning Proton Therapy with Real-Time Tumor-Tracking," PTCOG51 (2012).
(9) T. Matsuura et al., "Integration of a Real-time Tumor Monitoring System into Gated Proton Spot-scanning Beam Therapy: An Initial Phantom Study Using Patient Tumor Trajectory Data," Med Phys. **40**, 071729 (2013).
(10) S. Shimizu et al., "A Proton Beam Therapy System Dedicated to Spot-Scanning Increases Accuracy with Moving Tumors by Real-Time Imaging and Gating and Reduces Equipment Size," PLOS ONE, 9, 4, e94971 (2014).

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