**Table 1**
The patients' characteristics

| No. | Age | Site | TNM | Histology | Symptoms |
|---|---|---|---|---|---|
| 1 | 50 | Left | T4N3M0 | SCC[a] | Pain |
| 2 | 68 | Right | T4N0M0 | P/D ca.[b] | Pain, numbness |
| 3 | 66 | Left | T4N0M0 | Ad[c] | Pain |
| 4 | 67 | Right | T4N0M0 | NSCC[d] | Pain |
| 5 | 51 | Left | T4N0M0 | Ad[c] | Pain, numbness |

[a] SCC, squamous cell carcinoma.
[b] P/D ca., poorly differentiated carcinoma.
[c] Adenocarcinoma.
[d] Non-small-cell carcinoma.

**Table 2**
The treatments' characteristics

| No. | RT[a] dose (Gy) | Chemotherapy | RT dose at HT (Gy)[b] | HT sessions |
|---|---|---|---|---|
| 1 | 70 | Cisplatin + etoposide (BAI[c]) | 58 | 2 |
| 2 | 70 | – | 50 | 3 |
| 3 | 68 | Cisplatin + irinotecan[#] | 36 | 4 |
| 4 | 68 | Cisplatin + irinotecan[#] | 36 | 3 |
| 5 | 70 | Carboplatin + paclitaxel[#] | 40 | 4 |

[a] RT, radiation therapy.
[b] HT, hyperthermia.
[c] BAI, bronchial arterial infusion chemotherapy (before radiotherapy).
[#] Concurrent with radiotherapy.

that the addition of hyperthermia to radiotherapy or chemotherapy could enhance the tumor control. Here, we present 5 Pancoast tumor cases that were not eligible for surgery and were treated with hyperthermia-inclusive multimodality therapies.

## 2. Material and methods

Five patients with inoperable Pancoast tumor were treated with hyperthermia-inclusive multimodality therapies. Age ranged 50–68 years with median 66 years. The patients' characteristics are shown in Table 1. They suffered from severe symptoms such as pain and/or numbness which were considered to be related with the tumor. Tumor-node-metastasis (TNM) stages were established using the International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer and the Union Internationale Centre le Cancer [13]. All patients were diagnosed in T4 with vertebral invasion, and only one patient had N3 nodal lesion. These patients were not eligible for curative operation due to deep vertebral body involvement with/without poor performance status and complications. The decision was made through medical consultants from; radiation oncologists, medical oncologists and thoracic surgeons whom discussed about the treatment plan. All patients were fully informed about the possibility of severe or unexpected toxicity and agreed to this treatment.

Radiation therapy was delivered using 10-MV X-rays in 2 Gy fractions 5 times weekly. The total radiation dose was 68–70 Gy. Of them, 3 patients received systemic chemotherapy concurrently with radiation therapy and 1 patient received bronchial arterial infusion chemotherapy before radiation therapy. In the latter half of the radiation therapy hyperthermia was performed for 2–4 sessions once a week with 8 MHz radiofrequency capacitive heating equipment (Thermotron-RF 8, Yamamoto Vinita Co. Ltd., Japan). The treatment characteristics are demonstrated in Table 2.

The patients were then followed-up every 1 month for the first 2–3 years and every 2–3 months thereafter unless they had symptoms that required immediate examination or intervention. Radiographic examination by chest X-ray was performed at each follow-up visit. Computed tomography (CT) and positron emission tomography (PET) with the glucose analog [18F]-fluorodeoxyglucose (FDG) were performed by the discretion of the attending physician and radiation oncologist. The tumor response was judged according to the Response Evaluation Criteria in Solid Tumors (RECIST) [14]. The tumor-related symptoms were analyzed in order to evaluate the effectiveness. The symptom relief was assessed according to the scoring system created by Kramer et al. [15] which is defined as follow; vanished is complete resolution of the symptom, diminished is any improvement without complete resolution, stabilized is no change, or progressive is deterioration and the best response at any time was reported. The late pulmonary and skin toxicities were graded using the toxicity criteria of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC) [16].

## 3. Results

Median follow-up was 65.8 months (range, 9.0–78.5 months). Clinical outcomes are listed in Table 3. For primary response, 4 tumors showed partial response and 1 tumors showed stable disease (SD) on RECIST. All patients survived 3 years or more without recurrence except for 1 patient who was shortly followed-up (9 months). Of them, 2 patients were recognized with local recurrence at 38.7 and 42.7 months after treatment, and died at 66.9 and 78.5 months after treatment, respectively. The other 2 patients are disease-free survivors for 4 and 5 years after treatment. The symptoms were scored to be vanished in 3 patients and diminished in 2 patients, respectively. No severe late complication (RTOG/EORTC criteria grade 3 or worse) was observed.

### 3.1. Short case report

A 67-year-old male was admitted to our hospital with right shoulder pain and numbness in right arm. A chest radiography showed abnormal shadow in right apical region. A CT scan and magnetic resonance image (MRI) showed the tumor invading the thoracic vertebra and the 1st and 2nd right ribs which associated with bone destruction (Fig. 1a). The tumor exhibited uptake of FDG on PET (Fig. 1b). A fine-needle CT guided aspiration biopsy proved a non-small-cell carcinoma, and the disease was diagnosed clinically T4N0N0, Stage IIIB lung cancer; Pancoast tumor. He was treated with thoracic irradiation up to 68 Gy with conventional fractionation. Hyperthermia was performed using Thermotron-RF 8 once a week after the total irradiation dose reached 36 Gy. Coupling of the applicator to the patient was usually achieved with plastic

**Table 3**
Clinical outcomes

| No. | Tumor response | Symptom relief | Time to local progression | Follow-up period (months) | Status |
|---|---|---|---|---|---|
| 1 | PR | D | 38.7 months | 66.9 | Dead |
| 2 | PR | V | 42.7 months | 78.5 | Dead |
| 3 | PR | V | No recurrence | 65.8 | Alive |
| 4 | SD | V | No recurrence | 55.1 | Alive |
| 5 | PR | D | No recurrence | 9.0 | Alive |

V, vanished (complete resolution of the symptom); D, diminished (any improvement without complete resolution).

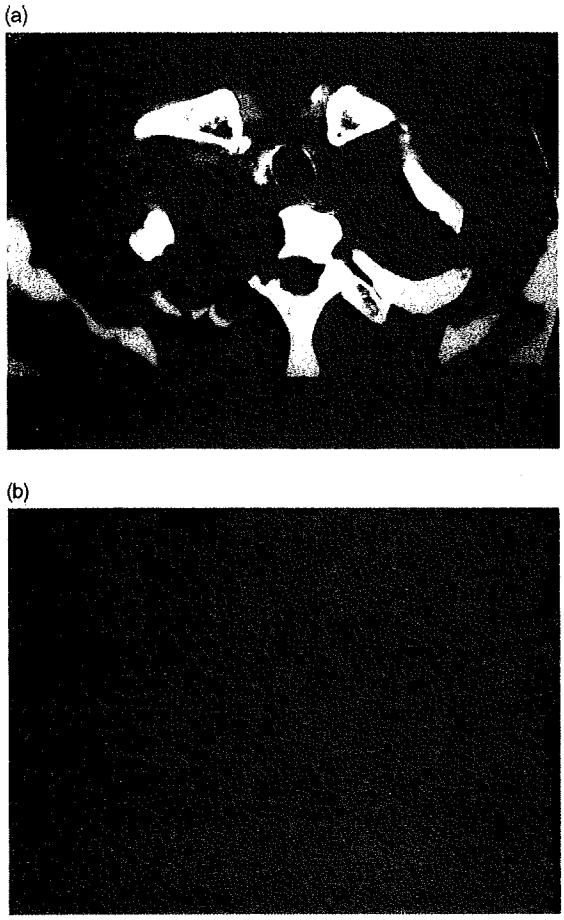


**Fig. 1.** (a) A Chest CT revealed the tumor invading the thoracic vertebra and the 1st and 2nd right ribs with bone destroyed. (b) FDG-PET. The tumor exhibited uptake of 18F-FDG.

bags filled with deionized water. Active skin cooling was applied. He received 3 sessions of hyperthermia. Systemic chemotherapy including 45 mg/body cisplatin (CDDP) and 30 mg/body irinotecan (CPT-11) was administered just before every hyperthermia session. At the end of the treatment the primary tumor was assessed as SD on RECIST. In spite of the SD, he relieved from all symptoms. No severe non-hematological toxicity was observed. Four years later the tumor continued to be SD and did not uptake on FDG-PET (Fig. 2a and b). He is surviving without recurrence till this moment (55.1 months).

## 4. Discussion

During the past 40 years, the local control and the overall survival for patients with Pancoast tumors have improved using intensive local treatments which consisted of radiotherapy with or without chemotherapy followed by surgery [2]. There is a large prospective multicenter phase II trial (Intergroup Trial 0160) tested the feasibility of induction chemoradiotherapy for Pancoast tumors [9]. In this trial, 110 eligible patients were enrolled in the study. Induction therapy was completed by 104 (95%) patients. Of them, 95 patients were eligible for surgery. Five-year survival rate was 44% for all patients and 54% after complete resection. Although the treatment approach was very attractive and encouraging, all patients were not suitable for it and 2 patients (2.3%) died postoperatively of multisystem failure.

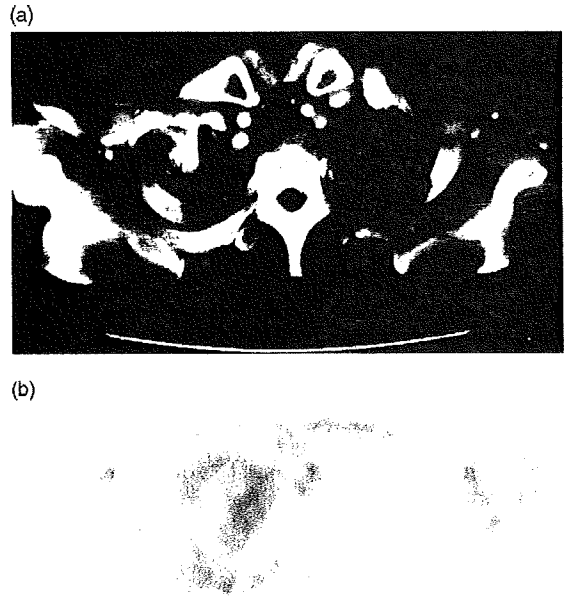


**Fig. 2.** (a) Four years after treatment, a chest CT showed the same size tumor comparing with the pretreatment. (b). Four years after treatment, FDG-PET showed no uptake in the tumor.

Radiotherapy is the mainstay for inoperable Pancoast tumor. However, radiotherapy alone is not considered to be sufficient. Komaki et al. conducted a retrospective study at The University of Texas M.D. Anderson Cancer Center to identify the outcome predictors for 143 patients with superior sulcus tumors (SST), including Pancoast tumors treated by a multidisciplinary approach [6]. Twenty-three patients survived longer than 3 years. Only 4 patients (17%) received radiation therapy alone or in combination with chemotherapy, while 19 patients (83%) had surgical resection combined with radiation therapy and/or chemotherapy. This study suggested that surgery was an important component of the multidisciplinary approach to those patients with SST.

In Intergroup Trial 0160 [9], patients received two cycles of CDDP and VP-16 concurrently with 45 Gy radiation. Pathologic complete response (CR) or minimal microscopic disease was seen in 61 (56%) resection specimens and pathologic CR led to better survival than when any residual disease was present. This suggests a direct relationship between local control and survival, hence increasing the tumor dose is expecting an improvement of the local control. Kwong et al. [8] researched the surgical resection of Pancoast tumors after neoadjuvant high-dose radiation. Mean total radiation dose was 56.9 Gy. Pathologic complete response was found in 40.5% of patients. In spite of increasing the radiation dose (56.9 Gy), pathological response is similar to the Intergroup Trial 0160 (45 Gy). It is not clear that whether the higher radiation dose would improve the survival. The similar pathological response between different radiation doses might mean the existence of radio- and/or chemo-resistant tumor cells.

In the present study 5 inoperable Pancoast tumor patients received hyperthermia-inclusive multimodality therapies. Hyperthermia was added to radiotherapy alone or in combination with chemotherapy. In this study, Except for 1 patient with short follow-up periods (9 months), other patients survived 3 years or more without evidence of recurrence. One speculation for the disease-free long survivors in the current treatment is that hyperthermia might have sterilizing effect on the radio and/or chemo-resistant tumor cells. The cells in hypoxic and low pH conditions that are

specifically found within tumor tissue due to insufficient blood perfusion are radio and/or chemo-resistance but thermo-sensitive. Drug concentration will be less in the insufficiently perfused tumor regions. The most important mechanisms for an interactive effect are an increased intracellular drug uptake, enhanced DNA damage and higher intratumor drug concentrations, resulting from an increase in blood flow. Furthermore many drugs including cisplatin and carboplatin are potentiated by heat and the addition of hyperthermia to chemotherapy can counteract drug resistance [12]. It is well known as well the cells in the S phase are radioresistant, while these cells are sensitive to heat [17]. Therefore, the combination of radiotherapy with hyperthermia could increase the cytotoxic effects, in so called hyperthermia radiosensitization. The optimal combination of hyperthermia and irradiation is unclear. In this study, hyperthermia sessions were performed in the latter half of conventional radiation therapy, because hyperthermia could cause tumor necrosis due to injury to the tumor vessels. If hyperthermia causes tumor necrosis in the initial phase of conventional radiation therapy, numerous hypoxic cells near the necrosis become to be radioresistant.

## 5. Conclusion

Regional hyperthermia combined with chemo-radiotherapy could improve the local control in Pancoast tumors and result in long-term survival.

## Conflicts of interest statement

Financial support for this study was not provided by any company, foundation and so on. The authors report no conflicts of interest.

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## References

[1] Bradley J, Govindan R, Komaki R. Lung. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK, editors. Principles and practice of radiation oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 1201–43 [Chapter 44].
[2] Rusch VW. Management of Pancoast tumours. Lancet Oncol 2006;7: 997–1005.
[3] Chardack WM, MacCallum JD. Pancoast tumor: five-year survival without recurrence or metastases following radical resection and postoperative irradiation. J Thorac Surg 1956;31:535–42.
[4] Shaw RR, Paulson DL, Kee Jr JL. Treatment of the superior sulcus tumor by irradiation followed by resection. Ann Surg 1961;7:29–40.
[5] Paulson DL. Carcinomas in the superior pulmonary sulcus. J Thorac Cardiovasc Surg 1975;70:1095–104.
[6] Komaki R, Roth JA, Walsh GL, Putnam JB, Vaporciyan A, Lee JS, et al. Outcome predictors for 143 patients with superior sulcus tumors treated by multidisciplinary approach at the University of Texas M.D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 2000;48(2):347–54.
[7] Wright CD, Menard MT, Wain JC, Donahue DM, Grillo HC, Lynch TJ, et al. Induction chemoradiation compared with induction radiation for lung cancer involving the superior sulcus. Ann Thorac Surg 2002;73: 1541–4.
[8] Kwong KF, Edelman MJ, Suntharalingam M, Cooper LB, Gamliel Z, Burrows W, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. J Thorac Cardiovasc Surg 2005;129:1250–7.
[9] Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Winton T, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of southwest oncology group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313–8.
[10] Komaki R, Mountain CF, Holbert JM, Garden AS, Shallenberger R, Cox JD, et al. Superior sulcus tumors: treatment selection and results for 85 patients without metastasis (Mo) at presentation. Int J Radiat Oncol Biol Phys 1990;19(1): 31–6.
[11] Hagan Michael P, Choi Noah C, Mathisen Douglas J, Wain John C, Wright Cameron D, Grillo Hermes C. Superior sulcus lung tumors: impact of local control on survival. J Thorac Cardiovasc Surg 1999;117:1086–94.
[12] van der Zee J. Heating the patient: a promising approach? Ann Oncol 2002;13(8):1173–84.
[13] Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–23.
[14] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[15] Kramer GW, Gans S, Ullmann E, van Meerbeeck JP, Legrand CC, Leer JW. Hypofractionated external beam radiotherapy as retreatment for symptomatic non-small-cell lung carcinoma: an effective treatment? Int J Radiat Oncol Biol Phys 2004;58:1388–93.
[16] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
[17] Bradley J, Govindan R, Komaki R. Lung. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK, editors. Principles and practice of radiation oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 736–56 [Chapter 44].

# Current status of the HIBMC and results of representative diseases

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**Abstract.** The proton radiotherapy (PRT) has been spreading, since 1990 when 250MeV proton beams with rotation gantry was developed for medical use. On the other hand, carbon-ion radiotherapy (CRT) that has both physical and biological features is available at 4 facilities in the world. HIBMC is the only facility to be able to use both particles. From Apr 2001 to Dec 2008, 2486 patients were treated with PRT in 2030 patients or with CRT in 456. Treatment to the Head and Neck (H&N: in 405 patients), the lung (245), the liver (371), and the prostatic carcinoma (1059) was a major subject. The 2-year local control rates is 72% in H&N (n=163, T1:9, T2:18, T3:36, T4:79, malignant melanoma 48, adenoid cystic carcinoma 35, squamous cell carcinoma (SCC) 32, adenocarcinoma 14, others 34), 88% in lung (n=116, T1:59, T2:42,T3:4, T4:6, SCC 30, adenocarcinoma 59, others 27), and 89% in liver cancer (n=153, Proton: 130, carbon: 23). Biochemical disease free 3-year survival of 291 prostate cancer is 100% in 9 patients with initial prostate-specific antigen (PSA) level <=4 ng/ml, 99% in 140 with PSA 4.1-10 ng/ml, 90% in 71 with PSA 10.1-20 ng/ml, and 79% in 71 with PSA>20 ng/ml. These results are excellent comparable or superior to those of surgery. Thus, particle therapy is sophisticated radiotherapy, however the only problem to prohibit the progress is high costs for construction and maintenance. Facilities at which both proton and carbon ion beams can be used, including the HIBMC, have to investigate the differential use. We started clinical randomized trial to compare both ion beams, and started biological examinations in a project aiming at the development of a laser driven proton radiotherapy. We stated about the current status of the HIBMC and the results of representative diseases.

**Keywords:** Proton Radiotherapy, Carbon-ion Radiotherapy
**PACS:** 14.20.Dh, 41.75.-i

## INTRODUCTION

Proton-beam radiation therapy proposed by R. R. Wilson (1946) was initiated at the Lawrence Berkeley National Laboratory (LBL) of the U.S. (1954), Uppsala in Sweden (1957), and Moscow in the former Soviet Union (1967). The Paul Scherrer Institute (PSI) of Switzerland, Clatterbridge of the U.K., Lubin of Belgium, and TRIUMF of Canada also started proton-beam radiation therapy by diverting cyclotrons previously used in fast neutron and negative pi meson beam research facilities. These early proton-beam radiation therapies for cancers were limited because accelerators installed in physical research facilities were used for medical purposes.

The instrument introduced in the Loma Linda University Medical Center (LLUMC) in 1990 emitted 250-MeV proton beams and was equipped with a gantry, being the model for later proton-beam radiation systems for medical use.

When the human body is irradiated with accelerated protons or carbon ions, particles reach a depth corresponding to the acceleration energy. Particles slow as they lose energy, forming a Bragg peak emitting the maximum energy right before they stop. The adjustment of beams to form the Bragg peak at tumor sites exhibits the maximum therapeutic effect on the tumor, while normal tissue distant from the tumor is not irradiated, providing

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safe cancer therapy lacking in conventional X-ray radiation. In addition, particle-beam radiation therapy exhibits a higher biological effect than conventional radiation, enabling the 'cure of cancer without resection'. Particle-beam radiation therapy may be the most promising in this era in which a consideration of the quality of life (QOL) is essential for cancer therapy.

## OUTLINE OF THE HYOGO ION BEAM MEDICAL CENTER (HIBMC)

Construction of a prefectural particle-beam radiation medical center was planned as a leading project of the 'Hyogo Cancer Strategy' of Hyogo Prefecture, and the center was opened in May 2001 9 years after the plan was proposed. It is located in the Harima Science Garden City, and the facility consists of a radiation therapy building (12,000 $m^2$) composed of ion sources, accelerators, and 5 irradiation rooms, and a hospital building (4,500 $m^2$) composed of wards with 50 beds, examination rooms, testing laboratories, and dining halls. There is a Japanese garden on the premises, and the facility is designed in consideration of patient amenity.

The maximum acceleration energy of the synchrotron at the HIBMC is 230 MeV/u for proton beams and 320 MeV/u for carbon ion beams. Three irradiation rooms installed with 45-degree, horizontal/vertical, and horizontal fixed ports can be used for carbon ion irradiation therapy, and 2 gantry rooms can be additionally used for proton beams. The acceleration system of the particle-beam irradiation system consists of 2 ion sources, RFQ and Alvarez linear accelerators, and a synchrotron. Carbon ions and protons can be accelerated at a maximum of 5 MeV/u using the RFQ and Alvarez linear accelerator, and 320 MeV/u by the synchrotron. For clinical usages, proton and carbon ion beams are irradiated at 70-230 and 70-320 MeV/u, and the maximum ranges in water are 40-300 and 40-200 mm, respectively. Irradiated beams are transported to 5 treatment rooms: 45-degree (A), horizontal/vertical (B), and horizontal (C) irradiation rooms, and 2 gantry rooms (G1 and G2) (transport system). The gantry system rotates and irradiates the human body from various directions. Beams are irradiated through an irradiation field-forming system installed in each treatment room (irradiation system). The irradiation field-forming system consists of wobbler magnets which expands the beam laterally, a ridge filter which expands the beam to the optimum spread out Bragg peak (SOBP), collimator which focuses the lateral direction of the beam to the shape of the target volume, range shifter which determines the beam depth in the body, and bolus which optimizes the maximum range, and beams which pass through these devices form an irradiated volume almost consistent with the target volume.

Physical, biological, and preclinical studies of the particle-beam radiation system were performed before clinical trials, and the safety and efficacy of the system were confirmed[1]. Clinical trials with proton and carbon ion beams were performed in 2001 and 2002 following the Pharmaceutical Affairs Law, respectively, and general medical practice was initiated in 2003. Clinical trials were required for the final step in the application for approval of system manufacture, and performed following a protocol prepared based on the Good Clinical Practice (GCP) for Medical Devices. Proton- and carbon ion-beam radiation therapies were approved as advanced medical care in 2004 and 2005, respectively. Advanced medical care is positioned as a pre-step before becoming insurance-covered treatment, and patients have to pay the fee for particle-beam radiation therapy: 2,883,000 yen, by themselves, but other treatments are covered by national insurance.

## INDICATION OF PARTICLE-BEAM RADIATION THERAPY

Proton and carbon ion beams exhibit a physical characteristic of charged particle-beams called the Bragg peak, distinctively different from X-rays. In simulation images of ionizations along the ranges of various radiations (FIGURE 1), the ionization density per unit length (Linear energy transfer: LET) increases in the order of X-rays, proton beams, and heavy ion beams, and are designated as low-, medium -, and high-LET radiations, respectively. At present, it is unclear whether differences in the radiation type are directly associated with the outcomes of clinical treatment, and close investigation is necessary.

Historically, particle-beam radiation therapy started with the treatment of diseases arising from relatively shallow sites, such as malignant ocular choroidal melanoma, basal skull chordoma, and chondrosarcoma, using proton beams at about 80-100 MeV. Employing beams at 230-250 MeV, which the current medical device can output, deep tumors in any region of the trunk are treatable.

Our facility started with treatment of H&N tumors, lung, liver, and prostate cancers, and bone soft tissue tumor, and the indication gradually expanded. As a rule, the presence of cancers at single sites is required. Therapy is safely applicable for non-operable patients, such as elderly patients and those with complications. Tumors in the abdominal and pelvic regions were previously excluded from the indication because the regions are close to the digestive tract including the stomach and intestine, but spacer placement surgery, surgeons place several devices between the tumor and digestive tract before particle-beam irradiation, enabled safe and reliable particle-beam irradiation.

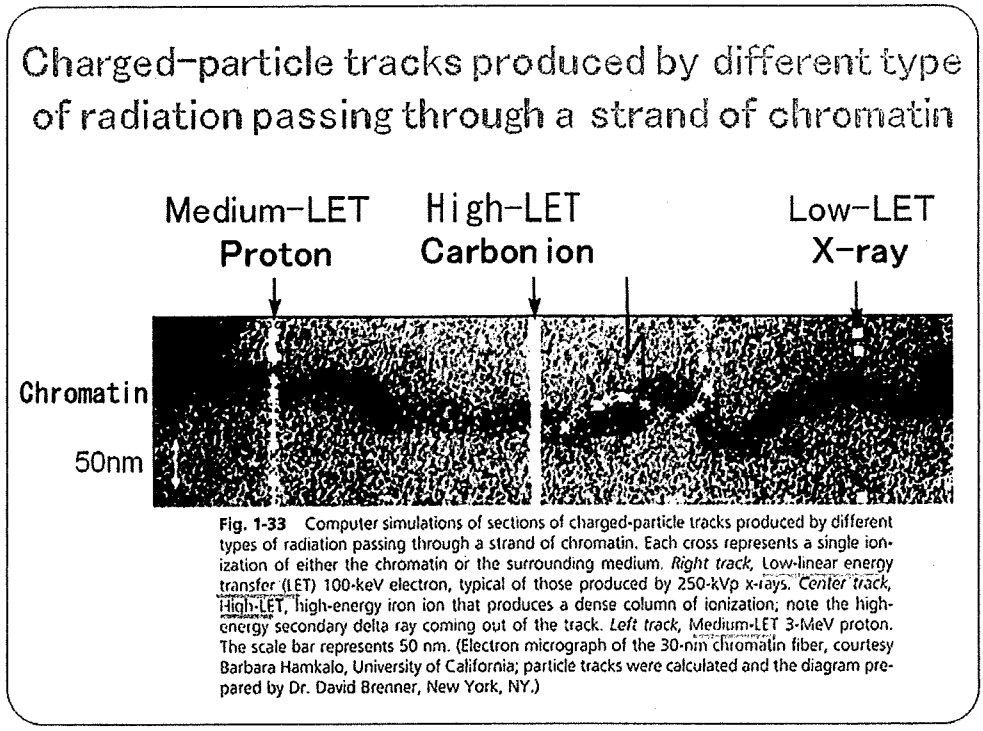


Fig. 1-33 Computer simulations of sections of charged-particle tracks produced by different types of radiation passing through a strand of chromatin. Each cross represents a single ionization of either the chromatin or the surrounding medium. *Right track*, Low-linear energy transfer (LET) 100-keV electron, typical of those produced by 250-kVp x-rays. *Center track*, High-LET, high-energy iron ion that produces a dense column of ionization; note the high-energy secondary delta ray coming out of the track. *Left track*, Medium-LET 3-MeV proton. The scale bar represents 50 nm. (Electron micrograph of the 30-nm chromatin fiber, courtesy Barbara Hamkalo, University of California; particle tracks were calculated and the diagram prepared by Dr. David Brenner, New York, NY.)

**FIGURE 1.** Ionizations and DNA injuries with causative ranges of radiation
Preparation for particle-beam radiation therapy (partially modified from Radiation Oncology Rationale, Technique, Results James D Cox, K Kian Aug (ed) Mosby 8th edition p 44)

## PREPARATION FOR TREATMENT

Preparation for treatment takes about one week. (1) Appropriate fixing devices are prepared for individual patients. The fixation device is attached to the patient, and imaged by plain X-ray CT (Toshiba ASTEION CT Port) at a 2-mm slice thickness and cross-sectional MRI (Phillips Gryroscan Intera 1.5 T Master) for the planning of treatment. The region from the parietal to the lower neck region is imaged in H&N cancer cases, the supraclavicular fossa over the periphery of the lower lung field in lung cancer cases, the region 2 cm from the cranial side of the diaphragm to the lower end of the liver in liver cancer cases, and the upper margin of the 5th lumbar vertebra to the perineal region in prostate cancer. (2) For the treatment of lung and liver cancers, treatment plans are prepared using a respiratory-gated irradiation unit developed by the National Institute of Radiological Sciences (NIRS)[2]. (3) The CT and MRI images are sent on-line to a treatment planning system (FOCUS-M, CMS Co.) (4) Contrast X-ray CT and

MRI diagnostic images are referred to on contour input (gross tumor volume (GTV), clinical target volume (CTV), and organs at risk (OR)), in which treatment plan CT and MRI images can be fused using the FOCAL FUSION system of CMS Co. (5) The planning target volume (PTV) including a margin around the CTV corresponding to the disease is established according to the 3-dimensional treatment plan prepared based on CT images. (6) Based on the 3-dimensional simulation prepared using the CT image and treatment planning system, the optimum beam direction is set corresponding to the anatomical position and tumor-expanded area, and the dose distribution is calculated in consideration of a penumbra, which is defined as the distance between a point irradiated doses of 80% to maximum dose and a point of 20% in the isocenter plane (proton beam: 5-12 mm, carbon beam: 1-3 mm which is depend on the distance between collimator and the position of tumor). The dose is set so as to avoid the exposure of normal tissues, such as the lens, brain, spinal cord, lung, liver, kidney, and intestine to doses higher than their tolerance, and a dose volume histogram (DHV) is prepared to investigate the dose volume histogram in the CTV, PTV, and OR. (7) Parameters of each port, such as the wobble diameter, scatterer, ridge filter, range shifter, and SOBP, are determined using the treatment planning system. The collimator, bolus preparation data, dose of each port, and digitally reconstructed radiographic (DRR) image collated in the irradiation room are calculated, and transmitted to the milling machine or irradiation system. A bolus, which compensates the position of distal end of beams, is made by milling machine. A rehearsal is performed on the day before irradiation to help the patient mentally prepare, confirm the fixation and transmission of parameters, and prepare reference images. Reference images are DRR X-ray photographs in 2 midlateral directions and X-ray beams eye view (BEV) images acquired in the treatment room, compared with those sent from the treatment planning system. After confirming the equivalence, the reference images are saved in the irradiation system server. These are used as standard images to confirm the patient's position in daily irradiation.

The number of treatment fractions varies between 4 in the liver or lung and 37 in the prostate. Physicians, radiologists, and medical physicists prepare for treatment in cooperation, and the optimum treatment plan is selected. Autoactivation positron emission tomography (PET) images are acquired using a PET camera immediately after the first radiation exposure, and collated with the planned images. This is a characteristic of particle-beam irradiation therapy not exhibited by conventional X-ray therapies. Treatment can be progressed without anxiety by confirming whether treatment is performed as planned.

## NUMBER OF PATIENTS

Proton-beam radiation therapy has been performed in a total of more than 52,000 patients at 33 facilities in Japan and other countries. Eight of the facilities have completed their operation, and the remaining 25 facilities are currently operating. The construction of 14 and at least 4 facilities is planned overseas and in Japan, respectively, showing that proton-beam radiation therapy plays the main role in charged-particle radiation therapy. There are 4 facilities for carbon-beam radiation therapy in the world (the NIRS Heavy Ion Medical Center, HIBMC, GSI of Germany, and Lanzhou National Institute of Physics of China), and about 4,000 patients had undergone carbon-beam radiation therapy as of August 2007. Six facilities will introduce carbon-beam radiation therapy in Japan, Germany, Italy, and France including Gunma University in Japan.

The HIBMC had performed particle-beam radiation therapy in 2,486 patients as of December 2008, and nearly 600 patients underwent therapy yearly in recent years (Fig. 2). Prostate cancer cases accounted for the highest ratio, but the number has recently been decreasing, while head and neck and liver cancer cases are increasing (Fig. 3).

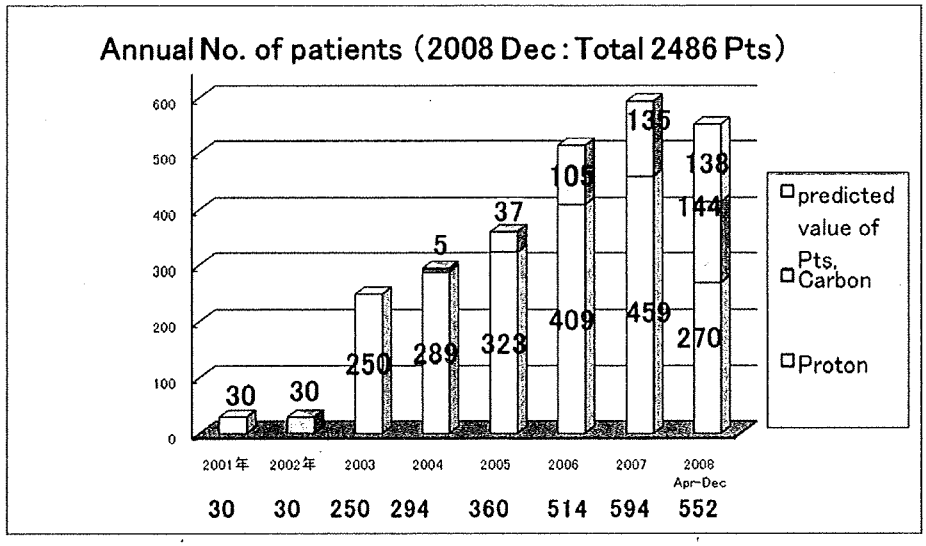


**FIGURE 2.** Annual number of patients treated in the HIBMC

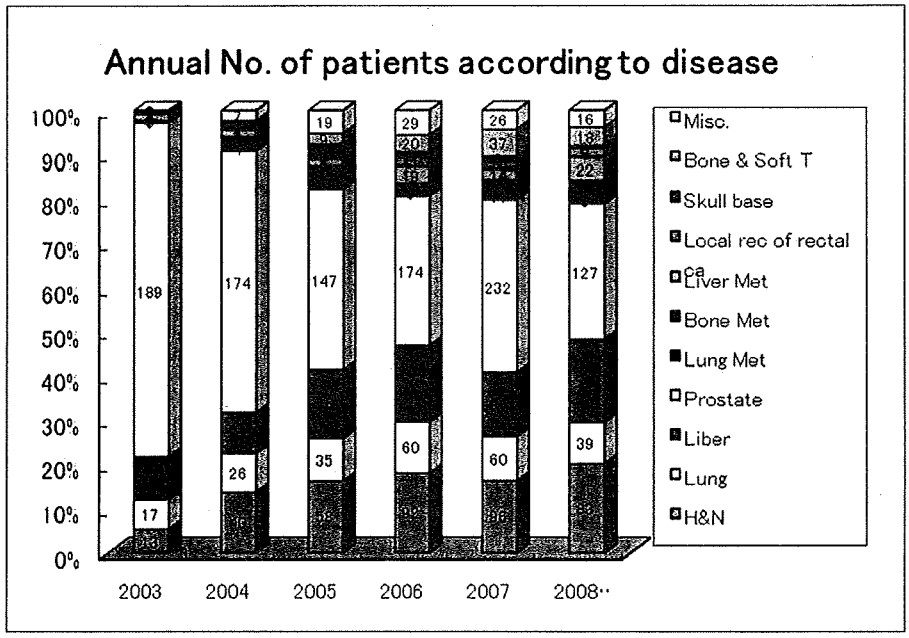


**FIGURE 3.** Annual number of patients according to disease treated in the HIBMC

## CHARACTERISTICS OF DISEASES AND EXAMPLES

### Head and neck tumors

Anatomically, organs with important functions for daily living activities, such as visual, auditory, gustatory, and olfactory sensations, vocalization, chewing, and swallowing, are concentrated in the head and neck regions, and the cranial side is adjacent to the brain via the basal skull. Tumors in this region are non-operable in many cases because they invade the basal skull and internal carotid artery. Not only are lymphoma and squamous cell carcinoma relatively sensitive to chemotherapy and X-ray radiation but also radiation-resistant tumors, such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, and sarcoma, frequently develop in this region. Carcinogenesis is associated with smoking and alcohol in many cases, and the incidence of double cancer involving lung and esophageal cancers is high. Moreover, it involves the face and esthetics important for social lives, and, thus, the development of a treatment method which completely cures diseases while maintaining functional morphology is awaited. Particle-beam radiation therapy may become a new therapeutic modality providing promising means to overcome these problems which the current major treatments, surgery and radiochemotherapy, cannot resolve.

*Proton-beam radiation plan for head and neck tumors*

The treatment plan should be prepared for individual cases considering the tumor development site (subsegment), size, expansion, relationship with the adjacent organs, histologic type, clinical stage, age, and the presence or absence of previous treatment. A wider CTV may be set in malignant melanoma and adenoid cystic carcinoma because of mucosal pigmented spots and nerve invasion, respectively. Organs at risk include the brain, spinal cord, eye ball, optic nerve, auditory organs, parotid gland, temporomandibular joint, larynx, and skin, and the dose should be set within their tolerance doses. In the broad beam method, 2-3 ports, non-coplanar radiation, bolus and a collimator are employed in many cases.

*Examples of particle-beam radiation therapy for head and neck tumors*

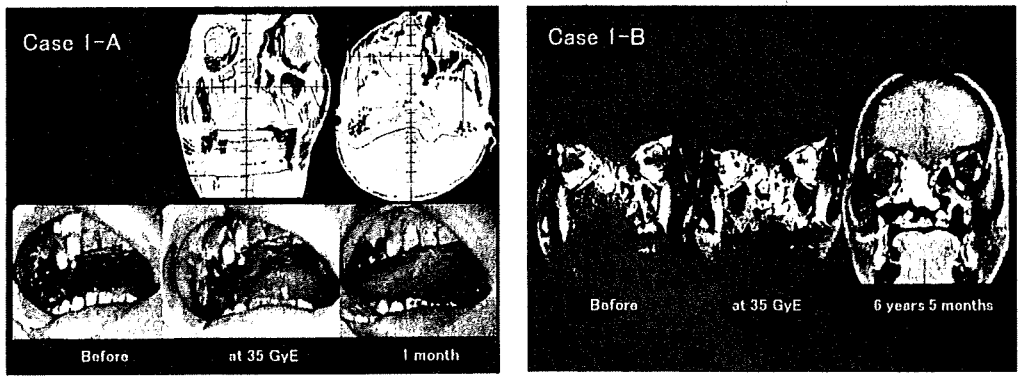


**FIGURE 4.** Case 1 A 54-year-old male with T4pN1M0 right maxillary squamous cell carcinoma
The tumor invaded the right oral cavity. Cervical lymph node dissection was previously performed. The tumor was irradiated with 65 GyE/26 Fr/5.2 w proton beams using 2 orthogonal ports in the anterior-posterior (AP) and right-left (RL) directions (Upper pictures in the Case 1-A). At the time of 35 GyE, the tumor mostly disappeared on visual examination of the oral cavity, and a marked effect on the tumor in the maxillary sinus was observed on MRI. The tumor in the oral cavity disappeared after 1 month, and acute mucositis was also improved. The patient was doing well without recurrence on MRI as of 6 years and 5 months after therapy.

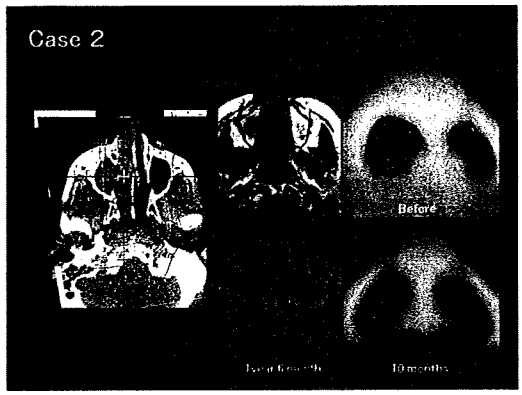


**FIGURE 5.** Case 2 A 55-year-old female with malignant melanoma in the right nasal cavity
The tumor invaded the right maxillary sinus. The tumor was irradiated with 65 GyE/26 Fr/5.2 w proton beams using 2 ports in the AP and RL directions. The tumor obstructing the right nasal cavity disappeared after 10 months, and no recurrence was noted on MRI at 1 year and 6 months after therapy. Malignant melanoma is a typical tumor resistant to conventional radiation, but proton-beam radiation exhibited a marked local effect.

*Results of particle-beam radiation therapy for head and neck tumors (Table 1)*

There are many subregional and histologic types of tumor in the head and neck region, and surgery and chemotherapy are performed as pretreatment in many cases. For a fair evaluation of the therapeutic results, the accumulation of many cases is necessary.

The National Cancer Center Hospital East reported therapeutic results involving nasal and paranasal sinus tumors. Regarding the histologic type, not only squamous cell carcinoma, which frequently develops in this region, but also olfactory neuroblastoma, malignant melanoma, and adenoid cystic carcinoma accounted for high ratios of cases. These were considered resistant to conventional radiation, but the local control rate by proton beams was favorable. The results obtained in Hyogo Prefecture showed a similar tendency.

**TABLE 1** Results of particle-beam radiation therapy for head and neck tumors

| Year, Author, Institution, Report | No. of cases | Region | Histology | Dose (GyE) | Local control rate (%) | Survival rate (%), | Late adverse events |
|---|---|---|---|---|---|---|---|
| 2007 Ogino NCCE ECCO14 | 93 | NCPC | SCC27, ONB22, MM18, ACC13, Other13 | 65 (58.8-70) | 87(2Y) | 71(2Y) | Blindness: 0, cataract: 3, asymptomatic brain necrosis: 2, bone necrosis: 1, spinal fluid leakage: 1, hemorrhage: 1, skin graft: 2 |
| 2007 Nishimura NCCE IJROBP | 14 | NCPC | ONB | 65 | 84(5Y) | 93(5Y) | No grade-3 or severer case |
| 2007 HIBMC | 163 | All | SCC32, adenoca14, | 65(P) 57.6(C) | 72%(2Y) | 64%(2Y) | Blindness: 2, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | regions | MM48, ACC35, Other34 | | | | skin necrosis: 1, mucosal ulcer: 4, asymptomatic brain necrosis: 0 |
| NCCE:National Cancer Center Hospital East, IJROBP: International journal of radiation oncology biology physics, NCPC: Nasal cavity and paranasal sinuses, SCC: squamous cell carcinoma, ONB: olfactory neuroblastoma, MM: malignant melanoma, ACC: adenoid cystic carcinoma | | | | | | | |

## Lung cancer

Lung cancer is a malignant tumor ranked the number one cause of cancer-related death, and the prognosis is poor. The number of patients has been increasing: 60,000 people develop it yearly, and the number is expected to reach 135,000 in 2015 in Japan. Lung cancer is roughly divided into non-small cell and small cell carcinoma. Peripheral stage-I non-small cell lung cancer is considered to be an indication for particle-beam radiation therapy at many facilities, and this type accounts for about 1/4 of all lung cancer cases. The standard treatment is surgery, but non-operable cases due to an elderly age and complications account for about 10%, for which radical particle-beam radiation therapy is indicated.

*Particle-beam radiation treatment plan for lung cancer*

As a physical problem regarding planning treatment, the lung is a low-density organ. It should be noted that abruptly stopping proton beams is difficult in the lung compared to parenchymal organs, such as the liver. Moreover, it is necessary to start SOBP from the inner chest wall to ensure tumor coverage, otherwise the normal lung in the entrance region before the tumor may be irradiated at a relatively high dose. When a bolus is used, the density difference between the tumor and surrounding lung is large, which increases the variation of bolus thickness, resulting in a low dose being administered to the tumor with a wide lateral scattering distribution. Regarding problems on the patient side, many lung cancer patients are elderly and have chronic respiratory diseases, such as interstitial pneumonia, and reducing the tolerance dose of the lung, for which a consideration of radiation pneumonia after irradiation is necessary. In addition, caution regarding the doses administered to the esophagus and skin is necessary. When long-term survival is expected, an extra dose for the heart should be avoided. Treatment plans should be prepared in consideration of the tumor location (peripheral or central site in the lung field) and size. Particle-beam radiation facilities in Japan employ respiratory-ordered irradiation to reduce the irradiated volume of the normal lung.

*An example of particle-beam radiation therapy for lung cancer*

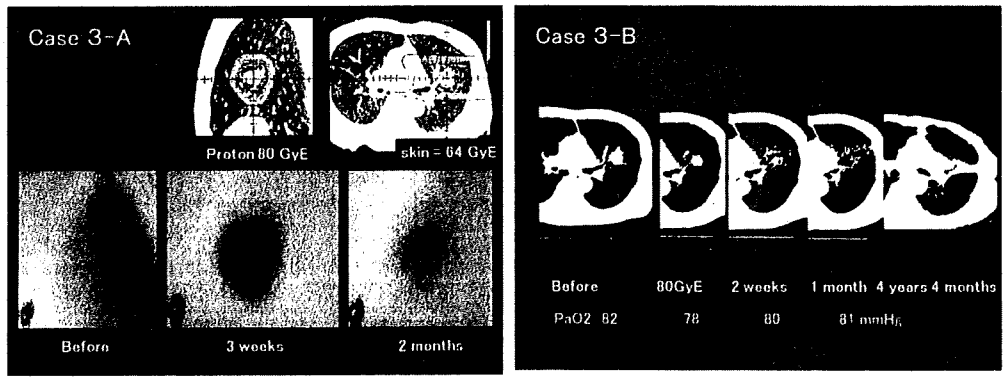


**FIGURE 6.** Case 3 A 77-year-old male with T1N0M0 left lung squamous cell carcinoma

A tumor measuring about 3 cm was irradiated with 80 GyE/20 Fr proton beams using a port in the lateral direction. SOBP starting at the chest wall continued to a site over the tumor, and the beam stopped at the left hilum. On CT, the tumor size was already reduced when 80 GyE was completed, and the tumor disappeared after one month. Radiation-induced pneumonia continuous from the beam entrance region occurred, and severe fibrosis was present 4 years and 4 months after therapy. The patient died of pulmonary emphysema-associated pulmonary dysfunction 4 years and 9 months after therapy, but no tumor recurred.

**TABLE 2** Results of particle-beam radiation therapy for non-small cell lung carcinoma

| Year, Author, Institution, Report | No. of cases | Stage | Histology | Dose (GyE) | Median duration of follow-up (months) | Local control rate (%) | Survival rate (%), | Grade3 or more of late adverse events |
|---|---|---|---|---|---|---|---|---|
| 2004 Bush LLUMC Chest | 68 | I | NS | 51–60 | 30 | 74(3Y) | 44(3Y) | No |
| 2006 Nihei NCCE IJROBP | 37 | I | SCC, AD, Other | 70–94 | 24 | 95(2Y) | 71(2Y) | No |
| 2007 Hata Tsukuba IJROBP | 21 | I | SCC, AD, Other | 60Gy/10Fr (3 例は 50Gy) | 25 | 95(2Y) | 74(2Y) | No |
| 2007 HIBMC | 116 | I-IV | SCC, AD, Other | 60GyE/10Fr-80GyE/20Fr | 21 | 88(2Y) | 78(2Y) | No |
| SCC: squamous cell carcinoma, AD: adenocarcinoma, NS: note stated | | | | | | | | |

*Results of particle-beam radiation therapy for non-small cell lung carcinoma*

In an early report (Bush, Chest 1999) from Loma Linda University in the U.S., 37 cases of non-small cell lung carcinoma (stage I: 27, II: 2, IIIA: 8) were irradiated with a combination of proton beams and X-rays (cases with normal cardiopulmonary function: 45 Gy X-ray + 28.8 CGE proton beam, total dose: 73.8 CGE) or proton beams alone (cases with reduced cardiopulmonary function: 51 CGE/10 times), the 2-year disease-free survival rate was 63% (stage I: 86%), and the local control rate was 87%. There was no adverse event excluding pneumonia requiring oral steroid treatment in 2 of 8 cases in the X-ray combined group. The dose distribution of proton-beam radiation was favorable, it allowed elevation of the target dose without increasing adverse events, and the local control and survival rates exceeded those in conventional radiotherapy. In the results of stage-I lung cancer in 2004, the 3–year local control group was 74%, as described above.

In a clinical study performed in stage-I non-small cell lung carcinoma patients at the National Cancer Center Hospital East, the dose was sequentially increased from the starting dose of 70 GyE/20 fr/5 weeks to 80, 88, and 94 GyE/20 fr/5 weeks, and the outcomes were favorable, with a local control rate of 95%.

Tsukuba University also reported that the 2-year local control rate was 95% with no Grade-3 or severer late adverse event in 21 patients treated with short-term radiation at 60 GyE/10 fr (50 GyE/10 fr in 3). Based on the previous achievements, proton-beam radiation therapy is safe and effective for stage-I lung cancer.

## Liver cancer

Liver cancer is ranked the 3rd most common cause of death from malignant tumors. It is predicted that 45,000 persons will develop liver cancer in 2010, and the cancer occupies an important position in Japan. Cancer progresses from viral hepatitis in many cases, but also from non-viral cases, such as alcoholic hepatitis. Hepatitis progresses to hepatic cirrhosis and liver cancer. There are various local treatment methods, such as surgical resection,

transcatheter arterial embolization, transcatheter arterial infusion chemotherapy, percutaneous ethanol infusion, and radiofrequency ablation. The radiation dose tolerated by the liver is low. Moreover, digestive organs are present near the liver, such as the stomach, duodenum, large intestine, and pancreas, which excluded liver cancer from the indication of conventional radiation therapy. Recent high-precision radiotherapy facilitated the application of X-ray radiation.

Liver cancer has characteristics different from those of solid tumors of other organs, such as poor liver function due to hepatic cirrhosis in the background, the presence of multicentric lesions in many cases, from which new liver cancer may arise, despite a solitary lesion being well controlled. Accordingly, a low-invasive radical method inducing only liver functional disorder with a small influence on the later treatment is desired to select local treatment. In this regard, particle-beam radiation therapy is expected.

*Particle-beam radiation treatment plan for liver cancer*

Respiratory-gated irradiation is employed because the liver moves with respiration. When portal and hepatic venous invasions are present, caution is necessary for setting GTV and CTV. To avoid impairing liver function, many cases are irradiated using 1-2 ports. Organs at risk, such as the skin, stomach, duodenum, large intestine, and kidney, may be present in the irradiated volume depending on the tumor-occupying region. Particular caution is necessary for the upper intestine because its exposure to a high dose always causes ulcer. In the treatment of large tumors, costal fracture, dermatitis, pleuritis, and the retention of pleural effusion may occur as late adverse events.

*Examples of proton-beam radiation therapy for liver cancer*

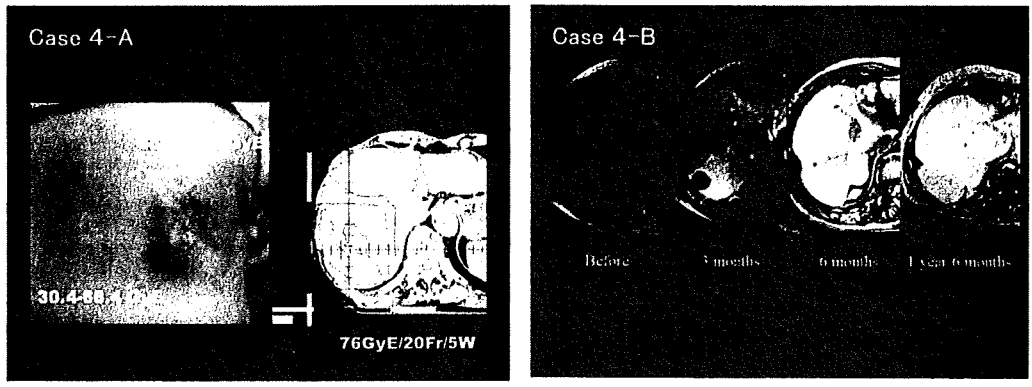


**FIGURE 7.** Case 4 An 81-year-old female with TN0M0 primary liver cancer
A tumor measuring 6 x 5 cm was irradiated with 150 MeV proton beams for 76 GyE/20 fr using 2 ports in the lateral and postroanterior directions. In the picture of the skin 1 month after therapy, dermatitis (Grade 2) was noted in the high-dose region in which 2 beams overlapped, and flare (Grade 1) and mild dermatitis were noted in the region irradiated with a single beam. These acute dermatitis reactions following proton-beam treatment remitted remaining pigmentation after 2 weeks. The tumor size was markedly reduced on MRI 3 months after therapy, and mostly disappeared at 6 months. Radiation-induced hepatitis and hepatic fibrosis occurred in the irradiated volume, but remitted with time, and became liver deformities 1 year and 6 months after therapy. The patient was doing well at 6 years and 7 months after therapy.

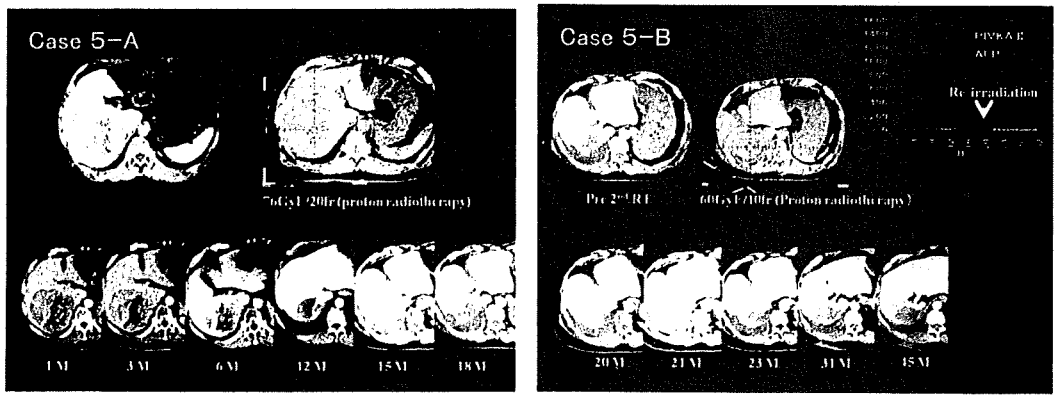

**FIGURE 8.** Case 5 Re-irradation for recurrence (proton-beam re-radiation) A 67-year-old male with T3N0M0 primary liver cancer:

A non-B non-C giant liver cancer with a 13-cm diameter was irradiated with 76 GyE/20 fr proton beams. Normalized tumor marker levels rose after 18 months, and a nodular mass was present in a local mass on CT and MRI, being diagnosed as local recurrence. The tumor was re-irradiated with 60 GyE/10 fr proton beams, and the tumor markers and imaging findings were improved. As late adverse events, pleural effusion, costal fracture, and skin induration occurred, and chest pain requiring analgesics temporarily developed, but slowly remitted. No recurrence had occurred as of about 5 years after the initial treatment.

*Results of particle-beam radiation therapy for liver cancer*

**TABLE 3** Results of particle-beam radiation therapy for liver cancer

| Year, Author, Institution, Report | No. of cases | Stage | Tumor size (median), | Dose/fraction (GyE/Fr), | Median duration of follow-up (months) | Local control rate (%) | Survival rate (%), | Late adverse events |
|---|---|---|---|---|---|---|---|---|
| 2005 Chiba Tsukuba Clin Cancer Res | 162 (192) | StageI-III | 3.8 | 50-88/10-20 median72/16 | 31.7 | 86.9 (5Y) | 23.5 (5Y) | Common bile duct stenosis: 1, cholerrhagia: 2, stomach ulcer: 1, large intestinal ulcer: 1 |
| 2004 Bush LLUMC J.Gastro | 34 (36) | T1-3, T4(selected) N0M0 | 5.7 (mean) | 63/15 | 20 | 75 (2Y) | 55 (2Y) | NS |
| 2005 Kawashima NCCE JCO | 30 | StageI-III | 4.5 | 76/20 | 31 | 96 (2Y) | 66 (2Y) | liver disorder: 8 |
| 2007 HIBMC | 153 | NS | NS | 52.8-76/4-38 P:130, C:23 | 29 | 88.1 (3Y) | 66.7 (3Y) | liver disorder: 5 Duodenal ulcer: 1 |

NS: not stated

Tsukuba University has been performing proton-beam radiation therapy for liver cancer for a long time. In the latest report from Chiba et al., the outcomes were stable, with a 5-year local control rate of 86.9%. Bile duct and intestinal disorders are late adverse events to be paid attention to. In a report from the National Cancer Center Hospital East, superior local control was achieved by a schedule of 76 GyE/20 Fr.

In a report on re-irradiation for recurrence following proton-beam radiation therapy (Hashimoto, IJOBP 2006), 27 cases which underwent re-irradiation with proton beams (66 Gy/16 Fr) after the second treatment were analyzed. The median dose in the first therapy was 72 Gy/16 Fr. The second therapy could be safely performed when the lesion was located in the marginal region of the liver with favorable liver function (Child A).

## Prostate cancer

Prostate cancer frequently develops in elderly men. It is ranked as the most common cause of cancer death in men in Western countries, and the incidence is also showing an increasing tendency in Japan. The tumor marker PSA is useful for early discovery and follow-up after treatment. It is a hormone-dependent tumor, along with breast cancer, and responds to hormone therapy. Surgery and radiotherapy are performed for radical treatment, and there are various radiotherapies, such as external X-ray irradiation, brachytherapy, and particle-beam radiation therapy. Because of strong QOL demands, there are high expectations for particle-beam radiation therapy, which has only small influences on urination, defecation, and sexual function.

The clinical stage, Gleason score, and PSA are known as prognostic factors, and various risk classifications based on combinations of these have been proposed. Local therapy alone is possible in the low-risk group, but possibilities of seminal vesicle invasion and regional lymph node and distant metastases are high in medium- and high-risk cases, even though these are unclear on the imaging diagnosis. For medium- and high-risk cases, combined treatment is employed in many cases, such as the addition of irradiation of the pelvic lymph node region and hormone therapy to local treatment.

*Proton-beam irradiation treatment plan for prostate cancer*

Lateral opposing portal irradiation is employed in many cases. Because of its location between the urinary bladder and rectum, the position of the prostate readily alters due to the states of urination, defecation, and gas retention. Accordingly, attention is paid to avoid constipation during the irradiation period, and an enema, gas discharge, and laxative treatment may be performed, as needed. Some facilities use a rectal balloon. To maintain a specific urinary bladder volume during irradiation, patients drink a specified volume of water following urination 30-60 minutes before irradiation as a pretreatment. The irradiated volumes of the urinary bladder and rectum increase as the complicating benign prostatic hypertrophy. Since diabetes was related to late adverse events in many reports, long-term blood glucose management after treatment is also necessary.

*An example of proton-beam radiation therapy for prostate cancer*

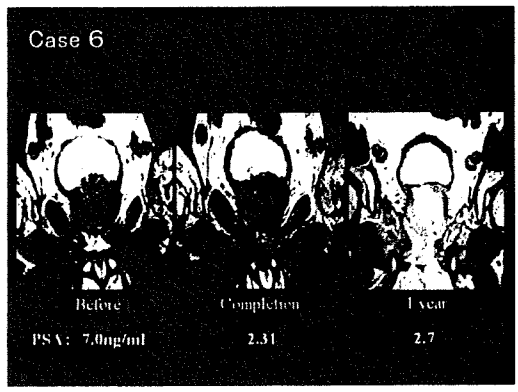


**FIGURE 9.** Case 6 A 74-year-old male with T4N0M0 hormone-refractory prostate cancer:

A locally advanced prostate cancer found with a PSA level of 104.9 ng/ml was definitely diagnosed as poorly differentiated adenocarcinoma based on biopsy of the bilateral lobes. The PSA level was reduced to 0.9 ng/ml by hormone therapy, but became unresponsive in the 31st month, and proton-beam radiation therapy was introduced. The tumor invaded the urinary bladder. Hematuria associated with the tumor was noted, but remitted after irradiation at 74 GyE/37 fr. and the tumor size was reduced on MRI.

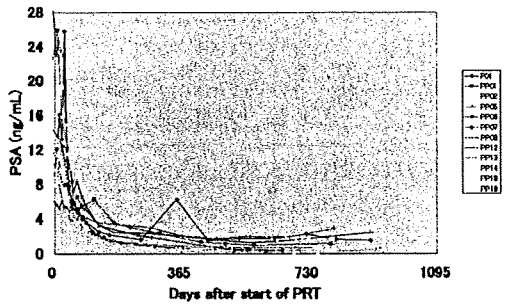


**FIGURE 10.** Changes in the PSA level following proton-beam radiation therapy

The PSA level transiently rose immediately after the initiation of irradiation (2-6 weeks), but rapidly decreased thereafter, followed by a slow, continuous decrease for more than one year. The PSA level increases when the tumor recurs, serving as an important index for follow-up.

*Results of proton-beam radiation therapy for prostate cancer*

A randomized controlled study was performed in T3T4 prostate cancer patients at the Massachusetts General Hospital (MGH), in which patients were divided into those treated with X-ray radiation alone, designated as a normal-dose group (64.8 Gy), and those with 50.4 Gy pelvic X-ray irradiation boosted with proton-beam radiation as a high-dose group (75.6 Gy). Single portal irradiation via the perineal region in the lithotomy position was employed because the proton beam output was slightly low (160 MeV). There was no significant difference in the survival rate. The 5- and 8-month local control rates were 81 and 61% in the normal-dose group, and 92 and 77% in the high-dose group, respectively, showing an improvement, but the differences were not significant (p=0.069). However, when cases were limited to poorly differentiated adenocarcinoma, the 5- and 8-month local control rates were 60 and 19% in the normal-dose group, while they were 94 and 85% in the high-dose group, respectively, showing that the addition of proton-beam boost radiation to X-ray radiotherapy significantly increased the local control rate. Since the incidence of poorly differentiated adenocarcinoma is reportedly high in Japanese, proton-beam radiation therapy may be useful for Japanese.

**TABLE 4** Results of proton-beam radiation therapy for prostate cancer

| Year, Author, Institution, Report | No. of cases | Dose of proton-beam radiation | Radiation method | Hormone therapy | stage | Survival rate | Biochemical disease-free survival rate | Local control rate | G2GU | G3GU | G2GI | G3GI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1995 Shipley MGH IJROBP | 202 | 50.4Gy[X]+X (total 68.4 Gy) (99) VS. 50.4Gy[X]+P (total 75.6CGE)(103) | 4 [X] and 1 [P] ports via the perineal region | - | T3T4 | 60%(8Y:X) VS. 77%(8Y:P) | - | 60%(8Y:X) VS. 77%(8Y:P) (p = .089) | 6% (X) VS. 14% (P) | | 9% (X) VS. 27% (P) | |
| 1998 Slater LLUMC IJROBP | 643 | 75CGE/40Fr (45Gy/25Fr[X]+30CGE/15Fr[P]) または 74CGE/37Fr [P] | 4 [X] and 2 (RL, LR) [P] ports using a rectal balloon | - | T1a -T3 | 89%(5-Y clinical disease-free survival rate)) | 79% | 95% | 5.4% | 0.3% | 21% | 0% |
| 1999 Slater LLUMC Urology | 319 | | | - | T1a – T2b | 95% (5-Y clinical disease-free survival rate)) | 88% (5Y) | - | 5% (3Y) | 0% | 6% (3Y) | 0% |
| 2004 Slater LLUMC IJROBP | 1255 | | | - | T1a-T3 | - | 75% (5Y) 73% (8Y) | - | - | 1% (G3) | - | 1% (G3) 0.2% (G4) |
| 2005 Zietmann MGH JAMA | 393 | 70.2Gy (L: 50.4[X]+[P]) VS. 79.2GyE (H:50.4[X]+[P]) | 4 [X] and 2 (RL, LR) [P] ports using a rectal balloon or 1 port [P] via the perineal region | - | T1b-T2b | | 61.4% (5Y:L) VS 80.4%(5Y:H) | | | | | |
| 2005 Nihei NCCE IJROBP | 30 | 50Gy/25Fr[X]+26GyE /13Fr[P] | 2 ports (RL, LR) | ± | T1-T3N0M0 | | 80% (2Y) | | 10% | 0% | 10% | 0% |
| 2007 Murakami HIBMC ECCO14 | 291 | 74CGE/37Fr [P] | 2 ports (RL, LR) | ± | T1-T3N0M0 | 98.1%(3Y) | 92%(3Y) | 99.3%(3Y) | 4% | 0% | 4% | 0% |

At the Loma Linda University Medical Center (LLUMC), lateral opposing portal irradiation with proton beams at 250 MeV (74 GyE/37 Fr) alone is applied for T1-3N0M0 prostate cancer with a low possibility of pelvic lymph node metastasis, and the combination of whole pelvic X-ray and proton-beam radiations (18-23 MeV X-ray: 45 Gy/25 fr, proton beam: 30 CGE/15 fr) for cases in which pelvic lymph node metastasis cannot be ruled out. In their early study of 643 patients, the 5-year clinical and biochemical disease-free survival rates were 89 and 79%, respectively, showing favorable outcomes. The incidences of intestinal Grade-2 and -3 radiation disorders were 21 and 0%, respectively, and those of the urinary tract were 5.4 and 0.3%, respectively. The LLUMC also reported a study limiting the target to T1-2BN0M0 prostate cancer performed in 319 patients, in which the 5-year clinical disease-free survival rate was as high as 97%, and this was more favorable than those achieved by conventional X-ray radiotherapy reported by the MD Anderson Cancer Center and Michigan University, and equivalent or superior to that of radical prostatectomy for T1-2 prostate cancer reported by the Johns Hopkins University, concluding that the outcome of proton-beam radiation therapy was comparable to that of radical prostatectomy. In a study performed in 1,255 patients with T1-3 prostate cancer between October 1991 and December 1997, the incidence of Grade-3 adverse events in the gastrointestinal and urinary tracts was less than 1%, showing the safety of therapy, and marked influences of the initial PSA level, Gleason score, and lowest PSA level after therapy on the biochemical disease-free survival rate were re-confirmed. The 5-year biochemical disease-free survival rates were 90, 84, 65, and 48% when the initial PSA level was 4.0 or lower, 4.1-10.0, 10.1-20.0, and 20.1 ng/ml or higher, respectively.

The LLUMC and MGH performed a collaborative comparative study between doses of 70.2 and 79.2 GyE X-ray radiation combined with proton-beam boost for T1b-2b prostate cancer with a PSA level <15 ng/ml, and the 5-year biochemical disease-free survival rates were 61.4 and 80.4%, respectively, showing a favorable prognosis in the high-dose group (P=0.00001) and dose-effect responses in not only the high- but also low-dose group. The incidence of Grade-3 adverse events in the intestine was 1% in both high- and low-dose groups, and those in the urinary tract were 1 and 2%, respectively, showing no significant differences.

Nihei et al. reported the status of proton-beam radiation therapy in Japan. Currently, a multicenter phase II study is being performed by 3 facilities in Japan: the NCCE, SCC, and HIBMC. At the HIBMC, trials of lateral opposing portal irradiation with 190-230 MeV proton beams (74 GyE/37 Fr) alone and in combination with hormone therapy are underway. In a report on acute adverse events in 287 cases treated at the HIBMC (Mayahara, IJROBP 2007), no Grade-2 intestinal adverse events occurred in proton beam-treated cases (0%), unlike those in cases treated with conventional radiation (14-64%), showing that very safe treatment can be realized.

## PROSPECT OF PARTICLE-BEAM RADIATION THERAPY

In the static range modulation method using a passive scatterer (broad beam method) employed by many facilities, the maximum irradiation field is about 15-25 cm, smaller than that of lineac X-ray (about 40 cm), limiting its application. Moreover, since SOBP is determined by the longest target length in the beam axial direction, the adjacent normal tissue before the target is exposed to a high dose when the target length (the yellow region in FIGURE 11) is shorter than SOBP, resulting in dermatitis and encephalopathy. The spot scanning and layer-stacking methods are more advantageous in this regard. Conditions vary among facilities, such as some facilities are equipped with a gantry but incapable of non-coplanar radiation, and others are not equipped with a multileaf collimator, and perform collimation using a patient collimator. The preparation of conditions identical to those for lineac X-ray is not always possible.

In intensity modulated radiation therapy (IMRT), organ failure or carcinogenesis may occur in regions irradiated at a dose of 20-40 Gy, whereas proton beams are advantageous because the irradiated volume is small[3], particularly for whole spinal cord irradiation in children[4]. Although particle-beams are not frequently used for pediatric tumors in Japan, its future development is expected.

Particle-beam radiation therapy was previously performed at physical research institutes because of the requirement of large-scale facilities, but since the LLUMC installed equipment in 1990, instruments for hospital installment have been introduced, and particle-beam radiation is being slowly adopted clinically. However, at present, the medical fee paid at patients' own expense is about 3,000,000 yen, even though the treatment is specified as advanced medical care. Coverage by national heath insurance is awaited, for which the development of instruments for general use with reduced costs for construction and maintenance and human resources are necessary.

A laser-driven accelerator not using a synchrotron or cyclotron was proposed by Tajima et al. in 1979[5]. The development of an accelerator for medical use is underway, and a table-top accelerator will be realized[6]. Facilities at which both proton and carbon ion beams can be used, including the HIBMC, have to investigate the differential use

and combination radiation of the two beam types. We started clinical randomized trial to compare both ion beams, and started biological studies including laser-driven proton beams (FIGURE 12). Furthermore, the fusion of particle-beam irradiation techniques including spot-scanning with image-guided treatment planning using autoactivation PET may lead to the realization of individualized particle-beam radiation therapy corresponding to individual tumor sensitivity and intractability.

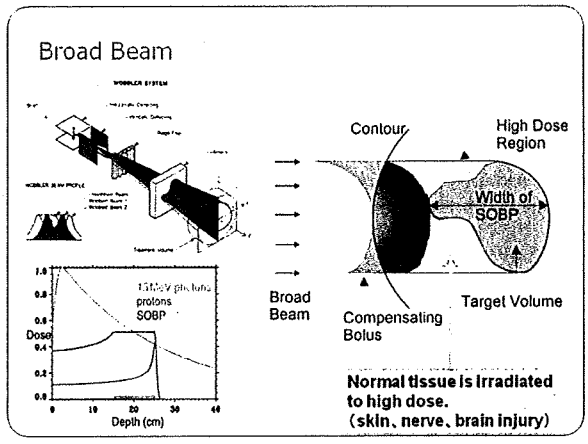


**FIGURE 11.** Problem in the broad beam method

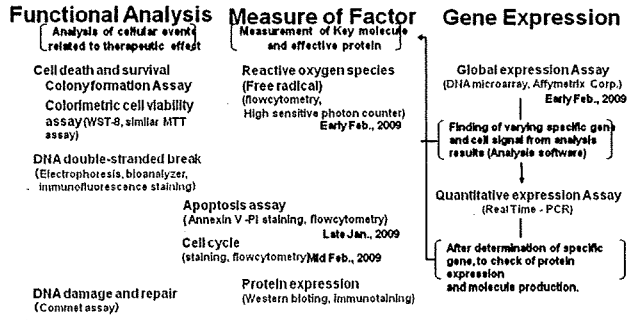


**FIGURE 12.** Plan of in vitro experiment at HIBMC toward the development of laser driven proton radiotherapy

## REFERENCES


1 Kagawa K, Murakami M, Hishikawa Y, et al. *Int J Radiat Oncol Biol Phys* **51**:239 (2001)
2 Minohara S, Kanai T, Endo M, et al. *Int J Radiat Oncol Biol Phys* **47**:1097-1103 (2000).
3 Jones B, et al. *Clinical Oncology.* **16**: 324-325 (2004).
4 Miralbell R, et al. *Int J Radiat Oncol Biol Phys.***54**: 824-829 (2002).
5 Tajima T, et al. *Phys Rev Lett.* **43**:267 (1979).
6 Katsouleas T. *Nature* **431**: 515-516 (2004).

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**5TH JUCTS AND THE 5TH S. TAKAHASHI MEMORIAL INTERNATIONAL JOINT SYMPOSIUM**

# PHYSIOLOGIC REACTIONS AFTER PROTON BEAM THERAPY IN PATIENTS WITH PROSTATE CANCER: SIGNIFICANCE OF URINARY AUTOACTIVATION

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**Purpose: Proton therapy is a sophisticated treatment modality for prostate cancer. We investigated how physiologic factors affected the distribution of autoactivation as detected by positron emission tomography (PET) after proton beam therapy.**

**Methods and Materials: Autoactivation was evaluated in 59 patients treated with a 210-MeV proton beam. Data acquisition for autoactivation by PET started 5minutes after proton irradiation to assess activation. In the first 29 patients, five regions of interest were evaluated: planning target volume (PTV) center, urinary bladder inside the PTV, urinary bladder outside the PTV, rectum (outside the PTV), and contralateral femoral bone head (outside the PTV). In the remaining 30 patients, urine activity was measured directly. In a phantom study autoactivation and its diffusion after proton beam irradiation were evaluated with water or an ice block.**

**Results: Mean activities calculated by use of PET were 629.3Bq in the PTV center, 555.6Bq in the urinary bladder inside the PTV, 332.5Bq in the urinary bladder outside the PTV, 88.4Bq in the rectum, and 23.7Bq in the femoral bone head ($p < 0.001$). Mean urine activity was 679.4Bq, recorded 10minutes after therapy completion, and the half-life for urine autoactivation was 4.5minutes.**

**Conclusions: Urine is a major diffusion mediator of autoactivation after proton beam therapy. Our results indicate that physiologic factors can influence PET images of autoactivation in the context of proton beam therapy verification.** © **2009 Elsevier Inc.**

**Proton beam, Autoactivation, $\beta^+$ decayed nuclei, Positron emission tomography, Prostate cancer.**

## INTRODUCTION

Proton beam therapy is a sophisticated treatment modality for prostate cancer. The proton beam is associated with a low entry dose and reaches the target volume at its maximal dose before stopping at the prescribed depth, known as the Bragg peak (1). This property allows the proton beam to form a high-dose region known as a spread-out Bragg peak (SOBP). The proton beam can achieve an excellent dose distribution by delivering greater doses to the target while minimizing the dose to surrounding normal tissues (2).

The Hyogo Ion Beam Medical Center (Tatsuno, Japan) has offered proton beam therapy since 2001 and carbon-ion beam therapy since 2002 (3–5). Our proton therapy program started in April 2003. More than 500 patients with prostate cancer have been treated with proton beam therapy at our facility to date. Recently, Mayahara *et al.* (6) reported acute morbidities in patients with prostate cancers who underwent proton beam therapy that resulted in a low incidence of acute gastrointestinal morbidity and a 40% incidence rate (Grade 2 or greater) of acute genitourinary (GU) toxicity. Although the

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