Published OnlineFirst March 31, 2011; DOI:10.1158/0008-5472.CAN-10-2926

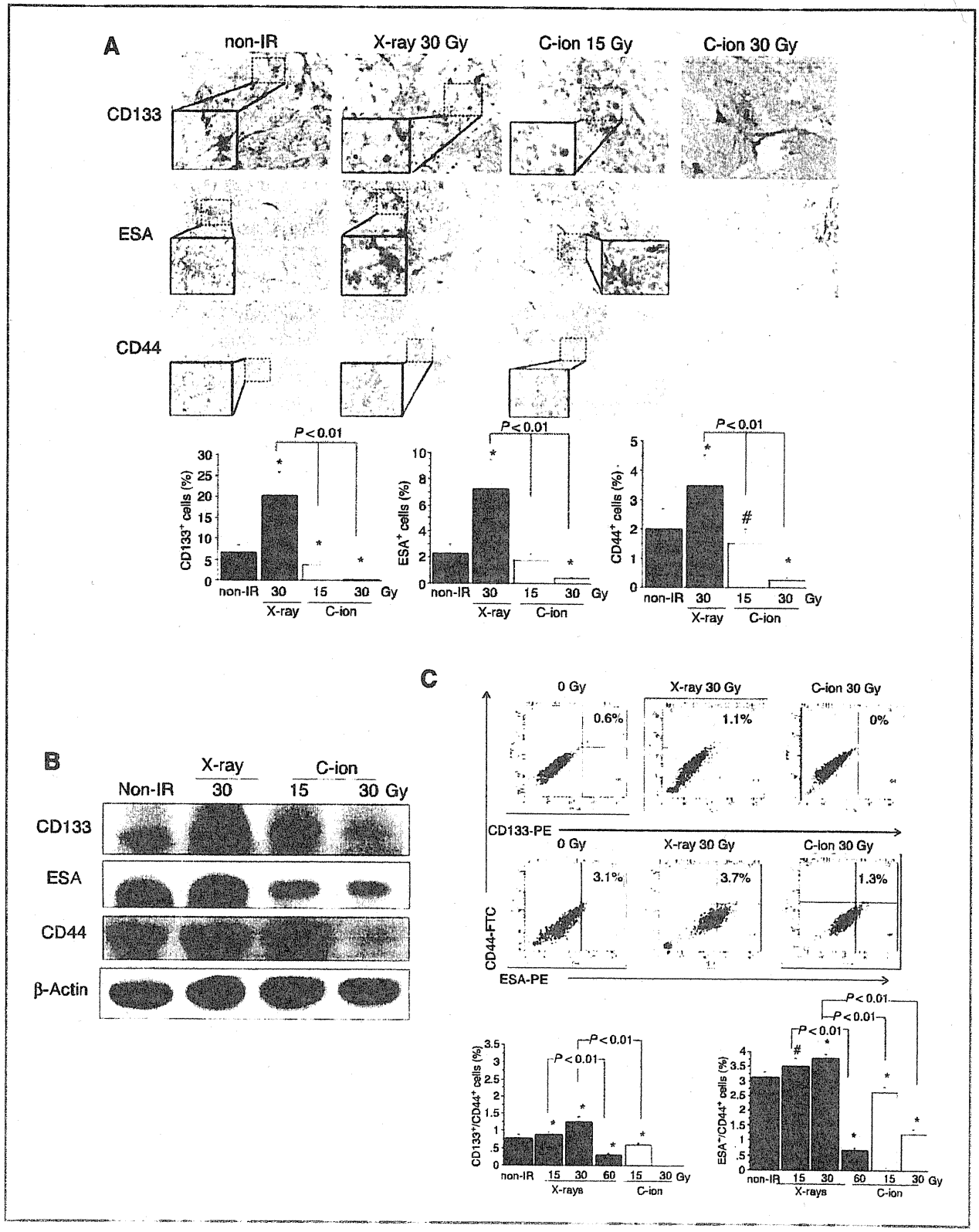


Figure 5. A, immunohistochemistry for the expression changes of CD133, CD44, and ESA in the HCT116 xenograft tumors at 4 weeks after treated with carbon-ion or X-ray irradiation. Original magnification × 100. #, $P < 0.05$, *, $P < 0.01$, compared with unirradiated tumors. B, Western blotting for the expression changes of CD133, CD44, and ESA in the HCT116 xenograft tumors at 4 weeks after being treated with carbon-ion or X-rays irradiation. β-Actin was used as loading control. C, percentage changes of $CD133^+/CD44^+$ and $CD44^+/ESA^+$ cancer stem–like cells by FACS analysis at 4 weeks after X-ray or carbon ion irradiation in HCT116 xenograft tumors. #, $P < 0.05$; *, $P < 0.01$, compared with unirradiated tumors.

Downloaded from cancerres.aacrjournals.org on February 15, 2012
Copyright © 2011 American Association for Cancer Research

Published OnlineFirst March 31, 2011; DOI:10.1158/0008-5472.CAN-10-2926

radioresistance (22). To determine cancer stem properties of $CD133^+$, $CD44^+/ESA^+$ cells in HCT116 and SW480, we have sorted cancer stem–like positive and negative cells and confirmed that $CD133^+$, $CD44^+/ESA^+$ cells have a significantly higher possibility for colony and tumor sphere formation than $CD133^-$, $CD44^-/ESA^-$ cells. *In vivo* tumorigenicity study showed that the tumorigenicity of $CD133^+$, $CD44^+/ESA^+$ colorectal cancer cells exactly much higher than $CD133^-$ or $CD44^-/ESA^-$ cells.

In the present study, FACS analyses showed that the proportion of cancer stem–like cells which were positive for CD133, ESA, and CD44 was more highly enriched after X-ray compared with carbon ion irradiation, particularly, the population of $CD133^+$, $CD44^+$ cells was increased more than 2-fold (2–4 Gy) by X-ray irradiation. In contrast, $CD133^+$ and $CD44^+$ cells were unchanged or decreased by carbon-ion irradiation (1–2 Gy). Interestingly, the proportion of ESA^+ cells was increased by 6 Gy X-ray irradiation but without changes by carbon-ion irradiation even the dose was up to 4 Gy. The proportion changes of double positive $CD133^+/CD44^+$ and $ESA^+/CD44^+$ cells by X-ray versus carbon-ion irradiation were showed same responses. These finding suggests that low LET X-ray irradiation may mainly kill the non–stem-like tumor cells, as a result the radioresistant cancer stem–like cell population was predominantly enriched. In contrast, carbon-ion irradiation may concurrently kill both non–stem-like and stem-like tumor cells; consequently, the population of cancer stem–like cells was only slightly increased or unchanged. To directly determine the radiosensitivity of cancer stem–like cells between carbon ion and X-ray irradiation, a colony assay was conducted. On the basis of the dose–response curves for cell killing effect on cancer stem–like cells and noncancer stem–like cells after irradiation with either X-rays or carbon ion beams, the cancer stem–like cells showed resistance to both X-rays and carbon ions. The surviving fractions for the cancer stem–like cells after irradiation with X-rays or carbon ions decreased exponentially with increasing doses. The RBE values calculated at the D10 level for cancer stem–like cells were about 2.05 to 2.28, suggesting that carbon ion beam has a promising potential to destroy cancer stem–like cells. In contrast, RBE values at the D10 level for noncancer stem–like cells were only 1.22 to 1.44, implying that there are no significant differences in the killing of noncancer stem–like cells between the carbon ion beam and X-ray irradiation. Altogether, these results can also partially explain why the proportion of cancer stem–like cells after irradiation with X-rays is more enriched than those of carbon-ion beams.

In vivo study showed that 15 or 30 Gy carbon-ion irradiation predominantly induced colon cancer cell cavitations, fibrosis, and completely disrupted the duct-like structure, whereas 30 Gy X-ray irradiation only partially disrupted colon cancer cells and the duct-like structure still remained when the xenograft tumors were histopathologically examined after 4 weeks. The tumor-supplying vessels were exactly reduced in carbon-ion irradiated mice compared with those of X-rays irradiated mice. This finding is in agreement with a previous report that heavy-ion irradiation inhibits *in vitro* angiogenesis (29). Several previous studies reported that the *in vivo* RBE values for high LET carbon-ion beams ranged from 2.0 to 3.1 (30, 31). In the present study, the *in vivo* RBE was calculated as 3.05 to 3.25 from the slope of the dose–response curve for tumor growth suppression by carbon ions relative to X-rays, which is almost in line with previous reports (30, 31). It is known that RBE is a complex quantity, depending on many factors such as particle type, dose per fraction, and LET, as well as on biological factors like cell or tissue type and the selected biological endpoint. The extent of TGD determined from tumor growth curves is highly dependent on the end volume chosen because of tumor bed effects (32). This may be the reason why the RBE values calculated in this study are a little higher than other reports. In addition, because a low number of dose levels were applied in this study, further studies are needed on *in vivo* RBE of carbon ions for local tumor control.

Recently, accumulating evidence showed that expression of cancer stem–like cell markers such as CD133, CD44 were closely related with patient's clinical outcome and prognosis as well as chemoresistance (33–36). In the present study, we surprisingly found that 15 Gy carbon-ion irradiation induced more severe tumor cell disruption without significant increment of putative cancer stem cell markers CD133, CD44, and ESA, whereas X-rays irradiation remarkably increased these protein levels. All these cancer stem–like cell markers were remarkably inhibited after treatment with 30 Gy carbon-ion irradiation. Furthermore, *in vivo* FACS analyses showed that the proportion of cancer stem–like cells which were positive for CD133, ESA were enriched by 15 and/or 30 Gy but significantly decreased by 60 Gy X-ray irradiation after 4 weeks. In comparison, carbon-ion irradiation with 15 Gy did not change the percentage of these positive cancer stem–like cells, whereas irradiation with 30 Gy significantly reduced the percentage of positive cancer stem–like cells. However, none of cancer stem–like cells were detectable by FACS analysis after the tumors were irradiated with 30 Gy carbon ions or 60 Gy X-rays for 2 to 3 months. Presumably, the doses to completely destroy the cancer stem cells are dependent on the tumor cell type as well as cancer stem cell population in the tumor bulk.

Altogether, according to the cancer stem cell model, therapeutic approaches that are not capable of eradicating the cancer stem cell subset are unlikely to be successful because they might be able to kill the majority of tumor cells and induce regression of tumor lesions but fail to prevent disease relapse and metastatic dissemination (23–25, 37, 38). Based on this understanding, although carbon ion beam facilities are very expensive, to achieve better outcomes as well as a better quality of life for patients with some types of cancer, such as unresectable sacral chondromas (39) or locally recurrent rectal cancer (40), carbon-ion beam therapy may be worth the cost. In conclusion, our findings presented here are the first to show that carbon ion beam therapy may have advantages over photon beam therapy in targeting putative colon cancer stem–like cells.

Downloaded from cancerres.aacrjournals.org on February 15, 2012
Copyright © 2011 American Association for Cancer Research

Published OnlineFirst March 31, 2011; DOI:10.1158/0008-5472.CAN-10-2926

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank Mrs. Noda Y, Mr. Maeda T, Mr. Takano H, Mrs. Koike S, and Mrs. Uzawa A for their kind technical support. They also thank Drs. Ando K and Niwa O for their helpful suggestions.

Grant Support

This work was a part of Research Project with Heavy-ion at NIRS-HIMAC.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 11, 2010; revised March 25, 2011; accepted March 28, 2011; published OnlineFirst March 31, 2011.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–30.
2. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, et al. The benefit of leucovorin modulated 5-fluorouracil as post-operative adjuvant therapy for primary colon cancer: results from the National Surgery and Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879–87.
3. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys 1999;44:201–10.
4. Suzuki M, Kase Y, Yamaguchi H, Kanai T, Ando K. Relative biological effectiveness for cell-killing effect on various human cell lines irradiated with heavy-ion medical accelerator in Chiba (HIMAC) carbon-ion beams. Int J Radiat Oncol Biol Phys 2000;48:241–50.
5. Griffin TW. Particle-beam radiation therapy. In:Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. 2nd ed. Philadelphia, PA: J.B. Lippincott Co.; 1992. p. 368–87.
6. Okayasu R, Okada M, Okabe A, Noguchi M, Takakura K, Takahashi S, et al. Repair of DNA damage induced by accelerated heavy ions in mammalian cells proficient and deficient in the non-homologous end-joining pathway. Radiat Res 2006;165:59–67.
7. Kamada T, Tsujii H, Tsuji H, Yanagi T, Mizoe JE, Miyamoto T, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. J Clin Oncol 2002;20:4466–71.
8. Tsujii H, Mizoe JE, Kamada T, Baba M, Kato S, Kato H, et al. Overview of clinical experiences on carbon ion radiotherapy at NIRS. Radiother Oncol 2004;73Suppl 2:S41–9.
9. Tsujii H, Mizoe J, Kamada T, Baba M, Tsuji H, Kato H, et al. Clinical results of carbon ion radiotherapy at NIRS. J Radiat Res 2007;48 Suppl A:A1–13.
10. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 2007;25:953–64.
11. Zou GM. Cancer initiating cells or cancer stem cells in the gastro-intestinal tract and liver. J Cell Physiol 2008;217:598–604.
12. Marhaba R, Klingbeil P, Nuebel T, Nazarenko I, Buechler MW, Zoeller M, et al. CD44 and EpCAM: cancer-initiating cell markers. Curr Mol Med 2008;8:784–804.
13. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. Nature 2004;432: 396–401.
14. Yin AH, Miraglia S, Zanjani ED, Almeida-Porada G, Ogawa M, Leary AG, et al. AC133, a novel marker for human hematopoietic stem and progenitor cells. Blood 1997;90:5002–12
15. Vander Griend DJ, Karthaus WL, Dalrymple S, Meeker A, DeMarzo AM, Isaacs JT, et al. The role of CD133 in normal human prostate stem cells and malignant cancer-initiating cells. Cancer Res 2008;68:9703–11.
16. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 2007;445:106–10.
17. Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, et al. Identification and expansion of human colon-cancer-initiating cells. Nature 2007;445:111–5.
18. Vermeulen L, Todaro M, de Sousa Mello F, Sprick MR, Kemper K, Perez Alea M, et al. Single-cell cloning of colon cancer stem cells reveals a multi-lineage differentiation capacity. Proc Natl Acad Sci U S A 2008;105:13427–32.
19. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006;444:756–60.
20. Hambardzumyan D, Squatrito M, Holland EC. Radiation resistance and stem-like cells in brain tumors. Cancer Cell 2006;10:454–6.
21. Rich JN. Cancer stem cells in radiation resistance. Cancer Res 2007;67:8980–4.
22. Baumann M, Krause M, Hill R. Exploring the role of cancer stem cells in radioresistance. Nat Rev Cancer 2008;8:545–54.
23. Diehn M, Clarke MF. Cancer stem cells and radiotherapy: new insights into tumor radioresistance. J Natl Cancer Inst 2006;98:1755–7.
24. Dingli D, Michor F. Successful therapy must eradicate cancer stem cells. Stem Cells 2006;24:2603–10.
25. Ischenko I, Seeliger H, Schaffer M, Jauch KW, Bruns CJ. Cancer stem cells: how can we target them? Curr Med Chem 2008;15:3171–84.
26. Cui X, Wakai T, Shirai Y, Yokoyama N, Hatakeyama K, Hirano S, et al. Arsenic trioxide inhibits DNA methyltransferase and restores methylation-silenced genes in human liver cancer cells. Hum Pathol 2006;37:298–311.
27. Cui X, Wakai T, Shirai Y, Hatakeyama K, Hirano S. Chronic oral exposure to inorganic arsenate interferes with methylation status of p16INK4a and RASSF1A and induces lung cancer in A/J mice. Toxicol Sci 2006;91:372–81.
28. Matsui Y, Asano T, Kenmochi T, Iwakawa M, Imai T, Ochiai T. Effects of carbon-ion beams on human pancreatic cancer cell lines that differ in genetic status. Am J Clin Oncol 2004;27:24–8.
29. Takahashi Y, Teshima T, Kawaguchi N, Hamada Y, Mori S, Madachi A, et al. Heavy ion irradiation inhibits *in vitro* angiogenesis even at sublethal dose. Cancer Res 2003;63:4253–7.
30. Koike S, Ando K, Oohira C, Fukawa T, Lee R, Takai N, et al. Relative biological effectiveness of 290 MeV/u carbon ions for the growth delay of a radioresistant murine fibrosarcoma. J Radiat Res 2002;43:247–55.
31. Peschke P, Karger CP, Scholz M, Debus J, Huber PE. Relative biological effectiveness of carbon ions for local tumor control of a radioresistant prostate carcinoma in the rat. Int J Radiat Oncol Biol Phys 2011;79:239–46.
32. Beck-Bornholdt HP, Würschmidt F, Vogler H. Net growth delay: a novel parameter derived from tumor growth curves. Int J Radiat Oncol Biol Phys 1987;13:773–7.
33. Diehn M, Clarke MF. Cancer stem cells and radiotherapy: new insights into tumour radioresistance. J Natl Cancer Inst 2006;98:1755–7.
34. Ma S, Lee TK, Zheng BJ, Chan KW, Guan XY. CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. Oncogene 2008;27:1749–58.
35. Pallini R, Ricci-Vitiani L, Banna GL, Signore M, Lombardi D, Todaro M, et al. Cancer stem cell analysis and clinical outcome in patients with glioblastoma multiforme. Clin Cancer Res 2008;14:8205–12.
36. Horst D, Kriegl L, Engel J, Kirchner T, Jung A. CD133 expression is an independent prognostic marker for low survival in colorectal cancer. Br J Cancer 2008;99:1285–9.
37. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer 2008;8:755–68.

Downloaded from cancerres.aacrjournals.org on February 15, 2012
Copyright © 2011 American Association for Cancer Research

Published OnlineFirst March 31, 2011; DOI:10.1158/0008-5472.CAN-10-2926

38. Clarke MF, Dick JE, Dirks PB, Eaves CJ, Jamieson CH, Jones DL, et al. Cancer stem cells–perspectives on current status and future directions: AACR Workshop on cancer stem cells. Cancer Res 2006;66:9339–44.
39. Imai R, Kamada T, Tsuji H, Yanagi T, Baba M, Miyamoto T, et al. Working Group for Bone, Soft Tissue Sarcomas. Carbon ion radiotherapy for unresectable sacral chordomas. Clin Cancer Res 2004;10:5741–6.
40. Mobaraki A, Ohno T, Yamada S, Sakurai H, Nakano T. Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer. Cancer Sci 2010;101:1834–9.

Downloaded from cancerres.aacrjournals.org on February 15, 2012
Copyright © 2011 American Association for Cancer Research

The British Journal of Radiology, 83 (2010), S48–S53

Carbon ion radiotherapy for sacral chordoma

R IMAI, MD, PhD, T KAMADA, MD, PhD, S SUGAHARA, MD, PhD, H TSUJI, MD, PhD and H TSUJII, MD, PhD

Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan

ABSTRACT. The National Institute of Radiological Sciences in Chiba, Japan has offered carbon ion radiotherapy (CIRT) since 1994 using carbon ion beams generated by the heavy ion medical accelerator in Chiba (HIMAC). The total number of cases treated with the HIMAC exceeded 5000 in July 2009. Here, we present a retrospective analysis of CIRT for sacral chordoma. The study included 95 patients with medically unresectable sacral chordomas treated between 1996 and 2007. The median age of the patients was 66 years. Of all the patients, 84 had not been treated previously and 11 had a locally recurrent tumour following previous resection. The carbon ion dose ranged from 52.8 to 73.6 GyE (median 70.4 GyE) in a total of 16 fixed fractions over 4 weeks. The median clinical target volume was 370 cm^3. The overall survival rate at 5 years for all 95 patients was 86%, and follow-up survival time was 42 months (range, 13–112 months). The 5-year local control rate was 88% and median time to local failure was 35 months (range, 13–60 months). Of the 95 patients, 91% remained ambulatory with or without a supportive device. Two patients experienced severe skin or soft tissue complications requiring skin grafts. 15 patients experienced severe sciatic nerve complications requiring continuing medication. CIRT appears effective and safe in the management of patients with sacral chordoma and offers a promising alternative to surgery.

Received 10 November 2009
Accepted 2 April 2010

DOI: 10.1259/bjr/13783281

© 2010 The British Institute of Radiology

The National Institute of Radiological Sciences (NIRS) began using photon beams for cancer therapy in 1961. Fast neutron therapy was used between 1975 and 1994, and proton therapy began in 1975. Building upon its accumulated skills and knowledge related to particle therapy, the NIRS launched heavy ion radiotherapy in June 1994 using carbon ion beams generated by the heavy ion medical accelerator in Chiba (HIMAC). The clinical trials were initiated by conducting Phase I/II dose-escalation studies on various types of tumours treated with carbon ion radiotherapy (CIRT). Their aim was to verify the safety of CIRT, to evaluate its anti-tumour effects and to identify the types of tumours eliminated more effectively by CIRT than by sophisticated conformal photon therapy.

All patients were treated according to clinical protocols (Phase I/II or Phase II) previously approved by the Ethics Committee of the NIRS. It has been our policy to use carbon ion beams to their best advantage, thereby reducing treatment time to less than that required for conventional treatment. In October 2003, the total number of patients treated with CIRT reached 1674, with a total of 1742 lesions. After completing these trials, CIRT was approved by the Japanese Ministry of Health in October 2003 as highly advanced medical technology (HAMT). In October 2006, the Health Insurance Law was partially changed and the name "HAMT" was changed to "Advanced Medicine". This level of approval is an intermediate step to being approved as a treatment under the national health insurance system in Japan. In the near future, the treatment of some cancers with CIRT will be covered by the national health insurance system [1, 2]. In July 2009, the number of cases treated with CIRT exceeded 5000. The HIMAC was the first medically dedicated heavy ion accelerator worldwide. Subsequently, two other facilities started to offer CIRT: in 1997 a facility opened at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany; in 2004, another opened at the Hyogo Ion Beam Medical Centre in Hyogo, Japan; and finally in 2006 an accelerator opened at the Institute of Modern Physics Lanzhou in China [3]. In 2005, the NIRS succeeded in developing a synchrotron that is smaller than the HIMAC and designed to make CIRT more widely available [4].

The major cancers that have been treated with CIRT at NIRS are prostate cancer, bone and soft tissue sarcoma, head and neck cancer, recurring rectal cancer, lung cancer and hepatocellular carcinoma [1, 2]. CIRT for bone and soft tissue sarcomas at NIRS was started in 1996 as a Phase I/II dose-escalation study for medically inoperable cases. Details of the study have been described in previous articles [1, 2, 5]. Until February 2000, only 64 tumours in 57 patients were treated. Following the trial, a Phase II fixed-dose clinical trial for medically inoperable cases and a HAMT trial with the same clinical eligibility criteria as the Phase II fixed-dose clinical trial were conducted between April 2000 and February 2009; 387 patients with 406 tumours were enrolled. The majority of these patients had tumours arising from the pelvis, spine, paraspinal and retroperitoneal regions (Table 1).

Carbon ion beams

The HIMAC has a 100 m linear accelerator and a synchrotron of about 40 m in diameter. It accelerates

Address correspondence to: Dr Tadashi Kamada, Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Anagawa 4-9-1, Inage-ku, Chiba 263-8555, Japan. E-mail: t_kamada@nirs.go.jp

Table 1. Characteristics of patients with bone and soft tissue sarcomas treated in National Institute of Radiological Sciences trials

Characteristics	*n*
Number of tumours	406 (387 patients)
Sex	
Male	223
Female	164
Tumour sites	
Pelvis	305
Spine/paraspine	75
Extremities etc.	26
Histology	
Bone	303
Chordoma	134
Chondrosarcoma	60
Osteosarcoma	60
Others	49
Soft tissue	84
Irradiation dose (GyE total in 16 fractions)	
64.0	27
67.2	43
70.4	326
73.6	10

carbon ions to 800 MeV n^{-1}, which is almost 80% of the speed of light. Beams of three different energies (290, 350 and 400 MeV n^{-1}) are available for use as vertical beams (290 MeV n^{-1}, 350 MeV n^{-1}) or horizontal beams (290 MeV n^{-1}, 400 MeV n^{-1}) in treatment. The water-equivalent path length of all three energy beams ranges between 15 and 25 cm. For modulation of the Bragg peak to conform to a target volume, the beam lines for treatment are equipped with a pair of wobbler magnets, beam scatters, ridge filters, multileaf collimators and a compensation bolus. The ridge filter is designed to produce biologically equal effects along the spread-out Bragg peak (SOBP). The compensation bolus is fabricated for each patient to make the distal configuration of the SOBP similar to the irregular shape of any target volume. The collimator is used to define the lateral outline of the target volume [6–8].

Before the clinical studies began, radiobiological studies were carried out *in vitro* and with mouse skins to estimate the biological effectiveness values relative to the megavoltage of photons or fast neutrons. The relative biological effectiveness (RBE) of carbon ions varies with depth, therefore the point at which the RBE value is specified has to be reported. On the basis of linear energy transfer (LET) comparisons, this point was taken at NIRS to be in the distal part of the SOBP. Irrespective of the size of the SOBP, the RBE value of carbon ions for acute skin reaction was assessed to be 3.0. Several ridge fitters were designed to produce a physical dose gradient that makes the biological effect along the SOBP more uniform. These improvements were made on the basis of the biological response of human salivary gland tumour cells [6]. To express carbon doses in terms comparable with the megavoltage of photon beams, the biologically effective dose of carbon beams is measured in GyE [or cobalt gray equivalents (CGE)], defined as the absorbed carbon physical dose (Gy) multiplied by the RBE value. Although the RBE value may differ for the various types of tissue and time-dose fractionations employed, a single RBE value of 3.0 was used at NIRS to calculate GyE [6–8].

Chordoma

Between 1% and 4% of primary bone tumours are chordomas, with >50% of these being sacral chordomas [9]. Chordomas, which arise from notochordal remnants, have slower local growth and metastasise less frequently than other bone and soft-tissue malignant tumours. Surgery is the mainstay of treatment for sacral chordomas. Complete radical resection produces both longer continuous local control and an extended disease-free period compared with subtotal resection, but by the time symptoms first appear, chordomas are often already too large to be removed completely [10–14]. Chordoma has poor sensitivity to photon radiotherapy, although some studies have reported that photon radiation therapy delays recurrence after incomplete resection and can relieve symptoms caused by recurrences [15]. Sacral chordomas also have poor sensitivity to chemotherapy [9]; they are almost impossible to cure without surgery and there is little possibility of survival. Hence, chordoma is considered to be one of the most challenging mesenchymal tumours to treat effectively. CIRT has the physical advantage of good dose distribution. With high LET and high Bragg peak intensity, it is expected to be safer and more effective for the treatment of sacral chordomas than low-LET radiation, such as photon radiation.

Data from 30 patients with sacral chordoma treated with carbon ion radiotherapy were reported in 2003 [16]; a study of a further 38 patients in Phase I/II and II clinical trials observed for almost 5 years was described 2009 [17]. This work has begun to establish the effectiveness of CIRT for sacral chordoma. Here, the results from 95 patients treated between 1996 and 2007 are evaluated.

Material and methods

CIRT for sacral chordoma

The specific technique of CIRT used at NIRS has been described in detail in previous publications [1–8]. Briefly, patients were positioned in a customised cradle and immobilised with a low-temperature thermoplastic sheet. The irradiated position was usually prone. A series of CT images of 5 mm slice thickness were acquired for treatment planning. Respiratory gating of both the acquired CT images and the therapy beam was performed. The motion of markers (lines) placed on the skin surface was observed on CT images before respiratory gating was applied [18]. Three-dimensional treatment planning for CIRT was performed using the HIPLAN software program (NIRS, Chiba, Japan) [19]. The planning target volume (PTV) included the clinical target volume (CTV) plus a 5 mm safety margin for positioning errors. Tumour extent was evaluated by MRI, CT and sometimes positron emission tomography. The CTV received at least 90% of the prescribed dose (Figure 1). However, in cases where

Figure 1. The dose distribution of carbon ion radiotherapy for sacral chordoma. The red line indicates 95% of the total dose.

the tumour was located very close to critical organs, such as the bowel and skin, the margin was reduced and consequently <90% of the dose was applied to some tumours. The cradle could be tipped ±20 degrees to ensure that the beam was pointed in the appropriate direction. The therapy was performed once a day, 4 days per week (Tuesday to Friday), at doses ranging from 52.8 to 73.6 GyE for a total of 16 fixed fractions over 4 weeks. Two to four irregularly shaped ports were applied. 91 patients were irradiated with 3 ports: from posterior to anterior, from left side to right side, and from right side to left side. In two patients, dose conformity was achieved using the patch technique, a method of irradiation that uses the special characteristics of carbon ion beams and divides the target into two segments to avoid excess dose irradiation to critical organs. One port was used in each session. At every treatment session, positioning was confirmed with a computer-aided, on-line positioning system and four doctors on shift checked all sessions each day.

The median CTV of the tumours in this study was 370 cm^3 (range, 47–1468 cm^3). 1 patient received a total dose of 54.8 GyE, 1 patient 64.0 GyE, 86 patients 70.4 GyE and 7 patients 73.6 GyE (Table 2).

Patients

Between June 1996 and February 2007, a total of 95 patients with sacral chordoma received CIRT. 9 patients were registered in Phase I/II clinical trials; 29 patients in Phase II clinical trials; and 57 in HAMT trials. All patients signed an informed consent form approved by the local institutional review board. Details of eligibility for both trials have been described in previous articles. The eligibility criteria applied were the same as those for the HAMT protocols:

- tumour judged to be medically inoperable by the referring surgeon
- tumour histopathologically diagnosed as chordoma

Table 2. Characteristics of patients with chordoma

Characteristics	*n*
Number of patients	95
Sex	
Male	68
Female	27
Prior surgery	
Yes	11
No	84
Most cranial level of tumour	
L5	10
S1	29
S2	29
S3	9
S4	7
Recurrence after resection	11
Irradiation dose (GyE total in 16 fractions)	
52.8	1
64.0	1
70.4	86
73.6	7
Total	95

- no distant metastasis at the time of initial referral for treatment
- no prior radiation therapy at the same site
- Karnofsky performance status score >60
- tumour grossly measurable.

All tumours were pathologically confirmed as chordomas by our pathologists.

The median Karnofsky performance status score of the 68 males and 27 females was 80 (range, 70–90). The median age was 66 years (range, 30–85 years). Among the 95 patients, 84 had received no previous treatment, whereas 11 had tumours that had recurred after prior surgical resection. All the tumours originated in the sacrum. Their median diameter was 9 cm (range, 3–17 cm). The site distribution of spinal cord tumours was as follows: L5, 10 patients; S1, 29 patients; S2, 29 patients; S3, 9 patients; and below S4, 7 patients. More than 80% of the tumours were located at spinal cord levels higher than S2 (Table 2).

Statistical analysis

Patients were closely followed with physical, CT and MRI examinations at the end of their CIRT, and again 1–2 months after the completion of CIRT. Subsequent follow-ups were planned at least every 6 months at our hospital. For some patients (the elderly and those living in remote places), we depended on imaging films taken at local hospitals and medical reports from local doctors. The follow-up period was calculated from the initial date of carbon ion irradiation. Recurrence was defined as tumour regrowth, *i.e.* an increase in tumour volume observed in two consecutive MRI or CT scans. Modes of failure were defined as:

- local failure—relapse within the PTV
- marginal failure—relapse within 2 cm of the PTV

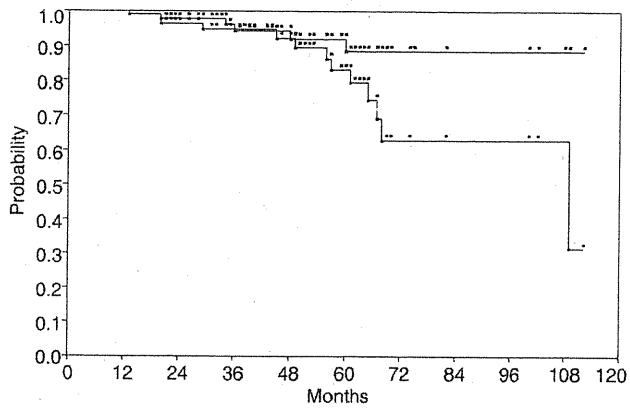


Figure 2. The overall survival (bottom line) and the local control rate (top line) in 95 patients with sacral chordoma treated with carbon ion radiotherapy.

- distant failure—tumour growth identified >2 cm from the PTV.

Local control and overall survival rates were calculated using the Kaplan–Meier method. The last follow-up date was February 2008. Radiation morbidity was classified according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Acute/Late Radiation Morbidity Scoring System criteria in addition to the Late Effects of Normal Tissue/Subjective, Objective, Management and Analytic scoring system [20, 21].

Results

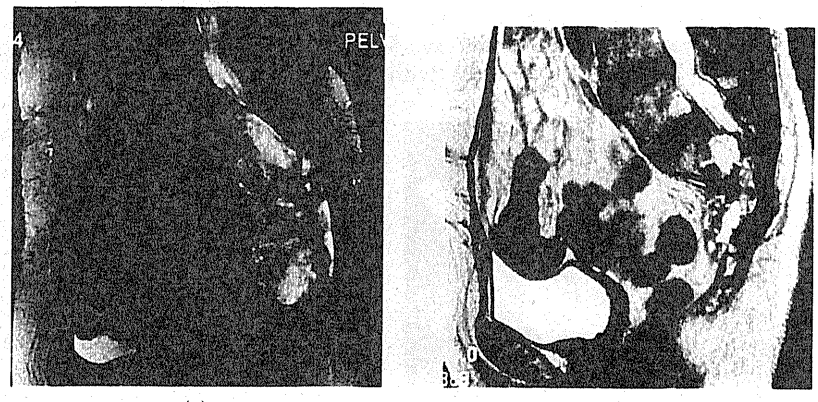
All patients completed CIRT. 83 patients were alive and 12 patients had died at the time of the evaluation. The overall survival rate in all 95 patients at 5 years was 86% (Figure 2). Median follow up time was 42 months (range, 13–112 months). All survivors were followed-up for >1 year. The 5-year local control rate was 88% (Figures 2 and 3). Six patients had local recurrence after CIRT, and median time to local failure was 35 months (range, 13–60 months). Of the 95 patients, 91% remained ambulatory with or without a supportive device.

Three patients had Grade 3 acute skin reactions and two had Grade 3 late skin reactions. Two patients treated with a total dose of 73.6 GyE experienced Grade 4 late skin and soft tissue complications requiring skin grafts on the buttocks. No patient required a colostomy as a result of toxicity from CIRT but one patient experienced transient Grade 1 rectal bleeding 20 months after CIRT. No other treatment-related surgical intervention (*e.g.* urinary diversion) was carried out. 15 patients, including 3 who were surgically treated before CIRT, required continuing medication for sciatic nerve neuropathy. 5 of these 15 patients received a total dose of 73.6 GyE.

Discussion

Sacral chordoma is one of the most challenging malignancies to treat [1]. Surgery is the mainstay but complete excision is sometimes difficult to achieve if the tumour volume is large and/or the tumour invades the upper levels of the sacrum (*e.g.* S1–2) and lumbar spine. The reported proportion of lesions for which complete tumour resection is achieved ranges from 20% to 70% [10–14]. The local control rate is approximately 60–80% in total excision cases, compared with 25–50% in subtotal resection cases [10–13]. Although >80% of tumours occurred at levels higher than S2 and all tumours were judged medically inoperable in our study, the 5-year local control rate was 88%. In the 38 Phase I and Phase I/II clinical trial patients receiving CIRT and observed over 56 months, the 5-year local control rate was 89%. This rate is similar to, or better than, those reported for patients treated by surgical resection.

Approximately 90% of the 95 patients given CIRT remained ambulatory. As already mentioned in a previous report, 30 of 38 patients in these clinical trials had no previous surgery [17]. Although the tumours of 26 of these 30 patients were located above the spinal cord level S2, approximately 90% remained ambulatory (with or without canes) almost 5 years after CIRT, and 50% needed no pain medication. No colostomies or urinary diversions were carried out as a consequence of CIRT [17]. Severe sciatic nerve neuropathy was observed in 15 of the 95 patients, which to some extent influenced their quality of life. We speculate that the main reason for this severe reaction is that all of these patients were irradiated above the S2 vertebra. On the other hand, 12 of 16 patients with S3–4 tumours had no symptoms after CIRT, even though referral surgeons had judged that these patients had medically inoperable tumours. The tumours in all 12 patients were controlled and their activities of daily living were the same before and after CIRT.



(a) (b)

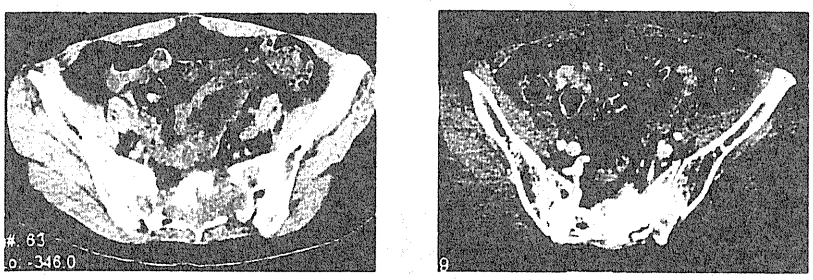
Figure 3. Sagittal T_2 weighted MRI of a sacral chordoma (a) before carbon ion radiotherapy (CIRT), and (b) 4 years after CIRT the tumour shrank and the sacral bone deformity was shown.

An analysis of DVHs of 44 sciatic nerves in 22 patients with sacral chordoma (receiving total doses ranging from 70.4 to 73.6 GyE and followed for >2 years) indicated that the length of irradiated sciatic nerves and dose of irradiation were possibly related to nerve injury. A length of >10 cm and a total dose of >70 GyE were possible thresholds for sciatic nerve injury (data not shown). DeLaney et al [22] at Massachusetts General Hospital (MGH), Boston, MA, reported Grade 3 sacral neuropathy in two patients who received 77.4 Gy RBE and no neural injuries in patients who received ≤70.2 Gy RBE. This result is in accord with their previous finding that the maximum tolerance dose to the cauda equina resulting in a 50% complication rate 5 years after treatment (TD50/5) was 72 GyE for males and 84 GyE for females [23]. This result would be difficult to apply to our results. MGH used fractional doses of <2 Gy RBE, whereas we used fractional doses of 4.4 and 4.6 GyE, corresponding to total doses of 70.4 and 73.6 GyE, respectively. The RBE of carbon ion beams for the sacral nerve or chordoma itself has not yet been elucidated. Furthermore, we speculate that other factors influence sciatic nerve symptoms in our cases. Among these factors, calcium deposits in nerve roots and defective remodelling of the sacral bone structure after CIRT were observed in patients with sciatic nerve injury and symptoms (Figure 4). Yanagi et al [24] used dose–surface histogram (DSH) to analyse the skin reaction of patients with bone and soft tissue sarcoma after CIRT. The area irradiated with >60 GyE (S_{60}>20 cm^2) on DSH was found to correlate significantly with late skin reactions that were worse than Grade 3. With regard to proton therapy, DeLaney et al [22] reported that recommended posterior skin dose was ≤66 Gy RBE.

Several reports have examined charged particle therapies for sacral chordoma, and the results for proton radiotherapy have been compared with those for CIRT. In 1993, Schoenthaler et al [25] at the Lawrence Berkley Laboratory, Berkeley, CA, reported a 5-year local control rate of 55% in 14 post-operative patients with sacral chordomas treated by charged neon and helium particles. This study further demonstrated a trend towards improved local control rate when neon (high LET) was used rather than helium (low LET). The authors recommended maximum debulking of tumour by radical surgery before the charged particle therapy. In 2004, Shulz-Ertner et al [26] reported the results of CIRT in 8 patients with sacral chordoma who were among 152 patients studied at GSI. The treatment sequence consisted of surgery, post-operative intensity-modulated radiotherapy and a carbon ion boost to the macroscopic residual tumour. The median photon dose was 50.4 Gy, and the carbon ion boost 18 GyE. Of the eight patients treated with combined photon radiotherapy to the sacrum and a carbon ion boost to the macroscopic tumour, one had local recurrence inside the irradiated field. DeLaney et al [22] reported results from a Phase II trial involving 50 spinal tumours, including 29 spinal chordomas, at MGH; high-dose photon/proton radiotherapy was part of the treatment regimen, which also included surgery. Before that trial, the results of a pilot study looking at the use of combined high-dose proton–photon radiation for axial skeleton tumours suggested that a primary target dose >77 Gy RBE and total resection of the visible tumour might improve local control rate [27]. In the Phase II trial, the median dose was 76.6 Gy RBE and none of the 23 patients with primary spinal chordoma had local failure. Detailed location-specific analysis of the primary chordomas was not presented in this study. The treatment of one primary sacral chordoma (of 5.5 cm in diameter) with 77.4 Gy RBE led to Grade 3 sacral neuropathy 5.5 years after proton therapy. Treatment of another primary sacral chordoma (of 8.4 cm in diameter) with 77.4 GyE was associated with erectile dysfunction within 3 years. Both tumours were controlled.

Rutz et al [28] reported results from the Paul Scherrer Institute (PSI) in Switzerland. Their treatment protocol involved either a combination of function-preserving surgery and spot-scanning proton therapy or a combination of function-preserving surgery, spot-scanning proton therapy and photon therapy. The study included 7 sacrococcygeal chordomas out of a total 26 spinal chordomas. Patients with residual tumour volume of <500 cm^3 were enrolled. Median total dose was 72 CGE. This report did not present location-specific results, but the 3-year local control rate for all cases was 86%. The applicable dose constraint for centre cauda equina was 64 CGE, which was a lower dose than that applied at MGH [22]. All patients without local failure maintained their full independent status. They retained control over bladder, anal sphincter and ambulatory functions. This result was excellent but the follow-up period was short (35 months).

Regarding local control rate, the results from our study, assuming all our tumours were unresectable, are superior to those previously published, and indicate that CIRT for sacral chordoma is both a promising alternative to surgery and possibly the best charged particle therapy. Patients with sacral chordomas tend to be elderly at the time of diagnosis [1]. The median age in our study was 66 years, whereas in the 2006 MGH study, the average ages of patients with primary chordoma and with recurrent chordoma were 56 and 55



(a) (b)

Figure 4. Contrast CT images of a sacral chordoma (a) before carbon ion radiotherapy (CIRT) and (b) 5 years after CIRT calcification deposited in the tumour bed.

years, respectively [29]. The PSI study showed good results but, compared with our study, the patients were younger (median age, 49 years) and with smaller tumour volume [28]. Even for older patients, our study shows that the direct effects of treatment on patient activity may be acceptable.

There are some problems that need to be overcome if CIRT is to become more prevalent. The major issue is cost per treatment, which depends on manufacturing and operational costs [30]. To increase access to CIRT, the NIRS completed research and development on a compact charged particle therapy system in 2005. The NIRS expects that this system, which is about one-third the size of the HIMAC system and has one-third its manufacturing cost, will perform comparably. This type of accelerator was installed at Gunma University and launched on 16 March 2010. It is expected that this compact system will be installed at institutions throughout Japan.

Data from the present study indicate that CIRT has efficacy against sacral chordoma and limited toxicity. To prove the effectiveness and safety of CIRT, further investigations including clinical trials need to be conducted comparing CIRT with proton beam therapy and surgery.

Acknowledgement

This study was supported by the Research Project with Heavy Ions at NIRS-HIMAC of the NIRS.

References

1. Tsujii H, Kamada T, Baba M, Tsuji H, Kato H, Kato S, et al. Clinical advantages of carbon-ion radiotherapy. New J Phys 2008;10. Available from: http://www.iop.org/EJ/abstract/1367-2630/10/7/075009/.
2. Tsujii H, Mizoe JE, Kamada T, Baba M, Kato S, Kato H, et al. Overview of clinical experiences on carbon ion radiotherapy at NIRS. Radiother Oncol 2004;73:S41–9.
3. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. J Clin Oncol 2007;25:953–64.
4. Noda K, Furukawa T, Fujisawa T, Iwata Y, Kanai T, Kanazawa M, et al. New accelerator facility for carbon ion radiotherapy. J Radiat Res 2007;48:A43–54.
5. Kamada T, Tsujii H, Tsuji H, Yanagi T, Mizoe JE, Miyamoto T, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. J Clin Oncol 2002;20:4466–71.
6. Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys 1999;44:201–10.
7. Murakami T, Tsujii H, Furusawa Y, Ando K, Kanai T, Yamada S, et al. Medical and other application of high-energy heavy-ion beams from HIMAC. J Nucl Materials 1997;148:360–8.
8. Kanai T, Furusawa Y, Fukutsu K, Itsukaichi H, Eguchi-Kasai K, Ohara H. Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat Res 1997;147:78–85.
9. Sundaresan N. Chordomas. Clin Orthop 1986;204:135–42.
10. York JE, Kaczaraj A, Abi-Said D, Fuller GN, Skibber JM, Janjan NA, et al. Sacral chordoma: 40-year experience at a major cancer center. Neurosurgery 1999;44:74–9.
11. Ozaki T, Hillmann A, Winkelmann W. Surgical treatment of sacrococcygeal chordoma. J Surg Oncol 1997;64:274–9.
12. Yonemoto T, Tatezaki S, Takenouchi T, Ishii T, Satoh T, Moriya H, et al. The surgical management of sacrococcygeal chordoma. Cancer 1999;85:878–83.
13. Cheng EY, Ozerdemoglu RA, Transfeldt EE, Thompson RC Jr. Lumbosacral chordoma. Prognostic factors and treatment. Spine 1999;24:1639–45.
14. Bergh P, Kindblom LG, Gunterberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. Cancer 2000;88:2122–34.
15. Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, et al. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol 1996;41:67–72.
16. Imai R, Kamada T, Tsuji H, Yanagi T, Baba M, Miyamoto T, et al. Carbon ion radiotherapy for unresectable sacral chordomas. Clin Cancer Res 2004;10:5741–6.
17. Imai R, Kamada T, Tsuji H, Sugawara S, Serizawa I, Tsujii H, et al. Effect of carbon ion radiotherapy for sacral chordoma: results of phase I–II and phase II clinical trials. Int J Radiat Oncol Biol Phys 2010;77:1470–6.
18. Minohara S, Kanai T, Endo M, Noda K, Kanazawa M. Respiratory gated irradiation system for heavy-ion radiotherapy. Int J Radiat Oncol Biol Phys 2000;47:1097–103.
19. Endo M, Koyama-ito H, Minohara S, Miyahara N, Tomura H, Kanai T. HIPLAN—a heavy ion treatment planning system at HIMAC. J Jpn Soc Ther Radiol Oncol 1996;8:231–8.
20. 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.
21. Anon. LENT SOMA tables. Radiother Oncol 1995;35:17–60.
22. DeLaney TF, Liebsch NJ, Pedlow FX, Adams J, Dean S, Yeap BY, et al. Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. Int J Radiat Oncol Biol Phys 2009;74:732–9.
23. Pieters RS, Niemierko A, Fullerton BC, Munzenrider JE. Cauda equina tolerance to high-dose fractionated irradiation. Int J Radiat Oncol Biol Phys 2006;64:251–7.
24. Yanagi T, Kamada T, Tsuji H, Imai R, Serizawa I, Tsujii H. Dose–volume histogram and dose–surface histogram analysis for skin reactions to carbon ion radiotherapy for bone and soft tissue sarcoma. Radiother Oncol 2010;95:60–5.
25. Schoenthaler R, Castro JR, Petti PL, Baken-Brown K, Phillips TL. Charged particle irradiation of sacral chordomas. Int J Radiat Oncol Biol Phys 1993;26:291–8.
26. Schulz-Ertner D, Nikoghosyan A, Thilmann C, Haberer T, Jäkel O, Karger C, et al. Results of carbon ion radiotherapy in 152 patients. Int J Radiat Oncol Biol Phys 2004;58:631–40.
27. Hug EB, Fitzek MM, Liebsch NJ, Munzenrider JE. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. Int J Radiat Oncol Biol Phys 1995;31:467–76.
28. Rutz HP, Weber DC, Sugahara S, Timmermann B, Lomax AJ, Bolsi A, et al. Extracranial chordoma: outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. Int J Radiat Oncol Biol Phys 2007;67:512–20.
29. Park L, DeLaney TF, Liebsch NJ, Hornicek FJ, Goldberg S, Mankin H, et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. Int J Radiat Oncol Biol Phys 2006;65:1514–21.
30. Pijls-Johannesma M, Pommier P, Lievens Y. Cost-effectiveness of particle therapy: current evidence and future needs. Radiother Oncol 2008;89:127–34.

書籍

著者名	論文タイトル	編集者	書籍名	出版地	出版年	頁
Kamada T, Yamamoto N, Baba M	Carbon Ion Radiotherapy for Perupheral Stage1 Non-Small Cell Lung Cancer	U.Linz(ed)	Ion Beam Therapy	Germany	2012	223-228
Kamada T, Tsujii H	HIMAC: A New Start for Heavy Ions	U.Linz(ed)	Ion Beam Therapy	Germany	2012	611-621

Chapter 14
Carbon Ion Radiotherapy for Peripheral Stage I Non-Small Cell Lung Cancer

Tadashi Kamada, Naoyoshi Yamamoto, and Masayuki Baba

Abstract The National Institute of Radiological Sciences in Chiba, Japan (NIRS) has the highest number of patients with lung cancer treated with carbon ion beams in the world. This report describes the techniques and clinical trials that have been undertaken at NIRS and preliminary results of a current study on single-fraction irradiation. The data are compared to recent results for the treatment of peripheral stage I lung cancer from the literature.

14.1 Introduction

Non-small cell lung cancer (NSCLC) is divided into two groups for radiotherapy (RT). One group is advanced lung cancer, including invasion of the chest wall, mediastinum, and/or mediastinal lymph nodes. The other group is early-stage disease, i.e., peripherally localized T1 or T2 tumors without evidence of lymph node metastases. In general, only early-stage lung cancer is expected to have a long survival.

Surgical resection has played a pivotal role in the treatment of peripherally localized lung cancer and can achieve 5-year survival rates of 60% and 5-year local control rates of more than 80% [1, 2]. The first recommendation for the treatment of early-stage peripheral lung cancer has been surgical resection. However, this is not always feasible or can increase morbidity due to patients' medical conditions, such as pulmonary or cardiovascular disease. RT has played an important role as an alternative treatment. However, conventional RT achieves only poor control of the primary tumor resulting in 5-year survival rates of 30% at best [3]. Dose escalation is essential to improve the effectiveness of RT, but this involves an increasing risk of

T. Kamada (✉)
National Institute of Radiological Sciences, Research Center of Charged Particle Therapy, Anagawa 4-9-1, Inage-ku, Chiba, 263-8555, Japan
e-mail: t_kamada@nirs.go.jp

U. Linz (ed.), *Ion Beam Therapy*, Biological and Medical Physics, Biomedical Engineering, DOI 10.1007/978-3-642-21414-1_14,
© Springer-Verlag Berlin Heidelberg 2012

normal tissue toxicity, especially pulmonary toxicity [4]. As it can even cause fatal reactions, it limits the applicable dose to the tumor. The goal of RT for lung cancer must, therefore, be a higher dose to the target and lower doses to normal tissues, such as lung parenchyma, esophagus, and spinal cord.

As a substitute for conventional RT, which could only be a palliative treatment for medically inoperable localized NSCLC, various modalities of RT have recently been developed, such as stereotactic body radiotherapy using photon beams (SBRT) and ion beam therapy (IBT). SBRT is spreading worldwide and a variety of new machines and techniques are being developed [5–9]. The radiation doses are usually divided into multiple fractions given in multiple sessions. Hypofractionated SBRT, where few fractions of higher doses are administered, is usually applied for the treatment of peripheral stage I lung cancer [6–10]. Onishi et al. reported SBRT results for 257 patients with stage I NSCLC, which showed lower toxicity and good local control rates (5.4% for the pulmonary complications above grade 2, and 14% for the local progression) [9]. Japan is one of the leading countries in the use of hypofractionated SBRT for early stage lung cancer [5].

Ion beams with their improved dose distribution are a novel promising method to apply a higher dose to the tumor while minimizing the dose to surrounding normal tissues. In particular, carbon ion radiotherapy (CIRT) seems to be an attractive modality due to its excellent dose distribution and increased biological effects in the Bragg peak region (cf. Chap. 4 for details). Our clinical trials led us to conclude that irradiation with ion beams, notably carbon ions, offers a significant potential for improving tumor control without increasing the risk of toxicity [11–15].

14.2 CIRT for Lung Cancer at NIRS

NIRS has conducted clinical trials on CIRT for lung cancer since 1994. For peripheral early-stage NSCLC, a dose-escalation study using 18 fractions in 6 weeks was started in 1994. Between 1994 and 1999, a phase I/II dose-escalation study of the treatment of stage-I peripheral NSCLC was conducted to determine the optimal dose and to evaluate if progression to hypofractionated CIRT was feasible [11]. Another purpose of these trials was to develop precise and safe irradiation techniques with maximum sparing of normal tissue.

The phase I/II study provided the following results:

1. The local control rate was dose dependent. Local control reached more than 90% at 90.0 GyE with a regimen of 18 fractions over 6 weeks and 72.0 GyE with a regimen of 9 fractions over 3 weeks. Both doses were determined to be optimal in each fractionation.
2. Damage to the lung was minimal; grade 3 radiation pneumonitis occurred in 2.7% of the cases. Respiratory-gated and 4-portal oblique irradiations, which excluded opposed ports, proved successful for reducing the incidence of radiation pneumonitis.

3. Survival was significantly related to the local control and tumor size of the primary lesion. Local failure, distant metastasis, and malignant pleurisy accounted for decreases in survival.

After the phase I/II study using this optimized schedule, a phase II clinical trial that enrolled a total of 127 patients was initiated in April 1999 and was closed in December 2003 [12, 13]. In the phase II clinical trial, the total dose was fixed at 72.0 GyE in 9 fractions within 3 weeks, and at 52.8 GyE for stage IA NSCLC and 60.0 GyE for stage IB NSCLC in 4 fractions within 1 week. After confirming the feasibility to irradiate in 4 fractions, a phase I/II dose-escalation clinical trial for single-fraction irradiation for peripheral stage I NSCLC was initiated in April 2003. The initial total dose was 28.0 GyE administered in a single fraction using respiratory-gated and 4-portal oblique irradiation. The total dose was escalated in increments of 2.0 GyE up to 48.0 GyE. This clinical trial is still in progress at this moment (February 2011). This article describes the preliminary results of the phase I/II clinical trial and the recent results of the phase II clinical trial in terms of local control and survival rate after CIRT.

14.3 Treatment Methodology

14.3.1 Staging

Computed tomography (CT) scans of the chest and the whole abdomen, enhanced magnetic resonance imaging (MRI) of the brain, bone scans, and bronchoscopy are routinely performed to permit staging. Enrollment in clinical trials is subject to clear pathological diagnosis of NSCLC based on transbronchial tumor biopsy (TBB), transbronchial aspiration cytology (TBAC), or CT-guided percutaneous needle biopsy (PCNB). If regional lymph nodes are greater than 1 cm in the short axis on contrast-enhanced CT images, as well as positive on a ^{11}C-methionine positron emission tomography (PET) scan, the regional lymph nodes are considered positive for metastasis [16]. Recently, it has been introduced that in such a case endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the hilar and mediastinal lymph nodes is performed to determine the metastasis status, more clearly. Clinical staging is performed according to the UICC TNM classification [17].

14.3.2 Marker Insertion

Small iridium markers (length: 3 mm, diameter: 0.5 mm) are inserted into the lung to verify position and direction of a patient's body during the irradiation. The markers do not interfere with planning and implementation of the treatment. Routinely, two iridium rods are bronchoscopically placed into the patient's lung (Fig. 14.1). The

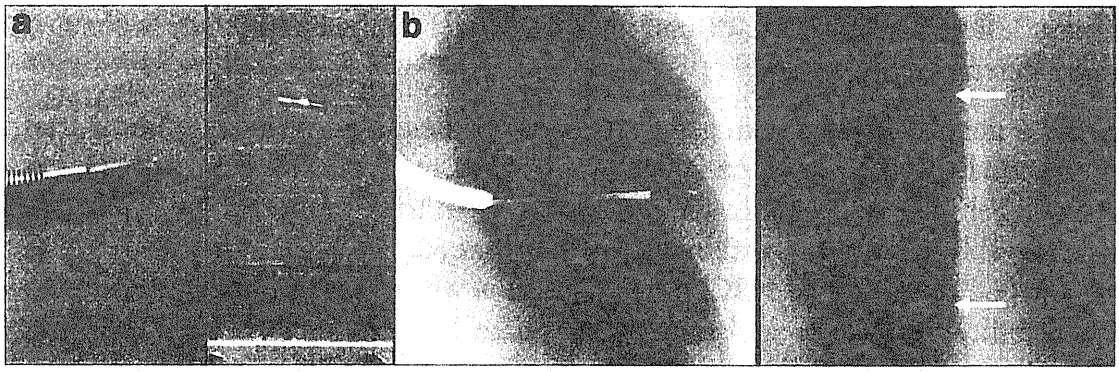


Fig. 14.1 (**a**) *Left*: Size comparison of an iridium marker and the tip of a large-diameter biopsy needle. *Right*: iridium marker with ruler of millimeter gradations. (**b**) X-ray image of bronchoscopic placement of an iridium marker in the lung. (**c**) X-ray image after placement of two iridium markers. The *white arrows* mark their positions

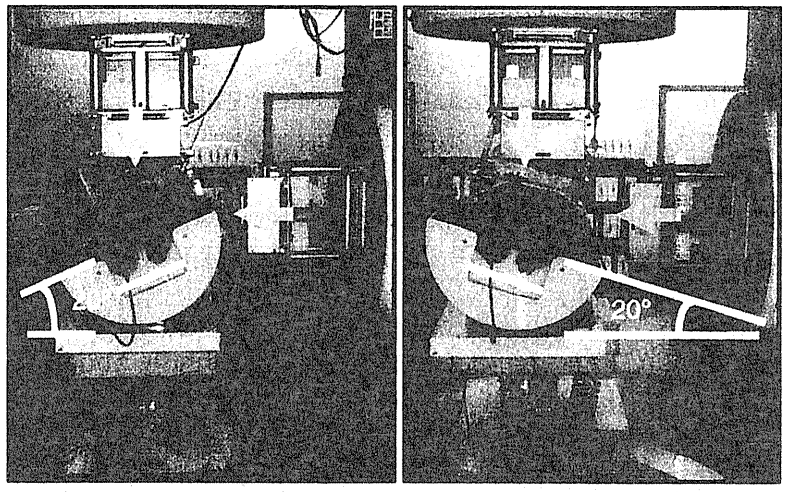


Fig. 14.2 Treatment room with patient fixed in cradle. Irradiation is from four directions. The *yellow arrows* indicate the vertical and horizontal position of the beams. They are directed onto the patient, who is tilted to the left or right by 20°, each

markers serve as fiducial centers to verify the position of the tumor in the lung. In each treatment session, they are visualized by X-ray radiography [18].

14.3.3 Immobilization

The immobilization devices consist of polyurethane fixtures and thermoplastic plates. The fixtures and plates are personalized for each patient before CT scanning for treatment planning. Usually, the patient is in supine position. If the tumor is in the posterior lung, the patient assumes a prone position (Fig. 14.2).

Irradiation is typically from four directions. As the beam lines are fixed in vertical and horizontal directions, respectively, the other two directions are achieved by tilting the patient to the left or right [18].

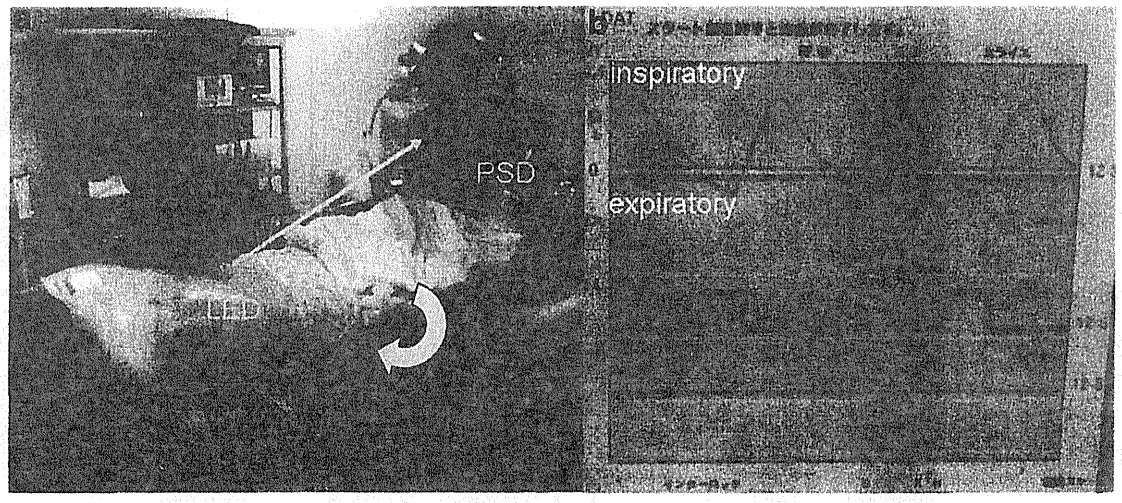


Fig. 14.3 (**a**) Positioning for planning CT-scan. The patient is fixed onto the couch in prone position. The couch is rotated by 20°. A light emitting diode (LED) is attached to the patient's back and the light spot of the LED is focused onto a position-sensitive detector (PSD). (**b**) Respiratory waveform. The *green line* is the threshold of the lung excursion. The *blue line* is the on–off signal of the beam

14.3.4 Respiratory Gating

CT images for treatment planning are taken in synchronization with respiratory motion. Because the displacement of a tumor is generally lowest at the end of the expiratory phase, this is applied for the actual irradiation. Respiration is monitored by measuring the excursions of the chest wall.

The respiratory sensing system uses a position-sensitive detector (PSD) as camera and an infrared light-emitting diode (LED). The LED (5×5 or $3 \times 10\,mm^2$) is attached to the patient's body around the chest wall, and the light spot from the LED is focused on the PSD through a lens system [19]. A change in position is amplified by the zoom lens of the camera. The analog signals of the PSD are directly proportional to the spot position without any software. The camera is typically mounted on the treatment couch at the feet of the patient, where it does not disturb the irradiation and does not interfere with the patient's fixation device. Set-up of the respiratory sensor takes less than 30 s (Fig. 14.3).

Prompt start and stop of beam extraction according to the gate signal are warranted by a special extraction method that provides an efficiency of more than 85% of that of the standard extraction at HIMAC [19, 20].

14.3.5 Treatment Planning

The targets are typically irradiated from four oblique directions without prophylactic elective nodal irradiation. A margin greater than 10 mm is set outside the gross target volume (GTV) to determine the clinical target volume (CTV). Spicula formations

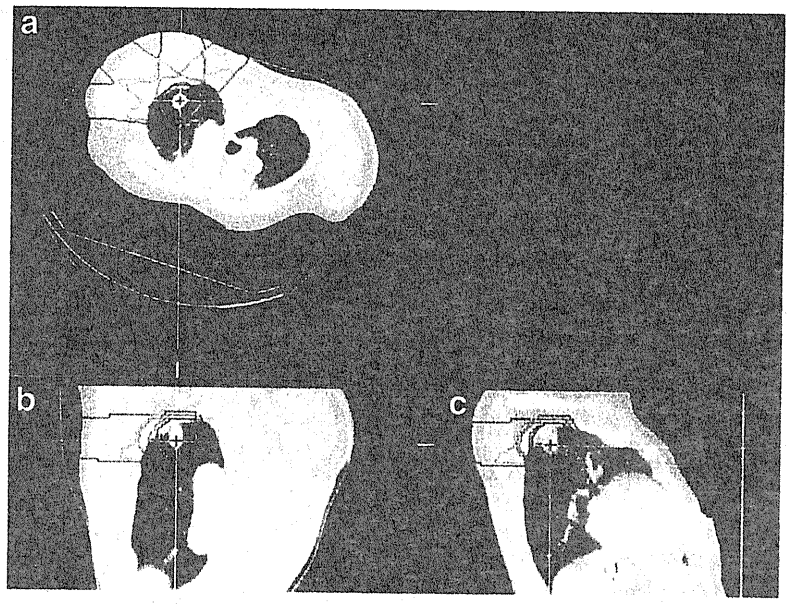


Fig. 14.4 Dose distribution of a single-fraction carbon ion treatment for an 80-year-old male patient with T1 NSCLC. CIRT Dose–Volume histograms showing percentage of prescribed dose of 44.0 GyE. *Red line*: 96%; *orange line*: 90%; *green line*: 50%; *blue line*: 30%; *violet line*: 10%. (**a**) Axial plane. (**b**) Coronal plane. (**c**) Sagittal plane

and pleural indentations are included in the CTV where possible. An internal margin (IM) is set outside the CTV, in order to allow for target motion during gating. The planning target volume (PTV) is defined as CTV plus IM. Three-dimensional treatment planning is performed using the HIPLAN software, developed at NIRS [21]. The IM is determined by extending the target margin in the head and tail direction by a width of 5 mm, which has resulted in the successful prevention of marginal recurrences caused by respiration movement. The dose is prescribed at 90% of the dose distribution. A representative case is illustrated in Fig. 14.4.

14.3.6 Irradiation

For patient positioning, fluoroscopic images are used along with the superposition of the respiration waveform. Each treatment room of the HIMAC has a pair of orthogonal fluoroscopic devices. Fluoroscopic images of the patient in the setting position are digitized and transferred to the positioning computer. They are displayed on the computer monitor screen together with reference images, such as simulation images or digital reconstruction radiography, which is calculated based on the planning CT images. Fluoroscopy is taken from the beam's eye view. The patient's respiration waveform and the gate signal are also superimposed on the TV screen. The treatment couch is then moved to the matching position until the largest deviation from the field edge and the isocenter position is less than 2 mm. The whole procedure including irradiation takes about 20–30 min.

14.4 Clinical Results

14.4.1 Phase II Clinical Trial with 9 or 4 Fractions

After a preliminary report by Miyamoto et al. on phase II clinical trials using a fixed total dose of 72 GyE in 9 fractions over 3 weeks or 52.8/60.0 GyE in 4 fractions over 1 week, a total of 129 patients having 131 tumors were enrolled into a phase II clinical trial on 9- or 4-fraction irradiation [12, 22]. Fifty-one primary tumors of 50 patients were treated using a fixed total dose of 72 GyE in 9 fractions within 3 weeks. The remaining 79 patients with 80 tumors received an applied total dose of 52.8 or 60.0 GyE in 4 fractions within 1 week. A total of 92 males and 37 females were enrolled; their mean age was 74.5 years. Seventy-two tumors were T1 and 59 were T2. The mean tumor size was 31.5 mm in diameter. Of these patients, 75% were inoperable for medical reasons. The median follow-up time was 50.8 months and ranged from 2.5 months to 70.0 months (Table 14.1). The 5-year local control rate for the 131 primary lesions was 91.5%. The 5-year cause-specific survival rate and the overall 5-year survival rate were 67% and 45.3%, respectively (Fig. 14.5).

The 5-year local control rates for the T1 ($n = 72$) and T2 ($n = 59$) tumors were 96.3% and 84.7%, respectively. This difference was statistically significant ($p = 0.0156$). Even more dramatic were the 5-year overall survival rates for the two subgroups with 53.9% for stage IA and 34.2% for stage IB and the cause-specific survival rates with 84.8% and 43.7%, respectively. No significant differences in the local control and survival were observed according to the dose and fractionation pattern. Of 62 (48.8%), who died, half died due to disease progression, the others due to intercurrent diseases.

Toxicities to the skin and lung caused by CIRT were assessed according to the criteria of the RTOG for early, and RTOG/EORTC for late effects [23]. No acute

Table 14.1 Patient characteristics in the studies with 4 and 9 fractions (fx)

Total number of patients (lesions)		129(131)
Gender	Male	92[a]
	Female	37
Mean age (years)		74.5
Tumor stage (no.)	T1	72
	T2	59
Mean tumor diameter (mm)		31.5
Medically inoperable (%)		75
Follow-up (months)	Median	50.8
	Range	2.5–70
Carbon ion dose (GyE)	72/9 fx	51
	52.8 or 60 in 4 fx	80

[a]92 patients with 94 lesions

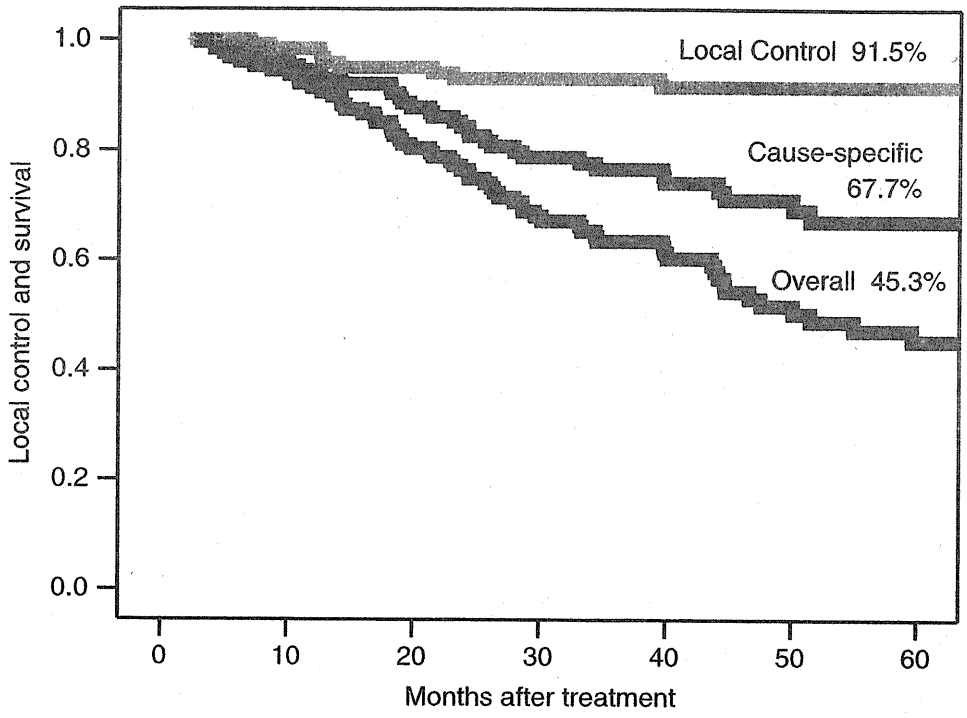


Fig. 14.5 Phase II trial of 9- and 4-fraction CIRT for early-stage NSCLC. The local control rate for 131 primary lesions was 91.5%. The 5-year cause-specific survival rate and the 5-year overall survival rate of 127 patients was 67% and 45.3%, respectively

and only one late grade 3 skin reaction was observed. Of 129 patients assessed, there was no grade 3 early or late reaction. Just two acute and three late grade 2 lung reactions were observed [22].

14.4.2 Phase I/II Clinical Trial: Single Fractionation

More than 200 patients have been enrolled in the dose-escalating clinical trial using a single fraction until February 2011. The trial is still ongoing and the preliminary results are so far quite promising.

The outcome of a first cohort of 72 patients treated between April 2003 and August 2007 was analyzed. The group consisted of 47 patients with T1 and 25 patients with T2 tumors (see Table 14.2). The average tumor size was 28 mm (mean) in diameter and 65% of the patients were medically inoperable. All patients were followed up until death.

The treatment dose was gradually increased from 36.0 GyE per single fraction ($n = 18$) to 38.0 GyE ($n = 14$), 40.0 GyE ($n = 15$), 42.0 GyE ($n = 15$), and 44.0 GyE ($n = 10$), respectively.

The 2-year local control rate for the whole cohort was 89.3%; for patients with T1 tumors, it was 94.6%, and for T2 tumors 78.7%. The overall 2-year survival rate was 85.4% and the cause-specific survival rate an excellent 98.0%.

Table 14.2 Patient characteristics of phase I/II trial with single fractions

Total number of patients		72
Gender (no.)	Male	49
	Female	23
Mean age (years)		75
Tumor stage (no.)	T1	47
	T2	25
Mean tumor diameter (mm)		28
Medically inoperable (%)		65
Follow-up (months)	Median	16.1
	Range	1.6–21.6
Carbon ion dose (GyE)	36	18
	38	14
	40	15
	42	15
	44	10

Skin reactions were, in general, minor with only one acute lesion and one late reaction being of grade 2. None of the 72 patients assessed clinically developed grade 2 or higher acute reactions and no late lung reactions including pneumonitis or fibrosis were observed [24].

The low incidence of complications in patients treated with single-fraction CIRT demonstrated its feasibility not only for patients who refuse surgery but also for medically inoperable candidates.

14.5 Comparisons of CIRT and Other Modalities

Table 14.3 summarizes the clinical results of four institutions treating NSCLC patients with proton therapy (PT).

The first report on PT for NSCLC was published in 1999 by Bush et al. from the Loma Linda University Medical Center (LLUMC) [25]. This report had a heterogeneous patient population with stages I to IIIA, and described a number of irradiation regimens ranging from 10 to 41 fractions. A subsequent report by Bush et al. in 2004 showed good local control rates with hypofractionated PT using 51 or 60 GyE in 10 fractions [26]. In Japan, the same 10-fraction regimen was successfully repeated at the Proton Medical Research Center (PMRC), Tsukuba, and the Hyogo Ion Beam Medical Center (HIBMC) with local control rates ranging from 74 to 95% [27, 28, 30]. A significant improvement in survival was noted for patients who received 60 rather than 51 GyE; their 3-year overall survival rate increased from 27% to 55% [26].