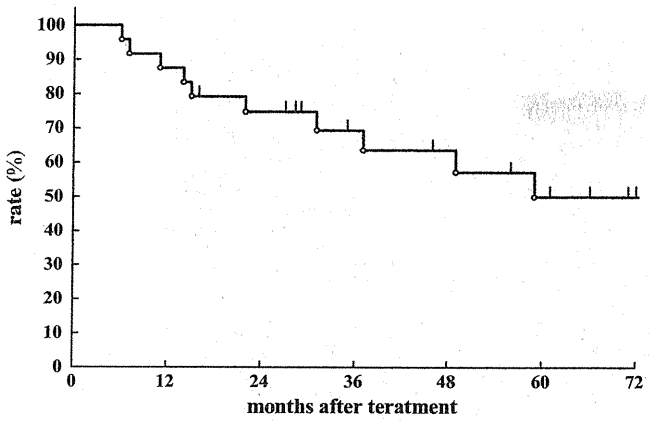

Fig. 2. Overall survival curve for all 24 patients. The 5-year overall survival rate was 50%.

volume. In cases in which the tumor was located close to critical organs such as the bowel, the margin was reduced accordingly. The clinical target volume was covered with at least 90% of the prescribed dose. The planning target volume included the clinical target volume plus a 5-mm safety margin for positioning errors (Fig. 1).

The CIRT was given once daily, 4 days a week (Tuesday through Friday), for a fixed 16 fractions in 4 weeks. Patients were treated with two or three irregularly shaped ports. The doses delivered were 52.8 GyE (3.3 GyE/fraction) in 2 patients, 64.0 GyE (4.0 GyE/fraction) in 1 patient, 70.4 GyE (4.4 GyE/fraction) in 19 patients, and 73.6 GyE (4.6 GyE/fraction) in 2 patients (mean dose, 68.9 GyE; median dose, 70.4 GyE).

The Heavy Ion Medical Accelerator in Chiba generates carbon ion beams, with accelerations of energy of carbon ion beams of 290, 350, and 400 MeV/n. The range of these energy beams has an in-water depth of 15 to 25 cm. The patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. The cell mortality rate from a carbon ion beam is higher than that from a photon beam when the same physical dose is irradiated. This cell-killing effect ratio is expressed by the relative biologic effectiveness (RBE). The RBE of a carbon ion beam has been reported to be 2 to 3, meaning that the cell-killing effect of a carbon beam is two to three times stronger than that of a photon beam (12).

The patients were closely followed with physical examinations, CT, and MRI. Initial follow-up examinations were performed 1 to 2 months after the completion of CIRT, then every 3 to 6 months. The follow-up period was calculated from the initial date of carbon ion irradiation. Recurrence was defined as tumor regrowth and increase in tumor volume observed in two consecutive MRI or CT scans.

Actuarial OS and LC were calculated using the Kaplan-Meier method. Toxicity attributable to RT was scored using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0, for acute toxicity and the Radiation Therapy Oncology Group and the European Organization for Research Treatment of Cancer scale for late toxicity (13). Significant toxicity was defined as any event scored as Grade 3 or greater.

RESULTS

All patients were able to complete the planned CIRT without interruption. Median survival time of all patients was 41 months (range, 6–88 months). At 2 and 5 years, actuarial overall survival rates were 75% and 50% (Fig. 2). Six patients experienced local failure, with time from carbon ion therapy to local failure ranging from 3 to 36 months. One of the 6 patients who had local failure showed marginal recurrence close to the irradiated area. The remaining 18 patients had no evidence of local failure at the last follow-up date (Figs. 3, 4). Distant failure was observed in 12 patients, regional failure in 7 patients, distant metastasis in 2 patients, and both in 3 patients. At 2 and 5 years, actuarial LC rates were 77% and 69% (Fig. 5). There was no case of fatal toxicity during the follow-up period after RT. Grade 1 skin acute reactions were observed in 20 patients (83%) and Grade 2 skin late reactions in 4 patients (17%). Grade 1 skin late reactions were observed in 22 patients (92%) and Grade 2 skin late reactions in 1 patient (4%). Skin reaction higher than Grade 2 was not observed, and skin toxicity decreased in a few months. One patient (4%) developed Grade 1 pulmonary acute reaction. There were no other acute reactions.

Five patients (21%) developed Grade 2 late neurologic toxicity. Three of them had primary tumors and the other 2

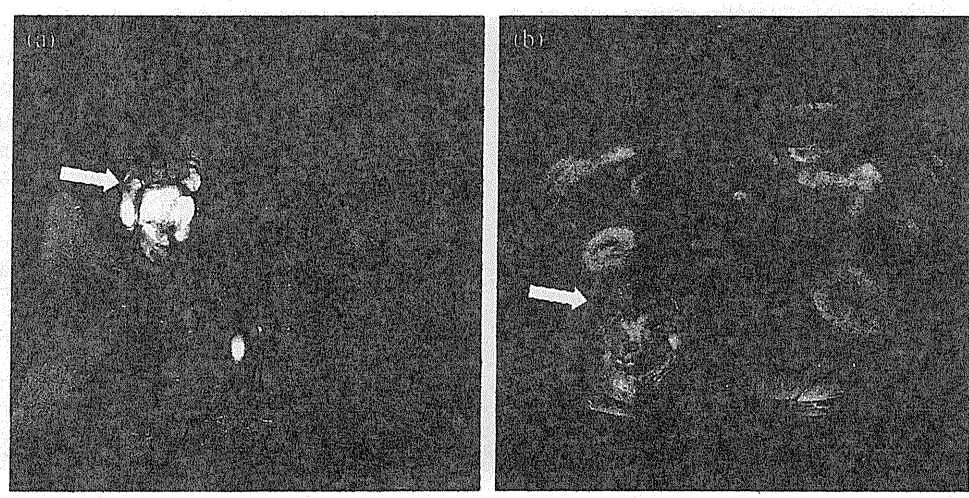

Fig. 3. The tumor revealed intermediate to high intensity on T2-weighted image (a) and enhancement on contrast-enhanced T1-weighted image before carbon ion radiotherapy (b).

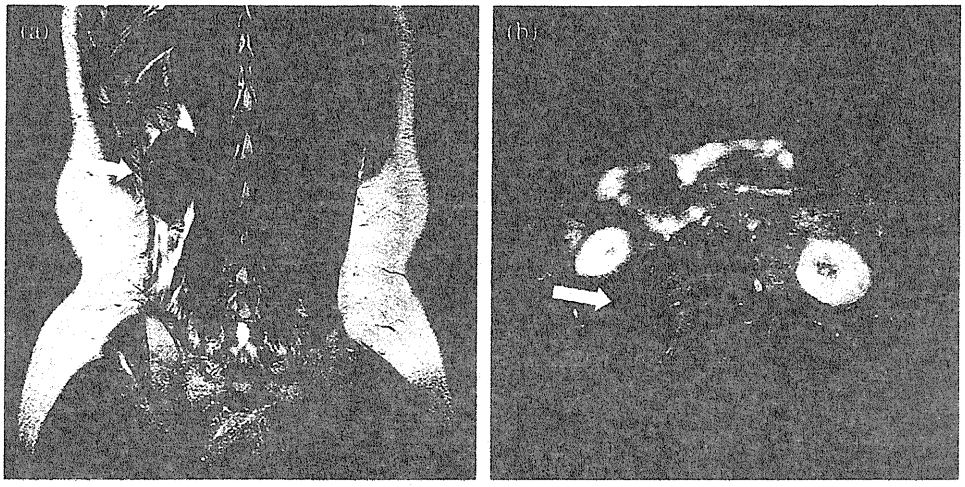

Fig. 4. Fifty-six months after carbon ion radiotherapy, T2-weighted image showed obvious reduction of tumor volume (a) and low intensity and contrast-enhanced T1-weighted image showed no enhancement lesion (b).

had recurrent tumors. Complications of the gastrointestinal tract did not occur. No severe reactions (≥Grade 3) were observed (Table 2).

DISCUSSION

Our institution started a Phase I/II clinical study using CIRT and demonstrated the clinical efficacy of this RT on various kinds of malignant tumors (10, 11). The study produced good LC of BSTSs, including RPSs, generally considered to be photon resistant and inoperable. Despite the fact that patients with RPSs in our series had been considered mostly to involve tumors that were unresectable, radioresistant, and located deep in the trunk, we experienced good LC, OS and a relatively low incidence of complications with CIRT. The facts that more than 83% of the patients in this study had high-grade (≥Grade 2) tumors, and that high grade is reported as a risk factor of LC and OS, means that CIRT resulted in good tumor control.

Most studies with surgical resection with or without conventional radiotherapy have reported 5-year OS and LC of RPSs of 36% to 64% and 28% to 71%, respectively (2, 4, 14–19), as shown in Table 3. A number of reports concluded that the status of the surgical margin is significantly associated with OS and that a complete surgical margin improves OS. However, patients with RPSs often present with large tumors; because of the anatomic location of these tumors and their propensity for spreading invasively, they can be difficult to remove completely. Even after complete resection, most investigators report high local recurrences rates for RPSs, with a mean rate of approximately 50% (14, 20). It is even more difficult to completely resect recurrent tumors after surgery. Such conditions reduce the rate of complete surgical resection and worsen tumor control.

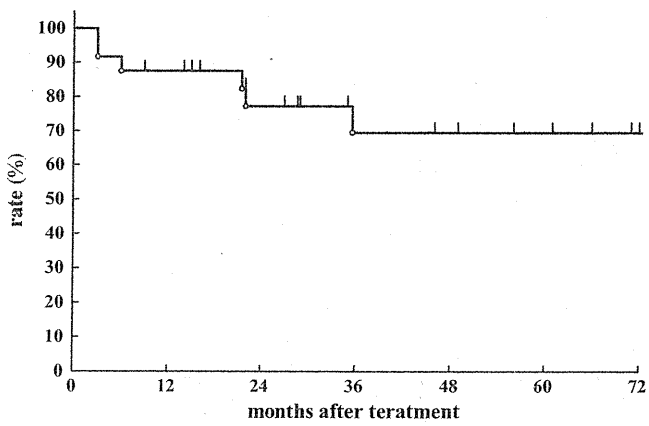

Fig. 5. Local control rate for all 24 patients. Five-year local control rate was 69%.

Although one-third of the patients in present study had recurrent tumor and most of the tumors were diagnosed as unresectable, CIRT shows favorable OS and LC (OS at 5 years, 50%; LC at 5 years, 69%) compared with other reports on surgery.

Some investigators have reported that higher doses of external beam radiation or the specific use of IORT improve LC of RPSs. Catton *et al.* set a lower limit of 35 Gy, based on the experience that irradiation doses greater than 35 Gy after complete surgery delayed local recurrence (2). Stoeckle *et al.* found a significant reduction of local recurrence and longer survival in patients who received an adjuvant RT (14). Fein *et al.* insisted on using doses greater than 55 Gy for RPSs to improve the likelihood of local control (20). In a series of 198 patients with RPS who were long-term (>5

Table 2. Toxicity in study patients

Acute reaction	G1 *n*	G2 *n*	G3 *n*	G4 *n*
Skin	20	4	0	0
Gastrointestinal	0	0	0	0
Late reaction	**G1 n**	**G2 n**	**G3 n**	**G4 n**
Skin	22	1	0	0
Gastrointestinal	0	0	0	0
Neurologic	0	5	0	0

Table 3. Overall survival (OS) and local control (LC) in various studies

First author, year	Treatment	n	Resection (%)	Complete resection (%)	Microscopically positive margin (%)	5-y OS (%)	5-y LC (%)
Catton, 1994 (2)	Op+EBRT	104	43			36	28
Stoeckle, 2001 (14)	Op+EBRT	145	65			49	41
Van Dalen, 2001 (15)	Op	142		54	ND	ND	32
Lewis, 1998 (4)	Op+EBRT	278	67	49	18	54	59
Gronch, 2004 (16)	Op+EBRT+IORT	167	88			53	54
Gilbeau, 2002 (17)	Op+EBRT	45		38	58	60	40
Krempien, 2006 (18)	Op+IORT ± EBRT	67		31	51	64	40
Youssef, 2002 (19)	Op+EBRT ± BT	60		45	30	56	71
Current study (2009)	CIRT	24	–			50	69

Abbreviations: BT = brachytherapy; CIRT = carbon ion radiotherapy; EBRT = external beam radiation therapy; IORT = intraoperative radiation therapy; ND = no description; Op = operation.

years) survivors, Heslin *et al.* reported that radiation therapy was the only significant factor associated with improved local control, concluding that postoperative high dose (>50–55 Gy) XRT was effective in local control (1).

To give a high dose to the target is very important in radiation therapy of RPSs, but such doses are associated with higher rates of toxicity. Methods for dose-escalating radiation include BT and IORT; but some series have reported significant complications, including neuropathy as well as gastrointestinal and genitourinary complications (Table 4) (21, 22). Jones *et al.* reported six patients with life-threatening complications, including duodenitis, and 1 patient died of liver failure. Petersen *et al.* reported severe (Grades 3–5) toxicities such as elevating creatinine levels, ureteral injury required stenting, and neuropathy. When external radiation therapy with effective doses is performed, small bowel toxicity is generally emphasized; but other organs such as kidneys, liver, and spinal cord are also dose-limiting organs. Tzeng *et al.* reported preoperative IMRT with selective dose escalation of radiation therapy for RPS (23). Their study enrolled 16 patients who could undergo operation, and their follow-up time was shorter (median, 28 months). Six patients showed acute and late gastrointestinal tract complications (>G1).

In the present study, no gastrointestinal tract complications occurred, indicating that CIRT can deliver better dose distribution than photon beams. Compared with other reports, our results showed higher incidence of late neurologic toxicity (5 patients developed Grade 2 late neurologic toxicity) (Table 4). However, most patients in our study were inoperable and their tumors invaded nerves before treatment, so the nerve could not be spared from the high-dose area of CIRT. In fact, 3 of the 5 patients had neurologic disabilities before CIRT. It was also reported that, in the treatment of sacral chordoma, tumor location and pretreatment neurologic status are important predictors of treatment outcome (11). Therefore our data on neurologic toxicity are considered to be acceptable.

Lewis *et al.* reported that a pathologic high grade was a risk factor of metastasis, and their analysis showed distinctly longer survival among patients with low-grade tumors than among those with high-grade tumors (low-grade: mean, 149 months; high-grade: mean, 33 months) (4). Stoeckle *et al.* reported that histologic subtypes had an influence on outcome, as patients with nonliposarcoma tumors had a higher risk of metastasis and poorer LC and OS than patients with liposarcoma (14). Feng *et al.*, from their survival analysis, indicated that grade is a strong predictor, with a 5-year OS rate of 66% and 25%, respectively, for patients with low-grade vs. intermediate/high-grade tumors. They observed that high-grade plus unresectability was also associated with poor survival (24). Guadagnolo *et al.* reported good outcomes in patients with liposarcoma, indicating a clear relationship between pathologic features and outcomes of treatment (25).

In our study, most of the tumors were high-grade sarcomas (≥Grade 2), including 3 patients with lioposarcoma. In light of this situation, CIRT is suggested to be an effective and safe treatment for retroperitoneal sarcomas.

Table 4. Complications in studies reported

First author, year	Treatment protocol	n	2-y LC (%)	Acute ≥G2(%)		Late I ≥G2(%)		Death(%)
				GI	NT	GI	NT	
Gilbeau, 2002 (17)	Op+EBRT ± IORT	45	70	77	0	9	19	0
Fein, 1995 (20)	Op+EBRT	19	72	5	0	0	0	0
Jones, 2002 (21)	Op+EBRT ± BT	41	80	15	0	10	2	7
Peterson, 2002 (22)	Op+EBRT + IORT	87	84	14	10	–	–	0
Tzeng, 2006 (23)	Op+IMRT	14	80	6	0	6	0	0
Current study (2009)	CIRT	24	77	0	0	0	21	0

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; GI = gastrointestinal (toxicity); IORT = intraoperative radiation therapy; IMRT = intensity modulated radiotherapy; LC = local control; NT = neurotoxicity; Op = operation.

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Changes in Tumor Volume of Sacral Chordoma After Carbon Ion Radiotherapy

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Objective: We evaluated changes in tumor volume in cases of sacral chordoma after carbon ion radiotherapy.

Methods: Thirty-four patients with sacral chordoma underwent carbon ion radiotherapy between June 1996 and June 2003. We assessed 23 patients without previous surgery using T2-weighted magnetic resonance imaging. The tumor volume was calculated semiautomatically.

Results: Two cases showed local recurrence. The median interval of this examination was 46 months. At the end of the treatment, the tumor showed an enlargement larger than 10% of its volume in 13 of the 23 cases, no change in 4 cases, and regression in 6 cases. At the last examination, 20 cases showed a reduction in tumor volume, and the median ratio, determined as the tumor volume at the last examination divided by that before the treatment, was 0.36.

Conclusions: An increase in tumor volume at the end of the treatment does not indicate the ineffectiveness of carbon ion radiotherapy.

Key Words: chordoma, charged particle therapy, radiotherapy, magnetic resonance (MR) imaging

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Chordomas are rare malignant bone tumors that constitute between 1% and 4% of all primary bone malignancies.[1] About 50% of all chordomas originate in the sacrum.[1] Complete resection is the preferred method for treating chordomas for continuous local control and survival prolongation.[1] However, chordomas are often too large at the time of diagnosis for successful resection. Currently, there is no effective chemotherapy regimen for chordomas.[2–4] Because chordomas are radioresistant, photon radiotherapy is not sufficient as a curative local treatment.[2,3] As previously reported, we have treated unresectable sacral chordomas using carbon ion radiotherapy since 1996 and have achieved good results.[5] Carbon ion radiotherapy provides excellent dose distribution and high biological effectiveness. These advantages are useful for the treatment of chordomas.[5–7] In this study, we report on changes in the tumor volume of sacral chordomas after carbon ion radiotherapy. There have been no previous reports on longitudinal changes in images of chordomas that could not be surgically treated because local control could rarely be accomplished by photon radiotherapy in unresectable cases.[2–4,8] This is the first report on the longitudinal changes in images of chordoma after carbon ion radiotherapy.

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MATERIALS AND METHODS

Patient Characteristics

We examined 34 patients with sacral chordoma who were candidates for clinical trials and underwent carbon ion radiotherapy between June 1996 and June 2003 at the National Institute of Radiological Sciences in Chiba, Japan.[5,6] Patients eligible for phase I/II or phase II trials of carbon ion radiotherapy for bone and soft tissue sarcomas were those with tumors judged unresectable by orthopedic surgeons or those who were refused surgery. Details regarding these trials are described in a previous report.[6] Pathological specimens from each patient were reviewed, and all were confirmed as chordomas. All patients signed an informed consent form that was approved by the local institutional review board. The 34 patients consisted of 25 men and 9 women, with a median age of 66 years (range, 41–85 years). Eight patients had recurrent tumors after surgical resection, and 26 patients had not received any previous treatment. The median clinical target volume was 510 cm^3.

Study Design

Imaging was performed before irradiation and at the end of treatment and then, in general, followed up at least every 12 months at our institution. For this study, we used magnetic resonance (MR) imaging as the main evaluation tool; however, if serial MR imaging could not be performed, a serial computed tomography (CT) was performed to replace MR imaging. In some patients, CT and MR imaging examinations were mixed during the follow-up period. For those patients, serial examinations performed with more regularity were adopted for this study. Magnetic resonance examination was performed with 1.5-T imagers (Magnetom Vision and Intera from Siemens, Erlangen, Germany, and Philips Medical Systems, Best, the Netherlands, respectively) with a phased array coil. The acquisition protocols were as follows: nonenhanced transverse turbo spin echo T1-weighted (620/13) and T2-weighted sequences (2300/90) with a slice thickness of 4 mm, an intersection gap of 1 mm, a field of view of 330 × 280 mm, and a matrix of 512 × 330, followed by fat-suppressed enhanced axial and sagittal T1-weighted sequences (620/13) with a slice thickness of 4 mm and an intersection gap of 1 mm after intravenous injection of 0.1 to 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany).

Computed tomographic examination was performed with a 16–detector row CT scanner (Sensation 16; Siemens). Our standardized CT scan protocol included an initial unenhanced scanning pass of the pelvis with a 0.75-mm collimation. This was followed by a contrast-enhanced pass with a 0.75-mm collimation 80 seconds after the start of an intravenous power injection of 100 mL of noniodinated material (iopamidol, Iopamiron 300; Bayer, Osaka, Japan) at 1.5 mL/s. The slice thickness of the MR and CT images was 5 mm.

We excluded from the study 8 patients with recurrence after resection. Another patient was excluded because her follow-up

was performed at the local hospital and we could not calculate the tumor volume. One patient who died of intercurrent disease within 1 year of the treatment was also excluded. Another patient was excluded because of multiple small skip lesions around the primary tumor site in the sacrum that were included in the original irradiated field during the first treatment. In this case, it was difficult to define the effectiveness of carbon ion radiotherapy for each lesion.

Analysis of Images for the Measurement of Tumor Volume

All procedures were conducted with the consensus of 3 authors from this study (R.I., T.K., and R.K.). T2-weighted imaging clearly delineated the chordomas from the surrounding tissue, allowing excellent assessment of the tumors. T2-weighted axial images were used to describe the region of interest with reference to T1-weighted and postcontrast T1-weighted axial images. In the evaluations by CT, postcontrast images were primarily used. In questionable cases, especially those with calcification and bone degeneration, both MR and CT images were used for reference, even if they were not examined at the same time. For quantification of the tumor volume, the tumor area on each tumor-containing section was delineated by an operator-defined region of interest, and the tumor volume was automatically calculated. In addition, the tumor volume ratio (VR) at each examination divided by the volume before irradiation was examined. For verification of tumor calcification, we used the latest CT images, which were taken at least 2 years after carbon ion radiotherapy. Computed tomographic images examined within 2 years were not regarded as appropriate for this assessment. We only compared the initial CT images with the last CT images. There were 14 patients who were candidates for the CT analysis.

Carbon Ion Radiotherapy

The specific techniques for carbon ion radiotherapy have been described in detail in previous reports.[6,9] The Heavy Ion Medical Accelerator in Chiba generates carbon ion beams. A carbon ion beam has the benefit of excellent dose distribution and better biological effectiveness compared with a photon beam. Tumors that are difficult to treat make good use of these advantages and are good controls.[5,6,9] For the definition of target volume, tumor spreading was estimated by MR, CT, and positron emission tomography. Carbon ion radiotherapy was performed

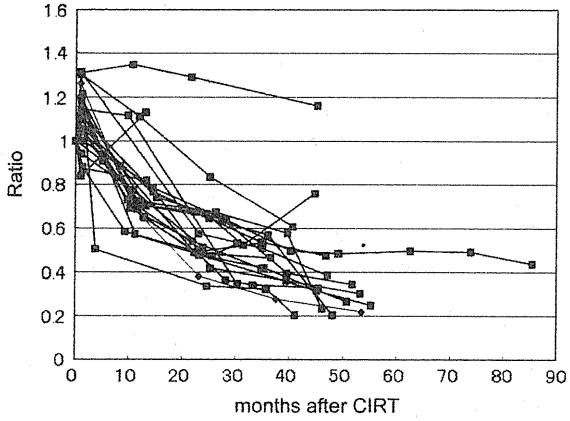

FIGURE 1. Changes in the tumor VR at the time of examination. The vertical axis indicates the tumor VR at each examination divided by the volume before irradiation, and the transverse axis is the number of months after carbon ion radiotherapy (CIRT). At the end of CIRT, temporary enlargement was observed in 13 cases.

TABLE 1. The Comparison of Tumor VR After CIRT (Cases)

	At the End of CIRT	Last Examination*
VR ≥ 1.1	13	1
1.1 > VR > 0.9	6	0
0.9 ≥ VR	4	20

*Excluding 2 recurrent cases.

once a day for 4 days a week (Tuesday to Friday), for a total of 16 fixed fractions in 4 weeks. A range of 2 to 4 irregularly shaped ports were applied, and 1 port was treated in each session. We used doses from 52.8 to 73.6 Gy equivalents (carbon physical dose [gray] multiplied by the relative biological effectiveness).[5,8] Relative biological effectiveness was evaluated by both radiobiological and physical studies.[7,9]

Statistics

The follow-up period was calculated beginning from the initial date of carbon ion radiotherapy. The last follow-up date was on September 1, 2006. Local control and overall survival rates were calculated using the Kaplan-Meier method. The correlation between the tumor volume and the VR at the end of the treatment was tested. To assess tumor calcification changes, t test was used. All statistics were performed using Stat View 5.0 (SAS Institute Inc, Cary, NC). $P < 0.05$ was considered significant.

RESULTS

Treatment Results

Only 2 of the 34 patients in this study demonstrated local recurrence, 1 after 13 months and the other after 35 months. Four patients died because of disease, and another 4 died of intercurrent disease. The 5-year overall survival rate was 85.4%, and the 5-year local control rate was 93.8%.

Changes in Tumor Volume

Of the remaining 23 patients, including the 2 recurrent cases, 18 were examined by serial MR imaging and 5 by serial CT. Two patients did not have annual examinations, and we decided to add them to this analysis because their last images were obtained more than 2 years after carbon ion therapy, and we judged that using these images were appropriate for this study. By excluding the 2 recurrent cases, the median interval between the first and the last examinations was 46 months. The interval was longer than 3 years in 17 patients and between 2 and 3 years in 4 patients.

Figure 1 shows a plot of VR. At the end of the carbon ion radiotherapy, the VR had increased in most patients. The volume ratio at the end of the carbon ion radiotherapy was higher than 1.1 in 13 cases and lower than 0.9 in 4 cases (Table 1). In 12 of the 13 cases with a larger than 10% increase in size, continuous regression was observed after the initial enlargement. There was only 1 case in which the tumor volume did not revert back to the primary volume after the initial enlargement. The median VR was 0.36 in the last evaluation of 20 cases with decreasing size. In 4 cases, an enlargement larger than 20% of the initial volume occurred; however, at the time of the second examination, there was no continuous progression in size, and VR at the last evaluation was between 0.2 and 0.6 in 3 of the 4 cases and 1.16 in 1 case. The first regression of tumor volume to a ratio lower than 1.0 was observed between 1 and 25 months after carbon ion radiotherapy in 22 cases (Fig. 2).

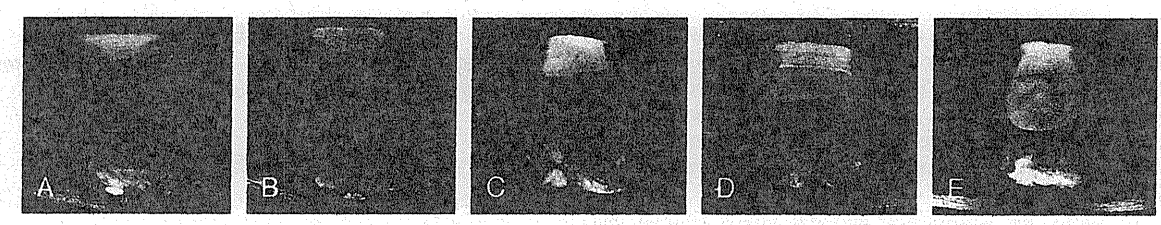

FIGURE 2. Serial axial T2-weighted images of sacral chordoma in a 61-year-old man. The tumor was temporary enlarged after carbon ion radiotherapy and then gradually shrank. A, Before carbon ion radiotherapy. B, At the end of carbon ion radiotherapy. C, Thirteen months after CIRT. D, Twenty-three months after CIRT. E, Forty-five months after CIRT.

We compared the annual mean VR in 11 available cases. We defined 1 year as occurring between 10 and 12 months after carbon ion radiotherapy, 2 years as 22 to 26 months, and 3 years as 34 to 38 months. The mean VR was 1.06, 0.72, 0.56, and 0.44, respectively, at the end of the carbon ion radiotherapy, and 1, 2, and 3 years, respectively, after the carbon ion radiotherapy.

Changes of Tumor Calcification

Tumor calcification was evaluated in 14 of the 23 cases by CT more than 2 years after carbon ion radiotherapy. Changes in tumor calcification were categorized into 3 patterns. The first was a pattern of calcification observed in tumors with both original bony structures, such as the sacral bone, and nonbony structures, such as where a tumor protrudes from the bone (n = 6; Fig. 3A). Another calcification pattern was observed in tumors with original bone structures only (n = 3; Fig. 3B). The third pattern consisted of areas where less calcification was observed in the tumor (n = 5; Fig. 3C). The extent of the pattern of calcification was not significantly correlated with the shrinkage ratio at the end of the treatment ($P = 0.5298$).

DISCUSSION

There have been few reports of sacral chordomas treated with modalities other than surgery because, before the appearance of carbon ion radiotherapy, only surgery could achieve long survival rates.[2–4,8] As we reported previously, carbon ion radiotherapy can achieve good results for sacral chordomas.[5] For this study, we made an effort to check the progress of our patients at least every 6 months; however, most of the candidates in this study were elderly and lived far from our hospital. Occasionally, our only recourse was to estimate a patient's tumor volume using imaging films taken at the local hospital, and we could not use such examinations as part of this study. Thus, there was some dispersion in the time when examinations for each patient were performed.

In 80% of the patients, we observed that tumors had increased or remained unchanged in size at the end of the carbon ion radiotherapy. It has been reported that the same phenomenon occurs in vestibular schwannomas after gamma knife radiotherapy.[10] In the study of schwannomas, 41% of the cases demonstrated temporary enlargement, and the local control rate was 81%. In a similar fashion, in our study, the tumor volume gradually decreased after initial enlargement. The tumor may enlarge owing to developing areas of necrosis and edema. Hemorrhage may also stimulate tumor growth that is often appearing as areas of high signal intensity on T1-weighted MR images. Nakamura et al[10] report that microsurgical resection of tumors show hyalinized thrombosis, thickening of the vascular wall, vascular obstruction, and granulomatous change, and this change help our inference. Even tumors with an enlargement larger than 20% demonstrated shrinkage upon the second examination. Considering these results, we could not conclude that recurrence would occur immediately upon observing initial enlargement. In 1 case, the tumor volume did not revert to the primary volume, but we did not confirm this change as recurrence because the tumor did not maintain a successive increase. Furthermore, the patient's symptoms were gradually relieved. Upon admission, he was bedridden with epidural anesthesia, but at the time of the last examination, he was active enough to maintain a part-time job.

In 4 cases, we observed that the tumor volume decreased lower than 10% and then rose higher than 10%. In 2 of these cases, a progressive increase in tumor volume was found by the local hospitals, and these were defined as local recurrence. One patient underwent CT examination after the last MR imaging. According to the findings of the last CT, regression of the tumor was apparent. In this case, the original tumor existed within the sacrum and did not protrude into the soft tissue around the sacrum. After treatment, calcification was observed to gradually accumulate in the soft part of the tumor on serial MR images. The last MR image revealed abnormal intensity, and the enhancement area by contrast medium was extended. The new CT examination performed did not reveal any apparent findings of local recurrence. It has been reported that radiation-induced insufficiency fractures show abnormal intensity on MR images.[11] Thus, we speculated that we misunderstood the abnormal intensity on the MR images caused by calcification change and degeneration of sacral bone as tumor spreading. In the other case, a compression fracture in the sacral bone occurred 2 years after carbon ion radiotherapy. Owing to the bone degeneration and misalignment caused by the fracture,

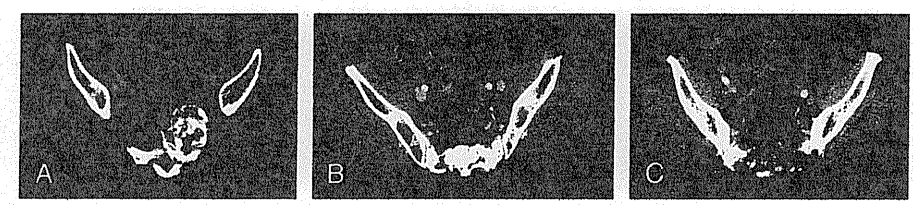

FIGURE 3. Changes of tumor calcification. A, Calcification in the tumor in both the original bony structures, such as the sacral bone, and the nonbony structures, such as where the tumor protruded from the bone. B, Calcification in the tumor in only the original bony structure. C, Less calcification in the tumor.

abnormal intensity was seen on the MR images, and we confused this abnormality with tumor spreading. For cases such as these, images from another axis of the body or a combination of several modalities would be useful. Except in cases of recurrence, sequential enlargement was generally not observed, and to judge recurrence, we will need to monitor regrowth 2 or more times in a row.

Regarding the relationship between tumor volume and tumor regression, the rate of regression at the end of carbon ion radiotherapy was not significantly correlated with the initial tumor volume. We could not speculate on the speed of shrinkage by considering the initial volume. The accumulation level of calcification was not significantly related to the initial ratio of regression. As for the prediction of local control, only 2 patients in this study had local recurrence, and it was hard to determine a relationship between recurrence and reaction to carbon ion radiotherapy.

In cases where the tumor volume has not decreased or there are residual findings on CT and MR images, to know whether tumor regression will occur is important for orthopedic surgeons referring patients. This data could indicate whether chordomas treated with carbon ion radiotherapy had sufficient potential to become reduced in size during observation. We suggest a waiting period and frequent monitoring of follow-up imagings before diagnosing cases of recurrence, unless symptoms deteriorate or the tumor continuously enlarges. Carbon ion radiotherapy does not have a long history, but we have been able to use it to treat a growing number of cases of chordoma. Chordoma is a slow-growing tumor that requires a long follow-up period, and a large number of cases are needed to establish the efficacy of carbon ion radiotherapy. However, we believe that carbon ion radiotherapy is an effective local treatment of chordoma.

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V. 研究成果の刊行物・別刷
（研究分担者）

Carbon Ion Radiotherapy for Treatment of Prostate Cancer and Subsequent Outcomes after Biochemical Failure

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Abstract. *Background/Aim: Carbon ion radiotherapy is expected to be suitable to treat localized prostate cancer because it yields great biological and physical effects. The aim of this study was to examine long-term results and subsequent outcomes after biochemical failure. Patients and Methods: A total of 254 patients were treated from the beginning of 2003 and followed through 2009. Long-term hormone therapy was also used for some intermediate-risk and high-risk patients. Results: Among the patients examined, 54 patients experienced biochemical failure. Failure-free survival was 76%, 91% and 76% at eight years in low-risk, intermediate-risk and high-risk patients, respectively. Clinical progression occurred only in high-risk patients, with 89% progression-free survival at eight years. After biochemical failure, diseases of most patients were well controlled by salvage therapy but twelve high-risk patients (5%) died of prostate cancer. Conclusion: Carbon ion radiotherapy had an excellent effect on localized prostate cancer. Factors influencing salvage therapy included PSA kinetics and duration between radiation and failure.*

In 2005 in Japan, 42,997 men were diagnosed with prostate cancer (an incidence of 42.0 per 100,000 men), and 9,264 men died of prostate cancer (1). The proportion of patients with cancer at a localized stage has increased and radiotherapy and surgery are critical curative treatments for such patients. Carbon ion beam is characterized by high cytocidal effects, high linear energy transfer and excellent radiation dose distribution. Based on its biological and physical effects, carbon ion radiotherapy is considered as a new treatment modality for solid tumors. The National Institute of Radiological Sciences in Japan constructed the Heavy Ion Medical Accelerator in Chiba (HIMAC) in 1993 and started to use carbon ion radiotherapy to treat localized and locally advanced prostate cancer in 1995. Preliminary short-term results have been reported (2-4). Since then, this is the first study to assess the long-term outcomes of patients who received carbon ion radiotherapy between 1995 and 2003. Because some patients experienced biochemical failure, the present study examined the influence of adjuvant therapy on the subsequent outcome.

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Key Words: External beam radiation therapy, PSA-doubling time, carbon radiotherapy, prostate cancer.

Patients and Methods

Patients. Patients with confirmed histological adenocarcinoma and T1b-T3N0M0 cancer were enrolled in the study. Between the start of treatment (October 1995) and October 2003, 254 consecutive patients had received carbon ion radiotherapy. Patients had not received previous treatment for prostate cancer. Clinical records for all patients were collected in 2009. The follow-up period lasted for a mean of 98 months, with a median of 96 months and a range of 5-178 months. To establish the radiation modality, the three following Protocols were adapted sequentially (2): 35 cases used Protocol 9402 with a dose escalation of 54.0-72.0 Gy equivalent (GyE), 62 cases used Protocol 9703 with a dose escalation of 60.0-66.0 GyE and a fixed dose of 66.0 GyE, and 157 cases used Protocol 9904 with a fixed dose of 66.0 GyE in 20 fractions. Stages were defined using the UICC (2002). Before treatment, prostate biopsy with eight or more cores was performed and Gleason scores were estimated by a central pathologist (MH). Patients were divided into low-risk, intermediate-risk and high-risk groups using the NCCN classification system (5).

Hormone therapy was used according to risk classification as follows: no hormone therapy for low-risk and intermediate-risk patients with T2ab, and two to six months of neoadjuvant hormone therapy and one year or more of adjuvant hormone therapy for other intermediate-risk patients with T2c or with Gleason score of 7 and all high-risk patients. Hormone therapy generally consisted of a luteinizing hormone-releasing hormone agonist and a daily dose of 80 mg of bicalutamide. After biochemical failure, conventional hormone therapy, second-line hormone therapy and chemotherapy were successively employed.

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Patients underwent digital rectal examinations and determination of prostate-specific antigen (PSA) every three to six months. If abnormal findings were suspected, an imaging examination including a bone scan and magnetic resonance imaging scan was carried out along with frequent PSA assays. The primary endpoint was biochemical failure, and overall and clinical progression-free survival rates were calculated.

Rates of acute and late morbidities were estimated using the RTOG/EORTG system (6).

PSA kinetics. Total PSA (PSA) was determined using commercial kits (AxSYM PSA Dainapack; Abbot, Chiba Japan). Biochemical failure was judged by Phoenix criteria, when PSA was elevated by 2 ng/ml or more over baseline (7). PSA-doubling time (PSA-DT) and velocity before biochemical failure were calculated by linear regression. A slope was obtained from three or more points by the least-squares fitting method using the natural logarithm (ln) of PSA (for calculation of PSA-DT) or PSA (for calculation of velocity). Consequently, PSA-DT was calculated as ln 2/slope (8) and velocity was determined as the difference in PSA increase per year (9). The response to salvage hormone therapy was evaluated as follows: a partial response (PR) was defined as a decrease in PSA ≥50% from baseline, progressive disease (PD) was designated as an increase in PSA ≥25% over baseline, and no change (NC) was denoted as any change between PR and PD.

Carbon ion radiotherapy. The technique of carbon ion radiotherapy was previously reported (2). Briefly, the head and feet of the patients were positioned in a customized cradle and the pelvis was immobilized with a thermoplastic sheet. The bladder was filled with 100 ml of sterilized water in the anterior direction at a computed tomography (CT) planning and at each session from the anterior direction. The rectum was emptied with a laxative or enema, if necessary.

The clinical target volume was designed for the prostate and seminal vesicle after referring to a 5-mm thick CT scan. The initial planning target volume was created by adding 10-mm anterior and lateral margins and 5-mm posterior margin. After the first 10 fractions, the posterior margin was set on the anterior wall of the rectum to limit the dose received by the rectum to <50 GyE. Radiation was performed with one anterior-posterior port and a pair of lateral ports which were alternated at each session once a day in four fractions per week for five weeks.

Statistical analysis. Survival was calculated with the Kaplan-Meier method. Statistical differences were determined by the unpaired two-group *t*-test and *p*-value of ≤0.05 was considered statistical significant. All calculations were performed with SPSS statistical computer program (SPSS Inc, Tokyo, Japan).

Results

Risk groups and outcomes. The risk distribution of the patients was 11%, 26% and 63% in the low-risk, intermediate- risk and high-risk groups, respectively (Table I).

Five patients showed local recurrences (2%), some of which were due to insufficient radiation doses in the initial protocols. Distant metastases were detected in a total of 15 patients (6%) distributed as follows: ten in bone, three in abdominal lymph nodes, one in liver and one in lung. Twelve patients (5%) died of cancer-specific causes, all of them were high-risk patients (8% of the high-risk group). Forty-three patients (17%) died of other diseases: four (14%), nine (14%) and thirty (19%) belonged to the low-, intermediate- and high-risk groups, respectively. These patients showed no signs of biochemical failure until death.

Table I. *Risk classification. The number of patients with biochemical failure is shown in parentheses.*

		Low-risk	Intermediate-risk	High-risk
No. of cases		29 (7)	66 (7)	159 (40)
Age (years)	≤60	2	7	10
	61-65	6	12	22
	66-70	8	15	52
	71-75	10	23	54
	76-80	3	8	18
	≥81	0	1	3
Stage	T1bc	19	27	14
	T2ab	10	12	9
	T2c	0	27	37
	T3	0	0	99
Gleason score	≤6	29	26	27
	7	0	40	73
	≥8	0	0	59
Initial PSA (ng/ml)	≤4	4	1	0
	>4-<10	25	21	17
	≥10-20	0	49	29
	>20-50	0	0	69
	>50-100	0	0	31
	>100	0	0	13

The rates of overall survival in all patients at five and eight years after radiotherapy were 90% and 84%, respectively, while the respective rates of biochemical failure-free survival were 85% and 79%. Three-, five- and eight-year overall survival rates were 93%, 93% and 93% in the low-risk group, 96%, 94% and 90% in the intermediate-risk group, and 95%, 88% and 79% in the high-risk group, respectively (Figure 1). The respective rates for biochemical failure-free survival were 93%, 85% and 76% in the low-risk group, 97%, 95% and 91% in the intermediate-risk group and 85%, 79% and 76% in the high-risk group, respectively (Figure 2). No clinical progression was detected in the low-risk and intermediate-risk groups. Three-, five- and eight-year progression-free survival rates in the high-risk group were 96%, 93% and 89% (Figure 3, p=0.005).

At G0, G1, G2, G3 and G4, the incidence of morbidities in the bladder/urethra were 70%, 27%, 3%, 0% and 0% (acute morbidities) and 70%. 21%, 6%, 3% and 0% (late morbidities), respectively, and the incidence of morbidities in the rectum were 97%. 3%, 0%, 0% and 0% (acute morbidities) and 85%. 9%, 4%, 2% and 0% (late morbidies), respectively.

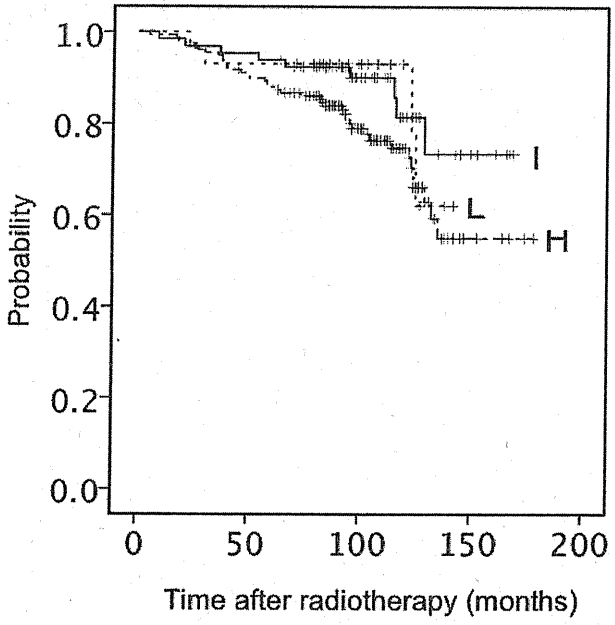

Figure 1. *Overall survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates overall survival probability.*

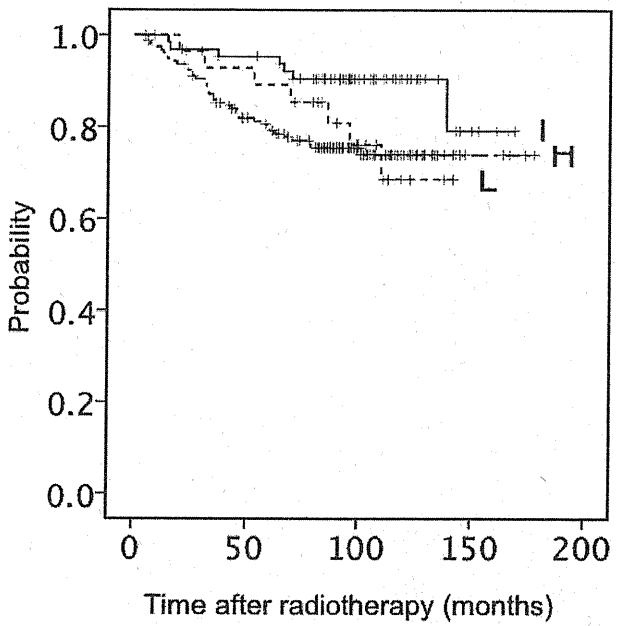

Figure 2. *Biochemical failure-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates biochemical failure-free survival probability*

Effect of hormone therapy. Patients were treated with hormone therapy or left untreated according to the risk classification (Table II). Of 254 patients, 54 (21%) experienced biochemical failure; 24%, 11% and 25% in the low-, intermediate- and high-risk groups, respectively. The relatively high rate of biochemical failure in the low-risk patients may be partially due to the small number of patients in this group compared to the others; moreover, the low-risk group may contain underdiagnosed cases without adjuvant hormone therapy. Biochemical failure occurred infrequently in the intermediate-risk patients, due perhaps to the long-term adjuvant hormone therapy provided to T2c patients. In contrast, no hormone therapy was scheduled for T2ab patients. As the failure rate was rather low in the high-risk patients, hormone therapy seemed to be beneficial and a two-year treatment duration appeared to be better for avoiding biochemical failure compared to shorter treatments.

After biochemical failure, the patients without or after adjuvant hormone therapy were treated with conventional hormone therapy for two years or more. Most patients in the low- and intermediate-risk groups responded well with PR. No cancer deaths were observed in these groups.

Of 159 high-risk patients, 40 (25%) experienced biochemical failure. Twenty-six patients showed failure without or after

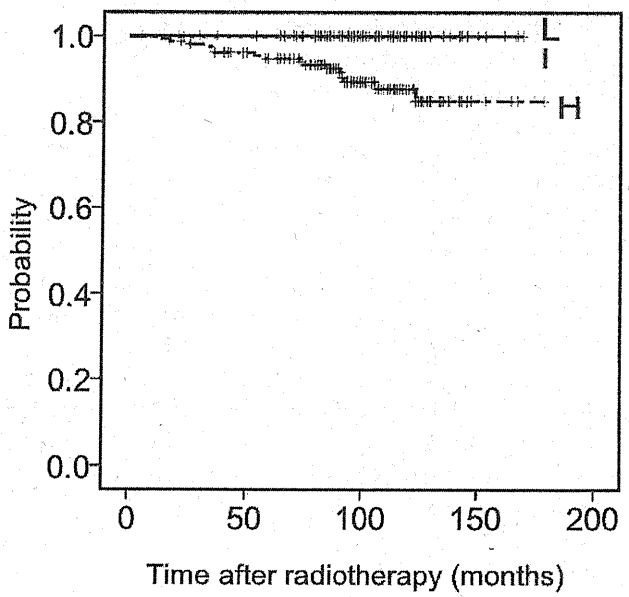

Figure 3. *Clinical progression-free survival rates of prostate cancer patients treated with carbon ion radiotherapy. The patients are separated into the following risk groups: L, low-risk (29 patients); I, intermediate-risk (66 patients); H, high-risk (159 patients). The vertical axis indicates clinical progression-free survival probability.*

Table II. *Relationship between hormone therapy and biochemical failure. Other failures occurred after termination of hormone treatment.*

	Low risk		Intermediate risk		High risk	
Hormone therapy	No failure	Failure	No failure	Failure	No failure	Failure
None or <1 year	21	7	22	6	15	10
1-2 years	1	0	13	0	32	12
>2 years			24	1	72	4
During treatment[a]						14

[a]Biochemical failure during hormone treatment.

Table III. *Response to salvage therapy after biochemical failure. Data are shown as mean, median (range).*

	PR (37)[a]	NC and PD (17)[a]	*p*-value
Low: intermediate: high risk	7 : 7 : 23	0 : 0 : 17	
Initial PSA (ng/ml)	31.0, 19.0 (2-174)	50.2, 29.1 (8.2-260)	0.24
Radiation-failure (months)	47, 43 (6-112)	33, 19 (6-139)	0.15
Nadir PSA (ng/ml)	0.81, 0.24 (0.003-10.3)	0.62, 0.2 (0.06-2.8)	0.60
PSA-DT (months)[b]	8.9. 6.5 (1.2-24.9)	4.5, 2.9 (0.65-17.5)	0.009
Velocity (ng/ml/year)[b]	5.4, 1.7 (0.34-68.2)	29.8, 3.0 (0.6-205.2)	0.12

PR: PSA decrease ≥50%, PD: PSA increase ≥25%, NC: any change between PR and PD; [a]number of cases; [b]Value from one case (a patient with lymph node metastasis) was excluded.

adjuvant hormone therapy. These patients were treated with conventional hormone therapy repeatedly and 23 patients showed PR and three showed PD. Of these patients, three died of prostate cancer after an average period of 62 months (range 32-106 months) after radiotherapy.

Fourteen high-risk patients progressed to a castration-resistant state despite continuous hormone treatment, nine of whom died of prostate cancer after an average period of 43 months (range 16-91 months) from radiotherapy (Figure 4). The period between radiotherapy and biochemical failure was shorter for these patients (average 20 months: range 6-38 months) than for the other high-risk patients who experienced biochemical failure (average 42 months: range 6-95 months; p=0.0002).

The factors influencing the salvage therapy for biochemical failure were examined (Table III). PSA-DT was found to significantly affect response, and a PSA-DT greater than ten months indicated a good response to salvage hormone therapy (data not shown).

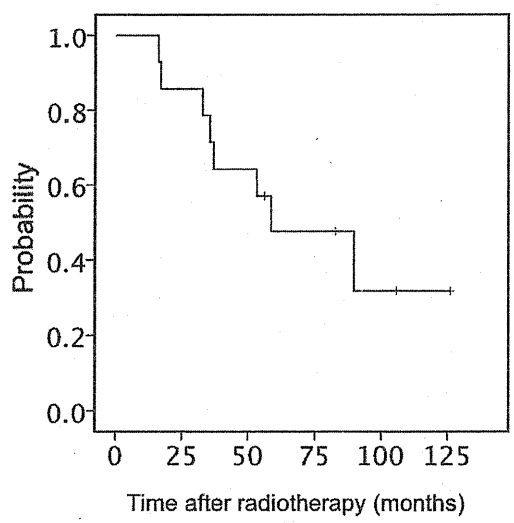

Figure 4. *Cause-specific survival of fourteen high-risk patients with disease progression under continuous hormone treatment after radiotherapy.*

Discussion

Radiotherapy for prostate cancer in Japan is generally reserved for rather advanced stages of the disease. Based on the results determined from 162 patients with prostate cancer at 50 facilities in 1999-2000, 80% of the patients were high-risk, and overall and biochemical failure-free survival rates at three years were 86.7% and 86.1%, respectively. Two-thirds of patients received hormone therapy (10). In the present study, 63% of patients were high-risk.

Low-risk patients are candidates for radiotherapy alone, and such patients achieved favorable outcomes. Treatment for intermediate-risk patients involves consideration of whether or not radiotherapy alone is sufficient. Some of the patients experienced biochemical failure with carbon ion radiotherapy alone. However, patients with more advanced stage disease in the intermediate-risk group, namely T2c, showed favorable outcomes after the addition of hormone therapy. This suggests that hormone therapy may be advisable as a supplement for certain intermediate-risk patients.

In the case of high-risk patients, radiotherapy alone is considered to be insufficient. The five-year biochemical failure-free survival rate after radiotherapy with 66 Gy was approximately 30% (11). Increasing the radiation dose to 78 Gy using three-dimensional conformal radiotherapy or intensity-modulated radiation therapy improved biochemical failure-free survival rates compared to radiation with less than 72 Gy for high-risk patients (12-13). A radiation dose of 74 Gy for T3 patients with hormone therapy for 1-6 months yielded a biochemical failure-free survival rate of 46% after four years (14). For high-risk prostate cancer, therefore, high radiation doses greater than 72 Gy may be required for treatment, and such high doses may be used without serious adverse effects (15). The extension of the target volume to the pelvic area has been proposed (16), but because of the possible adverse effects on the neighboring organs, this technique is still controversial (17). Proton beam radiotherapy resulted in five-year biochemical-free survival rate of 48% in high-risk patients (18). Establishment of radiation modality was arranged from the results of initial protocols referring to carbon ion beam properties (19). After the initial protocols, the appropriate radiation dose was set at 66.0 GyE in 20 fractions. The cytocidal effect of this dose was assumed to be comparable to that of high doses of photons. Taking into account other beneficial properties, carbon ion radiotherapy may be considered to be one of the best treatment methods for prostate cancer. Acute and late morbidities associated with treatment are only minor and comparable to those associated with photon radiation (20).

The addition of hormone therapy has generally been recommended before, during and/or after radiotherapy to improve results for high-risk patients (21). In the literature, the reported durations of hormone therapy range between four months and five years (22). A consensus on the optimal duration has not yet been achieved. Hormone therapy for four months led to improved biochemical failure (22), but longer durations of hormone therapy, ranging from eight to thirty-six months, showed increased biochemical failure-free survival compared to either radiation alone or short-term hormone therapy (23-25). The RTOG 92-02 Trial showed that for high-risk patients 70 Gy of radiation with two years of hormone therapy led to 67% and 44% of biochemical failure-free rates at five and ten years, respectively (26-27). External beam radiotherapy with hormone therapy showed outcomes similar to those achieved with surgery (28-29). In the present study, high-risk patients were treated with adjuvant hormone therapy and this treatment seems to have achieved considerable biochemical failure-free outcomes in conjunction with carbon ion radiotherapy. Hormone therapy for two years may be sufficient. It is claimed that the addition of hormone therapy is generally credited with improving biochemical failure-free and clinical progression-free survivals, but has no benefit on overall survival. This is an important issue that needs to be further clarified. Recently, studies have reported adverse effects of hormone therapy (30), and trivialized its beneficial effects (31). On the contrary, the addition of hormone therapy is protective to the genitourinary and gastrointestinal tracts (32). Based on these findings, careful use of adjuvant hormone therapy may be beneficial. After biochemical failure, early induction of hormone therapy is more effective than delayed therapy (33). Salvage hormone treatment after failure as judged by the Phoenix criteria was also effective as shown in the present cohort. Factors influencing the response to hormone therapy included PSA-DT before the time of failure and the duration between radiotherapy and biochemical failure, suggesting a correlation with rapidly growing tumors.

A subset of high-risk patients progressed to a castration-resistant state, despite radiotherapy to the prostate and continuous hormone treatment. Most of these patients scarcely showed response to second-line hormone therapy. Clinically distant metastases may occur at certain times after biochemical failure (34, 35). Treatments for these patients were performed following EAU guidelines (36), but the patients progressed to a more severe disease state in general. The duration from the start of hormone therapy to biochemical failure in highly advanced prostate cancer patients, such as those at the metastatic stage, was generally one to two years and similar disease progression intervals were observed after radiotherapy. Factors affecting the rapid progression to a castration-resistant state included the time between radiotherapy and biochemical failure, and PSA kinetics including velocity and PSA-DT (37, 38), but other influencing factors have not been determined yet (39). Further advances are awaited in the development of treatment strategies for rapidly growing prostate cancer.

In summary, carbon ion radiotherapy is suitable and tolerable for the treatment of localized prostate cancer, especially for locally advanced stages.

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前立腺癌患者における quality of life（QOL）効用値の評価：QOL 効用値指標 EQ-5D および VAS と健康関連 QOL 質問表 SF-36 および EPIC との比較

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EVALUATION OF UTILITY INDEX OF QUALITY OF LIFE (QOL) IN PROSTATE CANCER PATIENTS : COMPARISON OF QOL UTILITY INDEX EuroQol-5D (EQ-5D) AND VISUAL ANALOGUE SCALE (VAS) WITH HEALTH-RELATED QOL QUESTIONNAIRES SF-36 AND EPIC

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前立腺癌患者における quality of life（QOL）効用値の評価：QOL 効用値指標 EQ-5D および VAS と健康関連 QOL 質問表 SF-36 および EPIC との比較

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要旨：

（目的）局所前立腺癌の治療法として様々な選択肢があるが，その比較には医療経済的評価が不可欠である．また，費用対効用分析においては，単なる生存期間の比較ではなく QOL を加味した質調整生存年（QALY：quality adjusted life year）の評価が重要である．そこで，QALY 算出に最も広く用いられている QOL 効用値指標である EuroQol-5D（EQ-5D）ならびに visual analogue scale（VAS，0～100 points）の前立腺癌患者における有用性を検討した．

（対象と方法）前立腺癌患者 81 例を対象として，包括的および前立腺癌特異的 QOL 調査票である SF-36 と EPIC を用いて，EQ-5D と VAS との関連を調べた．

（結果）SF-36 の全ての下位尺度において EQ-5D および VAS との有意な相関を認めた．一方，EPIC の下位尺度である排尿，排便，性，ホルモンに関しては QOL 効用値指標に大きな影響はなかった．SF-36 の結果から VAS 効用値を変換算出すると，実際に得られた値と有意で強い相関がみられた（相関係数 0.53, $p<0.0001$）．

（結論）前立腺癌患者において EQ-5D ならびに VAS を用いた QOL 効用値指標の算出が妥当であり，費用対効用分析に用いる可能性が示された．また，これまでに蓄積されている SF-36 のデータを用いて QOL 効用値指標を変換算出できる可能性が示唆された．

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キーワード：前立腺癌，費用対効用分析，質調整生存年（QALY）

緒　言

我が国においては，前立腺癌の罹患率および死亡率は近年上昇を続けており，今後も増加傾向を示すと推測されている[1]．また，人口の高齢化が進行するため，高齢者に多い前立腺癌の有病率は極めて高く，患者総数はさらに増大すると考えられる[2]．したがって，前立腺癌の治療法としては，治療効果が優れているのみならず，費用が適切であることが要求される．このため，前立腺癌に対する治療法の比較にあたっては医療経済的評価が不可欠である[3]．局所前立腺癌の治療法としては，様々な選択肢が存在している．いずれの治療法にも特徴，長所，短所があるが，その比較に際しては，抗腫瘍効果，有害事象やQOL(quality of life)への影響が考慮されるべきである．

一方，治療法別の費用対効用分析においては，単なる生存期間の比較ではなく，QOL 評価を加味した質調整生存年（QALY：quality adjusted life year）の評価が重要である[4]．健康関連 QOL の評価にはさまざまな調査票があるが，いずれも複数の測定尺度を含むため QALY 算出に直接用いることはできない．QALY 算出に最も広く用いられている QOL 効用値指標は EuroQol-5D（EQ-5D）ならびに visual analogue scale（VAS）[5][6]である．そこで，前立腺癌患者におけるこれらの QOL 効用値指標の有用性を明らかにするために，包括的および前立腺癌特異的 QOL 調査票である SF-36[7][8]と EPIC[9]を用いて，EQ-5D と VAS との関連を調べた．

対象・方法

東京厚生年金病院に通院中の前立腺癌患者 81 例を対象とした．年齢は 51～82 歳，平均 70.4±6.9 歳であった．主たる治療法としては，active surveillance（PSA 監視療法）5 例，手術療法（前立腺全摘除術）22 例，放射線療法 38 例，内分泌療法 16 例であり，放射線療法の内訳は，小線源治療 3 例，リニアック外部照射 14 例，粒子線照射 21 例であった．14 例に再発ないし再燃を認め，67 例では再発・再燃なしであった．

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付表　患者効用値（VAS：0～100点）の算出式

VAS＝社会生活機能得点×0.007＋身体機能得点×0.143＋心の健康得点×0.1＋日常役割機能（精神）得点×0.01＋体の痛み得点×0.04＋日常役割機能（身体）得点×0.024＋活力得点×0.182＋全体的健康感得点×0.31

表1　QOL効用値とSF36の関連

SF36（下位尺度8項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
身体機能	0.474	0.000	0.400	0.000
心の健康	0.251	0.025	0.254	0.030
日常役割機能（身体）	0.400	0.000	0.324	0.006
日常役割機能（精神）	0.295	0.008	0.291	0.013
体の痛み	0.455	0.000	0.401	0.000
全体的健康感	0.439	0.000	0.517	0.000
活力	0.376	0.001	0.401	0.000
社会生活機能	0.232	0.037	0.362	0.002

表2　QOL効用値とEPICの関連

EPIC（下位尺度4項目）	EQ-5D		VAS	
	相関係数	有意確率	相関係数	有意確率
排尿	0.125	0.273	0.300	0.010
排便	0.138	0.232	0.091	0.452
性	0.023	0.843	−0.023	0.852
ホルモン	0.167	0.147	0.120	0.322

2008年9月から12月に自己記入式の質問表によりアンケート調査を行った．QOL効用値指標としては，EQ-5DとVASスケールを用いた．EQ-5Dは，移動の程度，身の回りの管理，ふだんの活動，痛み/不快感，不安/ふさぎ込み，の5項目について3段階で評価する質問表であり，回答結果からQOL効用値が計算される．VASは，想像できる最も悪い健康状態（0ポイント）から想像できる最も良い健康状態（100ポイント）までの直線上に，現在の健康状態を自己評価しプロットするスケールである．包括的および前立腺癌特異的QOL尺度としては，それぞれSF-36およびEPICを使用した．また，SF-36の結果からVASへの変換式（付表）を用いてQOL効用値を算出し，実際の測定値と比較した[10]．

解析はDr. SPSS II（エス・ピー・エス株式会社，東京）を用いて行った．相関の解析にはPearsonの相関分析を使用し，$p<0.05$を有意とした．

結　果

全患者におけるEQ-5DおよびVASとSF-36との関連を下位尺度項目別に示す（表1）．SF-36の全ての下位尺度において，EQ-5DおよびVASとの相関が認められた．両者の相関係数は小さいものの統計学的に有意な相関であった．SF-36の8つの下位尺度のうちでは，身体機能とEQ-5D，全体的健康感とVASとの相関係数が比較的大きかった（図1，2）．全患者におけるEQ-5Dおよび

図1　EQ-5Dと身体機能（SF-36）

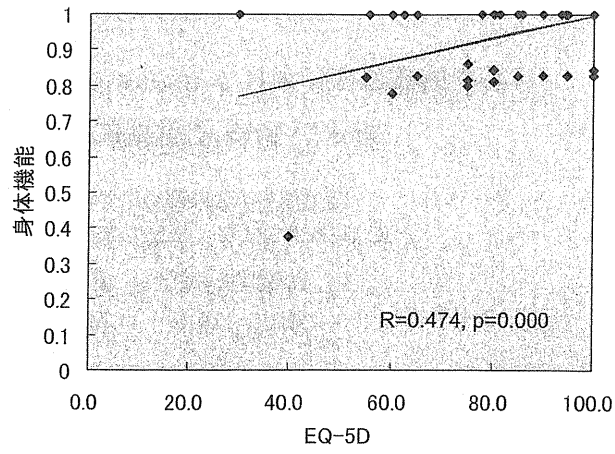


図2　VASと全体的健康感（SF-36）

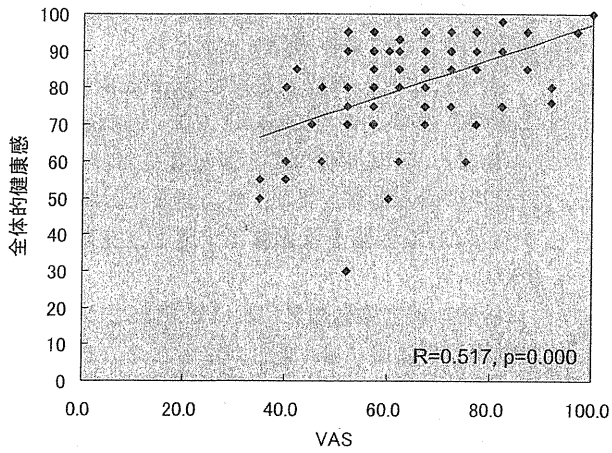
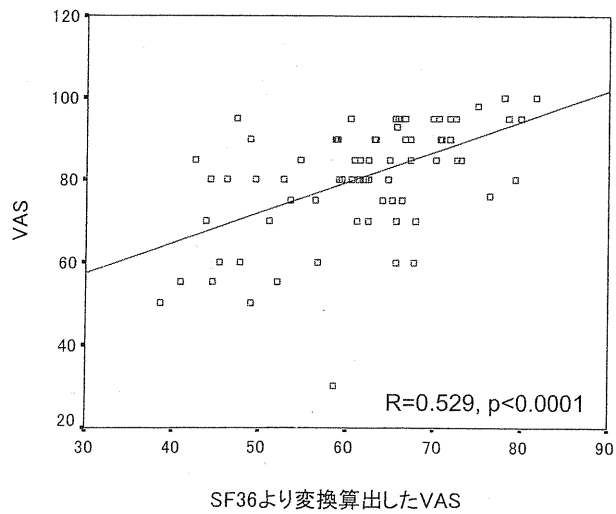


図3　SF-36より変換算出したVASとVAS実測値



VASとEPICとの関連を下位尺度項目別に示す(表2). EPICの排尿尺度とVASとの間に弱い相関を認めたが, それ以外に有意な相関を示すものはなかった. 放射線療法を受けた患者38例のみで解析を行ったところ, 同様に, EQ-5DおよびVASは, SF-36のすべての下位尺度との相関を認め, EPIC下位尺度との強い関連はなかった(data not shown).

EQ-5DとVASとの関連を検討すると, 両者には有意な相関が認められた(相関係数0.36, $p=0.0008$)[11]. 報告された方法によりSF-36の結果からVASスケールの効用値を変換算出すると, 実際に得られた値と有意で強い相関がみられた(相関係数0.53, $p<0.0001$, 図3).

年齢とEQ-5DおよびVASの間には相関はなかった. また, 治療法別にEQ-5DおよびVASを比較したが, 有意な差は認められなかった. 再発・再燃例では, EQ-5DおよびVASが低かったが, 有意な差ではなかった.

考　察

転移のない局所前立腺癌患者に対しては, 手術療法, 放射線療法, 内分泌療法, あるいはそれらの組み合わせなど, 多くの治療選択肢が提示される[12]. これらの比較においては, 抗腫瘍効果に基づく治療効果, 予測される有害事象のリスク以外に, QOLへの影響が重要視されるべきである. また, 医療経済的側面からみると, QOLへの影響を加味した質調整生存年(QALY)による評価が有用である[4].

前立腺癌患者における健康関連QOL評価には種々の質問票が用いられてきた. 包括的質問表としてはSF-36やSF-8, 癌特異的質問票ではEORTC QLQ-C30やFACT-G, 前立腺癌特異的質問表としてはFACT-PやUCLA-PCIやEPICなどが代表的である[7][13]~[17]. これらの質問票はいずれも複数の下位尺度からなっており, 全体として各患者のQOLを評価測定してQALYを算出することは困難であった. 一方, 各種治療法の費用対効用分析においては, QOLへの影響を加味した生存期間を比較することが要求される. そこで, QOL効用値指標を算出するためにEQ-5DやVASスケールが開発され使用されてきた.

今回の検討により, 前立腺癌患者において治療後のQOL効用値指標は一般的QOL評価の全ての下位尺度を反映することが明らかになった. すなわち, EQ-5DおよびVASは健康関連QOLのあらゆる側面から影響をうけていることが示唆され, 効用値評価として用いることは妥当であると考えられた. 一方, 前立腺癌に特異的なQOL下位尺度である排尿, 排便, 性, ホルモンに関しては, QOL効用値指標に大きな影響はなかった. 日本人前立腺癌患者では, 包括的QOL評価に挙げられているすべての下位尺度項目が, 自身の健康評価に重要であり, 疾患やその治療に関連する事象は容認可能であると推測される. また, SF-36のデータから変換算出したQOL効用値指標が, 直接測定したVASと強い相関を示したことより, SF-36質問表のデータが蓄積された前立腺癌患者コホートを費用対効用分析研究の対象として使用可能であることが示唆された.

以上より, 前立腺癌患者においてもEQ-5DならびにVASを用いたQOL効用値指標の算出が妥当であり, 費用対効用分析に用いる可能性が示された. 今回の検討は横断的研究であり, 患者背景や治療期間にばらつきがあったために, 治療法別にみてQOL効用値指標に有意差は認められなかった. 今後, 症例数を増やした縦断的研究により治療法別の比較が可能となると思われる. さらに, 生存期間とあわせてQALYを算出して, 各治療法を評価し比較することが望まれる.

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