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CASE REPORT

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Avascular necrosis of bilateral femoral head as a result of long-term steroid administration for radiation pneumonitis after tangential irradiation of the breast

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Abstract We report a patient with avascular necrosis of the bilateral femoral head resulting from long-term steroid administration for radiation pneumonitis that occurred after tangential irradiation of the breast. The patient was a 50-year-old postmenopausal woman with breast cancer, stage IIIB (T4bN0M0) in the right C area. Following wide excision of right breast carcinoma and level III axillary lymph node dissection, whole-breast X-ray irradiation was given, at a dose of 2 Gy per fraction; the total dose was 50 Gy. On day 84 after the initiation of radiation therapy, she developed radiation pneumonitis. As the lung shadow expanded to the contralateral lung, she received steroid medication. Despite the steroid medication, the symptoms were exacerbated; therefore, she underwent steroid pulse administration with subsequent oral steroid medication. She improved immediately, but subsequently the radiation pneumonitis relapsed three times when the steroid medication was stopped. The period of medication was 423 days and the cumulative amount of steroids was 7365 mg before complete resolution occurred. In the 19 months after she stopped the steroid administration, she developed avascular necrosis (AVN) of the bilateral femoral head. This was regarded as a complication of the steroid treatment. Patients treated with long-term or high-dose steroid administration have been suggested to be at great risk of developing AVN, but this hypothesis remains controversial. The probability of AVN occurrence may be very small, but it should be considered as one of the complications of steroids, which are often used to treat radiation pneumonitis.

Key words Avascular necrosis · Breast cancer · Breast-conserving therapy · Radiation pneumonitis · Steroid

Introduction

Radiation pneumonitis in patients treated with breast-conserving therapy (BCT) is not uncommon. Radiation pneumonitis after BCT is usually mild and can be treated at an outpatient clinic. When the pneumonitis expands beyond the irradiated volume of the lung, it sometimes becomes symptomatic. It is extremely rare for radiation-induced pneumonitis to involve the contralateral nonirradiated lung. In this situation, symptoms may become severe, and hospitalization may be necessary to treat the patient with medication and oxygen inhalation. In this case report, we present a patient who developed avascular necrosis (AVN) of the bilateral femoral head as a result of prolonged steroid administration for refractory radiation-induced pneumonitis after BCT.

Case report

The patient was a 50-year-old postmenopausal woman with stage IIIB (T4bN0M0) in the right C area. The tumor had invaded her breast skin, but BCT was performed with the hope of breast conservation. Following a wide excision of the right breast carcinoma and level III axillary lymph node dissection, she was medicated with tamoxifen and 5′-deoxy-5-fluorouridine, and whole- breast 6-MV X-ray irradiation was given, at a dose of 2 Gy per fraction; the total dose was 50 Gy. A boost to the tumor bed was not given. The size of the tangential field was 22.0 cm by 8.0 cm and the central lung distance (CLD) was 2.5 cm (Fig. 1). The radiation therapy was completed uneventfully.

On day 84 after the initiation of the tangential radiation therapy, the patient complained of right chest pain and

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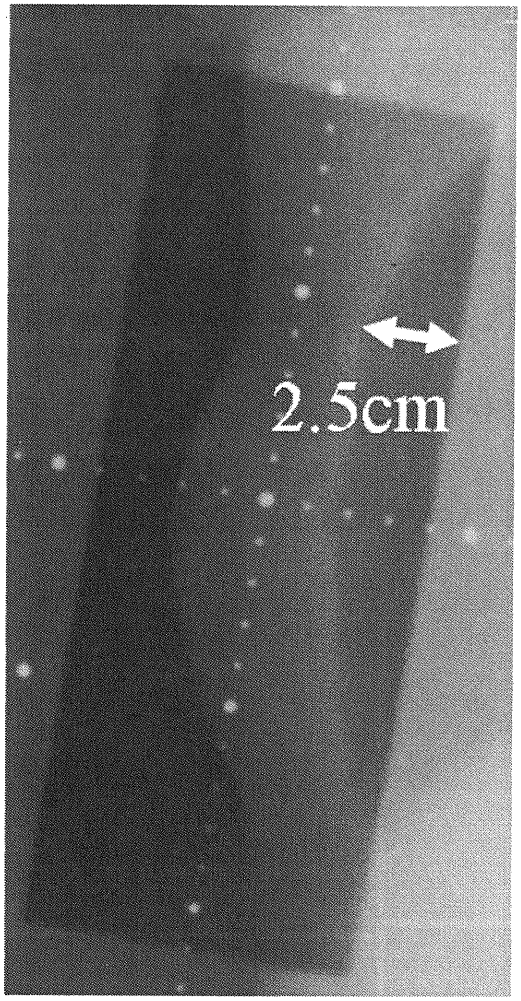

Fig. 1. Linacgraphy. Whole-breast irradiation was given with 6-MV X-rays, using a tangential field. The size was 22.0 cm by 8.0 cm, and the central lung distance was 2.5 cm

fever. Chest X-ray (Fig. 2B) and computed tomography (CT) scan revealed consolidation in the right lung. She was diagnosed with pneumonia and was treated with antibiotics, but the lung shadow expanded despite the treatment. About 1 month later, consolidation in the contralateral lung appeared on CT, and prednisolone, at a daily dose of 20 mg, was started, with a diagnosis of radiation pneumonitis (Fig. 2A). Although steroid administration was started, her clinical symptoms and the lung shadows were exacerbated (Fig. 2C). Oxygen inhalation and steroid pulse medication were administered for 3 days and her condition improved. Oral prednisolone medication was then given, with the dose being tapered every 2 weeks.

After 2 months of the steroid treatment, the pneumonitis gradually recovered, with scars, and the treatment was stopped (Fig. 2D). Low-grade fever and cough developed immediately after the steroid therapy was stopped. Bilateral lung shadows were confirmed on chest X-ray film (Fig. 2E). She was diagnosed with relapse of the radiation pneumonitis. Prednisolone administration, at a dose of 15 mg daily, was resumed immediately. The prednisolone was tapered every 4 weeks. When the dose of prednisolone had been decreased to 2.5 mg daily, the lung shadow relapsed again. Therefore, the dose of prednisolone was increased, to 10 mg daily. The prednisolone was again tapered every 4 weeks. Four months after the relapse, the lung shadows disappeared, and the steroid treatment was stopped.

However, within 1 month, a lung shadow in the lower lobe of the right lung was seen again on CT. The patient restarted the prednisolone administration, at a daily dose of 5 mg. As the pneumonitis gradually recovered, she stopped the steroid treatment, after 3 months. From that time, no lung shadow was seen on X-ray film, except for the shadow of an inflammatory scar.

She complained of bilateral hip joint pain 19 months after she stopped the prednisolone administration, 38 months after the initiation of the radiation therapy. Bone scintigraphy and magnetic resonance imaging (MRI) disclosed AVN of the bilateral femoral head (Fig. 3A,B). Bone scintigraphy showed ^{99m}Tc-HMDP (hydroxymethylenedisphosphonate) accumulation in the left femoral head, and on T1- and T2-weighted images, MRI showed a low signal intensity in the contralateral femoral head, as well as in the ipsilateral one.

The AVN was thought to be due to the prolonged steroid administration. She received conservative medical treatment and did not undergo femoral head replacement. Regarding the breast cancer, she has been recurrence-free for 4 years, up to the present.

Discussion

Generally, symptomatic radiation pneumonitis is rare, especially bilateral pneumonitis. Reported risk factors include patient factors such as age, sex, performance status, pulmonary function, and preexisting pulmonary diseases, and treatment factors such as chemotherapy, total radiation dose, dose per fraction, accelerated radiation schedule, and radiation field size.[1–6] Recently it has been reported that tamoxifen administration during radiation therapy also enhances the risk of radiation pneumonitis.[7]

Patients with lung cancer have radiation pneumonitis more frequently and more severely than those with breast cancer. In the literature, the incidence of symptomatic pneumonitis is 0%–10% of patients with breast cancer, and 5%–15% of patients with lung cancer.[8] No case has been reported in which a patient with breast cancer has died of radiation pneumonitis, while it has been reported that 1%–6% of patients with lung cancer have died of radiation pneumonitis.[9,10]

The number of patients with asymptomatic radiation pneumonitis is about four times that of those with symptomatic pneumonitis.[8] Asymptomatic patients can be cured without any treatment. Even symptomatic patients can usually be cured with symptomatic treatment such as medication with bronchodilators, antitussives, or expectorants. Only some patients with symptomatic pneumonitis or pulmonary diseases need to be treated with steroid medication.

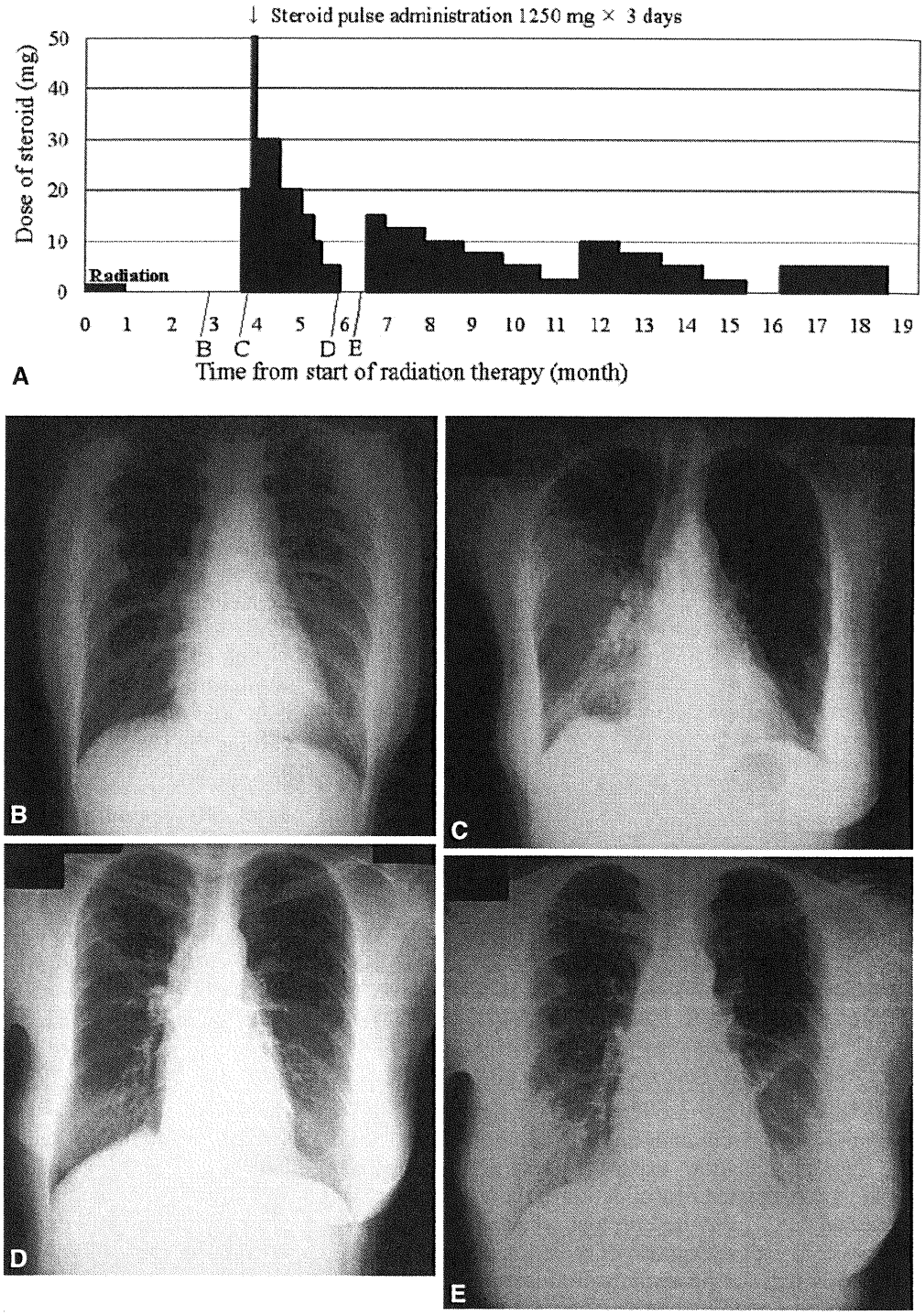

Fig. 2. **A** This figure shows the dosage of steroids and the clinical course. The *horizontal axis* expresses the time from the beginning of radiation therapy. Radiation therapy was performed during the first month. **B, C, D,** and **E** are the chest X-ray films at the times shown in the graph in **A**. **B** X-ray the first time right chest pain and fever appeared, on day 84 after the initiation of radiation therapy. Consolidation was observed in the peripheral middle parts of the right lung. **C** X-ray just before steroid pulse administration, day 120. The shadow had expanded to lower parts of the right lung. **D** X-ray the first time the radiation pneumonitis resolved, day 184; the shadow had disappeared. **E** X-ray at the time the condition recurred and the steroid treatment was resumed, day 204. The shadow appeared in the lower parts of the right lung and in the middle parts of the left lung

There are no apparent criteria for steroid use in radiation pneumonitis, but steroids are effective for patients in whom symptoms get worse despite other medication, or for those in whom pneumonitis expands outside the radiation field (sporadic radiation pneumonitis or bronchiolitis obliterans organizing pneumonia (BOOP)-type pneumonitis).

In such cases, the patients are cured soon after they start steroid medication. Radiation pneumonitis sometimes relapses after the dose of steroid is decreased. The probability of occurrence of refractory radiation pneumonitis varies from 33% to 100%.[11–16] In refractory radiation pneumonitis, steroids need to be used for a long time, so various side effects of steroids can arise.

Our patient developed severe symptomatic bilateral radiation pneumonitis, recurring several times, and needed steroid medication for a long time, so she came to

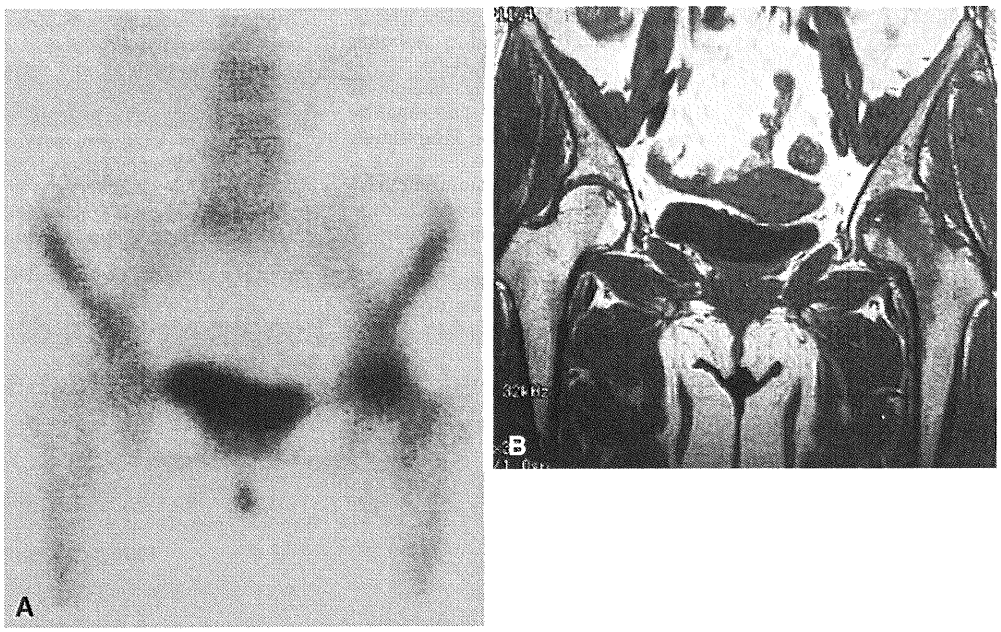

Fig. 3. **A** Bone scintigraphy and **B** magnetic resonance imaging (MRI). Bone scintigraphy shows ^{99m}Tc-HMDP (hydroxymethylenedisphosphonate) accumulation in the left femoral head. The MRI shows a low signal intensity in the left femoral head on a T1-weighted image. A small low signal intensity area is also seen in the contralateral femoral head. A T2-weighted image (not shown) showed similar low signal intensity areas in the same regions. The findings suggested avascular necrosis of the bilateral femoral head, predominantly on the left side

suffer from AVN, one of the major side effects of steroids.

Steroids have many side effects. Moon face, diabetes mellitus, gastrointestinal ulcer, osteoporosis, induced infection, and mental disorder arise with high frequency.

AVN is also a major complication of steroid medication. The precise mechanism by which steroids cause AVN is not known. Current research has implicated the development of a hypercoaguable state, with subsequent impaired fibrinolysis and venous thrombosis in the bone.[17,18]

Patients treated with long-term or high-dose steroid administration have been suggested to be at great risk of developing AVN. In the Italian literature, either a period of medication of more than 216 days or a cumulative steroid amount over 6g was reported as a risk factor for AVN.[19] However this causal relationship is controversial. Some reports suggest that there is little association between AVN and the duration of steroid therapy or the total cumulative dose, but note that a high cumulative steroid dose during the first few months of therapy is a more important risk factor for AVN.[20] These relationships remain as a matter to be discussed further. In our patient, the duration of therapy was 423 days and the cumulative steroid dose was 7365mg. Moreover, the cumulative dose of steroid during the first few months was also high, mainly due to pulse administration.

The probability of AVN occurrence may be very low, but it should be considered as one of the complications of steroid administration. Patients receiving long-term high-dose steroid therapy must be informed about this risk.

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ORIGINAL ARTICLE

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Results of radiation therapy combined with neoadjuvant hormonal therapy for stage III prostate cancer: comparison of two different definitions of PSA failure

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Abstract

Background. We herein report the clinical outcome of radical radiation therapy combined with neoadjuvant hormonal therapy (NHT) for stage III (International Union Against Cancer [UICC] 1997: UICC 97) prostate cancer. Prostate-specific antigen (PSA) failure-free survival was assessed according to two different definitions, and the appropriateness of each definition is discussed.

Methods. Between October 1997 and December 2000, 27 patients with stage III prostate cancer were enrolled in this study. The median pretreatment PSA level was 29 ng/ml (range, 7.4–430 ng/ml). The Gleason score (GS) was 7 or more in 22 patients (81%). All patients received 3 months of NHT with a luteinizing hormone-releasing hormone (LH-RH) analogue, in combination with an antiandrogen (flutamide), given during the first 2 weeks, followed by 70-Gy external-beam radiation therapy (EBRT) in 35 fractions. The initial 46 Gy was given with a four-field technique, while the remainder was given with a dynamic conformal technique. No adjuvant hormonal therapy (AHT) was given.

Results. The median follow-up time was 63 months. PSA levels decreased to the normal range (<4 ng/ml) after irradiation in all but one patient. The 5-year PSA failure-free survival was 34.8% according to the American Society for Therapeutic Radiology and Oncology (ASTRO) definition and it was 43.0% according to the "nadir plus 2" definition. Discordance of the results between the two definitions was seen in two patients. The 5-year overall and cause-specific survivals were 83.0% and 93.3%, respectively. No severe acute or late adverse effects were observed.

Conclusion. Seventy Gy of EBRT following 3 months of NHT produced therapeutic results comparable to those reported in other studies which used long-term AHT. The value of long-term AHT for Japanese men should be tested in a clinical trial.

Key words Prostate cancer · Radiation therapy · Neoadjuvant hormonal therapy · PSA failure

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Introduction

In Japan, the incidence of prostate cancer was 25.5 per 100000 in 1998, and the mortality rate was 12.4 per 100000. It was the eighth commonest cause of cancer death in Japanese men in 2001 (7645 deaths; 4.21%).[1] Although this number has been increasing rapidly, it is still approximately one-fifth that in Western countries.

Many studies have reported treatment options for stage III (International Union Against Cancer [UICC] 1997) prostate cancer, including surgery, hormonal therapy, external-beam radiation therapy (EBRT), and a combination of these alternatives. Watchful waiting is an option only for selected patients, while early hormonal therapy seems to result in better survival than deferred treatment until progression in the few studies available.[2–4] Surgical treatment of these patients remains controversial and is not widely accepted, owing to the relatively high incidence of associated nodal metastases and the potential for incomplete removal of the tumor.[4] Reports from several institutions in Western countries suggest that EBRT, when combined with hormonal therapy, achieves cancer control results comparable

to those for radical prostatectomy (RP).[5–8] However, the optimal timing and duration of hormonal therapy is still under investigation, and the definition of prostate-specific antigen (PSA) failure for patients with neoadjuvant hormonal therapy remains controversial.

We herein report the clinical outcome, prognostic factors, and toxicity of EBRT following 3 months of neoadjuvant hormonal therapy for stage III prostate cancer. We also compared the results using two different definitions of PSA failure.

Patients and methods

Patient selection

This research was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions. This study was a retrospective analysis of a cohort of patients who received uniform treatment. Patients who fulfilled the following requirements were selected for this analysis: (1) histologically proven adenocarcinoma of the prostate; (2) clinical stage III (UICC 2002); (3) no prior treatment for prostate cancer; (4) no history of malignant disease in the past; (5) age less than 80 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less[9] at the time of diagnosis; (6) at least 5 years from the initiation of treatment.

Consequently, 27 patients were selected for analysis. They were treated between October 1997 and December 2000. Their diagnoses of prostate cancer were confirmed before the initation of any treatment, by extended biopsy, guided by transrectal ultrasonography (TRUS). Eight specimens were routinely obtained from each patient. The median pretreatment PSA level was 29 ng/ml (range, 7.4–430 ng/ml) and the median pretreatment prostate volume was 31 ml (range, 12–79 ml). Twenty-two of the 27 patients (81%) had a Gleason score (GS) of 7 or more. Patient characteristics are detailed in Table 1.

Table 1. Patient characteristics

Number of patients	27
Age (years)	72 (55–79)[a]
Pretreatment PSA (ng/ml)	29 (7.4–430)[a]
0.0–4.0	0
4.1–10	2
10.1–20	6
>20	19
PSA after hormonal therapy (ng/ml)	0.586 (0.068–17)[a,b]
<0.5	14
>=0.5, <4.0	10
>4	3
Gleason score	
2–5	0
6	5
7	12
8	2
9	8
10	0
Prostate volume before hormonal therapy (cm^3)	31 (12–79)[a]
Prostate volume after hormonal therapy (cm^3)	15 (8–30)[a]
Reduction in prostate volume (%)	51 (34–77)[a]

[a] Median (range)
[b] Excluding two patients whose data were reported as "<0.2"

Pretreatment evaluation

Pretreatment evaluation consisted of complete physical examination, including digital rectal examination; determination of PSA and the GS; transrectal ultrasound, including measurement of prostate volume; pelvic computed tomography (CT); bone scan; and urethrogram.

Neoadjuvant hormonal therapy (NHT)

A luteinizing hormone-releasing hormone (LH-RH) analogue (3.6 mg goserelin acetate or 3.75 mg leuprorelin acetate) was administered on day 1 of treatment and every 4 weeks for 3 months. An antiandrogen (flutamide, 375 mg daily) was also started 3 months prior to the initiation of radiotherapy and was continued for 2 weeks.

Radiation therapy

EBRT was initiated immediately after the fourth administration of hormonal therapy. As the effect of the LH-RH analogue persists for 1 month, at least part of the radiation therapy can be regarded as having been administered concurrently with the hormonal therapy. Planning CT scans were obtained by using a CT simulator (CTS-20; Shimadzu, Kyoto, Japan) with a slice thickness of 5 mm. Target delineations and treatment planning were performed with the Cadplan system (Varian Medical System, Palo Alto, CA, USA).

The clinical target volume (CTV) included the prostate and seminal vesicle. Organs at risk included the rectum and urinary bladder. The planned radiation dose for the CTV was 70 Gy/2.0 Gy/7 weeks to the isocenter with 15-MV X-ray. Patients were treated in the supine position with no fixation devices, and were instructed to urinate just before the treatment. The initial 46 Gy was delivered with the static four-field box technique with multileaf collimation. A planning target volume (PTV) was not created in this protocol. With the four-field irradiation, the multi-leaf collimator (MLC) edges were placed directly to the CTV with margins of 15 mm in all directions, based on the beam's eye-view of each field. If part of the posterior rectal wall was included in the lateral opposing fields, the MLC positions were manually adjusted to completely shield the posterior wall from the area irradiated by the bilateral fields. The remaining 24 Gy was given with the dynamic arc conformal technique. With this technique, two lateral arcs of 100° of rotation (from 36° to 136°, and 226° to 326°) were used with dynamic conformal fitting of MLCs to the CTV with a 7-mm margin. This technique enables continuous beam delivery with dynamic changing of the MLC positions conforming to the target as the gantry rotates.[10,11]

Follow-up strategies

After completion of the EBRT regimen, patients were followed-up by both urologists and radiation oncologists every 3–6 months. Follow-up evaluation included physical examination; laboratory examination, including serum PSA level; and radiological examination, if necessary.

Acute and late toxicity were evaluated using the National Cancer Institute common toxicity criteria, version 2.0 (NCI-CTC ver. 2.0) and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria,[12] respectively. If PSA failure was confirmed, the hormonal therapy could be resumed at the discretion of the presiding urologist.

Study endpoint and definition of PSA failure

The primary endpoint of this study was PSA failure-free survival. Secondary endpoints were overall survival, cause-specific survival, and the incidence of significant treatment-related morbidity.

Two different definitions of PSA failure were used in this study. The first was according to the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria, which define the date of failure as the midpoint of the current nadir and the first date of three consecutive rises.[13] As the original statement recommends that each PSA measurement should be separated by at least 3 to 4 months, any rise observed within an interval of less than 3 months was ignored in this study. The other definition we used was according to the "nadir plus 2" criteria, which define the date of failure as the date when the PSA value exceeds the current PSA nadir plus 2 ng/ml.[14] A temporary rise in PSA, which is often observed within several months of radiation therapy and stabilizes thereafter, was not regarded as PSA failure for either of the definitions.

Statistical analysis

Biochemical disease-free survival was measured from the date of initiation of NHT, and was calculated by the Kaplan-Meier method. The log-rank test was used for statistical comparisons. A P value of less than 0.05 was considered as significant.

Results

All patients completed their planned course of treatment as scheduled and none were lost to follow-up at the time of writing. The median follow-up for surviving patients was 63 months (range, 40–90 months).

Effect of NHT

In 18 patients in whom the prostate volume was measured both before and after NHT, a significant reduction of prostate volume was observed ($29.8 \pm 16.3\,cm^3$ vs $15.3 \pm 4.7\,cm^3$, mean ± SD; $P < 0.005$).

PSA levels went down to the normal range (<4 ng/ml) after NHT in 24 patients (falling below 0.5 ng/ml in 14; Table 1). Two of the remaining 3 patients showed normalization of PSA levels after the completion of radiotherapy.

Survival

At the time of analysis, there had been 4 deaths among the patients, 1 from prostate cancer and 3 from intercurrent disease (cerebral infarction, gastric cancer, and perforation of the small intestine which was not related to prostate cancer). Clinical failure was seen in 2 patients; both had bone metastases. Consequently, at 5 years, overall survival (OAS) was 83.0% and cause-specific survival (CSS) was 93.3% (Figs. 1 and 2, respectively). Of note, 6 of the 27 patients (22%) had a second malignancy (4 in the stomach, 1 in the colon, and 1 in the urinary bladder).

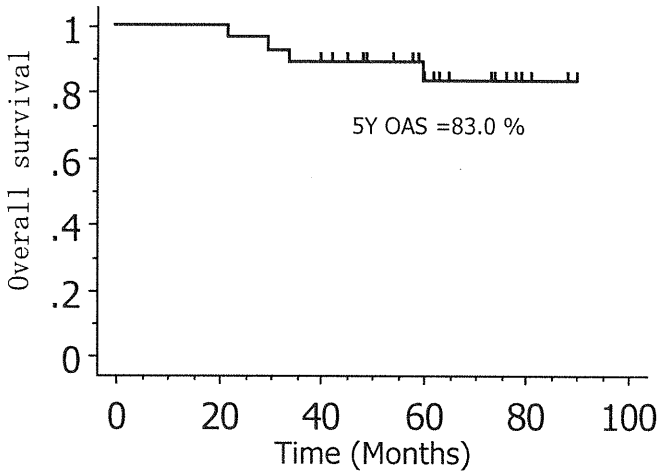

Fig. 1. Overall survival (*OAS*). *Y*, year

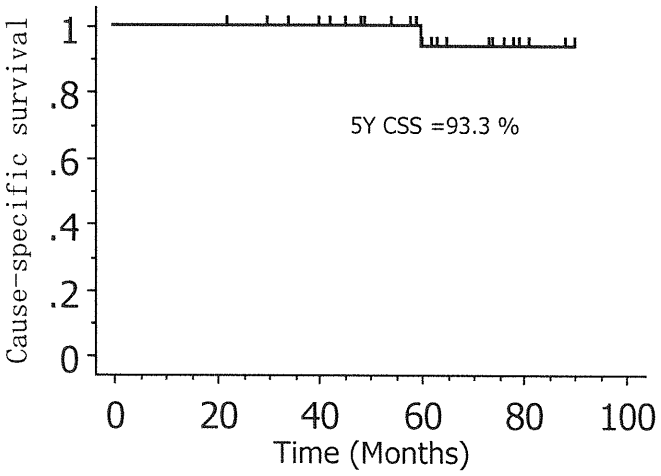

Fig. 2. Cause-specific survival (*CSS*)

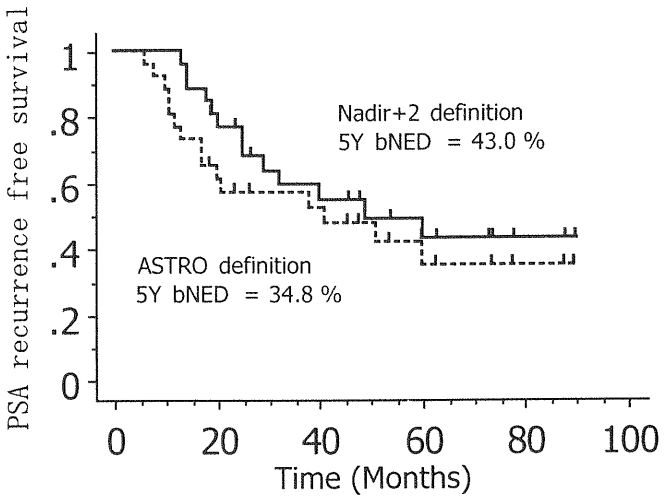

Fig. 3. Prostate-specific antigen (PSA) recurrence-free survival according to two different definitions. *ASTRO*, American Society for Therapeutic Radiology and Oncology; *bNED*, biochemical no evidence of disease

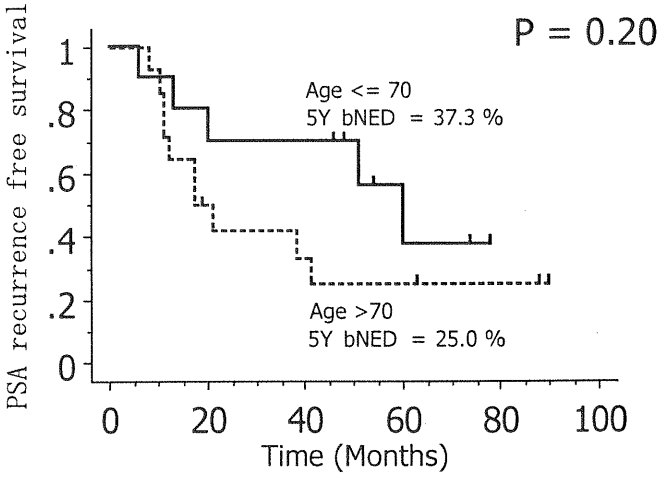

Fig. 4. PSA recurrence-free survival according to age at diagnosis

PSA control

The biochemical relapse-free survival rates at 5 years, using the ASTRO definition and the "nadir plus 2" definition, were 34.8% and 43.0%, respectively (Fig. 3). Of note, no patient resumed hormonal therapy before being judged as having PSA failure according to both definitions. Disagreement between the results according to the two definitions was observed in two patients. Both patients were judged as biochemical no evidence of disease (bNED) according to the "nadir plus 2" definition, and as showing PSA failure according to the ASTRO definition. In patients who were judged as failure in both definitions, the average difference between the two definitions in the duration of PSA failure-free survival was 175 days. Failure dates according to the ASTRO definition preceded those according to the "nadir plus 2" definition in all but two cases.

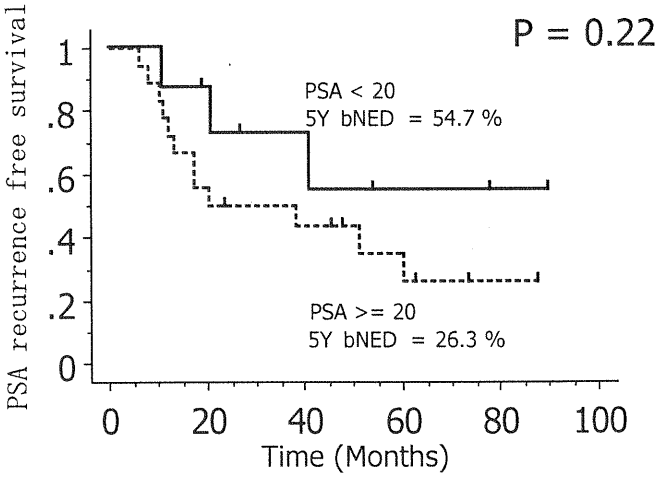

Fig. 5. PSA recurrence-free survival according to initial PSA

Prognostic factors (Figs. 4–7)

Univariate analysis was performed, in terms of prognostic factors for PSA recurrence-free survival. Older age (>70 years), higher pretreatment PSA level (>=20 ng/ml), higher PSA level after NHT (>0.5 ng/ml), and higher GS (>7) were related to a worse result ($P = 0.20$, $P = 0.22$, $P = 0.18$, and $P = 0.01$, respectively).

Toxicity (Table 2)

Acute toxicity

Seventeen patients (63%) experienced acute urinary symptoms (pollakisuria, micturition pain, etc.), rectal symptoms (anal bleeding, etc.), or both, related to the treatment, but the extent of symptoms was generally mild and there was no interruption of the planned treatment (NCI-CTC grade <=2).

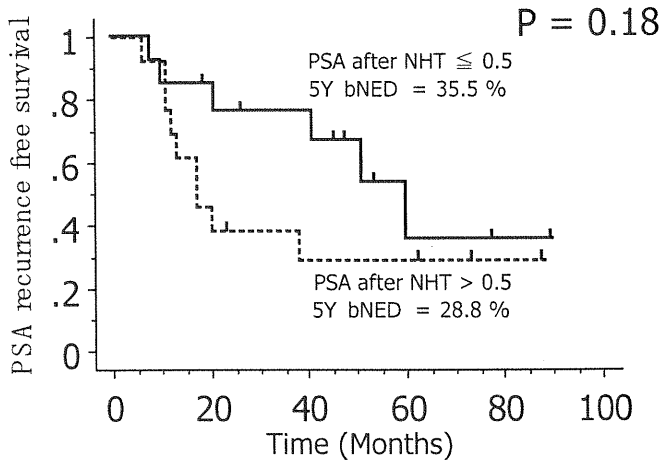

Fig. 6. PSA recurrence-free survival according to PSA after neoadjuvant hormonal therapy (NHT)

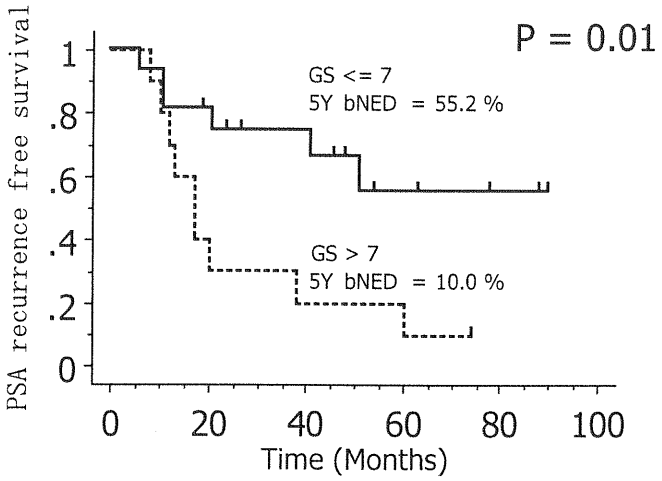

Fig. 7. PSA recurrence-free survival according to Gleason score (*GS*)

Table 2. Toxicity

	Grade 0	Grade 1	Grade 2	Grade 3–4
Acute toxicity (n = 27)				
Urinary	14	12	1	0
Rectal	24	3	0	0
Skin	0	1	0	0
Late toxicity (1 year or more follow-up; n = 27)				
Urinary	24	1	2	0
Rectal	20	6	1	0

Late toxicity

Three patients had grade 2 late complications (RTOG/EORTC late-toxicity criteria). One suffered rectal bleeding, which required a steroid suppository and hyperbaric oxygenation therapy (HBO). Two had an episode of solitary macrohematuria, and one of the two also experienced urethral stenosis, which was managed using a bougie. Symptoms of mild and intermittent rectal bleeding or microhematuria (grade 1) were seen in seven patients.

Discussion

Reports from Western countries suggest that similar results for PSA control are achieved with either EBRT or RP in men at all stages of prostate cancer.[15–17] It has also been suggested that there are no large differences in terms of survival among RP, EBRT, and endocrine therapy, especially for locally advanced prostate cancer.[18,19]

In spite of these findings and the fact that the results of RP for clinical stage III patients are clearly inferior to those for clinical stages I and II,[20,21] RP remains the mainstay of treatment for localized prostate cancer in Japan. The use of RP treatment was supported by the results of a randomized trial conducted in Japan. It compared RP and EBRT, in which endocrine therapy was applied in both arms, and concluded that there was a survival benefit in the surgery arm.[22] However, the results of this study are obsolete, because it used an obviously insufficient radiation dose for curative treatment. Many studies have revealed the dose-dependency of radiation therapy,[23] and it is considered that at least 70 Gy is necessary to achieve acceptable local control for locally advanced prostate cancer.[24,25]

Under these circumstances, the aim of the present study was to determine the effectiveness of EBRT as an alternative to surgery in the management of patients with stage III prostate cancer.

It has been established that NHT improves local control and disease-free survival in locally advanced prostate cancer.[7,26,27] In our series, the average reduction in the prostate volume after the completion of NHT was 51%. Whether the use of NHT is advantageous for radiation therapy is still controversial. Theoretically, it decreases the dose scattered to adjacent normal tissues by decreasing the volume of the prostate gland.[28] However, an increase in late rectal as well as acute and late genito-urinary toxicity has been reported in some studies.[29–31]

Adjuvant hormonal therapy was not used in the present study, because clinical evidence of a survival advantage with adjuvant hormonal therapy was not well established when this study was initiated. Moreover, the effectiveness of EBRT cannot be determined under adjuvant hormonal treatment, because biochemical failure is masked until the disease becomes refractory to hormonal therapy. Recently, several randomized studies concluded that prolonged adjuvant hormonal therapy improved overall survival, especially in patients with high-risk disease.[6,7,32,33] However, as overall survival in our series was comparable to that with adjuvant hormonal therapy in these clinical trials, and as improved survival with radiation dose escalation[25,34] or whole pelvic irradiation [35] has been suggested in some trials, the use of a sophisticated technique such as intensity modulated radiation therapy (IMRT) might be an alternative to adjuvant hormonal therapy for Japanese men. With IMRT, dose escalation to the prostate and the seminal vesicles, as well as elective irradiation to pelvic lymph nodes, can be performed simultaneously, without increasing the radiation dose to adjacent normal tissue.

The definition of PSA failure is another problem with this type of treatment. Once hormonal therapy is initiated, the PSA value usually drops below the cutoff level. However, the baseline level of PSA often rises after the termination of hormonal therapy even in patients whose tumors are controlled by radiation therapy. Moreover, a temporary rise, or spike, in PSA is sometimes observed immediately after completion of radiation therapy. This is considered to be due to the breakdown of the tumor cells and/or normal cells caused by irradiation. Strict application of the existing definitions entails the risk of an increased false-failure rate, especially in a population consisting of patients with advanced/high-risk cancer, in whom early failure and a temporary rise in PSA are mixed. In the present retrospective analysis, a temporary rise of PSA within 1 year of radiation therapy was not regarded as failure. We also felt that the