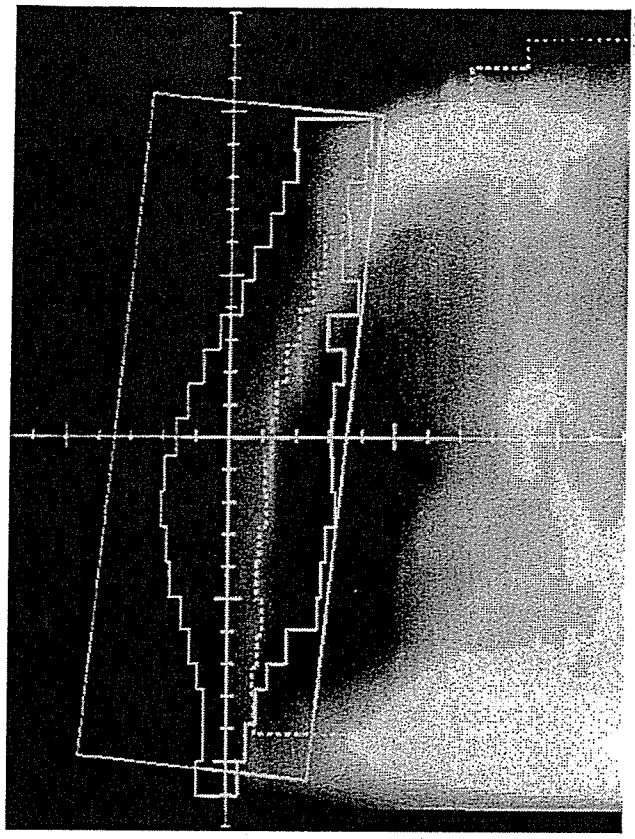

Fig 4. The irradiated field to the whole left breast with 6 MV X rays. The field includes level I/II axillary lymph nodes for prophylactic irradiation.

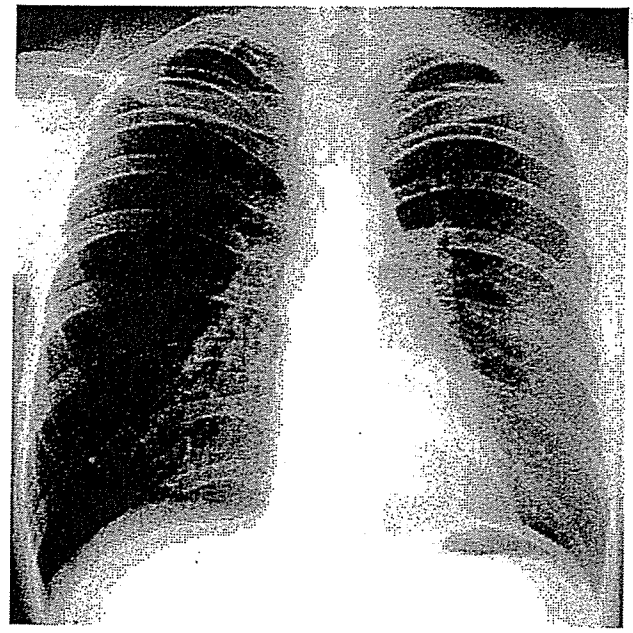

Fig 5. Four months after irradiation, chest X-ray showed an increased density in the left lung.

which includes both synchronous and metachronous disease, has been reported to range from 1.4% to 11.8%[1]. Metachronous bilateral breast cancer is known to occur at a constant annual rate of about 0.5% to 1% per year[2]. In addition, the incidence of radiation pneumonitis with clinical symptoms is reported to be around 1.0 percent. Therefore, it is extremely rare to encounter a case like this patient. There are several factors which are related to the development of radiation pneumonitis. First, the volume of the irradiated lung is important. Inclusion of supraclavicular and/or parasternal lymph nodes in clinical target volume is associated with a significantly higher incidence of radiation pneumonitis[3, 4]. Another treatment-related factor for developing radiation pneumonitis is the use of systemic therapy. The use of chemotherapy is associated with higher incidence of radiation pneumonitis especially when used concurrently with radiation therapy[4]. However, there have been no reports that concurrent use of tamoxifen with tangential breast irradiation induces radiation pneumonitis[5, 6]. This patient received concurrent oral 5-FU and tamoxifen during whole breast radiation therapy for both breasts. Although the influence of these chemo-hormonal agents on the development of radiation pneumonitis is difficult to estimate, we should have considered delaying systemic therapy for the second breast cancer. In addition to these treatment-related factors, certain patient factors such as younger age, smoking history, female sex, and prior thoracic irradiation are related to the development of radiation pneumonitis. Therefore, it is reasonable to assume that such patients are at higher risk of developing radiation pneumonitis than usual[7, 8]. Radiation therapy after breast-conserving surgery is known to significantly decrease the incidence of recurrence within the treated breast[9]. A subgroup of patients among whom radiation therapy can be safely omitted has not been identified in any clinical trial[10-12]. Consequently, if we pursue the highest possible local control, whole breast radiation therapy might be justified because there have not been any reports of fatal outcome due to radiation pneumonitis after BCT. However, there are some patients for whom prolonged treatment with steroids is required due to the development of bronchiolitis obliterans organizing pneumonia (BOOP)-like radiation pneumonitis which is refractory to steroid therapy[13, 14]. In such circumstance, patients face an increased risk of major adver-

se effects of steroids, such as avascular necrosis of the femoral head and opportunistic infections. Possible alternatives for these patients could be (1) breast-conserving surgery without radiation therapy or (2) accelerated partial breast irradiation[15]. The former has the advantage of avoiding all risk of developing radiation pneumonitis but the risk of ipsilateral breast recurrence is estimated to be three times higher than that after whole breast irradiation[9]. Although the latter has the advantage that the radiation dose delivered to the ipsilateral lung is quite low, the feasibility of this technique in Japanese women, whose breast size is much smaller than that of Western women, has not yet been fully verified. Moreover, the use of partial breast irradiation with a broad indication might compromise local control, compared with that achieved by whole breast irradiation[16].

Conclusion

It is essential to discuss the adequacy of whole breast irradiation and the possibility of alternative approaches, such as omitting breast irradiation or partial breast irradiation, with a patient who has a history of radiation pneumonitis in the treatment of contralateral breast cancer who wishes to undergo BCT.

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Jpn J Clin Oncol 2006;36(8)499–503
doi:10.1093/jjco/hyl056

Patterns of Care Study for Postmastectomy Radiotherapy in Japan: Its Role in Monitoring the Patterns of Changes in Practice

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Received March 18, 2006; accepted April 30, 2006; published online June 27, 2006

Background: Three prospective randomized clinical trials (RCT) in the 1990s demonstrated the survival benefit of postmastectomy radiotherapy (PMRT) for patients with locally advanced breast cancer. The present study was performed to evaluate whether the Patterns of Care Study (PCS) fulfills a role in monitoring the patterns of changes in clinical practices in Japan.
Methods: The first survey (JPCS-1) involved 79 Japanese facilities by two-stage cluster sampling of facilities and patients, and was carried out during 1998–2000. JPCS-1 included 1124 patients with breast cancer who were treated between 1995 and 1997. The second survey (JPCS-2) was carried out during 2001–2003, involving 827 patients who were treated between 1999 and 2001 in 76 facilities.
Results: Patients with adverse risk factors, including pathologically axillary positive nodes (≥4) and/or advanced primary disease (pT3–4) accounted for 57% of the patients who received PMRT in JPCS-1 and 72% of those in JPCS-2 ($P = 0.039$). The multiple radiotherapy target volume including the chest wall and regional lymph nodes was applied in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$). However, the dose distribution was calculated in only 42% of the patients in both surveys ($P = 0.467$).
Conclusions: The eligibility and the target volume for PMRT were influenced by the outcome of RCT, but the quality of radiotherapy did not improve sufficiently. The PCS survey is useful to monitor the changes in patterns of clinical practice and can clarify some problems with radiotherapy techniques.

Key words: breast cancer – mastectomy – patterns of care – radiotherapy

INTRODUCTION

Over the last two decades, prospective randomized clinical trials (RCT) and meta-analysis demonstrated that postmastectomy radiotherapy (PMRT) improved the loco-regional control of patients with locally advanced breast cancer, but failed to improve overall survival (1–3). Any reduction in breast cancer mortality has been offset by mortality from late adverse effects of radiotherapy, including heart disease (1). In the late 1990s, three prospective RCT demonstrated that PMRT improved not only loco-regional control but also overall survival of patients with locally advanced breast cancer (3–6). Recent meta-analysis demonstrated that PMRT with an optimal dose and optimal radiotherapy target volume was significantly associated with improved survival for up to 10 years (7). The adequate radiotherapy technique of PMRT should be established to provide the effectiveness of PMRT without increases in lethal toxicity. The recent development of three-dimensional radiotherapy planning and quality assurance of radiotherapy technique has facilitated the reduction of severe radiation-induced toxicity. In 2001, the American Society of Clinical Oncology (ASCO) proposed the clinical guidelines for PMRT to improve the level of clinical practice (8).

The Patterns of Care Study in the United States (USPCS) sponsored by the American College of Radiology has made significant contributions to improvements in the care of patients with breast cancer and with other types of cancer (9,10). The Japanese Patterns of Care Study (JPCS) Working

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Group collaborated with USPCS to evaluate each radiotherapy practice pattern and improved the research method (11–13). We conducted two national surveys to evaluate the clinical practice of radiotherapy in Japan. The first goal of this study was to evaluate whether PCS surveys fulfill the role of monitoring changes in practice patterns in Japan after three prospective randomized trials, which demonstrated the efficacy of PMRT in the late 1990s (3,5,6). In addition, the second goal of this study was to clarify whether the radiotherapy technique has been improved sufficiently to provide effectiveness of PMRT.

METHODS

We developed a data format system, which we installed on portable computers. The extramural audits of facilities were conducted by the JPCS Working Group. The audits were performed by member physicians of the working group. The audits reviewed the patients' clinical records and input the data into the portable computer on-site. The method of data collection and the JPCS data format have been reported in detail previously (14).

In 1995, according to the Japanese facility master list, a total of 556 facilities nationwide were stratified into four classifications according to the category of facility type and the number of patients, and 79 facilities were sampled at random. The first survey (JPCS-1) was carried out during 1998-2000, and collected data of 1124 patients with breast cancer treated with radiotherapy between 1995 and 1997 using two-stage cluster sampling of facilities and patients (15). In 1999, a total of 641 facilities nationwide were stratified using the same method, and 76 facilities were sampled at random. The second survey (JPCS-2) was carried out in 2001–2003, and involved 827 patients who were treated between 1999 and 2001. We could not keep the same number of facilities in the two surveys because of difficulties in gaining approval for an extramural audit from the institutional review board (14). The eligibility criteria for these surveys were as follows: (1) absence of distant metastases, (2) no bilateral lesions, (3) females, (4) no gross multiple tumors, (5) no diffuse micro-calcification on pretreatment mammography, (6) absence of prior or concurrent malignancies, (7) absence of prior history of radiotherapy for beast cancer and (8) absence of collagen vascular disease other than rheumatoid arthritis. These eligibility criteria for the patients who received breast conservative therapy were the same as those for patients who underwent PMRT. The study office sampled the patients at random from the patient list regardless of the treatment procedures, including breast conservative therapy and PMRT.

The clinical and pathological stages were classified according to the Fifth Classification of the International Union against Cancer (UICC) (16). Academic facilities were defined as university hospitals or cancer centers and non-academic facilities were defined as other hospitals. Differences in proportion were evaluated by chi-squared test.

RESULTS

JPCS-1 included 866 patients treated with breast conservative therapy and 258 patients treated with mastectomy and PMRT. JPCS-2 included 746 patients treated with breast conservative therapy and 81 patients treated with mastectomy followed by PMRT. The patient characteristics are shown in Table 1. The proportion of patients who received PMRT among those who received postoperative radiotherapy decreased from 22.9% to 9.7% ($P < 0.001$). Among the patients who received PMRT, the proportions of those with adverse risk factors, including four or more axillary positive nodes and/or advanced primary disease (pT3-4), were 57% in JPCS-1 and 72% in JPCS-2 ($P = 0.039$).

The radiotherapy target volume included the chest wall in 31% and in 63% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). The radiotherapy target volume included the regional lymph node area, such as the supraclavicular fossa and/or internal mammary lymph nodes in 87% of the patients in JPCS-1 and in 79% of those in JPCS-2 ($P = 0.083$). The radiotherapy target volume included both chest wall and regional lymph node area in 18% of the patients in JPCS-1 and 44% of those in JPCS-2 ($P < 0.001$) (Fig. 1). The majority of the patients in JPCS-1 received irradiation of the regional lymph node area alone. In the academic facilities, the proportions of patients who received both chest wall irradiation and regional lymph node irradiation were 28% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P = 0.001$). In the non-academic facilities, the proportions of patients receiving both treatments were 10% in JPCS-1 and 36% in JPCS-2 ($P < 0.001$).

The dose distribution at the iso-center plane was calculated in only 42% of the patients both in JPCS-1 and in JPCS-2 ($P = 0.467$). In the academic facilities, the dose distribution was calculated in only 46% of the patients in JPCS-1 and 52% of those in JPCS-2 ($P = 0.120$). In the non-academic facilities, the dose distribution was calculated in only 39% and in 36% of the patients in both surveys, respectively ($P = 0.894$). Among all facilities, the multiple-plane dose distribution was calculated in 4% of the patients in JPCS-1 and 15% of those in JPCS-2 ($P < 0.001$).

The immobilization cast was used in 14 and in 35% of the patients in JPCS-1 and in JPCS-2, respectively ($P < 0.001$). In the academic facilities, the immobilization cast was used in 21% of the patients in JPCS-1 and 58% of those in JPCS-2 ($P < 0.001$). In the non-academic facilities, the immobilization cast was used in 9% of the patients in JPCS-1 and 20% of those in JPCS-2 ($P = 0.018$).

No marked differences were found between the two surveys regarding the daily fraction size, total irradiation dose or photon beam energy (Table 2).

DISCUSSION

The effectiveness and the safety of breast conservative therapy have been confirmed by many randomized trials and pooled-

Table 1. Patient characteristics in two surveys

	JPCS-1 (95–97) (n = 258)	JPCS-2 (99–01) (n = 81)	P-value
Age (y)	53.6 ± 11.5	56.5 ± 10.7	0.482
Menstrual status			0.063
Pre-	86/258 (33.3)	19/81 (23.4%)	
Peri-	17/258 (6.6)	2/81 (2.5)	
Post-	106/258 (41.1)	46/81 (56.8)	
Unknown/missing	49/258 (19.0)	14/81 (17.3)	
Pathologically T stage			0.548
pTis	0/258 (0.0)	0/81 (0.0)	
pT0	1/258 (0.4)	0/81 (0.0)	
pT1	43/258 (16.7)	13/81 (16.1)	
pT2	116/258 (44.9)	33/81 (40.8)	
pT3	45/258 (17.4)	13/81 (16.0)	
pT4	27/258 (10.5)	15/81 (18.5)	
Unknown/missing	26/258 (10.1)	7/81 (8.6)	
Number of pathologically positive axillary lymph nodes			0.010
0	48/258 (18.6)	10/81 (12.3)	
1–3	51/258 (19.8)	19/81 (23.5)	
⩾4	119/258 (46.1)	49/81 (60.5)	
Unknown/missing	40/258 (15.5)	3/81 (3.7)	
Final microscopic margin			<0.001
Positive	11/258 (4.3)	17/81 (21.0)	
Close (⩽2 mm)	10/258 (3.9)	2/81 (2.5)	
Close (2–5 mm)	0/258 (0.0)	1/81 (1.2)	
Close (>5 mm)	0/258 (0.0)	0/81 (0.0)	
Negative	183/258 (70.9)	51/81 (63.0)	
Unknown/missing	54/258 (20.9)	10/81 (12.3)	
Estrogen receptor status			0.012
Not done	35/258 (13.6)	7/81 (8.6)	
Positive	61/258 (23.6)	28/81 (34.6)	
Negative	57/258 (22.1)	26/81 (32.1)	
Unknown/missing	105/258 (40.7)	20/81 (24.7)	
Progesterone receptor status			<0.001
Not done	39/258 (15.1)	7/81 (8.6)	
Positive	48/258 (18.6)	23/81 (28.4)	
Negative	50/258 (19.4)	29/81 (35.8)	
Unknown/missing	121/258 (46.9)	22/81 (27.2)	

JPCS, Japanese Patterns of Care Study.

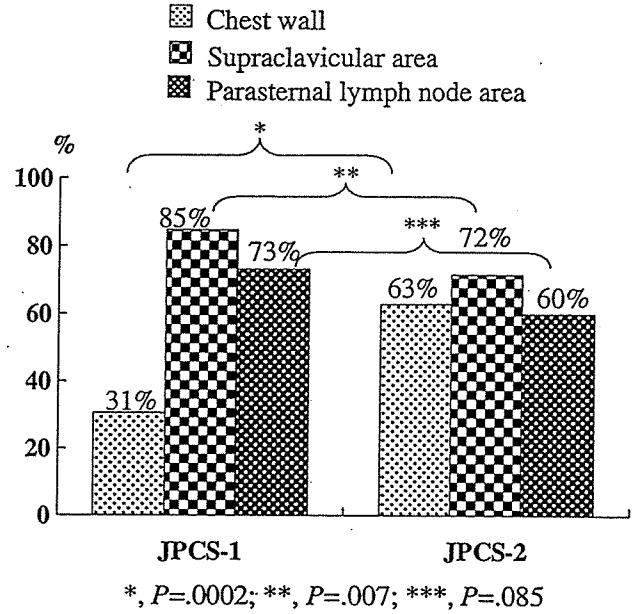

Figure 1. The radiotherapy target volume in patients who received PMRT. The majority of patients in the first survey received irradiation of the regional lymph node area alone. In the second survey, the radiotherapy target volume including the chest wall and regional lymph nodes was applied more frequently. JPCS, Japanese Patterns of Care Study

analyses (17–20). For the last two decades, breast conservative therapy has become more frequently performed in Japan. The national survey conducted by the Japanese Breast Cancer Society indicated that ~40% of patients with breast cancer received breast conservative therapy in 2000, and that nowadays more than half of the patients receive such treatment (21). However, three prospective randomized trials indicated that PMRT improved the overall survival of pre-menopausal and post-menopausal patients with locally advanced breast cancer who had pathologically four or more axillary positive nodes, and that PMRT has been used widely in the United States and in the other Western countries (2–5). Fowble reviewed a large number of reports regarding chest wall recurrence after mastectomy, and reported that 8–36% of patients with four or more pathologically positive nodes underwent treatment with mastectomy and adjuvant systemic chemotherapy (2). However, in Japan PMRT has been used infrequently in patients with adverse risk factors, because many Japanese surgeons consider that chest wall recurrence is infrequent after mastectomy and systemic therapy alone (22). However, the evidence-based guidelines for clinical practice conducted by the Japanese Breast Cancer Society recommended that PMRT should be applied in patients with pathologically four or more axillary positive nodes. These clinical guidelines may have affected the increment in a number of patients receiving PMRT in Japan. The dissemination of high-quality evidence that does not result in the progress of practical techniques would expose patients to severe adverse effects. We should monitor clinical practice to evaluate whether appropriate radiotherapy for PMRT is being performed.

PMRT has been recommended for patients with four or more pathologically proven axillary positive nodes and/or advanced primary disease (8). The clinical benefit of PMRT for patients without adverse risk factors is controversial (23,24). Smith

Table 2. Radiotherapy technique in two surveys

	JPCS-1‡ (n = 258)	JPCS-2 (n = 81)	P-value
Total radiation dose (Gy) (median, range)	49 (10–60)	49 (18–60)	0.738
Fraction size (Gy) (median ± standard deviation)	2.0 ± 0.2	2.0 ± 0.1	0.490
Beam quality of chest wall irradiation*			<0.001
Photon (≤6 MV) (%)	59/79 (74.7)	26/51 (51.0)	
Photon (>6 MV) (%)	6/79 (7.6)	2/51 (3.9)	
Electron (%)	13/79 (16.5)	23/51 (45.1)	
Mixed beam (^{60}Co and X-ray 15 MV) (%)	1/79 (1.2)	0/51 (0.0)	
Wedge filter (yes)† (%)	11/66 (16.7)	11/28 (39.3)	0.001
Boost (yes) (%)	7/258 (2.7)	5/81 (6.2)	0.141

*Calculations were performed only for patients who received chest wall irradiation.
†Calculations were performed only for patients who received chest wall irradiation using photon beam.
‡JPCS, Japanese Patterns of Care Study.

et al. (23) reported that PMRT provided clinical benefits for patients with T1-2 disease and positive axillary nodes. However, some other investigators argued that the role of PMRT had not been defined for patients with T1-2 disease and positive axillary nodes (25). Hence further studies should be performed to establish the indications for PMRT. Our surveys showed that among patients with breast cancer who received postoperative radiotherapy, the proportion of PMRT decreased from 22.9% in JPCS-1 to 9.7% in JPCS-2. This observation does not imply a decrease in the absolute number of patients who received PMRT in Japan, but rather suggests an increment in the number of patients who received breast conservative therapy. The proportions of patients with adverse risk factors, including four or more pathologically proven axillary positive nodes and/or advanced T stage, increased from 57 to 72% between the two studies. The eligibility for PMRT may be influenced by the outcome of the prospective randomized trials in the late 1990s, and PMRT came to be avoided for patients with low risk factors (3–5).

A recent meta-analysis demonstrated that PMRT with an optimal radiation dose ranging from 40 to 60 Gy in 2 Gy fractions, and an appropriate target volume, including chest wall and regional lymph node area, was associated with a statistically significant 6.4% increase in absolute survival (7). However, an inappropriate PMRT technique with an inadequate or excessive dose of radiotherapy or an inappropriate target volume failed to show clinical benefit. Our two surveys demonstrated some problems in radiotherapy techniques for PMRT. In the first survey, the majority of patients received regional lymph node irradiation alone, which was known as the hockey-stick technique. In the second survey, the radiotherapy target volume more frequently included the chest wall and regional lymph nodes. Multiple radiation fields covering anatomically complex sites require a high-quality radiotherapy technique, including three-dimensional radiation planning and quality assurance to avoid severe toxicities. The dose distribution is essential to determine the administration of wedge filter and to evaluate the irradiated lung and heart volume. In the United States, dose distribution in the iso-center plane was calculated in ~95% of patients (11). However, in our survey the dose distribution in the iso-center plane was calculated only in 40% patients, and the multiple-plane dose distribution was calculated only in 15% patients. No improvement of quality assurance was found either in the academic or in the non-academic facilities. Although the immobilization cast is an important item to reproduce the irradiation field in daily treatment, it was used in less than half of the patients in our surveys.

The main limitation of our surveys was the eligibility criteria used. The aim of our surveys was to clarify the clinical procedures applied in patients with breast cancer who received postoperative radiotherapy. The eligibility criteria for our surveys were set up to collect data for patients who received postoperative radiotherapy, including breast conservative therapy and PMRT. The population of patients who received breast conservative therapy has been increasing, and the relative size of the population receiving PMRT has decreased. We could not collect data for patients with PMRT to determine the changes in the clinical procedure sufficiently. Our surveys excluded patients with multiple gross tumors and/or diffuse microcalcification on pretreatment mammography, but the survey for PMRT should include these patients to determine the nationwide status of PMRT. In future studies, we should consider the eligibility criteria to determine the changes in the clinical procedure of PMRT.

Donabedian emphasized three components of quality of care: structure, process and outcome (15). Good processes of care help to achieve good clinical outcome for the patients, while poor processes are associated with insufficient outcome. However, we did not evaluate the correlation between poor radiotherapy technique and clinical outcome, including survival and adverse effects, because of the short follow-up time and small sample size. A survey with small sample size cannot clarify the interactions between poor processes and insufficient clinical outcome. "No difference" in the survey with small sample size does not necessarily mean the "same." Even if the poor process is not significantly associated with poor clinical outcome, this hasty interpretation does not justify by any means that a poor radiotherapy technique is acceptable. In addition, repeated analyses of the correlation between each clinical parameter and the outcome may lead to misunderstanding of the observed phenomenon because of multiplicity. A process survey including large sample size may not be efficient and economical. In contrast, a process survey using a relatively small sample size is convenient and useful to compare the observed clinical practice with the optimal radiotherapy technique that is considered appropriate according to the textbooks or previously reported evidence. However, the definition of optimized sample size for a survey is controversial.

A recent meta-analysis demonstrated that use of an inappropriate radiotherapy technique that applied excessive radiation dose and/or inappropriate target volume was associated with an increment in non-breast cancer mortality (7). In Japan, the infrastructure of radiation oncology units has been insufficient to provide safe medical service in both academic and non-academic facilities (13). The radiation oncology staff, including radiation oncologists, technologists, dosimetrists and oncology nurses, should be enriched to provide good clinical practice for the patients. An efficient monitoring system using optimized surveys combining the structure survey and process survey should be established for good clinical practice.

Acknowledgments

This study was presented in part at the 46th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Salt Lake City, UT, in October 2004.

This study was supported by a Grant-in-Aid for Cancer Research (14–6,16–12) from the Ministry of Health, Labor and Welfare of Japan. We thank all radiation oncologists who participated in this study whose efforts in providing information made these surveys possible.

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Int J Clin Oncol (2006) 11:482–486
DOI 10.1007/s10147-006-0607-0

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

Received: April 26, 2006 / Accepted: July 23, 2006

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.

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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

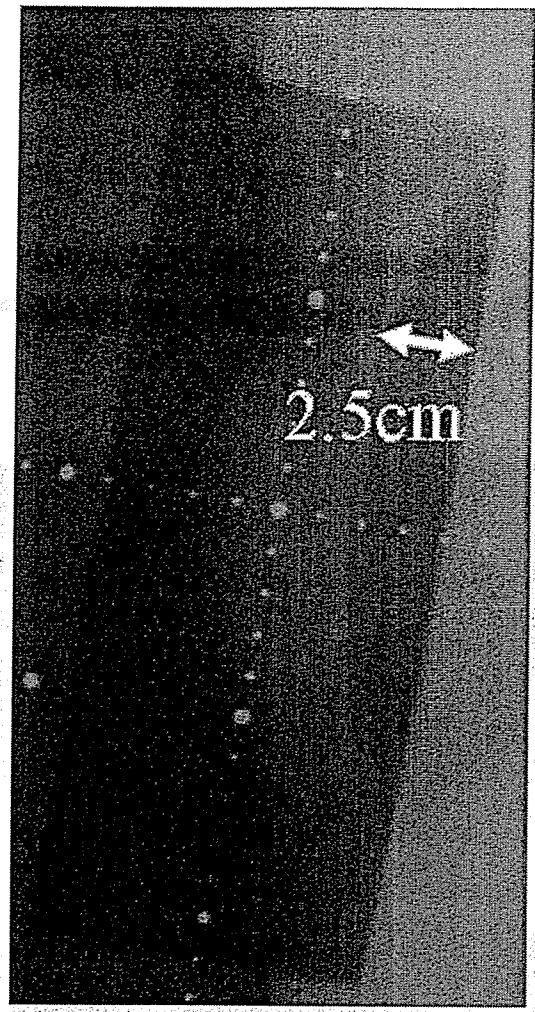

Fig. 1. Linacgraphy. Whole-breast irradiation was given with 6-MV X-rays, using a tangential field. The size was 22.0 cm by 8.0 cm, and the central lung distance was 2.5 cm

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.

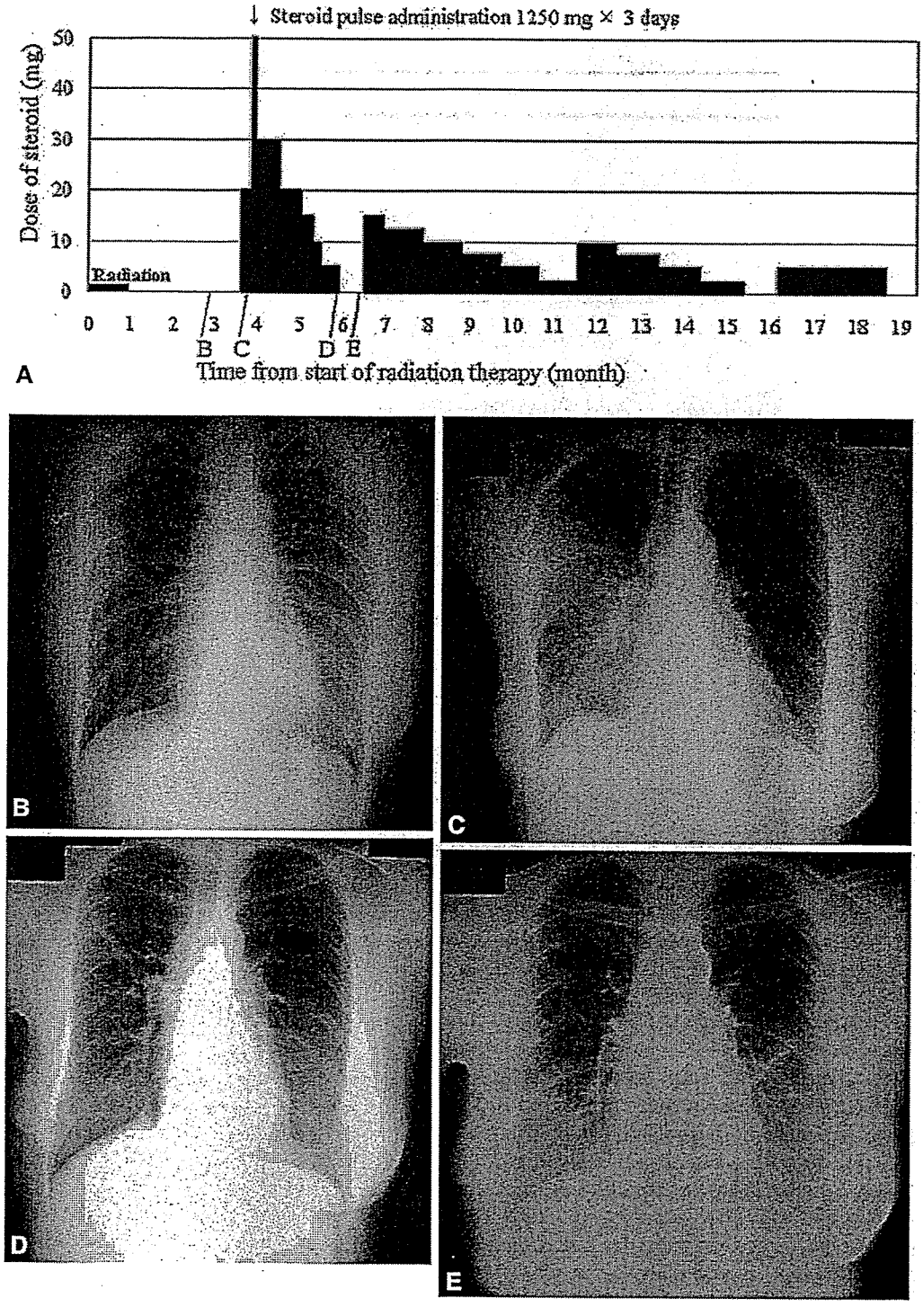

Fig. 2. **A** This figure shows the dosage of steroids and the clinical course. The *horizontal axis* expresses the time from the beginning of radiation therapy. Radiation therapy was performed during the first month. **B, C, D,** and **E** are the chest X-ray films at the times shown in the graph in **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

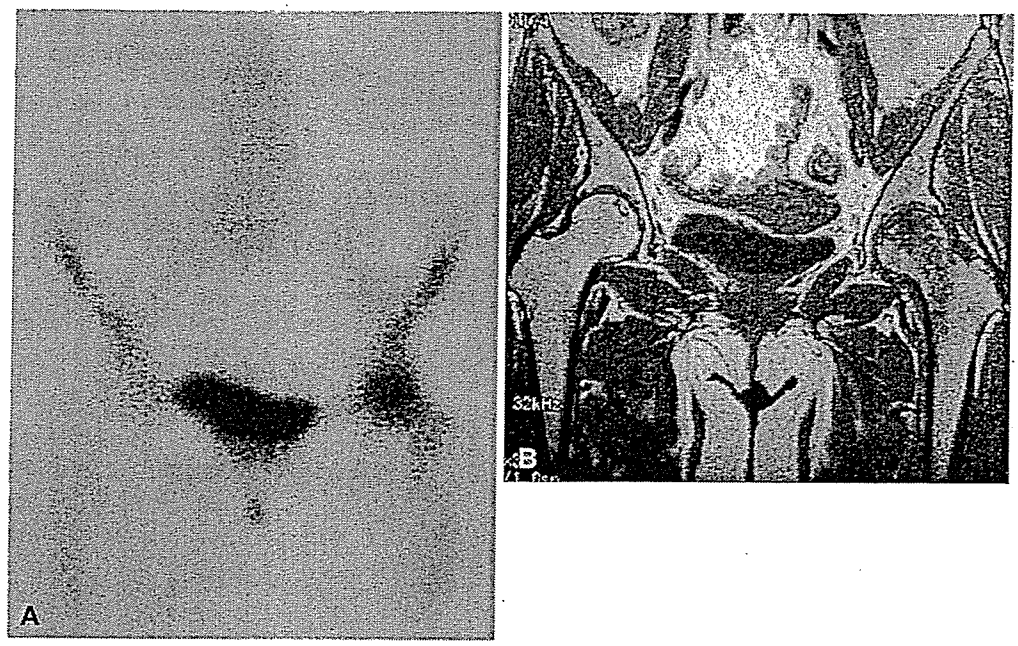

Fig. 3. **A** Bone scintigraphy and **B** magnetic resonance imaging (MRI). Bone scintigraphy shows ^{99m}Tc-HMDP (hydroxymethylenedisphosphonate) accumulation in the left femoral head. The MRI shows a low signal intensity in the left femoral head on a T1-weighted image. A small low signal intensity 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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Int J Clin Oncol (2006) 11:396–402
DOI 10.1007/s10147-006-0600-7

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

Received: April 10, 2006 / Accepted: June 13, 2006

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 2ng/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 (<4ng/ml) after NHT in 24 patients (falling below 0.5ng/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).

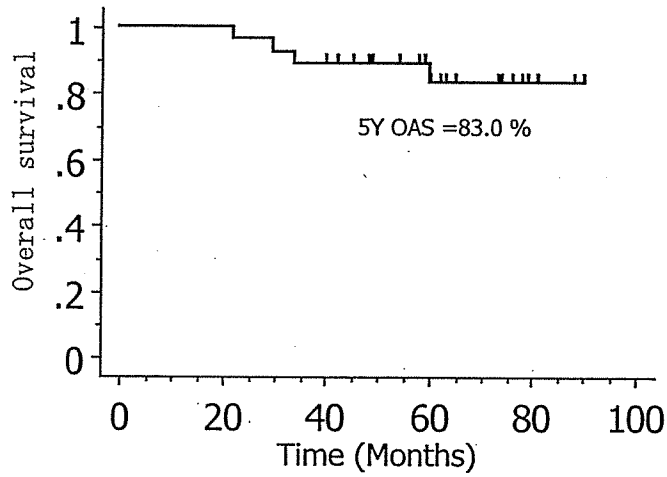

Fig. 1. Overall survival (*OAS*). *Y*, year

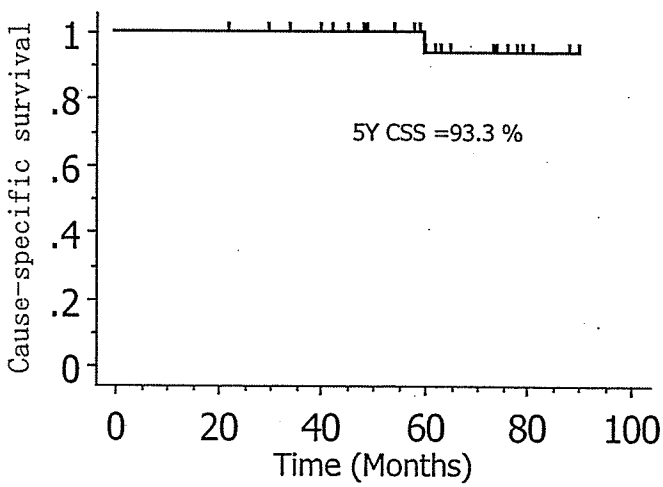

Fig. 2. Cause-specific survival (*CSS*)

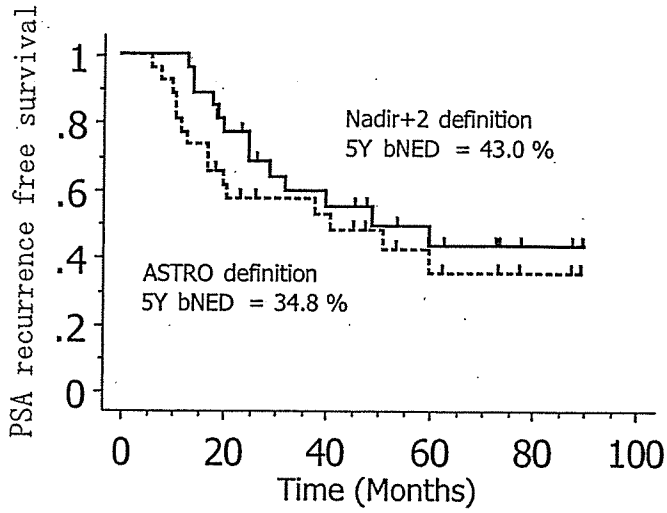

Fig. 3. Prostate-specific antigen (PSA) recurrence-free survival according to two different definitions. *ASTRO*, American Society for Therapeutic Radiology and Oncology; *bNED*, biochemical no evidence of disease

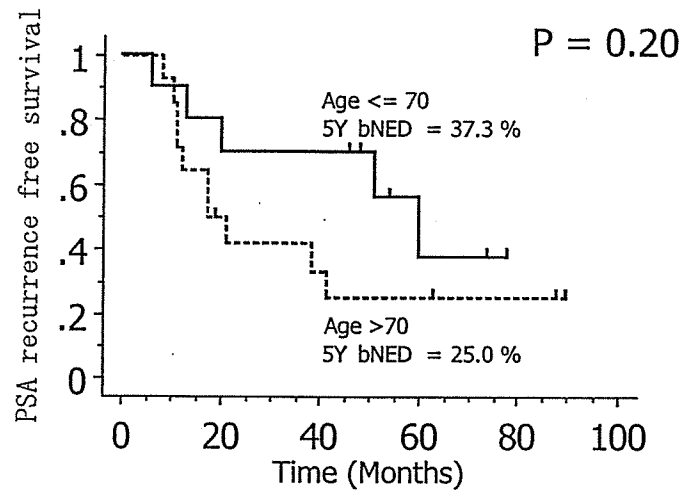

Fig. 4. PSA recurrence-free survival according to age at diagnosis

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.

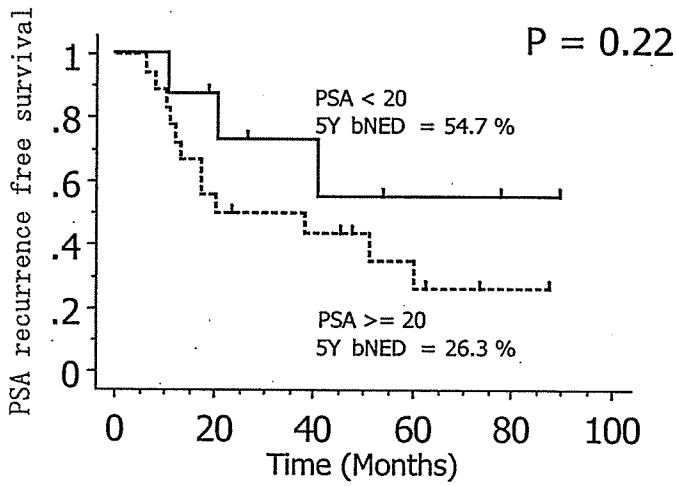

Fig. 5. PSA recurrence-free survival according to initial PSA

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).

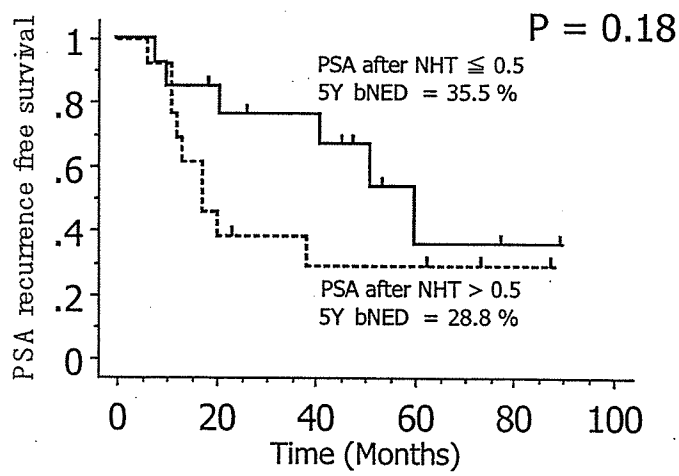

Fig. 6. PSA recurrence-free survival according to PSA after neoadjuvant hormonal therapy (NHT)

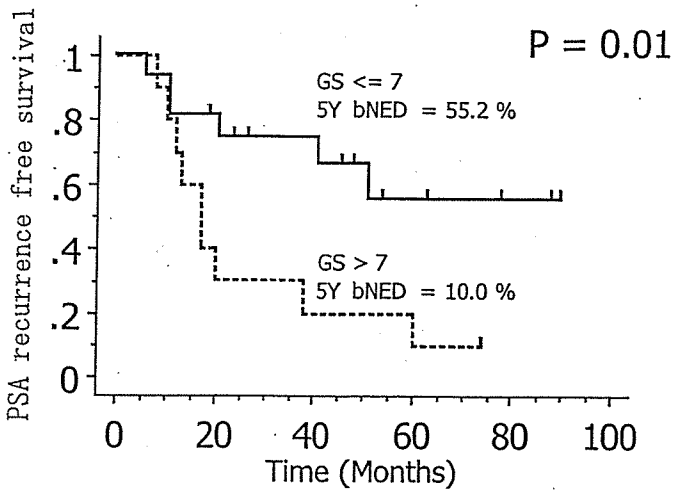

Fig. 7. PSA recurrence-free survival according to Gleason score (*GS*)

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

judgment of PSA failure is often difficult and vague with the ASTRO definition, especially when the intervals between measurement are shorter than recommended, which sometimes occurs as a result of a patient's desire to monitor their PSA levels as often as possible. Therefore, we employed the criteria of "nadir plus 2", reported by Coen et al.,[14] with a modification so as not to misinterpret the temporary rise in PSA after the initial treatment as PSA failure. The results with these two definitions matched in 93% of our patient cohort for the judgment of PSA failure; however, time to failure was approximately 6 months shorter with the ASTRO definition.

It is notable that as many as 22% of the patients in our series developed a second primary malignancy; this is significantly higher than the figure reported by Movsas et al.[36] It should be emphasized that none of these malignancies fulfilled the classic definition of radiation-induced malignancy (arising within the radiation field and a minimum 5-year interval between prior radiotherapy and the development of a second malignancy). Considering the high incidence of death from intercurrent disease, including a second primary cancer, less invasive treatment, such as radiation therapy, is a reasonable option for this elderly population.

Based on the results of the present study, we are now undertaking a phase II study with dose escalation to 78 Gy, using IMRT, for patients with stage III disease. The role of adjuvant hormonal therapy following EBRT for Japanese men will be assessed in our next study.

In conclusion, NHT followed by 70 Gy of EBRT, using a dynamic conformal technique, is feasible for Japanese men and produced a favorable survival result. Assessment of the effect of an increased radiation dose and/or the use of adjuvant hormonal therapy is warranted in future studies.

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Lung Cancer (2007) xxx, xxx–xxx

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Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan

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Received 29 November 2006; received in revised form 4 January 2007; accepted 17 January 2007

KEYWORDS
Non-small-cell lung cancer;
Postoperative radiation therapy;
Patterns of care study;
Practice;
Survey;
PORT meta-analysis

Summary To investigate the practice process of postoperative radiation therapy for non-small-cell lung cancer (NSCLC) in Japan. Between April 2002 and March 2004, the Patterns of Care Study conducted an extramural audit survey for 76 of 556 institutions using a stratified two-stage cluster sampling. Data on treatment process of 627 patients with NSCLC who received radiation therapy were collected. Ninety-nine (16%) patients received postoperative radiation therapy between 1999 and 2001 (median age, 65 years). Pathological stage was stage I in 8%, II in 17%, IIIA in 44%, and IIIB in 20%. The median field size was 9 cm × 11 cm, and median total dose was 50 Gy. Photon energies of 6 MV or higher were used for 64 patients, whereas a cobalt-60 unit was used for five patients. Three-dimensional conformal treatment was used infrequently. Institutional stratification influenced several radiotherapy parameters such as photon energy and planning target volume. Smaller non-academic institutions provided worse quality of care. The study confirmed continuing variation in the practice of radiotherapy according to stratified institutions. Outdated equipment such as Cobalt-60 units was used, especially in non-academic institutions treating only a small number of patients per year.

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0169-5002/$ — see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2007.01.017

Please cite this article in press as: Uno T, et al., Postoperative radiotherapy for non-small-cell lung cancer: Results of the 1999–2001 patterns of care study nationwide process survey in Japan, Lung Cancer (2007), doi:10.1016/j.lungcan.2007.01.017