**TABLE 1.** Patient Characteristics

| | Younger Patients (n = 72) | | Elderly Patients (n = 14) | |
|---|---|---|---|---|
| | No. Patients (%) | Median (range) | No. Patients (%) | Median (range) |
| Age | | 57 y (9-70) | | 74 y (71-77) |
| Performance status | | | | |
| 0-1 | 44 (61%) | | 2 (14%) | |
| 2-4 | 28 (39%) | | 12 (86%) | |
| RPA | | | | |
| Class 3 | 14 (19%) | | 0 (0%) | |
| Class 4 | 19 (26%) | | 2 (14%) | |
| Class 5 | 25 (35%) | | 6 (43%) | |
| Class 6 | 14 (20%) | | 6 (43%) | |
| Tumor size | | 4.5 cm (1.4-8.0) | | 4.0 cm (3.0-6.5) |
| Surgery | | | | |
| Total or subtotal resection | 44 (61%) | | 8 (57%) | |
| Partial resection or biopsy | 28 (39%) | | 6 (43%) | |
| Systemic therapy | | | | |
| Chemotherapy | 66 (92%) | | 9 (64%) | |
| Interferon-β | 62 (86%) | | 8 (57%) | |
| External radiotherapy | | | | |
| Fraction size | | 2 Gy (1.8-2) | | 2 Gy (2-3) |
| Total dose | | 54 Gy (42-66) | | 60 Gy (30-70) |

RPA indicates recursive partitioning analysis proposed by the Radiation Therapy Oncology Group.

preoperative computed tomography (CT) and magnetic resonance imaging (MRI) studies, and included the enhanced tumor and peritumoral edema with 1.5 to 2 cm margins. The planning target volume (PTV) was based on clinical target volume with a 0.5 cm margin. If the PTV included critical organs, such as the brainstem, optic chiasm, optic nerve, or retina, PTV was reduced to a 1 to 1.5 cm margin of the preoperative gross tumor volume after a radiation dose of 50 Gy. A photon energy of 4 MV, 6 MV, or 10 MV was used. Treatment plans included lateral-opposed fields, wedged-pair fields, rotation techniques, or multiple-field techniques. Computer-aided treatment planning was performed after the late 1990s. The prescribed dose was calculated at the center of the radiation field or that of the PTV. A 74-year-old man with poor PS, who was grouped into class 6 by recursive partitioning analysis (RPA), was treated with 30 Gy in a fraction size of 3 Gy over 2 weeks. The remaining 85 patients were treated with 42 to 70 Gy in a fraction size of 1.8 to 2 Gy over 4 to 7 weeks. The median and mean radiation doses were 60 and 55 Gy (range, 30 to 70 Gy) in elderly patients, and 54 and 54 Gy (range: 42 to 66 Gy) in younger patients. There was no difference between the total radiation dose in elderly and younger patients ($P = 0.22$).

Seventy-nine patients (92%) received anticancer agents, including cytotoxic agents and/or interferon-β, during or after radiotherapy. Sixty-nine younger patients (96%) and 10 elderly patients (71%; $P$=0.008) received anticancer agents. Nitrosourea alone or nitrosourea-containing combination chemotherapy was administered to 75 patients, usually concomitant with radiotherapy and/or in a postradiotherapy adjuvant setting. Seventy patients received intravenous interferon-β at a dose of 3,000,000 IU daily during radiotherapy and weekly in a postradiotherapy adjuvant setting. As a basic procedure, patients received these anticancer agents until disease progression or development of severe adverse events. Temozolomide, an oral alkylating agent, was not used in the initial treatment of all patients. Temozolomide was approved for clinical use by the Ministry of Health, Labor, and Welfare of Japan in July 2006. Only a 59-year-old man, who was grouped into RPA class 4, was treated with temozolomide after local progression.

Overall survival time and progression-free survival (PFS) was measured from the date of treatment initiation. PFS was calculated using disease progression and death due to any cause such as events, and overall survival was calculated using death due to any cause such as an event. Disease progression was defined as an increase in tumor size compared with the initial tumor volume visualized on CT/MR images or the appearance of a new lesion separate from the initial tumor volume. Local progression was defined as a tumor size increase or new lesion in the surgical cavity seen on CT/MR images, and distant progression was defined as the appearance of new lesions separated from the initial tumors by at least 2 cm on CT/MR images. We used the Kaplan-Meier method to estimate survival distributions for each group and the log-rank test to compare survival distributions using a significance level of <0.05. The Mantel-Haenszel $\chi^2$ test was used to compare patients and tumor characteristics at baseline. We carried out a multivariate analysis of prognostic factors using the Cox proportional hazards model. Statistical analysis was carried out using JMP version 5.1J (SAS Institute Inc.).

## RESULTS

The median follow-up for all patients was 11.6 months (range, 1.4 to 105.8 mo). The median PFS and median survival time (MST) of all 86 patients were 5.8 months [95% confidence interval (CI), 4.7-7.4] and 12.8 months (95% CI, 10.8-14.9), respectively. One-year and 2-year overall survival rates of all patients were 53% and 16%, respectively. Thirteen patients (15%) showed disease progression at the end of radiotherapy. Twelve younger patients (17%) and 1 elderly patient (7%) showed local progression at the end of radiotherapy ($P$=0.36). The MST of the 35 patients in classes 3 and 4 was 16.9 months (95% CI, 14.2-22.7), and that of the 51 patients in classes 5 and 6 was 11.0 months (95% CI, 9.3-12.6; $P < 0.001$; Fig. 1).

Among the patients in classes 3 and 4, the MST of 2 elderly patients was 14.8 months (95% CI, 10.5-N/A), and that of 33 younger patients was 18.1 months (95% CI, 14.2-24.4;

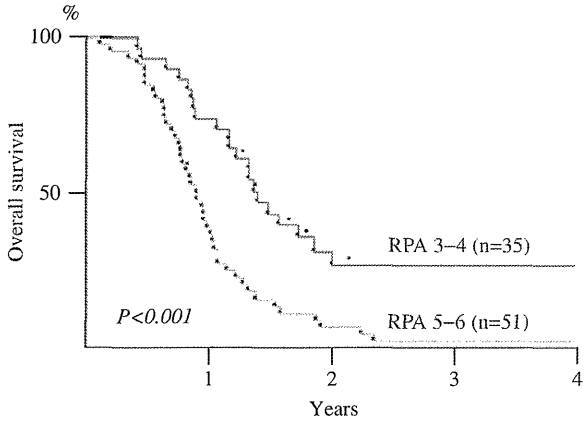


**FIGURE 1.** Comparison of overall survival rates based on recursive partitioning analysis (RPA) classes.

$P = 0.10$). Twelve elderly patients (86%) and 39 younger patients (54%) were grouped in RPA classes 5 and 6 ($P$=0.01). Among these patients, the MST of the 12 elderly patients was 10.5 months (95% CI, 5.8-12.8), and that of 39 younger patients was 11.7 months (95% CI, 9.3-13.0; $P$=0.32; Fig. 2). The 2-year overall survival rates of elderly and younger patients in classes 5 and 6 were 0% and 9%, respectively. The MST of the 20 middle-aged patients (61 to 70 y) in classes 5 and 6 was 8.8 months (95% CI, 6.7-12.0), and the 2-year overall survival rate was 0%. There was no difference between the MST of middle-aged patients and that of elderly patients (>70 y) ($P = 0.48$). The median PFS of elderly patients in classes 5 and 6 was 5.3 months (95% CI, 1.1-9.4), and that of younger patients was 5.8 months (95% CI, 3.2-7.2; $P = 0.74$). The median PFS of middle-aged patients in classes 5 and 6 was 3.6 months (95% CI, 1.7-7.2), and there was no difference between that of the middle-aged patients and that of elderly patients ($P = 0.70$). Among patients in classes 5 and 6, there was no difference between the extension of surgery and total radiation dose between elderly and younger patients ($P = 0.36$ and 0.69). However, younger patients received anticancer agents more frequently than elderly patients ($P = 0.03$).

We carried out a multivariate analysis including RPA class (3 to 4 vs. 5 to 6), age (60 to 70 y vs. >70 y), total radiation dose, and treatment with anticancer agents (yes vs. no). Only RPA class was an independent prognostic factor for overall survival rate ($P = 0.009$), whereas age ($P = 0.85$), total radiation dose ($P$=0.052), and treatment with anticancer agents ($P = 0.32$) were not. We also carried out a multivariate analysis including these prognostic factors for PFS, but found no independent prognostic factors (RPA classes, $P$=0.67; age, $P = 0.25$; total radiation dose, $P = 0.11$; anticancer agents, $P = 0.13$).

Sixty-five patients (75%) showed disease progression during the follow-up period: 54 patients (83%) had local progression, 8 (12%) had both local and distant progression, and 3 (5%) had only distant progression. Salvage therapies, including chemotherapy or best supportive care (BSC), were performed according to each physician's policy.

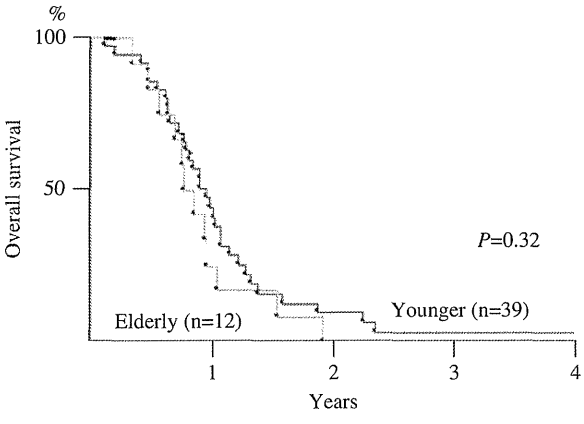


**FIGURE 2.** Overall survival rates of the 12 elderly patients and 39 younger patients in recursive partitioning analysis classes 5 and 6.

## DISCUSSION

Data from the cancer registry in Switzerland demonstrated that 27% of patients with GBM aged 55 to 64 years, 44% of the patients aged 65 to 74 years, 75% of the patients aged >75 years received BSC alone without effective treatment.[12] The Surveillance, Epidemiology, and End Results-Medicare linked data demonstrated that increased age was associated with noneffective treatment and hence, worse prognosis.[13] Although these large population-based cancer registries demonstrate that an increase in age is associated with less intensive treatment, there is little information to define the standard of care for elderly patients with GBM.[9] In particular, there are no prospective randomized studies that evaluate the effectiveness and safety of combination therapy, including postoperative radiotherapy and chemotherapy, for patients aged $\geq$70 years.

Adjuvant systemic chemotherapy after surgery prolongs survival in patients with GBM.[6,14] A meta-analysis of 12 randomized controlled trials, including more than 3000 patients, compared postoperative radiotherapy alone with postoperative radiotherapy and chemotherapy, and demonstrated that the addition of chemotherapy decreased the risk of death by 15% (hazard ratio, 0.85; 95% CI, 0.78-0.91).[5] The European Organisation for Research and Treatment of Cancer/the National Cancer Institute of Canada Intergroup conducted a randomized clinical trial for patients aged 18 to 70 years with newly diagnosed GBM, and reported that the 2-year survival rate was 26% for the temozolomide and radiotherapy group compared with only 10% for the radiation only group.[4] This trial demonstrated the clinical benefit of temozolomide in patients with GBM, but subset analysis showed that the benefit was not statistically significant in patients undergoing diagnostic biopsy only or those with poor PS.[4,15] The 5-year analysis of this trial demonstrated that patients aged 60 to 70 years benefited from combined therapy (hazard ratio for overall survival, 0.7; range, 0.5 to 0.97).[16] Grant et al[17] retrospectively analyzed 148 patients with malignant gliomas or recurrent astrocytomas who received nitrosourea-based chemotherapy, and reported that age was strongly predictive of the likelihood of responding to chemotherapy, time to progression, and survival, and patients aged $\geq$60 years had a lower chance of benefiting from chemotherapy. On the other hand, Combs et al[18] conducted a retrospective study including 43 patients aged $\geq$65 years (range, 65 to 76 y) who received postoperative radiotherapy and chemotherapy, and reported that radiochemotherapy was safe and effective in this population. Prospective studies are required to clarify the benefit of chemotherapy for elderly patients with GBM.

The Medical Research Council conducted a randomized trial comparing 45 Gy in 20 fractions over 4 weeks with 60 Gy

in 30 fractions over 6 weeks for patients aged 18 to 70 years with grade 3 or 4 malignant glioma, and reported that the 60 Gy course produced a modest lengthening of PFS and overall survival.[19] Keime-Guibert et al[6] conducted a randomized trial that compared BSC only with radiotherapy (50 Gy in daily fractions of 1.8 Gy over 5 wk) in patients with GBM aged ≥ 70 years. Radiotherapy improved MST from 16.9 weeks to 29.1 weeks, and the hazard ratio for death in the radiotherapy group was 0.47 (95% CI, 0.29-0.76; $P$=0.002). Roa et al[20] conducted a prospective randomized trial that compared standard radiation therapy (60 Gy in 30 fractions over 6 wk) and a short course of radiotherapy (40 Gy in 15 fractions over 3 wk) in patients aged ≥ 60 years. There was no difference in survival between the 2 groups, and short-course radiotherapy led to a decrease in posttreatment corticosteroid dosage. Although radiotherapy has been effective and safe in elderly patients, it is unclear whether a total dose of 60 Gy represents the standard dose for these patients.[6,19] A limitation of this study is that the median radiation dose for younger patients was <60 Gy. However, there was no statistical difference between the radiation dose in elderly, middle-aged, and younger patients and multivariate analysis showed that total radiation dose was not associated with overall survival. This study is also limited due to the lack of evaluation of MGMT methylation status, quality of life, and long-term neurotoxicity.

Although age is an important factor for predicting survival of patients with GBM, there is a room for discussion as to whether less intensive therapy is suitable for the majority of elderly patients.[8,9] RPA proposed by the Radiation Therapy Oncology Group has been a useful tool for predicting the prognosis of patients with malignant glioma.[21] RPA includes age, histology, mental status, PS, and the extent of surgical excision. The median survival time was 4.7 to 58.6 months for the 12 subgroups resulting from this analysis. This study showed that the MST of the 35 patients in classes 3 and 4 was superior to that of 51 patients in classes 5 and 6 ($P < 0.001$). However, a limitation of the RPA classification is that it requires the extent of surgical excision, which cannot be assessed before treatment, and this prognostic system is not used for the initial pretreatment decision-making process. The Organisation for Research and Treatment of Cancer/the National Cancer Institute of Canada Clinical Trials Group developed nomograms for predicting survival in patients with GBM. The nomograms include methylated MGMT promoter status, age, PS, extension of surgical excision, and Mini-Mental State Examination score.[7] Patients with GBM with a methylated MGMT promoter benefit from temozolomide and have a good prognosis.[22] This additional molecular information may be useful for estimating the treatment outcome of patients with GBM, and other molecular characteristics and predictive markers may facilitate individually tailored therapy.

In this study, the majority of elderly patients were grouped in RPA classes 5 and 6. However, an analysis adjusting for RPA classification showed that the treatment outcome of patients aged >70 years in classes 5 and 6 and that of younger patients in classes 5 and 6 was likely to be equal. Treatment decision-making should be performed in the same manner in elderly patients as for younger patients, and definitive treatment should not be withheld based on age alone.

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Clinical Investigation

# Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: A Survey in Japan

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## Summary

To determine the current patterns of practice in Japan and to investigate factors that may make clinicians reluctant to use single-fraction radiotherapy, members of the Japanese Radiation Oncology Study Group completed an Internet-based survey and described the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful bone metastases. Single-fraction radiotherapy

**Purpose:** To determine the current patterns of practice in Japan and to investigate factors that may make clinicians reluctant to use single-fraction radiotherapy (SF-RT).

**Methods and Materials:** Members of the Japanese Radiation Oncology Study Group (JROSG) completed an Internet-based survey and described the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful bone metastasis (BM). Case 1 described a patient with an uncomplicated painful BM in a non-weight-bearing site from non-small-cell lung cancer. Case 2 investigated whether management for a case of uncomplicated spinal BM would be different from that in Case 1. Case 3 was identical with Case 2 except for the presence of neuropathic pain. Case 4 investigated the prescription for an uncomplicated painful BM secondary to oligometastatic breast cancer. Radiation oncologists who recommended multifraction radiotherapy (MF-RT) for Case 2 were asked to explain why they considered MF-RT superior to SF-RT.

**Results:** A total of 52 radiation oncologists from 50 institutions (36% of JROSG institutions) responded. In all four cases, the most commonly prescribed regimen was 30 Gy in 10 fractions. SF-RT was recommended by 13% of respondents for Case 1, 6% for Case 2, 0% for Case 3, and 2% for Case 4. For Case 4, 29% of respondents prescribed a high-dose MF-RT regimen (*e.g.*, 50 Gy in 25 fractions). The following factors were most often cited as reasons for preferring MF-RT: "time until first increase in pain" (85%), "incidence of spinal cord compression" (50%), and "incidence of pathologic fractures" (29%).

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was recommended by 0%–13% of respondents. "Time until first increase in pain" was most often cited as a reason for preferring multifraction radiotherapy.

**Conclusions:** Japanese radiation oncologists prefer a schedule of 30 Gy in 10 fractions and are less likely to recommend SF-RT. Most Japanese radiation oncologists regard MF-RT as superior to SF-RT, based primarily on the time until first increase in pain. 

**Keywords:** Radiotherapy, Bone metastasis, Japan, Single fraction, Oligometastasis

## Introduction

Radiotherapy (RT) provides successful palliation of painful bone metastasis (BM), with 50% to 80% overall response rates (1).

Numerous prospective randomized controlled trials have demonstrated the equivalence of multifraction (MF) and single-fraction (SF) RT for the palliation of painful BM (2–10). Owing to patient convenience, resource advantages, and cost effectiveness, clinical practice guidelines have recommended that SF-RT should be in widespread use (11–13).

However, according to previous surveys, SF regimens have remained underused globally (14–18). In addition, regional and national differences in prescribing patterns for painful BM have been described (15, 16). To our knowledge, no previous surveys have focused on the prescribing patterns in Japan. This study investigated the current patterns of practice in Japan and factors that may make clinicians reluctant to use SF-RT.

## Methods and Materials

Members of the Japanese Radiation Oncology Study Group (JROSG) completed an Internet-based survey. All JROSG members were radiation oncologists (ROs). The respondents indicated their name, their institutions, and the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful BM (Table 1). Case 1 described a patient with an uncomplicated painful BM in a non-weight-bearing site from non-small-cell lung cancer. Case 2 investigated whether management for a case of uncomplicated spinal BM would be different from that in Case 1. Case 3 was identical with Case 2 except for the presence of neuropathic pain. Case 4 investigated the prescription for an uncomplicated painful BM secondary to oligometastatic breast cancer. ROs who recommended MF-RT for Case 2 were asked to explain why they considered MF-RT superior to SF-RT.

## Results

A total of 52 ROs from 50 institutions (36% of JROSG institutions) responded. Of those, 32 respondents (61%) work at university hospitals or cancer centers, 15 (29%) at public hospitals, and 5 (10%) at private hospitals.

A total of 14 different dose schedules were cited, ranging from 8 Gy in one fraction to 60 Gy in 30 fractions. The recommended treatments for Cases 1 through 4 are summarized in Table 2. In all four cases, the most commonly prescribed regimen was 30 Gy in 10 fractions. None of the respondents recommended SF-RT for neuropathic pain (Case 3). For oligometastasis (Case 4), 29% of respondents prescribed a high-dose MF-RT regimen (*e.g.*, 50 Gy in 25 fractions).

Table 3 summarizes why these respondents regarded MF-RT as superior to SF-RT for Case 2. The following factors were most often cited as reasons for preferring MF-RT: "time until first increase in pain" (85%), "incidence of spinal cord compression" (50%), and "incidence of pathologic fractures" (29%).

## Discussion

Our results show that SF-RT was used by the minority of Japanese ROs, a finding consistent with previous reports from other regions or nations. Japanese ROs preferred a schedule of 30 Gy in 10 fractions.

In our study, the first case described uncomplicated BM in a non-weight-bearing site, and the second case described uncomplicated spinal BM. Both cases fit the eligibility criteria for most previously completed randomized trials (2–10). Only 13% and 6% of our respondents recommended SF-RT for Case 1 and Case 2, respectively.

As many as 85% of the respondents who recommended MF-RT for Case 2 regarded MF-RT as superior to SF-RT based on the time until first increase in pain. The randomized trials do not support the superiority of MF-RT to prevent recurrence, even with

**Table 1** Hypothetical cases

| | |
|---|---|
| Case 1 | A 65-year-old man was diagnosed with squamous cell lung cancer 1 year earlier and was treated by radical surgery. He now has pain in the right shoulder. Radiologic examinations detected osteolytic bone metastasis at the right scapula and multiple lung metastases. His ECOG performance status is 1. |
| Case 2 | A 65-year-old man was diagnosed with squamous cell lung cancer 1 year earlier and was treated by radical surgery. He now has back pain. Radiologic examinations detected osteolytic bone metastasis at L1 and multiple lung metastases. There is no evidence of vertebral collapse or of spinal or thecal sac compression. His ECOG performance status is 1. |
| Case 3 | Same setting as in Case 2, with the addition of paresthesias in a distribution consistent with the L1 dermatome, compatible with neuropathic pain. |
| Case 4 | A 64-year-old woman was diagnosed with breast cancer 7 years earlier and was treated by radical surgery, followed by tamoxifen. She now has pain in the right shoulder. Radiologic examinations detected solitary osteolytic metastasis at the right scapula. Her ECOG performance status is 1. |

*Abbreviation:* ECOG = Eastern Cooperative Oncology Group.

**Table 2** Recommended dose schedules for cases of painful bone metastases (BM) ($n$ = 52)

| Case | Single fraction (8 Gy), $n$ (%) | Fractionated low dose (20 Gy in 5 fractions), $n$ (%) | 30 Gy in 10 fractions, $n$ (%) | Fractionated intermediate dose other than 30 Gy in 10 fractions, n (%)* | Fractionated high dose, $n$ (%)† | External beam irradiation not recommended, $n$ (%) |
|---|---|---|---|---|---|---|
| Case 1: Uncomplicated peripheral BM | 7 (13) | 5 (10) | 34 (65) | 5 (10) | 0 (0) | 1 (2) |
| Case 2: Uncomplicated spinal BM | 3 (6) | 2 (4) | 40 (77) | 6 (12) | 0 (0) | 1 (2) |
| Case 3: Neuropathic pain | 0 (0) | 3 (6) | 41 (79) | 8 (15) | 0 (0) | 0 (0) |
| Case 4: Ologometastasis | 1 (2) | 0 (0) | 26 (50) | 10 (19) | 15 (29) | 0 (0) |

* Eight different dose schedules (25 Gy in five fractions, 36 Gy in 12 fractions, 37.5 Gy in 15 fractions, 39 Gy in 13 fractions, 40 Gy in 20 fractions, 40 Gy in 16 fractions, 45 Gy in 15 fractions, and 46 Gy in 23 fractions) are included.

† Three different dose schedules (50 Gy in 25 fractions, 50 Gy in 20 fractions, and 60 Gy in 30 fractions) are included.

extended follow-up (2, 3). Higher rates of reirradiation for SF patients have been reported despite equivalent response and progression rates between SF-RT and MF-RT. This is interpreted as reflecting a lower threshold for both clinicians and patients after lower doses.

Half of our respondents who recommended MF-RT for Case 2 were concerned about the high incidence of spinal cord compression subsequent to SF-RT. Three randomized trials have reported spinal cord compression rates with uncomplicated spinal metastases, but none of the trials have shown a statistically significant difference between SF-RT and MF-RT (2, 3, 7).

Another concern about SF-RT is the risk of pathologic fracture. Twenty-nine percent of our respondents who recommended MF-RT for Case 2 were concerned about the high incidence of pathologic fracture subsequent to SF-RT. Recalcification of osteolytic bone lesions seems to be dose dependent (6). However, the contribution of recalcification to prevent fracture remains unclear. In the Dutch trials, there was a significantly higher risk of pathologic fracture in the SF arm than in the multifraction arm (24 Gy in six fractions), 4% vs. 2% ($p$ = 0.05) (2). In the randomized trials performed in Scandinavia, however, there was a significantly higher risk in the multifraction arm (30 Gy in 10 fractions) than in the SF arm, 11% vs. 4% (5). In other randomized trials, there has not been any significant difference in the rate of pathologic fracture between SF-RT and MF-RT (3, 4, 7–9, 19).

Case 3 was identical with Case 2 except for the presence of neuropathic pain. None of our respondents recommended SF-RT. Neuropathic pain due to BM has been the subject of one randomized trial comparing an SF arm with a multifraction arm (20 Gy in five fractions). Treatment in the SF arm was not shown to be as effective as that in the multifraction arm, nor was it statistically significantly worse (19). Our study suggests that Japanese ROs considered that greater doses were needed to relieve nerve impingement or to reduce the risk of spinal cord compression.

**Table 3** The basis on which respondents regarded multifraction radiotherapy superior to single-fraction therapy (48 respondents who recommended multifraction radiotherapy for Case 2)

| Factor | $n$ (%) |
|---|---|
| Response rates of pain relief | 7 (15) |
| Time until first increase in pain | 41 (85) |
| Survival duration | 1 (2) |
| Quality of life | 12 (25) |
| Pathologic fracture | 14 (29) |
| Spinal cord compression | 24 (50) |
| Acute side effects | 9 (19) |
| Late side effects | 7 (15) |

Our final case described an uncomplicated painful BM secondary to breast cancer in which oligometastasis developed after a long disease-free interval. A considerable number of our respondents recommended a high-dose MF-RT regimen (*e.g.*, 50 Gy in 25 fractions). A practice guideline for palliative radiotherapy of metastatic breast cancer from Germany also recommends a full-dose fractionated regimen (*e.g.*, 40–50 Gy in 20–25 fractions) for oligometastases (12).

Regional and national differences in prescribing patterns for painful BM have been previously described (15, 16). SF regimens have been most frequently reported by ROs in the United Kingdom and least frequently by ROs in the United States (15, 20). Our results suggest that Japanese ROs prescribe SF-RT as often as do ROs in the United States. The reasons proposed for regional and national differences have included the influence of reimbursement and participation in related randomized controlled trials (17, 18). Reimbursement depends on the number of treatments in Japan, and most Japanese ROs have never participated in related randomized controlled trials. In addition, where ROs train has a variable effect on the patterns of treatment. Those trained in the United States were as much as 80% less likely to use SF-RT than were those trained in Canada or Europe (15). We think that Japanese ROs prefer to learn from United States resources, resulting in similar patterns of practice as those in the United States. These factors may result in the underuse of SF-RT by Japanese ROs.

Our study has certain limitations. Because of the relatively low response rate (36%) and the small absolute sample size ($n$ = 52), our results might not accurately represent the practice of ROs in Japan. Those willing to participate might have been more knowledgeable. Furthermore, recommendations for hypothetical cases might not reflect clinical management.

## Conclusions

Japanese ROs prefer a schedule of 30 Gy in 10 fractions and are less likely to recommend SF-RT. Most Japanese ROs regard MF-RT as superior to SF-RT, based primarily on the time until first increase in pain.

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Clinical Investigation: Breast Cancer

# Identifying Patients Who Are Unsuitable for Accelerated Partial Breast Irradiation Using Three-Dimensional External Beam Conformal Techniques

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## Summary

Fifty consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) accelerated partial breast irradiation (APBI) techniques. Dose–volume histogram (DVH) constraints were satisfied in 20% of patients with a long cranio-caudal surgical clip distance (CCD; ≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Patients with long CCDs might be unsuitable for 3D-CRT APBI due to nonoptimal DVH constraints.

**Purpose:** Several recent studies reported that severe late toxicities including soft-tissue fibrosis and fat necrosis are present in patients treated with accelerated partial breast irradiation (APBI) and that these toxicities are associated with the large volume of tissue targeted by high-dose irradiation. The present study was performed to clarify which patients are unsuitable for APBI to avoid late severe toxicities.
**Methods and Materials:** Study subjects comprised 50 consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery, and in whom five or six surgical clips were placed during surgery. All patients were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) APBI techniques according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. The beam arrangements included mainly noncoplanar four- or five-field beams using 6-MV photons alone.
**Results:** Dose–volume histogram (DVH) constraints for normal tissues according to the NSABP/RTOG protocol were satisfied in 39 patients (78%). Multivariate analysis revealed that only long craniocaudal clip distance (CCD) was correlated with nonoptimal DVH constraints ($p = 0.02$), but that pathological T stage, anteroposterior clip distance (APD), site of ipsilateral breast (IB) (right/left), location of the tumor (medial/lateral), and IB reference volume were not. DVH constraints were satisfied in 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Median IB reference volume receiving ≥50% of the prescribed dose (IB-$V_{50}$) of all patients was 49.0% (range, 31.4–68.6). Multivariate analysis revealed that only a long CCD was correlated with large IB-$V_{50}$ ($p < 0.0001$), but other factors were not.
**Conclusion:** Patients with long CCDs (≥5.5 cm) might be unsuitable for 3D-CRT APBI because of nonoptimal DVH constraints and large IB-$V_{50}$. © 2012 Elsevier Inc.

**Keywords:** Partial breast irradiation, Breast cancer, Radiotherapy, 3D-conformal radiotherapy, Toxicity

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## Introduction

Breast-conserving therapy including partial resection and postoperative whole breast irradiation has constituted standard care for patients with early breast cancer (1). Some Phase III trials of postoperative radiotherapy and systematic reviews have revealed that omission of postoperative radiotherapy increases recurrence in breasts by threefold, and increases absolute breast cancer mortality by more than 5% (1, 2). Several reasons, including the long-term radiation schedule, level of surgeon involvement in the radiation decision, patient refusal, and comorbidity, lead to omission of postoperative radiotherapy. In fact, approximately 25% of patients who underwent conservative surgery did not receive postoperative radiotherapy in the United States (1991–2002) (3).

Approximately 85% of breast recurrences after breast conservative therapy develop in the vicinity of the tumor bed; several percent appear "elsewhere" in the breast, and the absolute number of such failures is very low (4). In the past decade, prospective clinical trials and retrospective studies evaluated the efficacy and safety of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size. These studies reported good treatment outcome and minimal late toxicities after a short follow-up duration (4–6). However, two recent studies reported that the large volume of irradiated breast tissue was correlated with higher incidences of late severe toxicities including soft-tissue fibrosis and fat necrosis of the breast, which were clearly associated with marked cosmetic compromise (7, 8). Appropriate eligibility criteria and treatment schedules for APBI should be established to avoid late severe toxicities. The present study aimed to identify patients who are unsuitable for APBI because of the potential risk of late toxicities including soft-tissue fibrosis and fat necrosis after APBI using three-dimensional conformal radiotherapy (3D-CRT).

## Methods and Materials

### Patients

The study population consisted of 50 consecutive patients with unilateral breast cancer, at Union for International Cancer Control 7th Stage 0–II, who received breast-conserving therapy between April 2009 and September 2009. Median patient age was 49 years (range, 33–73). The right-to-left ratio of the ipsilateral breast (IB) was 25:25, and the medial-to-lateral ratio of the tumor location was 19:31. All patients underwent partial breast resection, and five or six surgical clips were placed at the borders of the surgical bed. Thirty-one patients had pathological T stage 1 (pT1), 7 patients had pT2, and 12 patients had pTis. Sentinel node biopsy and/or axillary node dissection revealed that 47 patients had pathological N stage 0 (pN0), and 2 patients had pN1. pN stage was not evaluated for 1 patient.

### Radiation treatment planning

All patients were placed in the supine position and underwent computed tomography (CT) as part of the standard planning for whole breast irradiation. CT scanning was performed using a 2-mm thick-slice and a slice step of 2 mm; slices extended to completely cover the bilateral whole breast, lung, heart, thyroid, and a 5-cm margin in the cranial and caudal directions. No respiratory control was used. The following structures were contoured for the planning of 3D-CRT: surgical clips, clinical target volume (CTV), planning target volume (PTV), ipsilateral whole breast (IB) reference, IB reference excluding PTV (IB-PTV), contralateral breast, heart, bilateral lungs, and thyroid. To keep the probability of comparison consistent with outcomes of other studies, the contouring of IB reference was made up using an automated contouring method applied by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-39) and Radiation Therapy Oncology Group (RTOG 0413) protocol (9). CTV was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoralis muscles, chest wall, lung, heart, pericardial fat, and 5 mm beneath the skin (9). PTV was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. PTV_EVAL, the volume for dose–volume histogram (DVH) analysis, was defined as the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung, heart, and pericardial fat.

All 50 patients were replanned using 3D-CRT planning system software (Pinnacle$^3$ version 8.0m, Pinnacle Treatment System; Philips, Milpitas, CA). To correctly evaluate heterogeneous tissue density, the convolution algorithm was used. The NSABP B-39/RTOG 0413 protocol dose limitation was used as a guideline for specified normal tissue constraints (9). Beam arrangements included noncoplanar mainly four- or five-field beams using 6-MV photons referring to the method reported by Vicini *et al.* (10). No electron beam was used. The exertion of simulation planning was for minimizing doses to organs at risk, and improving a homogeneous dose to the target volume. Beam weights, beam angle, and wedge angles were manually optimized, such that the targeted goal was to cover $\geq$90% of the PTV_EVAL by a dose $\geq$90% of the prescribed dose (9). The DVH constraints adopted for plan optimization are shown in Table 1.

A total dose of 30 Gy in five fractions was prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (isocenter) (11). The isocenter was placed in the center of the PTV. This treatment schedule was proposed by the Department of Radiation Oncology at New York University using the prone position and parallel-opposed minitangents external beam therapy (12). The New York University study demonstrated that this abbreviated regimen was well tolerated, with only mild acute adverse events and excellent or good cosmetic outcome. However, given the typical Japanese woman's breast size and shape, we had patients assume a supine position and used a noncoplanar three-, four-, five-, and six-beam technique.

### Data analysis

IB volume, target volumes, and distance of surgical clips were measured by CT images on the radiation treatment planning (RTP) system. The craniocaudal surgical clip distance (CCD) was defined as the longitudinal distance along the body axis between head-side clip and foot-side clip, and the anteroposterior surgical clip distance (APD) was defined as the vertical distance between anterior-side clip and posterior-side clip. The IB reference volume receiving 50% of the prescribed dose (IB-$V_{50}$) was calculated. The homogeneity index (HI) was defined as the ratio of maximum dose

**Table 1** DVH constraints for planning

| | | | |
|---|---|---|---|
| IB reference | ≤60% | ≥50% of the prescribed dose | IB-V50 ≤60% |
| | ≤35% | ≥100% of the prescribed dose | IB-V100 ≤35% |
| Contralateral breast | Any point | ≤3% of the prescribed dose | 0.9 Gy |
| Ipsilateral lung | ≤15% | ≥30% of the prescribed dose | V30 ≤15% |
| Contralateral lung | ≤15% | ≥5% of the prescribed dose | V5 ≤15% |
| Heart | | | |
| Right-sided lesions | ≤5% | ≥5% of the prescribed dose | V5 ≤5% |
| Left-sided lesions | ≤40% | ≥5% of the prescribed dose | V5 ≤40% |
| Thyroid | Any point | ≤3% of the prescribed dose | 0.9 Gy |

*Abbreviations:* DVH = dose–volume histogram; IB = ipsilateral breast.

of PTV_EVAL to minimum dose of PTV_EVAL. The conformity index (CI) was defined as the ratio of volume that was covered by the minimal dose of PTV_EVAL to the volume of PTV. The associations between categorical variables (*e.g.*, site of IB) and patient and tumor characteristics at baseline were analyzed using Fisher's two-tailed exact test. Statistically significant differences between two sample means and medians for continuous variables (*e.g.*, IB reference volume) were analyzed using the Student's unpaired *t*-test. A $p$ value of less than 0.05 was considered statistically significant. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards model. Statistical analyses were performed with JMP software, version 5.1 (SAS Institute, Cary, NC).

## Results

### Outcome of 3D-CRT planning

Median IB reference volume of all patients was 824 $cm^3$ (range, 425–1868) (Table 2). Median right IB reference volume was 794 $cm^3$ (range, 463–1556) and the left IB reference volume was 849 $cm^3$ (range, 425–1868), respectively ($p = 0.63$). Median CCD and APD for all patients were 4.5 cm (range, 2.0–9.5) and 4.2 cm (range, 0.8–7.6), respectively.

Median CTV for all patients was 56.3 $cm^3$ (range, 11.3–83.6), and median PTV for all patients was 246.9 $cm^3$ (range, 113.4–370.9) (Table 3). The median ratio between IB-PTV and IB reference volume was 74.9% (range, 54.0–86.9). The number of external beams ranged from three to six; the four-beam technique was mainly used for patients with the right breast region, and the five-beam technique was mainly used for patients with the left breast region. The median value of mean dose of PTV_EVAL was 30.2 Gy (range, 29.5–30.8). The median value of HI for all patients was 1.24 (range, 1.14–1.39), and the median value of CI for all patients was 1.38 (range, 1.01–2.40).

### Unsuitable patients for the NSABP B-39/RTOG 0413 protocol

DVH constraints for organs at risk according to the NSABP B-39/RTOG 0413 protocol were satisfied in 39 patients (78%). Seven patients showed nonoptimal DVH for the ipsilateral lung; 5 patients for the contralateral breast; 4 patients for IB-$V_{50}$; 2 patients for the heart; and 1 patient for the thyroid. Univariate logistic regression analysis revealed that long CCD and medial tumors were correlated with nonoptimal DVH constraints ($p < 0.0001$ and $p = 0.007$, respectively), but pathological T stage excluding pTis (T1a/T1b/T1c/T2), APD, site of IB (right/left), and IB reference volume were not ($p = 0.98$, $p = 0.54$, $p = 0.73$, and

**Table 2** Patients characteristics

| | | | | Univariate analysis |
|---|---|---|---|---|
| | All patients ($n = 50$) | Optimal DVH ($n = 39$) | Nonoptimal DVH ($n = 11$) | $p$ value |
| Pathological T stage | | | | |
| pTis/pT1/pT2 | 12/31/7 | 10/24/5 | 2/7/2 | 0.82 |
| pT1a/pT1b/pT1c/pT2* | 5/5/20/7 | 4/4/15/5 | 1/1/5/2 | 0.98 |
| Site of IB | | | | |
| Right/left | 25/25 | 20/19 | 5/6 | 0.73 |
| Location of tumor | | | | |
| Mediolateral | 19/31 | 11/28 | 8/3 | 0.007 |
| IB reference volume ($cm^3$) | | | | |
| Median (range) | 824 (425–1868) | 828 (425–1868) | 725 (528–1032) | 0.10 |
| CCD (cm) | | | | |
| Median (range) | 4.5 (2.0–9.5) | 3.5 (2.0–5.5) | 6.0 (4.5–9.5) | <0.0001 |
| APD (cm) | | | | |
| Median (range) | 4.2 (0.8–7.6) | 4.2 (0.8–7.6) | 4.6 (1.0–7.5) | 0.54 |

*Abbreviations:* APD = anteroposterior clip distance; CCD = craniocaudal clip distance; DVH = dose–volume histogram; IB = Ipsilateral breast.
* 1 patient was not classified according to subcategory of pathological T stage.

**Table 3** Dosimetric characteristics

| Dosimetric characteristics | Mean | Median | Range |
|---|---|---|---|
| CTV ($cm^3$) | 55.5 | 56.3 | 11.3–83.6 |
| PTV ($cm^3$) | 247.4 | 246.9 | 113.4–370.9 |
| IB–PTV/IB reference (%) | 74.3 | 74.9 | 54.0–86.9 |
| IB-$V_{100}$ (%) | 12.7 | 12.5 | 5.6–23.4 |
| IB-$V_{95}$ (%) | 24.7 | 24.6 | 14.6–44.8 |
| IB-$V_{50}$ (%) | 48.6 | 49.0 | 31.4–68.6 |
| Ipsilateral mean lung dose (Gy) | 4.1 | 4.2 | 1.2–7.6 |
| Ipsilateral lung-$V_{9\ Gy}$ (%) | 12.5 | 12.6 | 3.6–23.1 |
| Contralateral lung-$V_{1.5\ Gy}$ (%) | 0.3 | 0 | 0–10.1 |
| Heart-$V_{15\ Gy}$ (%) | 1.0 | 0 | 0–7.4 |
| Heart-$V_{6\ Gy}$ (%) | 2.7 | 0 | 0–17.1 |
| Thyroid-$V_{0.9\ Gy}$ (%) | 0.5 | 0 | 0–25.5 |
| Contralateral breast-$V_{0.9\ Gy}$ (%) | 0.1 | 0 | 0–3.6 |
| Mean dose of PTV_EVAL (Gy) | 30.2 | 30.2 | 29.5–30.8 |
| PTV_EVAL-$V_{27\ Gy}$ (%) | 99.4 | 99.7 | 96.2–100 |
| Homogeneity index | 1.23 | 1.24 | 1.14–1.39 |
| Conformity index | 1.45 | 1.38 | 1.01–2.40 |

*Abbreviations:* CTV = clinical target volume; IB = ipsilateral breast; PTV = planning target volume; PTV_EVAL = volume of PTV for evaluation.

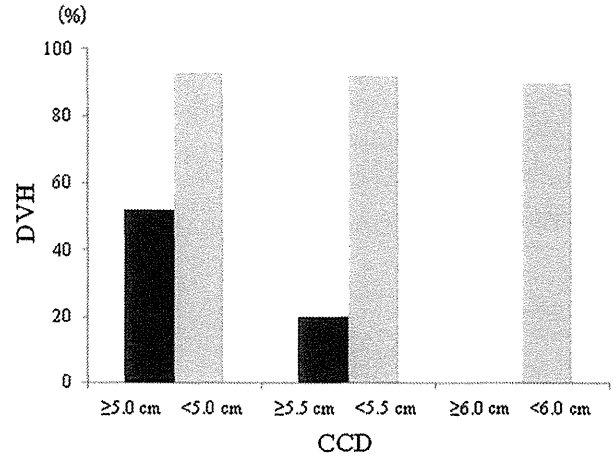


**Fig. 1.** Frequency of optimal dose–volume histogram (DVH) constraints according to craniocaudal surgical clip distance (CCD). Left column indicates that 52% of patients with long CCD (≥5 cm) satisfy DVH constraints, whereas the center and right columns show that only a few patients with long CCD of ≥5.5 cm and those with long CCD of ≥6.0 cm satisfy DVH constraints.

$p$ = 0.10, respectively). Multivariate analysis revealed that only a long CCD was correlated with nonoptimal DVH constraints ($p$ = 0.02). DVH constraints were satisfied in only 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD (<5.5 cm) ($p < 0.0001$) (Fig. 1). Of the 2 patients with a short CCD (<5.5 cm), 1 patient with a left upper-inner primary tumor and a 5-cm CCD, did not satisfy optimal DVH for the ipsilateral lung and contralateral breast, and the other patient, who had a right upper-outer primary tumor and a 4.5-cm CCD, did not satisfy optimal DVH for the heart and IB-$V_{50}$. DVH constraints were satisfied in 52% of patients with a long CCD (≥5.0 cm) and 93% of those with a short CCD (<5.0 cm) ($p$ = 0.0007). DVH constraints were satisfied in 0% of patients with a long CCD (≥6.0 cm) and in 90% of those with a short CCD (<6.0 cm) ($p <$ 0.0001). A long CCD was correlated with not only nonoptimal DVH constraints, but also a large ipsilateral mean lung dose (MLD) ($r$ = 0.48, $p$ = 0.0003).

## High-risk patients with large IB-$V_{50}$

Median IB-$V_{50}$ of all patients was 49.0% (range, 31.4–68.6). Univariate logistic regression analysis revealed that long CCD ($r$ = 0.72, $p < 0.0001$) and medial tumors ($p$ = 0.02) were correlated with large IB-$V_{50}$ (Fig. 2, 3). The site of the IB (right/left), pathological T stage (T1a/T1b/T1c/T2), IB reference volume, and APD were not correlated with a large IB-$V_{50}$ ($p$ = 0.47, $p$ = 0.92, $p$ = 0.13, $p$ = 0.10, respectively). Multivariate analysis revealed that only a long CCD was correlated with large IB-$V_{50}$ ($p< 0.0001$).

## Discussion

The Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology Breast Cancer Working Group and the American Society for Radiation Oncology Health Services Research Committee proposed the patient selection criteria for use of APBI based on available clinical evidence complemented by expert opinion (13, 14). The main eligibility criteria proposed by these task groups included patient age (≥60 years), pathological tumor size (≤3 cm), negative surgical margin, unicentric lesion, and pN0 (13, 14). These recommendations were mainly based on the probability of breast recurrence after APBI. To maintain the efficacy and safety of APBI, potential risk for late severe toxicities should be considered in addition to the probability of breast recurrence. The NSABP B-39/RTOG 0413 protocol requires that the ratio of lumpectomy cavity to IB volume must be <30% based on postoperative/prerandomization CT

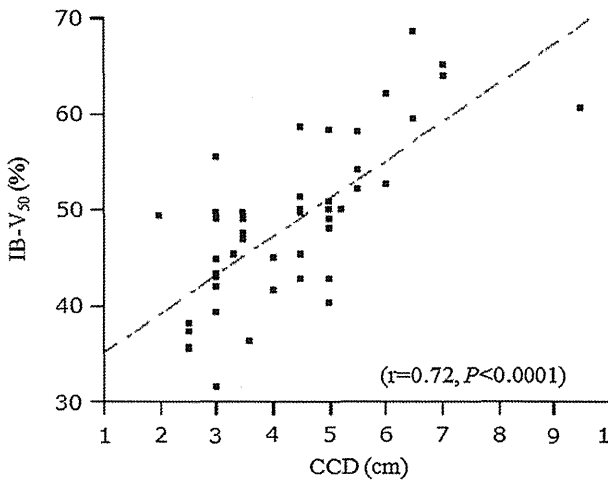


**Fig. 2.** Scatter plots for craniocaudal surgical clip distance (CCD) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-$V_{50}$). Long CCD was strongly correlated with large IB-$V_{50}$ ($r$ = 0.72). IB-$V_{50}$. The dotted line indicates the fitting line.

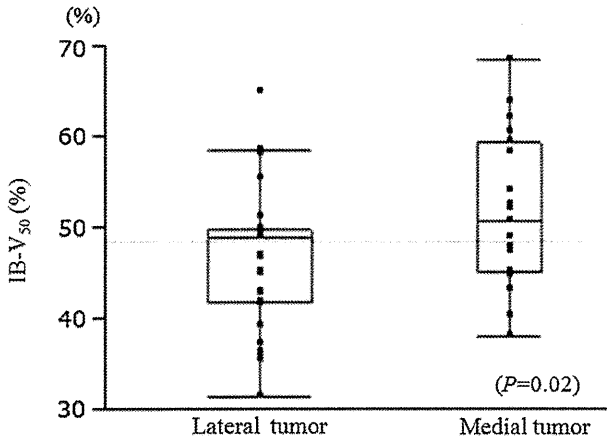


**Fig. 3.** Box plots for tumor location (lateromedial) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-$V_{50}$). The gray line indicates the median value of IB-$V_{50}$.

imaging (9). Unfortunately, the ratio of lumpectomy cavity to IB volume and that of PTV to IB reference volume are not calculated until the RTP system operation. Thus, eligibility criteria that require complex calculations serve as obstacles toward seamless execution of clinical trials. In the majority of contemporary APBI series, patients for whom the maximal tumor size is less than 3 cm have been eligible (5, 14). In our study, pathological T stage (pT1a/pT1b/pT1c/pT2), which was classified according to pathological maximum diameter of the invasive carcinoma component, was not associated with nonoptimal DVH constraints of the NSABP B-39/RTOG 0413 protocol. Some likely explanations for this are that the pathological T stage does not include the noninvasive carcinoma component and that it does not correlate with specimen shape (*e.g.*, fan shape, slender oval) or the direction of the long axis of the specimen. On the other hand, the distance of surgical clips is directly associated with the size of the resected specimen, and the CCD strongly correlated with the field length in the craniocaudal direction and the breast irradiated volume. Distances between surgical clips are easy to measure with digital chest X-rays rather than the RTP system operation and they serve as tools to help predict which patients are unsuitable for 3D-CRT APBI. However, APD was not closely correlated with either nonoptimal DVH constraints or large IB-$V_{50}$. We applied the noncoplanar beam technique using tangential beam with a 10–20° steeper gantry angle and couch angles of 0–30°. With this technique, the gantry angle arrangement allows one to reduce the field width in the anteroposterior direction and the irradiated volume, in which case APD does not correlate closely with field size, irradiated volume, or nonoptimal DVH constraints.

Hepel *et al.* reported that high-, intermediate-, and low-dose volumes (IB-$V_5$–IB-$V_{80}$) all correlated with incidence of breast fibrosis after 3D-CRT APBI (7). Improved target coverage with external beam techniques comes at the cost of a higher integral dose to the remaining normal breast. With the 3D-CRT APBI technique, the volume of high-dose region (*e.g.*, IB-$V_{100}$, IB-$V_{80}$) and that of low-dose region (*e.g.*, IB-$V_2$, IB-$V_{20}$) are closely related. Jagsi *et al.* reported on the unacceptable cosmesis that developed in 7 patients among 34 patients after APBI using Intensity-modulated radiotherapy, noting that IB-$V_{50}$ and IB-$V_{100}$ correlated with cosmetic outcome (8). They indicated that there seemed to be a possible threshold at 40%, in which the 5 of 10 patients (50%) with an IB-$V_{50}$ >40% experienced unacceptable cosmesis vs. the 2 of 22 (9%) below that threshold who experienced it ($p = 0.02$). On the other hand, Formenti *et al.* reported good cosmetic outcomes in most patients after performing APBI with the 3D-CRT technique in a prone position with 30 Gy in five fractions, noting that IB-$V_{50}$ ranged from 23 to 75%, and IB-$V_{100}$ ranged from 10 to 45% (12). In our simulation study, median IB-$V_{50}$ of patients with optimal DVH constraints was 46.9% (31.4–58.1), and that for patients with nonoptimal DVH constraints was 59.4% (49.9–68.6) ($p < 0.0001$, data not shown). The appropriate threshold of IB-$V_{50}$ and that of other parameters (*e.g.*, IB-$V_{20}$, IB-$V_{80}$, maximum dose) as predictive factors of late soft tissue toxicities has yet to be clarified. Further studies should be conducted to clarify predictive factors for late soft tissue toxicities.

Recht *et al.* reported that the risk of pneumonitis appeared to be related to the irradiated ipsilateral lung volume treated, and recommended that ipsilateral lung volume receiving 20 Gy or higher should be lower than 3%, and that receiving 5 Gy lower than 20% (6). They indicated that relatively low-dose lung irradiation might better help to determine the risk of pneumonitis after radiotherapy. In our study, a long CCD was correlated with large ipsilateral MLD ($r = 0.48$, $p = 0.0003$), and ipsilateral lung volume receiving 6 Gy or higher (≥20% of the prescribed dose) ($r = 0.63$, $p < 0.0001$).

A limitation of the present study was that we used simulation data rather than clinical outcomes. A prospective clinical trial should be conducted to evaluate the utility of these eligibility criteria and treatment outcomes. In addition, we could not verify the geometric couch and gantry angle limitations for the Varian linear accelerator in all patients. However, before the beginning of this study, we did verify the geometric couch and gantry angle limitations using a human-body phantom placed on a couch.

## Conclusions

Patients with a long CCD, especially 5.5 cm or longer, might be unsuitable for 3D-CRT APBI from nonoptimal DVH constraints and large IB-$V_{50}$. Pathological T stage, APD, site of IB (right/left), tumor location (medial/lateral), and IB reference volume could not predict whether patients were unsuitable for 3D-CRT APBI.

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ORIGINAL ARTICLE

# The relationship between the bladder volume and optimal treatment planning in definitive radiotherapy for localized prostate cancer

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**Abstract**

*Background.* There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. The aim of this study was to clarify the relationship between the bladder volume and optimal treatment planning in radiotherapy for localized prostate cancer. *Material and methods.* Two hundred and forty-three patients underwent definitive radiotherapy with helical tomotherapy for intermediate- and high-risk localized prostate cancer. The prescribed dose defined as 95% of the planning target volume (PTV) receiving ≧ 100% of the prescription dose was 76 Gy in 38 fractions. The clinical target volume (CTV) was defined as the prostate with a 5-mm margin and 2 cm of the proximal seminal vesicle. The PTV was defined as the CTV with a 5-mm margin. Treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for PTV and organs at risk (rectum wall, bladder wall, sigmoid colon and small intestine). If all dose constraints were satisfied, the plan was defined as an optimal plan (OP). *Results.* An OP was achieved with 203 patients (84%). Mean bladder volume (± 1 SD) was 266 ml (± 130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$). Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP. However, the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. *Conclusions.* Bladder volume is a significant factor affecting OP rates. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

The bladder is filled to various volumes during fractionated radiotherapy. Changing bladder volumes affects both bladder dose volumes and the position of adjacent organs (the prostate, seminal vesicles, small intestine and sigmoid colon) [1]. Furthermore, significant variations in bladder volume can affect planned three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) dose distributions. For all these reasons, bladder volumes must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity to the surrounding normal tissue.

There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. One possible advantage of maintaining a full bladder is that part of the bladder moves away from the target volume, thereby reducing bladder toxicity [2,3]. A full bladder also moves the small intestine and the sigmoid colon out of the irradiation field, reducing toxicity in these organs [1,4–7]. However, if we target larger bladder volumes on planning using computed tomography (CT) and during radiotherapy, such volumes tend to show marked variability [8–10]. On the other hand, excessively small bladder volumes make it difficult to meet planning dose constraints for the bladder and adjacent organs. For these reasons, the optimal bladder volume may be the minimum bladder volume that can satisfy dose constraints. Based on this reasoning, several institutions target a half-full bladder or a comfortably full bladder [8,9]. However, no previous

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reports have focused on the relationship between the bladder volume and optimal treatment planning.

We evaluated the relationship between the bladder volume on planning CT and the percentage satisfying the dose constraints as a reference what bladder volumes should be targeted.

## Material and methods

Between June 2007 and February 2009, 243 patients underwent definitive radiotherapy with helical tomotherapy using the Hi-Art System (Tomotherapy Inc.) for intermediate- and high-risk localized prostate cancer (cT1-4N0M0) according to D'Amico's classification at Edogawa Hospital (Tokyo, Japan) (Table I).

The patients were irradiated in a supine position, with a knee support. They were instructed to refrain from urinating for 60–90 minutes before the planning computed tomography (CT) scan and before daily irradiation. They were also encouraged to drink an unspecified volume of water to ensure a clear but tolerable urge to urinate before the planning CT scan and before daily irradiation. They were instructed to take laxatives before the planning CT scan, although no specific instructions were issued regarding bowel movements before daily irradiation.

Table I. Patient characteristics.

| | no. |
|---|---|
| cT stage (TNM 6th ed.) | |
| 1–2a | 101(42%) |
| 2b | 32 (13%) |
| 2c | 40 (16%) |
| 3a | 61 (25%) |
| 3b | 8 (33%) |
| 4 | 1 (0.4%) |
| Gleason score | |
| 2–6 | 41 (17%) |
| 7 | 102 (42%) |
| 8–10 | 100 (41%) |
| Pretreatment PSA | |
| 0–10 | 104 (43%) |
| 10–20 | 67 (28%) |
| >20 | 72 (30%) |
| D'Amico's risk group | |
| Intermediate | 71 (29%) |
| High | 172 (71%) |
| Neoadjuvant hormone therapy | |
| No | 81 (33%) |
| Yes | 162 (67%) |
| Mean age (range) | 70 (42–85) |
| Mean prostate volume (range) | 21 ml (6–178) |
| Mean PTV (range) | 112 ml (61–273) |
| Mean bladder volume (range) | 235 ml (45–653) |

cT stage, clinical tumor stage; PSA, prostate-specific antigen; PTV, planning target volume.

The clinical target volume (CTV) was defined as the prostate that was delineated by the fusion images of CT and magnetic resonance imaging (MRI) with a 5-mm margin and 2 cm of the proximal seminal vesicle. Exceptionally, the whole seminal vesicle was included in the CTV for cases of clinical T3b stage disease. The planning target volume (PTV) was defined as the CTV with a 5-mm margin. The prescribed dose defined as 95% of the PTV receiving ≧ 100% of the prescription dose (D95) was 76 Gy in 38 fractions. The treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for the PTV and organs at risk (OAR) (Table II). No specific protocols were used for the order of prioritization among the constraints. Cases in which all dose constraints were satisfied were defined as an optimal plan (OP).

We assessed the relationship between the bladder volumes on planning CT and the percentage of patients achieving an OP. Univariate logistic regression analysis was used to examine the predictive value of covariates including clinical T stage (T1–2a, T2b, T2c, T3a, T3b, and T4), Gleason score (2–6, 7, 8–10), pretreatment PSA (0–10, 10–20, and >20), D'Amico's risk group (intermediate or high), neoadjuvant hormone therapy (yes or no), age, PTV, and bladder volume. Those showing significant associations in univariate logistic regression analysis were further tested by multivariate logistic regression analysis.

We used GraphPad Prism version 5 (GraphPad Software Inc.) and SPSS version 17 (IBM) for statistical analysis. Differences were deemed significant when two-tailed p-values were less than 0.05.

## Results

Of the subjects, 203 patients (84%) met the definitions for an OP. Among these patients, the mean of

Table II. Dose constraints.

| Target/Organ | | Dose constraint |
|---|---|---|
| PTV | D95 | 100% (76 Gy) |
| | Maximum | <110% (83.6 Gy) |
| | Mean | <105% (79.8 Gy) |
| Rectum wall* | V40 | <65% |
| | V60 | <35% |
| | V70 | <25% |
| | V78 | <10% |
| Bladder wall | V40 | <60% |
| | V70 | <35% |
| Sigmoid colon | V65 | <0.5 ml |
| Small bowel | V60 | <0.5 ml |

*Rectum wall within 5 mm above and below the PTV, Vx<y% (or ml) means that no more than y% (or ml) of the volume of the organ receive a dose>x Gy.
PTV, planning target volume.

the mean PTV dose and the maximum dose were 77.4 Gy (range 76.7–79.2 Gy) and 80.7 Gy (range 78.2–83.3 Gy), respectively.

The mean bladder volume (±1 standard deviation; SD) was 266 ml (±130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$, by unpaired t-test).

Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP (Table III). Figure 1 shows the percentage of patients with an OP according to bladder volumes, indicating that the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. On univariate analysis, higher clinical T stage, younger age, treatment with neoadjuvant hormone therapy, and larger bladder volume were predictors for achieving an OP (Table IV). On multivariate analysis, larger bladder volumes ($p = 0.04$), younger age ($p = 0.01$), and higher clinical T stage ($p = 0.03$) were independent predictors for achieving an OP.

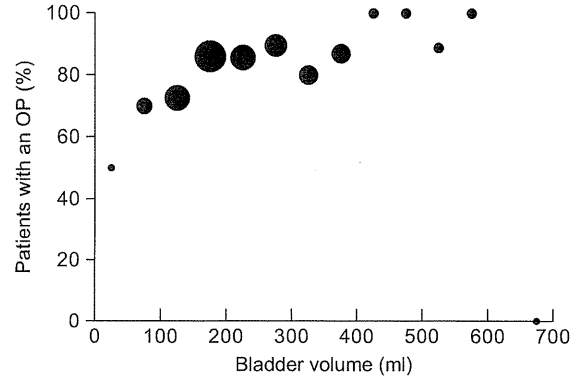


Figure 1. The percentage of patients with an OP according to bladder volume. Patients were divided into subgroups according to their bladder volume by 50 ml. The percentage of patients with an OP was defined by dividing the number of patients with an OP by the number of patients in each subgroup. The size of each dot represents the number in each subgroup.
n, number of patients; OP, optimal plan.

## Discussion

We found that bladder volumes among patients with an OP were significantly larger than among patients without an OP. This indicates that bladder volume is a significant factor affecting whether OP is achieved. However, we also found that bladder volumes larger than 150 ml did not contribute to OP rates. We could meet the dose constraints on the bladder even with considerably small bladder volumes. However, small bladders moved the small intestine and the sigmoid colon inside the irradiation field, which made it impossible to meet the dose constraint on those organs. This may explain why we found the plateau effect at bladder volumes above 150 ml.

Table III. Logistic regression analysis between bladder volume and the percentage of patients with an optimal plan.

| Bladder volume | Number of patients | Patients with an OP | p | Odds ratio (95% CI) |
|---|---|---|---|---|
| <100 ml | 21 | 15 (71%) | 0.069 | 0.34 (0.11–1.09) |
| 100–149 ml | 34 | 24 (71%) | 0.028 | 0.33 (0.12–0.89) |
| 150–199 ml | 43 | 37 (86%) | 0.761 | 0.85 (0.29–2.50) |
| 200–249 ml | 35 | 30 (86%) | 0.739 | 0.82 (0.26–2.61) |
| 250–299 ml | 27 | 24 (89%) | 0.896 | 1.10 (0.28–4.31) |
| >300 ml | 83 | 73 (88%) | | 1 |

OP, optimal plan.

Our logistic regression analysis did not show a statistically significant difference in the percentage of patients with an OP in the subgroup with the smallest bladder volume. We think the relatively small number of subjects in the subgroup caused the false negative.

Our results suggested that younger age and higher clinical T stage were also independent predictors for achieving an OP. It is difficult to interpret why age affects OP achievement. There may be some anatomic features among younger patients that make it easier to achieve an OP. It is also difficult to interpret why clinical T stage affects OP achievements although we used the same definition of CTV for all clinical T stages except for the few cases of clinical T3b.

The existence of a clear dose effect for genitourinary (GU) toxicity is well-known in cases in which the entire bladder is irradiated [11]. In the case of prostate irradiation, the cranial portion of the bladder is generally spared, whereas the bladder neck and urethra are irradiated at levels close to the prescribed dose. Most of the published results fails to support a correlation between bladder dose volume histograms (DVH) and GU toxicity [12,13], whereas several studies indicate that the absolute volume of the bladder receiving >78 Gy to 80 Gy is most predictive of late GU toxicity [14,15]. Regarding GU toxicity, a half-full bladder and an empty bladder appear to be acceptable bladder volumes [16]. However, an excessively small bladder volume may move the small intestine and sigmoid colon within the high dose irradiated field [1,4–6]. Therefore, we also imposed dose constraints on the small intestine and sigmoid colon.

Table IV. Univariate logistic regression analysis of association with achieving an optimal plan.

| | Patients with an OP (n, 203) | Patients without an OP (n, 40) | p |
|---|---|---|---|
| cT stage (TNM 6th ed.) | | | 0.03 |
| 1–2a | 77 (38%) | 24 (60%) | |
| 2b | 26 (13%) | 6 (15%) | |
| 2c | 35 (17%) | 5 (13%) | |
| 3a | 57 (28%) | 4 (10%) | |
| 3b | 7 (3%) | 1 (3%) | |
| 4 | 1 (0.5%) | 0 (0%) | |
| Gleason score | | | NS |
| 2–6 | 39 (19%) | 2 (5%) | |
| 7 | 83 (41%) | 19 (48%) | |
| 8–10 | 81 (40%) | 19 (48%) | |
| Pretreatment PSA | | | NS |
| 0–10 | 85 (42%) | 19 (48%) | |
| 10–20 | 58 (28%) | 9 (23%) | |
| >20 | 60 (30%) | 12 (30%) | |
| D'Amico's risk group | | | NS |
| Intermediate | 60 (30%) | 11 (28%) | |
| High | 143 (70%) | 29 (73%) | |
| Neoadjuvant hormone therapy | | | 0.10 |
| No | 63 (31%) | 18 (45%) | |
| Yes | 140 (69%) | 22 (55%) | |
| Mean age (range) | 70 (42–85) | 73 (59–83) | 0.01 |
| Mean prostate volume (range) | 21 ml (6–178) | 22 ml (12–103) | NS |
| Mean PTV (range) | 109 ml (61–225) | 115 ml (77–273) | NS |
| Mean bladder volume (range) | 266 ml (45–594) | 214 ml (48–653) | 0.04 |

cT stage, clinical tumor stage; OP, optimal plan; PSA, prostate-specific antigen; PTV, planning target volume.



Several previous studies have reported that the greatest variation in bladder volume is found in patients with large initial bladder volumes [8,9,17]. Significant variations in bladder volume can confound planned dose distributions. A half-full bladder of 150 ml or slightly larger may represent a reasonable target, offering the potential to improve bladder volume consistency without compromising the dose constraints for the adjacent organs.

A limitation of this investigation is the lack of the clinical correlation. We need to investigate the correlation between bladder volumes on planning CT and clinical outcomes in a future study. In most cases, we use a shrinking PTV if we can not satisfy the dose constraints for OARs. Our concern is that the compromise might cause inferior local control and survival rates. However, long-term follow-up is necessary to clarify the clinical impact. We consider achieving an optimal plan a surrogate marker for clinical outcomes; therefore, we report the correlation between bladder volumes and achieving an optimal plan as the first step.

While optimal bladder volumes vary from institution to institution according to the protocol used, we believe that each institution must seek to recognize what bladder volumes are optimal in definitive radiotherapy for localized prostate cancer.

In conclusions, bladder volume is a significant factor affecting the achieving of an optimal plan. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

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Clinical Investigation

# Dose-Volume Histogram Predictors of Chronic Gastrointestinal Complications After Radical Hysterectomy and Postoperative Concurrent Nedaplatin-Based Chemoradiation Therapy for Early-Stage Cervical Cancer

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## Summary

In this study, dose-volume histogram parameters of the small bowel loops were predictive for the development of chronic gastrointestinal (GI) complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. Multivariate analysis indicated that V40 (volume receiving more than 40 Gy) of the small bowel loops and smoking were independent predictors of GI complications.

**Purpose:** The purpose of this study was to evaluate dose-volume histogram (DVH) predictors for the development of chronic gastrointestinal (GI) complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

**Methods and Materials:** This study analyzed 97 patients who underwent postoperative concurrent chemoradiation therapy. The organs at risk that were contoured were the small bowel loops, large bowel loop, and peritoneal cavity. DVH parameters subjected to analysis included the volumes of these organs receiving more than 15, 30, 40, and 45 Gy (V15-V45) and their mean dose. Associations between DVH parameters or clinical factors and the incidence of grade 2 or higher chronic GI complications were evaluated.

**Results:** Of the clinical factors, smoking and low body mass index (BMI) (<22) were significantly associated with grade 2 or higher chronic GI complications. Also, patients with chronic GI complications had significantly greater V15-V45 volumes and higher mean dose of the small bowel loops compared with those without GI complications. In contrast, no parameters for the large bowel loop or peritoneal cavity were significantly associated with GI complications. Results of the receiver operating characteristics (ROC) curve analysis led to the conclusion that V15-V45 of the small bowel loops has high accuracy for prediction of GI complications. Among these parameters, V40 gave the highest area under the ROC curve. Finally, multivariate analysis was performed with V40 of the small bowel loops and 2 other clinical parameters that were judged to be potential risk factors for chronic GI complications: BMI and smoking. Of these 3 parameters, V40 of the small bowel loops and smoking emerged as independent predictors of chronic GI complications.

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**Conclusions:** DVH parameters of the small bowel loops may serve as predictors of grade 2 or higher chronic GI complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. © 2012 Elsevier Inc.

## Introduction

Adjuvant whole-pelvic radiation therapy (RT) after radical hysterectomy reduces locoregional recurrence in cervical cancer patients after surgery with adverse risk factors (1, 2). However, patients undergoing whole-pelvic RT after radical hysterectomy may suffer severe gastrointestinal (GI) complications with an incidence varying from 3%-13% for patients treated with pelvic RT alone (1-3). Moreover, while adjuvant concurrent chemoradiation therapy has been shown in several studies to improve survival rates for high-risk cervical cancer patients compared with adjuvant RT alone, GI complications were observed more frequently in conjunction with concurrent chemoradiation therapy than with RT alone (4). Therefore it is important to improve the feasibility of adjuvant concurrent chemoradiation therapy by reducing GI complications.

Because the small bowel is one of the critical organs involved in GI complications, a predictive model of acute GI complications of the small bowel has been established with the aid of Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (5). However, the correlation between dose-volume effect and chronic GI complications of the small bowel has not been extensively investigated.

Since 2000, we have been using postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer patients with adverse risk factors (6). The purpose of the study reported here was to evaluate dose-volume histogram (DVH) predictors for the development of chronic GI complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

## Methods and Materials

### Patients

A total of 131 patients with cervical cancer received radical hysterectomy and postoperative RT at our institute between April 2000, when we started to use postoperative concurrent nedaplatin-based chemoradiation therapy, and September 2010. Treatment criteria for postoperative RT were previously described (6, 7). Thirty-four of these patients were excluded from the study: 18 who received extended-field radiation therapy alone because of multiple lymph node metastases (7), 9 who refused concurrent chemotherapy, 3 who received intracavitary brachytherapy with whole-pelvic RT because of a close surgical margin, and 4 early patients who did not undergo radiation treatment planning computed tomography (CT) with a 2-dimensional (2D) era. The remaining 97 patients treated with concurrent chemoradiation therapy were analyzed for this study with a minimum follow-up period of 3 months. This study was approved by our institutional review board.

### Radiation therapy and chemotherapy

Whole-pelvic RT was delivered with 2D planning in 65 patients between April 2000 and March 2008 and with 3-dimensional (3D) conformal treatment planning in 32 patients starting April 2008. During the 2D era, RT was delivered using 10-megavolt X rays from a linear accelerator with the anteroposterior parallel opposing technique. The superior margin of the whole-pelvic RT was at the upper edge of the fifth lumbar vertebra and the inferior margin was the inferior edge of the obturator foramen. Laterally, the field extended 2 cm beyond the lateral margins of the bony pelvic wall. After we defined an isocenter or field-shape in the X-ray simulator, CT with the isocenter position marked was performed with 5.0-mm slices without filling the bladder to calculate the monitor unit and check the dose distribution. The CT scan range was from the upper edge of L3 to at least 7 cm below the bottom of the obturator foramen. The dose distribution was calculated using a commercial treatment planning system (FOCUS; Elekta, Stockholm Sweden). The prescribed RT doses were 50 Gy administered in 25 fractions over 5 weeks at the center of the body. Multileaf collimators were used to block the upper and lower corners of the radiation field. No target volume or organ at risk was delineated before treatment. Since April 2008, all patients have been treated with 3D conformal treatment planning. RT planning CT was performed with 2.5-mm slices with normal quiet breathing and a full-bladder scan. The CT scan range was the same as that used in 2D planning. A commercial treatment planning system (XiO TPS; Elekta) was used to design the radiation fields. The clinical target volume (CTV) comprised a central vaginal CTV and a regional nodal CTV. The former included the proximal vagina and paravaginal tissues and the latter consisted of the common iliac, external and internal iliac, and presacral lymph nodes. CTVs were contoured according to the consensus guidelines of the Radiation Therapy Oncology Group (RTOG) 0418 (8) and its atlas on the RTOG website. The planning target volume (PTV) was generated by using 1.0-cm uniform expansion of the CTV. The prescribed RT doses were 50 Gy at the center of the PTV, administered in 25 fractions over 5 weeks by means of the 3D 4-field box technique. Multileaf collimators were used to cover the PTV with a margin of approximately 5 mm. No organ at risk was delineated before treatment. Nedaplatin (40 mg/$m^2$) was given intravenously on a weekly basis during the course of whole-pelvic RT for 5 weeks as previously described (6).

### Contouring and evaluation of normal structures

The organs at risk that were contoured comprised the small bowel loops, large bowel loop, and peritoneal cavity. All contouring was done retrospectively. The superior and inferior extents of critical organs were outlined on all CT slices containing portions of the PTV (3D) or field margins (2D), including an additional area 2-cm superior and inferior to the limit of the PTV or field margins. Therefore, the organs at risk, including the large bowel loop, small bowel loops, and peritoneal cavity, could not be contoured in full volume. The large bowel loop was contoured first as a single loop continuing from the end of the sigmoid colon to the ascending colon, and the remaining bowel loops were classified as the small bowel loops. A preoperative diagnostic CT scan using oral and intravenous contrast media was performed in 92/97 patients (95%). This preoperative CT scan