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Phase I study of daily cisplatin and concurrent radiotherapy in patients with cervical carcinoma

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Abstract

Objective. Chemoradiation based on cisplatin is the standard treatment for locally advanced cervical carcinoma; however, the optimal scheduling and dosing have still not been established. This study was conducted to determine the maximum-tolerated dose (MTD) of cisplatin for daily administration during pelvic radiotherapy (RT).

Methods. Fourteen patients with locally advanced cervical carcinoma and 13 who required postoperative RT were registered. A low dose of cisplatin was given daily concurrently with RT. Cisplatin dosing was started at 6.0 mg/m^2/day, which was incremented by 0.5 mg/m^2/day. RT was delivered at 2 Gy/day to a total dose of 50 Gy. The MTD was defined as the dose level immediately below that causing dose-limiting toxicity (DLT) in over one-third of treated patients.

Results. Twenty-five patients were treated with a maximum of six escalating dose levels. In 22/25 patients (88%), cisplatin was administered continuously as planned without interruption. The MTD was determined to be 8 mg/m^2 and the DLT was indicated by the onset of neutropenia.

Conclusion. Daily cisplatin, at 8 mg/m^2/day, is a well-tolerated radiosensitizer in cervical carcinoma patients.

Keywords: Cervical carcinoma; Phase I; Cisplatin; Chemoradiation

Introduction

Cervical carcinoma is the most frequent cause of death by cancer in women worldwide [1]. Radiation therapy is considered to be the gold standard of treatment for stage IIB–IVA patients. Recently, several phase III studies showed that concurrent chemoradiation could improve outcomes more than radiotherapy alone [2–6]. Cisplatin and cisplatin plus 5-fluorouracil have been the two most common radiosensitizer regimens used in cervical cancer. However, the Gynecologic Oncology Group 120 study showed that 40 mg/m^2 of cisplatin weekly for 6 weeks was as effective as, yet less toxic than, a combination of cisplatin plus 5-fluorouracil. Thus, weekly 40 mg/m^2 cisplatin with concurrent radiotherapy seems to have the better therapeutic ratio [5]. Although the new paradigm of cisplatin-based concurrent chemoradiotherapy is a step forward, questions remain regarding optimal scheduling, dosing, and systemic agents.

In non-small-cell lung cancer, phase III studies demonstrated that radiotherapy combined with daily administration of 6 mg/m^2 cisplatin offered improved local control and improved actuarial survival in comparison with the radiation alone group (significantly) and the weekly administration group (not significantly) in inoperable patients [7]. Several

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authors who combined high-dose radiotherapy with 6 mg/m^2 cisplatin daily did not observe either renal or severe hematological toxicity in head, neck, or non-small-cell lung cancers [8–11].

On these grounds, we thought that daily administration of cisplatin was as effective as weekly administration given concurrently with pelvic radiation in patients with cervical carcinoma. We also initiated a phase I study to evaluate the maximum tolerated dose of daily cisplatin given concurrently with pelvic radiation to patients with cervical carcinoma.

Methods

Patient selection

Fourteen patients with locally advanced cervical carcinoma and 13 who required postoperative RT were entered in this study. Eligibility criteria for postoperative radiation included the presence of at least one of the following: positive pelvic lymph node metastasis, a positive surgical margin, deep stromal invasion, and parametrium invasion. Patients with either disease outside the pelvis or para-aortic lymph node swelling were not eligible. The following were the other inclusion criteria: (1) aged ≤ 75 years; (2) ECOG performance status ≤ 2; (3) no previous chemotherapy or radiotherapy; (4) leukocytes ≥ 3000/mm^3; (5) neutrophils ≥ 2000/mm^3; (6) platelets ≥ 100,000/mm^3; (7) serum creatinine ≤ 1.5 mg/dl; (8) normal chest radiograph and electrocardiogram; and (9) informed consent.

This study was approved by the Institutional Review Board of Chiba University.

Radiotherapy

Patients were treated with 10 MV X-rays from a linear accelerator using four-field box technique, with the fields encompassing the whole pelvis extending from the lower margin of the obturator foramen to the upper margin of the fifth lumbar vertebra, and laterally to at least 1.5 cm outside of the true pelvis. Anterior and posterior borders of lateral fields were carefully determined based on the pretreatment diagnostic imaging such as CT and MRI, with an adequate coverage of the pelvic lymph node area and the primary tumor bed. Typically, the anterior margin was placed just anterior to the symphysis pubis and the posterior margin included the anterior aspect of the entire sacrum. A CT-simulator with three-dimensional treatment planning system was used for all patients.

No attempt was made to irradiate the para-aortic lymph node region. A total dose of 50 Gy was delivered in 25 daily fractions of 2.0 Gy, administered on 5 days a week (from Monday to Friday). All fields were treated each day. Low dose-rate brachytherapy was applied for curative cases 1–2 weeks after the end of external-beam radiotherapy. Brachytherapy was not performed in the adjuvant setting.

Chemotherapy

Each dose of cisplatin was administered i.v. over 30 min, and was completed 1 h before irradiation. The daily dose of cisplatin was reconstituted in 100 ml of normal saline. All patients received 5 mg of granisetron 1 h before cisplatin to prevent emesis. Post-cisplatin hydration was performed with 1 L of normal saline given over 2 h.

Study design

A phase I study was designed to define the MTD of daily cisplatin and pelvic radiotherapy. The starting dose of cisplatin was 6 mg/m^2/day and increments of 0.5 mg/m^2/day were planned at each level until DLT occurred. The MTD was defined as the highest safely tolerated dose with toxicity levels that did not exceed the DLT. DLT was defined as grade 3 or 4 neutropenia or thrombocytopenia and grade 3 or 4 nonhematologic toxicity except for alopecia, nausea, and vomiting. Toxicity was evaluated according to National Cancer Institute common toxicity criteria and the Radiation Therapy Oncology Group toxicity criteria. Cisplatin was suspended if grade ≥3 toxicity appeared, and was resumed once the counts rose above grade 3 levels at the dose level below that which produced DLT. Radiotherapy was suspended if grade 4 hematological toxicity appeared or in the event of grade 4 radiation-related gastrointestinal or genitourinary toxicity, and treatment was resumed once the counts rose above those levels.

The dose was escalated to the next level if none of the patients experienced DLT. If the incidence of DLT was >33% (seen in 2 or 3) at a given dose level, then dose escalation was stopped. If one of three patients at any level developed treatment-related DLT, three additional patients were then treated at the same dose level. The MTD was defined as the dose level below that which produced DLT in more than one-third of the treated patients. If DLT appeared in only one or two of the six patients, the dose was escalated to the next level.

Laboratory studies, including chemistry panels and a complete blood cell count, were obtained twice weekly, or more frequently if clinically indicated.

Chemoradiation with weekly cisplatin

From December 1999 to March 2002, 10 patients with cervical carcinoma, stages IIB–IIIB, were treated with five weekly courses of cisplatin 40 mg/m^2 during standard pelvic radiation. Radiation was administered according to the same schedule as daily cisplatin. Cisplatin was withheld in any case of grade 3 toxicity (except nausea/vomiting) until the toxicity regressed to

less than grade 3. If grade 3 neutropenia appeared, G-CSF was administered.

Results

Between April 2002 and December 2003, a total of 27 patients were enrolled in the study. (Table 1). The mean age was 51.0 (range 29–71) years. The mean BMI was 24.1 (range 16.8–30.6). Two were not eligible because of non-dose-related toxicity (grade 2 nausea/vomiting) and were refused chemotherapy (2× and 15× cisplatin). Twenty-five patients were evaluable for toxicity analysis. Six dose levels were studied (Table 2). DLT was observed in six patients: in two patients at level 3, in one at level 5 and in three at level 6 (Table 3). Thus, the MTD of daily cisplatin was defined 8 mg/m^2/day.

In 22/25 patients (88%), daily cisplatin could be administered continuously as planned with no interruption. Cisplatin administration had to be interrupted in only two patients and terminated in only one.

Hematological toxicity was mild overall. As shown in Table 3, grade 3 or 4 leukopenia or neutropenia was recorded in nine cases (including five after treatment). Only one patient was treated with G-CSF because of grade 4 leukopenia (level 6); in no case was febrile neutropenia recorded. Grade 3 thrombocytopenia was observed in one patient after treatment. No grade 3 nonhematological toxicity was seen. Four patients observed grade 2 nausea and vomiting. Grade 1 and 2 diarrhea was frequent, being recorded in almost all patients. But no grade 3 diarrhea was not found. No late toxic event was observed during follow-up of patients. There was no correlation between BMI and side effects.

Fourteen patients were receiving primary treatment and were evaluated for response. Thirteen patients achieved responses: 11 (78.6%) complete responses and 2 (14.3%) partial. At the median follow-up period of 14.2 months (range 7–26), one patient with progression had died of the disease, and two patients suffered relapses at sites outside radiation field.

Table 1
Patient characteristics

Number of patients	27
Age(years)	
Mean	51.0
Range	29–71
BMI	
Mean	24.1
Range	16.8–30.6
Histology	
Squamous	19 (8)[a]
Adeno	6 (4)[a]
Small cell	1 (1)[a]
Carcinosarcoma	1 (0)[a]
Stage	
IB	6 (6)[a]
IIB	9 (7)[a]
IIIB	11 (0)[a]
IVA	1 (0)[a]
Radiation	
Adjuvant	13
Primary therapy	14

[a] Parentheses indicate members of the adjuvant group.

Table 2
Toxicity and dose levels

Toxicity	Dose levels of cisplatin (mg/m^2/day)					
	1 (n = 5)[a]	2 (n= 3)	3 (n = 7)[a]	4 (n = 3)	5 (n = 6)	6 (n = 3)
Hematological						
Leukopenia						
1	1	1	3	1	1	0
2	2	1	0	1	3	0
3	0	0	4	0	2	2
4	0	0	0	0	0	1
Neutropenia						
1	1	1	3	1	2	0
2	2	0	2	1	3	1
3	0	0	2	0	1	1
4	0	0	0	0	0	1
Thrombocytopenia						
1	2	4	6	2	4	2
2	0	0	0	0	0	0
3	0	0	0	0	0	1
4	0	0	0	0	0	0
Nonhematological						
Nausea/vomiting						
1	3	2	3	2	4	1
2	1	0	1	0	0	2
3, 4	0	0	0	0	0	0
Diarrhea						
1	1	3	2	2	4	1
2	3	0	4	1	1	2
3, 4	0	0	0	0	0	0

[a] One patient from this group was not eligible for this study.

Table 3
Dose regimens administered, toxicity, and interruption of administration

Dose level	Dose of cisplatin (mg/m^2/day)	No. of patients with DLT[a]	DLT[a]	Interruption of cisplatin administration
1	6	0/4		
2	6.5	0/3		
3	7	2/6	grade 3 neutropenia	D-21, 23,24
			grade 3 neutropenia	D-22, 24
4	7.5	0/3		
5	8	1/6	grade 3 neutropenia	7 days after treatment
6	8.5	3/3	grade 4 neutropenia	D-24
			grade 3 neutropenia	4 days after treatment
			grade 3 thrombo-cytopenia	4 days after treatment

[a] DLT: dose-limiting toxicity.

Chemoradiation with weekly cisplatin; the mean course of cisplatin was 4.2 cycle (mean total dose 168 mg). The proportion of patients who received the total course of treatment was 30%. Grade 3 and 4 hematologic toxicity was recorded in six cases (60%): Five cases of grade 3 and one of grade 4 leukopenia/neutropenia and two cases of grade 4 thrombocytopenia. Grade 3 nonhematologic toxicity occurred in one patient.

Discussion

In the present study, we sought the MTD of daily 8 mg/m^2 administration of cisplatin given concurrently with pelvic radiotherapy in patients with cervical cancer. Neutropenia was the DLT at daily cisplatin dose level of 8.5 mg/m^2.

Cisplatin-based concurrent chemoradiation was regarded as standard treatment for locally advanced cervical carcinoma. Despite the increasing use of cisplatin to exploit its powerful radiosensitizing properties, its nephrotoxicity has been recognized as its main dose-limiting feature since its early clinical trials. Therefore, another agent, namely carboplatin, was tried as a radiosensitizer [12–14]. In this study, no patient recognized any alteration of renal function. Even if the patient has a urinary tract obstruction, as long as the serum creatinine level <1.5, daily administration of cisplatin is considered to be safe. Other authors, who combined radiotherapy with 6 mg/m^2 cisplatin daily in the treatment of lung carcinoma, observed neither renal nor severe hematological toxicity [8–11].

Daily cisplatin administration led to milder adverse side effects than weekly cisplatin. Weekly cisplatin 40 mg/m^2 was accompanied with grade 3 or 4 gastrointestinal and hematological side effects, in 14% and 28.3% of patients, respectively [4]. In our study, weekly cisplatin 40 mg/m^2 caused grade 3 or 4 gastrointestinal and hematological side effects, in 10% and 60% of patients, respectively. However, only 30% of patients received the entire course of weekly cisplatin 40 mg/m^2, and a complete course of daily cisplatin 8 mg/m^2 could be administered to Japanese women. There was no phase I study of weekly cisplatin concurrent with radiotherapy in Japanese cervical carcinoma patients. We suggest that 40 mg/m^2 of cisplatin weekly is not the optimal dose for Japanese women. With daily cisplatin (≤8 mg/m^2), grade 3 gastrointestinal side effects were uncommon and 6 of 22 patients had grade 3 or 4 hematological toxicity (27.3%). We regard the daily administration of cisplatin to be more tolerable than its weekly administration. Moreover, we considered that 8 mg/m^2 could be administered daily in an outpatient situation.

Although the evaluation of response was not the primary objective of this study, the overall response rate was higher than 90%, which suggests that this treatment is clinically relevant. However, the small sample size of this phase I study precludes any conclusions about the response. The results of the present study warrant further phase II study of cervical cancer using a daily administration of 8 mg/m^2 cisplatin concurrently with pelvic radiotherapy.

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CLINICAL INVESTIGATION **Brain**

LONG-TERM RESULTS OF RADIOTHERAPY FOR INTRACRANIAL GERMINOMA: A MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW OF 126 PATIENTS

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Purpose: Optimal management of radiotherapy (RT) for intracranial germinoma remains controversial. This study was conducted to evaluate the long-term results of RT in patients with these tumors.

Methods and Materials: The study group consisted of 126 patients with intracranial germinoma (50 patients with pathologically verified germinoma and 76 clinically diagnosed with germinoma by clinical and neuroradiologic signs) who were treated by RT alone between 1980 and 2001. The median age at diagnosis was 17 years (range, 2–47), and various radiation doses and treatment fields were used. Serum human chorionic gonadotropin (hCG) levels were elevated in 18 patients. The median follow-up of the 114 surviving patients was 122 months (range, 13–263).

Results: The 10-year actuarial overall survival and cause-specific survival rate for all patients was 90% and 95%, respectively. The 10-year actuarial cause-specific survival rate for patients with and without elevated hCG levels was 94%. Relapses were noted in 10 patients, 7 of whom died of the disease. No in-field relapses at primary sites were observed in 72 patients treated with total doses of 40–50 Gy. The incidence of spinal relapses was 4% (2 of 56) for patients treated with spinal irradiation and 3% (2 of 70) for those without spinal irradiation. After a median 10-year follow-up, 54 (92%) of 59 patients with tumors not involving the neurohypophyseal region and 42 (76%) of 55 patients with tumors involving the neurohypophyseal region had Karnofsky performance status scores of 90–100%. With regard to school education and occupation, 54 (92%) of 59 patients with tumors not involving the neurohypophyseal region and 39 (71%) of 55 patients with tumors involving the neurohypophyseal region were attending school or undertaking occupations. Hormonal replacement therapy was required in 50 (44%) of 114 surviving patients before RT; only 4 patients (4%), all with neurohypophyseal tumors, required hormonal replacement therapy after RT. Clinically evident severe neurocognitive dysfunctions were documented in 10 patients before RT, and no patients treated with total doses of <55 Gy developed apparent neurocognitive dysfunctions or other complications after RT.

Conclusion: RT was a curative treatment for intracranial germinoma, and elevated serum hCG levels did not affect the prognosis of patients treated by RT alone. A total dose of 40–50 Gy to adequate treatment fields was effective in preventing intracranial relapse, and the incidence of spinal relapses was too low to warrant routine spinal irradiation. Karnofsky performance status scores, educational achievement, and the ability to work were generally good, particularly in patients with tumors that did not involve the neurohypophyseal region. Because most complications, such as hormonal deficiency and neurocognitive dysfunction, were documented before RT and newly diagnosed complications after RT were infrequent, the treatment toxicity faced by germinoma patients appears to be less than anticipated. © 2004 Elsevier Inc.

Germinomas, Radiotherapy, Pineal, Suprasellar, hCG, Quality of life, Complication.

INTRODUCTION

Intracranial germinomas represent 0.5–2.5% of all intracranial tumors and are more common in Japan than in Western countries (1–5). These tumors occur primarily in the pineal or neurohypophyseal regions and most often affect adolescents and young adults. In contrast to intracranial nongerminomatous germ cell tumors, germinomas are one of the

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most radiosensitive tumors known and are curable by radiotherapy (RT) alone (1, 5–13). Although RT has been the standard treatment for intracranial germinoma for many years, agreement on the optimal management of these tumors with respect to treatment volume, dose, and use of chemotherapy has not been reached. Also, the prognosis and treatment of human chorionic gonadotropin (hCG)-secreting germinoma remain controversial (14–19).

Because patients with intracranial germinoma can expect long-term survival, the adverse effects of RT and late sequelae in survivors are of major concern. However, the late effects of RT alone have not been well documented in such patients. In the current study, we reviewed a retrospective and multi-institutional series of 126 patients with intracranial germinoma treated by RT alone and evaluated the long-term results of RT.

METHODS AND MATERIALS

Patient characteristics

A retrospective review of medical records from 1980 to 2001 identified 126 patients with documented intracranial germinoma treated by RT alone at the departments of radiology, University of the Ryukyus Hospital, Shinshu University Hospital, Kyushu University Hospital, Chiba University Hospital, Yamanashi University Hospital, or the International Medical Center of Japan. Of the 126 patients, 31 were female (25%) and 95 were male (75%), and none had received chemotherapy during initial treatment. The median age at diagnosis was 17 years (range, 2–47), with 23 patients (18%) <12 years old, 54 patients (43%) 12–19 years old, and the remaining 49 patients (39%) ≥20 years old. All patients were evaluated by CT and/or MRI before the initial treatment. Fifty patients (40%) were diagnosed pathologically and 76 (60%) were diagnosed clinically with germinoma by clinical and neuroradiologic signs. These signs included age within the typical age range (8–32 years), tumor site (pineal and/or neurohypophyseal region or basal ganglia), serum hCG levels not increased to >100 mIU/mL or α-fetoprotein levels >10 ng/mL, appropriate CT and/or MRI findings (homogenously enhanced mass), and a rapid response to RT (gt;80% reduction in the product of the perpendicular diameters of the contrast-enhancing tumor at 15–20 Gy) (6, 9, 20). All 76 patients who were clinically diagnosed underwent CT scanning after RT of 15–20 Gy, and the average reduction rate was 89% (range 81–100%).

Table 1 presents the tumor characteristics in the 126 patients with intracranial germinoma. For 51 patients (40%), the primary site of the germinoma was the pineal region only, and in 33 patients (26%), the primary site was the neurohypophyseal region only. Seven patients (6%) had tumors in the thalamus or basal ganglia only, 21 patients (17%) had multifocal tumors involving more than one intracranial site, and the remaining 14 (11%) had disseminated disease. Of the patients with disseminated disease, 2 patients had tumor cells in their cerebrospinal fluid, and 1 patient had a tumor in the spinal cord as detected by MRI. The median diameter of the maximal tumor size in the 126 patients was 2.5 cm (range, 0.8–7). Serum hCG levels were elevated in 18 patients (14%), who as a group had a median hCG value of 41 mIU/mL (range, 8–890). The patients with hCG levels >100 mIU/mL all had pathologically verified germinomas. No patients had an elevated α-fetoprotein or carcinoembryonic antigen titer.

Table 1. Tumor characteristics

Characteristic	Patients (*n*)
Tumor location	
Pineal	51 (40)
Neurohypophyseal	33 (26)
Thalamus or basal ganglia	7 (6)
Multifocal	21 (17)
Disseminated	14 (11)
Maximal tumor size (cm)	
<2	28 (22)
≤2–≤4	84 (67)
>4	14 (11)
Serum hCG level	
Normal	108 (86)
High	18 (14)

Abbreviation: hCG = human chorionic gonadotropin.
Data in parentheses are percentages.

Radiotherapy

RT was administered using a ^{60}Co teletherapy unit (8 patients) or a 4-, 6-, or 10-MV linear accelerator. Daily fraction sizes of 1.8–2.0 Gy for the primary tumor and 1.6–2.0 Gy for the cerebrospinal axis, 5 d/wk, were mostly used. In most cases, treatment fields were determined using conventional X-ray simulators. More recently, in an effort to spare normal brain tissue from the high-dose volume of RT, CT simulators were also used to boost the primary disease site. The radiation field and dose varied according to the tumor extent, patient age, cerebrospinal fluid results, spinal MRI findings, and serum hCG values. Localized-field RT was defined as a partial brain field covering the primary tumor with a generous margin but not including the third ventricle and lateral ventricles.

Fifty-six patients (44%) were treated using a radiation field encompassing the whole central nervous system with a boost; 62 patients, the whole brain with a boost, 2 patients, the whole ventricle; and 6 patients, a localized field smaller than the whole ventricle. The field was varied during RT for 114 patients; for instance, a localized field followed by craniospinal irradiation, or whole brain RT followed by a localized field. The total dose to the primary site ranged from 20 to 64 Gy (median, 50), with 11 patients (9%) receiving total doses of >55 Gy. For 18 patients with elevated hCG levels, the median total dose was 50.4 Gy (range, 20–55.7) compared with 50 Gy (range, 38–64) for the 108 patients with normal hCG levels. Whole brain doses ranged from 19.5 to 44 Gy (median, 30), and the whole

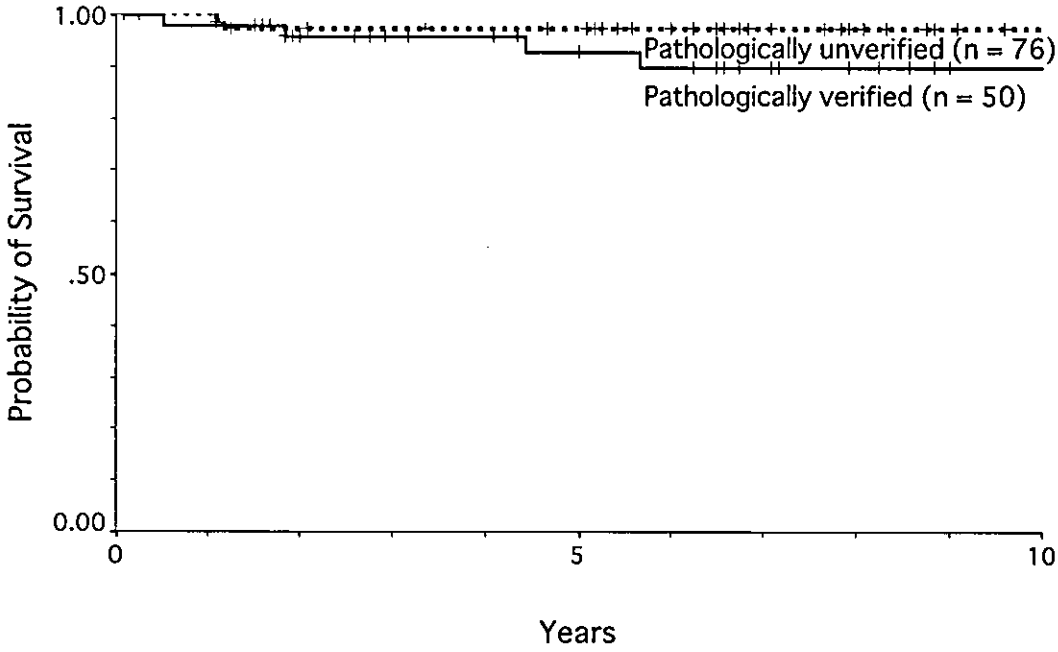

Fig. 1. Actuarial overall survival rates according to pathologic status.

ventricle dose for the 2 patients who received them was 40 Gy and 42 Gy. Localized-field doses ranged from 20 to 55.8 Gy (median, 53), and prophylactic dose to the whole spine ranged from 7.2 to 37.2 Gy (median, 30.4). One patient with a spinal tumor detected by MRI received a total dose of 46.2 Gy to the spinal tumor site.

Analysis of late effects

Data from the 114 surviving patients were analyzed to assess the late effects. The median patient age at the time of investigation was 28 years (range, 12–61). In the current study, patients were divided into two groups according to tumor involvement at the neurohypophyseal region. Of the 114 patients, 55 patients had tumors involving the neurohypophyseal region and 59 patients had tumors that did not involve the neurohypophyseal region. Assessments were made according to Karnofsky performance status (KPS), school education/job attainment, need for hormonal replacement, and the presence of complications, such as severe neurocognitive dysfunctions or intracranial hemorrhage. In the current study, 12 patients, who provided written informed consent (the patients or their guardians), underwent formal neurocognitive testing, such as the Wechsler Intelligence Scale for Children-Revised or the Wechsler Adult Intelligence Score-Revised. However, the remaining 102 patients did not undergo the testing before and after RT. Therefore, we defined "severe neurocognitive dysfunction" as a clinically evident situation that hampered social activity (i.e., the patient could not lead a normal life without assistance from others). Data were collected from patient records, follow-up visits, and a questionnaire dealing with psychosocial development (education and current occupation).

Statistical analysis

The median follow-up time of the 114 surviving patients was 122 months (range, 13–263), and no patients were lost to follow-up. The overall and cause-specific survival rates were calculated actuarially according to the Kaplan-Meier method (21) and were measured from the beginning of RT. Differences between groups were estimated using the log–rank test (22). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences, version 6.1, software (SPSS, Chicago, IL).

RESULTS

Survival

Twelve (10%) of 126 patients died during the period of this analysis. Seven patients (6%) died of germinoma and the remaining 5 patients died without any sign of clinical relapse (2 died of pneumonia, 1 of meningitis, 1 of hypernatremia, and 1 of convulsions of unknown cause). The 10-year actuarial overall and cause-specific survival rate for all patients was 90% and 95%, respectively.

The 10-year actuarial cause-specific survival rate for patients with pathologically diagnosed germinoma and those diagnosed clinically as having germinoma by clinical and neuroradiologic signs was 90% and 97%, respectively (Fig. 1). The difference between these two groups was not statistically significant ($p = 0.25$). The 10-year actuarial cause-specific survival rate was 94% for patients both with and without elevated serum hCG levels (Fig. 2), also not a statistically significant difference ($p = 0.95$).

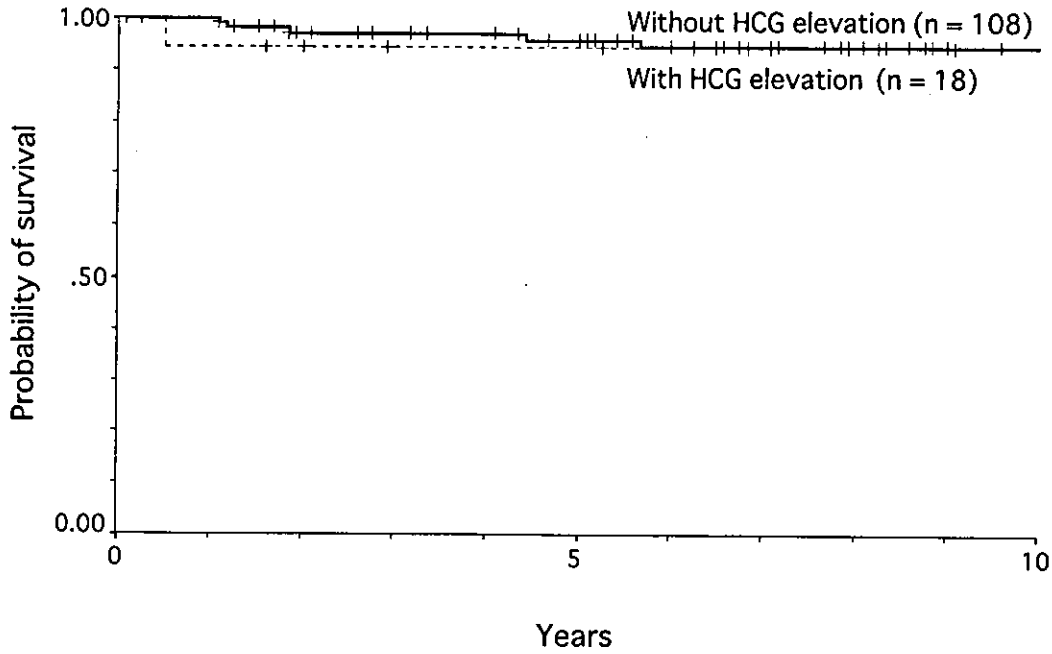

Fig. 2. Actuarial overall survival rates according to the presence of elevated hCG.

Relapse patterns

Overall, 10 patients experienced tumor relapse, with the relationship between radiation field and relapse site summarized in Table 2. Concerning intracranial relapses, 3 (50%) of 6 patients treated with localized-field RT developed recurrence, and only 1 (1%) of 118 patients treated with whole brain or craniospinal RT had an intracranial relapse. Spinal relapses were less common, with 2 (4%) of 56 patients treated with spinal RT and 2 (3%) of 70 patients not treated with spinal RT developing a spinal relapse. Concerning extracranial relapses, 1 patient developed bone metastasis as a first relapse and was successfully salvaged with cisplatin-based chemotherapy (23).

Intracranial relapse patterns according to total radiation dose

Five patients experienced intracranial relapse. Table 3 indicates the incidence of intracranial relapse according to the total radiation dose to the primary site, with "in-field" defined as the field receiving the total RT dose. One patient treated with a total dose of 20 Gy had an in-field relapse; none of the 124 patients treated with a total dose of ≥40 Gy had in-field relapses at the primary site. The site of relapses was a marginal relapse at the primary site in 2 patients and an out-field relapse at the ventricles in 2 patients. The median maximal diameter of the tumors was 2.75 cm (range, 2.5–3) for patients treated with total doses of <40 Gy, 2.5 cm (range, 0.8–4.8) for patients treated with total doses between 40 and 50 Gy, and 2.5 cm (range, 1–7) for patients treated with total doses of >50 Gy.

Table 2. Relapse patterns according to radiation field

Radiation field	Total patients (*n*)	Site of first relapse (*n*)		
		Intracranial	Spinal	Extracranial
Localized field	6	3 (50)	0	0
Whole ventricle	2	1	0	0
Whole brain + boost	62	1 (2)	2 (3)	0
Craniospinal + boost	56	0	2 (4)	1 (2)
Total	126	5 (4)	4 (3)	1 (1)

Data in parentheses are percentages.

KPS and school education/occupation

Table 4 indicates the KPS scores before and after RT. Before RT, 39 (66%) of 59 patients with nonneurohypophyseal tumors and 39 (71%) of 55 patients with neurohypophyseal tumors had KPS scores of 90–100%. After a median 10-year follow-up period, 54 (92%) of 59 patients with nonneurohypophyseal tumors and 42 (76%) of 55 patients with neurohypophyseal tumors had KPS scores of 90–100%. Improvement in KPS (≥10%) after RT was observed in 18 (31%) of 59 patients with nonneurohypophyseal tumors and 11 (20%) of 55 patients with neurohypophyseal tumors.

With regard to school education and job attainment (Table 4), 54 (92%) of 59 patients with tumors not involving the neurohypophyseal region and 39 (71%) of 55 patients with tumors involving the neurohypophyseal region attended school (junior high school, high school, college, or university) or had an occupation (permanent or part time). In the current study, 3 female patients, who had married and led normal daily lives as housewives, were regarded as having an occupation.

Table 3. Intracranial relapse patterns according to total radiation dose

Total dose (Gy)	Total patients (*n*)	Site of first relapse (*n*)			
			Marginal and out of field		
		In-field*	Primary site	Ventricle	Other sites
<40	2	1	0	0	0
≤40–≤50	72	0	0	2 (3)	0
>50	52	0	2 (4)	0	0
Total	126	1 (1)	2 (2)	2 (2)	0

Data in parentheses are percentages.
* In-field defined as field receiving total dose of radiotherapy.

Hormonal replacement therapy before and after RT

Table 5 shows the incidence of hormonal replacement therapy before and after RT. Before RT, 50 (44%) of 114 patients required continual hormonal replacement therapy alone or in combination with desmopressin, thyroxin, cortisol, growth hormone, and gonadotropin. After a median 10-year follow-up period, 4 patients (4%) with neurohypophyseal tumors newly required hormonal replacement therapy, and none of the 52 patients with nonneurohypophyseal tumors required the initiation of hormonal replacement therapy after RT. The incidence of patients requiring hormonal replacement therapy after RT was greater for patients with tumors involving the neurohypophyseal region (47 of 55 patients) than for those with tumors outside the neurohypophyseal region (7 of 59 patients).

Complications before and after RT

Table 5 shows the incidence of complications before and after RT. Before RT, 10 (8%) of 114 patients had documented clinical evidence of severe neurocognitive dysfunction that hampered social activity. Of the 10 patients, 3 underwent formal neurocognitive testing using the Wechsler Intelligence Scale for Children-Revised or Wechsler Adult Intelligence Score-Revised before RT, and all 3 patients had full-scale IQ scores of <70 (62, 64, and 68). Most patients (9 of 10) with neurocognitive dysfunctions before RT had disease involving the neurohypophyseal region. After the median 10-year follow-up period, 2 patients experienced new neurocognitive dysfunctions and 1 patient developed an intracranial hemorrhage. The total radiation dose to the primary site was 60.5 and 64 Gy in the 2 patients who developed neurocognitive dysfunction and 55.2 Gy in the 1 patient with intracranial hemorrhage. Conversely, none of the remaining 101 surviving patients, who were generally treated with a total dose of <55 Gy, experienced apparent neurocognitive dysfunction or other complications.

With regard to visual function, 57 patients were documented to have visual impairment before RT, and all showed improvement or no change after RT. Before RT, 2 female patients with tumors involving the neurohypophyseal region were reported to have a short stature (<10th percentile), but no additional patients developed apparent short stature after RT.

DISCUSSION

The results of the current study confirmed the efficacy of RT for intracranial germinomas, and the excellent long-term survival of patients with these tumors treated by RT alone.

Table 4. Karnofsky Performance status before and after radiotherapy and school or job status after radiotherapy in 114 patients with germinomas treated with radiotherapy alone*

	Before RT†			After RT‡		
	N (+)	N (−)	Total	N (+)	N (−)	Total
Patients (*n*)	55	59	114	55	59	114
KPS (%)						
90–100	39 (71)	39 (66)	78 (68)	42 (76)	54 (92)	96 (84)
70–80	5	11	16	6	2	8
≤60	11	9	20	7	3	10
School or job (yes)	—	—	—	39 (71)	54 (92)	93 (82)

Abbreviations: KPS = Karnofsky performance status; RT = radiotherapy; N (+) = tumors involving neurohypophyseal region; N (−) = tumors without involving neurohypophyseal region.
Data in parentheses are percentages.
* Median follow-up 122 months (range, 13–263).
† Median age before RT 18 years (range, 6–47).
‡ Median age at analysis 28 years (range, 12–61).

Table 5. Incidence of hormonal replacement therapy and complications before and after radiotherapy in 114 available patients treated with radiotherapy alone*

	Before RT (*n*)			After RT (*n*)		
	N (+)	N (−)	Total	N (+)	N (−)	Total
Total patients	55	59	114	55	59	114
Hormonal replacement therapy (yes)	43 (78)	7 (12)	50 (44)	47 (85)	7 (12)	54 (47)
Complications						
Severe neurocognitive dysfunction†	9	1	10	10‡	2§	12
Intracranial hemorrhage	0	0	0	1‖	0	1
Others	0	0	0	0	0	0

Abbreviations as in Table 4.

* Median follow-up 122 months (range, 13–263).

† Severe neurocognitive dysfunctions defined as clinically evident situations that hampered their social activity (could not lead daily life without assistance from others).

‡ One patient developed new neurocognitive dysfunction with a total dose of 60.5 Gy to primary site.

§ One patient developed new neurocognitive dysfunction with a total dose of 64 Gy to primary site.

‖ One patient had new intracranial hemorrhage with a total dose of 55.2 Gy to primary site.

The findings of 90% actuarial overall survival and 95% cause-specific survival rates at 10 years are similar to those reported previously (1, 5–10, 14). The current findings also indicated that elevated serum hCG levels did not significantly affect patient prognosis. The prognostic significance of hCG elevation has been controversial owing to the limited information available. Some authors have reported poorer prognoses for germinoma patients with elevated hCG compared with those with normal hCG levels and recommended more intensive treatment (16–19). Yoshida *et al.* (17) indicated that germinoma with elevated hCG was resistant to cisplatin/etoposide chemotherapy and such patients had a 2-year survival rate of 50%. Aoyama *et al.* (16) found that localized-field RT at a total dose of 24 Gy in combination with effective chemotherapy was insufficient to control the disease. However, others have reported favorable prognoses for patients with elevated hCG levels when treated by standard RT (14, 15). Shibamoto *et al.* (14) indicated that the prognosis of intracranial germinoma with hCG elevation after RT did not differ from that of pure germinoma, with both groups exhibiting 10-year survival rates of 100%. In the current study, elevated hCG did not affect patient prognosis after RT alone, with a 10-year cause-specific survival rate of 94% for patients both with and without hCG elevation. It is possible that the prognosis of germinoma patients with high hCG levels is dependent on treatment intensity. Chemotherapy alone or chemotherapy followed by low-dose involved-field RT may be associated with a high recurrence rate in intracranial germinoma with hCG elevation, and standard RT may be sufficient to prevent recurrence.

For the treatment of intracranial germinoma, the standard radiation field has usually been whole brain or craniospinal irradiation with a boost to the primary tumor site (1, 4–6, 10, 14, 24–26). In contrast, several authors have recommended partial brain fields; for instance, tumors with 2–4-cm margins (3, 27). However, localized-field RT has been associated with a high intracranial relapse rate (4, 10). Haddock *et al.* (10) indicated that partial-brain RT was associated with brain and spinal failure, with a 5-year disease-free survival rate of only 29% after partial brain treatment vs. 88% after whole brain RT and 100% after craniospinal RT. Aoyama *et al.* (4) indicated that even with the use of CT imaging, localized-field RT without the inclusion of the ventricles resulted in 10-year relapse-free survival rates as low as 22%. In the current study, 3 (50%) of 6 patients treated with localized-field RT experienced intracranial relapse; patients treated with whole brain or craniospinal RT had extremely low intracranial relapse rates (1 of 118 patients). These results indicate that localized-field RT without ventricle inclusion is associated with a high relapse rate and that whole brain RT is effective in preventing intracranial tumor relapse. Recently, Shirato *et al.* (6) reported the absence of germinoma relapse in 10 patients who received 40 Gy of whole ventricle RT only using CT simulation. Whole-ventricle RT using precise CT simulation may be appropriate as a standard treatment for most cases of nonmetastatic intracranial germinoma.

Although the optimal RT dose to the primary tumor is still unclear, recent findings have suggested that intracranial germinomas can generally be cured with doses of between 40 and 50 Gy (3, 5, 6, 9, 10, 12, 23, 24, 28–30). Shirato *et al.* (6) found no increase in tumor control rate by increasing the dose to the primary tumor site >40 Gy. Hardenbergh *et al.* (5) found no relapse in 14 patients receiving <50 Gy. In the current study, no in-field relapses at the primary site were observed in 72 patients treated with total doses of 40–50 Gy for tumors with a median size of 2.5 cm (range 0.8–4.8). These results suggest that total radiation doses of 40–50 Gy are effective in preventing intracranial tumor relapse. Recently, Shibamoto *et al.* (9) indicated that intracranial germinomas ≤4 cm in diameter were usually cured by radiation doses of 40–45 Gy. Several other authors also found no local relapses after total doses of 45 Gy (1, 4, 13, 18). Therefore, a total dose of 50 Gy appears to be unnecessary for intracranial germinoma, except for large tumors,

and investigation into additional dose reduction seems worthwhile.

The optimal radiation dose required for the control of microscopic disease has also not been determined. Although most authors have recommended doses of 25–30 Gy for microscopic disease (7, 10, 13, 31), Shibamoto *et al.* (28) recommended a lower craniospinal dose of 20–24 Gy, because similar results were obtained for patient groups with positive or negative cytology. Additional studies are needed to determine whether even lower doses can suffice for the control of microscopic disease.

It has been widely recognized that the risk of spinal metastases is too low to warrant routine prophylactic spinal RT (3, 7, 10, 25, 27, 28). Haddock *et al.* (10) indicated that none of 9 patients diagnosed by CT exhibited spinal relapse when treated with whole brain RT. Linstadt *et al.* (28) found that of 31 patients treated without adjuvant spinal RT, only 1 (3%) developed a spinal relapse. In the current study, the incidence of spinal relapse was 4% (2 of 56) for patients treated with spinal RT and 3% (2 of 70) for those treated without spinal RT. With modern imaging procedures, the proportion of patients presenting with spinal disease at diagnosis is low, and the risk of secondary spinal seeding in germinoma did not exceed 15% in a large series (8, 25). However, for patients with positive tumor cells in the cerebrospinal fluid or tumor deposits by MRI, craniospinal RT is still recommended as standard therapy (6, 28).

As survival has improved for certain brain tumors, issues related to the quality of that survival have become increasingly important. This is particularly true for patients undergoing treatment for germinomas, because survival can be almost ensured when treated by radical RT alone. However, in most cases, the occurrence of late effects have been extrapolated from studies involving other patient groups with favorable outcomes, such as those with medulloblastomas (32, 33). Because most germinoma patients are postpubertal at diagnosis, the effects of cranial or craniospinal RT, such as neurocognitive dysfunction or spinal growth alterations, appear to be less marked in this patient group than in younger children given RT for medulloblastomas (1, 9). The quality of life in long-term survivors of germinoma has been investigated by several retrospective studies and found to be acceptable or reasonable (1, 2, 8, 9). Bamberg *et al.* (1) indicated that of 60 germinoma patients treated with RT, nearly all patients in complete remission were living active and useful lives. With regard to KPS, Shibamoto *et al.* (9) indicated that treatment-related declines in KPS were generally not observed in patients treated by RT alone. In the current study, the KPS scores for patients treated by RT were also generally good, particularly in patients without neurohypophyseal tumors. Using school education and occupation as indicators of psychosocial development, we found no overt deficits in the vast majority of patients, especially for patients with nonneurohypophyseal tumors. Matsutani *et al.* (8) indicated that 19 (83%) of 23 long-surviving patients achieved a good quality of life with respect to school and employment. In a recent retrospective review by Sutton *et al.* (2), all 22 patients treated by radical RT had completed high school, 9 had completed or were in college, and 5 had advanced degrees. However, the methods used to evaluate the quality of life of young patients can be difficult to interpret and require additional investigation.

Endocrine dysfunction is often linked to cranial irradiation in the treatment of brain tumors (34). However, several studies have indicated that most intracranial germinoma patients present with substantial preexisting morbidity at diagnosis (5, 35). Merchant *et al.* (24) found that preirradiation endocrine deficiencies were present in 6 of 6 patients with neurohypophyseal tumors and 1 of 6 patients with pineal tumors. Kitamura *et al.* (29) found that 9 (60%) of 15 patients diagnosed with panhypopituitarism before RT included 9 of 11 patients with tumors involving the neurohypophyseal region, but no patients with solitary pineal tumors. Bamberg *et al.* (1) reported that although 23 (50%) of 46 patients had at least one endocrine abnormality that required continual hormonal replacement at diagnosis, at follow-up, no additional impairments in endocrine function were noted. In the current study, of 114 available patients, 50 (44%) had at least one endocrine abnormality requiring hormonal replacement before RT. After RT, 4 patients (4%), all with neurohypophyseal tumors, developed newly impaired endocrine function that required hormonal replacement. These results suggest that endocrine-related abnormalities are primarily linked to tumor effects, contrary to the traditionally held view that endocrine abnormalities are mainly induced by RT. Because many germinoma patients present with endocrine deficiencies before treatment, it is difficult to assess the true late effects of RT on endocrine function without precisely evaluating the baseline endocrine function before therapy.

Despite its effectiveness, craniospinal RT may be responsible for complications such as neurocognitive dysfunction, vascular pathologic findings, spinal growth impairment, and leukoencephalopathy (36–39). The long-term effects of craniospinal RT, especially neurocognitive dysfunction, are well known and mainly affect very young children. However, with regard to germinoma patients, the extent of late effects on neurocognitive function due to RT has been controversial. Jenkin *et al.* (40) reported that brain damage as a consequence of a tumor and/or its treatment occurred to some extent in all patients, and only one-third of long-term survivors with pineal germinoma did not experience gross late effects. Shirato *et al.* (6) indicated that 5 (19%) of 27 available patients experienced significant late neurocognitive dysfunction after RT, with some patients treated by daily doses of 2.5 or 3.0 Gy. In contrast, Shibamoto *et al.* (9) found no treatment-related decline of severe neurocognitive dysfunction in 38 patients treated with total doses of 40–52 Gy (1.6–1.8 Gy/fraction), with a median follow-up of 10 years. Merchant *et al.* (24) indicated that after a median follow-up of 69 months, no statistically significant differences were found in full-scale, verbal, and performance IQ scores before and after RT in 12 patients treated with craniospinal irradiation plus a boost, with a median total

dose of 50.4 Gy. Sutton *et al.* (2) evaluated the 22 adult survivors with germinoma treated with prophylactic whole-neuraxis irradiation. The standard dose was 36 Gy to the neuraxis, with a boost of 50.4 Gy to the primary site, and the emotional and psychological measures were better than those in the normal population. In the current study, with a median follow-up of 10 years, no patients developed new clinically evident severe neurocognitive dysfunction when treated with total doses of <55 Gy. These results suggest that, in general, neurocognitive function in germinoma patients appears not to be compromised by standard RT regimens.

Moreover, in the current study, clinically evident neurocognitive dysfunctions were documented in 10 patients before RT, especially in patients with tumors involving the neurohypophyseal region. Several authors have also reported a decline in neurocognitive function in patients with neurohypophyseal tumors before treatment (29). Therefore, differentiating between treatment- and tumor-related side effects is important for adolescent and young adult patient populations diagnosed with substantial preexisting morbidity. Treatment of intracranial germinoma should be based on a balanced assessment of the probability of disease control weighed against the probability of treatment-related side effects, and it is imperative that patient age and preexisting morbidity be included in this assessment (24).

Because the risk of neurocognitive dysfunction is mainly age dependent, it is important to investigate the possibility of dose reduction, especially for very young patients (1, 39, 41). However, chemotherapy alone has been associated with an unacceptably high relapse rate, and this approach cannot be justified (42, 43). The combination of chemotherapy and low-dose RT is being increasingly investigated (16, 26, 44–46). The approach of delivering reduced-dose limited-field RT after a complete response to chemotherapy appears to be meritorious. The findings of these studies have suggested generally favorable outcomes, but the follow-up periods were short.

However, in addition to the delayed injury induced by RT, the late injury induced by chemotherapy is becoming increasingly evident. Cisplatin is considered an indispensable drug, but it may cause renal damage, ototoxicity, peripheral neuropathy, and sterility, and etoposide is associated with an excess frequency of secondary neoplasms (7, 29, 47). Because many germinoma patients are diagnosed with substantial preirradiation morbidity and are likely to be of an age at which the potential for radiation-related side effects is relatively small, the toxicity of standard RT faced by these patients might be less than anticipated. Additional prospective studies comparing conventional RT with combination chemotherapy and low-dose irradiation, with regard to both long-term survival and complications, should be planned, especially for adolescent and young adult patients.

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PHYSICS CONTRIBUTION

EVALUATION OF NOVEL MODIFIED TANGENTIAL IRRADIATION TECHNIQUE FOR BREAST CANCER PATIENTS USING DOSE–VOLUME HISTOGRAMS

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Purpose: We have previously reported that entire axillary lymph node regions could be irradiated by the modified tangential irradiation technique (MTIT). In this study, MTIT was compared with a conventional irradiation technique (CTIT) using dose–volume histograms to verify how adequately MTIT covers the breast and axillary lymph node region and the extent to which it involves the lung and heart.

Methods and Materials: Forty-four patients with early-stage breast cancer were treated by lumpectomy, axillary dissection, and postoperative radiotherapy. Twenty-two patients were treated with MTIT and 22 with CTIT. In 25 patients, the breast tumor was on the left and in 19 on the right. During axillary dissection, surgical clips were left as markers at the border of the axillary lymph node region. MTIT was planned by setting the dorsal edge of the radiation field on a lateral-view simulator film at the dorsal edge of the humeral head and the cranial edge of the radiation field at the caudal edge of the humeral head. CTIT was planned to ensure radiation of the breast tissue without considering the axillary region. In this study, all patients underwent computed tomography, and the CT data were transmitted on-line to a radiotherapy planning system, in which the dose-distribution computed tomography images and dose–volume histograms were calculated by defining the breast, axillary region (levels I, II, and III), lung, and heart region.

Results: Dose–volume histogram analysis demonstrated that breast tissue was radiated with an 86.5–100% volume (median 96.5%) by MTIT and an 83–100% volume (median, 95%) by CTIT at >95% of the isocenter dose. The axillary lymph node regions at Levels I, II, and III were irradiated with 84–100% (median, 94.5%), 59–100% (median, 89%), and 70–100% (median, 89.5%) volumes, respectively, by MTIT and with 2–84% (median, 38%), 0–53% (median, 15%), and 0–31% (median, 0%) volumes, respectively, by CTIT at >70% of the isocenter dose. The ipsilateral lung was irradiated with a 5–22% volume (median, 11.5%) by MTIT and 5–15% volume (median 9%) by CTIT at >90% of the isocenter dose. In all 25 left-sided breast cancer patients, the volumes irradiated with an 80% isocenter dose were <30 cm^3.

Conclusion: The results of our study demonstrated that the breast tissue was sufficiently irradiated with both CTIT and MTIT planning, the axillary lymph node areas irradiated by MTIT were much wider than those irradiated by CTIT at all levels, and the lung and heart volumes irradiated by MTIT were small. © 2004 Elsevier Inc.

Breast cancer, Modified tangential irradiation technique, Axillary lymph nodes, Dose–volume histogram analysis.

INTRODUCTION

The role of routine axillary dissection is controversial in the management of localized breast cancer (1–3), and the option to perform axillary radiotherapy (RT) without axillary dissection or with only sentinel node biopsy is only available for clinically node-negative patients (4–10). Recently, three-dimensional conformal tangential RT and intensity-modulated RT using computed tomography (CT)-based three-dimensional treatment planning have been applied (11, 12) in an effort to improve the local control rate and reduce toxicity. However, many

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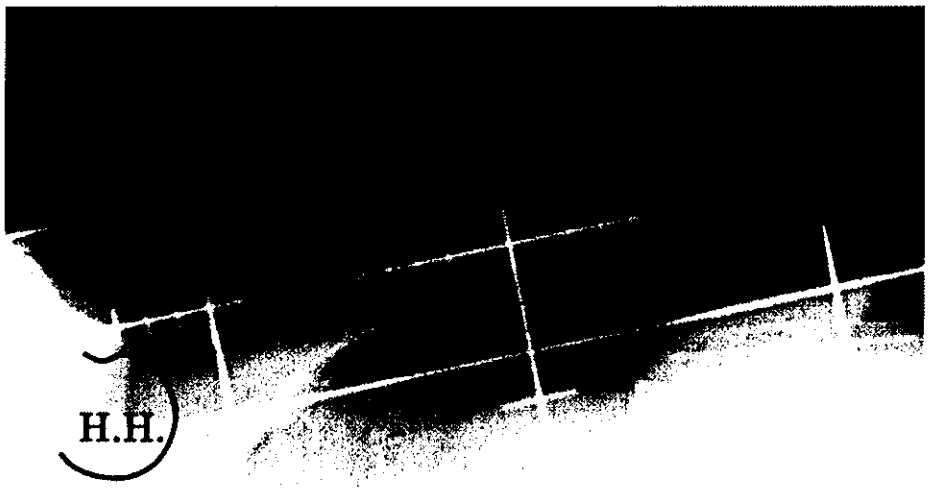
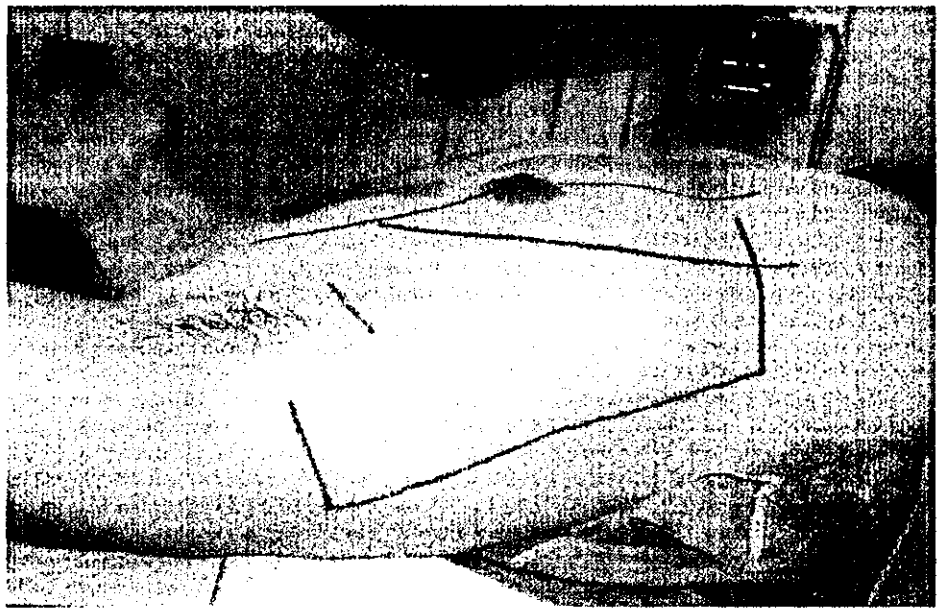


(a)



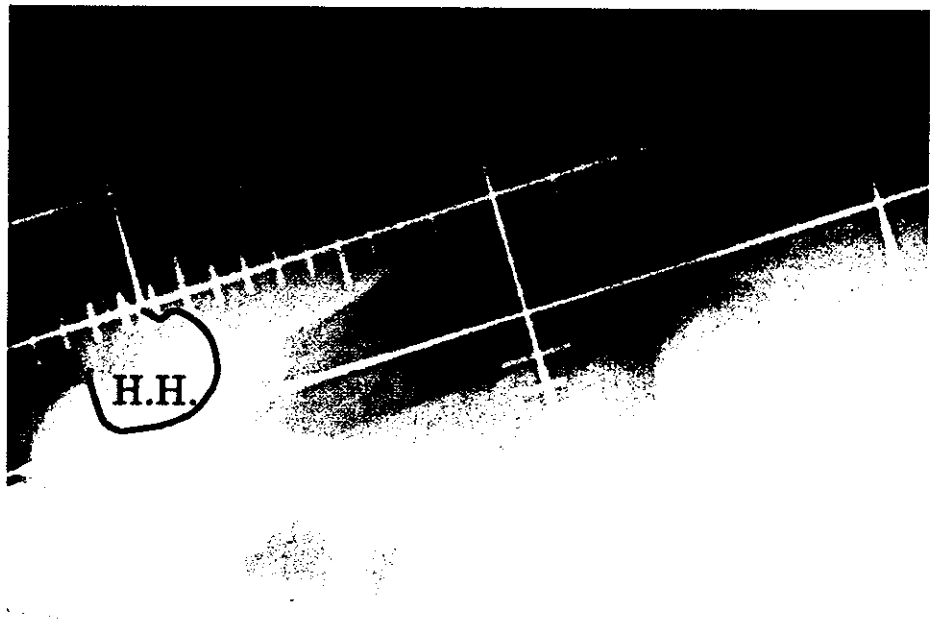
(b)

Fig. 1. Simulation films (anterior oblique view) and photographs of patients treated with (a,b) conventional irradiation technique and (c,d) modified tangential irradiation technique (MITT). In treatment with MTIT, field size tends to be wider in caudal and posterior directions and collimator and gantry angles tend to be deeper. Field from the anterior oblique view covers one-half of humeral head. H.H. = humeral head.

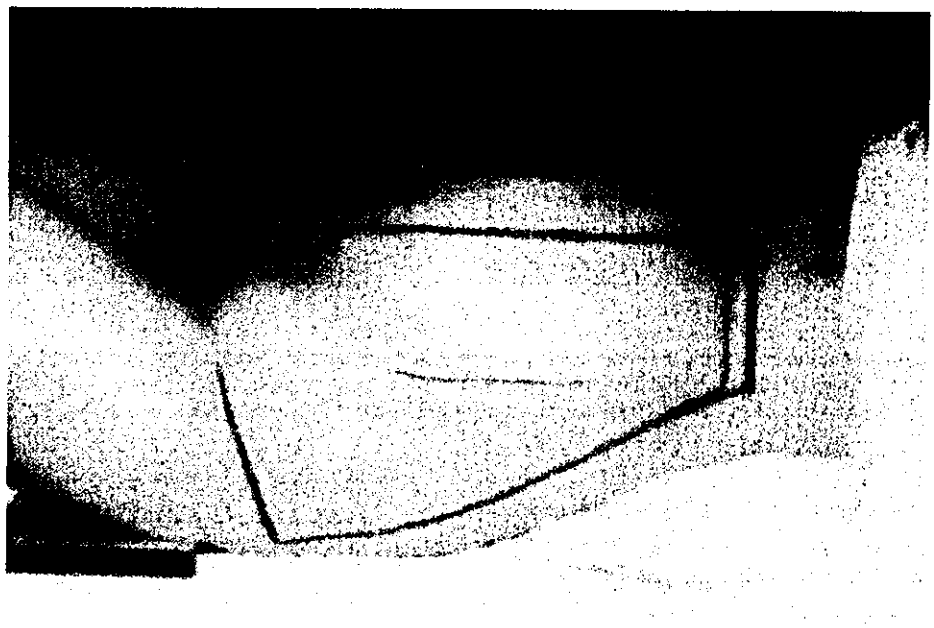
patients still undergo fluoroscopic simulation or planning without three-dimensional data (13), and coverage of the axillary lymph node region and involved lung and heart volumes by two-dimensional planning remains controversial (13, 14). As we previously reported, it is possible to irradiate almost the entire axillary lymph node region using the modified tangential irradiation technique (MTIT) (15). In this study, MTIT was compared with a conventional tangential irradiation technique (CTIT) using dose–volume histograms (DVHs) to verify how adequately MTIT covers the breast and axillary lymph node region and to estimate the extent of lung and heart RT.

METHODS AND MATERIALS

Between October 2000 and July 2001, 44 patients with early-stage breast cancer were treated by lumpectomy and axillary dissection at the Department of Surgery, Keio Uni-



(c)



(d)

Fig. 1. (*Cont'd*)

versity Hospital. During axillary dissection, surgical clips were left as markers at the following sites: in the chest wall under the pectoralis minor muscle at the level of the axillary vein; immediately adjacent to the subscapular vein; in the latissimus dorsi muscle at the level of the axillary vein; in the latissimus dorsi muscle at the level of the inferior margin of the dissection area; and in the latissimus dorsi muscle between the level of the axillary vein and the level of the inferior margin of the dissection area. All patients were female with an age range of 35–73 years (median, 49 years). Patients' height, weight, and above and below breast measurements were done before starting RT.

Postoperative RT was performed with a dose of 50 Gy (in 25 fractions) at the Department of Radiology, Keio University Hospital or Tokyo Metropolitan Hiroo Hospital. Twenty-two patients (11 with left- and 11 with right-sided breast cancer) with no, or minimal, lymphatic infiltration were treated with CTIT. CTIT was planned to irradiate the breast tissue without considering the axillary region. Figure 1a shows a simulation film, and Fig. 1b shows a patient treated

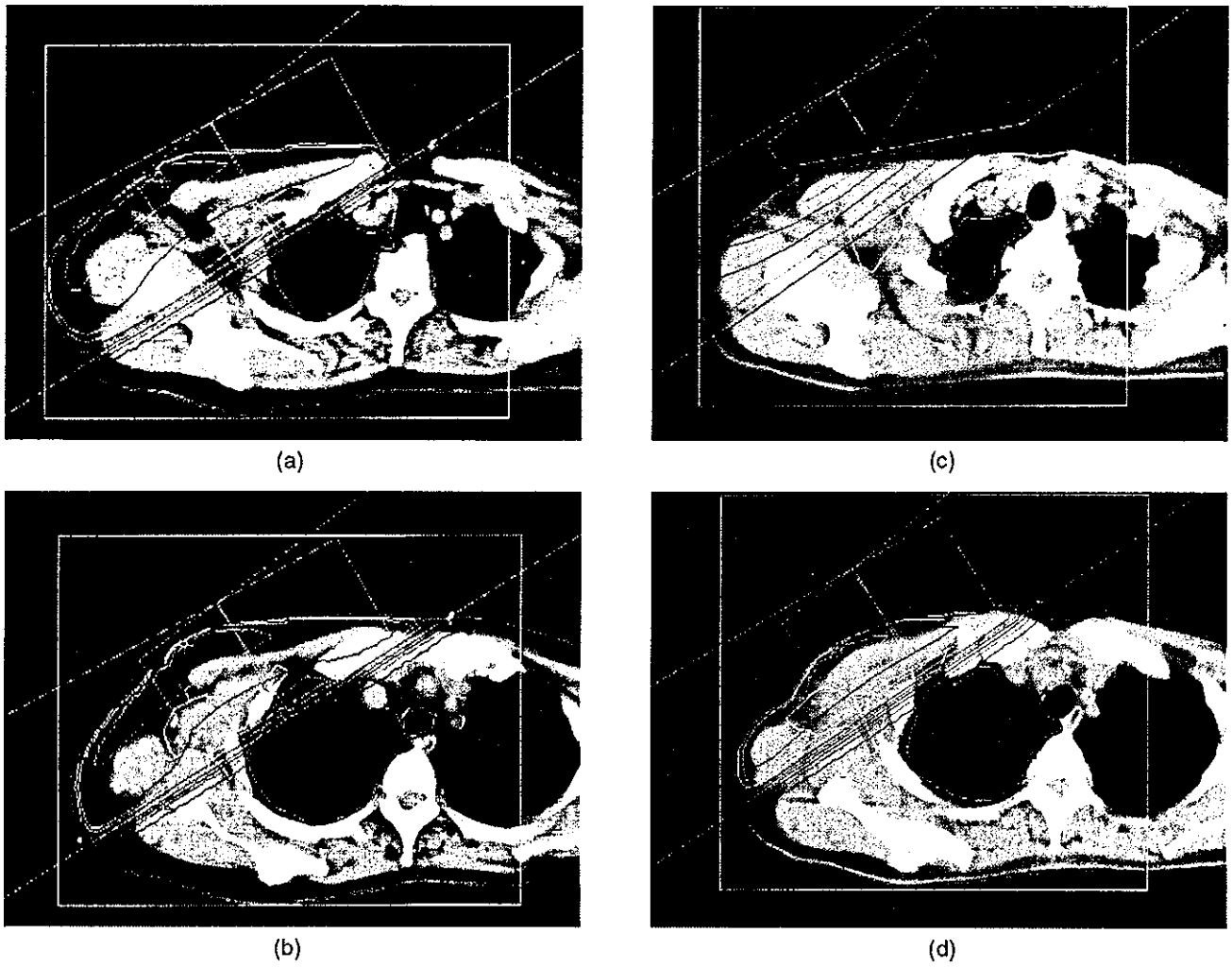


Fig. 2. Dose-distribution curve on CT slices: levels just below humeral head and axilla of patient treated with (a,b) MTIT and (c,d) CTIT. Surgical clips, seen in axillary region, were left as axillary dissection markers. White lines show limits of Levels I, II, and III. Green line is 100% isocenter dose line, blue 90%, yellow 80%, and so on.

with CTIT. The medial margin of the field was set up at the midline of the chest wall. The lateral margin was set up at the mid-axillary line. The cranial margin was 1–2 cm below the caudal edge of the humeral head. The caudal margin was 1 cm below the caudal edge of the palpable breast tissue. Twenty-two patients (14 with left- and 8 with right-sided breast cancer) with apparent lymphatic infiltration were treated with MTIT. MTIT was planned to irradiate the breast tissue and axillary region. Figure 1c shows a simulation film, and Fig. 1d shows a patient treated with MTIT. In this study, a conventional X-ray simulator was used to set the radiation field. MTIT was planned by setting the dorsal edge of the radiation field on a lateral-view simulator film at the dorsal edge of the humeral head and the cranial edge of the radiation field at the caudal edge of the humeral head, as previously reported (15). As a result, a 2–3-cm area of the humeral head was within the anterior-oblique radiation field. The collimator angle for MTIT thus had to be somewhat steeper than that of CTIT to decrease the lung volume

Table 1. Dose and volume analysis of breast, axillary regions, and lung

	MTIT (%)	CTIT (%)	95% Confidence limit
Breast			
105% dose	1–49 (22.5)	0–70 (10)	Not significant
95% dose	86–100 (96.5)	83–100 (95)	Not significant
Level I			
80% dose	79–100 (90)	1–79 (30.5)	Significant
70% dose	84–100 (94.5)	2–84 (38)	Significant
Level II			
80% dose	39–100 (81)	0–40 (8)	Significant
70% dose	59–100 (89)	0–53 (15)	Significant
Level III			
80% dose	45–100 (76)	0–20 (0)	Significant
70% dose	70–100 (89.5)	0–31 (0)	Significant
Ipsilateral lung			
90% dose	5–22 (11.5)	5–15 (9)	Significant
30% dose	12–32 (19)	10–22 (14.5)	Significant

Abbreviations: MTIT = modified tangential irradiation technique; CTIT = conventional tangential irradiation technique.
Data presented as range, with median in parentheses.

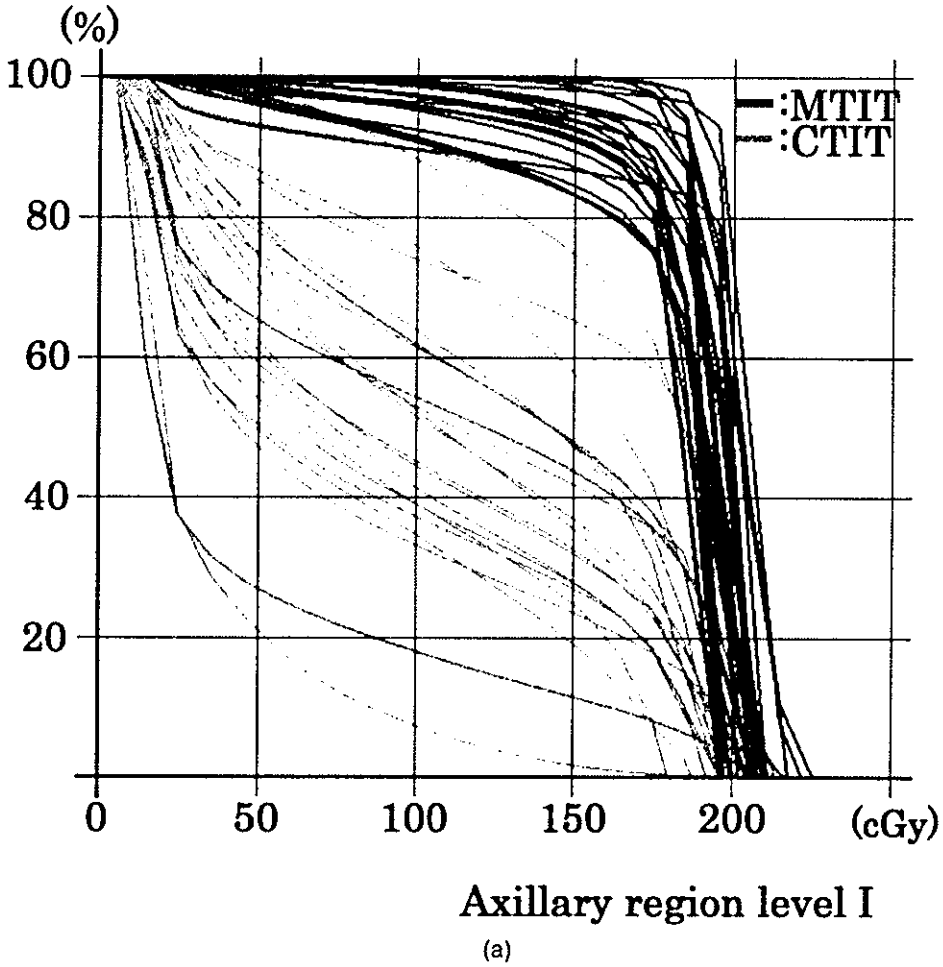


Fig. 3. DVH for patients treated with MTIT (black line) and CTIT (gray line) at (a) Level I, (b) Level II, and (c) Level III. DVHs show tolerable radiation doses at each axillary region level treated with MTIT in contrast to CTIT results.

irradiated. The medial and cranial margins were sometimes crossed over the mid-line of the chest wall.

All patients in this study underwent CT scanning with marking of the field margins and the isocenter, and the CT data were transmitted on-line to a RT planning system (FOCUS, version 2.50, Computerized Medical Systems, St. Louis, MO). The breast region was defined as the region exhibiting greater density than the surrounding fatty tissue on the CT images (displayed with a window width of 400 Hounsfield Units and a window level of 30 Hounsfield Units). The breast regions of patients >50 years, who might have had fatty degenerative changes in their breasts, were defined with 5-mm wider than margins used in other patients. Axillary lymph node regions (Levels I–III) were defined by referring to the position of the pectoralis minor muscle and the surgical clips inserted during surgery. The ipsilateral lung region was automatically defined and circumscribed by the system. The dose-distribution CT images and the DVHs for the breast, axillary lymph node region (Levels I–III), and lung were calculated for all patients. The heart volume irradiated was also calculated for the 25 patients with left-sided breast cancer.

Statistical analyses were performed using Welch's *t* test.

RESULTS

The height, weight, and above and below breast measurement for the CTIT and MTIT patients was 157.0 ± 5.0 cm and 157.0 ± 6.4 cm, 53.7 ± 5.3 kg and 54.0 ± 4.6 kg, 87.0 ± 7.0 cm and 86.6 ± 6.2 cm, and 76.8 ± 5.2 cm and 77.1 ± 5.4 cm, respectively. No differences were statistically significant between the two groups.

The dose distributions for MTIT are shown in Fig. 2a,b. and those for CTIT in Fig. 2c,d. The dose distributions on CT slices just below the humeral head level showed whole axillary regions were irradiated with MTIT; CTIT did not achieve full irradiation (Fig. 2a,c). At the CT slice level 2–3 cm below the humeral head, dorsal axillary regions were underdosed but almost the entire axillary region was covered by MTIT; however, dorsal axillary regions were not irradiated with CTIT (Fig. 2b,d).

Dose volume histogram analyses for the breast, axillary region (Levels I–III), and ipsilateral lung were performed in patients treated with MTIT and CTIT (Table 1). The breast tissue was irradiated with an 86.5–100% volume (median, 6.5%) by MTIT and 83–100% volume (median, 95%) by CTIT at >95% of the isocenter dose (Table 1). The DVHs

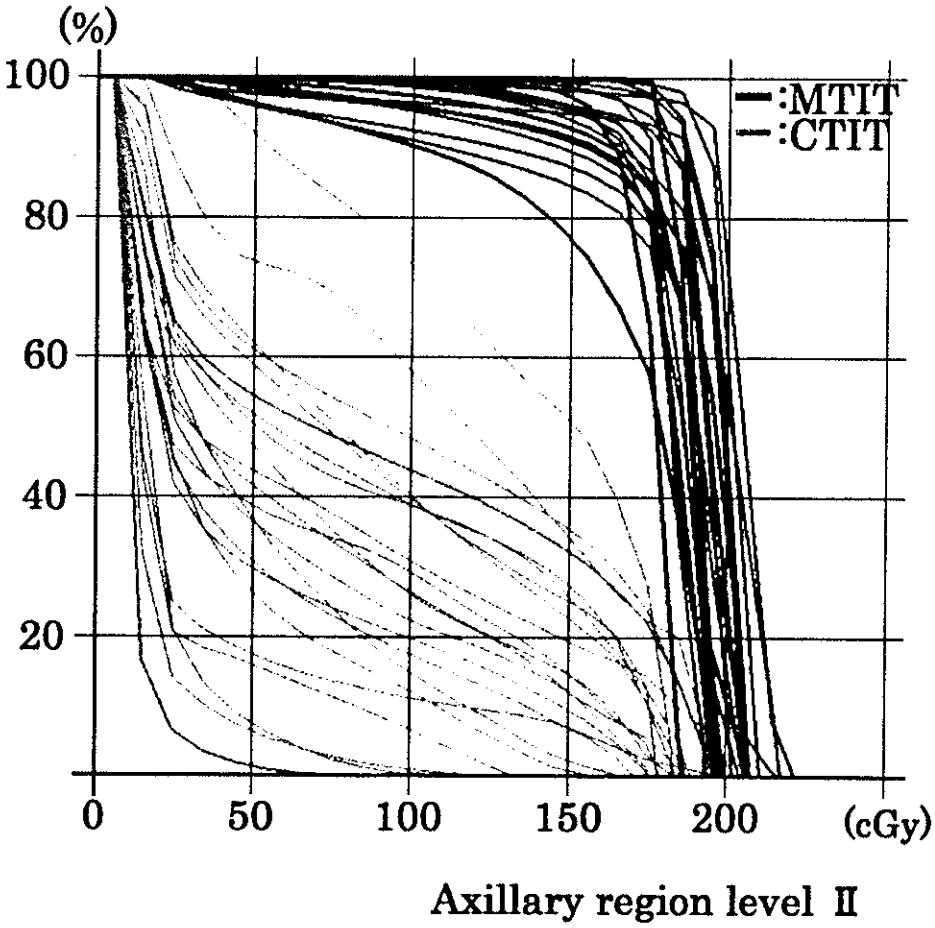


Fig. 3. (*Cont'd*).

for the axillary region Levels I, II, and III for all patients treated with MTIT and CTIT are shown in Fig. 3. DVH analyses demonstrated all axillary region levels to be well covered with MTIT compared with those treated with CTIT. The axillary lymph node regions at Levels I, II, and III were irradiated with 84–100% (median, 94.5%), 59–100% (median, 89%), and 70–100% (median, 89.5%) volumes by MTIT and 2–84% (median, 38%), 0–53% (median, 15%), and 0–31% (median, 0%) volumes by CTIT, respectively, at >70% of the isocenter dose (Table 1). The ipsilateral lung was irradiated with a 5–22% volume (median 11.5%) by MTIT and a 5–15% volume (median, 9%) by CTIT at >90% of the isocenter dose (Table 1). The irradiated dose and volume analysis of the heart for the 14 and 11 patients with left-sided breast cancer treated with MTIT and CTIT, respectively, are presented in Table 2. In all patients, the volumes irradiated with an 80% isocenter dose were <30 cm^3.

DISCUSSION

The role of routine axillary dissection in the management of localized breast cancer is controversial (1–3). Recently, early-stage breast cancer patients without clinically palpable axillary lymph nodes have reportedly been offered axillary RT without dissection (4–9). A randomized controlled study of early-stage breast cancer (National Surgical Adjuvant Breast and Bowel Project Breast-32 [NSABP B-32] is in progress, and the long-term survival and incidence of side effects will be compared between patients treated with sentinel lymph node biopsy and those receiving axillary lymph node dissection (11). Because the surgical procedures for breast cancer are smaller in scope, the radiation fields should be planned to cover wider regions. As we previously reported, it is possible to irradiate almost the entire axillary lymph node region by MTIT (15). In this study, we calculated the dose distribution and DVHs of the breast, axillary lymph node region, ipsilateral lung, and heart for all patients and demonstrated MTIT to be an adequate treatment method after breast-conserving surgery.

The breast region was defined as the area exhibiting greater density than the surrounding fatty tissue on CT. However, it is sometimes difficult to define the breast tissue in elderly patients in whom fatty degenerative change may be present in the breast. The breast region of patients >50 years old (about one-half of our patients) was determined with margins 5-mm wider than margins used in other pa-