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**CLINICAL INVESTIGATION** **Thoracic Cancer**

# PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

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**Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).**

**Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more ($V_{20}$) ≤30% received three to four cycles of cisplatin (80 mg/m$^2$ Day 1) and vinorelbine (20 mg/m$^2$ Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.**

**Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were $V_{20}$ >30% ($n$ = 10) and overdose to the esophagus ($n$ = 8) and brachial plexus ($n$ = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.**

**Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints.** © **2012 Elsevier Inc.**

**Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.**

## INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

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Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

## PATIENTS AND METHODS

### *Study design*

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more ($V_{20}$) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

### *Patient selection*

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age $\geq 20$ years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin $\geq 9.5$ g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin $\leq 1.5$ mg/dL and transaminase $\leq 80$ IU/L), renal function (serum creatinine $\leq 1.5$ mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

### *Pretreatment evaluation*

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

### *Treatment schedule*

Chemotherapy consisted of cisplatin 80 mg/m$^2$ on Day 1 and vinorelbine 20 mg/m$^2$ on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung $V_{20}$ was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

*Toxicity assessment and treatment modification*

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

*Dose-limiting toxicity and maximum tolerated dose*

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

*Response evaluation*

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

*Follow-up*

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

*Statistical analyses*

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

## RESULTS

*Registration and characteristics of the patients*

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis ($n = 1$) and anemia ($n = 2$) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of $V_{20}$ higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

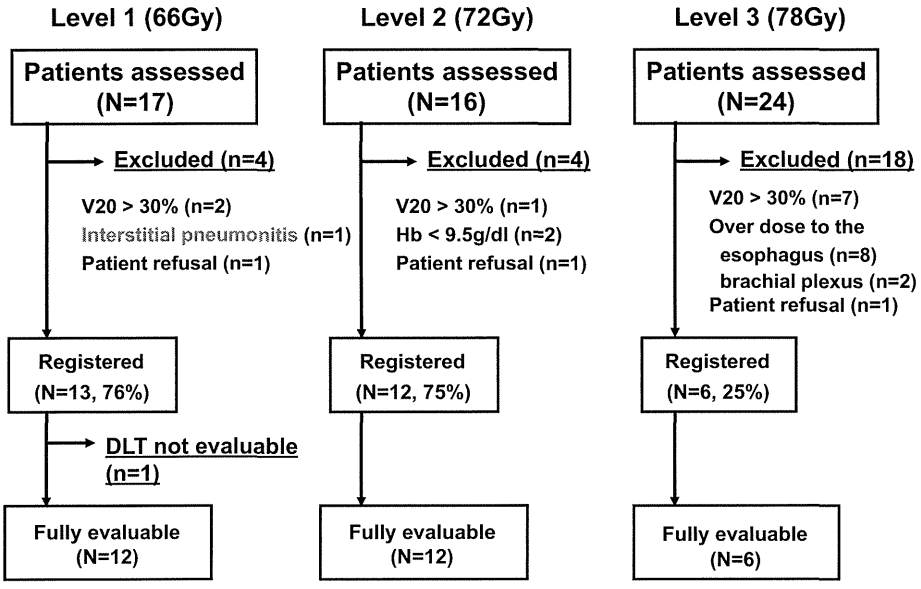


Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

*Treatment delivery*

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

*Toxicity and DLTs*

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

| Characteristic | *n* | (%) |
|---|---|---|
| Sex | | |
| M | 26 | (84) |
| F | 5 | (16) |
| Age (y) | | |
| Median (range) | 60 | (41–75) |
| Performance status | | |
| 0 | 25 | (81) |
| 1 | 6 | (19) |
| Body weight loss (%) | | |
| 0 | 26 | (84) |
| 0.1–5.0 | 2 | (6) |
| ≤5.0 | 3 | (10) |
| Histology | | |
| Adenocarcinoma | 23 | (74) |
| Squamous cell carcinoma | 4 | (13) |
| NSCLC, not otherwise specified | 4 | (13) |
| Stage | | |
| IIIA | 20 | (65) |
| IIIB | 11 | (35) |

*Abbreviation:* NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

| | Level 1 (*n* = 13) | Level 2 (*n* = 12) | Level 3 (*n* = 6) |
|---|---|---|---|
| Radiotherapy | | | |
| Total dose (Gy) | | | |
| 66 | 13 (100) | – | – |
| 72 | – | 12 (100) | – |
| 78 | – | – | 6 (100) |
| Delay (days) | | | |
| ≤5 | 11 (85) | 5 (42) | 5 (83) |
| 6–10 | 2 (15) | 6 (50) | 0 |
| 11–15 | 0 | 1 (8) | 1 (17) |
| Chemotherapy | | | |
| No. of cycles | | | |
| 4 | 6 (46) | 6 (50) | 4 (67) |
| 3 | 6 (46) | 4 (33) | 2 (33) |
| 2 | 0 | 1 (8) | 0 |
| 1 | 1 (8) | 1 (8) | 0 |
| No. of VNR omissions | | | |
| 0 | 10 (77) | 7 (58) | 2 (33) |
| 1 | 2 (15) | 4 (33) | 3 (50) |
| 2 | 0 | 0 | 1 (17) |
| 3 | 1 (8) | 1 (8) | 0 |

*Abbreviation:* VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

| | Grade | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Level 1 | | | ($n$ = 13) | Level 2 | | | ($n$ = 12) | Level 3 | | | ($n$ = 6) |
| Toxicity | 2 | 3 | 4 | (3+4 %) | 2 | 3 | 4 | (3+4 %) | 2 | 3 | 4 | (3+4 %) |
| Leukopenia | 4 | 6 | 2 | (62) | 1 | 3 | 8 | (92) | 1 | 3 | 2 | (83) |
| Neutropenia | 4 | 4 | 4 | (62) | 0 | 1 | 10 | (92) | 1 | 3 | 2 | (83) |
| Anemia | 8 | 2 | 2 | (31) | 7 | 3 | 1 | (33) | 2 | 2 | 0 | (50) |
| Thrombocytopenia | 0 | 0 | 0 | (0) | 1 | 1 | 0 | (8) | 0 | 0 | 0 | (0) |
| Febrile neutropenia | – | 1 | 0 | (8) | – | 3 | 0 | (25) | – | 1 | 0 | (17) |
| Infection | 0 | 0 | 1 | (8) | 0 | 1 | 0 | (8) | 2 | 0 | 0 | (0) |
| Esophagitis | 1 | 1 | 0 | (8) | 2 | 1 | 0 | (8) | 0 | 0 | 0 | (0) |
| Lung toxicity | 2 | 0 | 0 | (0) | 0 | 0 | 0 | (0) | 0 | 1 | 0 | (17) |
| Anorexia | 3 | 0 | 0 | (0) | 2 | 2 | 0 | (17) | 0 | 0 | 0 | (0) |
| Nausea | 3 | 0 | 0 | (0) | 3 | 0 | 0 | (0) | 0 | 0 | 0 | (0) |
| ALT elevation | 1 | 1 | 0 | (8) | 0 | 0 | 0 | (0) | 1 | 0 | 0 | (0) |
| CRN elevation | 7 | 0 | 0 | (0) | 4 | 0 | 0 | (0) | 0 | 0 | 0 | (0) |

*Abbreviations:* ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

*Preliminary efficacy results*

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

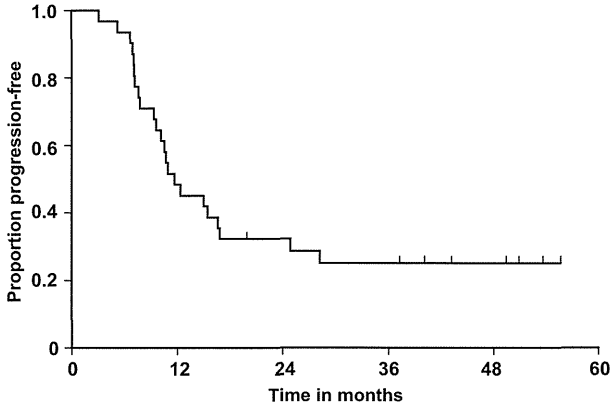


Fig. 2. Progression-free survival ($n$ = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

## DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites ($n$ = 31)

| Sites | $n$ | (%) |
|---|---|---|
| Local recurrence alone | 6 | (19) |
| Local and distant metastasis | 6 | (19) |
| Distant metastasis alone | 11 | (35) |
| Brain alone | 7 | (23) |
| No relapse | 8 | (26) |

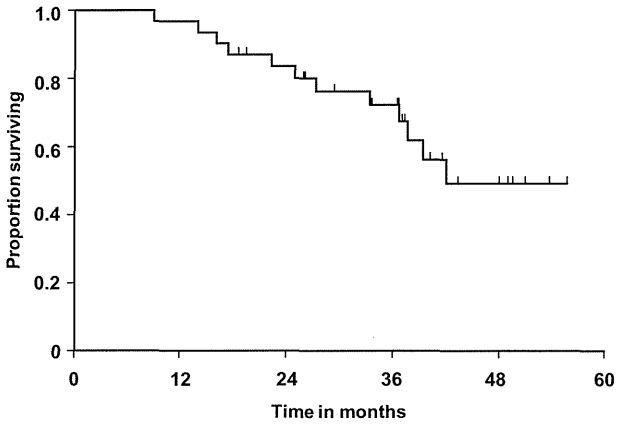


Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung $V_{20}$ often exceeded 30% when the total dose was increased to 78 Gy. This lung $V_{20}$ dose constraint might have been too strict. According to a recent review, it is prudent to limit $V_{20}$ to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of $V_{20}$ were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the $V_{20}$ was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

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ORIGINAL ARTICLE

# Japanese structure survey of radiation oncology in 2009 with special reference to designated cancer care hospitals

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**Abstract**
*Background* The structure of radiation oncology in designated cancer care hospitals in Japan was surveyed in terms of equipment, personnel, patient load, and geographic distribution, and compared with the structure in other radiotherapy facilities and the previous survey.

*Methods* The Japanese Society for Therapeutic Radiology and Oncology surveyed the national structure of radiation oncology in 2009. The structures of 365 designated cancer care hospitals and 335 other radiotherapy facilities were compared.

*Results* Designated cancer care hospitals accounted for 50.0 % of all the radiotherapy facilities in Japan. The patterns of equipment and personnel in designated cancer

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care hospitals and the other radiotherapy facilities were, respectively, as follows: linear accelerators per facility: 1.4 and 1.0; dual-energy function: 78.6 and 61.3 %; three-dimensional conformal radiotherapy function: 88.5 and 70.0 %; intensity-modulated radiotherapy function: 51.6 and 25.3 %; annual number of patients per linear accelerator: 301.3 and 185.2; Ir-192 remote-controlled afterloading systems: 31.8 and 4.2 %; and average number of full-time equivalent radiation oncologists per facility: 1.8 and 0.8. Compared with the previous survey, the ownership ratio of equipment and personnel improved in both designated cancer care hospitals and the other radiotherapy facilities. Annual patient loads per full-time equivalent radiation oncologist in the designated cancer care hospitals and the other radiotherapy facilities were 225.5 and 247.6, respectively. These values exceeded the standard guidelines level of 200.

*Conclusions* The structure of radiation oncology in designated Japanese cancer care hospitals was more mature than that in the other radiotherapy facilities. There is still a shortage of personnel. The serious understaffing problem in radiation oncology should be corrected in the future.

**Keywords** Radiotherapy · Medical engineering · Epidemiology

## Introduction

In Japan, the current utilization rate of radiotherapy (RT) for new cancer patients in Japan is only 27.7 % and surgery remains predominant [1]. This rate is very low when compared to those for western developed countries. The main reason for this is that there is not enough personnel, such as radiation oncologists (ROs), medical physicists (MPs), and radiotherapy technologists (RTTs) [2, 3]. The Cancer Control Act was implemented in 2007 in response to patients' urgent petitions to the Japanese government [4]. This law strongly advocates the promotion of RT and an increase in the number of ROs and MPs. At the same time, the Ministry of Health, Labour and Welfare began the accreditation of "designated cancer care hospitals (DCCHs)" with the aim of correcting regional differences in the quality of cancer care and strengthening cooperation among regional cancer care hospitals [5, 6]. The Japanese Society for Therapeutic Radiology and Oncology (JASTRO) has conducted national structure surveys of RT facilities in Japan every 2 years since 1990 [7]. Findings of these surveys indicate that the structure of radiation oncology in Japan has improved in terms of equipment and functioning in response to the increasing numbers of cancer patients who require RT.

In the study presented here, the structure of radiation oncology in DCCHs in Japan was analyzed in terms of equipment, personnel, patient load, and geographic distribution, and compared with these features in other RT facilities in Japan. In addition, the recent structure of RT facilities was compared with that surveyed in 2007 [2] and the medical care situation in Japan was compared with that in European countries and the USA.

## Methods and materials

A national survey in the form of a questionnaire on the structure of radiation oncology in Japan in 2009 was conducted by JASTRO from March 2010 to January 2011 [1]. The questionnaire consisted of items related to the number of treatment machines and type of modality, the number of personnel by job category, and the number of patients by type and disease site. The response rate was 90.9 % (700 out of 770) from all actual RT facilities in Japan. The number of DCCHs certified by the Ministry of Health, Labor and Welfare was 375 as of April 1, 2011 [8]. Of this total, 51 were designated prefectural and 324 were designated regional cancer care hospitals. The surveys were not returned by 20 facilities, and 3 facilities did not have departments of RT at the time of the survey, so that the structures of 365 DCCHs and 335 other RT facilities were analyzed. In this survey, full-time equivalent (FTE) (40 h/week for radiation oncology work only) data were surveyed in terms of the clinical working hours for RT of each staff member. SAS® 8.02 (SAS Institute Inc., Cary, NC, USA) [9] was used for the statistical analysis and statistical significance was determined by means of the $\chi^2$ test and Student's $t$ test.

The Japanese Blue Book Guidelines (JBBG) [10, 11] were used for comparison with the results of this study. These guidelines pertain to the structure of radiation oncology in Japan based on Patterns of Care Study (PCS) [12, 13] data. The standard guidelines for annual patient load per external beam equipment were set at 250–300 (warning level 400), those for annual patient load per FTE RO at 200 (warning level 300), and those for annual patient load per FTE RT technologists at 120 (warning level 200).

## Results

### Current situation of radiation oncology

Table 1 shows the current situation of radiation oncology in Japan. DCCHs accounted for 50.0 % (385/770) of all the RT facilities in Japan. The numbers of new patients and total patients in all RT facilities in Japan were estimated at approximately 201,000 (182,390 × 770/700) and 240,000 (205,087 × 770/700), respectively. For DCCHs,

**Table 1** Numbers of new patients and total patients (new plus repeat) requiring radiotherapy in designated cancer care hospitals and other radiotherapy hospitals

| | DCCHs | Other RT facilities | *p* value (95 % CI)[a] | Total |
|---|---|---|---|---|
| Facilities | 365 | 335 | – | 700 |
| New patients | 126,123[b] | 56,267 | – | 182,390[c] |
| Average new patients/facility | 345.5 | 168.0 | <0.0001 (146.7, 208.4) | 260.6 |
| Total patients (new + repeat) | 150,215[b] | 67,614 | – | 217,829[c] |
| Average total patients per facility | 411.5 | 201.8 | <0.0001 (171.6, 247.8) | 311.2 |

*DCCH* designated cancer care hospital, *RT* radiotherapy, *CI* confidence interval

[a] Student's *t* test

[b] The number of designated cancer care hospitals with RT was 385, and the number of new patients in DCCHs was estimated at approximately 134,000; the corresponding number of total patients (new plus repeat) was 159,000

[c] The number of radiotherapy facilities was 770 in 2009, and the number of new patients was estimated at approximately 201,000; the corresponding number of total patients (new plus repeat) was 240,000

the corresponding numbers were approximately 134,000 (126,123 × 385/365) and 159,000 (150,215 × 385/365). The number of new patients and total patients in DCCHs thus accounted for approximately 66.7 % (134,000/201,000) and 66.3 % (134,000/201,000 and 159,000/240,000) of the number of new patients and total patients in all RT facilities. The average numbers of new patients per facility were 345.5 for DCCHs and 168.0 for the other RT facilities, and for the average numbers of total patients per facility the corresponding figures were 411.5 and 201.8, respectively.

## Facility and equipment patterns and patient load per linear accelerator

The RT equipment patterns and related functions in Japan are shown in Table 2. In DCCHs, 496 linear accelerators (linacs) and 116 $^{192}$Ir remote-controlled after-loading systems (RALSs) were in current use, while the corresponding data for the other RT facilities were 320 and 14, respectively. The rate of equipment ownership at DCCHs was significantly higher than at the other RT facilities. As for the linac systems in DCCHs, the dual-energy function was used in 390 (78.6 %), the three-dimensional conformal radiotherapy (3D-CRT) function in 439 (88.5 %), and the IMRT function in 256 (51.6 %). For the other RT facilities, the corresponding figures were 196 (61.3 %), 224 (70.0 %), and 81 (25.3 %). The patient load per linac was 301.3 at DCCHs and 185.2 at the other RT facilities. Compared with the data for DCCHs in 2007 [2], the rate of linac ownership increased by 0.6 % while the rates of increase for installation of the various functions used with linacs were 3.8 % for dual-energy, 13.2 % for 3D-CRT, and 15.2 % for IMRT function. At the other RT facilities, the rate of linac ownership decreased by 0.4 %, while the rates of installation corresponding to those for DCCHs increased by 4.8, 9.5, and 5.5 %. The patterns for radiotherapy planning systems (RTPs) and other equipment are shown in Table 2. X-ray simulators were installed in 56.7 %, computed tomography (CT) simulators in 83.3 %, and RTPs in 97.3 % of the DCCHs, while the corresponding percentages for the other RT facilities were 44.2, 70.4, and 94.6 %. A noteworthy difference between the two types of facilities was found in the rates of X-ray simulator and CT simulator installation. Compared with the data for 2007 [3], X-ray simulator ownership at DCCHs decreased by 12.6 %, while CT simulator and RTP ownership increased by 8.2 and 0.5 %, respectively. At the other RT facilities, X-ray simulator ownership decreased by 8.8 % while CT simulator and RTP ownership increased by 13.7 and 0.8 %, respectively.

The distribution of annual patient load per linac in Japan is shown in Fig. 1. The patient load at 19.4 % of DCCHs and 4.6 % of the other RT hospitals exceeded the JBBG warning level of 400 patients per linac, but the average patient load per linac at the other facilities was below that level. Compared with the data for 2007 [2], the rate of facilities exceeding the JBBG warning level (400 patients per linac) decreased at both DCCHs (−0.8 %) and the other RT facilities (−0.7 %). However, the average number of total patients per facility increased at both DCCHs (1.6 %) and the other RT facilities (5.9 %).

## Staffing patterns and patient loads

Staffing patterns and patient loads in Japan are detailed in Table 3. The figures for total FTE ROs were 666.3 for DCCHs and 273.1 for the other RT facilities, while the corresponding average numbers of FTE ROs per facility were 1.8 and 0.8 and for patient load per FTE RO 225.5 and 247.6. The distribution of annual patient load per FTE RO in Japan is illustrated in Fig. 2. More than 300 patients per RO (JBBG warning level) were treated in 23.3 % of DCCHs and in 10.7 % of the other facilities. Figure 3 shows the distribution of facilities by patient load per FTE RO, with the largest number featuring a patient per FTE RO level in the 100–149 range for DCCHs and the other

**Table 2** Items of equipment, their function and patient load per unit of equipment in designated cancer care hospitals and other radiotherapy hospitals

| | DCCHs ($n$ = 365) | | Comparison with 2007 | Other RT facilities ($n$ = 335) | | Comparison with 2007 | $p$ value (95 % CI) | Total ($n$ = 700) | |
|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | % | $n$ | % | % | | $n$ | % |
| Linac | 496 | 98.6[a] | 0.6[c] | 320 | 90.4[a] | −0.4[c] | <0.0001[f] | 816 | 94.7[a] |
| With dual energy function | 390 | 78.6[b] | 3.8[c] | 196 | 61.3[b] | 4.8[c] | <0.0001[f] | 586 | 71.8[b] |
| With 3D-CRT function (MLC width ≤1.0 cm) | 439 | 88.5[b] | 13.2[c] | 224 | 70.0[b] | 9.5[c] | <0.0001[f] | 663 | 81.3[b] |
| With IMRT function | 256 | 51.6[b] | 15.2[c] | 81 | 25.3[b] | 5.5[c] | <0.0001[f] | 337 | 41.3[b] |
| Average no. linac per facility | 1.4 | – | 4.7[e] | 1.0 | – | 0.4[e] | <0.0001 (0.3, 0.4)[g] | 1.2 | – |
| Annual no. patients per linac | 301.3[d] | – | 1.6[e] | 185.2[d] | – | 5.9[e] | <0.0001 (86.8, 133.9)[g] | 255.8[d] | – |
| $^{192}$Ir RALS (actual use) | 116 | 31.8[a] | 2.3[c] | 14 | 4.2[a] | −1.2[c] | <0.0001[f] | 130 | 18.6[a] |
| X-ray simulator | 211 | 56.7[a] | −12.6[c] | 150 | 44.2[a] | −8.8[c] | 0.0009[f] | 361 | 50.7[a] |
| CT simulator | 324 | 83.3[a] | 8.2[c] | 251 | 70.4[a] | 13.7[c] | <0.0001[f] | 575 | 77.1[a] |
| RTP computer | 854 | 97.3[a] | 0.4[c] | 417 | 94.6[a] | 0.8[c] | 0.0757[f] | 1,271 | 96.0[a] |

*DCCH* designated cancer care hospital, *RT* radiotherapy, *CI* confidence interval, *Linac* linear accelerator, *IMRT* intensity-modulated radiotherapy, *RALS* remote-controlled after-loading system, *CT* computed tomography, *3D-CRT* three-dimensional conformal radiotherapy, *RTP* radiotherapy planning

[a] Percentage of facilities which have this equipment

[b] Percentage calculated from the number of systems using this function and the total number of linac systems

[c] Comparison with the data of 2007, calculated using the formula: data of 2009 (%) − data of 2007 (%)

[d] Percentage calculated from the number of patients and the number of linac units. Facilities without linacs were excluded from the calculation

[e] Rate of increase compared with the data of 2007, calculated using the formula: $\frac{\text{data of 2009 } (n) - \text{data of 2007 } (n)}{\text{data of 2007 } (n)} \times 100$ (%)

[f] $\chi^2$ test

[g] Student's $t$ test

RT facilities. Facilities with less than 1 FTE RO still account for about 31.2 % of DCCHs and 65.7 % of the other RT facilities. The average numbers of FTE ROs per facility and full-time JASTRO-certified ROs per facility at DCCHs increased by 11.5 and 6.7 %, respectively, compared with 2007 data, and for the other RT facilities, those numbers increased by 18.9 and 22.3 %. The annual patient load per FTE RO, on the other hand, decreased by 4.9 % at DCCHs and 9.4 % at the other RT facilities.

The total numbers of FTE RTTs were 1175.7 for DCCHs and 660.2 for the other RT facilities, and the corresponding average numbers of RTTs per facility were 3.2 and 2.0, while the patient loads per FTE RTT were 127.8 and 102.4. The distribution of annual patient load per FTE RTT in Japan is shown in Fig. 4. More than 200 patients per RTT (JBBG warning level) were treated in 11.0 % of DCCHs and in 7.5 % of the other RT facilities, while Fig. 5 shows the distribution of facilities by patient load per FTE RTT. The largest number of facilities featured a patient per FTE RTT level in the 100–119 range for DCCHs and the other RT facilities. The total numbers of FTE MPs and FTE RT nurses were 74.6 and 392.8, respectively, for DCCHs and 43.0 and 228.4 for the other RT facilities.

## Distribution of primary disease sites and palliative treatment

Table 4 shows the distribution of primary disease sites and palliative treatment at DCCHs and the other RT facilities. The most common disease site at DCCHs and the other RT facilities was the breast. Head/neck, esophagus, liver/biliary tract/pancreas, gynecologic, urogenital, prostate, hematopoietic/lymphatic, and skin/bone/soft tissue cancers were treated at higher rates at DCCHs than at the other RT facilities. The rates for other cancers were the reverse. Compared with the data for 2007, the percentage of breast cancers increased the most at DCCHs (1.4 %), and at the other RT facilities the percentage of head/neck and breast cancers increased significantly (2.4 and 2.3 %).

Brain metastasis was treated at higher rates at the other RT facilities (14.7 % of total patients) than at DCCHs (6.9 % of total patients), while the reverse was true for

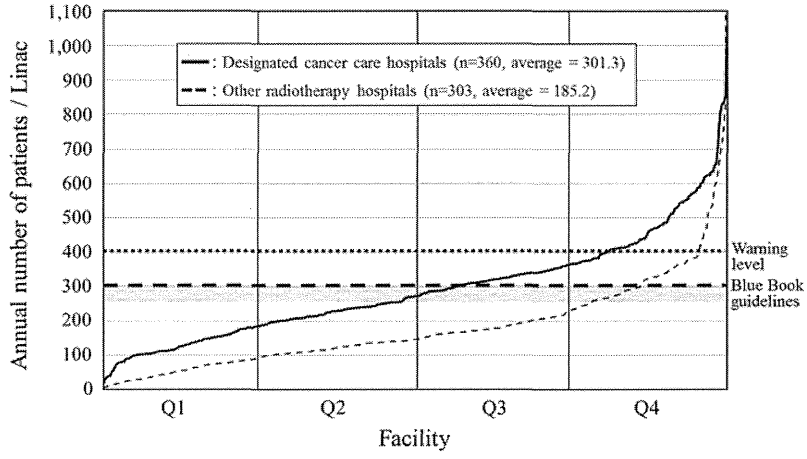


**Fig. 1** Distribution of annual patient loads per linear accelerator in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per treated equipment within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %

**Table 3** Structure and personnel of designated cancer care hospitals and other radiotherapy hospitals

| | DCCHs ($n$ = 365) | Comparison with 2007[a] (%) | Other RT facilities ($n$ = 335) | Comparison with 2007[a] (%) | $p$ value[b] | Total ($n$ = 700) |
|---|---|---|---|---|---|---|
| Facilities with RT beds | 190 | – | 108 | – | – | 298 (42.6) |
| Average no. RT beds per facility | 4.2 | −1.5 | 2.2 | 11.5 | – | 3.3 |
| Total (full + part-time) RO FTE | 666.3 | – | 273.1 | – | – | 939.4 |
| Average no. FTE ROs per facility | 1.8 | 11.5 | 0.8 | 18.9 | <0.0001 | 1.3 |
| JASTRO-certified RO (full-time) | 422 | – | 109 | – | – | 531 |
| Average no. JASTRO-certified ROs per facility | 1.2 | 6.7 | 0.3 | 22.3 | <0.0001 | 0.8 |
| Annual no. patients per FTE RO | 225.5 | −4.9 | 247.6 | −9.4 | <0.0001 | 231.9 |
| Total (full + part-time) RT technologist FTE | 1175.7 | – | 660.2 | – | – | 1836.0 |
| Average no. FTE RT technologists per facility | 3.2 | 16.8 | 2.0 | 9.1 | <0.0001 | 2.6 |
| Annual no. patients per FTE RT technologist | 127.8 | −9.2 | 102.4 | −1.3 | <0.0001 | 118.7 |
| Total (full + part-time) medical physicist FTE | 74.6 | 77.7 | 43.0 | 62.9 | – | 117.6 |
| Total (full + part-time) RT nurse FTE | 392.8 | 29.1 | 228.4 | 20.1 | – | 621.2 |

*DCCH* designated cancer care hospital, *RT* radiotherapy, *RO* radiation oncologist, *FTE* full-time equivalent (40 h/week only for RT practise), *JASTRO* Japanese Society for Therapeutic Radiology and Oncology

[a] Rate of increase compared with the data of 2007, calculated using the formula: $\frac{\text{data of 2009 } (n) - \text{data of 2007 } (n)}{\text{data of 2007 } (n)} \times 100\ (\%)$

[b] Student's $t$ test

bone metastasis (11.3 and 12.8 %, respectively). Compared with the data for 2007, the rate of brain and bone metastasis decreased in both DCCHs (−0.7 and −0.9 %) and the other RT facilities (−1.0 and −2.3 %).

## Discussion

The utilization rate of RT for new cancer patients in Japan is less than half of that in developed countries in Europe and in the USA [14]. However, RT is expected to play an increasingly important role in Japan because the increase in the elderly population is the highest among developed countries. The distribution of facilities by patient load per RO for DCCHs proved to be largely similar to that of the USA in 1989 [15]. While the numbers of ROs in both DCCHs and the other RT hospitals in Japan has increased, the facilities which have less than one FTE RO still account for 31.2 % of DCCHs and 65.7 % of the other RT facilities. In Japan, the majority of facilities still rely on

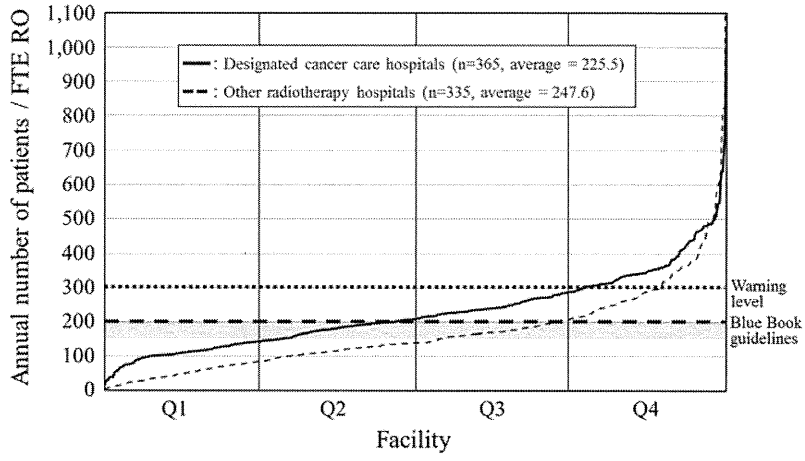


**Fig. 2** Distribution of annual patient loads per FTE RO in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per FTE RO within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %. Number of FTE RO for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RO

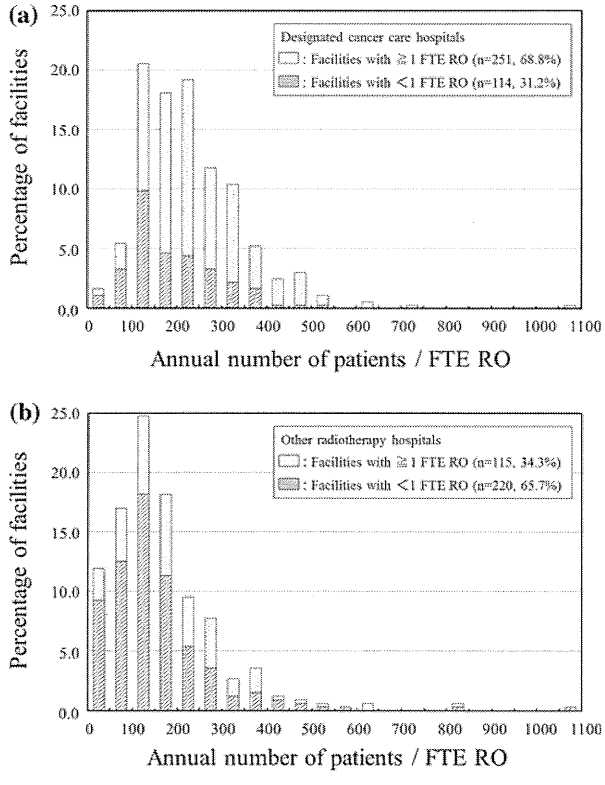


**Fig. 3** Percentage of facilities by patient loads per FTE RO in designated cancer care hospitals (**a**) and in the other radiotherapy hospitals (**b**). *Each bar* represents an interval of 50 patients per FTE RO. Number of FTE RO for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RO

part-time ROs, especially in facilities other than DCCHs, but in western developed countries, most facilities have at least 1 full-time RO. The distribution in Japan of facilities by patient load per RO for the other RT facilities in this study was similar to that in 1990 [15], so that a shortage of ROs has remained a major concern. More than 300 patients per RO (JBBG warning level) were treated in 17.6 % of all RT facilities. This is a matter of critical importance to the quality of radiotherapy.

A new educational system called "Cancer Professional Training Plan" by the Ministry of Education, Culture, Sports, Science and Technology, Japan is being developed in Japan to train specialists for cancer care, including ROs, MPs, medical oncologists, oncology nurses, and palliative care doctors. The average number of RT staff members at DCCHs was greater than that in the other RT hospitals. As noted above, there is still a shortage of Ros, although the numbers have increased. In Japan, many RT hospitals do not have an independent department for RT. One way to increase the number of ROs is to create an independent department for RT. The numbers of MPs in Japan are still smaller than those in western developed countries, and they work mainly in metropolitan areas or academic facilities, such as university hospitals or cancer centers. At present, no national license is available for MPs in Japan, but those with a master's degree in radiation technology or science and engineering can take the accreditation test for MPs administered by the Japanese Board of Medical Physics (JBMP). Compared with ROs and MPs, a sufficient number of RTTs is ensured in Japan. However, there is a significant number of hospitals with less than 1 FTE RTT in both DCCHs ($n = 13$) and the other RT hospitals ($n = 50$). In addition, many RTTs are extremely busy because they must also partially act as MPs. As for equipment, the ownership of equipment for advanced high-precision radiation therapy machines increased compared with 2007 at all RT facilities, especially DCCHs, indicating that the accreditation of DCCHs closely correlates with the maturity of the radiation oncology structure. Further accreditation of DCCHs by the Ministry of Health, Labor, and Welfare would be a move in the right direction towards a more balanced geographic consolidation of RT facilities in Japan.

The findings of this study show that, on a regional basis, DCCHs were located in the most suitable areas. There were

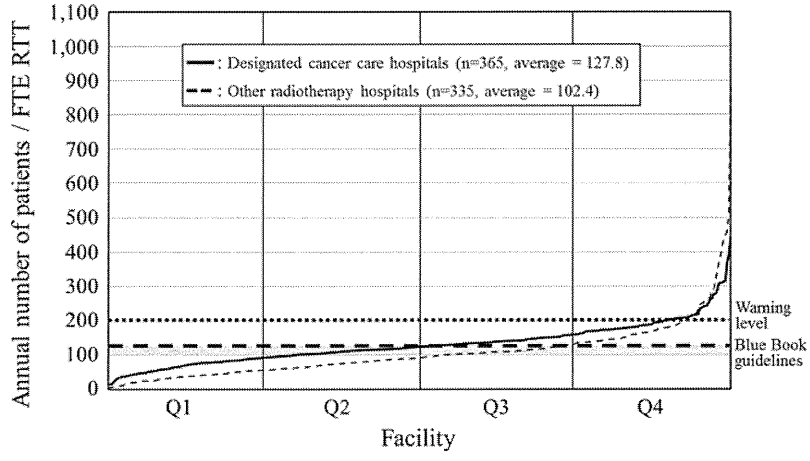


**Fig. 4** Distribution of annual patient loads per FTE RTT in designated cancer care hospitals and the other radiotherapy facilities. *Horizontal axis* represents facilities arranged in order of increasing value of annual number of patients per FTE RTT within facilities. *Q1* 0–25 %, *Q2* 26–50 %, *Q3* 51–75 %, *Q4* 76–100 %. Number of FTE RTT for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RTT

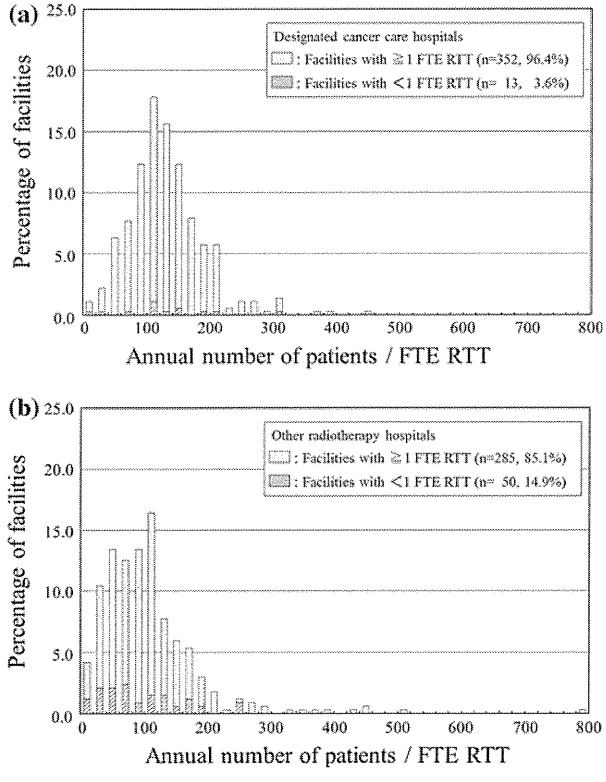


**Fig. 5** Percentage of facilities by patient loads per FTE RTT in designated cancer care hospitals (**a**) and in the other radiotherapy hospitals (**b**). *Each bar* represents an interval of 20 patients per FTE RTT. Number of FTE RTT for facilities with FTE <1 was calculated as FTE = 1 to avoid overestimating patient loads per FTE RTT

388 DCCH facilities by the end of fiscal year 2011 because some further university facilities with many patients undergoing RT had been certified as DCCHs since the previous survey, while some small-scale facilities were not certified as DCCHs by the Ministry of Health, Labor, and Welfare. In terms of nationwide distribution, there seem to be enough RT facilities in Japan. On the other hand, the RT potential of RT facilities other than DCCHs in Japan remains unrealized because of personnel shortages. The most frequent primary disease site treated with RT at the other RT facilities changed from lung/trachea/mediastinum to breast, compared with the data for 2007, while at DCCHs, the most frequently treated primary disease site, the breast, remained unchanged from 2007. Finally, the number of patients with brain and bone metastasis did not increase since 2007.

To evaluate medical care systems for cancer at regular intervals, it is very important to collect detailed information on all cancer care facilities. In Japan, the structural data for all RT facilities is regularly surveyed by JASTRO. In addition, the procedures and the outcome data of cancer care for patients undergoing RT have been conducted by PCS every 4 years, but insufficient outcome data is collected. In the USA, a National Cancer Data Base was established in 1989 and since then has been collecting comprehensive data on cancer care, and this database is used as the quality indicator for improvements in the processes and outcomes of cancer care [16, 17]. We have established a Japanese National Cancer Database based on the RT data in Japan and we are preparing to use this system for the collection of cancer care data.

In conclusion, the RT structure of DCCHs in Japan showed more maturity than that of other RT facilities in terms of equipment, functions, and staff. However, there is still a shortage of personnel (ROs, RTTs, MPs, RT nurses, and so on) in radiation oncology in Japan. The structure survey data presented and discussed here seemed to be both fundamental and important for a clear and accurate understanding of the medical care system for radiation oncology in Japan. As this survey data makes clear, a

**Table 4** Primary sites of cancer, brain metastasis, and bone metastasis treated with RT in designated cancer care hospitals and the other radiotherapy hospitals

| Primary site | DCCHs ($n$ = 344) | | Comparison with 2007[a] | Others ($n$ = 300) | | Comparison with 2007[a] | $p$ value[b] | Total ($n$ = 644) | |
|---|---|---|---|---|---|---|---|---|---|
| | $n$ | % | % | $n$ | % | % | | $n$ | % |
| Cerebrospinal | 4,719 | 3.9 | 0.2 | 4,342 | 8.5 | −1.1 | <0.0001 | 9,061 | 5.8 |
| Head and neck (including thyroid) | 13,084 | 10.9 | −0.2 | 5,021 | 9.8 | 2.4 | <0.0001 | 18,105 | 9.8 |
| Esophagus | 7,306 | 6.1 | −0.4 | 2,288 | 4.5 | −0.6 | <0.0001 | 9,594 | 6.0 |
| Lung, trachea, and mediastinum | 21,600 | 18.0 | −0.6 | 10,707 | 21.0 | −0.5 | <0.0001 | 32,307 | 19.5 |
| Lung | 19,532 | 16.2 | −0.6 | 9,659 | 18.9 | 0.7 | <0.0001 | 29,191 | 17.3 |
| Breast | 27,706 | 23.0 | 1.4 | 12,128 | 23.8 | 2.3 | 0.0008 | 39,834 | 21.5 |
| Liver, biliary, tract, and pancreas | 4,733 | 3.9 | −0.1 | 1,908 | 3.7 | 0.3 | 0.0577 | 6,641 | 3.8 |
| Gastric, small intestine, and colorectal | 5,693 | 4.7 | −0.2 | 2,586 | 5.1 | −0.4 | 0.0029 | 8,279 | 5.1 |
| Gynecologic | 6,851 | 5.7 | 0.0 | 1,365 | 2.7 | −0.6 | <0.0001 | 8,216 | 4.9 |
| Urogenital | 16,641 | 13.8 | 0.7 | 6,409 | 12.6 | −0.2 | <0.0001 | 23,050 | 13.0 |
| Prostate | 12,830 | 10.7 | 0.9 | 5,089 | 10.0 | 0.6 | <0.0001 | 17,919 | 9.6 |
| Hematopoietic and lymphatic | 6,176 | 5.1 | −0.3 | 1,773 | 3.5 | −0.1 | <0.0001 | 7,949 | 4.8 |
| Skin, bone, and soft tissue | 3,014 | 2.5 | −0.1 | 1,079 | 2.1 | −0.7 | <0.0001 | 4,093 | 2.7 |
| Other (malignant) | 1,359 | 1.1 | −0.2 | 582 | 1.1 | −0.3 | 0.8388 | 1,941 | 1.4 |
| Benign tumors | 1,407 | 1.2 | −0.3 | 813 | 1.6 | −0.4 | <0.0001 | 2,220 | 1.6 |
| Pediatric < 15 years (included in totals above) | 900 | 0.7 | 0.0 | 192 | 0.4 | −0.1 | <0.0001 | 1,092 | 0.6 |
| Total | 120,289 | 100.0 | 0.0 | 51,001 | 100.0 | 0.0 | | 171,290[c] | 100.0 |
| Metastasis | ($n$ = 365) | | | ($n$ = 335) | | | | ($n$ = 700) | |
| Brain | 10,361 | 6.9 | −0.7 | 9,973 | 14.7 | −1.0 | <0.0001 | 20,334 | 10.4 |
| Bone | 19,293 | 12.8 | −0.9 | 7,613 | 11.3 | −2.3 | <0.0001 | 26,906 | 13.6 |

[a] Comparison with the data of 2007, calculated using the formula: data of 2009 (%) − data of 2007 (%)

[b] $\chi^2$ test

[c] Number of total new patients is different with these data, because no data on primary sites were reported by some facilities

national policy is needed to improve the establishment of DCCHs and overcome the shortage of personnel for cancer care.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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**Original Article**

# Survey of Advanced Radiation Technologies Used at Designated Cancer Care Hospitals in Japan

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**Objective:** Our survey assessed the use of advanced radiotherapy technologies at the designated cancer care hospitals in Japan, and we identified several issues to be addressed.
**Methods:** We collected the data of 397 designated cancer care hospitals, including information on staffing in the department of radiation oncology (e.g. radiation oncologists, medical physicists and radiation therapists), the number of linear accelerators and the implementation of advanced radiotherapy technologies from the Center for Cancer Control and Information Services of the National Cancer Center, Japan.
**Results:** Only 53% prefectural designated cancer care hospitals and 16% regional designated cancer care hospitals have implemented intensity-modulated radiotherapy for head and neck cancers, and 62% prefectural designated cancer care hospitals and 23% regional designated cancer care hospitals use intensity-modulated radiotherapy for prostate cancer. Seventy-four percent prefectural designated cancer care hospitals and 40% regional designated cancer care hospitals employ stereotactic body radiotherapy for lung cancer. Our multivariate analysis of prefectural designated cancer care hospitals which satisfy the institute's qualifications for advanced technologies revealed the number of radiation oncologists ($P = 0.01$) and that of radiation therapists ($P = 0.003$) were significantly correlated with the implementation of intensity-modulated radiotherapy for prostate cancer, and the number of radiation oncologists ($P = 0.02$) was correlated with the implementation of stereotactic body radiotherapy. There was a trend to correlate the number of medical physicists with the implementation of stereotactic body radiotherapy ($P = 0.07$). Only 175 (51%) regional designated cancer care hospitals satisfy the institute's qualification of stereotactic body radiotherapy and 76 (22%) satisfy that of intensity-modulated radiotherapy. Seventeen percent prefectural designated cancer care hospitals and 13% regional designated cancer care hospitals had a quality assurance committee.
**Conclusions:** The numbers of radiation oncologists and other operating staff might be essential factors in the implementation of advanced radiotherapy technologies. Small proportions of regional designated cancer care hospitals satisfy the institute's qualifications of advanced technologies.

*Key words: radiotherapy – stereotactic body radiotherapy – intensity-modulated radiotherapy – advanced radiotherapy technology*

## INTRODUCTION

Several advanced radiotherapy technologies have been introduced over the last decade, and their use has contributed to both reductions in the rates of treatment-related complications and improvements in patients' quality of life after cancer treatment (1–3). In the USA, the proportion of intensity-modulated radiotherapy (IMRT) used for patients with prostate cancer rose from 28.7% in 2002 to 81.7% in 2005 (4), and the proportion of IMRT for head and neck cancers rose from 1.3% in 2000 to 46.1% in 2005 (5). Pan et al. (6) conducted a survey on the use of advanced radiotherapy technologies in the USA, and they found that the cumulative adoption of stereotactic body radiotherapy (SBRT) for the treatment of any disease site was <5% in 2000 versus >60% in 2010. The percentage of physicians using SBRT was 63.9%, but nearly one-half of the physicians reported that they first used SBRT in 2008 or later. IMRT and SBRT have rapidly become widely adopted among American radiation oncologists (ROs).

The Japanese government enacted the Basic Act for Anti-Cancer Measures in June 2006 to promote comprehensive strategies against cancer. The government set basic guidelines and founded a system of designated cancer care hospitals (DCCHs). The prefectural DCCH (P-DCCH) is defined as the coordinating hospital of each prefecture (the 47 prefectures in Japan are akin to the states in the USA), and the regional DCCHs (R-DCCHs) are mainly cardinal hospitals in the secondary medical care area of prefecture. The DCCHs are required to cooperate with each other to deliver comprehensive cancer care, including adequate radiotherapy, surgical treatment, systemic chemotherapy and palliative care to all citizens.

We conducted the present study to survey the current situation regarding the use of novel radiotherapy technologies such as IMRT and SBRT at all of the DCCHs in Japan.

## PATIENTS AND METHODS

There are currently two national cancer centers: 51 P-DCCHs and 344 R-DCCHs in Japan (total, 397 DCCHs). We included the two national cancer centers in the grouping of P-DCCHS for a total of 53 hospitals that are defined as P-DCCHs in this analysis. We obtained the institutional information of the DCCHs from the Center for Cancer Control and Information Services of the National Cancer Center, Japan. The data from each DCCH were submitted to the Ministry of Health, Labor and Welfare of Japan in October 2011, and that of each DCCH has been updated on a regular basis.

We collected the data of all 397 DCCHs, which included the number of medical staff working in radiotherapy departments, such as ROs, medical physicists (MPs), radiotherapy quality managers (RQMs) and radiation therapists (RTs), the number of linear accelerators, the number of patients who were treated with radiotherapy per year and radiotherapy use for each disease site in detail (e.g. SBRT, IMRT and brachytherapy) as of November 2012. We calculated the proportion of implementation of the advanced radiation techniques for IMRT for head and neck and prostate cancers, and SBRT for lung cancer according to each kind of DCCH. The proportion of implementation means that of institutions which have potential availability of advanced radiation technologies.

Differences between the two sample medians for continuous variables were analyzed using Pearson's chi-squared test. $P$ values of $<0.05$ were considered significant. Multivariate analyses were performed using the logistic regression model. Statistical analyses were performed using JMP version 10.0.0 (SAS Institute, Inc.).

## RESULTS

### Institute's Qualification for Advanced Radiotherapy Technologies

Japanese health insurance providers cover the cost of SBRT and IMRT only at hospitals which satisfy the institute's qualification including the number and year of experience of full-time ROs, appropriate treatment machine and planning systems for these advanced radiotherapy techniques and adequate radiotherapy quality control (QC) system. The institute's qualification for IMRT includes (i) two or more full-time ROs, (ii) at least one of them who has over 5 years experience in radiotherapy, (iii) at least one full-time RT who has over 5 years experience in radiotherapy, (iv) appropriate treatment machine and inverse planning systems for IMRT and (v) adequate radiotherapy QC system. The institute's qualification for stereotactic radiotherapy (SRT) includes (i) at least one full-time RO, (ii) appropriate treatment machine for SRT and (iii) appropriate treatment system for SRT. Thirty P-DCCHs (57%) satisfy the institute's qualification for IMRT, and 76 R-DCCHs (22%) satisfy it ($P < 0.001$). Forty-seven P-DCCHs (89%) with institute's qualification for SRT, and 175 R-DCCHs (51%) satisfy it ($P < 0.001$).

### IMRT for Head and Neck Cancers

In November 2012, only 53% P-DCCHs and 16% R-DCCHs had been using IMRT for head and neck cancers. The results of our univariate analyses of the implementation of IMRT for head and neck cancers, which included the number of linear accelerators, those of medical staff such as ROs, RTs, RQMs and MPs are shown in Table 1 according to the types of DCCH. We analyzed the 30 P-DCCHs which satisfy the institute's qualification for IMRT, and the multivariate analysis including the five factors listed above revealed that there was no factor associated with IMRT implementation for head and neck cancers (Table 2). But there was a trend to correlate the number of ROs with IMRT implementation for head and neck cancers ($P = 0.08$). We analyzed the 76 R-DCCHs with institute's qualification for IMRT, and the multivariate analysis revealed that there was no factor associated with IMRT implementation for head and neck cancers (Table 2).

**Table 1.** Univariate analysis of implementation of IMRT and SBRT according to the type of designated cancer care hospital

| | Prefectural designated cancer care hospitals | | | Regional designated cancer care hospitals | | |
|---|---|---|---|---|---|---|
| | Implementation, median (range) | Non-implementation, median (range) | *P* value | Implementation, median (range) | Non-implementation, median (range) | *P* value |
| IMRT for head and neck cancer | | | | | | |
| No. of linear accelerators | 3 (2–4) | 2 (1–4) | 0.07 | 2 (1–3) | 1 (1–3) | 0.0001 |
| No. of ROs | 4 (1–11) | 2 (0–5) | 0.06 | 2 (0–36)[b] | 1 (0–8) | 0.0001 |
| No. of radiation therapists | 6.5 (2–15) | 4 (1–18) | 0.33 | 4 (1–11) | 2 (1–10) | 0.0001 |
| No. of radiation quality managers | 2 (1–18) | 2 (1–5) | 0.26 | 2 (1–8) | 2 (1–9) | 0.28 |
| No. of medical physicists | 1 (0–5) | 1 (0–3) | 0.41 | 1 (0–7) | 0 (0–4) | 0.0001 |
| IMRT for prostate cancer[a] | | | | | | |
| No. of linear accelerators | 3 (1–4) | 2 (1–4) | 0.16 | 2 (1–3) | 1 (1–3) | 0.0001 |
| No. of ROs | 4 (1–11) | 3 (0–7) | 0.38 | 2 (0–36)[b] | 1 (0–8) | 0.0001 |
| No. of radiation therapists | 7 (2–15) | 4 (2–18) | 0.01 | 4 (1–11) | 2 (1–10) | 0.0001 |
| No. of radiation quality managers | 2 (1–13) | 1 (1–18) | 0.49 | 2 (1–8) | 2 (1–9) | 0.20 |
| No. of medical physicists | 1 (0–5) | 0.5 (1–4) | 0.57 | 1 (0–7) | 0 (0–4) | 0.0001 |
| SBRT for lung cancer | | | | | | |
| No. of linear accelerators | 3 (1–4) | 2 (1–4) | 0.14 | 1 (1–3) | 1 (1–3) | 0.0001 |
| No. of ROs | 3 (1–11) | 2 (0–5) | 0.12 | 1 (0–9)[b] | 1 (0–36) | 0.0001 |
| No. of radiation therapists | 6 (1–18) | 4 (1–12) | 0.11 | 3 (1–11) | 2 (1–8) | 0.0001 |
| No. of radiation quality managers | 2 (1–18) | 1.5 (1–5) | 0.73 | 2 (1–8) | 2 (1–9) | 0.15 |
| No. of medical physicists | 1 (0–5) | 0.5 (0–4) | 0.16 | 1 (0–7) | 0 (0–4) | 0.007 |

Data are expressed as median (range) values unless otherwise specified.
ROs, radiation oncologists; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.
[a]The data of three hospitals were not available.
[b]A part of hospitals which have full-time radiation oncologists seem to submit under-reporting of them in error.

### IMRT for Prostate Cancer

Only 62% P-DCCHs and 23% R-DCCHs had been using IMRT for prostate cancer. The results of the univariate analysis of IMRT for prostate cancer, which included the five factors listed above, are shown in Table 1 according to the types of DCCHs. We analyzed the 30 P-DCCHs with institute's qualification for IMRT, and the multivariate analysis revealed that the number of ROs ($P = 0.01$) and that of RTs ($P = 0.003$) were significantly correlated with IMRT implementation for prostate cancers (Table 2). Our multivariate analysis of the 76 R-DCCHs with institute's qualification for IMRT revealed no factor associated with IMRT implementation for prostate cancer.

### SBRT for Lung Cancer

At the time of our survey, 74% P-DCCHs and 40% R-DCCHs were using SBRT for lung cancer. The results of the univariate analysis of SBRT for lung cancer are shown according to the types of DCCH (Table 1). We analyzed the 47 P-DCCHs with institute's qualification for SBRT, and the multivariate analysis including the five factors listed above revealed that the number of ROs was significantly correlated with SBRT implementation for lung cancers ($P = 0.02$) (Table 2). There was a trend to correlate the number of MPs with SBRT implementation for lung cancers ($P = 0.07$). We analyzed the 175 R-DCCHs with institute's qualification for SBRT, and the multivariate analysis revealed that there was no factor associated with SBRT implementation for lung cancers at these hospitals.

### Quality Assurance/Quality Control (QA/QC) System

The freedom of information act data from the Center for Cancer Control and Information Services showed that only nine P-DCCHs (17%) and 46 R-DCCHs (13%) had a radiotherapy quality assurance (QA) committee, and the output dose of linear accelerators was evaluated by a third party in only 26 P-DCCHs (49%) and 150 R-DCCHs (44%).

## DISCUSSION

IMRT reduces the dose to the organ at risk while maintaining good coverage of the target (1), and it has rapidly become a

**Table 2.** Multivariate analysis of implementation of IMRT and SBRT according to the type of designated cancer care hospital that has institute's qualification for advanced technologies

| IMRT | Prefectural designated cancer care hospitals ($n = 30$) | | Regional designated cancer care hospitals ($n = 76$) [a] | |
|---|---|---|---|---|
| Head and neck cancer | Implementation ($n = 23$), median (range) | *P* value | Implementation ($n = 40$), median (range) | *P* value |
| No. of linear accelerators | 3 (2–4) | 0.86 | 2 (1–3) | 0.64‘ |
| No. of radiation oncologists | 4 (2–11) | 0.08 | 2.5 (1–36) | 0.46 |
| No. of radiation therapists | 8 (2–15) | 0.62 | 5 (1–11) | 0.31 |
| No. of radiotherapy quality managers | 2 (1–18) | 0.29 | 2 (1–8) | 0.49 |
| No. of medical physicists | 2 (0–5) | 0.99 | 1 (0–7) | 0.64 |
| Prostate cancer | Implementation ($n = 28$) | | Implementation ($n = 61$) | |
| No. of linear accelerators | 3 (2–4) | 0.99 | 2 (1–3) | 0.69 |
| No. of radiation oncologists | 4 (2–11) | 0.01 | 2 (1–36) | 0.59 |
| No. of radiation therapists | 7 (2–15) | 0.003 | 5 (1–11) | 0.19 |
| No. of radiotherapy quality managers | 2 (1–13) | 0.99 | 2 (1–8) | 0.86 |
| No. of medical physicists | 1.5 (0–5) | 0.99 | 1 (0–7) | 0.90 |
| SBRT | Prefectural designated cancer care hospitals ($n = 47$) | | Regional designated cancer care hospitals ($n = 175$)[b] | |
| Lung cancer | Implementation ($n = 37$) | *P* value | Implementation ($n = 116$) | *P* value |
| No. of linear accelerators | 3 (1–4) | 0.52 | 1 (1–3) | 0.30 |
| No. of radiation oncologists | 4 (1–11) | 0.02 | 2 (0–9)[c] | 0.70 |
| No. of radiation therapists | 7 (1–18) | 0.29 | 3 (1–11) | 0.24 |
| No. of radiotherapy quality managers | 2 (1–18) | 0.73 | 2 (1–8) | 0.70 |
| No. of medical physicists | 1 (0–5) | 0.07 | 1 (0–7) | 0.31 |

Data are median (range) unless otherwise specified.
[a]The data of four hospitals were not available.
[b]The data of three hospitals were not available.
[c]A part of hospitals which have full-time radiation oncologists seems to submit under-reporting of them in error.

widely adopted treatment approach among American ROs. This increase in the use of IMRT could be attributed in part to the fact that multiple investigators have reported dosimetric advantages and consequent improvement in the xerostomia rate, rectal toxicity rate and quality of life measures following the use of IMRT (3,7,8).

In the UK, Mayles et al. performed a survey and found that in 2008 only 6.7% of the patients with head and neck cancers and 7.5% of the patients with prostate cancers received IMRT (9). Their survey included questions about the reasons for not using IMRT, and the respondents' answer showed that the main reasons for the lack of progress in using IMRT in the UK were the inadequate availability of MPs, the lack of funding, the lack of equipment and the inadequate availability of ROs. The present IMRT situations in the UK is thus similar in some ways to those in Japan, with the need for more ROs and other types of medical staff in the department of radiation oncology for the establishment of a training system for IMRT. In particular, in Japan's R-DCCHs, the proportion of implementation of IMRT is very small, and the insufficient number of medical staff working in radiotherapy departments and the small number of R-DCCHs with institute's qualification for IMRT have been serious problems. The high fee for IMRT might lead to its prevalence, but it causes the unnecessary implementation for the patients who do not receive its benefit. The appropriate indication of advanced radiation technologies should be established.

In contrast, in the USA, the rapid adoption of IMRT in the wider clinical practice has shown that there is great variability in IMRT delivery such as incorrect contouring and the various margins, dose and techniques used for anal cancer and other malignancies (10,11). The establishment of adequate IMRT requires not only sufficient number of operating staff, but also the preparation of IMRT training programs for each type of operating staff in the radiation department (12). Routsis et al. (13) proposed that the reason for the slow adoption of IMRT in the UK is associated with insufficient understanding and skills concerning IMRT among the operating staff. The Radiotherapy Development Board in the UK has begun education and training programs for IMRT for each type of medical staff in the radiation department. Our survey revealed that the proportion of IMRT for head and neck cancers in Japan was small. Especially, head and neck anatomy is complex, and the physical examination, image evaluation and radiation treatment of this region are technically demanding. Rosenthal et al. (14) emphasized the importance of the patient