## INTRODUCTION

External beam radiation therapy (EBRT) has developed rapidly in recent years (1,2) and treatment equipment with which intensity-modulated radiation therapy (IMRT) and/or image-guided radiation therapy (IGRT) can be conducted are being introduced into Japan (3). IMRT and IGRT are particularly useful in EBRT for prostate cancer and are routinely used in the USA (4) and recommended in worldwide guidelines (5,6).

In Japan, IMRT and IGRT were listed as eligible for insurance reimbursement in 2008 and 2010, respectively. However, the present situation regarding the use of these techniques in EBRT for prostate cancer remains unclear (7,8). Therefore, we conducted a survey that would clarify the operational situation, treatment planning and treatment processes of IMRT and/or IGRT when used in EBRT for prostate cancer.

## PATIENTS AND METHODS

In February 2010, we sent a questionnaire on EBRT for prostate cancer to 139 major facilities including university hospitals, cancer centers and designated prefectural cancer centers and hospitals. The questionnaire was also sent to the hospitals which had treatment machines with IGRT functions, including Novalis (BrainLAB, Heimstetten, Germany), Tomotherapy (Accuray Inc., Sunnyvale, USA) and MHI-TM2000 (Mitsubishi Heavy Industries, Ltd., Nagoya, Japan).

The survey was composed of categories regarding treatment planning, dose fractionation and methods of implementation of EBRT for prostate cancer. If methods differed according to the type of radiation techniques used such as three-dimensional radiation therapy (3DCRT) or IMRT, we required responses regarding the most precise radiation method presently used. Among the 139 facilities to which we sent the survey, 115 (82.7%) gave responses, which were then analyzed. The high response rate allowed an extensive and representative data analysis.

## RESULTS

### General Information

Figure 1 shows the distribution of the number of patients with prostate cancer treated with EBRT at facilities in 2009 over the course of 1 year. There were 30 facilities (26.1%) at which over 50 patients were treated in 1 year. Of the 115 total facilities, 67 (58.3%) conducted IMRT, 70 (60.9%) conducted IGRT and 58 (50.4%) conducted both.

### Treatment Planning

Figure 2 shows the condition of the bladder at the treatment planning stage and during the treatment. In approximately

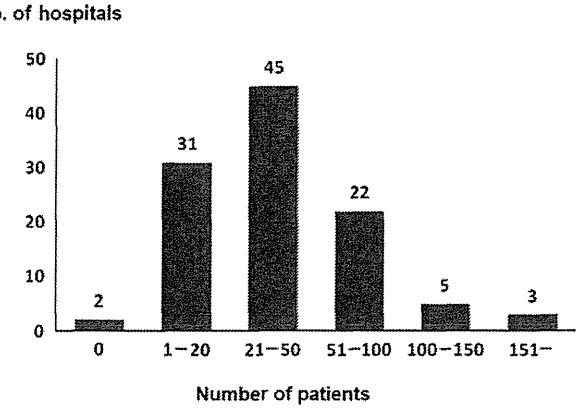


**Figure 1.** Total number of patients with prostate cancer treated with external-beam radiation therapy at facilities in 2009. Because some data were missing, the total numbers of patients were less than the actual number.

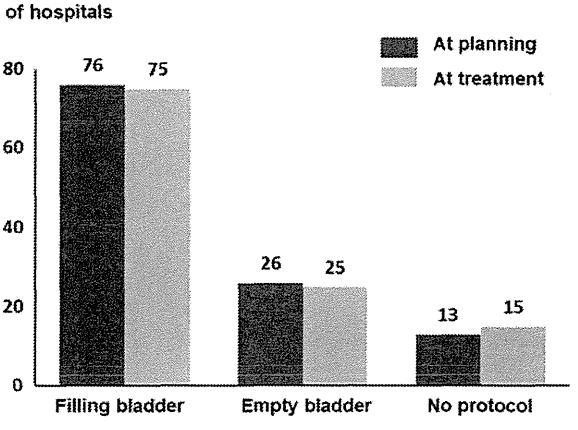


**Figure 2.** Condition of the bladder at the treatment planning stage and during treatment.

two-thirds of the facilities, a filling bladder was requested. The time spent pooling urine was 1 h at 56 facilities (48.7%), 1–2 h at 8 facilities (7.0%) and 30 min at 7 facilities (6.1%). Seven facilities (6.1%) also asked patients to drink water prior to treatment.

Figure 3 shows the condition of the rectum. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Laxative medication was used at one-quarter of the facilities.

Simulations and treatments were performed in the supine position at 105 facilities (91.3%) and the prone position at 10 facilities (8.7%). Figure 4 shows methods of patient fixation. Some kind of fixation method was used at 102 facilities (88.7%). Although various methods were reported, a vacuum cushion, thermoplastic shell and foot support were used most frequently.

Magnetic resonance imaging (MRI) was routinely performed for treatment planning at 32 facilities (27.8%). Of these, 15 facilities (13.0%) performed computed tomography

(CT)-MRI image fusion with treatment planning software. MRI taken at the time of diagnosis was used as a reference at 66 facilities (57.4%), while 17 facilities (14.8%) did not use MRI for treatment planning.

### Treatment

Radiation therapy was carried out with 2 Gy per fraction at 100 facilities (86.9%), 2.1–3 Gy at 14 facilities (12.2%) and 1.8 Gy at 1 facility (0.9%). Most facilities conducted treatment five times a week. Treatment was conducted three times a week at five facilities (4.3%) and four times a week at three facilities (2.6%).

Figure 5 shows the distributions of radiation doses delivered to the prostate at facilities using a fraction dose of 2 Gy. The median total dose was 76 Gy with IMRT and 70 Gy with 3DCRT. The doses were prescribed at the isocenter at the facilities that conducted 3DCRT. In contrast, the dose prescription varied greatly at the facilities that conducted IMRT. Of the 67 facilities that conducted IMRT, D95, which is the minimum absorbed dose that covers 95% of the planning target volume (PTV), was used as a dose prescription at 24 facilities (35.8%). A dose prescription requiring that 95% of the prescribed isodose line cover 95% of the PTV was used at 4 facilities (6.0%), the mean PTV dose was used at 13 facilities (19.4%) and other methods at 26 facilities (38.8%).

The most popular IGRT methods (54 facilities) involved 2D matching with X-ray fluoroscopy or 3D matching with a flat-panel cone-beam CT. Eight facilities used CT on rail and 4 facilities used ultrasonic devices. Of the 70 facilities that could perform IGRT, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. At the treatment of prostate cancer, 60 facilities (85.7%) always conducted IGRT, while 9 (12.9%) conducted IGRT at regular intervals.

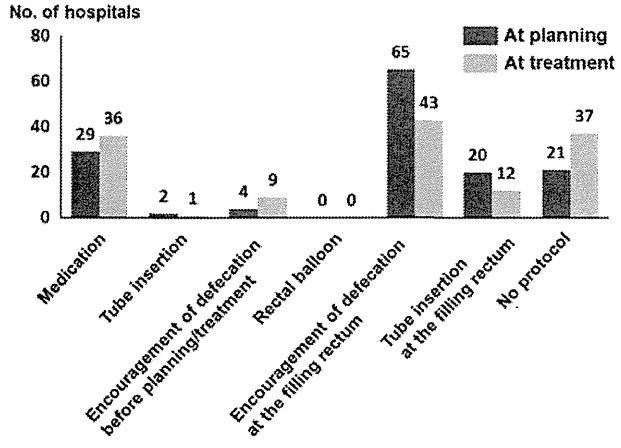


**Figure 3.** Condition of the rectum at the treatment planning stage and during treatment. Multiple answers allowed.

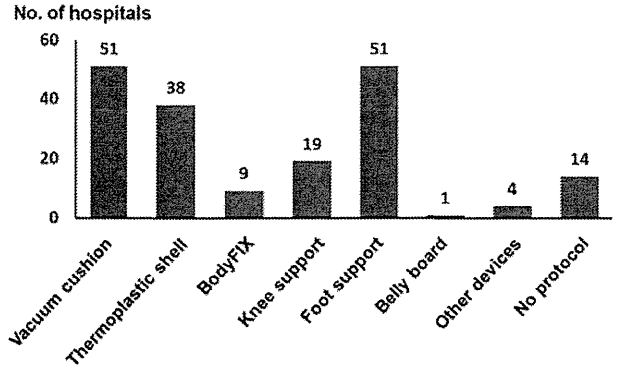


**Figure 4.** Fixation of the patients at the treatment planning stage and during treatment. Multiple answers allowed.

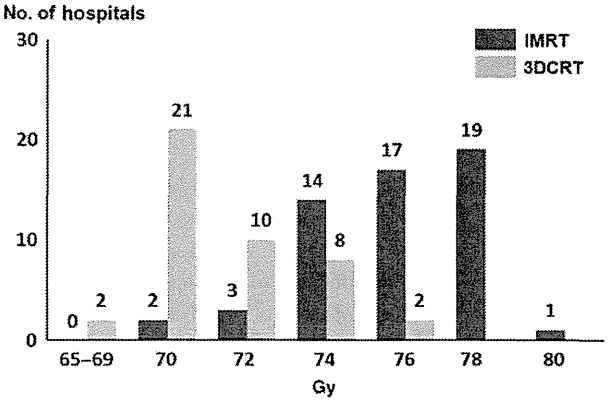


**Figure 5.** Total dose to the prostate.

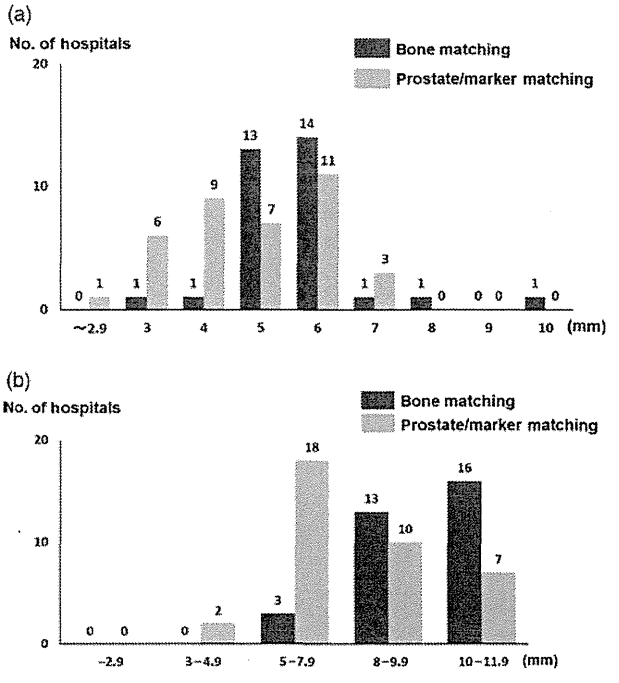


**Figure 6.** Margins from the prostate to planning target volume for patients with T1–2 tumors treated with IGRT: (a) rectal side and (b) other sides.

Figure 6 show the distribution of the prostate-PTV margins for patients with typical T1–2 tumors treated with IGRT. Prostate or metal marker matching tended to produce slightly smaller margins than bone matching.

## DISCUSSION

This study provides a clear picture of present practices of IMRT and/or IGRT for prostate cancer in Japan.

Simulations and treatments were performed in the supine position at most facilities. However, facilities employed various fixation methods. In most facilities, some kind of fixation method was used, although immobilization devices for body malignancies are not covered by health insurance in Japan. In the patterns of care study on prostate cancer patients who were treated with EBRT from 2003 to 2005, immobilization devices were used on only 15% of patients (7). One reason for the high frequency of the usage of patient immobilization devices in this study could be the gradual popularization of fixation methods over time. An additional reason is probably the fact that some sort of fixation method tends to be used in more precise radiation treatment, because patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (9).

The pretreatment condition of the bladder and rectum also varied greatly among facilities. Although fixation of the prostate is frequently conducted with a rectal balloon in Western countries (10), this method has not been used at all in Japan.

In this study, we did not investigate PTV margins when IGRT was not used. Therefore, we were unable to clarify whether IGRT causes decreased margins. However, PTV margins tended to be slightly smaller with prostate or fiducial marker matching than that with bone matching. PTV margins should be determined at each facility taking into account position errors caused not only by the IGRT method, but also by the patient position, fixation method and pretreatment condition of the bladder and rectum. Enmark et al. (11) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including the inter- and intrafraction motions, if IGRT with fiducial markers is performed on a daily basis. Some facilities have chosen prostate-PTV margins of $<4$ mm. Because of uncertainties such as intrafraction motion or uncertainty of the target delineation, decreases in the PTV margin should be carefully performed even when IGRT is applied.

The radiation dose administered at most facilities was 2 Gy per fraction. The median value of the total radiation dose was 76 Gy with IMRT and 70 Gy with 3DCRT. It is well known that the radiation dose is a strong independent predictor of failure (12), and IMRT can reduce the unwanted doses to nearby organs at risk. Therefore, as IMRT becomes more widespread in Japan, more appropriate higher dosages of radiation should be utilized. However, a significant problem is the fact that the IMRT dose prescription varies. It is necessary to define and develop recommended guidelines for dose prescription and a dose reporting system for IMRT in Japan (13).

IMRT and IGRT were being conducted at approximately half of the facilities in this study. However, our survey targeted large-scale facilities. If all radiation therapy facilities in Japan were to be surveyed, this proportion would probably be smaller (3). At present, high-precision radiation therapy devices such as IMRT and IGRT are being rapidly introduced (3,14), and an increasing number of facilities will surely come to adopt IMRT and IGRT. The results of the survey in this study will provide beneficial information to those facilities as they begin treatment.

### Acknowledgements

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### Conflict of interest statement

None declared.

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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).

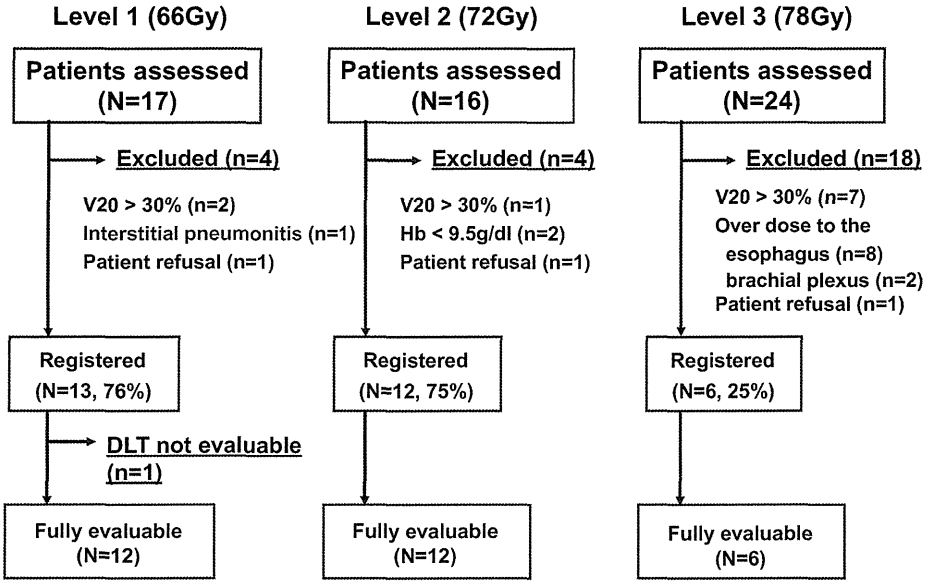


Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

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).

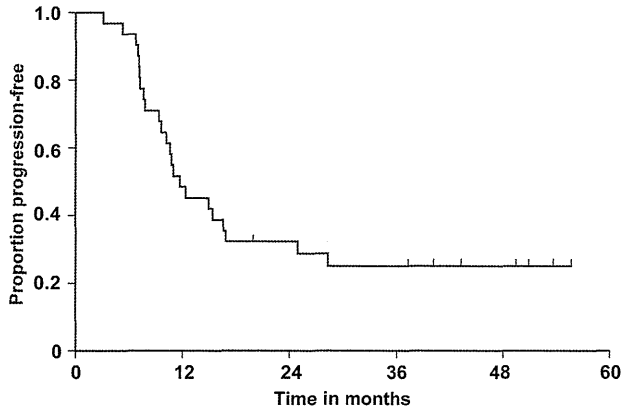


Fig. 2. Progression-free survival ($n$ = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

## 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) |

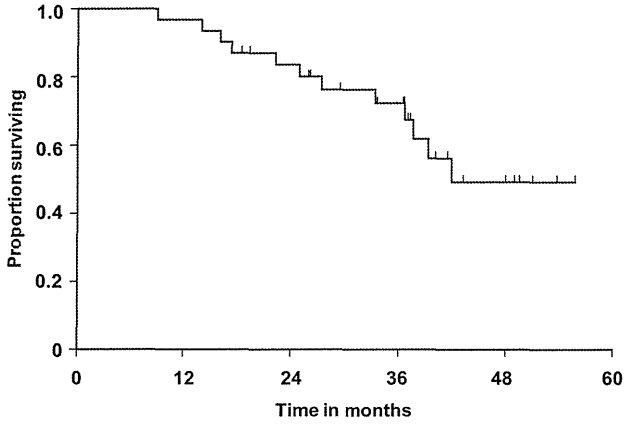


Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

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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**CLINICAL INVESTIGATION** **Gynecologic Cancer**

# INTERNATIONAL BRACHYTHERAPY PRACTICE PATTERNS: A SURVEY OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

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**Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/New Zealand (ANZ), Europe (E), and North America (NAm).**

**Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.**

**Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) ($p = 0.02$). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; $p = 0.02$ for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan ($p = 0.0002$).**

**Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials.** © 2012 Elsevier Inc.

**Brachytherapy, Cervical cancer, Radiation dose.**

## INTRODUCTION

Globally, cervical cancer represents the most common gynecologic malignancy (1). Patients with locally advanced cervical cancer (Stage IB2–IVA) require treatment with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (2). The recommended cumulative dose of EBRT and brachytherapy to cure locally advanced disease

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ranges from 80 to 90 Gy recorded at point A using low-dose-rate (LDR) brachytherapy (2).

Over the past 20 years, high-dose-rate (HDR) brachytherapy has increased and replaced LDR in many practices (3). The Patterns of Care for cervical cancer radiation practice in the United States reported a 16% HDR utilization rate in 1999 (4), whereas 85% of surveyed physician members of the American Brachytherapy Society (ABS) reported having HDR at their institution in 2007 (3). Overall, randomized studies indicate that outcomes with HDR resemble those with LDR, though many issues exist regarding the methodology of randomization and the follow-up duration across the studies (5). However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of computed tomography (CT) or magnetic resonance imaging (MRI) to determine doses to the tumor and the organs at risk (6).

The biologic equivalent dose formulas allow calculation of the brachytherapy dose (7, 8). However, these formulas require an assumption that the $\alpha/\beta$ ratio for tumor is 10, which may be an underestimation for squamous cell carcinoma. Furthermore, concerns regarding the validity of the linear quadratic model exist for very low or very high doses per fraction (9). Publication of standard fractionation regimens for HDR cervical cancer brachytherapy with point A–based standard loading (10, 11) led to widespread adoption in the United States of the regimen 6 Gy for five fractions over approximately 2.5 weeks. Preliminary results demonstrate a 2-year Grades 3 and 4 bowel toxicity rate of 11% with this HDR regimen (12). By contrast, with 2-year follow-up, only three (5%) Grade 3 or greater gastrointestinal complications occurred in a group of 65 patients treated with 6 Gy for five fractions in one report (13). It remains unknown whether 6 Gy for five fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR brachytherapy.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups to move the development of oncologic clinical trials forward in a highly constructive and cost-effective manner. Randomized trials with international participation will accrue cervical cancer patients rapidly and result in advances on a global stage. To determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. The goal is to clarify which regimen would be acceptable for future international collaborative clinical trials.

## METHODS AND MATERIALS

The GCIG represents an international association of member cooperative groups conducting large clinical trials for gynecologic malignancies. Since its inception in 1997, 18 cooperative groups have joined, including the AGO-Austria (Austria), AGO-OVAR (Germany), ACRIN (USA), ANZOG (Australia, New Zealand), DGOG (the Netherlands), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRI (Great Britain), NCIC (Canada), NSGO (Scandinavia), RTOG (USA), SGCTC (Scotland), and SWOG (USA).

A 32-question survey was designed to address questions regarding standard practice patterns for locally advanced cervical cancer management, such as routine doses of external beam and the use of concurrent chemotherapy, and also to determine baseline brachytherapy practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix EI available online at at www.redjournal.org). An e-mail providing background information, the purpose of the survey, and a link to a web page for easy retrieval of the survey was sent electronically to the chair of each GCIG member cooperative group in December 2008. Each cooperative group chair could choose to forward the email to six radiation oncology members from separate representative centers that had a large volume of cervical cancer cases. Respondents could complete only one survey on a computer, and entered their names and e-mail addresses to avoid duplicate submissions. The survey website closed in May 2009. Appendix E1 (available online at at www.redjournal.org) lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. For respondents that used a midline block, the total dose to the nodes and the dose to the cervix were summed separately. The EBRT and brachytherapy EQD2 doses were calculated at point A for patients with Stage IB–IIA and those with Stage IIB-IVA disease; then the average was taken for a cumulative sum for all stages. Analysis of reported HDR fractionation regimens was divided by country and by region, including Asia (Japan/Korea); Australia/New Zealand; Europe (Austria, Denmark, England, Finland, Germany, Italy, Ireland, the Netherlands, Scotland, Spain); and North America (USA, Canada). Quartiles of dose were evaluated to determine whether any particular region or country grouped into the highest or lowest dose ranges. The *t*-test statistic was performed to determine whether any significant differences in dose existed by region.

## RESULTS

*Respondent characteristics*

A total of 16 cooperative groups gave member responses to this survey. Of 74 respondents, two were excluded: one non-GCIG member and one GCIG member who did not answer questions regarding brachytherapy, yielding a final study population of 72 respondents. Cooperation was received from the AGO-Austria ($n$ = 3), ABO-Germany ($n$ = 2), ACRIN ($n$ = 1), ANZGOG ($n$ = 6), DGOG ($n$ = 6), EORTC ($n$ = 5), GEICO ($n$ = 1), GOG ($n$ = 5), JGOG ($n$ = 6), KGOG ($n$ = 4), MANGO ($n$ = 3), MITO ($n$ = 2), MRC/NCRI ($n$ = 9), NCIC ($n$ = 10), NSGO ($n$ = 3), and the RTOG ($n$ = 6). Regions of the world represented were Japan/Korea ($n$ = 10), Australia/New Zealand ($n$ = 6), Europe ($n$ = 34), and North America ($n$ = 22).

Of the 72 respondents, 63 (88%) practice radiation oncology; 8 (11%), both medical and radiation oncology; and one (1%), gynecologic oncology. Regarding the average number of cervical cancer patients treated per year, 7 (10%) treat 1 to 9, 18 (25%) treat 10 to 19, 11 (15%) treat 20 to 29, 9 (13%) treat 30 to 39, 6 (8%) treat 40 to 49, 10 (14%) treat 50 to 59, 6 (8%) treat 60 to 69, 4 (6%) treat 70 to 79, and 1 (1%) treats more than 140.

*External-beam radiation to the cervix*

Physicians were queried regarding the standard EBRT dose prescribed for treating cervical cancer. For those who reported administering a parametrial boost dose, the parametrial doses were excluded from the EBRT cumulative cervical dose calculation, since the goal of a midline block is to avoid significant radiation to the cervix during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose was 44.2 Gy (range, 19.8–50.4) for Stage IB–IIA patients and 47.2 Gy (range, 30.6–54) for Stage IIB–IVA patients. The average cervical dose for the Japanese respondents (not including the parametrial boost dose) was 23.3 Gy (range, 19.8–30) for Stage IB-IIA patients and 36.7 Gy (range, 30.9–40) for Stage IIB–IVA patients. All Japanese respondents commented that after insertion of a midline block, the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after insertion of the midline block). By contrast, all other countries reported a mean EBRT dose of 46.11 Gy (range, 40–50.4) for Stage IB–IIA patients and 48.2 Gy (range, 40–54) for Stage IIB–IVA patients. The most commonly added parametrial boost dose is 5.4 Gy after 45 Gy to the entire pelvis. For Stage IB–IIA patients, the most common EBRT doses are 45 Gy ($n$ = 41, 57%) and 50.4 Gy ($n$ = 15, 21%). For Stage IIB–IVA, the most common EBRT doses are 45 Gy ($n$ = 26, 36%), 50.4 Gy ($n$ = 27, 38%), and 54 Gy ($n$ = 5, 7%).

All respondents prescribe concurrent chemotherapy with EBRT. In addition, 4% (three respondents) consider giving neoadjuvant chemotherapy before concurrent chemoradiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-flourouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

*Brachytherapy*

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) had LDR, and 8 (11%) have pulse-dose-rate. Chemotherapy is given on the same day as an HDR fraction by four respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by three respondents (4%). A total of 38% of respondents might hospitalize patients overnight for HDR treatment. For those using LDR, an equal number of respondents use on average one or two fractions, with a per-fraction dose ranging from 10 to 40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, pulse-dose-rate, and LDR, with 54% using this applicator for more than 75% of their cases annually. The tandem and ring applicator is used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, 97% of respondents' patients receive anesthesia, consisting of general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%). Ultrasound is used for assistance with applicator insertion by 62% of respondents; 24% use ultrasound less than 10% of the time, 12% use it for 10–25% of cases, 7% use it for 26–50% of cases, 1% use it for 51–75% of cases, and 18% use it for more than 75% of their cases.

With regard to imaging the brachytherapy applicator after insertion, 17 centers (24%) reported that they use plain x-ray films, either alone or in combination with MRI and/or CT. By contrast, CT is the most commonly used imaging modality ($n$ = 41, 57%); 27 respondents use CT for every fraction, and 14 use CT for the first fraction only. MRI is used by 18 centers (25%), of which eight use MRI for every fraction and 10 for the first fraction only; of these 10, eight acquire a CT scan for every fraction. In terms of prescribing to the cervix, 56 (78%) prescribe to point A, 8 (11%) follow the GEC-ESTRO guidelines (14, 15) alone, 15 (21%) follow the GEC-ESTRO and report dose to point A, 4 (6%) follow the ABS guidelines alone, and 8 (11%) use both the ABS and point A.

The major HDR fractionation patterns are depicted in Fig. 1 and listed in the table. For Stage IB–IIA patients, the most common HDR fractionation pattern is 6 Gy for five fractions ($n$ = 11, 15%), as it is for Stage IIB–IVA patients ($n$ = 14, 19%). A total of 28 fractionation regimens are reported, of which 18 are used by only one institution. The most common fractionation regimen, 6 Gy for five fractions, is prescribed by centers in the United States, Canada, Australia, New Zealand, the United Kingdom, Spain, Italy, and Germany. The second most common regimen, 7 Gy for four fractions, is prescribed by centers in the United States, Australia, Austria, and the Netherlands. For HDR dose reporting, of the 68 respondents to this question, 32 (47%) calculate equivalent dose using the 2-Gy (EQD2) formula, whereas 31 (46%) use only the biologic equivalent dose formula, and five (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT plus brachytherapy EQD2 was 78.9 Gy (standard deviation [SD] 10.7) for Stage IB–IIA patients and 83.3 Gy (SD 11.2) for Stage IIB–IVA patients for all countries ($p$ = 0.02 Stage IB–IIA vs. IIB–IVA). For all stages and all countries, the mean EBRT plus brachytherapy dose was 80.9 (SD 10.14). By region, the mean combined EQD2 for Australia/New Zealand was 81.18 (SD 4.96); for Europe, 83.35 (SD 10.75); for North America, 81.66 (SD 6.05); and for Asia, 71.2 Gy (SD 12.65; $p$ = 0.02 for Asia vs. other regions). The mean EBRT plus brachytherapy dose for Japan was 62.73 (SD 6.7), and for Korea it was 83.9 (SD 6.86). Therefore, the only significant difference was between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, and 1 New Zealand) had EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) reported EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose was from a center that uses a fractionation regimen of 7 Gy for seven fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

The average ratio of brachytherapy dose to total sum (EBRT plus brachytherapy) dose was 0.45 (SD 0.08) for Stage IB–IIA and 0.44 (SD 0.08) for Stage IIB–IVA ($p$ = NS). However, for Japanese respondents, the all-stages ratio

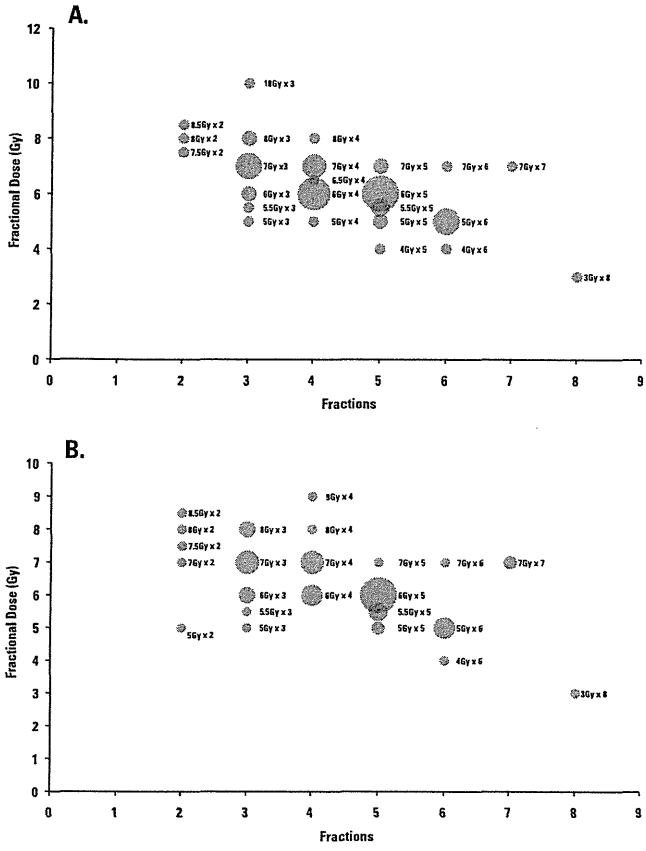


Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages IIB–IVA cervical cancer. The size of the circle is proportional to the number of respondents, with the largest number reporting 6 Gy for five fractions.

was 0.51 (SD 0.03), which was significantly different from the average ratio for all other countries ($p$ = 0.0002). When stratified by stage, this difference in brachytherapy ratio was seen only for the Stage IB–IIA subgroup. For Japanese respondents, the ratio of brachytherapy to EB plus brachytherapy was 0.58 (SD 0.05) for Stage IB–IIA and 0.45 (SD 0.06) for Stage IIB–IVA ($p$ = 0.002). In other words, to accommodate their reduced EBRT dose, the Japanese use a higher brachytherapy dose for patients with Stage I–IIA tumors than that typically used elsewhere.

*Complications*

When queried about the number of patients treated for cervical cancer who were hospitalized annually for a complication, most respondents indicated 0 ($n$ = 12, 17%), 1 ($n$ = 37, 60%), or 2 ($n$ = 9, 13%).

## DISCUSSION

The primary goal of this survey was to gauge variation in HDR fractionation for cervical cancer and to determine brachytherapy practice patterns internationally, in order to assist with the development of the brachytherapy portion of international randomized clinical trials. Inasmuch as cervical cancer remains a leading cause of mortality in developing countries, international collaborative randomized trials that can advance treatment approaches on a global level are needed. In particular, before undertaking this study, we questioned whether the heterogeneity of brachytherapy practice might hinder standardization. As part of this survey, other items of interest were queried, including the utilization of three-dimensional (3D) imaging during brachytherapy. Other questions were designed to provide a 3-year update to selected general management information queried on the 2007 survey (16).

With regard to the general management of cervical cancer, this survey showed that the use of concurrent chemoradiation is similar to that reported in the 2007 survey, as are EBRT doses. In terms of brachytherapy, a greater proportion of respondents in this survey reported the use of HDR than in a United States–based survey from 1999 (4). However, the use of HDR in the United States also seem to be increasing, with 85% of ABS members having HDR brachytherapy available in their practices in 2007, indicating a growing acceptance of HDR brachytherapy in the United States that matches international implementation (3). The transition from LDR to HDR has been based on an increased acceptance of the feasibility, safety, and efficacy of HDR when carefully administered, with a concomitant increase in the use of 3D imaging. Three-dimensional imaging allows dose optimization away from the normal tissues in an attempt to spare them the large fractional dose used in HDR brachytherapy.

Overall, a significant proportion of GCIG members have access to 3D imaging for gynecologic brachytherapy. The most frequently used method for brachytherapy imaging is CT. In a recent ABS survey, 70% of respondents used CT after brachytherapy applicator insertion, and 57% used CT imaging in this survey (3). Before the 1990s, plain x-ray film simulation was the standard of care. After the integration of CT into radiation oncology departments, 3D imaging use increased and now represents the standard for external beam. The integration of 3D imaging into brachytherapy has also expanded, albeit later than for EBRT. This study found a significant proportion using the best available 3D imaging modality available at their institution, either CT or MRI, for cervical cancer brachytherapy planning.

In this survey, HDR brachytherapy dose fractionation recommendations varied considerably. The most common fractionation internationally was 6 Gy for five fractions, although this regimen is used by fewer than 20% of reporting institutions. Despite the high degree of individuality in brachytherapy prescribing, the biologic equivalence was remarkably similar for all countries and regions except Japan. All six Japanese respondents follow a regimen of treating to 20 to 30 Gy for early stage disease, then place a midline block, which significantly reduce the cumulative EQD2 cervical dose compared to that used in other countries. Nevertheless, the EQD2 dose to the cervix was equivalent, on average 80 Gy for all regions of the world surveyed. The Japanese cervix dose reduction to approximately 70 Gy, instead of the

Table 1. Routine high-dose-rate brachytherapy fractionation regimens for cervical cancer as used by Gynecologic Cancer Intergroup surveyed physicians

| Standard fractionation for Stages IB–IIA cervical cancer | | | | Standard fractionation for Stages IIB–IVA cervical cancer | | | |
|---|---|---|---|---|---|---|---|
| % Respondents (*n*) | Dose/fraction | Fractions (*n*) | EQD2 | % Respondents (*n*) | Dose/fraction | Fractions (*n*) | EQD2 |
| 18% (11) | 6 | 5 | 40 | 23% (14) | 6 | 5 | 40 |
| 15% (9) | 6 | 4 | 32 | 10% (6) | 7 | 4 | 40 |
| 12% (7) | 7 | 3 | 29.75 | 10% (6) | 7 | 3 | 30 |
| 8% (5) | 5 | 6 | 37.5 | 8% (5) | 6 | 4 | 32 |
| 8% (5) | 7 | 4 | 39.7 | 7% (4) | 5.5 | 5 | 35.5 |
| 5% (3) | 5 | 5 | 31.25 | 5% (3) | 5 | 6 | 37.5 |
| 5% (3) | 5.5 | 5 | 35.52 | 5% (3) | 7 | 6 | 59.5 |
| 3% (2) | 8 | 3 | 36 | 5% (3) | 6 | 3 | 24 |
| 1.6% (1) | 3 | 8 | 26 | 5% (3) | 8 | 3 | 36 |
| 1.6% (1) | 4 | 5 | 23.3 | 3% (2) | 7 | 7 | 69.4 |
| 1.6% (1) | 4 | 6 | 28 | 3% (2) | 5 | 5 | 31.3 |
| 1.6% (1) | 5 | 3 | 18.75 | 1.6% (1) | 3 | 8 | 26 |
| 1.6% (1) | 5 | 4 | 25 | 1.6% (1) | 4 | 6 | 28 |
| 1.6% (1) | 5.5 | 3 | 21.3 | 1.6% (1) | 7 | 5 | 49.6 |
| 1.6% (1) | 6 | 3 | 24 | 1.6% (1) | 8 | 4 | 48 |
| 1.6% (1) | 6.5 | 4 | 35.75 | 1.6% (1) | 9 | 4 | 57 |
| 1.6% (1) | 7 | 5 | 49.6 | 1.6% (1) | 5 | 3 | 18.8 |
| 1.6% (1) | 7 | 6 | 59.5 | 1.6% (1) | 5.5 | 3 | 21.3 |
| 1.6% (1) | 7 | 7 | 69.4 | 1.6% (1) | 5 | 2 | 12.5 |
| 1.6% (1) | 7.5 | 2 | 21.9 | 1.6% (1) | 7.5 | 2 | 21.9 |
| 1.6% (1) | 8 | 2 | 24 | 1.6% (1) | 8 | 2 | 24 |
| 1.6% (1) | 8 | 4 | 48 | 1.6% (1) | 8.5 | 2 | 26.2 |
| 1.6% (1) | 8.5 | 2 | 26.2 | | | | |
| 1.6% (1) | 10 | 3 | 50 | | | | |

*Abbreviation*: EQD2 = Equivalent dose in 2 Gy fractions.
Results indicate the diversity of responses.
The EQD2 formula was used to convert the high-dose-rate dose and number of fractionations.

international standard of 80 Gy, must be further analyzed, including comparison of recurrence rates and toxicities; an upcoming abstract shows reasonable rates of local control (17). The Japanese regimen, in use for several decades, was implemented upon the observation that Japanese women, potentially because of their small body size, had very high bowel and bladder toxicity rates when treated with higher pelvic EBRT doses (18). The current Japanese regimen begins HDR intracavitary brachytherapy once per week after 20 Gy. Whether a genetic difference in sensitivity to radiation exists is unknown, but one implication of the successful outcomes in Japanese women is that brachytherapy may be the more critical component for treatment to the cervix, particularly for early stage disease with a lower risk of nodal spread.

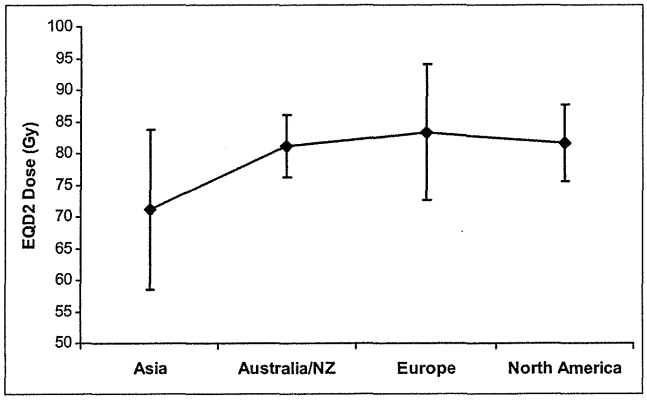


Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

A previously unassessed difference in brachytherapy administration was identified with regard to the proportional relationship of brachytherapy to the sum total dose. For early-stage patients, the Japanese respondents administer a significantly higher proportion of the dose using brachytherapy than practitioners from other countries. The reliance on HDR brachytherapy fractionation may indicate that a large dose given with HDR can compensate for a lower external beam dose in patients with small tumors. This assumption of proportionality must be corroborated with recurrence information.

For all respondents (including those from Japan), the mean EBRT plus brachytherapy cumulative EQD2 dose was 80.4 Gy, with a standard deviation of 10 Gy. Patients with higher-stage disease (Stage IIB–IVA) received a significantly higher dose than did those with earlier-stage cervical cancer. Therefore, a dose of 80 Gy may be considered the universally accepted international baseline dose overall, with on average 79 Gy for Stage IB–IIA and 84 Gy for Stage IIB–IVA cases. A dose of 80 Gy is approximately equivalent to 45 Gy delivered with EBRT and 5.5 Gy for five fractions delivered with HDR brachytherapy. A dose

of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for five fractions or 7 Gy for four fractions of HDR.

Standardization of HDR brachytherapy on an international level will assist institutions in terms of comparing toxicities and outcomes in patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR brachytherapy. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes in Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemoradiation may attempt radiation dose variation based on response and on improved sparing of normal tissues with 3D imaging, to determine the acceptable safe threshold level that results in equivalent eradication of disease while minimizing toxicities.

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Clinical Investigation: Thoracic Cancer

# Recursive Partitioning Analysis for New Classification of Patients With Esophageal Cancer Treated by Chemoradiotherapy

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## Summary

The objective of this study was to develop and validate a new staging system that incorporates lymph node size for esophageal cancer patients undergoing chemoradiotherapy. The new staging classification, which was based on the T stage and lymph node size, led to good separation of survival curves in both the developmental and validation datasets. The new staging system provided good prognostic power and discriminated effectively for esophageal cancer patients undergoing chemoradiotherapy.

**Background:** The 7th edition of the American Joint Committee on Cancer staging system does not include lymph node size in the guidelines for staging patients with esophageal cancer. The objectives of this study were to determine the prognostic impact of the maximum metastatic lymph node diameter (ND) on survival and to develop and validate a new staging system for patients with esophageal squamous cell cancer who were treated with definitive chemoradiotherapy (CRT).

**Methods:** Information on 402 patients with esophageal cancer undergoing CRT at two institutions was reviewed. Univariate and multivariate analyses of data from one institution were used to assess the impact of clinical factors on survival, and recursive partitioning analysis was performed to develop the new staging classification. To assess its clinical utility, the new classification was validated using data from the second institution.

**Results:** By multivariate analysis, gender, T, N, and ND stages were independently and significantly associated with survival ($p < 0.05$). The resulting new staging classification was based on the T and ND. The four new stages led to good separation of survival curves in both the developmental and validation datasets ($p < 0.05$).

**Conclusions:** Our results showed that lymph node size is a strong independent prognostic factor and that the new staging system, which incorporated lymph node size, provided good prognostic power, and discriminated effectively for patients with esophageal cancer undergoing CRT.


**Keywords:** Esophageal cancer, Chemoradiotherapy, TNM, Recursive partitioning analysis, Prognostic factor

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## Introduction

Staging systems for cancer have evolved over time and continue to change as knowledge of cancer increases. Based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of distant metastasis (M), the TNM staging system is one of the most widely used staging systems. The tumor stage is the most important prognostic factor for any type of cancer, and planning for optimal treatment is mainly decided according to the tumor stage (1).

The American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was revised in the 2009 7th edition. A major modification in the 7th edition was the subdivision of N according to the number of involved lymph nodes. The modification was based on retrospective analysis of pathologic data from patients treated only by primary surgical resection (2, 3), although the current standard treatment for esophageal cancer incorporates neoadjuvant chemotherapy or chemoradiotherapy (CRT). We therefore evaluated the prognostic impact of the 7th edition staging system on esophageal cancer patients undergoing CRT (4). The results indicated that the 7th edition TNM classification had several limitations in determining the prognosis of patients undergoing CRT. For example, the 7th TNM staging system poorly distinguishes the prognoses of patients with Stage III and Stage IV disease undergoing CRT with regard to nondistant organ metastasis (4). Additional detailed classification that more accurately predicts prognosis after treatment may be necessary for clinical decision-making.

Pathological lymph node size has been reported to be a meaningful prognostic factor for survival in patients with esophageal cancer who undergo surgery (5, 6). We hypothesize that the size of nodal disease as an additional prognostic criterion for overall survival in esophageal cancer patients may have an impact on clinical outcome after CRT. However, to the best of our knowledge, this has not been evaluated in esophageal cancer patients undergoing definitive CRT. Although lymph node size is already integrated into the N staging system of head-and-neck carcinoma, the only criterion determining N stage in esophageal cancer is the number of infiltrated nodes.

The objectives of the present study were to investigate the prognostic impact of the largest diameter of all the identified metastatic lymph nodes (ND) and to develop and validate a new staging system on patients with esophageal squamous cell cancer who were treated with definitive CRT.

## Methods and Materials

### Patient population

This was a retrospective cohort study of esophageal cancer patients treated with definitive CRT at two institutions. Criteria for inclusion were the following: (*1*) carcinoma of thoracic esophagus; (*2*) histological diagnosis of primary esophageal squamous cell carcinoma; (*3*) no distant organ metastasis; (*4*) total radiation dose ≥50 Gy; (*5*) concomitant chemotherapy consisting of 5-fluorouracil and platinum; (*6*) no previous thoracic radiotherapy (RT); (*7*) no previous thoracic surgery; and (*8*) no salvage surgery. Patients who received chemotherapy followed by CRT were also excluded from this analysis. The developmental database

**Table 1** Patient and tumor characteristics

| | Generation dataset | | Validation dataset | | |
|---|---|---|---|---|---|
| Characteristic | $n$ = 261 | (%) | $n$ = 141 | (%) | $p$ |
| Age (y) | | | | | <0.001 |
| Median | 65 | | 67 | | |
| Range | 39–82 | | 44–87 | | |
| Gender | | | | | 0.26 |
| Male | 224 | (86) | 115 | (82) | |
| Female | 37 | (14) | 26 | (18) | |
| PS | | | | | 0.27 |
| 0 | 75 | (29) | 48 | (34) | |
| 1 | 186 | (71) | 93 | (66) | |
| Cancer site | | | | | 0.37 |
| Ut | 50 | (19) | 25 | (18) | |
| Mt | 149 | (57) | 90 | (64) | |
| Lt | 62 | (24) | 26 | (18) | |
| T stage (7th) | | | | | 0.041 |
| 1 | 80 | (31) | 30 | (21) | |
| 2 | 17 | (6) | 19 | (14) | |
| 3 | 105 | (40) | 62 | (44) | |
| 4 | 59 | (23) | 30 | (21) | |
| N stage (7th) | | | | | 0.021 |
| 0 | 102 | (39) | 36 | (26) | |
| 1 | 91 | (35) | 69 | (49) | |
| 2 | 60 | (23) | 33 | (23) | |
| 3 | 8 | (3) | 3 | (2) | |
| M stage (7th) | | | | | 0.97 |
| 0 | 204 | (78) | 110 | (78) | |
| 1 | 57 | (22) | 31 | (22) | |
| Histological grade (7th) | | | | | 0.001 |
| 1 | 43 | (17) | 15 | (11) | |
| 2 | 112 | (43) | 43 | (31) | |
| 3 | 24 | (9) | 9 | (6) | |
| X | 82 | (31) | 74 | (52) | |
| Stage (7th) | | | | | 0.093 |
| I | 59 | (23) | 23 | (16) | |
| II | 55 | (21) | 22 | (16) | |
| III | 90 | (34) | 65 | (46) | |
| IV | 57 | (22) | 31 | (22) | |
| Maximum lymph node diameter (cm) | | | | | 0.008 |
| Median | 1.7 | | 1.6 | | |
| Range | 0.5–7 | | 0.5–7 | | |
| Total radiation dose (Gy) | | | | | 0.93 |
| Median | 60 | | 60 | | |
| Range | 50–64 | | 50–60 | | |
| Chemotherapy regimen | | | | | <0.001 |
| 5-FU + CDDP | 247 | (95) | 115 | (82) | |
| 5-FU + CDGP | 14 | (5) | 26 | (18) | |

*Abbreviations:* 5-FU = 5-fluorouracil; CDDP = cisplatin; CDGP = nedaplatin; Lt = lower thoracic portion; Mt = mid-thoracic portion; PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion.

consisted of 261 esophageal cancer patients treated at the Aichi Cancer Center Hospital between March 2003 and October 2009. The external validation database consisted of 141 esophageal cancer patients treated at Kansai Medical University between February 2006 and April 2010.

## Pretreatment staging

Pretreatment staging evaluations included physical examination, laboratory tests, esophagogastroduodenoscopy, barium esophagography, contrast-enhanced computed tomography (CT) from the neck to upper abdomen, and positron emission tomography (PET). Pretreatment staging was based on the 6th edition of the AJCC Cancer Staging Manual and was determined during a meeting of thoracic surgeons, radiologists, gastroenterologists, and medical oncologists. Treatment strategy was also determined at the meeting.

## RT treatment planning and treatment

RT was delivered using a linear accelerator (Clinac 21EX and Clinac 2100C at Aichi Cancer Center; Clinac 21EX at Kansai Medical University; Varian Medical Systems, Palo Alto, CA) with a 6- to 15-MV photon beam. In general, patients received 2 Gy per fraction, for a total of 60 Gy. A conventional beam arrangement that consisted of opposed anterior and posterior fields up to 36–40 Gy, and off-cord oblique fields was used. Spinal cords never received more than 45 Gy. Doses were prescribed according to Reports 50 and 62 of the International Commission on Radiation Units and Measurements (7, 8). Before treatment, all patients underwent three-dimensional treatment planning, which included tissue inhomogeneity correction. Treatment planning was based on CT scans of patients in the treatment position using 3- to 5-mm thick sections and 3- to 5-mm intervals. The gross tumor volume of the primary site (GTV-P) and the gross volume of involved lymph nodes (GTV-N) were determined. The primary clinical target volume (CTV-P) included the GTV-P plus 20–30 mm craniocaudal margins, and the lymph node clinical target volume (CTV-N) included the GTV-N without additional margins (9). The planning target volume (PTV) included both CTVs plus lateral and anteroposterior 5–10 mm margins and 10–20 mm craniocaudal margins. In addition, 5–8 mm leaf margins were added to the PTV.

The chemotherapy regimens used with RT consisted of 5-fluorouracil and cisplatin or nedaplatin. The doses and schedules were determined and administered as previously reported (9–13). Most of the Stage IIA-IVB patients received consolidation chemotherapy consisting of 5-fluorouracil and platinum after their chemoradiotherapy.

## Follow-up

History and physical examination, complete blood cell count, gastrointestinal endoscopy, chest X-ray, and CT scanning of the neck, chest, and abdomen were performed approximately every 2–3 months for the first year after initiation of treatment. Thereafter, patients were followed every 3–6 months until death or until lost to follow-up. There were no differences in pretreatment examinations and treatment strategy between the two institutions.

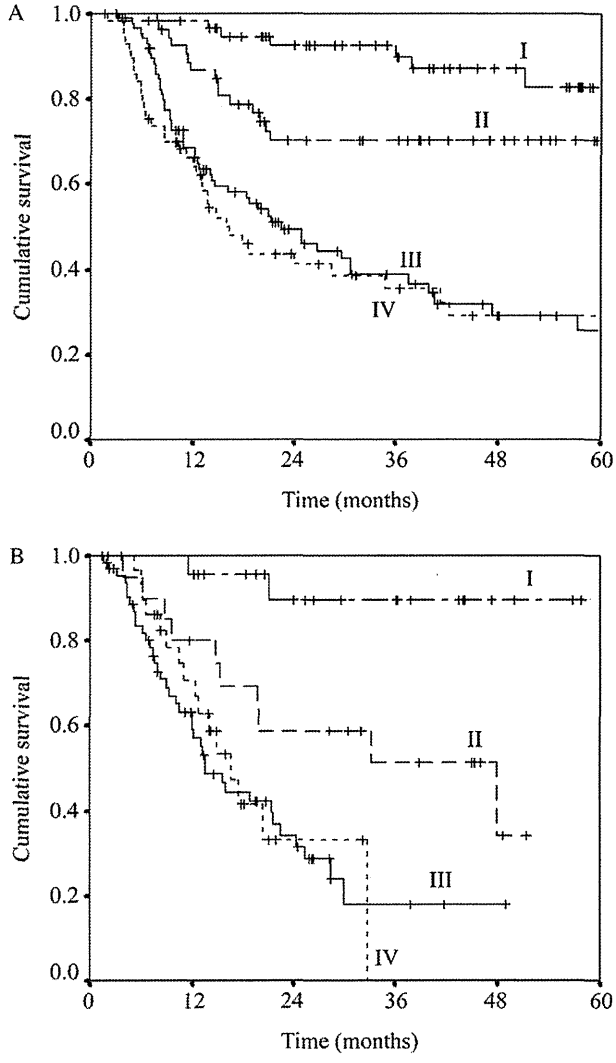


**Fig. 1.** Survival curves according to the TNM 7th classification of (A) the developmental dataset and (B) the validation dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.9%, 70.1%, 38.7%, and 35.5%, respectively, in the developmental dataset. The 3-year survival rates of disease Stages I, II, III, and IV according to the TNM 7th classification were 89.7%, 51.3%, 18.0%, and 0.0%, respectively, in the validation dataset.

## Data collection

The following information was recorded from the medical record and radiological images of each patient: treatment initiation date, age, sex, Eastern Cooperative Oncology Group performance status, cancer site, histological grade, clinical stage according to the 7th AJCC edition, total radiation dose, final date assessing survival, and date of death. ND measurements and TNM staging according to the 7th AJCC edition, including number of lymph nodes, were independently redetermined by two radiologists at each institution (M.N. and T.K. at Aichi Cancer Center; M.N. and M.K. at Kansai Medical University). A lymph node was considered as positive for metastasis if the short axis was greater than 5 mm on CT (14) and there was visual correlation on PET scan. PET-positive lymph node