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

We thank all radiation oncologists who participated in this study. We are also grateful to Y. Asazawa for making the questionnaire available to us.

Funding

This study was supported in part by Grant-in Aid from the Ministry of Health, Labor and Welfare of Japan [H21–018].

Conflict of interest statement

None declared.

References

1. Harmenberg U, Hamdy FC, Widmark A, Lennernas B, Nilsson S. Curative radiation therapy in prostate cancer. *Acta Oncol* 2011;50(Suppl 1):98–103.
2. Ghilezan M, Yan D, Martinez A. Adaptive radiation therapy for prostate cancer. *Semin Radiat Oncol* 2010;20:130–7.
3. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Sekiguchi K, et al. Japanese structure survey of radiation oncology in 2007 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2010;78:1483–93.
4. Kupelian P, Meyer JL. Image-guided, adaptive radiotherapy of prostate cancer: toward new standards of radiotherapy practice. *Front Radiat Ther Oncol* 2011;43:344–68.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer V1 2011. http://www.nccn.org/.
6. Horwich A, Parker C, Kataja V. Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20(Suppl 4):76–8.
7. Nakamura K, Ogawa K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Patterns of radiation treatment planning for localized prostate cancer in Japan: 2003–05 patterns of care study report. *Jpn J Clin Oncol* 2009;39:820–4.
8. Ogawa K, Nakamura K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Radical external beam radiotherapy for clinically localized prostate cancer in japan: changing trends in the patterns of care process survey. *Int J Radiat Oncol Biol Phys* 2011, in press.
9. Fiorino C, Reni M, Bolognesi A, Bonini A, Cattaneo GM, Calandrino R. Set-up error in supine-positioned patients immobilized

with two different modalities during conformal radiotherapy of prostate cancer. *Radiother Oncol* 1998;49:133–41.
10. Smeenk RJ, Teh BS, Butler EB, van Lin EN, Kaanders JH. Is there a role for endorectal balloons in prostate radiotherapy? A systematic review. *Radiother Oncol* 2010;95:277–82.
11. Enmark M, Korreman S, Nystrom H. IGRT of prostate cancer; is the margin reduction gained from daily IG time-dependent? *Acta Oncol* 2006;45:907–14.
12. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–18.
13. ICRU. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Report 83. Oxford: Oxford University Press 2010.
14. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Ito H, et al. Japanese structure survey of radiation oncology in 2005 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2008;72:144–52.

Risk Factors for Treatment-Related Death Associated with Chemotherapy and Thoracic Radiotherapy for Lung Cancer

Yuko Minami-Shimmyo, MD, Yuichiro Ohe, MD, PhD,* Seiichiro Yamamoto, PhD,† Minako Sumi, MD, PhD,‡ Hiroshi Nokihara, MD, PhD,* Hidehito Horinouchi, MD,* Noboru Yamamoto, MD, PhD,* Ikuo Sekine, MD, PhD,* Kaoru Kubota, MD, PhD,* and Tomohide Tamura, MD**

Introduction: The aim of the study is to evaluate the current status of treatment-related death (TRD) in lung cancer patients.

Methods: We retrospectively analyzed the incidence and risk factors of TRD in lung cancer patients who received chemotherapy and/or thoracic radiotherapy using logistic regression analyses.

Results: Between January 2001 and December 2005, 1225 (222 small cell and 1003 non-small cell lung cancers) patients received chemotherapy and/or thoracic radiotherapy as the initial treatment. Of these, 43 patients receiving chemotherapy followed by thoracic radiotherapy were included into both the chemotherapy-alone and radiotherapy-alone groups. There were a total of 23 (1.9%) TRDs. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 from drug-induced lung injury, 2 from pneumonia, and 1 from unknown cause. Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 from radiation pneumonitis and 1 from pneumonia. Thoracic radiotherapy-related deaths occurred in 4 of 96 (4.2%) patients. The incidence of chemotherapy-related death was correlated with poor performance status (odds ratio [OR]: 11.4, 95% confidence interval [CI]: 3.53–37.1), the presence of hypoxia (OR: 19.3, CI: 6.06–61.7), hyponatremia (OR: 45.5, CI: 13.4–154), and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (OR: 8.56, CI: 2.48–29.5), whereas the incidence of concurrent chemoradiotherapy-related death was correlated with pulmonary fibrosis (OR: 22.2, CI: 5.61–87.8). Radiotherapy results were not analyzed because there were too few patients.

Conclusions: TRD occurred in 1.9% of the patients as a result of treatment-related lung injury in the majority of the cases.

Key Words: Lung cancer, Treatment-related death, Risk factor, Chemotherapy, Thoracic radiotherapy.

(*J Thorac Oncol.* 2012;7: 177–182)

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital; †Division of Cancer Information and Epidemiology, National Cancer Center Research Institute; and ‡Division of Radiation Oncology, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo, Japan.

Disclosure: The authors declare no conflict of interests.

Address for correspondence: Ikuo Sekine, MD, PhD, Department of Medical Oncology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. E-mail: isekine@chiba-u.jp

ISSN: 1556-0864/12/0701-0177

Before any medical interventions are undertaken in patients with lung cancer, they must be clearly informed about the risks and benefits of the intervention(s) and about alternative treatment options. Careful delivery of this is particularly important if the planned treatment may not only result in cure but may also be harmful. Provision of accurate information to help patients make the most appropriate decision is therefore crucial. However, the risks of death from drug toxicity and the incidences of such events tend to be uncertain[1–4] and also constantly change with the wide use of newer agents, such as third-generation chemotherapy agents, and molecular-targeted agents. In addition, the incidence of treatment-related deaths (TRDs) has not been thoroughly examined in clinical settings outside of clinical trials. Prospective clinical trials for poor-risk patients are often difficult to perform because of poor accrual, reflecting the reluctance of physicians to subject patients with underlying comorbid illness to the toxic effects of chemotherapy and radiation.

Our ultimate goal is to prospectively identify individuals who are at a high risk of TRD so as to provide the most precise estimation of the possible risks to each patient. In this study, we retrospectively examined the data of patients with locally advanced or metastatic lung cancer who were treated at the National Cancer Center Hospital, Tokyo, Japan, focusing on the risks and incidences of TRD associated with chemotherapy and radiotherapy.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2005, a total of 1623 lung cancer patients were admitted to the thoracic oncology ward at the National Cancer Center Hospital. All patients were admitted in this period to be treated as part of standard practice in Japan. Patients who received chemotherapy alone usually stayed in the hospital for 7 to 10 days for one cycle of chemotherapy, and those who received concurrent chemoradiotherapy stayed for 6 weeks. Among these, a total of 1225 patients who had received first-line chemotherapy and/or radiotherapy on an inpatient basis were extracted from the institutional database. Additional details about the patients, including the diagnostic imaging findings, were then reviewed from the patients' medical records. The data of patients receiving chemotherapy and/or thoracic radiotherapy

as the initial treatment were evaluated. They included patients with stage III to IV disease and postoperative recurrent disease who received chemotherapy; those with stage III disease who received chemoradiotherapy or radiotherapy alone; and those with stage III disease who received preoperative induction therapy or postoperative adjuvant therapy. All the patients had been followed for at least 4 weeks after the completion of treatment.

Treatment Selection

After a thorough evaluation of the operability and/or curability, the eligibility of each patient for enrollment in an open clinical trial was determined. Although patient recruitment for protocol treatments is a priority of ours, patients were free to refuse treatment. If no appropriate clinical trials were scheduled or under way, the known best standard treatments were administered.

Best Standard Treatments

For first-line treatment, patients with non-small cell lung cancer (NSCLC) who were deemed inoperable but curable with good local control with chemoradiotherapy received three to four cycles of cisplatin (CDDP) 80 mg/m^2 on day 1 + vinorelbine (VNR) 20 mg/m^2 on days 1 and 8, every 4 weeks, along with early concurrent thoracic radiotherapy, usually at a total dose of 60 Gy/30 fractions.[5] Sequential chemoradiotherapy, rather than concurrent chemoradiotherapy, was offered if the calculated percentage of the total lung volume receiving radiation in excess of 20 Gy (V_{20}) was more than 40%.[6] Thoracic radiotherapy alone was selected if chemotherapy could not be given due to comorbidity. If the radiation field involved the contralateral hilum or if the patients had malignant effusion and/or distant metastasis, platinum doublet therapy was administered; the most common combination was four cycles of carboplatin (CBDCA) area under the curve = 6 on day 1 + paclitaxel (PTX) 200 mg/m^2 on day 1, every 3 weeks.[7] For limited-disease SCLC, four cycles of a combination of CDDP 80 mg/m^2 on day 1 + etoposide 100 mg/m^2 on days 1 to 3, every 4 weeks, were administered concurrently with hyperfractionated thoracic radiotherapy at a total radiation dose of 45 Gy in fractional doses of 1.5 Gy, administered twice a day.[8] In patients with extensive-disease SCLC, four cycles of a combination of CDDP 60 mg/m^2 on day 1 and irinotecan (CPT) 60 mg/m^2 on days 1, 8, and 15, every 4 weeks, were usually administered.[9] Radiotherapy was given using megavoltage photons (6–15 MV). The routine radiation schedule without chemotherapy for locally advanced NSCLC was a total radiation dose of 60 to 66 Gy, or as high as 70 Gy, administered in fractional doses of 2.0 Gy once a day.

Definition of TRD

Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment, without clear evidence of any other cause of death, or death obviously caused by treatment toxicity. Radiotherapy-related death was defined as death secondary to hypoxia or to complications of corticosteroid administration after the diagnosis of radiation pneumonitis. Steroid therapy was administered based on the attending physician's discretion, without a standardized treatment dose or duration, for the management of radiation-induced lung injury.[10]

Definition of Treatment-Induced Lung Injury

The criteria of drug-induced lung injury in this study were as follows: (1) appearance of new symptoms and radiological abnormalities in the course of chemotherapy with the onset within a few months of the start of the therapy; (2) diffuse or multifocal ground-glass opacities and intralobular interstitial thickening without segmental distribution in computed tomography (CT) scans of the chest; and (3) no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Lung biopsy was not routinely performed in our hospital because patients were frequently too frail to undergo biopsy. The criteria of radiation-induced lung injury were (1) appearance of new symptoms and radiological abnormalities with the onset within 6 months of the end of thoracic radiotherapy; (2) opacification, diffuse haziness, infiltrates, or consolidation conforming to the outline of the sharply demarcated irradiated area in CT scans; and (3) a reduction in lung volume within the irradiated area and linear, ground-glass opacities or reticular shadows beyond the irradiated area developing during clinical course. In contrast, the criteria of bacterial pneumonia were (1) clinical suspicion of pneumonia including rapidly developing fever and/or productive cough; and (2) consolidation spreading through anatomical structure of the lung in CT scans.

Statistical Analysis

We investigated the associations between chemotherapy-related or concurrent chemoradiotherapy-related death and the potential risk factors at the time of diagnosis. The following potential risk factors were investigated: sex, age (≥70 years versus <70 years), performance status (Eastern Cooperative Oncology Group criteria; 2–4 versus 0–1), smoking history (presence versus absence), partial pressure of oxygen (70 mmHg ≤ PO_2 versus >70 mmHg), hemoglobin (Hgb < 13.7 g/dl versus ≥ 13.7 g/dl), platelet (Plt > 367 × 10^9/L versus ≤367 × 10^9/L), albumin (Alb < 3.7 g/dl versus ≥3.7 g/dl), sodium (Na < 138 mEq/L versus ≥138 mEq/L), clinical trial (in versus out), and chemotherapy regimen (The cutoff values of hemoglobin, platelet, albumin, and sodium are the institutional normal limits [above or below]). For concurrent chemoradiotherapy-related factors, the presence of coincidental diseases such as emphysema (with versus without) or pulmonary fibrosis (with versus without) and the location of the primary tumor (lower lobe versus other lobes) were also included in the analyses. The diagnostic criteria of pulmonary fibrosis were a linear, ground-glass attenuation or reticular shadows on chest radiographs and CT scans before treatment that were predominant in the lower zone of the lung. Also, the influence of the chemotherapy regimens was evaluated.

In the univariate preliminary analysis, the relation between previously defined variables at the time of presentation and the occurrence of the outcome variable (toxic death) was assessed using the χ^2 test. To adjust for each factor, multivariate logistic regression analyses were planned. When the number of observed events was less than 10, multivariate

analysis was not performed. When the number of patients for each factor was small, the factor was excluded from the model, even when it appeared to be statistically significant. All the analyses were performed using the STATISTICA 4.1J program (StatSoft, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

The patient characteristics before treatment are listed in Table 1. Of the 1225 patients (SCLC: 222; adenocarcinoma: 652; squamous cell carcinoma: 194; NSCLC not otherwise specified: 111; large cell carcinoma: 7; others: 39), chemotherapy alone was administered in 884 patients, concurrent chemoradiotherapy in 245, sequential chemoradiotherapy in 43, and thoracic radiotherapy alone in 53 patients. To evaluate the incidence of TRD among the patients who received chemotherapy, radiotherapy, or a combination of these modalities, we included the 43 patients who received sequential chemoradiotherapy into both the chemotherapy-alone group and the thoracic radiotherapy-alone group. Therefore, the patients who received sequential chemoradiotherapy were regarded as having been exposed to the risks of treatment twice. The groups were therefore analyzed as chemotherapy alone in 927 patients, concurrent chemotherapy in 245 patients, and thoracic radiotherapy alone in 96 patients. In these groupings, the percentages of patients enrolled in clinical trials were 62, 53, and 23%, respectively.

Cumulative Incidence and Causes of TRD

The cumulative incidence and causes of TRD are listed in Table 2. Of the 1225 patients, a total of 23 (1.9%) TRDs occurred. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 (0.4%) from drug-induced lung injury (gefitinib, $n = 3$ and CBDCA + gemcitabine, $n = 1$), 2 (0.2%) from pneumonia (CBDCA + PTX, $n = 2$), and 1 (0.1%) from unknown cause. The patient who died of unknown cause experienced hemodynamic instability (shock) of unknown etiology within 24 hours of ingestion of the first dose of gefitinib (250 mg). No TRDs from sepsis occurred in this series.

Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 (4.5%) from radiation pneumonitis and 1 (0.4%) from pneumonia during the last planned cycle of CDDP + VNR. Radiotherapy-

TABLE 1. Patient Characteristics

Characteristics	Chemotherapy Alone[a] ($n = 927$)	Concurrent Chemoradiotherapy ($n = 245$)	Radiotherapy Alone[a] ($n = 96$)
Sex			
Male	639	201	43
Female	288	44	53
Age			
Median (range)	64 (27–86)	59 (18–77)	67 (35–81)
Performance status			
0–1	871	245	88
2	140	0	8
3–4	16	0	0
Stage			
III	297	235	71
IV	454	2	17
Postoperative recurrence	176	8	8
Histology			
Non-small cell carcinoma	760	191	88
Small cell carcinoma	167	54	8
Coincidental lung disease			
Pulmonary fibrosis	34	1	4
Pulmonary emphysema	69	30	1
Chemotherapy regimen			
Platinum + taxane	368	21	—
Platinum + irinotecan	133	1	—
EGFR-TKI	125	0	—
Platinum + etoposide	95	54	—
Platinum + antimetabolite	85	0	—
Platinum + vinca alkaloid	37	168	—
Others	84	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

TABLE 2. Treatment-Related Death and Its Cumulative Incidence

Characteristics	Chemotherapy Alone[a] (n = 927)	Concurrent Chemoradiotherapy (n = 245)	Radiotherapy Alone[a] (n = 96)
No. of treatment-related deaths	7	12	4
Cumulative incidence (%)	0.8	4.9	4.2
Sex			
Male	5	11	4
Female	2	1	0
Age of patients who died of treatment (yr)			
Median (range)	69 (46–77)	68 (50–77)	75 (65–77)
Causes			
Treatment-induced lung injury	4	11	4
Infectious pneumonia	2	1	0
Unknown	1	0	0
Chemotherapy regimen			
Platinum + taxane	2	2	—
EGFR-TKI	4	—	—
Platinum + antimetabolite	1	—	—
Platinum + etoposide	0	1	—
Platinum + vinca alkaloid	0	8	—
Others	0	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

related deaths occurred in 4 of 96 (4.2%) patients: all 4 (4.2%) patients died of radiation pneumonitis.

Risk Factors for TRD from Chemotherapy

Statistically significant factors identified by the univariate analysis were a performance status of 2 to 4, hypoxia, hypoalbuminemia, hyponatremia, out of clinical trials, and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Table 3). Although statistically significant, the degrees of hyponatremia in the events were neither clinically significant nor symptomatic for the range of 133 to 137 mEq/L. Pulmonary fibrosis and emphysema were noted in 34 and 69 patients, respectively, among the 927 patients. None of these patients with lung disease died of treatment in this study. Multivariate analysis was not performed because the number of observed events was too small (n = 7).

Risk Factors for TRD from Concurrent Chemoradiotherapy

None of the factors, except for pulmonary fibrosis, were found to be statistically significant in the univariate analysis, although a trend toward increase in the risk of TRD was observed in patients of advanced age (>70 years) and with lower lobe as the primary tumor site (Table 4). Pulmonary fibrosis appeared to be a statistically significant risk factor for TRD; however, it was excluded from the multivariate analysis because of its limited incidence. Thus, we did not perform multivariate analysis for chemoradiotherapy group, and an analysis of the risk of TRD associated with thoracic radiotherapy alone was not conducted because of the limited number of cases.

DISCUSSION

We identified a total of 23 TRDs out of the 1225 patients (1.9%) enrolled in this study, which is lower than the rate (2.7%) indicated in a previous report, particularly in relation to the number of TRDs from infections, including pneumonia and sepsis.[1] The reason for the decrease in the incidence of infection-related deaths is likely explained by the infrequent use of triplet regimens when compared with previous studies. Especially, mitomycin-C-containing regimens are regarded as effective regimens in the treatment of lung cancer; however, prolonged neutropenia has been observed with these regimens. Ohe et al.[1] reported that combined mitomycin-C + vindesine + CDDP (MVP regimen) therapy is a risk factor for chemotherapy-related TRD (toxic deaths occurred in 9 of 301 patients; odds ratio [OR] = 9.36, 95% confidence interval [CI] = 1.29–68.0, p = 0.027). In this study, only 35 patients, the majority (89%) of whom were enrolled in a clinical trial, received the MVP regimen. In the past, however, the MVP regimen was widely used as part of practice-based regimens (only 28% recorded under clinical trials). In most cases, patients who were not eligible for clinical trials ended up receiving the MVP regimen. Another reason is the relatively frequent use of EGFR-TKI (in 13.5% of the patients in this study) at present, which does not induce myelosuppression. The reduction in the frequency of TRD might also be explained by a progress in supportive care in the treatments given for cancer treatment toxicities.

This study revealed that drug-induced lung injury was the most frequent cause of TRD in the era of molecular-targeted therapy. Three (75%) of four TRDs from drug-induced lung injury were associated with gefitinib. The re-

TABLE 3. Risk Factors for Treatment-Related Death from Chemotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	288	0.8	1	
Male	639	0.7	1.13 (0.22–5.76)	0.89
Age				
<70	689	0.6	1	
≥70	238	1.3	2.17 (0.51–9.30)	0.30
PS				
0–1	870	0.5	1	
2–4	57	5.2	11.4 (3.53–37.1)	<0.001
Smoking history				
No	271	0.4	1	
Yes	656	0.9	2.49 (0.30–20.8)	0.40
PaO_2 (Torr)				
≥70	812	0.2	1	
<70	105	4.8	19.3 (6.06–61.7)	<0.001
Hemoglobin (g/dl)				
≥13.7	371	0.5	1	
<13.7	556	0.9	1.67 (0.33–8.39)	0.54
Albumin (g/dl)				
≥3.7	663	0.3	1	
<3.7	264	1.9	6.28 (1.51–26.1)	0.012
AST (IU/L)				
≤33	831	0.6	1	
>33	96	2.1	3.46 (0.75–16.0)	0.11
Na (mEq/L)				
≥138	819	0.1	1	
<138	108	5.6	45.5 (13.4–154)	<0.001
Clinical trial				
No	355	1.7	1	
Yes	572	0.2	0.10 (0.58–0.019)	0.001
Platinum + taxane				
No	559	0.9	1	
Yes	368	0.5	0.61 (0.12–3.14)	0.55
EGFR-TKIs				
No	802	0.4	1	
Yes	125	3.2	8.56 (2.48–29.5)	0.001
Platinum + antimetabolite				
No	842	0.7	1	
Yes	85	1.1	1.66 (0.20–13.9)	0.64

Multivariate analysis was not performed because the number of observed events was too small ($n = 7$).

OR, odds ratio; CI, confidence interval; PS, performance status; AST, aspartate transaminase; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

TABLE 4. Risk Factors for Treatment-Related Death from Concurrent Chemoradiotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	44	2.3	1	
Male	201	5.2	2.41 (0.35–16.6)	0.37
Age (yr)				
<70	221	4.1	1	
≥70	24	12.5	3.07 (0.92–10.3)	0.069
PS				
0	114	5.3	1	
1	131	4.6	0.87 (0.29–2.62)	0.81
Smoking history				
No	32	3.2	1	
Yes	213	5.2	1.65 (0.23–11.9)	0.24
Fibrosis				
No	244	4.5	1	
Yes	1	100	22.2 (5.61–87.8)	<0.001
Emphysema				
No	215	4.7	1	
Yes	30	6.7	1.43 (0.33–6.25)	0.63
Location of the tumor				
Other lobes	189	3.7	1	
Lower lobe	56	8.9	2.41 (0.82–7.13)	0.11
Histology				
SCLC	54	1.9	1	
NSCLC	191	5.8	3.11 (0.47–20.6)	0.24
Hemoglobin (g/dl)				
≥13.7	146	4.1	1	
<13.7	99	6.1	1.48 (0.49–4.42)	0.48
Albumin (g/dl)				
≥3.7	198	4.5	1	
<3.7	47	6.4	1.40 (0.40–4.99)	0.6
Na (mEq/L)				
≥138	219	5.0	1	
<138	26	3.8	0.77 (0.11–5.60)	0.79
Clinical trial				
No	114	5.3	1	
Yes	131	4.6	0.87 (0.29–2.62)	0.81
Platinum + taxane				
No	224	4.5	1	
Yes	21	9.5	2.25 (0.46–11.0)	0.32
Platinum + vinca alkaloid				
No	77	5.2	1	
Yes	168	4.8	0.91 (0.27–3.13)	0.88

Multivariate analysis was not performed because only fibrosis was significant in univariate analysis.

OR, odds ratio; CI, confidence interval; PS, performance status; NSCLC, non-small cell lung cancer.

ported risk factors for interstitial lung disease in NSCLC patients treated with gefitinib are male sex, history of smoking, and underlying interstitial pneumonitis.[11] In this study, however, none of these factors were associated with TRD from chemotherapy. Another TRD from drug-induced lung injury occurred in a patient who received gemcitabine, but this patient was also free from underlying pulmonary disease or concomitant use of taxanes, which are reported to be risk factors for gemcitabine-associated interstitial lung disease.[12]

For patients who receive concurrent chemoradiotherapy, we would like to emphasize the previous finding that the

presence of evidence of pulmonary fibrosis on a plain chest x-ray is an extremely strong risk factor for TRD (OR = 166, 95% CI = 8.79–3122, $p < 0.001$).[1] In this study, only one patient with pulmonary fibrosis was identified, and pulmonary fibrosis was not included in the multivariate analysis because of the small number of patients with this factor, because we generally exclude patients with evidence of pulmonary fibrosis on the chest x-ray from consideration of concurrent chemoradiotherapy. This study also suggested that advanced age may be a risk factor for TRD. This is consistent with the results of previous studies.[1,13–15] The association between advanced age and fatal radiation-induced lung injury may be explained by the increased likelihood of these patients developing comorbid lung disease, particularly among patients with a history of heavy tobacco exposure. A meta-analysis of chemoradiotherapy using individual data from 1764 patients with locally advanced NSCLC showed that the benefit of chemoradiotherapy was obtained in elderly patients (≥71 years) as well as in younger patients. However, it might be assumed that patients who are included in such trials are fit patients with minimal comorbidities. In addition, despite the increase in toxicity that accompanied chemoradiotherapy in elderly patients, it seemed that they had disease control and survival rates similar to those of younger patients.[16]

In conclusion, TRD occurred in a total of 1.9% of patients and was caused in the majority of the cases by treatment-related lung injury. This finding is in clear contrast with previous reports which suggested that the principal cause of TRD in lung cancer patients was septic shock.

ACKNOWLEDGMENTS

The authors thank Ms. Mika Nagai for her assistance in the preparation of this manuscript.

REFERENCES

1. Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.
2. Morittu L, Earl HM, Souhami RL, et al. Patients at risk of chemotherapy-associated toxicity in small cell lung cancer. *Br J Cancer* 1989;59: 801–804.
3. Radford JA, Ryder WD, Dodwell D, et al. Predicting septic complications of chemotherapy:an analysis of 382 patients treated for small cell lung cancer without dose reduction after major sepsis. *Eur J Cancer* 1992;29A:81–86.
4. Stephens RJ, Girling DJ, Machin D. Treatment-related deaths in small cell lung cancer trials: can patients at risk be identified? Medical Research Council Lung Cancer Working Party. *Lung Cancer* 1994;11: 259–274.
5. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
6. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
7. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18:317–323.
8. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20: 3054–3060.
9. Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
10. Sekine I, Sumi M, Ito Y, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. *Radiother Oncol* 2006;80:93–97.
11. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–2556.
12. Barlési F, Villani P, Doddoli C, et al. Gemcitabine-induced severe pulmonary toxicity. *Fundam Clin Pharmacol* 2004;18:85–91.
13. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–1960.
14. Schild SE, Stella PJ, Geyer SM, et al. North Central Cancer Treatment Group. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. *J Clin Oncol* 2003;21:3201–3206.
15. Schild SE, Stella PJ, Brooks BJ, et al. Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer* 2005;103:2349–2354.
16. Aupérin A, Le Péchoux C, Pignon JP, et al; Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 953–959, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.01.008

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

IKUO SEKINE, M.D., PH.D.,* MINAKO SUMI, M.D.,PH.D.,† YOSHINORI ITO, M.D.,† HIDEHITO HORINOUCHI, M.D.,* HIROSHI NOKIHARA, M.D., PH.D.,* NOBORU YAMAMOTO, M.D., PH.D.,* HIDEO KUNITOH, M.D., PH.D.,* YUICHIRO OHE, M.D., PH.D.,* KAORU KUBOTA, M.D., PH.D.,* AND TOMOHIDE TAMURA, M.D.*

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; and †Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

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).

Reprint requests to: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel : (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: isekine@ncc.go.jp

Presented at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29—June 2, 2006, Orlando, Florida.

Supported in part by Ministry of Health, Labour and Welfare, Health and Labour Science Research Grants, Research on Clinical Trials' Infrastructure Development, H21-RINKEN (Kikan)-IP-PAN-005.

Conflict of interest: none.

Acknowledgment—The authors thank Asako Sakamoto for her work as data manager and Mika Nagai for manuscript preparation.

Received June 7, 2010, and in revised form Dec 27, 2010. Accepted for publication Jan 10, 2011.

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 ≥ 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 ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 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).

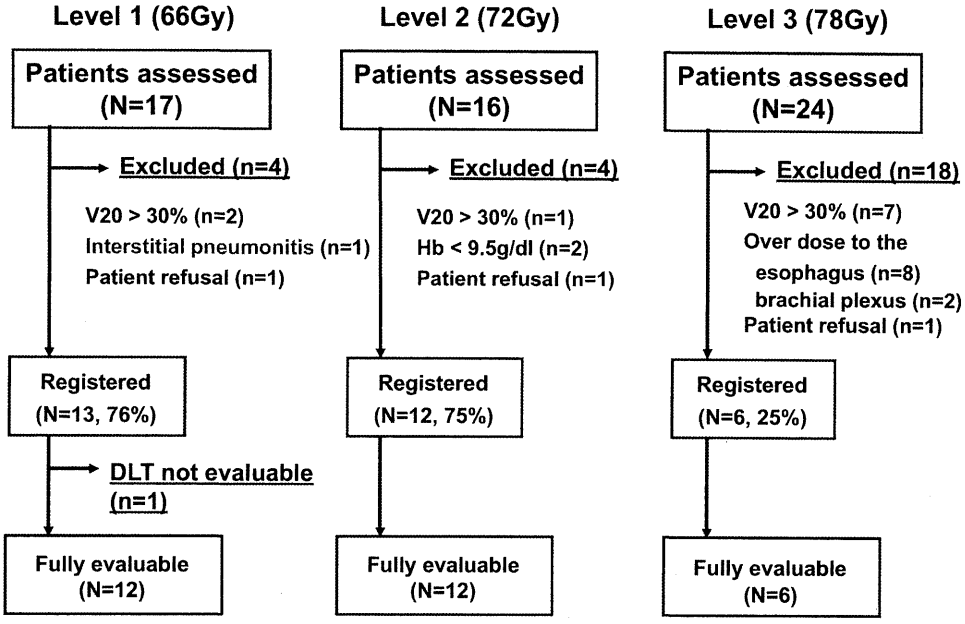

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

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).

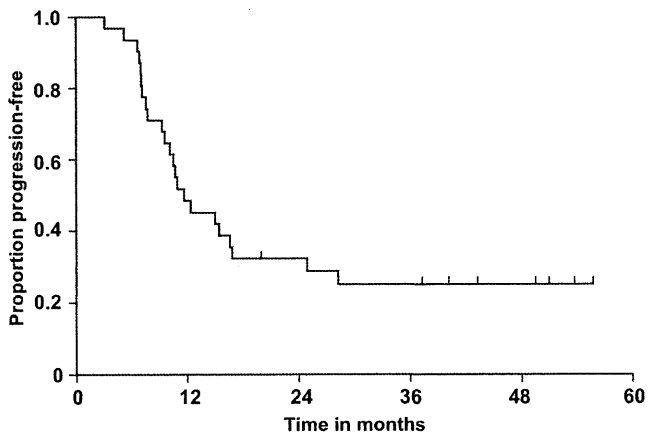

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

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)

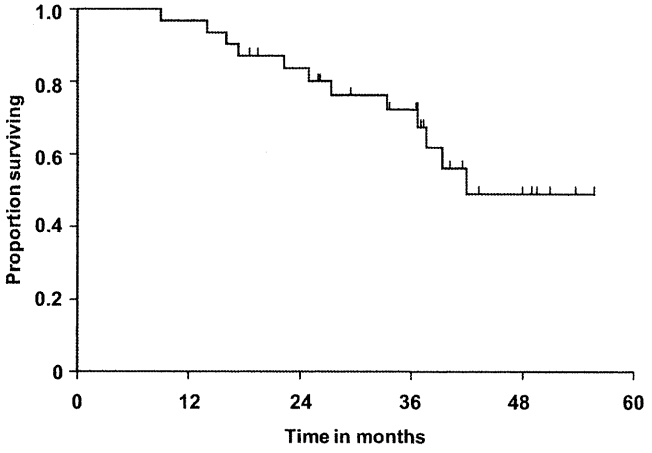

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

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.

REFERENCES

1. Yang P, Allen MS, Aubry MC, *et al.* Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452–462.
2. Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17: 2692–2699.
3. Curran WJ, Scott C, Langer C, *et al.* Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): Initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000;19: 484a.
4. Sekine I, Noda K, Oshita F, *et al.* Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for

unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
5. Sekine I, Nokihara H, Sumi M, *et al.* Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2006;1:810–815.
6. Kiura K, Takigawa N, Segawa Y, *et al.* Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer: OLCSG 0007. *J Clin Oncol* 2008;26(Suppl):400s (abstr. 7515).
7. Perez CA, Pajak TF, Rubin P, *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59:1874–1881.
8. Birim O, Kappetein AP, Stijnen T, *et al.* Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 2005;79:375–382.
9. Nestle U, Walter K, Schmidt S, *et al.* 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: High impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 1999;44:593–597.
10. Purdy J. Three-dimensional conformal radiation therapy: Physics, treatment planning, and clinical aspects. In: Halperin E, Perez C, Brady L, editors. Principles and practice of radiation oncology. 5th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008.
11. Rosenzweig KE, Sura S, Jackson A, *et al.* Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557–5561.
12. Sanuki-Fujimoto N, Sumi M, Ito Y, *et al.* Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol* 2009;91: 433–437.
13. Socinski MA, Morris DE, Halle JS, *et al.* Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: A dose-escalation phase I trial. *J Clin Oncol* 2004;22: 4341–4350.
14. Rosenman JG, Halle JS, Socinski MA, *et al.* High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: Technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002; 54:348–356.
15. Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. *Semin Radiat Oncol* 2004;14:298–307.
16. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
17. Marks LB, Bentzen SM, Deasy JO, *et al.* Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S70–S76.
18. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: Pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005;63:5–24.
19. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; 21:109–122.

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 250–255, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.10.030

CLINICAL INVESTIGATION **Gynecologic Cancer**

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

AKILA N. VISWANATHAN, M.D., M.P.H.,* CARIEN L. CREUTZBERG, M.D., PH.D.,† PETER CRAIGHEAD, M.B., CH.B.,‡ MARY MCCORMACK, FRCR PH.D.,§ TAKAFUMI TOITA, M.D.,¶ KAILASH NARAYAN, M.D., PH.D.,‖ NICHOLAS REED, M.B.B.S.,** HARRY LONG, M.D.,†† HAK-JAE KIM, M.D.,‡‡ CHRISTIAN MARTH, M.D.,§§ JACOB C. LINDEGAARD, M.D.,¶¶ ANNMARIE CERROTTA, M.D.,‖‖ WILLIAM SMALL, JR., M.D.,*** AND EDWARD TRIMBLE, M.D., M.P.H.†††

*Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; †Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; ‡Tom Baker Cancer Centre, Calgary, Alberta, Canada; §Department of Oncology, University College London Hospital, London, England; ¶Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan; ‖Division of Radiation Oncology, Peter MacCallum Cancer Centre and Department of Obstetrics and Gynecology, University of Melbourne, Melbourne, Australia; **Beatson Oncology Centre, Glasgow, Scotland; ††Division of Medical Oncology, Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN; ‡‡Department of Oncology, Seoul National University Hospital, Seoul, South Korea; §§Medical University Innsbruck, Innsbruck, Austria, ¶¶Aarhus University Hospital, Aarhus, Denmark; ‖‖Department of Radiation Therapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; ***The Robert H. Lurie Comprehensive Cancer of Northwestern University, Chicago, IL; and †††National Cancer Institute, Bethesda, MD

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

Reprint requests to: Akila N. Viswanathan, M.D., M.P.H., Brigham and Women's Hospital, Department of Radiation Oncology, 75 Francis Street L2, Boston, MA 02115. Tel: (617) 732-6331; Fax: (617) 278-6988; E-mail: aviswanathan@lroc.harvard.edu

Presented at the Cervical Cancer State of the Science Meeting, Manchester, UK, June 18, 2009.

Supplementary material for this article can be found at www.redjournal.org.

Conflict of interest: none.

Acknowledgment—The authors thank Barbara Silver for reviewing the manuscript and the physician respondents to this survey.

Received July 3, 2010, and in revised form Sept 3, 2010. Accepted for publication Oct 6, 2010.

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 α/β 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

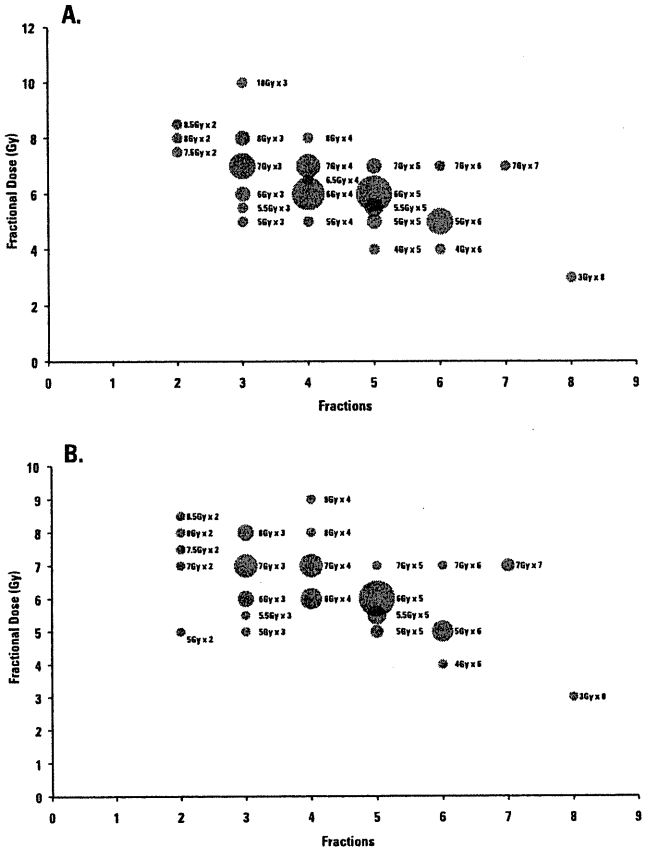

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages 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.

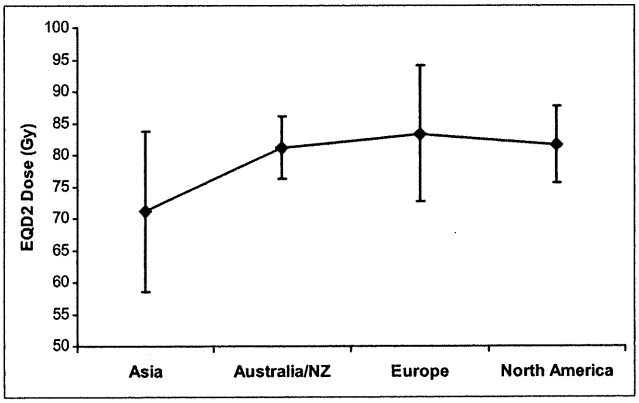

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

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