2. Hanks GE, Coia LR, Curry J. Patterns of care studies: past, present, and future. *Semin Radiat Oncol* 1997;7:97–100.
3. Yang L, Fujimoto J, Qiu D, *et al.* Trends in cancer mortality in Japanese adolescents and young adults aged 15-29 years, 1970-2006. *Ann Oncol* 2009;20:758–766.
4. Eifel PJ, Moughan J, Owen J, *et al.* Patterns of radiotherapy practice for patients with squamous carcinoma of the uterine cervix: Patterns of care study. *Int J Radiat Oncol Biol Phys* 1999;43:351–358.
5. Eifel PJ, Moughan J, Erickson B, *et al.* Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: A patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;60: 1144–1153.
6. Teshima T. Patterns of care study in Japan. *Jpn J Clin Oncol* 2005;35: 497–506.
7. Toita T, Nakamura K, Uno T, *et al.* Radiotherapy for uterine cervical cancer: Results of the 1995–1997 patterns of care process survey in Japan. *Jpn J Clin Oncol* 2005;35:139–148.
8. Toita T, Kodaira T, Shinoda A, *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999-2001): Patterns of care study in Japan. *Int J Radiat Oncol Biol Phys* 2008;70:788–794.
9. Rose PG, Bundy BN, Watkins EB, *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–1153.
10. Watanabe Y, Nakai H, Shimaoka M, *et al.* Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: A phase I study in Japanese patients with cancer of the uterine cervix. *Int J Clin Oncol* 2006;11:309–313.
11. Toita T, Kato S, Niibe Y *et al.* Prospective multi-institutional study of definitive radiotherapy with high-dose rate intracavitary brachytherapy in patients with nonbulky (<4 cm) stage I, II uterine cervical cancer (JAROG0401/JROSG04–2). *Int J Radiat Oncol Biol Phys.* In press.
12. Toita T, Kato S, Ishikura S, *et al.* Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): A cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer. *Int J Clin Oncol.* In press.
13. Cochrane Gynaecological Cancer Group. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: Individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010;1: CD008285. Review.
14. Nakano T. Status of Japanese radiation oncology. *Radiat Med* 2004; 22:17–19.
15. Ogawa K, Nakamura K, Sasaki T, *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.* In press.
16. Erickson B, Eifel P, Moughan J, *et al.* Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): A patterns of care study. *Int J Radiat Oncol Biol Phys* 2005;63: 1083–1092.
17. Nag S, Erickson B, Thomadsen B, *et al.* The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48: 201–211.
18. Toita T, Kakinohana Y, Ogawa K, *et al.* Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;56:1344–1353.
19. Nag S, Orton C, Young D, *et al.* The American brachytherapy society survey of brachytherapy practice for carcinoma of the cervix in the United States. *Gynecol Oncol* 1999;73:111–118.
20. Armesto Garcia S, Lapetra Gil ML, Wei L, *et al. Members of the Health Care Quality Indicators (HCQI) Expert Group.* Health Care-Quality Indicators Project 2006 Data Collection Update Report. OECD HealthWorking Papers No. 29, DELSA/HEA/WD/HWP. Paris: Organization for Economic Co-operation and Development; 2007.
21. Center for Cancer Control and Information Services, National Cancer Center, Japan. [In Japanese]. Available at: http://ganjoho.ncc.go.jp/professional/statistics/statistics.html. Accessed November 13, 2011.
22. Konno R, Sagae S, Yoshikawa H, *et al.* Cervical Cancer Working Group report. *Jpn J Clin Oncol* 2010;40(Suppl 1):i44–i50.

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

0360-3016/$ - see front matter

ELSEVIER

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

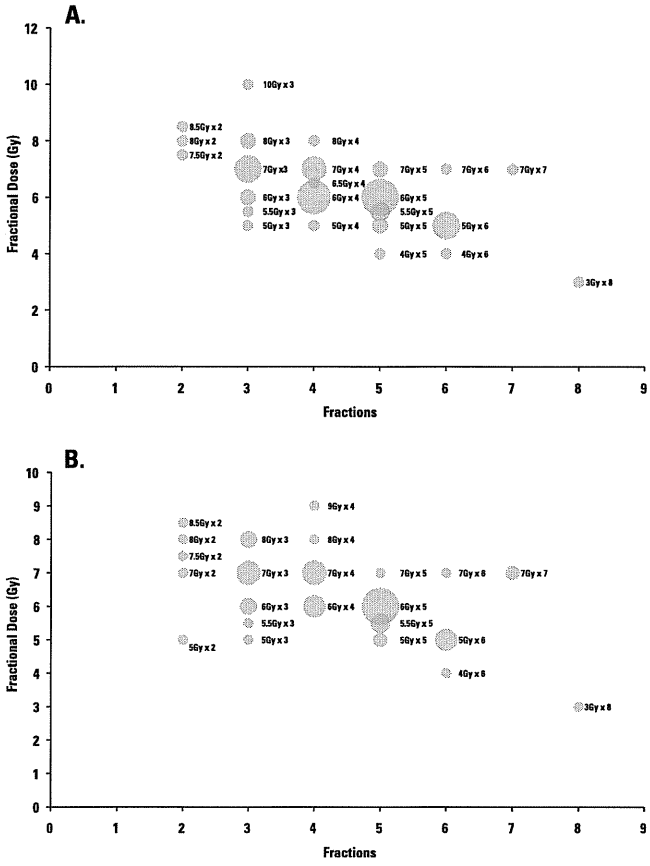

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages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

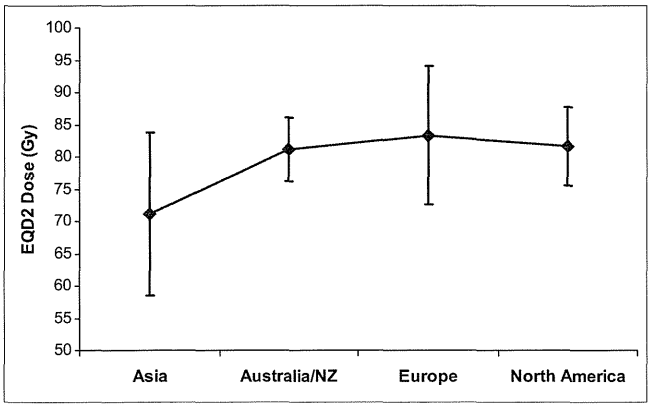

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

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

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

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

REFERENCES

1. Age-standardized incidence rates of cervical cancer. 2009. (Accessed May 22, 2010, at http://www.who.int/mediacentre/factsheets/fs297/en/).
2. Eifel PJ, Winter K, Morris M, *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. *J Clin Oncol* 2004;22:872–880.
3. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: A survey of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys* 2010;76:104–109.
4. Erickson B, Eifel P, Moughan J, *et al.* Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): A patterns of care study. *Int J Radiat Oncol Biol Phys* 2005;63:1083–1092.
5. Stewart AJ, Viswanathan AN. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. *Cancer* 2006;107:908–915.
6. Viswanathan AN, Dimopoulos J, Kirisits C, *et al.* Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: Results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007;68:491–498.
7. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–694.
8. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515–528.
9. Stewart AJ, Bentzen SM. Radiobiological aspects of brachytherapy in the era of 3-dimensional imaging. In: Viswanathan AN, Kirisits C, Erickson B, Poetter R, editors. Gynecologic radiation therapy: Novel approaches to image-guidance and management. Berlin: Springer; 2011.
10. Nag S, Erickson B, Thomadsen B, *et al.* The American Brachytherapy Society recommendations for high dose rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48:201–211.
11. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys* 1999;43:359–366.
12. Forrest J, Ackerman I, Barbera L, *et al.* Treatment outcomes for patients with advanced cervical cancer treated with GOG protocol definitive chemoradiotherapy and HDR brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:S151.
13. Anker CJ, Cachoeira CV, Boucher KM, *et al.* Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. *Int J Radiat Oncol Biol Phys* 2010;76:704–712.
14. Haie-Meder C, Potter R, Van Limbergen E, *et al.* Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74:235–245.
15. Potter R, Dimopoulos J, Kirisits C, *et al.* Recommendations for image-based intracavitary brachytherapy of cervix cancer: the GYN GEC ESTRO Working Group point of view: in regard to Nag, *et al.* (*Int J Radiat Oncol Biol Phys* 2004;60:1160–1172. *Int J Radiat Oncol Biol Phys* 2005;62:293–295. author reply 5–6).
16. Gaffney DK, Du Bois A, Narayan K, *et al.* Practice patterns of radiotherapy in cervical cancer among member groups of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys* 2007;68:485–490.
17. Toita T. Prospective multi-institutional study of definitive radiotherapy and high-dose-rate intracavitary brachytherapy in early stage uterine cervical cancer: A cooperative study of Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG). *Int J Radiat Oncol Biol Phys* 2010;77:S100.
18. Toita T, Kakinohana Y, Ogawa K, *et al.* Combination external beam radiotherapy and high dose rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;56:1344–1353.

Cancer Science
The official journal of the Japanese Cancer Association JCA

Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: Carcinoembryonic antigen as a potential predictive factor

Hidehito Horinouchi,[1,3] Ikuo Sekine,[1] Minako Sumi,[2] Yoshinori Ito,[2] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Division of Internal Medicine and Thoracic Oncology, [2]Division of Radiation Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

(Received September 5, 2011/Revised December 26, 2011/Accepted January 5, 2012/Accepted manuscript online February 9, 2012/Article first published online February 20, 2012)

The predictive factors for the development of brain metastases in patients with stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy remain unclear. Several studies have suggested adenocarcinoma as a predictive factor of brain relapses. In the current analysis, we tried to identify the factors associated with brain metastases in stage III lung adenocarcinoma. The demographic and clinical characteristics, site and date of recurrence, and date of death were reviewed in patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemoradiotherapy. In total, 116 patients were identified with a median (range) age of 57 (35–74) years. Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy. Of the 95 patients with disease progression or recurrence, 19 (16%) developed brain metastases as the sole site of initial recurrence. A total of 43 (37%) patients developed brain metastases at some time during follow-up. Time to brain metastases was significantly associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio (95% confidence interval) of 2.64 (1.39–5.02, $P = 0.003$). Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) than those with metastases other than brain. In conclusion, stage III lung adenocarcinoma patients with an elevated CEA value before treatment had a higher risk of developing brain metastases after chemoradiotherapy. Further effort is mandatory to control brain metastases in this patient population by a therapeutic strategy based on the tumor histology and pretreatment CEA value. (*Cancer Sci* 2012; 103: 756–759)

Recent advances in chemotherapy added to radiotherapy have dramatically improved the prognosis of patients with inoperable stage III non-small-cell lung cancer (NSCLC). The current standard treatment for these patients, concurrent thoracic radiotherapy and platinum-based chemotherapy, yields a 5-year survival rate of 16–23%, with acceptable acute and late toxicity.[1,2] However, many patients still die of recurrent disease. Brain metastases, as well as loco-regional recurrences, are the most frequent types of initial failure. Observational studies in patients with stage III NSCLC who underwent chemoradiotherapy with or without surgery showed that the first recurrent site was the brain in only 8–35% of patients, and brain and other sites in 4–10% of patients, resulting in brain metastases as the first recurrent site in 17–43% of patients.[1,3,4] Prophylactic cranial irradiation (PCI) has been tried to eradicate undetectable micrometastases before they become clinically apparent. Prospective randomized trials comparing PCI and observation in patients with locally advanced NSCLC treated by thoracic radiotherapy with or without chemotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, PCI is not indicated for all patients with stage III NSCLC treated with chemoradiotherapy, but it would improve prognosis if used to treat selected patients who are more likely to develop brain metastases. Several clinical factors have been identified to predict brain metastases in locally advanced NSCLC patients, but they are inconsistent among studies.[9–11] Of these clinical factors, adenocarcinoma histology was suggested to have a higher risk of brain relapses.[11–16] The objectives of this study were to identify factors associated with development of brain metastases in stage III adenocarcinoma patients who received concurrent chemoradiotherapy and to identify potential candidates for intervention to reduce brain relapses.

Materials and Methods

Patient selection. Patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital (Tokyo, Japan) between 1994 and 2005 were eligible for this study. Patients treated with sequential chemotherapy and thoracic radiotherapy were excluded because we have considered the standard care for the stage III NSCLC patients to be concurrent chemoradiotherapy, and therefore, the sequential treatment was given only to patients with poor general condition or to patients who had a tumor too large for radiotherapy initially but decreasing enough for radiotherapy after chemotherapy. All patients underwent a systematic pretreatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, CT scans of the chest and abdomen, a CT scan or MRI of the brain, a bone scintigram, and blood examinations including tumor markers.

Data collection and statistical analyses. Sex, age, performance status, body weight loss, carcinoembryonic antigen (CEA), clinical stage, nodal status, chemotherapy regimens, total dose of radiotherapy, tumor responses to treatment, sites and date of recurrence, and date of death were obtained from a retrospective medical chart review. As a routine clinical practice, tumor markers including CEA were examined in every patient eligible for chemotherapy and chemoradiotherapy before, during,

[3]To whom correspondence should be addressed.
E-mail: hhorinou@ncc.go.jp

doi: 10.1111/j.1349-7006.2012.02217.x

and just after the initiation of treatment. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the cut points of CEA values to predict brain metastasis as the sole, or one of the first, relapse sites. Tumor histological classification was based on the criteria of the World Health Organization.[17] Patients were staged using the 6th edition of Union for International Cancer Control TNM classification for lung cancer.

Time to brain metastases was measured from the start of initial chemoradiotherapy to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study after chemoradiotherapy, there might be diversity in the frequency and methods of monitoring. Patients who did not develop brain metastases at the last follow-up were censored at that time. Time to brain metastases was evaluated using the Kaplan–Meier method, the log–rank test, and Cox's proportional hazard model.

Sex, age, performance status, body weight loss, smoking status, CEA value, stage, T-factor, and nodal status were included as covariates in the multivariate analyses (Cox's proportional hazard model analyses). All of these analyses were carried out using STATA 11.1 software for Windows (StataCorp, College Station, TX, USA).

This study was approved by the president of the National Cancer Center Hospital. The institutional review board and ethics review committee decided to exempt this study from the usual review process because of its retrospective nature.

Results

In total, 116 patients were identified. Females accounted for 26% of the study group. The median age was 57 years. Almost all patients were in good general condition with a performance status of 0–1. Of the 116 patients, 63% had tumor factor (T-factor) 1–2 disease and 93% had nodal factor (N-factor) 2–3 disease. All patients received platinum-based chemotherapy, and 86% received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy (Table 1). The response rate was 82%, median survival time was 24.5 months, and the 5-year survival rate was 24% in this study group.

Disease progression or recurrence was noted in 95 (82%) patients. Brain metastases as the sole site of initial recurrence were noted in 19 (16%) patients, and both brain and other sites were involved in 17 (15%) patients (Table 2). Of the 19 patients who had isolated brain failure, 10 developed recurrences subsequently at additional sites other than the brain, three died of progressive brain metastases without progression in other sites, and two developed meningitis carcinomatosa. Another two patients also died, but the cause of death was not identified because they were lost to follow-up. Brain metastases were controlled by radiotherapy in the other two patients.

A total of 43 patients (37%) developed brain metastases at some time during the course of follow-up. We examined various cut points of CEA value and found 20 ng/mL gave a relatively better AUC (56.2%) by the ROC analysis. Time to brain metastasis was significantly associated with pretreatment CEA value. The responses of CEA during chemoradiotherapy and the CEA level just after chemoradiotherapy did not have significant correlation with brain relapses. The multivariate analysis using Cox's proportional hazard model showed that the hazard ratio (95% confidence interval [CI], *P*-value) of a CEA value $\geq$20 ng/mL was 2.64 (1.39–5.02, $P = 0.003$, Table 3) compared to a CEA value of < 20 ng/mL. Sex, age, performance status, body weight loss, smoking history, T-factor, nodal status, and stage were not associated with the time to brain metastasis (Table 3). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively (Fig. 1).

Overall survival according to the first relapse site is shown in Figure 2. Patients who developed brain metastases only as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

Table 1. Characteristics of patients with stage III lung adenocarcinoma who participated in this study (n = 116)

Characteristic	*n*	%
Sex		
Female	30	26
Male	86	74
Age (years)		
Median (range)	57 (35–74)	NA
Performance status		
0	36	31
1	79	68
2	1	1
Body weight loss		
$\leq$4.9%	95	82
$\geq$5.0%	21	18
Smoking (pack-years)		
$\leq$10	29	25
$\geq$11	87	75
CEA (ng/mL)		
< 20	89	77
$\geq$20	27	23
Stage		
IIIA	57	49
IIIB	59	51
T-factor		
1–2	73	63
3–4	43	37
N-factor		
0–1	8	7
2–3	108	93
Chemotherapy type		
Cisplatin + vinorelbine	75	65
Cisplatin + vindesine + mitomycin	26	22
Nedaplatin + paclitaxel	8	7
Other combinations	7	6
Total radiation dose (Gy)		
60	100	86
<60	16	14

CEA, carcinoembryonic antigen; NA, not applicable; N-factor, nodal factor; T-factor, tumor factor.

Table 2. Sites of first recurrence in patients with stage III lung adenocarcinoma (n = 95)

Site of recurrence	*n*	%
Relapses including brain	36	38
Brain only	19	20
Brain and other sites	17	18
Sites other than brain	56	59
Unknown	3	3

Discussion

This study showed that CEA values before treatment were associated with time to brain metastasis in patients with stage III

Table 3. Time to brain metastases according to clinical factors in patients with stage III adenocarcinoma: Cox proportional hazard model analysis

Characteristic	Cox proportional hazard model (HR [95% CI])			
	Univariate	*P*-value	Multivariate	*P*-value
Sex				
Male	1	0.03	1	0.660
Female	2.00 (1.08–3.69)		1.24 (0.48–322)	
Age (years)				
≤ 57	1	0.17	1	0.110
≥ 58	0.65 (0.34–1.21)		0.58 (0.30–1.13)	
Performance status				
0	1	0.96	1	0.830
1–2	0.98 (0.53–1.83)		0.92 (0.44–1.92)	
Body weight loss (%)				
≤ 4.9	1	0.91	1	0.630
≥ 5.0	1.05 (0.47–2.36)		1.25 (0.51–3.05)	
Smoking (pack-years)				
≤ 10	1	0.01	1	0.290
≥ 11	0.43 (0.23–0.79)		0.58 (0.21–1.59)	
CEA				
< 20	1	0.01	1	0.003
≥ 20	2.17 (1.17–3.99)		2.64 (1.39–5.02)	
T-factor				
1–2	1	0.39	1	0.880
3–4	0.75 (0.39–1.44)		0.84 (0.37–1.90)	
N-factor				
0–1	1	0.33	1	0.520
2–3	2.02 (0.49–8.38)		1.40 (0.50–3.88)	
Stage				
IIIA	1	0.93	1	0.770
IIIB	1.03 (0.57–1.87)		0.85 (0.30–2.46)	

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; N-factor, nodal factor; T-factor, tumor factor.

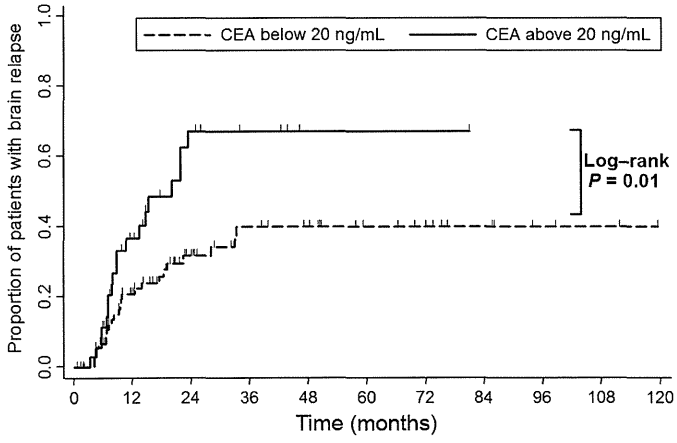

Fig. 1. Cumulative incidence of brain relapse in patients with stage III lung adenocarcinoma by carcinoembryonic antigen (CEA) value (ng/mL). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log-rank test, $P = 0.01$), respectively.

lung adenocarcinoma who received concurrent platinum-based chemotherapy and thoracic radiotherapy. This is the first report showing that the CEA value might be associated with a higher risk of brain metastases in locally advanced lung adenocarcinoma.

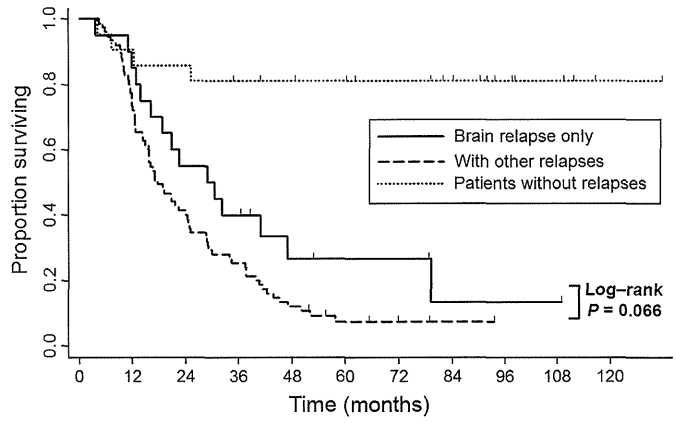

Fig. 2. Overall survival in patients with stage III lung adenocarcinoma according to the first relapse site. Dashed line, patients who developed extracranial recurrence with or without brain metastases; thick line, patients who developed brain relapse only; dotted line, patients who had no relapse. Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) compared to those with metastases other than brain.

The median survival time (24.5 months) in the present study seemed better than the results observed in the study of Cox *et al.* (median survival time, 12.2–18.9 months) that included four clinical trials involving chemoradiotherapy.[12,18–21] The proportion of the participants whose first recurrent sites included brain metastases (38%, Table 2) in this study was substantially higher than the results observed in the analysis of Cox *et al.*[12] (16% with adenocarcinoma). Because the concurrent chemoradiotherapy with better survival failed to improve the proportion of brain relapses, the importance of the prevention of brain metastases has increased in this patient group. Furthermore, overall survival in patients who developed brain metastases as the sole site of the initial recurrence was marginally better than in those with metastases to other sites (log-rank, $P = 0.066$, Fig. 2) in our observation of patients with locally advanced lung adenocarcinoma. In fact, some patients with only brain relapses as the first recurrent site survived without further metastases after local treatment for the brain lesions.

Prospective randomized trials evaluating the effect of PCI in patients with locally advanced NSCLC after chemoradiotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, it is necessary to identify the clinical factors of patients who are more likely to develop brain metastases and would be good candidates for PCI. In retrospective analyses of patients with locally advanced NSCLC, adenocarcinoma histology was suggested to have a higher risk of brain relapses and be worthy of more attention concerning brain metastases.[11–16] Therefore, locally advanced lung adenocarcinoma was specifically analyzed to identify clinical factors predicting brain metastases.

Among patients with disseminated adenocarcinoma without indications for definitive thoracic radiotherapy, a high CEA value (over 40 ng/mL) before treatment might be associated with a higher risk of brain relapses.[22] The present study involving patients with locally advanced lung adenocarcinoma after chemoradiotherapy showed that the CEA value was significantly associated with the time to brain metastasis on multivariate analysis (Table 3). This result suggested that patients with stage III lung adenocarcinoma and elevated CEA values might be good candidates for interventions to prevent brain metastases.

This study had several limitations. First, the number of patients included in the analysis was relatively small because we selected patients with stage III lung adenocarcinoma who

doi: 10.1111/j.1349-7006.2012.02217.x

underwent concurrent chemoradiotherapy. Second, there might be diversity in the frequency and methods of monitoring brain metastases because of the retrospective nature of the analysis. Third, we could not determine significant factors to predict solitary brain relapses which might be cured by prophylactic brain intervention, mainly because the number of patients with solitary brain relapse was too small for efficient statistical analysis.

In conclusion, the present analysis implies that patients with elevated CEA values before treatment have a higher risk of developing brain metastases after chemoradiotherapy for locally advanced lung adenocarcinoma. Further effort is mandatory to evaluate the clinical relevance of CEA value to predict brain relapses and select candidates for prophylactic interventions in future prospective trials.

Acknowledgment

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

Disclosure Statement

The authors have no conflicts of interest.

References

1 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**: 2692–9.
2 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 (abstr7515).
3 Albain KS, Rusch VW, Crowley JJ *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995; **13**: 1880–92.
4 Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007; **109**: 1668–75.
5 Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* 1981; **245**: 469–72.
6 Umsawasdi T, Valdivieso M, Chen TT *et al.* Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J Neurooncol* 1984; **2**: 253–9.
7 Russell AH, Pajak TE, Selim HM *et al.* Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1991; **21**: 637–43.
8 Gore EM, Bae K, Wong SJ *et al.* Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol* 2011; **29**: 272–8.
9 Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol* 2001; **19**: 1344–9.
10 Carolan H, Sun AY, Bezjak A *et al.* Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer* 2005; **49**: 109–15.
11 Gaspar LE, Chansky K, Albain KS *et al.* Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol* 2005; **23**: 2955–61.
12 Cox JD, Scott CB, Byhardt RW *et al.* Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. *Int J Radiat Oncol Biol Phys* 1999; **43**: 505–9.
13 Andre F, Grunenwald D, Pujol JL *et al.* Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer* 2001; **91**: 2394–400.
14 Keith B, Vincent M, Stitt L *et al.* Subsets more likely to benefit from surgery or prophylactic cranial irradiation after chemoradiation for localized non-small-cell lung cancer. *Am J Clin Oncol* 2002; **25**: 583–7.
15 Bajard A, Westeel V, Dubiez A *et al.* Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* 2004; **45**: 317–23.
16 Mamon HJ, Yeap BY, Janne PA *et al.* High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol* 2005; **23**: 1530–7.
17 Travis WD. *Pathology & Genetics of Tumours of the Lung, Thymus And Heart, World Health Organization Classification of Tumours*, 1st edn. Switzerland: WHO Press, 2004.
18 Sause WT, Scott C, Taylor S *et al.* Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995; **87**: 198–205.
19 Byhardt RW, Scott CB, Ettinger DS *et al.* Concurrent hyperfractionated irradiation and chemotherapy for unresectable nonsmall cell lung cancer. Results of Radiation Therapy Oncology Group 90-15. *Cancer* 1995; **75**: 2337–44.
20 Lee JS, Scott C, Komaki R *et al.* Concurrent chemoradiation therapy with oral etoposide and cisplatin for locally advanced inoperable non-small-cell lung cancer: radiation therapy oncology group protocol 91-06. *J Clin Oncol* 1996; **14**: 1055–64.
21 Komaki R, Scott C, Ettinger D *et al.* Randomized study of chemotherapy/radiation therapy combinations for favorable patients with locally advanced inoperable nonsmall cell lung cancer: Radiation Therapy Oncology Group (RTOG) 92-04. *Int J Radiat Oncol Biol Phys* 1997; **38**: 149–55.
22 Arrieta O, Saavedra-Perez D, Kuri R *et al.* Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. *BMC Cancer* 2009; **9**: 119.

Journal of Radiation Research, 2012, 53, 588–593
doi: 10.1093/jrr/rrs010 Advance Access Publication 15 June 2012

Regular Paper

Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer

Yuuki KURODA[1,*], Naoya MURAKAMI[1], Madoka MOROTA[1], Shuhei SEKII[1], Kana TAKAHASHI[1], Koji INABA[1], Hiroshi MAYAHARA[1], Yoshinori ITO[1], Ryo-ichi YOSHIMURA[1], Minako SUMI[1], Yoshikazu KAGAMI[1], Noriyuki KATSUMATA[2], Takahiro KASAMATSU[3] and Jun ITAMI[1]

[1]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan
[2]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[3]Department of Gynecologic Oncology, National Cancer Center Hospital, Tokyo, Japan
*Corresponding author. Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji Chuo-ku, Tokyo, Japan, 104-0045; Tel: 81-(3)3542-2511; Fax: 81-(3)3545-3567; Email: yuuki.kuroda.96@gmail.com

(Received 18 October 2011; revised 20 January 2012; accepted 7 February 2012)

The purpose of this retrospective study is to investigate the impact of concurrent chemotherapy on definitive radiotherapy for the International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer. Between 2000 and 2009, 131 women with FIGO IIIb cervical cancer were treated by definitive radiotherapy (i.e. whole pelvic external beam radiotherapy for 40–60 Gy in 20–30 fractions with or without center shielding and concomitant high-dose rate intracavitary brachytherapy with 192-iridium remote after loading system for 6 Gy to point A of the Manchester method). The concurrent chemotherapy regimen was cisplatin (40 mg/m^2/week). After a median follow-up period of 44.0 months (range 4.2–114.9 months) and 62.1 months for live patients, the five-year overall survival (OS), loco-regional control (LRC) and distant metastasis-free survival (DMFS) rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that lack of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; $P = 0.001$) and DMFS (HR = 2.53; 95% CI 1.39–4.61; $P = 0.002$), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; $P = 0.322$). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$). In conclusion, concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer.

Keywords: cervical cancer; IIIb; chemotherapy; radiotherapy; HDR

INTRODUCTION

External beam radiotherapy (EBRT) combined with intracavitary brachytherapy (ICBT) is the standard treatment for women with cervical cancer [1–3]. A combination of EBRT plus high-dose rate (HDR) ICBT for Japanese women with cervical cancer has provided acceptable outcomes and late complication rates despite the lower dose prescription in Japan than in the US [4–9]. In 2000s concurrent chemoradiotherapy (CCRT) became standard after the National Cancer Institute (NCI) announcement recommending concurrent chemotherapy in 1999 [10], however, the benefits of concurrent chemotherapy on definitive radiotherapy might not be applicable to concomitant EBRT plus HDR-ICBT and are not clear yet in Japan and other Asian countries [9]. We therefore performed a retrospective analysis in a mono-institutional group with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer treated by definitive radiotherapy, the purpose of this study being to investigate the impact of concurrent chemotherapy on definitive radiotherapy for Japanese women.

MATERIALS AND METHODS

Patients

We reviewed our database looking for women with newly diagnosed FIGO IIIb uterine cervical cancers with a

maximum diameter over 4 cm treated with definitive radiotherapy at the National Cancer Center Hospital between 2000 and 2009. Patients who received palliative EBRT alone, postoperative radiotherapy, interstitial brachytherapy or an experimental regimen of concurrent chemotherapy were excluded. A total of 131 women treated with EBRT plus HDR-ICBT were admitted to this retrospective analysis. All patients underwent pelvic examination, cystoscope, urography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and blood tests. Maximum tumor diameters were measured based on the MRI findings and/or US. FIGO staging was allocated for tumor boards of gynecological, medical and radiation oncologists. The pathological diagnosis was carried out with a central pathology review at our pathological division.

Treatment

Treatment selection was determined by the gynecological cancer board, our treatment policy for FIGO IIIb cervical cancer is CCRT to aim for loco-regional control (LRC) even if distant metastasis is not ruled out. Neoadjuvant chemotherapy was prohibited. The concurrent chemotherapy regimen was cisplatin (40 mg/m^2/week). Supportive treatments such as blood transfusions were encouraged during radiotherapy.

Radiotherapy

The radiotherapy field selected was the whole pelvis but exceptions were as follows: para-aortic node (PAN) area irradiation was acceptable in cases with suspicions of PAN metastasis, bilateral inguinal node area irradiation was acceptable in cases with vaginal involvement of more than two-thirds of total vaginal length. Radiotherapy doses of 40–60 Gy in 20–30 fractions were carried out with a 4-field box or the anterior–posterior technique. Center shield radiotherapy (CS) was performed for a shorter overall treatment time (OTT) reducing organ at risk (OAR) exposure depending on tumor shrinkage. CS was carried out 3–4 days/week, and HDR-ICBT 1–2 days/week, but both therapies were not carried out on the same day. All patients underwent EBRT with 10-, 15- and 20-MV X-rays from linear accelerators (Clinac IX, Varian, Palo Alto, CA, USA). Two-dimensional conventional radiotherapy (2DCRT) was employed between 2000 and 2005, and three-dimensional conformal radiotherapy (3DCRT) was used between 2005 and 2010. All patients underwent HDR-ICBT with 192-iridium remote after loading system (RALS, Microselectron). The point A dose prescription for 6 Gy using the Manchester method was performed with the ICBT planning system (Plato®, Nucletron). Image-guided optimization was not applicable even in the case of CT-based ICBT planning. A tandem-cylinder was used only in cases with vaginal involvement of more than one-third of total vaginal length or of an extraordinarily narrow vagina.

Follow-up

All patients were evaluated weekly for toxicity during radiotherapy through physical examinations and blood tests. CT and/or MRI scans and cytology were performed 1–3 months after radiotherapy for initial response, physical examination and blood tests were performed regularly every 1–6 months. Disease progression was defined by the response evaluation criteria in solid tumours (RECIST) version 1.1, new clinical symptoms or observable pelvic deficits.

Statistical analysis

Patient and treatment characteristics were compared using the Mann-Whitney *U* test and Pearson's chi-square test. OS was estimated from the beginning of radiotherapy to the date of death considered as an event, and censored at the time of last follow-up. LRC rate was estimated from the beginning of radiotherapy to the date of LRC failure including both central and lateral pelvic relapse considered as an event, and censored at the time of death or last follow-up. DMFS rate was estimated from the beginning of radiotherapy to the date of distant metastasis considered as an event, and censored at the time of death or last follow-up. The cumulative incidence rate of late rectal complication was estimated from the beginning of radiotherapy to the date of any grade rectal hemorrhage according to common terminology criteria for adverse events (CTCAE) version 4.0. [11] OS, LRC and DMFS, and the cumulative incidence rates of late rectal complication were calculated using the Kaplan–Meier method [12].

As a measure of radiotherapeutic intensity to point A, we used the equivalent dose in 2-Gy fractions (EQD_2) calculated from total irradiated dose (D) and each dose (d) with α/β for 10 Gy and potential doubling time (Tpot) defined as five days' subtraction from EQD_2 with correction for tumor proliferation associated with OTT (EQD_2T) as shown in the following formula:

$$EQD_2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$$

$$\mathrm{EQD_2}T = \mathrm{EQD_2} - \frac{\log_{e^2}}{\alpha}\frac{\mathrm{T}-\mathrm{T}}{T_{pot}} \Big/ \left(1+\frac{2}{\alpha/\beta}\right)$$

T_K is the kick-off time of accelerated repopulation and was defined as 21 days, and 0.3 for α [13]. These parameters are not well estimated for cervical cancer so we used those for head and neck squamous cell carcinoma (SCC) and extrapolated them. The survival curves were compared using the log-rank test and Cox's proportional hazards model. In order to carry out univariate and/or multivariate

analysis comparing OS, LRC and DMFS rates, patients were categorized as follows: age (<60 vs ≥60), tumor bulk (<55 vs ≥55 mm), OTT (<6 vs ≥6 weeks), hemoglobin (Hb) before (<11.9 vs ≥11.9 mg/dl) and concurrent chemotherapy. We added univariate and multivariate analysis to assess the impact of concurrent chemotherapy on OS, LRC and DMFS after stratified analysis for age and tumor bulk. All statistical analyses were performed using PASW statistics (Version 18.0, SPSS Japan Inc., an IBM company, Chicago, IL, USA). A P value of <0.05 was considered significant.

RESULTS

Patient and treatment characteristics are shown in Table 1. There were differences in age and Hb level after treatment between the radiotherapy alone and CCRT groups. After a median follow-up period of 44.0 months (range 4.2–114.9 months) collectively and 62.1 months for live patients, five-year OS, LRC and DMFS rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that default of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; $P = 0.001$) and DMFS (HR = 2.53; 95% CI 1.39–4.61; $P = 0.002$), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; $P = 0.322$). (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$) (Fig. 1). After stratifying 131 patients for age and tumor bulk, subgroup analysis with or without concurrent chemotherapy revealed that non-elderly women (HR = 2.78; 95% CI 1.25–6.18; $P = 0.012$) with even bulky length (HR = 2.53; 95% CI 1.26–5.07; $P = 0.009$) clearly benefit from concurrent chemotherapy (Table 3).

DISCUSSION

Various predictors such as treatment duration and anemia had been reported in the last decade before CCRT [14–18]. Concomitant EBRT with HDR-ICBT, which requires shorter treatment duration, was originally the mainstream treatment for women with cervical cancer in Japan [5]. Treatment durations of gross tumor irradiation had a median of 42 days, and were mostly 6 weeks, which is much shorter than the 8 weeks recommended by the American brachytherapy society (ABS) [14]. Concurrent chemotherapy has the potential hazard of treatment interruption associated with acute toxicities, however OTT was not significantly different between radiotherapy alone and CCRT (42 (30–69) vs 42 (36–62) days; $P = 0.217$). In this situation, OTT is no longer a prognostic factor [17]. Similarly, a low Hb value before radiotherapy has no impact on survival, and is no longer a prognostic factor if anemia has been actively corrected using blood transfusion during radiotherapy [18].

Randomized trials have shown survival benefits of CCRT for cervical cancer [19–23]. Incorporating concurrent chemotherapy contributed to improvement in both LRC and DMFS [19–23]. This impact is less in stages III–IV than in stages I–II [20–23]. Our study also supported this impact on OS and DMFS even in cases of FIGO IIIb, but not on LRC (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$) and reached a plateau (Fig. 1), though limited by the short follow-up period for late radiation-induced complications of other organs such as bladder or small intestine [7].

There were important limitations on this retrospective analysis: the advantage of concurrent chemotherapy might merely indicate that the reasons for not undergoing concurrent chemotherapy were associated with poor prognosis. Forty-two women with FIGO IIIb cervical cancer did not undergo concurrent chemotherapy in our study because of advanced age (77 (72–85) years) for 17 patients (40.4%), and the other half (53 (36–70)) had the following reasons for not undergoing concurrent chemotherapy:PAN irradiation for eight patients (19.0%), renal failure for three patients (7.2%), lack of patient's consent for five patients (11.9%), chronic hepatitis for two patients (4.8%), active pyometra, uncontrolled anemia, synchronous double cancer, hypertrophic cardiomyopathy, low white blood cell counts and sequential chemotherapy for one patient each (2.4%). These reasons not to perform concurrent chemotherapy seem to be clinically ordinary and acceptable, but could indicate a potential selection bias that modified the impact of concurrent chemotherapy. Our study revealed that concurrent chemotherapy is the most significant predictor of definitive radiotherapy, thus we conclude that concurrent chemotherapy combined with definitive radiotherapy for FIGO IIIb cervical cancer is advantageous for survival improvement.

Development of the optimal chemotherapy regimen and schedule to increase chemotherapeutic intensity as a cytotoxic agent but not a radiosensitizer seems to be warranted because our results indicated concurrent chemotherapy has impacts on DMFS but not on LRC. It is not reasonable for Japanese women with cervical cancer to undergo increased intensity of dose-dense concurrent chemotherapy due to a lack of relevant feasibility [24]. There is no evidence that platinum-doublet is superior to platinum-alone as concurrent chemotherapy for cervical cancer [22–23]. Therefore, devising the best form of concurrent chemotherapy is considered to be a limitation. The efficacy of adjuvant chemotherapy after definitive CCRT is unclear but worth testing as it is a feasible method [25].

Table 1. Patient and treatment characteristics for RT alone and CCRT

		RT alone ($n = 42$)	CCRT ($n = 89$)	P
Age	Median (range)	66 (36–85)	55 (29–73)	0.000
Tumor bulk	mm	55 (45–87)	55 (40–95)	0.302
Pathology	SCC	37 (88.1%)	82 (92.1%)	0.454
	non-SCC	5 (11.9%)	7 (7.9%)	
Hb before RT	mg/dl	11.9 (6.4–14.2)	11.9 (7.1–14.5)	0.653
Hb after RT	mg/dl	11.3 (7.6–14.4)	10.3 (6.9–12.3)	0.002
OTT	days	42 (30–69)	42 (36–62)	0.217
EQD_2	Gy	56.4 (44.0–74.0)	54.0 (52.2–74.0)	0.128
EQD_2T	Gy	50.0 (40.9–66.2)	48.2 (39.2–61.2)	0.177
wCDDP courses	1	0	5 (5.6%)	0.000
	2	0	6 (6.8%)	
	3	0	12 (13.5%)	
	4	0	23 (25.8%)	
	5	0	30 (33.7%)	
	6	0	13 (14.6%)	
Reason for RT alone	Advanced age	17 (40.4%)	0	0.000
	PAN irradiation	8 (19.0%)	0	
	No consent	5 (11.9%)	0	
	Renal function	3 (7.2%)	0	
	Hepatitis	2 (4.8%)	0	
	Others	7 (16.7%)	0	
Follow-up	months	30.7 (4.2–100.3)	48.8 (7.3–114.9)	0.001

RT = radiotherapy, CCRT = concurrent chemoradiotherapy, FIGO = International Federation of Gynecology and Obstetrics, SCC = squamous cell carcinoma, Hb = hemoglobin, OTT = overall treatment time, EQD_2 = the equivalent dose in 2-Gy fractions, $EQD_2T = EQD_2$ with correction for tumor proliferation associated with OTT, wCDDP = weekly cisplatin, ns = not significant.

Table 2. Univariate and multivariate analyses on OS, LRC and DMFS

		OS				LRC			DMFS		
Variants		***n***	**Five years**	**uni**	**multi**	**Five years**	**uni**	**multi**	**Five years**	**uni**	**multi**
Age	<60	72	51.4	0.631	0.121	73.3	0.129	0.076	56.0	0.173	0.033
	≥60	59	53.7			89.2			64.8		
Tumor bulk	<55 mm	54	59.8	0.358	0.486	79.5	0.768	0.856	74.4	0.010	0.027
	≥55 mm	77	47.6			80.6			50.2		
OTT	<6 weeks	75	53.1	0.789	0.639	78.5	0.532	0.258	63.5	0.626	0.918
	≥6 weeks	56	50.8			82.6			56.0		
Hb before RT	<11.9 mg/dl	62	53.1	0.627	0.934	74.5	0.380	0.599	59.3	0.527	0.988
	≥11.9 mg/dl	69	52.2			84.8			60.6		
Concurrent chemotherapy	Yes	89	60.4	0.002	0.001	82.6	0.583	0.322	66.6	0.005	0.002
	No	42	33.5			68.3			44.7		

OS = overall survival, LRC = loco-regional control, DFMS = distant metastasis free survival, uni = univariate analysis, multi = multivariate analysis, OTT = overall treatment time, Hb = hemoglobin, ns = not significant.

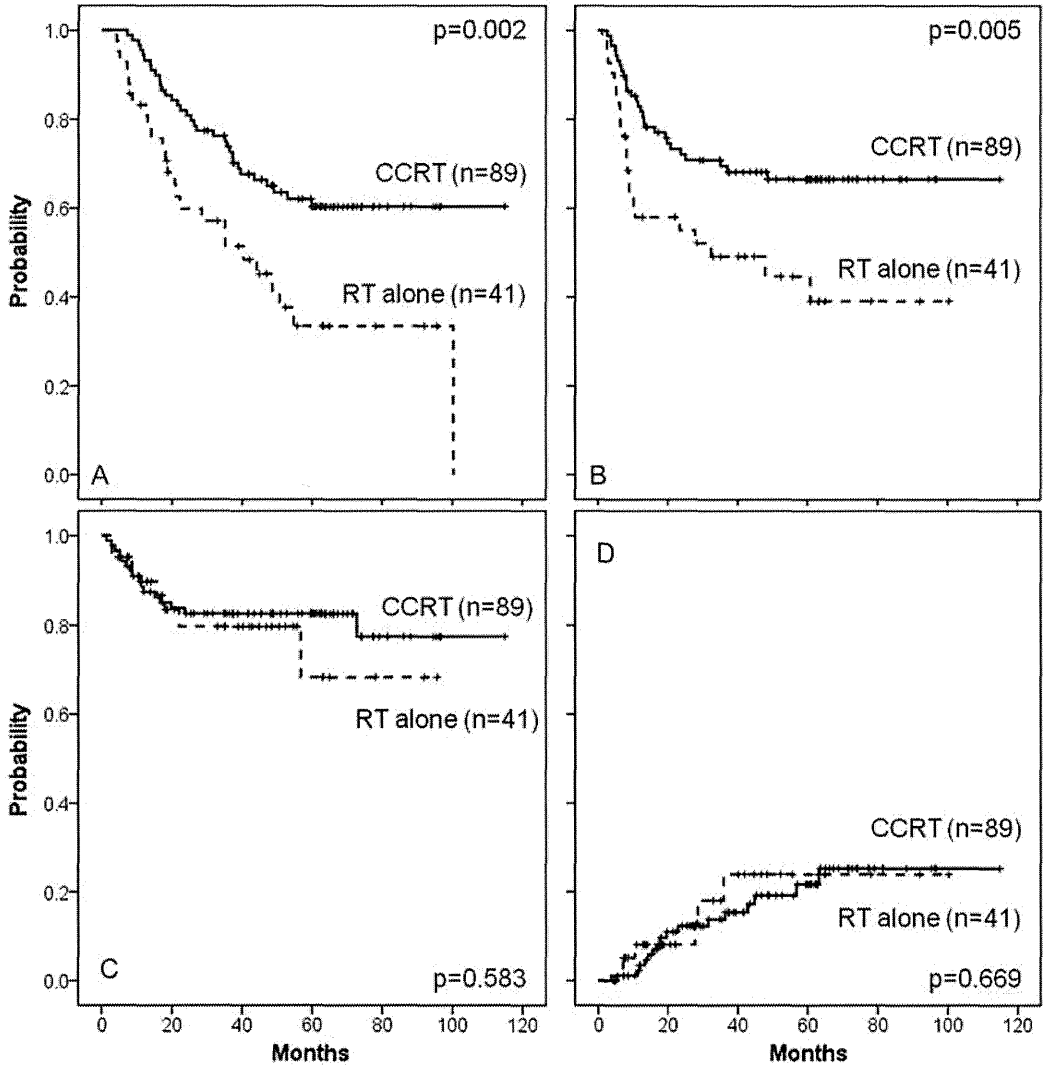

Fig. 1. OS (**A**), DMFS (**B**), LRC (**C**) and the cumulative incidence rates of late rectal complication (**D**) of women with FIGO IIIb cervical cancer after definitive radiotherapy with or without concurrent chemotherapy. Solid line for CCRT, dashed line for RT alone. OS = overall survival, DMFS = distant metastasis free survival, LRC = loco-regional control, CCRT = concurrent chemoradiotherapy, RT = radiotherapy.

Table 3. Impact of concurrent chemotherapy on OS, LRC and DMFS in the stratified analysis

		OS			LRC			DMFS		
		Log-rank	Cox's		Log-rank	Cox's		Log-rank	Cox's	
Variates		*P*	**HR (95%CI)**	*P*	*P*	**HR (95%CI)**	*P*	*P*	**HR (95%CI)**	*P*
Age	<60	0.005	2.78 (1.25–6.18)	0.012	0.145	2.31 (0.76–6.96)	0.136	0.001	2.83 (1.32–6.05)	0.007
	≥60	0.023	2.55 (1.10–5.89)	0.028	0.942	1.05 (0.23–4.85)	0.942	0.079	2.29 (0.88–5.94)	0.087
Tumor bulk	<55 mm	0.118	2.36 (0.85–6.52)	0.096	0.108	5.87 (1.27–27.0)	0.023	0.043	3.46 (1.01–11.9)	0.049
	≥55 mm	0.018	2.53 (1.26–5.07)	0.009	0.587	0.75 (0.22–2.49)	0.645	0.085	2.23 (1.12–4.44)	0.021

OS = overall survival, DMFS = distant metastasis free survival, ns = not significant.

In conclusion, though limited to a mono-institutional retrospective analysis, this study revealed that concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer. A randomized controlled trial is needed to establish the optimal chemotherapy combined with definitive radiotherapy for women with advanced cervical cancer.

ACKNOWLEDGEMENTS

We declare no conflict of interest. This work was partly supported by a Grant-in-Aid from the Tohoku Cancer EBM project of Yamagata University Faculity of Medicine, Cancer Research Development Fund, National Cancer Center.

REFERENCES

1. Thoms WW, Jr, Eifel PJ, Smith TL *et al.* Bulky endocervical carcinoma: a 23-year experience. *Int J Radiat Oncol Biol Phys* 1992;**23**:491–9.
2. Perez CA, Grigsby PW, Nene SM *et al.* Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* 1992;**69**:2796–806.
3. Landoni F, Maneo A, Colombo A *et al.* Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer *Lancet* 1997;**350**:535–40.
4. Eifel PJ, Moughan J, Erickson B *et al.* Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;**60**:1144–53.
5. Toita T, Kodaira T, Shinoda A *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. *Int J Radiat Oncol Biol Phys 2008*;**70**:788–94.
6. Toita T, Kato S, Niibe Y *et al.* Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage i and ii uterine cervical cancer (JAROG0401/JROSG04-2). *Int J Radiat Oncol Biol Phys* 2012;**82**:49–56.
7. Nakano T, Kato S, Ohno T *et al.* Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;**103**:92–101.
8. Toita T, Moromizato H, Ogawa K *et al.* Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. *Gynecol Oncol* 2005;**96**:665–70.
9. Nagase S, Inoue Y, Umesaki N *et al.* Evidence-based guidelines for treatment of cervical cancer in Japan: Japan Society of Gynecologic Oncology (JSGO) 2007 edition. *Int J Clin Oncol* 2010;**15**:117–24.
10. NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival. http://www.nih.gov/news/pr/feb99/nci-22.htm (11 April 2012, date last accessed).
11. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (10 April 2012, date last accessed).
12. Kaplan EL, Meier P Nonparametric estimation from incomplete observations *J Am StatAssoc* 1958;**53**:457–81.
13. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist: Time, Dose, and Fractionation in Radiotherapy, 6th edn.* Philadelphia: Lippincott Williams & Wilkins, 2006, 378–97.
14. Nag S, Erickson B, Thomadsen B *et al.* The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;**48**:201–11.
15. Lanciano RM, Martz K, Coia LR *et al.* Tumor and treatment factors improving outcome in stage III-B cervix cancer. *Int J Radiat Oncol Biol Phys* 1991;**20**:95–100.
16. Toita T, Kakinohana Y, Ogawa K *et al.* Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;**56**:1344–53.
17. Chatani M, Matayoshi Y, Masaki N *et al.* High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation. *Strahlenther Onkol* 1997;**173**:379–84.
18. Grogan M, Thomas GM, Melamed I *et al.* The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer* 1999;**86**:1528–36.
19. Rose PG, Bundy BN, Watkins EB *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;**340**:1144–53.
20. Morris M, Eifel PJ, Lu J *et al.* Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;**340**:1137–43.
21. Eifel PJ, Winter K, Morris M *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;**22**:872–80.
22. Green JA, Kirwan JM, Tierney JF *et al.* Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;**358**:781–6.
23. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;**26**:5802–12.
24. Watanabe Y, Nakai H, Shimaoka M *et al.* Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix. *Int J Clin Oncol* 2006;**11**:309–13.
25. Dueñas-González A, Zarbá JJ, Patel F *et al.* Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011;**29**:1678–85.

J Cancer Res Clin Oncol (2012) 138:1239–1247
DOI 10.1007/s00432-012-1198-y

ORIGINAL PAPER

Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis

Hiroshi Mayahara · Minako Sumi · Yoshinori Ito · Syuhei Sekii · Kana Takahashi · Kouji Inaba · Yuuki Kuroda · Naoya Murakami · Madoka Morota · Jun Itami

Received: 10 January 2012 / Accepted: 5 March 2012 / Published online: 23 March 2012

Abstract
Background and purpose Whether chemotherapy for systemic disease affects survival of patients with brain metastases or not has not been elucidated before. We performed comprehensive analysis of patients with newly-diagnosed brain metastases primarily treated with whole brain radiation therapy (WBRT) alone.
Materials and methods Data from 134 patients with newly-diagnosed brain metastases primarily treated with WBRT from 2007 to 2008 was retrospectively reviewed. Univariate and multivariate analyses were performed to identify significant prognostic factors.
Results Median survival time (MST) of this cohort from the start of WBRT was 5.7 months. MST of patients with RPA Class 1, 2 and 3 were 10.3, 7.8 and 2.2 months, respectively. Multivariate analysis revealed that karnofsky performance status ($\geq$70, $p < 0.0001$), gender (female, $p < 0.0001$), activity of extracranial disease (stable, $p = 0.015$), time to develop brain metastasis (<3 months, $p = 0.042$) and use of chemotherapy after WBRT (multiple regimens, $p < 0.0001$) were independent prognostic factors for better survival.
Conclusions Systemic chemotherapy for chemo-responsive cancer prolongs survival despite the presence of treated brain metastases. Irradiated brain metastases will lose their prognostic significance in a large number of patients. Systemic chemotherapy will be a treatment of choice for patients who have systemic disease after WBRT for brain metastases. These results should be validated in the future prospective clinical trials.

Keywords Brain metastasis · Brain metastases · Radiation therapy · Whole brain radiation therapy · Chemotherapy · Prognostic factors

Introduction

Brain metastasis affects 20–40 % of cancer patients (Soffietti et al. 2002). Brain metastasis is one of the major causes of morbidity in cancer patients. The prognosis of patients with brain metastasis is generally poor with a median survival time (MST) of 1–2 months with corticosteroids only (Weissman 1988; Lagerwaard et al. 1999).

The route of metastatic dissemination to the brain is often hematogeneous, therefore, the entire brain can be seeded with micrometastatic focus. Traditionally, whole brain radiation therapy (WBRT) has been regarded as the standard treatment for patients with brain metastasis. Overall survival of the patients after WBRT ranges 3–6 months (Lagerwaard et al. 1999; Gaspar et al. 2010; Tsao et al. 2005). Various dose/fractionation schedules of WBRT were tested in clinical studies, which resulted in no significant difference in median survival time after WBRT (Tsao et al. 2005; Gaspar et al. 2010).

Recently, significant progress has been made for a subset of patients with single or few brain metastases and well controlled systemic disease. Surgical resection or stereotactic radiosurgery (SRS) combined with WBRT significantly prolonged survival (Patchell et al. 1990; Vecht et al. 1993; Andrews et al. 2004). Median survival of

This study was presented in part at the 53rd Annual Meeting of the American Society for Radiation Oncology in Miami, October 2-6, 2011.

H. Mayahara (✉) · M. Sumi · Y. Ito · S. Sekii · K. Takahashi · K. Inaba · Y. Kuroda · N. Murakami · M. Morota · J. Itami
Division of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: hmayahar@ncc.go.jp

patients who received these aggressive therapies ranges 7–10 months. Unfortunately, patients who entered into these clinical trials represent only a small minority of the patients with brain metastases. For the majority of patients with multiple brain metastases and uncontrolled systemic disease, only WBRT is the standard treatment of choice.

The role of chemotherapy in brain metastasis has been limited because of the concern about the activity of chemotherapeutic agent to cross the blood–brain barrier (BBB). Recently, the activity of chemotherapy in brain metastasis is highlighted (Robinet et al. 2001; Walbert and Gilbert 2009; Mehta et al. 2010). Concurrent chemoradiation therapies with BBB permeable agents, such as Temozolamide or topotecan are currently under investigation in prospective clinical trials. Some investigators suggested that the permeability of BBB can alter after fractionated radiotherapy for brain metastasis (Yuan et al. 2006; Wilson et al. 2009). However, whether the use of chemotherapy affects survival of the patients with brain metastasis or not has not been elucidated before.

The primary aim of this study was to perform comprehensive analysis of 134 consecutive patients with newly-diagnosed brain metastases primarily treated by WBRT alone in a single institution. The secondary aim was to define independent prognostic factors associated with longer survival after WBRT. The final aim was to investigate the prognostic value of chemotherapy on survival after WBRT in patients with brain metastases.

Materials and methods

Patient characteristics

The database of patients who underwent radiotherapy for brain metastases at our institution was reviewed. A total of 264 patients were treated with WBRT between 2007 and 2008. Of these, 23 patients received WBRT as a salvage therapy after SRS. Another 39 patients received WBRT as an adjuvant therapy after resection of metastatic brain tumor. Forty-seven patients were metastases from radiosensitive primary tumor such as leukemia, lymphoma or small cell carcinoma. Excluding these patients, we reviewed the medical records of 155 patients with newly diagnosed brain metastases treated with WBRT as a primary therapy. Of these, 19 patients presented with symptoms or radiographic findings of leptomeningeal metastasis. We excluded these patients with leptomeningeal metastasis because they are known to have extremely limited survival. Two patients were ineligible for evaluation because of allergy to contrast media. Finally, a group of 134 patients were subjected to extensive analysis. The clinical and image interpretation data from these patients were entered into database in December 2010. Distribution of baseline patient and tumor characteristics is shown in Table 1.

Table 1 Distribution of baseline patient and tumor characteristics

Parameters	*n*	%	Parameters	*n*	%
Median age (years)	60		Extracranial distant metastases		
Gender			Absent	11	8
Male	69	51	Stable	16	12
Female	65	49	Progressive	107	80
Karnofsky performance status (KPS)			Activity of extracranical tumor		
100–90	46	34	Absent/stable	20	15
80–70	49	37	Progressive	114	85
60–50	29	22	Time to diagnosis of brain metastasis		
40–0	10	7	<3 months	21	16
Neurologic status			3–12 months	33	25
0	45	34	1–2 years	22	16
1	27	20	≥2 years	58	43
2	34	25	Type of the diagnostic brain image		
3	21	16	MRI	106	79
4	7	5	CT	28	21
RPA criteria			Number of brain metastases		
Class 1	5	4	1–4	40	30
Class 2	91	68	5–10	39	29
Class 3	38	28	11–24	29	22
Site of primary tumor			≥25	26	19
Lung	75	56	Size of the largest lesion		
Breast	27	20	≤10	31	23
Upper gastrointestinal tract	11	8	11–20	46	34
Colorectum	10	8	21–30	34	25
Genitourinary tract	5	4	>30	23	17
Others	6	5	Chemotherapeutic regimens before WBRT		
Histological type			None	22	16
Adenocarcinoma	114	85	Single	28	21
Squamous cell carcinoma	9	7	Multiple	84	63
Others	11	8	Chemotherapeutic regimens after WBRT		
Primary tumor status			None	70	52
Absent	57	42	Single	31	23
Stable	25	19	Multiple	33	25
Progressive	52	39	Molecular targeted therapy after WBRT (>1 month)		
			No	100	74
			Yes	34	26

RPA recursive partitioning analysis, *MRI* magnetic resonance imaging, *CT* computed tomography, *WBRT* whole brain radiation therapy

Imaging studies

Diagnosis of brain metastases was performed mainly with magnetic resonance images (MRI). In our institute, all patients with lung cancer routinely undergo brain imaging for initial staging or scheduled follow-up. Patients with other solid tumors underwent brain imaging when brain metastasis is clinically suspected. In this study, initial diagnostic brain images included MRI in 106 patients (79 %) and CT in 28 patients (21 %). Radiological features assessed included number, maximum tumor diameter and location. For follow-up brain images, change in size of the tumors and presence of new metastases were recorded. At least 20 % increase in diameter of the each preexisted tumor before WBRT, taking as reference on the smallest diameter after WBRT, was defined as local progression.

Treatment strategy

Treatment strategy for brain metastasis at our institution was previously described elsewhere (Narita and Shibui 2009; Hashimoto et al. 2011). Patients who received WBRT alone as a primary treatment for brain metastases were subjected for this study. Patients with brain metastases generally have extracranial systemic disease. After WBRT, patients with known systemic disease were indicated to start or continue chemotherapy if they still had active chemotherapeutic regimen with sufficient organ function and with Karnofsky performance status (KPS) of 70 or more. Salvage SRS was considered for recurrent brain metastases after WBRT. Some patients with known chemo-sensitive tumor continued palliative chemotherapy for recurrent brain metastases.

Consent for the treatment was obtained from each patient after the sufficient explanation of potential risks of treatment. All the patients provided written informed consent. Our institutional review board has approved this study.

Whole brain radiation therapy

One hundred and thirty-four patients were intended to receive WBRT. Of these, 128 patients were delivered to a dose of 30 Gy in 10 fractions. Another 3 patients were delivered to 37.5 Gy in 15 fractions, whereas one patient was delivered to 20 Gy in 5 fractions. Two patients discontinued irradiation course because of the deterioration of general condition at a dose of 12 and 24 Gy, respectively.

Retrospective analysis

All the medical charts of the eligible patients were reviewed. Information on potential prognostic factors (age, gender, KPS, neurologic status, site of primary tumor, primary tumor status, activity of extracranial distant metastases, time to develop brain metastasis, number of brain metastases, size of the largest lesion, use of chemotherapy before or after WBRT) was collected.

Initial neurological function was classified into 4 categories (No symptoms: grade 0, Minor symptoms; fully active without assistance: grade 1, Moderate symptoms; fully active but requires assistance: grade 2, Moderate symptoms; less than fully active: grade 3, Severe symptoms; totally inactive: grade 4). Radiation Therapy Oncology Group's (RTOG) recursive partitioning analysis (RPA) classes were coded into 3 categories as follows: Class 1: Patients with KPS $\geq$ 70, <65 years of age with controlled primary and no extracranial metastases; Class 3: KPS $<$ 70; Class 2: all the others (Gaspar et al. 1997).

For the evaluation of extracranial disease status, if there were no evidence of residual tumor after therapy, the activity was coded as "absent". If any tumor existed and there is no increase in size of the tumor for more than 6 months, the activity was coded as "stable". A continuous use of same chemotherapeutic regimen didn't impair the coding of "stable". If any tumor existed with any situation other than "stable", the activity was coded as "progressive".

Patients whose brain metastases were detected at the same time or soon after the diagnosis of primary tumor (so-called "synchronous" brain metastasis) may have different prognosis. We defined "synchronous" brain metastasis as those detected at the same time or detected within 3 months of the initial diagnosis of primary tumor.

For the analysis of prognostic effect of chemotherapy before or after WBRT, three different cohorts were defined: none, single regimen and multiple regimens. If a patient received two or more different types of chemotherapeutic regimens, the status was coded as multiple regimens. Any type of hormonal therapy was regarded as a single regimen. The status of the use of molecular targeted therapy was defined as "yes", if a patient continued to receive a specific regimen for more than 1 month.

Statistical analysis

Overall survival from the start of WBRT was calculated with the Kaplan–Meier method. For univariate and multivariate analysis, all the variables were dichotomized according to the clinical relevance from previous literature. Univariate analyses were performed by using log-rank test. Possible confounded variables were excluded from multivariate analysis. A Cox's proportional hazards model was developed to identify significant factors influencing survival after WBRT. All the tests of hypotheses were