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CLINICAL INVESTIGATION **Gynecologic Cancer**

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

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Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/ New Zealand (ANZ), Europe (E), and North America (NAm).
Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.
Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) (p = 0.02). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; p = 0.02 for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan (p = 0.0002).
Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials. © 2012 Elsevier Inc.

Brachytherapy, Cervical cancer, Radiation dose.

INTRODUCTION

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

250

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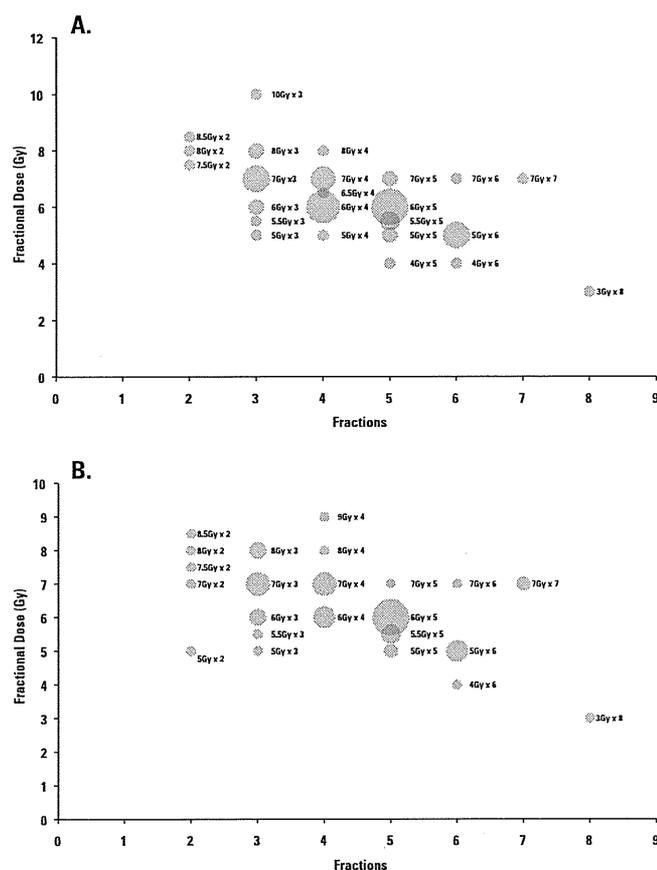
Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages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

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

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

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
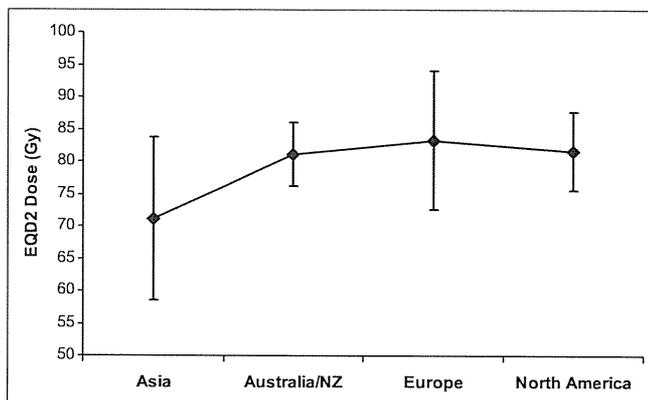

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

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.

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

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

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

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

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Intracavitary Combined with CT-guided Interstitial Brachytherapy for Locally Advanced Uterine Cervical Cancer: Introduction of the Technique and a Case Presentation

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Interstitial brachytherapy/Cervical cancer/Radiotherapy/CT-guided brachytherapy/Intracavitary brachytherapy.

We report a new technique of brachytherapy consisting of intracavitary combined with computed tomography (CT)-guided interstitial brachytherapy for locally advanced cervical cancer. A Fletcher-Suit applicator and trocar point needles were used for performing high-dose rate brachytherapy under in-room CT guidance. First, a tandem and ovoids were implanted into the patient's vagina and uterus by conventional brachytherapy method. Based on clinical examination and MRI/CT imaging, operating radiation oncologists decided the positions of insertion in the tumor and the depth of the needles from the upper surface of the ovoid. Insertion of the needle applicator was performed from the vaginal vault inside the ovoid within the tumor under CT guidance. In treatment planning, dwell positions and time adaptations within the tandem and ovoids were performed first for optimization based on the Manchester system, and then stepwise addition of dwell positions within the needle was continued. Finally, dwell positions and dwell weights were manually modified until dose-volume constraints were optimally matched. In our pilot case, the dose of D90 to high-risk clinical target volume was improved from 3.5 Gy to 6.1 Gy by using our hybrid method on the dose-volume histogram. D1cc of the rectum, bladder and sigmoid colon by our hybrid method was 4.8 Gy, 6.4 Gy and 3.5 Gy, respectively. This method consists of advanced image-guided brachytherapy that can be performed safely and accurately. This approach has the potential of increasing target coverage, treated volume, and total dose without increasing the dose to organs at risk.

INTRODUCTION

The combination of external beam radiotherapy (RT) and intracavitary brachytherapy (ICBT) is a standard treatment technique of RT for uterine cervical cancer, and concomitant chemotherapy is combined for locally advanced cases.[1-5] ICBT plays an important role because the brachytherapy system allows a much higher dose to the cervix while sparing adjacent bladder and bowels. Local control rates of cervical cancer have been reported at 80–90% for early stages.[6-8] However, those for advanced stages show a range of 67–75% and further improvement is needed.[4,5,9] One of the reasons for local failure is inadequate dose coverage to bulky and/or irregular-shape tumors.

In order to realize adequate dose coverage to cervical tumors, intracavitary combined with computed tomography (CT)-guided interstitial brachytherapy was developed at Gunma University. We introduce the new technique of hybrid-brachytherapy with a pilot case.

PATIENT

The patient was a 53-year-old woman with stage IIIB squamous cell carcinoma of the uterine cervix according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[10] On image diagnosis, CT detected a bulky tumor at the uterine cervix with left hydronephrosis. MRI before treatment revealed a cervical mass measuring 60 × 58 × 70 mm³. The tumor extension reaching the pelvic side-wall before RT still existed at the time of brachytherapy (Fig. 1).

The patient was treated with a combination of external

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before treatment   after 30 Gy
o   intrauterine cavity
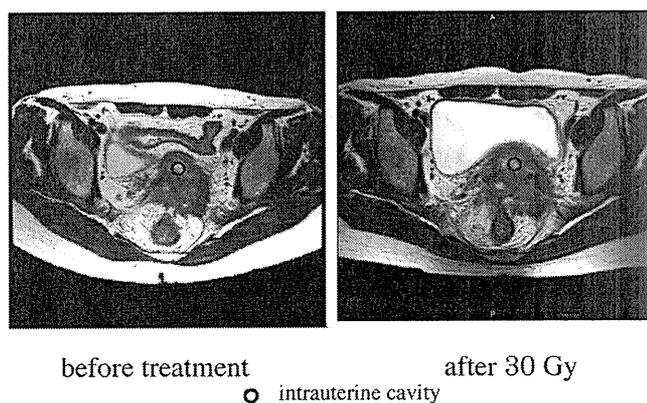
Fig. 1. MRI images before treatment and after 30 Gy.

A-P   R-L

Fig. 2. X-ray photographs of needle placement after implantation of a tandem and ovoids.

beam RT and high-dose rate (HDR) brachytherapy. She did not receive concurrent chemotherapy because of renal dysfunction. External irradiation to the whole pelvis was performed with antero-posterior and postero-anterior parallel-opposed ports with a total dose of 30 Gy at 2 Gy per fraction, 5 times per week. This was followed by a central shielding pelvis field up to a total pelvis irradiation dose of 50 Gy at 2 Gy per fraction, 5 times per week. Along with the central shielding irradiation, she was given HDR brachy-therapy by HDR-remote afterloading system (RALS) 5 times using an iridium-192 source. In the first three sessions, she received ICBT without interstitial brachytherapy adminis-tered once per week at fraction doses of 7.5, 7 and 7 Gy at Point A, with a total dose of 21.5 Gy. In the remaining two sessions, the hybrid method was used because the tumor showed poor response to radiotherapy. Written informed con-sent was obtained from the patient before this brachytherapy.

METHODS

In-Room CT Imaging

Brachytherapy was delivered in our unit, comprising HDR-RALS (microSelectron HDR; Nucletron, The Netherlands) coupled to a CT scanner and X-ray imager sharing a common couch. The couch rotates 230° at the CT-scanning position or 50° at the X-ray imaging position. During CT scanning, the gantry moves along rails on the floor while the table remains stationary. Applicators are implanted into the patient's vagina and uterus on the couch, and all processes including applica-tion, imaging, and irradiation can be performed on the same couch using the in-room CT brachytherapy system.[11,12]

Brachytherapy application

A set of Fletcher-Suit Asian Pacific applicator (tandem and half-size ovoids) and trocar point needles (Nucletron) was used. This hybrid application was done without general anesthesia or spinal anesthesia. The tandem and ovoids were implanted into the vagina and uterus by the procedure of
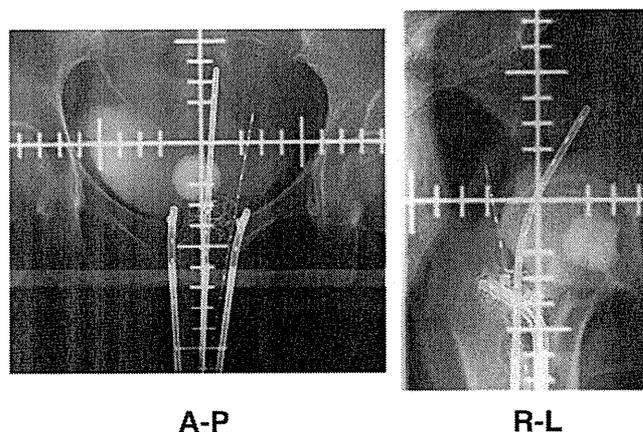
conventional brachytherapy. After implantation, CT scans were generated on the same couch at 3-mm slice thickness. Magnetic resonance images (MRI) were taken before brachytherapy and used as reference images of the tumor. Based on clinical examination and MRI/CT imaging, oper-ating radiation oncologists decided the positions of insertion in the tumor and the depth of the needles from the upper sur-face of the ovoid.

The CT-guided insertion of the needle applicator was per-formed along the inside of the half-size ovoid into the tumor (Fig. 2). After tumor location and needle position were con-firmed, anterior and posterior vaginal packing was done in a manner similar to the non-interstitial procedure. CT scans were generated again and used for treatment planning. Then, X-ray images were also taken in the same position while rotating the couch. After completion of irradiation, the appli-cator was removed in the order of tandem and ovoids, fol-lowed by the needles.

Treatment Planning

The applicator geometry was digitized, reconstructed and registered to the X-ray and CT images. Image registration was performed with the evaluation module of the PLATO Brachytherapy Planning System v14.3.6 (Nucletron).

The current brachytherapy planning process starts with a conventional pattern for tandem and ovoids planning based on the Manchester system. Point A was defined on the X-ray as being 2 cm superior to the external os, and 2 cm lat-eral from the axis of the intrauterine tandem. At first, the dose of point A at the opposite side of needle placement was normalized to 6 Gy. A dwell position and time adaptation were established first to optimize the initial standard dose distribution, and then continued with 2.5-mm stepwise addi-tions as dwell positions within the needle. Dose distribution by the resulting treatment plan was confirmed on CT images for the high-risk clinical target volume (HRCTV), which is

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defined as the parameter of ICBT in the GYN GEC ESTRO recommendation and for organs at risks (OARs) such as bladder, rectum and sigmoid colon.[13,14] HRCTV, which is a major risk for local recurrence because of residual macroscopic disease, is defined as the whole cervix and the presumed extracervical tumor extension at the time of brachytherapy. Certain dose coverage values can be defined to describe the specific shape of such a dose-volume histogram (DVH), e.g. D100 and D90, defining the minimum dose delivered to 100 and 90% of the volume of interest, respec-

tively. The OARs were contoured using the external wall contours. Cumulative DVHs were calculated for delineated organs of bladder, rectum and sigmoid colon, and the following parameters were reported: absolute volume and minimum dose to the most irradiated 0.1, 1, 2 cm^3 (D0.1 cc, D1 cc, D2 cc, respectively).[13,14]

Dwell positions and dwell weights in the tandem, ovoids and needles were manually modified until the dose distribution was optimally matched to cover HRCTV with a 6-Gy isodose line as much as possible. This planning was com-
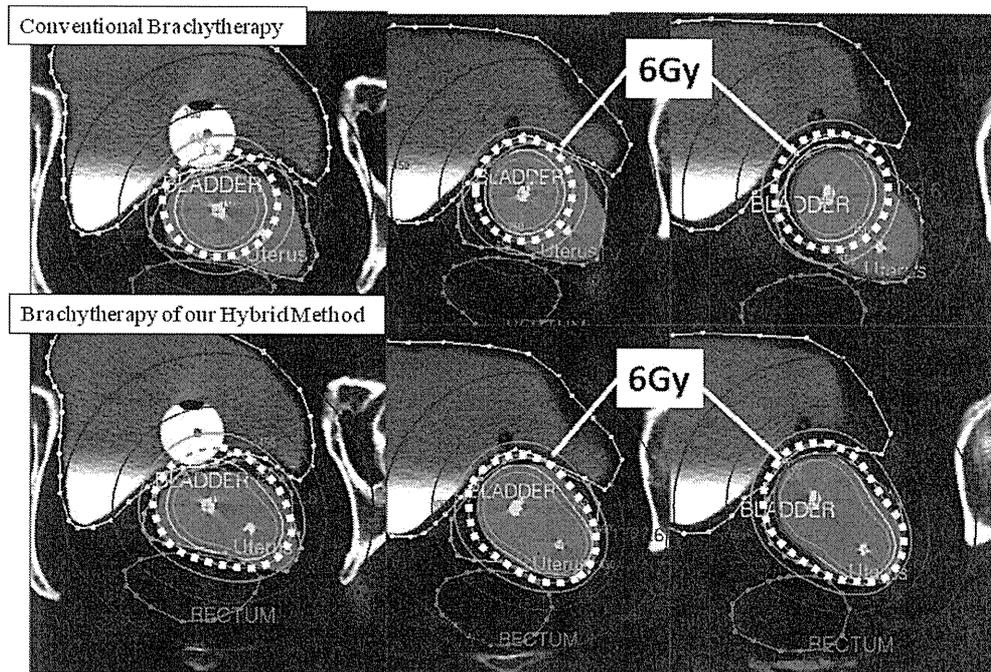

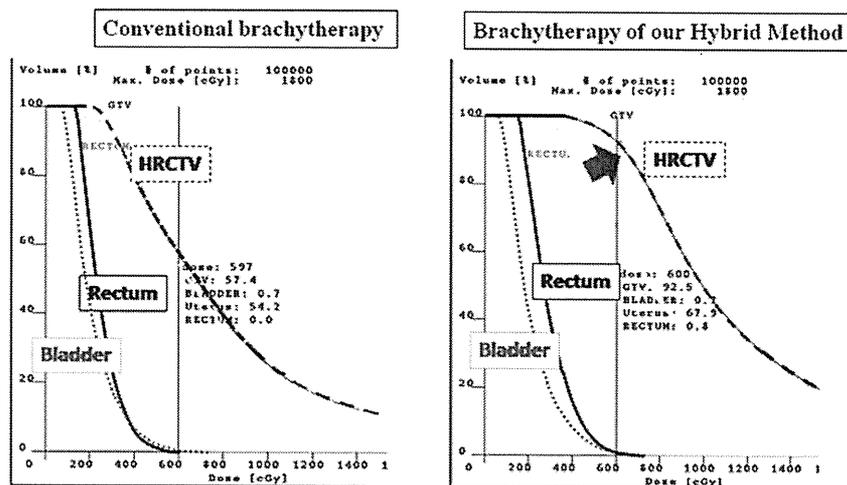**Fig. 3.** Dose distribution by conventional brachytherapy and our hybrid method. ⬭: HRCTV

Fig. 4. Dose-Volume histograms of conventional brachytherapy planning and our hybrid method planning. — — •: HRCTV ———: Rectum •••••••: Bladder

pared with conventional ICBT planning without interstitial needle by using DVH parameters for HRCTV and OARs. In conventional ICBT planning, the same source arrangement and irradiation conditions are used, and the dose distribution was based on the Manchester system. The prescribed dose was generated by the PLATO treatment planning system (TPS) with a dose of 6 Gy normalized to point A.

RESULTS

Dose distribution and dose volume histogram

Figures 3 and 4 show dose distributions and DVHs by our hybrid method and conventional ICBT. D90 to HRCTV by this hybrid method and conventional ICBT were 6.1 Gy and 3.5 Gy, respectively. D1cc of the rectum, bladder and sigmoid colon by this hybrid method were 4.8 Gy, 6.4 Gy and 3.5 Gy, respectively, whereas they were 5.7 Gy, 6.3 Gy and 3.4 Gy by conventional brachytherapy (Table 1, Fig. 4).

Table 1. Dose of HRCTV, Rectum, Bladder and Sigmoid Colon.

		Conventional brachytherapy	Our hybrid-brachytherapy
HRCTV	D100	1.9 Gy	3.4 Gy
	D90	3.5 Gy	6.1 Gy
Rectum	D0.1cc	5.8 Gy	6.7 Gy
	D1cc	4.8 Gy	5.7 Gy
	D2cc	4.4 Gy	5.2 Gy
Bladder	D0.1cc	8.0 Gy	8.0 Gy
	D1cc	6.4 Gy	6.3 Gy
	D2cc	5.8 Gy	5.8 Gy
Sigmoid colon	D0.1cc	4.5 Gy	4.3 Gy
	D1cc	3.5 Gy	3.4 Gy
	D2cc	3.2 Gy	3.2 Gy

Treatment Outcome

At 12 months after treatment, the tumor in the left parametrium had disappeared almost completely according to pelvic MRI findings. Serum levels of squamous cell carcinoma antigen and cytokeratin fragment 21-1 were reduced to 1.1 ng/ml and 3.3 ng/ml from 2.6 ng/ml and 7.6 ng/ml, respectively. No recurrent lesions and distant metastases were detected at 18 months after the treatment, and she did not experience grade 2 or higher late morbidity.

DISCUSSION

When bulky and/or irregular-shape cervical cancer is treated with brachytherapy, using increments of the prescribed dose at the reference point is one of the approaches. However, such increments may result in increasing doses to surrounding normal tissues including the bladder, rectum, and small intestine. In recent years, Japanese researchers reported the correlation of rectal bleeding with the dose-volume parameter of rectum in patients with cervical cancer.[15,16] Isohashi et al. reported that the mean biologically equivalent dose in 2-Gy fraction (EQD2) of rectum D1cc for patients with and without rectal bleeding was 76 Gy and 98 Gy, respectively, and there was a significant greater rectal bleeding risk for the high EQD2 group (≥ 82 Gy of D1cc rectum).[15] In the current case, EQD2 of rectum D1cc was 79.9 Gy, which was calculated as the linear quadratic model for incomplete sublethal damage repair. If the dose prescription at point A could be increased by conventional ICBT until the dose of D90 for HRCTV reached 6 Gy, D1cc of the rectum would increase from 4.8 Gy to 8.2 Gy, and EQD2 of rectum D1cc would increase to 96.8 Gy. This method was able to increase the HRCTV dose while keeping the rectum dose at tolerable levels even in the case of bulky and/or irregular-shape cervical cancer. In the present case, primary tumor was well controlled without severe toxicities. However, further follow-up will be needed to confirm long-term efficacy and toxicities.

Historically, interstitial brachytherapy was performed with free hand-placement, and ultrasound-guided, CT-guided and template-guided needles for locally advanced tumor.[17-21] To date, transperineal template techniques were the most commonly used methods for interstitial treatment in such cases. However, these techniques have difficulties in achieving accurate positioning of the implant and good parallelism of the needles. In addition, using these methods, the applicators have to be left in place for a few days after implantation. On the other hand, a major part of the procedure in the current hybrid method is derived from conventional brachytherapy. In-room CT-guided insertion of the interstitial needle could be performed after implantation of the Fletcher-Suit applicator. Furthermore, because this insertion is done for each brachytherapy session, the applicators do not need to be left in place. Therefore, this hybrid method is a non-complicated technique and is safe for patients compared with previous methods.

Considering the risk of perforation of the sigmoid colon or intestine, accurate positioning of the needle in interstitial brachytherapy is very important. Several researchers have reported achieving accurate positioning and avoiding perforation by several methods.[17-21] With the present hybrid method, CT-guided insertion is performed after implantation of tandem and ovoid applicators. In addition, an in-room CT system is used for the current method. This system enabled implantation of the applicator, CT-guided placement of the needle and irradiation by RALS to be performed on the same couch. Movement of the applicator and needle can be min-

imized during implantation, planning and irradiation. Because of the CT-guided insertion and in-room system, accurate positioning and safe insertion can be achieved with this hybrid method.

Dimopuolos *et al.* and Kirisits *et al.* reported a similar technique of intracavitary and interstitial brachytherapy that uses a modified tandem-ring applicator for cervical cancer at Vienna University.[22,23] In their method, needles are inserted through holes in the tandem-ring applicator. As it is limited to moderate lateral expansion of the HRCTV, for cases with involvement up to the pelvic wall, additional interstitial needles are required. Their method was also accurate and safe, based on an MRI-guided approach. However, the Vienna ring applicator is not commercially available, and in Japan the most common type of applicator is the Fletcher-Suit Asian Pacific applicator. In our hybrid method, similar to the Vienna ring applicator, needles can be placed in the tumor located at the posterior parametrium with high flexibility. The current technique of brachytherapy should be further investigated to confirm its safety and efficacy.

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Comparison of Intensity Modulated Radiotherapy and Dynamic Three-Dimensional Conformal Radiotherapy With Regard to Dose Distribution and Sparing of Organs at Risk

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Abstract

Dose escalation to the target while sparing the organs at risk near the lesion has been difficult over the last decade. However, recent radiotherapy techniques can deliver more sophisticated doses to the target. This study evaluated whether intensity modulated radiotherapy can deliver more homogeneous and conformal doses to the target than dynamic three-dimensional conformal radiotherapy while sparing organs at risk near the lesion in 13 patients with central nervous system tumors and other tumors around the central nervous system. Dynamic three-dimensional conformal radiotherapy and intensity modulated radiotherapy plans were calculated and dose distributions were compared for all patients with regard to the planning target volume and organs at risk. The plan of intensity modulated radiotherapy was significantly superior to that of dynamic three-dimensional conformal radiotherapy in target dose conformity (p = 0.0006) and organs at risk sparing (p = 0.0257). Intensity modulated radiotherapy could deliver more homogeneous and conformal doses to the target than dynamic three-dimensional conformal radiotherapy with sparing organs at risk near the lesion and may improve local control of radioresistant tumors via dose escalation.

Key words: intensity modulated radiotherapy, conformity, dose distribution, organ at risk, dose escalation

Introduction

The goal of radiotherapy is to treat patients with the best therapeutic ratio that provides the highest local control and the lowest toxicity rates. Dose escalation to the lesion improves local control of the tumors,[8,12] but also increases the risk of normal tissue complication. Therefore, radiation dose distributions should be designed conforming to the entire lesion while sparing the surrounding normal tissues, especially organs at risk (OARs) which are radiosensitive and related to late complications, such as cataract of the eye lens.

Recent advancements in radiotherapy technologies have allowed sophisticated radiation dose delivery, including the use of dynamic three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT).[1,17] Both dynamic 3D-CRT and IMRT are linear accelerator therapies using the multileaf collimator (MLC), a computer-controlled device that uses movable "leaves" to conform the radiation beam to the shape of the tumor while protecting normal adjacent tissue. Dynamic 3D-CRT stereotactically delivers doses which conform to the shape of the each projected target using the MLC. IMRT can also use MLC but the shapes are not restricted to the projected images. In IMRT, the fixed radiation beam from each angle can be turned off and on, or set to deliver dose at different intensities freely. Therefore, the plans of IMRT are highly complicated so inverse-planning is usually selected. The planner defines targets and OARs, and gives target doses. Then, the most suitable treatment plan is calculated automatically (Fig. 1).

The present study tried to evaluate whether IMRT can deliver more homogeneous and conformal dose distributions to irregular shaped tumors than dynamic 3D-CRT with sparing of OARs near lesions in
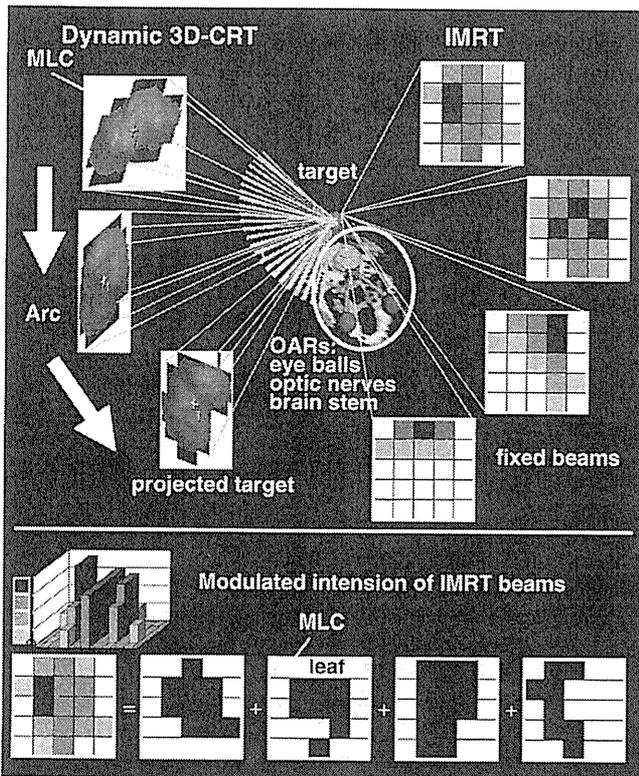
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Fig. 1 Features of dynamic three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). Dynamic 3D-CRT stereotactically delivers doses which conform to the shape of the each projected target using multileaf collimator (MLC). IMRT also uses MLC but not stereotactic technologies. The most suitable treatment plan using intensity modulated fixed beams is inversely calculated automatically. Arc: gantry arc, OARs: organs at risk.

Table 1 Thirteen patients with central nervous system tumors

Case No.	Age (yrs)	Sex	Lesion	Histology
1	45	M	skull base	squamous cell carcinoma
2	62	M	skull base	squamous cell carcinoma
3	62	M	skull base	squamous cell carcinoma
4	48	F	skull base	squamous cell carcinoma
5	69	M	skull base	adenoid cystic carcinoma
6	68	F	skull base	adenoid cystic carcinoma
7	62	M	skull base	multiple myeloma
8	37	M	skull base	olfactory neuroblastoma
9	50	F	skull base	plasmacytoma
10	8	F	brain stem	anaplastic ependymoma
11	32	F	vertebral body	myxoid liposarcoma
12	10	M	vertebral body	PNET
13	67	M	vertebral body	adenocarcinoma

F: female, M: male, PNET: primitive neuroectodermal tumor.

graphy (CT) and magnetic resonance (MR) imaging were used for planning, and three-dimensional geometrical registration of the CT and MR imaging data was performed. All patients were treated with IMRT.

The planning target volume (PTV), which was defined as the area of the enhanced lesion with 3 mm margin, and OARs, such as the brain stem, eye balls, optic nerves, chiasma, and spinal cord, were delineated in the corresponding MR imaging and CT slices. Three OARs were chosen and numbered from 1 to 3 in order of distance from the lesion in each patient. OAR1 was closer to the PTV than the other OARs.

Both dynamic 3D-CRT and IMRT treatment plans were calculated for each patient by the same treatment planning system, Brain SCAN (BrainLAB GmbH, Heimstetten, Germany). To eliminate interoperator variations, the same operator established all treatment plans. The same prescribed dose was determined in the dynamic 3D-CRT and IMRT plans to compare the two treatment plans for the same patient. The IMRT plan covered the entire PTV with higher than 95% of the prescribed dose (V95 was 100%). The dynamic 3D-CRT plan covered the entire PTV with higher than 80% of the prescribed dose (V80 was 100%). The percentage of the corresponding prescribed dose was calculated for the OARs to facilitate dosimetric comparison because each patient was treated with different prescribed doses.

To compare the dynamic 3D-CRT plan and the IMRT plan, we used dosimetric distribution and dose volume histogram (DVH) techniques. Dosimetric distribution is a two-dimensional contour map of

the central nervous system (CNS) and other tumors around the CNS. Various tumors have been already treated with these techniques[5,6,8,10,13,18,20] and recent studies compared the dose conformity of dynamic 3D-CRT with IMRT[7,9,14,19] but little attention has focused on the OARs, especially in the CNS.[3] Patients with CNS tumors and other tumors around the CNS were enrolled in this study because these tumors were very close to the OARs. We compared dynamic 3D-CRT with IMRT focusing on target dose homogeneity, target dose conformity, and mean dose to the OARs.

Patients and Methods

Thirteen patients, 8 males and 5 females aged 8–69 years (median 48 years), with 9 skull base tumors, 1 brain stem tumor, and 3 vertebral body tumors were randomly enrolled (Table 1). Both computed tomo-

delivered dose on some representative CT or MR imaging plane. The area inside the 80% contour line receives more than 80% of the prescribed dose. DVH is a three-dimensional dosimetric distribution in a graphical two-dimensional format, so DVH visualizes the volume not area. The vertical axis represents the percentage of total tissue volume that receives a dose more than a specified dose. The horizontal axis represents cumulative dose. Ideally, DVH displays 100% of the PTV receiving 100% of the prescribed dose and very low volumes of OARs receiving very low doses.

The homogeneity index (HI) was calculated using the following formula without using the prescribed dose: maximum dose within the PTV/minimum dose within the PTV. This formula is the simplest of several similar HIs. The HI is a useful tool to evaluate dose uniformity within the PTV and a value of HI close to 1 indicates better dose homogeneity in the treatment plan.[6]

The conformity index (CI) was calculated using the following formula: $1 + V_{normal}/V_{PTV}$. V_{normal} is the volume of the normal tissue and V_{PTV} is the volume of the PTV receiving the indicated dose; 95% of the prescribed dose in the IMRT plan and 80% in the dynamic 3D-CRT in this study. Therefore, V_{PTV} represented the entire PTV in both plans because we intended V95 as 100% in the IMRT plan and V80 as 100% in the dynamic 3D-CRT plan. A value of CI
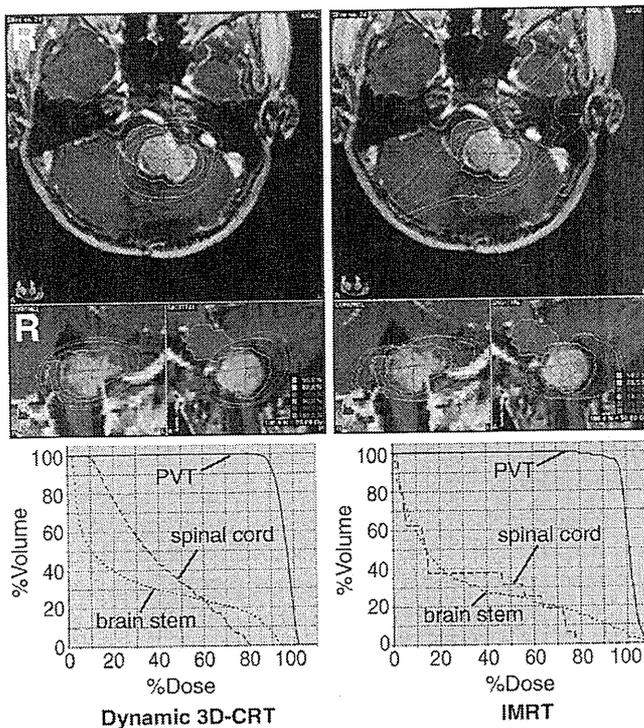

Fig. 2 Dosimetric distributions (upper row) and dose volume histograms (lower row) of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan (left column) and the intensity modulated radiotherapy (IMRT) plan (right column) in representative Case 10. An 8-year-old girl presented with recurrent brain stem anaplastic ependymoma. Magnetic resonance images showed an oval-shaped tumor which compressed the brain stem into a concave form. In the dynamic 3D-CRT plan, the conformal dose was delivered to the planning target volume (PTV) but the brain stem and the spinal cord were not spared. In the IMRT plan, flat dosimetric distribution spared the brain stem and the spinal cord. Dose volume histogram of the IMRT plan showed dose reduction to the spinal cord without dose reduction to the PTV.
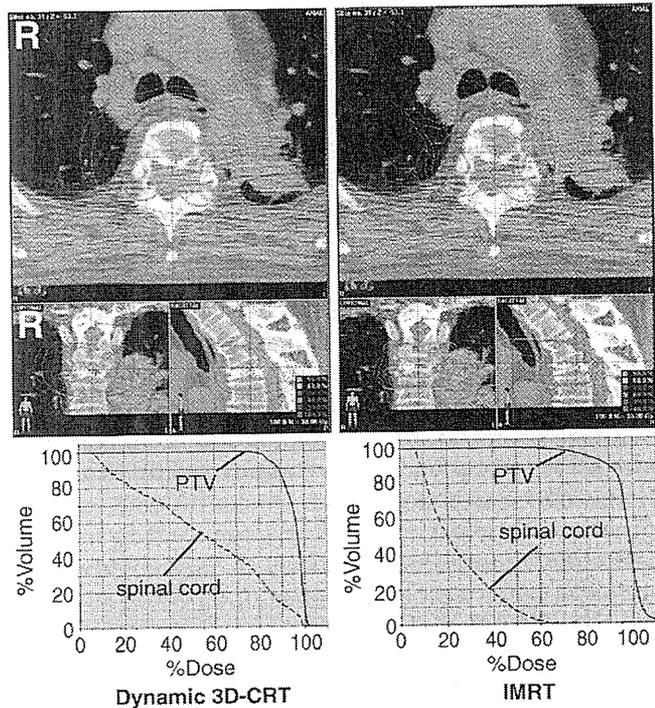

Fig. 3 Dosimetric distributions (upper row) and dose volume histograms (lower row) of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan (left column) and the intensity modulated radiotherapy (IMRT) plan (right column) in representative Case 13. A 67-year-old man presented with vertebral body metastasis from lung cancer. Computed tomography scans showed that the concave-shaped tumor surrounded the spinal cord. The dosimetric distribution of dynamic 3D-CRT was round and the spinal cord was not spared at all. The dosimetric distribution of IMRT was a conformal concave form corresponding with the planning target volume (PTV) and the spinal cord was spared. Dose volume histogram of the IMRT plan showed dose reduction to the spinal cord.

close to 1 indicates better reduction of normal tissue irradiation (V_{normal} is lower) in the treatment plan.[4]

The data were analyzed by the Mann-Whitney U test. A probability value of $p < 0.05$ was considered statistically significant. Statistical analyses were determined using StatView software (SAS Institute, Cary, North Carolina, USA).

Results

First, we show two representative cases in which IMRT was very effective.

Representative Case 10: An 8-year-old girl presented with recurrent brain stem anaplastic ependymoma. MR imaging showed an oval-shaped tumor which compressed the brain stem into a concave form. The brain stem, spinal cord, and optic nerve were defined as OARs, with the brain stem as OAR1. Dosimetric distributions are shown in Fig. 2. In the dynamic 3D-CRT plan, the conformal dose was delivered to the PTV but the brain stem and the spinal cord were not spared. In the IMRT plan, the flat dose distribution spared the brain stem and the spinal cord. DVH showed dose reduction to the spinal cord without dose reduction to the PTV. This patient was treated with IMRT using a prescribed dose of 50 Gy. MR imaging showed obvious tumor shrinkage. However, local recurrence was observed 9 months after IMRT treatment and the patient died 6 months after the recurrence. There was no complication due to IMRT.

Representative Case 13: A 67-year-old man presented with vertebral body metastasis from lung cancer. This lesion was impossible to treat with conventional radiotherapy because he had been already treated with conventional radiotherapy to the neighboring vertebral body with a total dose of 30 Gy in 10 fractions. The OAR of this patient was the spinal cord. CT showed that the concave-shaped tumor surrounded the spinal cord (Fig. 3). The dosimetric distribution of dynamic 3D-CRT was round and the spinal cord was not spared at all. We expected that this lesion would be difficult to treat with dynamic 3D-CRT practically because of the high dose to the spinal cord. The dosimetric distribution of IMRT was a conformal concave form corresponding with the PTV and the spinal cord was spared. DVH showed dose reduction to the spinal cord. This patient was treated with IMRT using a prescribed dose of 30 Gy. The patient had no local recurrence or radiological complication, such as paraparesis of the lower limbs, for 3.5 years.

Nine patients with skull base tumors were enrolled, 6 cases located at the maxillary sinus and the others
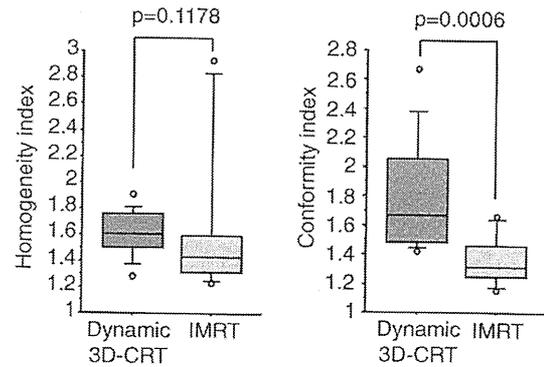

Fig. 4 Homogeneity index and conformity index of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan and the intensity modulated radiotherapy (IMRT) plan. In 11 of the 13 cases, the homogeneity index of the IMRT plan was lower than that of the dynamic 3D-CRT plan but the IMRT plan was not significantly superior to the dynamic 3D-CRT plan (p = 0.1178). The conformity index of the IMRT plan (mean 1.358) was significantly better (p = 0.0006) than that of the dynamic 3D-CRT plan (mean 1.802). Statistical analyses were determined using StatView software.

at the orbit, the upper pharynx, and the cribriform plate. The OARs were usually the eye balls, optic nerves, optic chiasm, and brain stem. The optic nerve was most frequently designated as the OAR1. Almost all PTVs of skull base cases were not concave and sparing the OARs was easier than in the 2 representative cases. The most frequent disease of the skull base was maxillary squamous carcinoma. All 4 patients had new lesions and underwent chemotherapy and IMRT with a prescribed dose of 54 Gy. All patients remained alive with mean overall survival of 1770 ± 253 days, although one patient experienced local recurrence. No radiological complication was observed.

The IMRT and dynamic 3D-CRT plans were compared for target dose homogeneity, target dose conformity, and mean dose to OARs. In 11 of the 13 patients, the HIs of the IMRT plans were lower than those of the dynamic 3D-CRT plans but the IMRT plan was not significantly superior to the dynamic 3D-CRT plan (p = 0.1178) because the HIs of IMRT plans of only two cases were extremely close to 3 (Fig. 4). In those cases, the PTV attached and surrounded the OAR1 (one of the two cases was representative Case 13) and the minimum dose within the PTV was very low to decrease the dose to the OAR1. The CI of the IMRT plan (mean 1.358) was significantly better (p = 0.0006) than that of the dynamic 3D-CRT plan (mean 1.802) (Fig. 4). The percentage of the corresponding prescribed dose of the
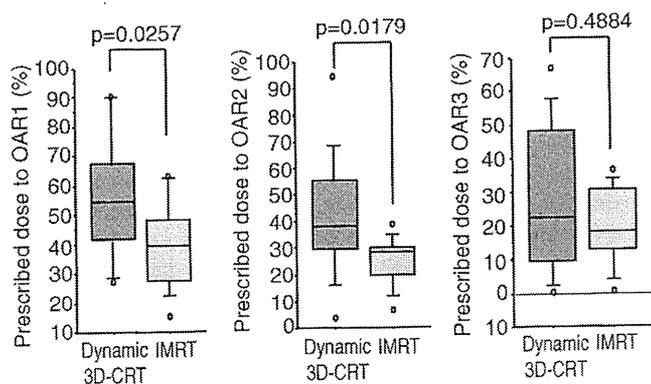
IMRT plan in mean dose to the PTV (mean 98.8%) was obviously higher (p = 0.0052) compared to that of the dynamic 3D-CRT plan (mean 96.3%) (figure not shown). The percentage of the corresponding prescribed dose of the IMRT plan in the OAR1 (mean 41.0%) was significantly lower (p = 0.0257) than that of the dynamic 3D-CRT plan (mean 58.2%) (Fig. 5). The percentage of the corresponding prescribed dose of the IMRT plan in the OAR2 (mean 25.5%) was also lower (p = 0.0179) than that of the dynamic 3D-CRT plan (mean 41.9%). However, there was no significant difference in the OAR3 between the plans (p = 0.4884).

Discussion

The aim of radical radiotherapy is to deliver a high dose to the tumor target while minimizing the dose to surrounding normal tissues. Recent innovations of irradiation technique may meet these contradictory requirements. Stereotactic radiosurgery/radiotherapy (SRS/SRT) is one of these novel irradiation techniques. SRS/SRT was chiefly developed in recent years for dose escalation sparing the OARs, and can deliver much conformal doses to spherical tumors. For spheroidal tumors, the two-isocenter plan is more effective than the one-isocenter plan.[11] However, SRS/SRT is not suitable for irregularly shaped tumors. The multiple-isocenter plan can deliver a more conformal dose, but is more complex and the technique has limits.[9] Dynamic 3D-CRT is one of the most excellent stereotactic radiothera-

pies.[2,16] Dynamic 3D-CRT with the MLC can deliver more conformal doses to the irregularly shaped tumors than SRS/SRT (Fig. 1), but sophisticated doses are still difficult to deliver to the concave form. In addition, SRS/SRT usually delivers a higher dose to the center of the PTV and the high dose spot over the prescribed dose is accrued within the PTV when the peripheral region receives a sufficient treatment dose.

IMRT is another advanced irradiation method without using stereotactic technologies, can modulate radiation intensity with MLC and deliver more homogeneous and conformal radiation doses using fixed beams based on inversely calculated planning (Fig. 1). The most important feature of IMRT is the excellent dose delivery conforming to irregularly shaped tumors, especially concave shaped tumors (representative Case 13). Our study showed that IMRT could deliver more homogeneous and conformal doses to irregularly shaped tumors than dynamic 3D-CRT, but the superior homogeneity was not statistically important because of sparing of the OAR surrounded by the PTV. In the treatment phase, the surgeon must determine whether the PTV has priority over the OAR or not. The decision is probably case-by-case.

Sparing of the OARs is very important as well as to treat the PTV with homogeneous and conformal dose. In our study, we intended that the entire PTV received higher than 95% of the prescribed dose in IMRT and 80% in dynamic 3D-CRT. Therefore, the percentage of the corresponding prescribed dose of the IMRT plan in the mean dose to the PTV was higher than that of the dynamic 3D-CRT plan. However, the receiving doses of the OARs were significantly lower in IMRT using the same planning. In OAR1 and OAR2, the differences in the dynamic 3D-CRT plan and the IMRT plan were significant but the difference in the OAR2 was greater than that in the OAR1. Therefore, the OAR adjoining the PTV is difficult to spare. In our case of brain stem tumor (representative Case 10), the lesion had compressed the brain stem into a concave form, but IMRT delivered a conformal dose to the PTV, sparing the spinal cord but not sparing the brain stem adequately. On the other hand, the difference in the OAR3 was not significant. Both dynamic 3D-CRT and IMRT plans could deliver treatment doses to the PTV sparing the OARs distant from the target.

Heavy charged particle radiotherapy is another promising treatment. Heavy charged particles, such as carbon ions, have excellent dose localizing properties compared with fast neutrons. The Bragg peak of the energy loss occurs immediately before the particles come to rest and the maximum depth of

penetration of a charged particle beam can be adjusted by varying the energy. These features of the particles result in excellent dose conformity. Comparisons of heavy charged particle radiotherapy and IMRT showed that heavy charged particle radiotherapy delivered a more sophisticated conformal dose to the target than IMRT.[15] However, few establishments worldwide have heavy ion medical accelerator equipment and the cost performance is usually poor. Presumably heavy charged particle radiotherapy will not become common as standard radiotherapy at the present time.

All of our 13 patients were treated with IMRT, and radiosensitive tumors were successfully controlled for several years with sufficient sparing of OARs. However, in radioresistant tumor such as anaplastic ependymoma, we could not inhibit tumor proliferation using IMRT with the usual irradiation dose. Dose escalation to the PTV improves local control of the tumors,[7,11] but also increases the risk of normal tissue complication. Safe irradiation requires delivery of homogeneous and conformal dose to the PTV and minimum doses to the OARs. Although IMRT is one of the best radiotherapies for dose escalation, the complex treatment plan and long treatment time are problems. In the choice of irradiation modality, we have to consider the cost/benefit ratio, and IMRT is suitable for irregularly shaped tumors close to OARs.

In this study, dynamic 3D-CRT and IMRT were compared with regard to dose distribution and sparing of OARs. IMRT was superior to dynamic 3D-CRT for irradiation of irregularly shaped tumors near the OARs. Therefore, dose escalation using IMRT will improve local control of radioresistant tumors in the future.

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