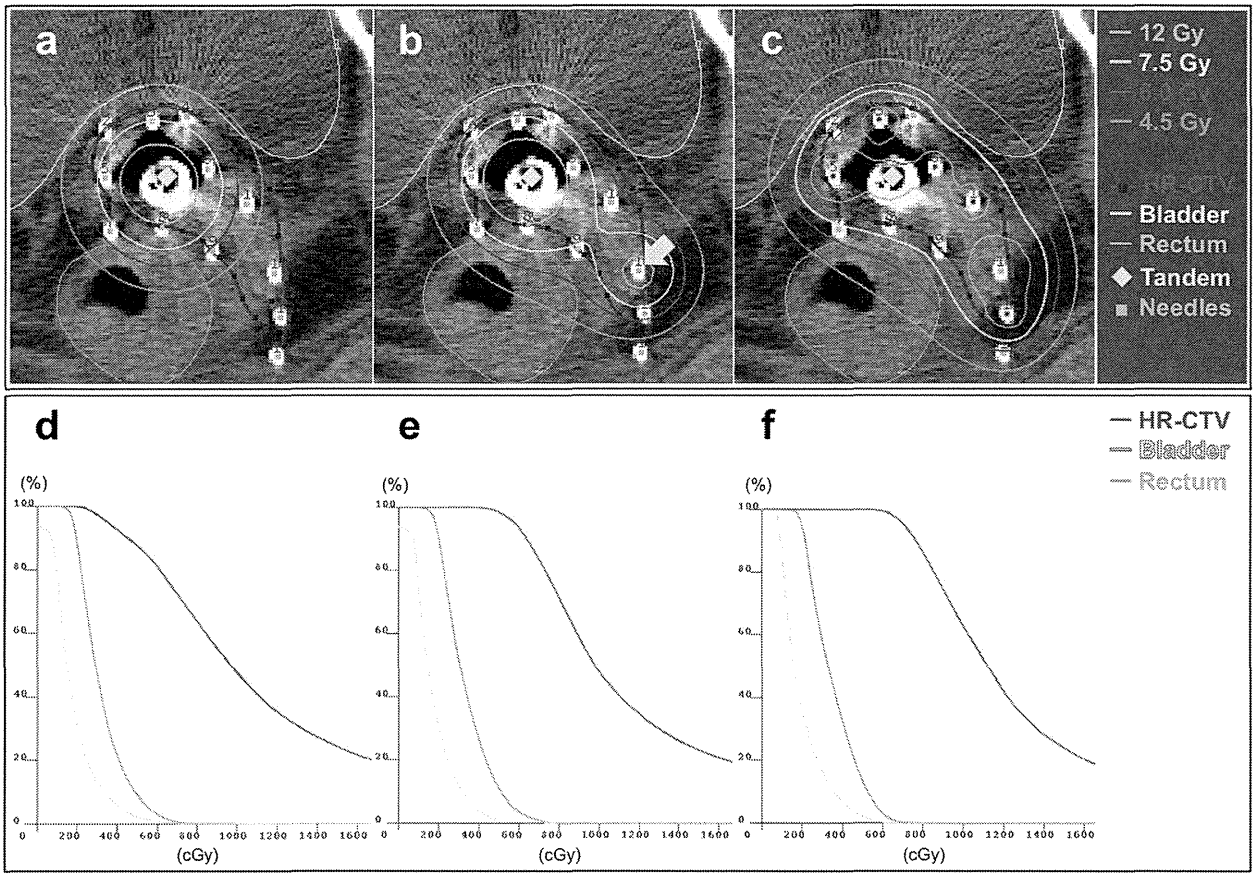


**Figure 3 Representative dose distributions in transverse planes (a-c) and DVH curves (d-f) provided by the IC plan (a, d), the IC/IS plan with 1 needle (b, e), and the IS plan (c, f).** The case is a 55-year-old patient with newly diagnosed cervical cancer, FIGO stage IIIB, treated with concurrent chemoradiotherapy using weekly cisplatin. **(a)** Source loading via only the tandem shows insufficient coverage of HR-CTV (D90, 4.6 Gy; D98, 2.9 Gy; $V_{6Gy}$, 81%). **(b)** Addition of source loading via 1 needle (arrow) in expanded tumour in the left laterodorsal direction improved HR-CTV coverage (D90, 6.3 Gy; D98, 5.1 Gy; $V_{6Gy}$, 93%). **(c)** Usage of the tandem and all 12 needles for source loading further improved HR-CTV coverage (D90, 7.6 Gy; D98, 6.5 Gy; $V_{6Gy}$, 100%).

which MRI images can be directly registered onto CT images, which should further improve the identification of HR-CTV.

The IS plans achieved more conformal coverage of HR-CTV than the IC/IS plans, leading to further improvement of HR-CTV coverage and GFs compared to the IC/IS plans (Figure 2a-e, Figure 3c, Table 1). The D90 HR-CTV, $GF_{rectum}$, $GF_{bladder}$, D98 HR-CTV and $V_{6Gy}$ HR-CTV values of the IS plan were significantly higher than those of the IC/IS plan ($P < 0.01$, $P < 0.01$, $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively). In fact, a previous study has pointed out the existence of cases with extremely bulky and/or irregularly shaped tumours in which even the combined IC/IS approach resulted in insufficient coverage for HR-CTV [8]. Together, ISBT with MUPIT can still be advantageous for such cases.

The number and geometrical distribution of interstitial needles affect the conformality of HR-CTV coverage. Therefore, the conformality of HR-CTV coverage is of particularly high importance in the combined IC/IS

**Table 1 DVH parameters in IC, IC/IS and IS plans**

| | HR-CTV | | | | Gain factor | |
|---|---|---|---|---|---|---|
| | D90 (%) | D98 (%) | V6Gy (%) | V12Gy (%) | Rectum | Bladder |
| IC plan | 77 (20) | 53 (15) | 77 (14) | 39 (12) | 0.8 (0.2) | 0.9 (0.2) |
| IC/IS plan | 118 (22) | 97 (18) | 95 (3.5) | 45 (16) | 1.3 (0.3) | 1.4 (0.3) |
| IS plan | 140 (25) | 115 (25) | 98 (2.1) | 50 (21) | 1.5 (0.3) | 1.6 (0.3) |

Averages (SD) are shown.

approach using less needles than ISBT. Meanwhile, several indices such as the conformality index (COIN) to evaluate the conformality of target coverage in brachytherapy have been proposed [16]. Interestingly, in the setting of the current study where maximal dose was prescribed to HR-CTV while keeping the dose constraint for the rectum (6 Gy) and bladder (7 Gy), COIN becomes identical to $V_{6Gy}$ HR-CTV. As shown in Figure 2e, $V_{6Gy}$ HR-CTV in the IC/IS plans has been dramatically improved compared to that in the IC plans, nearing that in the IC/IS plans. These data indicate that the IC/IS approach improves its conformality compared with the IC approach, and is close to ISBT in terms of the conformality of HR-CTV coverage in bulky and/or irregularly shaped gynecological tumours.

On the other hand, there was no significant difference in $V_{12Gy}$ among the three plans (Figure 2f, Table 1). Although V150 and V200 are recommended as DVH parameters for the high dose volume by GEC-ESTRO [11], the clinical significance of the high dose volume has not been elucidated by various IGABT techniques, which certainly warrants further investigation.

The present study has limitations. First, the study design of employing ICBT with a tandem alone as a control is weak and is not suitable for clinical use in locally advanced gynecological tumours. However, there are many types of applicators for ICBT used in combination with a tandem, including ovoids and a ring applicator. In treatment planning using these applicators, large numbers of variables such as three-dimensional spatial disposition of the applicators and dwell time setting make it difficult to standardize the scheme for optimization of a control ICBT plan among patients, leading to the difficulty of evaluating the pure dosimetric gain of additional needles. Furthermore, dosimetric study comparing a combined IC/IS technique using tandem, ovoids and a few interstitial needles with ISBT in the same patient is almost impossible because ovoids are not usually used in ISBT in the clinic. Thus, if we aim to perform such dosimetric study, comparison of the two methods using different patients with different anatomical characteristics in terms of tumours and OARs is inevitable. Such a study design also results in a weak conclusion. Upon taking these issues into consideration, in the present study, we employed the IC plan with only a tandem as a control. The optimal number and spatial disposition of needles in combination with a tandem and other applicators including ovoids should be further investigated. Second, the present study was carried out based on the assumption that the anatomy among the IC, the IC/IS and the IS approach remains the same. However, in the clinical setting, the anatomy, in particular the 3D-configuration of HR-CTV, can be different among the three methods according to the number and distribution of inserted needles. This issue should be carefully considered in the clinical application of the combined IC/IS approach as an alternative to ISBT with MUPIT.

## Conclusions

Here we have demonstrated a treatment plan consisting of a tandem and at most 2 needles, which is a simplified model for the combined IC/IS approach, achieving our dose prescription criteria (i.e., D90 HR-CTV > 6.0 Gy, $D_{2cc}$ rectum < 6.0 Gy and $D_{2cc}$ bladder < 7.0 Gy per fraction) in all 21 consecutive patients with gynecological malignancies actually treated with CT-guided ISBT using MUPIT. This indicates the potential of the combined IC/IS approach as an alternative to ISBT with MUPIT in CT-guided adaptive brachytherapy for bulky and/or irregularly shaped gynecological tumours. Further research to assess the clinical feasibility of the combined IC/IS approach should be carried out with an optimal number and spatial disposition of needles in combination with a tandem and ovoids, and also anatomical change by the insertion of a tandem and needles should be taken into consideration.

## Additional file

**Additional file 1: Figure S1.** Representative CT image of an implant for the recurrent ovarian cancer case. The tumour shows bilateral parametrial involvement predominant in the right side. An intrauterine tandem and 11 interstitial needles (white dots) were applied.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

The study conception and design: T. Oike and T. Ohno. Acquisition, analysis and interpretation of data: T. Oike, SEN, HK, KA, KS, TT, YT, HS and T. Ohno. Drafting of manuscript: T. Oike, TT and T. Ohno. Critical revision: SEN, HK, KA, KS, YT, HS, and TN. Final approval: T. Oike, T. Ohno, SEN, HK, KA, KS, TT, YT, HS and TN. All authors read and approved the final manuscript.

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RADIATION ONCOLOGY

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# Optimal hypofractionated conformal radiotherapy for large brain metastases in patients with high risk factors: a single-institutional prospective study

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## Abstract

**Background:** A single-institutional prospective study of optimal hypofractionated conformal radiotherapy for large brain metastases with high risk factors was performed based on the risk prediction of radiation-related complications.

**Methods:** Eighty-eight patients with large brain metastases ≥10 $cm^3$ in critical areas treated from January 2010 to February 2014 using the CyberKnife were evaluated. The optimal dose and number of fractions were determined based on the surrounding brain volume circumscribed with a single dose equivalent (SDE) of 14 Gy (V14) to be less than 7 $cm^3$ for individual lesions. Univariate and multivariate analyses were conducted.

**Results:** As a result of optimal treatment, 92 tumors ranging from 10 to 74.6 $cm^3$ (median, 16.2 $cm^3$) in volume were treated with a median prescribed isodose of 57% and a median fraction number of five. In order to compare the results according to the tumor volume, the tumors were divided into the following three groups: 1) 10–19.9 $cm^3$, 2) 20–29.9 $cm^3$ and 3) ≥30 $cm^3$. The lesions were treated with a median prescribed isodose of 57%, 56% and 55%, respectively, and the median fraction number was five in all three groups. However, all tumors ≥20 $cm^3$ were treated with ≥ five fractions. The median SDE of the maximum dose in the three groups was 47.2 Gy, 48.5 Gy and 46.5 Gy, respectively. Local tumor control was obtained in 90.2% of the patients, and the median survival was nine months, with a median follow-up period of seven months (range, 3-41 months). There were no significant differences in the survival rates among the three groups. Six tumors exhibited marginal recurrence 7-36 months after treatment. Ten patients developed symptomatic brain edema or recurrence of pre-existing edema, seven of whom required osmo-steroid therapy. No patients developed radiation necrosis requiring surgical resection.

**Conclusion:** Our findings demonstrate that the administration of optimal hypofractionated conformal radiotherapy based on the dose-volume prediction of complications (risk line for hypofractionation), as well as Kjellberg's necrosis risk line used in single-session radiosurgery, is effective and safe for large brain metastases or other lesions in critical areas.

**Keywords:** Large brain metastases, Hypofractionated conformal radiotherapy, Multi-session radiosurgery, Prediction of complications, Radiation necrosis, Brain edema, Optimal dose and fraction, V14

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## Background

Surgical removal is the gold standard therapy and is essential for treating large brain metastases causing progressive symptoms due to increased intracranial pressure, as the symptoms improve immediately after surgery. However, surgical removal carries a risk of causing neurological deficits after dissecting critical areas, especially in cases of tumors situated deep within the white matter. Surgery also requires hospitalization for at least one week, with higher medical expenses than that observed for radiosurgery in this country. In addition, there are many patients with general risks for surgery, as well as those who refuse surgical procedures, due to having primary malignancies and/or a poor performance status.

Whole brain radiotherapy (WBRT) and chemotherapy are not adequate to control large brain metastases, and radiosurgery is an important therapeutic tool for treating brain metastases in multiple clinical settings. Moreover, radiosurgery is increasingly being used as a primary treatment modality in an attempt to prevent disturbances in the neurocognitive function after WBRT [1]. However, single-session radiosurgery is also inadequate for managing large brain metastases due to dose limitations resulting from the need to prevent adverse effects on the surrounding structures, such as the optic pathway, internal capsule and brainstem [2].

Hypofractionated radiotherapy appears to be beneficial in case of metastases not causing clinical signs of impending cerebral herniation, and its use is supported by the findings of previously published series employing varying radiation dose and fractionation schedules [3-7]. However, the optimal dose and number of fractions have yet to be established [8], and the exact incidence of adverse effects on the surrounding brain is unclear in patients with tumors with high risk factors, such as a large size or location in a critical area. Therefore, in order to determine the optimal dose and fractionation schedule, dose escalation following low-dose treatment is required.

We previously reported that the brain volume circumscribed with a single dose equivalent (SDE) of 14 Gy (V14) is an indicator of radiation necrosis [9] and that the incidence of radiation-related complications after hypofractionated conformal radiotherapy is best predicted according to the dose-volume relationship using the SDE of the maximum dose and V14 [10]. In January 2010, we initiated a prospective study of optimal hypofractionated conformal radiotherapy based on risk prediction in order to avoid radiation necrosis after hypofractionation treatment for large brain metastases in addition to the Kjellberg's necrosis risk line used in single-session radiosurgery [11].

This report presents the results of our single-institution prospective study of optimal hypofractionated conformal radiotherapy performed in this institute as useful treatment for patients with large brain metastases in critical areas and/or those with general risks for surgery.

## Methods

All patients provided their written informed consent prior to the procedure with institutional ethics committee approval. Ninety-seven patients with large brain metastases measuring 10 $cm^3$ in volume or more were treated with optimal hypofractionated radiotherapy based on the dose-volume prediction of complications in order to avoid radiation necrosis and subsequently followed more than three months at Kanto Neurosurgical Hospital between January 2010 and February 2014. An evaluation of the rates of local tumor control, overall survival and complications was performed as a prospective single-institutional analysis.

### Definition of variables and end points

The treatment dose is expressed as the marginal dose used in hypofractionated conformal radiotherapy. The maximum dose was automatically obtained from the marginal dose and the prescribed isodose delivered to the lesion margin. A complication was defined as neurological impairment (either the development of a new deficit or the significant deterioration of a preexisting or recurrent deficit) with a change on either computerized tomography scans or magnetic resonance imaging studies. Clinical follow-up was considered to have stopped at the time of the most recent report from the patient and/or a representative or the time of death.

### Inclusion and exclusion criteria

Ninety-seven patients followed for more than three months after treatment were found to be eligible for inclusion in this study. Nine patients (9.3%) were excluded from the analysis due to a lack of available imaging findings after treatment. All other patients (88) were included in the analysis.

### Patient characteristics

The median age of the patients was 64 years; 42 patients (47.7%) were 65 years of age or older. The primary cancers were located in the lung, breast, gastrointestinal tract, ovary, kidney, thyroid, larynx, uterus, or other regions (liver, testis, etc.). The tumors (n =92) treated according to the hypofractionation protocol were situated in the frontal lobe (close to the optic pathway, Broca's area or motor cortex), parietal lobe (sensory cortex or dominant angular cortex), temporal lobe (close to the optic pathway or Wernicke's area), occipital lobe (visual cortex), thalamus, basal ganglia or cerebellum close to the brainstem. The median Karnofsky Performance status (KPS) score was 70, and 34 patients (38.6%) had a KPS score of less than 70. The initial tumor volume was measured using the MultiPlan (Accuray, Sunnyvale, CA)

software program, which determines the treatment volume based on the findings of enhanced T1-weighted magnetic resonance imaging (MRI). The median tumor volume of 92 lesions was 16.2 $cm^3$. Forty-nine tumors (53.3%) were larger than 15 $cm^3$ (more than 3 cm in diameter). Thirteen tumors measured 30 $cm^3$ or more (4 cm in diameter) up to 74.6 $cm^3$. Table 1 shows the patient characteristics.

### Prescribed marginal and SDE of the maximum dose

The maximum dose was calculated based on the marginal dose and prescribed isodose. For the purpose of the dose-volume analysis, the maximum dose in three- to ten-fraction treatment was converted to the SDE using the equation reported by Park et al. and Eaton et al. [8,12], as previously reported [10].

### Optimal hypofractionated conformal radiotherapy

Hypofractionated conformal radiotherapy was administered under CT and MRI guidance as previously reported [9]. When setting a dose and fraction schedule as the first plan, a marginal dose of 27–30 Gy in three fractions was intended to use to treat tumors measuring 10–19.9 $cm^3$. A marginal dose of 31–35 Gy in five fractions and a marginal dose of 35–42 Gy in eight to 10 fractions were intended to use to treat tumors measuring 20–29.9 $cm^3$ and tumors measuring 30 $cm^3$ or more, respectively. The isodose volume of the surrounding brain (excluding the GTV) circumscribed with an SDE of 14 Gy (V14), as well as the tumor volume, was measured using the MultiPlan software program for the G4 system (Accuray, Sunnyvale, CA) and recorded in each patient in order to obtain the optimal dose and fractionation schedule. The SDE of 14 Gy used in three- to ten-fraction treatment was 23.1 to 38.4 Gy according to Timmerman's values [13], as previously reported [10]. The V14 of each tumor was maintained at less than 7 $cm^3$ in order to prevent radiation necrosis for optimal treatment based on the dose-volume prediction of complications [10]. If the V14 value was more than 7 $cm^3$ in the first dose-plan, it was lowered to less than 7 $cm^3$ using a decreased marginal isodose or dose or an increased number of fractions in the revised or re-revised dose-plan, maintaining an effective marginal dose (SDE: 18–20 Gy) on the target.

### Follow-up evaluations and complications

Changes in the patients' neurological symptoms, such as paresis, sensory disturbances, aphasia or visual disturbances, were examined after treatment. Serial imaging studies (MRI or CT) were requested six weeks after treatment and every two to three months thereafter. Symptomatic brain edema was identified in association

**Table 1 Pretreatment characteristics of the 88 patients with large brain metastases in critical areas**

| | | | |
|---|---|---|---|
| Number of patients | 88 | Location of tumor | 92 lesions |
| Median age (range) | 64 (33–93) | Cerebral hemisphere | 61 |
| Age ≥65 | 42 | Frontal | 27 |
| Age <65 | 46 | Parietal | 10 |
| Sex | | Temporal | 13 |
| Male | 42 | Occipital | 21 |
| Female | 46 | Thalamus, basal ganglia | 4 |
| Primary cancer | | Cerebellum | 17 |
| Lung | 41 | Median KPS score | 70 (50–100) |
| Breast | 23 | KPS ≥70 | 54 |
| Gastro-intestinal tract | 9 | KPS <70 | 34 |
| Ovary | 4 | Tumor volume, median ($cm^3$) | 16.2 |
| Kidney | 3 | ≥ 30.0 | 13 |
| Thyroid | 2 | 20.0-29.9 | 18 |
| Larynx | 2 | 10.0-19.9 | 61 |
| Uterus | 2 | Image follow-up period (months) | |
| Others | 6 | Median | 7 |
| Multiple vs single | | Range | 1-37 |
| Multiple metastases | 45 | Survival period (months) | |
| Single metastases | 43 | Median | 9 |
| Metastases to other organs | 50 | Range | 3-41 |

with neurological deterioration and imaging changes in the concomitant perifocal regions after treatment. The tumor response was divided into three groups, reduced (a decrease in the tumor volume of >15%), stable (a change in the tumor volume within ±15%) or enlarged (an increase in the tumor volume of >15%), in order to compare the response with that observed in former reports of large brain metastases [9,10]. The incidence of complications was examined in relation to the V14 of the surrounding brain.

### Statistical analysis

Univariate and multivariate analyses were conducted using logistic regression and Cox hazard models. Differences between the groups were evaluated using Student's *t*-test. Overall survival was estimated according to the Kaplan-Meier method and examined for significance using the log-rank and generalized Wilcoxon tests. All analyses employed the conventional $p < 0.05$ level of significance.

## Results

Nineteen patients received osmo-steroid therapy during hypofractionation treatment for symptoms of perifocal edema and/or the further oral administration of steroids depending on the presence of other symptoms at the outpatient clinic.

### Follow-up evaluations

No new neurological deficits from direct damage to the optic pathway, brainstem or functional areas were noted, although symptoms recurred or appeared in 10 patients due to adverse effects (brain edema) on the surrounding brain.

### Treatment-related variables of optimal hypofractionation

The prescribed isodoses ranged from 50% to 70% (median, 57%) for the target. The SDE of the maximum dose ranged from 36.8 to 61.9 Gy (median, 47.4 Gy) delivered in three to 10 fractions (median, five). Twenty-one tumors were treated with more than five fractions. The median V14 value was 5.0 $cm^3$ (Table 2). The results are shown for each of the three groups divided according to the tumor volume in Table 3. The prescribed isodose declined according to the tumor volume, although no significant differences were found among the three groups. Large tumors measuring 20 $cm^3$ or more were treated with five fractions or more in order to maintain a V14 of less than 7 $cm^3$. A large number of fractions (more than five) was used, even in tumors measuring less than 20 $cm^3$, in order to decrease the V14 to less than 3 $cm^3$ or 1 $cm^3$ for tumors in critical areas, such as the motor cortex, basal ganglia, thalamus or pyramidal tract (concerning normal tissue dose constraints), or those associated with extensive brain edema. There were no significant differences in the SDE of the maximum dose or V14 values among the three groups.

**Table 2 Treatment-related variables of the 92 large brain metastases in the 88 patients**

| | |
|---|---|
| Prescribed isodose (%) | |
| Median | 57 |
| Range | 50-70 |
| Fraction number | |
| Median | 5 |
| Range | 3 – 10 |
| Lesion treated with 3 fraction | 14 |
| 4 fraction | 2 |
| 5 fraction | 55 |
| 6 fraction | 7 |
| 8 fraction | 12 |
| 10 fraction | 2 |
| Maximum dose (single fraction equivalent dose, Gy) | |
| Median | 47.4 |
| Range | 36.8-61.9 |
| V14 ($cm^3$) | |
| Median | 5 |
| Range | 0.3-6.9 |

### Tumor response, local control and overall survival after treatment

All 92 lesions in the 88 patients were subjected to sequential imaging studies from one to 37 months (median, seven months) after treatment. All but five of the 92 lesions (three enlarged and two stable) showed tumor regression on follow-up images (Table 3, Figure 1). Six lesions exhibited marginal recurrence and required additional treatment. A second cycle of treatment was performed at the recurrent areas only, excluding the central areas treated with higher doses (Figure 1C). The local tumor control rate was 90.2%, with a median survival of nine months (Figure 2). There were no significant differences in the survival rates among the patients with tumors measuring 10–19.9 $cm^3$, 20–29.9 $cm^3$ or ≥30 $cm^3$ after treatment (log-rank test: $p = 0.50$, generalized Wilcoxon test for group 1&2 vs. 3: $p = 0.32$) although the rate of survival was lower in the patients with tumors measuring ≥30 $cm^3$ than in the other groups (Figure 3).

### Tumor recurrence

Marginal regrowth of the treated lesions occurred in six patients seven to 36 months after treatment; all tumors were located in the cerebral hemisphere (Table 4). The tumors were treated with a median prescribed isodose of 57% and median SDE of the maximum dose of 48.4 Gy.

**Table 3 Results of optimal hypofractionation in the three groups divided according to the tumor volumes**

| | | | |
|---|---|---|---|
| Tumor volume ($cm^3$) (median) | 10–19.9 (13.4) | 20–29.9 (23.8) | 30–74.6 (37.5) |
| Median isodose (%) (range) | 57 (50–70) | 56 (51–64) | 55 (51–64) |
| Median fraction Number (range) | 5 (3–10) | 5 (5–10) | 5 (5–8) |
| Median SDE of the max. dose (Gy) (range) | 47.2 (36.8-61.9) | 48.5 (38.1-61.5) | 46.5 (39.7-56.0) |
| Median V14 ($cm^3$) | 5.1 | 4.4 | 5.2 |
| (range) | (0.3-6.9) | (0.7-6.1) | (0.4-6.1) |
| Median KPS | 70 | 70 | 65 |
| (range) | (50–100) | (50–80) | (50–90) |
| Tumor response | | | |
| Reduced (87) | 58 | 17 | 12 |
| Stable (2) | 0 | 1 | 1 |
| Enlarged (3) | 3 | 0 | 0 |
| Marginal recurrences (6) | 4/61 (6.6%) | 2/18 (11.1%) | 0/13 (0%) |
| Complications (10) (brain edema) | 5/61 (8.2%) | 4/18 (22.2%) | 1/13 (7.7%) |

No significant factors were found in the univariate and multivariate analyses. However, the difference in the tumor volumes (10–19.9 $cm^3$ vs 30–74.6 $cm^3$) between the groups was significant (p =0.02), whereas the difference in the tumor location (cerebrum vs. others) was not (p =0.16). All tumors recurred more than six months after treatment, and the difference between the groups (followed for <6 months vs. ≥6 months) was found to be significant (p =0.001).

### Adverse effects (brain edema)

Six patients who experienced recurrent symptoms and one patient who developed new symptoms due to extensive brain edema required osmo-steroid therapy. The symptoms and edema rapidly improved after the osmo-steroid therapy. Each of these patients received further oral administration of steroids at the outpatient clinic. Two patients who displayed recurrent symptoms and one patient who exhibited new symptoms due to perifocal edema required the oral administration of steroids at the outpatient clinic. These 10 patients showed both clinical and radiological deterioration one to 16 months after treatment. Two of these patients demonstrated newly developed brain edema, while the remaining eight patients presented with the extension of pre-existing brain edema that had been present prior to treatment. The median age of these patients was 69 years, which was older than that of the total population (Table 5). Each of these patients were treated with 5–10 fractions (median, 6). The V14 of the patients with brain edema ranged from 3.6 to 6.1 $cm^3$. In the univariate analyses, age and the number of fractions were found to be significant factors for complications; however, only the number of fractions was found to be significant in the multivariate analyses. Differences between the groups were significant for each of the following factors: age (≥60, p = 0.02), number of fractions (≥5, p = 0.0006) and duration of edema (<6 months, p = 0.001). In contrast, the differences in tumor volume between the three groups were not significant, nor were the differences in the number of patients treated with or without osmo-steroid therapy during hypofractionation treatment.

## Discussion

The prognosis of patients with brain metastases is related to the stage of the primary cancer, age and the KPS score [14,15]. The worst survival is seen in patients with a KPS of less than 70. In the present series, 38.6% of the patients had a KPS of less than 70 and 65.9% of the patients were 60 years of age or older. Although 78 patients (88.6%) were in RTOG-RPA class 2 or 3, the median survival of our patients was nine months. Furthermore, no statistically significant differences were found between the three groups of patients divided according to the tumor volume, although the survival rate and median KPS score were lowest in the largest group. Optimal hypofractionated conformal radiotherapy helps to increase the KPS, at least in patients with symptomatic lesions not directly affecting functional areas, and contributes to improving the prognosis of patients with large brain metastases, as previously reported [9].

Single-session radiosurgery is increasingly being used to treat brain metastases and has the benefits of a short treatment time, high tumor control rate and low risk of complications. However, large metastases are not suitable for treatment with single-session radiosurgery, as lower tumor control rates (85%) and higher complication rates (15%) than those for smaller metastases have been reported [2,16].

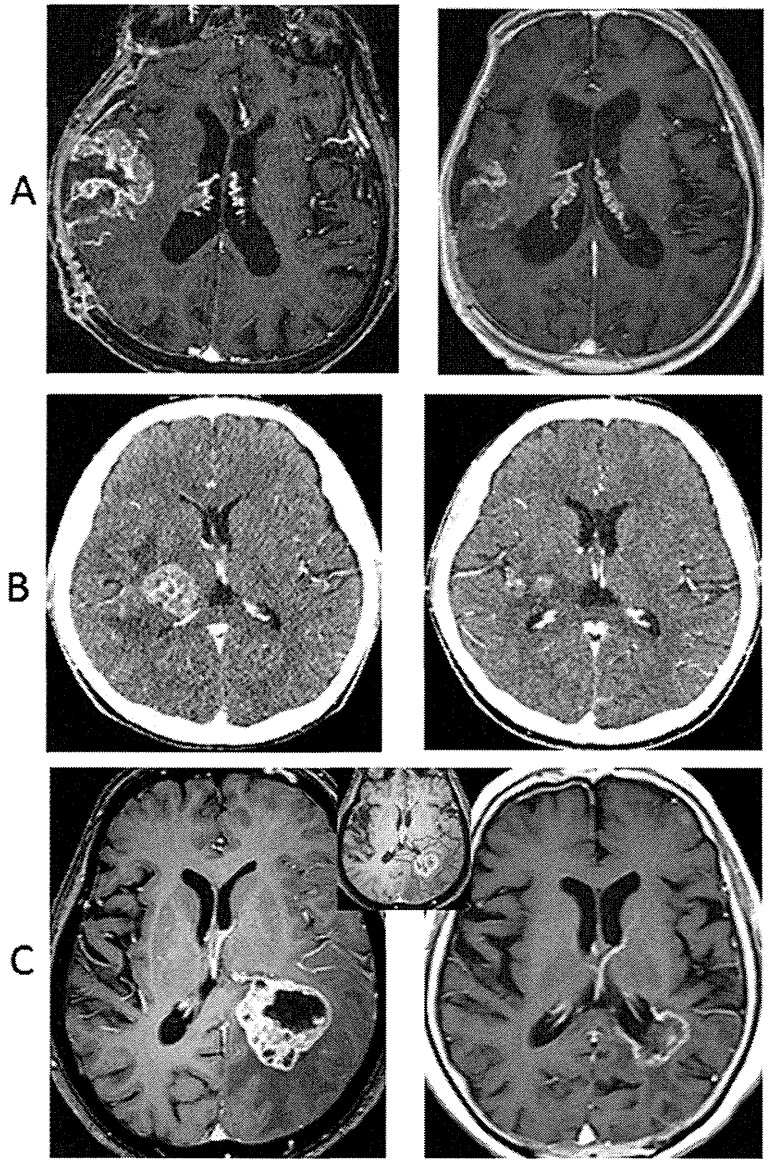


**Figure 1 Tumor regression after optimal hypofractionated conformal radiotherapy. A**: Gd-enhanced T1-weighted MR images. Lung cancer brain metastasis in a 73-year-old male. A large residual tumor (74.6 $cm^3$) obtained after partial removal due to an impending brain hernia was treated with a marginal dose of 27 Gy in five fractions at an isodose of 56% (left). A significant tumor response with no adverse imaging effects was found four months after the administration of conformal radiotherapy (right). The patients' left hemi-paresis disappeared, and the KPS improved from 60 to 70. **B**: Contrast-enhanced CT scans (MR images not available for the pace maker implant). Lung cancer brain metastasis in a 52-year-old female. A tumor in the thalamus (10.6 $cm^3$) with perifocal edema was treated with a marginal dose of 31 Gy in five fractions at an isodose of 63% (left). A tumor response was observed seven months after the administration of conformal radiotherapy (right). The patients' left hemiparesis was ameliorated, and the KPS improved 60 to 70 (walking with a stick 32 months after treatment). **C**: Gd-enhanced T1-weighted MR images. Breast cancer brain metastasis in a 70-year-old female. A large tumor in the parietal lobe (23.5 $cm^3$) with perifocal edema was treated with a marginal dose of 35 Gy in eight fractions at an isodose of 57% (left). A tumor response was found two months after treatment, Gerstmann's syndrome disappeared, and the KPS improved 60 to 70. Marginal recurrence was noted 20 months after the first treatment, and the recurrent lesion (1.7 $cm^3$) was treated with a marginal dose of 20 Gy at an isodose of 69% in single-session radiosurgery (center). A tumor response with no adverse imaging effects was found 34 months after the first treatment (right).

The optimal hypofractionation treatment in this series yielded a tumor control rate of 90.2% in the patients with large tumors. The median maximum dose (SDE) of 47.4 Gy at a median prescribed isodose of 57% in a median of five fractions appeared to be effective for most large brain metastases, in addition to a marginal dose of 20 Gy at the prescribed isodose of 50-60% for small tumors in single fraction radiosurgery. However, more

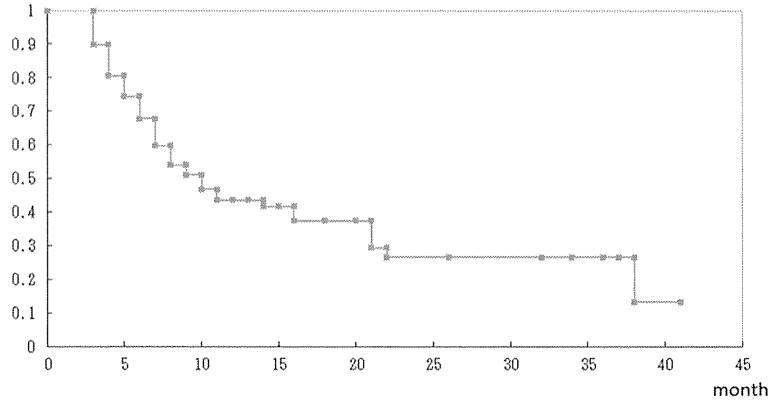


**Figure 2** Kaplan-Meier survival curves of the 88 patients with large brain metastases treated with optimal treatment.

than five fractions were used in cases involving large tumors measuring more than 20 $cm^3$ or tumors associated with extensive brain edema in order to decrease the V14 values.

Consequently, tumor recurrence appeared in six patients more than six months after treatment, all of which originated from marginal areas treated with the prescribed isodose. Additional treatment was easily performed in these patients, because the volume of the recurrent tumors was not large, and the risk of radiation necrosis after the second treatment was assessed to be very low. As to risk factors for recurrence, a larger tumor volume, lower prescribed isodose and lower SDE of the maximum dose are potential candidates; however, no factors were found to be significant in the univariate or multivariate analyses in this study. The difference in tumor volume (10–19.9 $cm^3$ vs 30–74.6 $cm^3$) between the groups was significant; however, recurrence occurred in only four of 61 patients with smaller tumors. Although greater sample size is required for further statistical analyses, our findings indicate that optimal hypofractionated conformal radiotherapy is effective for treating large lesions with a low rate of recurrence.

Brain edema developed in 10 patients, mostly within six months. With respect to risk factors, age and the number of fractions were found to be significant in this series. Older patients' brains with large metastases may be sensitive to irradiation stress or possibly exhibit greater vulnerability than the normal adult brain. More than five fractions were used to treat large tumor measuring more than 20 $cm^3$, tumors associated with extensive edema or tumors located in critical areas. Tumors situated deep within the white matter have a tendency to cause brain edema, and factors related to the onset of edema may promote the development or re-appearance of brain edema. In contrast to that observed for radiation necrosis, most cases of brain edema developed several months after treatment, and all were reversible and recovered after either osmo-steroid therapy or oral steroid treatment. Therefore, optimal hypofractionated conformal radiotherapy is a safe treatment for patients with large metastases with high risk factors.

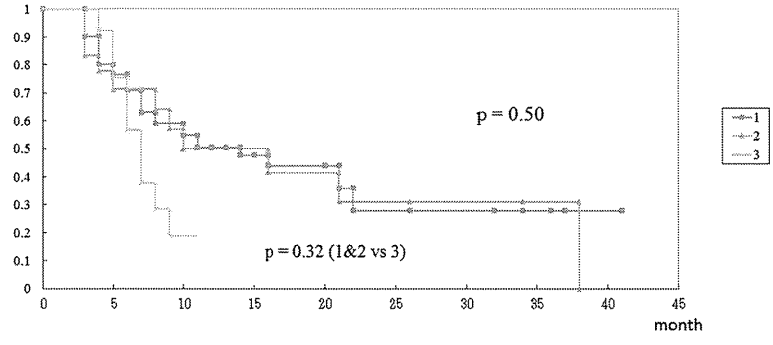


**Figure 3 Kaplan-Meier survival curves of the patients with large brain metastases in the three groups.** Group 1): patients with tumors measuring 10–19.9 $cm^3$, group 2): patients with tumors measuring 20–29.9 $cm^3$, group 3): patients with tumors measuring ≥30 $cm^3$. No statistically significant differences were found between the groups.

**Table 4 Characteristics of the six patients with recurrences after optimal hypofractionated conformal radiotherapy**

| | Median (range) | Univariate | Multivariate | | |
|---|---|---|---|---|---|
| | | p value | p value | HR | 95% CI |
| Age | 68.5 (56–82) | 0.17 | 0.20 | 1.09 | 0.95-1.25 |
| Sex | M: 3, F: 3 | 0.91 | 0.29 | 0.23 | 0.01-3.63 |
| Tumor location | Cerebrum (P: 2, F: 2, T: 1, O: 1) | 0.85 | 0.75 | 1.13 | 0.53-2.39 |
| Tumor volume ($cm^3$) | 18.0 (11.9-24.0) | 0.69 | 0.69 | 1.04 | 0.85-1.29 |
| Prescribed isodose (%) | 57 (52–66) | 0.97 | 0.73 | 0.93 | 0.63-1.37 |
| Fraction number | 5 (3–8) | 0.89 | 0.73 | 0.82 | 0.27-2.49 |
| SDE of the max. dose (Gy) | 48.4 (36.8-54.3) | 0.72 | 0.40 | 0.85 | 0.58-1.25 |
| V14 ($cm^3$) | 4.9 (3.7-5.1) | 0.78 | 0.90 | 1.07 | 0.35-3.32 |

HR: Hazard ratio, CI: Confidence interval, P: Parietal, F: Frontal, T: Temporal, O: Occipital.

Conducting dose-volume prediction of complications is essential for providing optimal hypofractionation treatment. We previously reported a method for predicting radiation necrosis using a model that accounted for the SDE of the maximum dose and V14 [10]. Long-term experience with single-session radiosurgery has also confirmed the optimal treatment doses for individual pathologies in the brain. For example, a marginal dose of 12 Gy or 20 Gy is used to treat vestibular schwannoma or AVM, respectively. The long-term results have been shown to be satisfactory, with low rates of complications [17,18]. The optimal dose and fraction number for hypofractionation treatment for such pathologies may be determined by predicting the incidence of complications with respect to avoiding adverse effects on the surrounding brain.

In this prospective study, our findings demonstrated a rate of high tumor control and a low rate of complications in the treatment of large brain metastases with high risk factors. No patients with radiation necrosis required surgical resection during the median follow-up of seven to 41 months. Therefore, the administration of defined optimal hypofractionation treatment based on the dose-volume prediction of complications is effective and safe for the treatment of large lesions. However, the V14 may need to be further reduced to less than 3 $cm^3$ when treating tumors situated deep within the white matter and/or exhibiting extensive perifocal edema, as the rate of recurrence of pre-existing edema was not low in the patients with a V14 of 3 $cm^3$ or more after treatment in this series. Conformal radiotherapy with a prescribed isodose of 50% to 60% has the benefits of decreasing the V14 value due to a sharp fall-off in the dose distribution, as noted with single-session radiosurgery. Optimal treatment using a large fraction number also has the benefits of decreasing the V14 value and helps to avoid radiation necrosis, as demonstrated in this prospective study.

## Conclusion

This prospective study of optimal dose and fractionation treatment for large brain metastases with high risk factors showed satisfactory results for local tumor control and survival, with limited complications. Conducting dose-volume prediction of complications using the V14 is beneficial for preventing irreversible complications in the treatment of large brain metastases or other lesions in the brain.

**Table 5 Characteristics of the 10 patients with adverse effects after optimal hypofractionated conformal radiotherapy**

| | Median (range) | Univariate | Multivariate | | |
|---|---|---|---|---|---|
| | | p value (CH model) | p value | HR | 95% CI |
| Age | 69 (59–84) | 0.04* (0.03*) | 0.14 | 1.05 | 0.99-1.11 |
| Sex | M: 7, F: 3 | 0.15 | 0.08 | 0.26 | 0.06-1.18 |
| Tumor location | Cerebrum: 9, cerebellum: 1 | 0.63 | 0.67 | 0.91 | 0.59-1.90 |
| Tumor volume ($cm^3$) | 20.5 (10.0-32.9) | 0.86 | 0.34 | 0.96 | 0.88-1.05 |
| Prescribed isodose (%) | 57 (51–65) | 0.77 | 0.88 | 0.98 | 0.79-1.22 |
| Fraction number | 6 (5–10) | 0.007* (0.004*) | 0.007* | 2.04 | 1.21-3.43 |
| SDE of the max. dose (Gy) | 48.0 (40.5-55.3) | 0.50 | 0.51 | 0.94 | 0.77-1.13 |
| V14 ($cm^3$) | 4.7 (3.6-6.1) | 0.92 | 0.88 | 0.96 | 0.57-1.61 |

CH: Cox hazard, HR: Hazard ratio, CI: Confidence interval, *: Significant.

**Competing interests**
The authors declare that they have no competing interests.

**Authors' contributions**
HKI developed the concept of study, contributed to the collection and analysis of the data and wrote the manuscript, SH, SY, SJ and NS conducted the treatment planning, SK and TK contributed to administering the treatment and supported the data analysis, SH and NT provide administrative support. All authors approved the final manuscript.

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RADIATION ONCOLOGY

RESEARCH Open Access

# Assessing cumulative dose distributions in combined radiotherapy for cervical cancer using deformable image registration with pre-imaging preparations

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## Abstract

**Background:** The purpose of the study was to evaluate the feasibility of deformable image registration (DIR) in assessing cumulative dose distributions of the combination of external beam radiotherapy (EBRT) and fractionated intracavitary brachytherapy (ICBT) for cervical cancer.

**Materials and methods:** Three-dimensional image data sets of five consecutive patients were used. The treatment plan consisted of whole pelvic EBRT (total dose: 45 Gy in 25 fractions) combined with computed tomography (CT)-based high-dose rate ICBT (≥24 Gy in 4 fractions to the high risk clinical target volume (HR-CTV)). Organs at risk and HR-CTV were contoured on each CT images and dose-volume parameters were acquired. Pre-imaging preparations were performed prior to each ICBT to minimize the uncertainty of the organ position. Physical doses of each treatment were converted to biologically equivalent doses in 2 Gy daily fractions by the linear quadratic model. Three-dimensional dose distributions of each treatment were accumulated on CT images of the first ICBT using DIR with commercially available image registration software (MIM Maestro®). To compare with DIR, 3D dose distributions were fused by rigid registration based on bony structure matching. To evaluate the accuracy of DIR, the Dice similarity coefficient (DSC) was measured between deformed contours and initial contours.

**Results:** The cumulative dose distributions were successfully illustrated on the CT images using DIR. Mean DSCs of the HR-CTV, rectum, and bladder were 0.46, 0.62 and 0.69, respectively, with rigid registration; and 0.78, 0.76, and 0.87, respectively, with DIR ($p < 0.05$). The mean DSCs derived from our DIR procedure were comparable to those of previous reports describing the quality of DIR algorithms in the pelvic region. DVH parameters derived from the 2 methods showed no significant difference.

**Conclusions:** Our results suggest that DIR-based dose accumulation may be acceptable for assessing cumulative dose distributions to assess doses to the tumor and organs at risk in combined radiotherapy for cervical cancer under pre-imaging preparations.

**Keywords:** Radiotherapy, Cervical cancer, Deformable image registration

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## Background

The combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the standard treatment for cervical cancer [1]. In conventional ICBT, two orthogonal X-rays are taken and "point A" is used as the reference point for dose prescription. "Rectal and bladder points" have also been used as reference points for the assessment of rectal and bladder doses, according to Report 38 of the International Commission on Radiation Units and Measurements [2]. However, these points are hypothetical, and do not always represent the actual tumor volume or the exact locations of the highest doses in the rectum and bladder [3,4]. Recently, three-dimensional (3D) image modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), have become available for use in planning ICBT treatment. Treatment planning based on 3D images allows for assessment of 3D dose distributions and dose-volume evaluation. The Group Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) working group for gynecologic brachytherapy has provided recommendations for 3D image-based treatment planning in cervical cancer brachytherapy [5-7]. Several studies have demonstrated that 3D dose-volume parameters of the target volume and organs at risk (OARs) are useful for predicting treatment response and toxicity development [8-12].

For assessment of cumulative dose-volume relationships for the target volumes and OARs in the combined radiotherapy, the GYN GEC-ESTRO working group suggests several parameters, including D90 of HR-CTV, and D2cc of the rectum and bladder. These 3D dose-volume histogram (DVH) parameters are calculated by simply adding DVH parameters for the target volume and OARs in EBRT for each ICBT session. However, simple addition of DVH parameters is based on the assumption that the location of the region of interest is identical in each therapy. If the high dose area is not consistent in each therapy, simple addition of DVH parameters does not reflect the absolute dose-volume relationship. Under such circumstances, it is necessary to illustrate cumulative dose distributions and calculate DVH in order to estimate the dose-volume relationship. However, assessing cumulative dose distributions with a conventional treatment planning system is difficult due to the following reasons. First, as EBRT and ICBT have different dose profiles and fractionations, it is generally difficult to calculate DVH [13]. Second, organ motions of the uterus, bladder, and rectum, and changes in target volume during treatment, are significant during cervical cancer treatment [14]; therefore dose accumulation with conventional rigid registration is inaccurate and unreliable.

Recently, a few studies have demonstrated the efficacy of DIR for evaluating cumulative dose distributions and DVHs in combined radiotherapy for various tumors [15-17]. Therefore, we aimed to conduct a pilot study to evaluate the feasibility of DIR for assessment of cumulative dose distributions and DVHs of combined radiotherapy for cervical cancer using a commercially available DIR algorithm (MIM Maestro®).

## Methods

### Patients

Data were collected from five consecutive patients with locally advanced cervical cancer, who were treated with EBRT and high-dose rate (HDR)-ICBT in our institution between August and October 2013. All the data collections were performed after the approval of institutional review board and acquiring written informed consent from patients.

### Treatment

EBRT was delivered to the whole pelvis with a total dose of 45 Gy in 25 fractions using the four-field box technique with 10-MV X-ray. The clinical target volume (CTV) of EBRT consisted of the cervical tumor, whole uterus, bilateral parametria, at least the upper half of the vagina, and pelvic lymph nodes (including the common, external, and internal iliac, and presacral lymph nodes). The planned target volume (PTV) of EBRT included the CTV plus a ≥10-mm safety margin.

High-dose-rate (HDR) ICBT was performed weekly for four consecutive weeks using $^{192}$Ir sources. A combination of tandem and ovoid applicators was used. CT-based 3D image guided brachytherapy was performed for every session of ICBT. A series of transverse CT images with 1 mm slice thickness were obtained with the applicators in place. The high risk CTV (HR-CTV), rectum, and bladder were delineated according to GEC-ESTRO recommendations [6]. For precise delineation, references were always made to the MRI at diagnosis and those obtained within a week prior to the first brachytherapy session. The minimum dose delivered to 90% of the most irradiated volume of HR-CTV (HR-CTV D90) and the minimum doses delivered to 2 cm$^3$ (D2cc) of the most irradiated volumes of the rectum and the bladder were calculated and recorded. At least 6 Gy was prescribed to HR-CTV D90 in each ICBT session. Dose constraint was 75 $Gy_{EQD2}$ in D2cc of the rectum. Dose prescription and target coverage were modified based on dose constraints for OARs.

### Pre-imaging preparations for deformable image registration

Pre-imaging preparations were carefully performed before every ICBT session, as large variation in organ position and volume may produce fusion uncertainties and affect the quality of DIR [18,19]. Patients were required to collect urine one hour before undergoing CT imaging for EBRT treatment planning. Bladder volume was confirmed by this

CT image. In every ICBT session, the bladder was filled with this volume of normal saline to stabilize its size and position. The original angle and length of the longitudinal axis of the uterus were also confirmed by treatment planning CT for EBRT. In all ICBT sessions, the angle of uterus was kept constant by adjusting the inserting angle of tandem applicator. Patients were required to defecate before any treatment. Distension of the rectum was confirmed by treatment planning CT for EBRT and brachytherapy. If gas was observed in the rectum at ICBT, gas drainage was performed to reduce rectal distention. CT was retaken if gas drainage was performed.

### Dose accumulation

In all cases, image registration was performed using MIM maestro ver.6.2 (MIM Software Inc., Cleveland, OH, USA). Doses of radiotherapy were converted into biologically equivalent doses in 2 Gy daily fractions ($Gy_{EQD2}$) using the linear quadratic model with $\alpha/\beta$ = 10 Gy for tumor tissues, and $\alpha/\beta$ = 3 Gy for normal tissues [20]. At first, CT image data sets of EBRT were rigidly fused by matching bony structures on CT images of the first ICBT. Next, CT image data sets of the second, third, and fourth ICBT sessions were rigidly fused, referring to the applicator position in the CT images of the first ICBT. Finally, DIR was performed to accumulate doses of the second, third, and fourth ICBT on the first ICBT dose (Figure 1). Results of the DIR were carefully reviewed using the function of MIM maestro (Reg Review) and modified by another function (Reg Refine).

### Cumulative dose-volume evaluations

Cumulative DVHs of the HR-CTV, rectum, and bladder were calculated based on accumulated dose distributions. DIR-based DVH parameters such as HR-CTV D90, D2cc of the rectum and bladder were derived from cumulative DVHs.

HR-CTV D90 and D2cc of the rectum and bladder were also calculated using conventional simple addition of DVH parameters. In this method DVH parameters were calculated by adding the components of EBRT and ICBT sessions.

### Quantitative evaluation of DIR performance

Although no established method exists for estimating the quality of DIR, the Dice similarity coefficient (DSC) is commonly used to evaluate the accuracy of DIR [18,21,22], DSC was calculated by the following formula [23]:

$$DSC = \frac{2(V_{\mathrm{DIR}} \cap V_{\mathrm{initial}})}{V_{\mathrm{DIR}} + V_{\mathrm{initial}}}$$

In this formula, $V_{DIR}$ represents the volume of deformed contour after DIR, and $V_{initial}$ represents the volume of contours manually delineated on the CT image of the first ICBT session. The DSC is used to evaluate the spatial overlap accuracy of automated segmentation of images. Values for DSC range from 0 to 1, with higher values indicating larger volumes of overlap between two images. DSC is also calculated to estimate overlap of the contours in case of rigid fusion.

### Statistical analysis

DIR-based cumulative DVH parameters and simple DVH parameter addition were compared using the paired t-test. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (SPSS Inc., Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

## Results

### Patient characteristics

Among the 5 patients included in the study, 3 had Stage IIB disease and 2 had Stage IIIB disease. The mean transverse tumor diameter was 5.2 cm at diagnosis and 3.8 cm at the initiation of ICBT.

### Performance of DIR

Cumulative dose distributions, consisting of EBRT and four sessions of ICBT, were successfully illustrated using DIR (Figure 2). Inspection by 3 radiation oncologists (TA, TT, SK) revealed that dose distributions were illustrated without any irregular dose warp or irresponsible isodose lines. A high dose area (>200 $Gy_{EQD2}$) was observed around the center of the tumor and steep dose decline was observed toward the peripheral area of the tumor. HR-CTV was covered with 70–80 $Gy_{EQD2}$. The parametria were covered with 50–60 $Gy_{EQD2}$. External iliac, internal iliac, and obturator lymph nodes were covered with 40–50 $Gy_{EQD2}$ depending on the distance from the uterus. The doses to the rectum were approximately 60–70 GyEQD2.

The mean DSCs for the HR-CTV, rectum, and bladder were 0.46, 0.62, and 0.69, respectively, with rigid fusion, and 0.78, 0.76, and 0.87, respectively, with DIR. Volumetric parameters related to our DIR procedure and DSCs are shown in Tables 1, 2 and 3. The difference in DSCs between the two methods was statistically significant, suggesting the improved spatial overlap accuracy of automated image segmentation with DIR.

### DVH Parameters

The mean HR-CTV D90 and D2cc of the rectum and bladder were 81.4 $Gy_{EQD2}$, 65.7 $Gy_{EQD2}$, and 82.8 $Gy_{EQD2}$, respectively, with DIR; and 83.1 $Gy_{EQD2}$, 67.2 $Gy_{EQD2}$, and 86.6 $Gy_{EQD2}$, respectively, with conventional simple DVH parameter addition. There was no statistically significant difference in the dosimetric parameters between the two calculation methods (Table 4). DVH parameters calculated

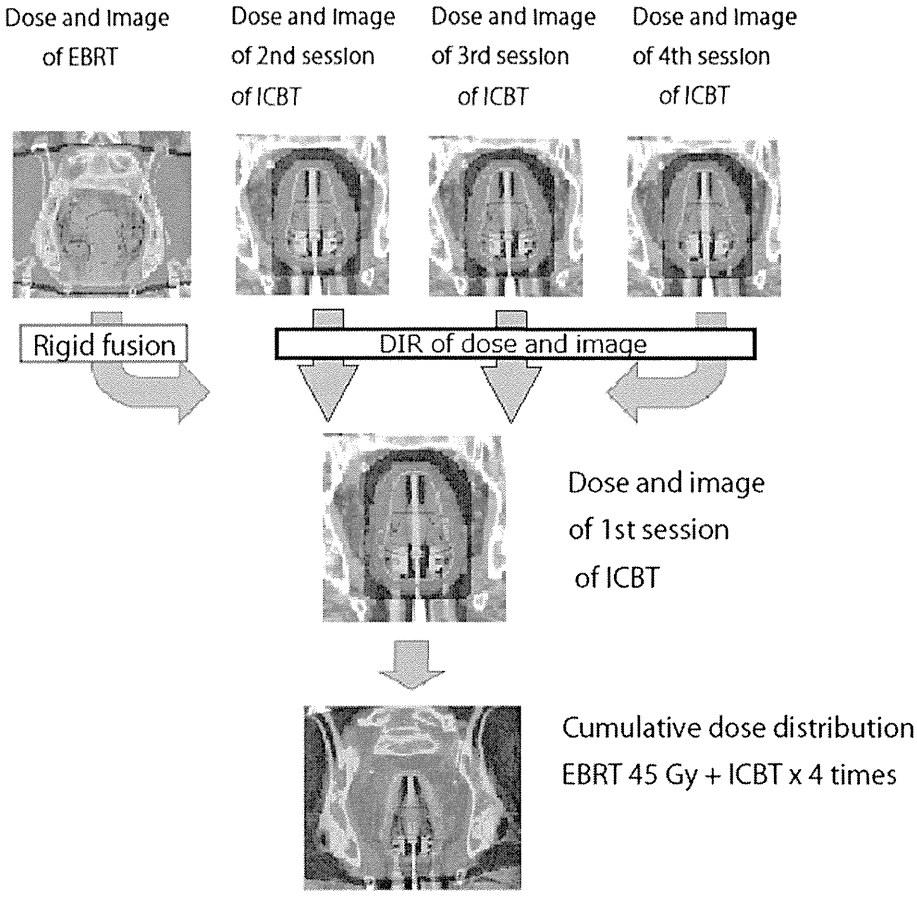


**Figure 1 The flow chart of dose accumulation.** Doses of radiotherapy were converted to biologically equivalent doses in 2 Gy per fraction using the linear quadratic model with $\alpha/\beta = 10$ Gy for tumor tissues and $\alpha/\beta = 3$ Gy for normal tissues. First, dose and image of EBRT were rigidly fused on the CT image of the first ICBT. Then, using DIR, doses and images of the second, third, and fourth ICBT were accumulated on those of the first ICBT.

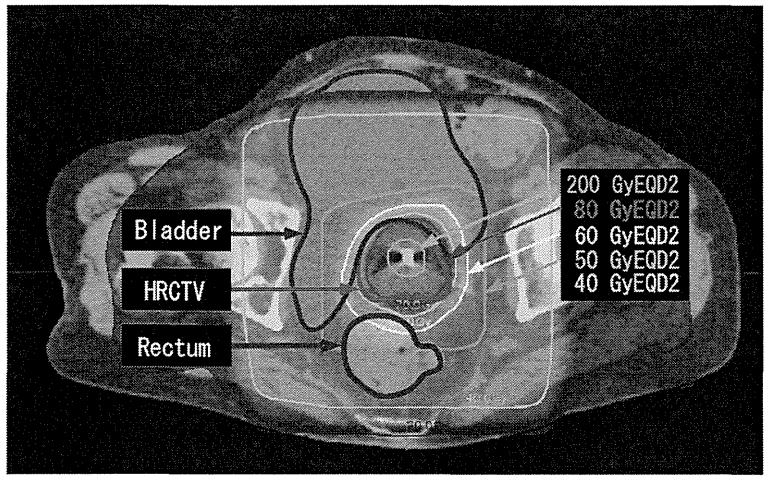


**Figure 2 Cumulative dose distribution.** A large dose gradient was observed in the irradiated field. There is an area with a very high dose at the center of the tumor. HR-CTV was covered by a 70–80 GyEQD2 isodose line. Pelvic lymph node areas were covered by 40–50 GyEQD2 isodose lines, depending on their distances from the central axis of the uterus.

**Table 1 Volume of the original contour and deformed contour and the results of dice similarity coefficient (HR-CTV)**

| | | Original contour ($cm^3$) | Deformed contour ($cm^3$) | Original contour ∩ deformed contour ($cm^3$) | DSC by DIR | DSC by rigid fusion |
|---|---|---|---|---|---|---|
| Case1 | DIR1 | 25.4 | 29.9 | 25.4 | 0.79 | 0.70 |
| | DIR2 | - | 20.5 | 16.4 | 0.71 | 0.49 |
| | DIR3 | - | 20.0 | 16.6 | 0.73 | 0.57 |
| | Mean | | | | 0.75 | 0.59 |
| Case2 | DIR1 | 17.8 | 20.6 | 15.3 | 0.80 | 0.35 |
| | DIR2 | | 18.0 | 13.4 | 0.75 | 0.69 |
| | DIR3 | | 18.1 | 13.4 | 0.75 | 0.14 |
| | Mean | | | | 0.76 | 0.39 |
| Case3 | DIR1 | 40.0 | 48.7 | 36.5 | 0.82 | 0.25 |
| | DIR2 | | 32.8 | 26.8 | 0.73 | 0.46 |
| | DIR3 | | 33.7 | 27.7 | 0.75 | 0.30 |
| | Mean | | | | 0.77 | 0.34 |
| Case4 | DIR1 | 18.1 | 21.4 | 16.5 | 0.83 | 0.66 |
| | DIR2 | - | 13.1 | 10.9 | 0.70 | 0.48 |
| | DIR3 | - | 17.6 | 12.5 | 0.70 | 0.42 |
| | Mean | | | | 0.74 | 0.52 |
| Case5 | DIR1 | 27.5 | 24.0 | 20.8 | 0.85 | 0.47 |
| | DIR2 | - | 27.5 | 21.8 | 0.83 | 0.53 |
| | DIR3 | - | 24.8 | 21.7 | 0.88 | 0.43 |
| | Mean | | | | 0.86 | 0.48 |
| Total | Mean ± SD | | | | 0.78 ± 0.06 | 0.46 ± 0.16 $p < 0.05$ |

with DIR were comparable with those derived by the conventional method, when the anatomical locations of the uterus, rectum, and bladder were adequately matched.

## Discussion

Assessing cumulative dose distributions in combined therapy with EBRT and ICBT for cervical cancer has been challenging due to the difficulty in combining different types of fractionated radiation therapy, organ motion uncertainty, and tumor volume regression during treatment. Dose distributions provided by the DIR appeared to represent the characteristic dose profiles of combined radiotherapy for cervical cancer. The cervical tumor was covered with an adequately high dose, while the surrounding normal tissues including the rectum and bladder received minimum doses.

When evaluating DIR-based cumulative dose distributions and DVHs of the tumor and OARs, the accuracy of DIR is of the most importance. Although there are many uncertainties related to brachytherapy for cervical cancer [24], the accuracy of DIR can be influenced significantly by large inter-fractional variation in the organ volume and position [18,19]. In this study, therefore, pre-imaging preparations for the bladder, rectum, and uterus were performed so as to minimize such variation. In spite of preparations, in some cases, there were still variations in volume, shape and position of OARs which require some adjustment by manual procedure. This adjustment may result in variability in DIR results. With these methods, the mean DSCs for the HR-CTV, rectum, and bladder were 0.78, 0.72, and 0.81, respectively, which were significantly higher than those derived from the cumulative images by rigid fusion based on bony structure matching (Tables 1, 2 and 3). Although DSC is limited in that it does not include information of the deformation amount inside the overlapped contours, these data suggest that improved spatial overlap accuracy was obtained with the DIR method. There has been no definite consensus regarding the optimum DSC range. Kirby et al. reported that the mean DSC of the rectum was 0.85 in their study comparing 11 DIR algorithms using kilovoltage CT images of phantom [22]. Thörnqvis et al. reported that the mean DSCs of the bladder and rectum were 0.89 and 0.78, respectively, using one DIR algorithm, and 0.81 and 0.71, respectively, using another DIR algorithm [18].

Other factors which may affect the accuracy of DIR-based dose-volume evaluation are voxel size and energy conservation [25,26]. If voxel sizes of the two CT images are different, they will be normalized to the larger one

**Table 2 Volumes of the original and deformed contours and dice similarity coefficients (rectum)**

| | | Original contour ($cm^3$) | Deformed contour ($cm^3$) | Original contour ∩ deformed contour ($cm^3$) | DSC by DIR | DSC by rigid fusion |
|---|---|---|---|---|---|---|
| Case1 | DIR1 | 47.8 | 40.9 | 32.4 | 0.73 | 0.72 |
| | DIR2 | - | 26.9 | 24.6 | 0.74 | 0.66 |
| | DIR3 | - | 50.2 | 33.3 | 0.68 | 0.62 |
| | Mean | | | | 0.72 | 0.66 |
| Case2 | DIR1 | 46.6 | 54.1 | 42.5 | 0.85 | 0.74 |
| | DIR2 | - | 55.3 | 42.4 | 0.80 | 0.73 |
| | DIR3 | - | 48.1 | 40.7 | 0.75 | 0.67 |
| | Mean | | | | | 0.71 |
| Case3 | DIR1 | 46.7 | 53.7 | 32.5 | 0.72 | 0.60 |
| | DIR2 | - | 47.0 | 29.6 | 0.71 | 0.70 |
| | DIR3 | - | 79.3 | 39.5 | 0.62 | 0.57 |
| | Mean | | | | 0.68 | 0.62 |
| Case4 | DIR1 | 95.4 | 59.9 | 56.7 | 0.76 | 0.52 |
| | DIR2 | - | 77.6 | 68.5 | 0.71 | 0.51 |
| | DIR3 | - | 75.7 | 69.0 | 0.84 | 0.41 |
| | Mean | | | | 0.77 | 0.48 |
| Case5 | DIR1 | 51.0 | 51.7 | 40.1 | 0.76 | 0.73 |
| | DIR2 | - | 36.9 | 31.4 | 0.74 | 0.50 |
| | DIR3 | - | 38.4 | 33.4 | 0.80 | 0.62 |
| | Mean | | | | 0.77 | 0.61 |
| Total | Mean ± SD | | | | 0.76 ± 0.05 | 0.62 ±0.10 p <0.05 |

during DIR process, and this process may cause some errors in cumulative dose-volume assessment. In this study, however, CT images were acquired with the same setting of field of view and the same slice thickness so as to generate same voxel size. Regarding energy conservation, the energy of radiation to one voxel may not be conserved during DIR, especially in some situation where more than one voxels which have different density are deformed to a single voxel. This may also cause some errors in DIR-based dose-volume assessment. We could not measure the energy loss with commercially available DIR software. This is another limitation of our study.

In this study, the values of the DIR-based DVH parameters were comparable to those derived from the conventional simple DVH parameter addition (Table 4). However, these results have to be carefully interpreted. According to the GEC-ESTRO recommendations, the DVH parameters for the target volumes and OARs in EBRT and each ICBT session are simply added for estimating cumulative DVH parameters. In this method, however, it has to be assumed that the location of the region of interest is identical each time [5-7]. Therefore, the cumulative DVH parameters derived from this method could be overestimated. However, there have been several reports that demonstrated positive correlation between cumulative DVH parameters derived from the simple DVH parameter addition and clinical outcomes [8-12]. It is also necessary to evaluate the correlation between DIR-based cumulative DVH parameters and clinical outcomes.

Theoretically, D2cc for OARs is an overestimation for simple DVH parameter addition, while D90 for HR-CTV is an underestimation. In our study, however, D2cc for the rectum and bladder with DIR-based DVH accumulation was higher than those with simple DVH parameter addition in one case, respectively. D90 for the HR-CTV with DIR-based DVH accumulation was lower in four cases (Table 4). Four-field box technique was used in EBRT. Inhomogeneity of EBRT doses to the uterus, rectum and bladder was within ±2% with a mean dose in a volume of interest. Therefore, inhomogeneity of dose distributions in EBRT did not greatly affect the results. One possible reason for the above results may be fusion uncertainties in DIR. In our study, we fused images and produced cumulative dose distributions for the fourth, third and second sessions of ICBT onto those of the first ICBT using DIR. During fractionated brachytherapy, most cases showed rapid diminishment of the tumors. The position and volume of the rectum and bladder also varied greatly in Case 4 despite our attempts with pre-imaging preparations. In addition, change in the volume

**Table 3 Volumes of the original and deformed contours and dice similarity coefficients (bladder)**

| | | Original contour ($cm^3$) | Deformed contour ($cm^3$) | Original contour ∩ deformed contour ($cm^3$) | DSC by DIR | DSC by rigid fusion |
|---|---|---|---|---|---|---|
| Case1 | DIR1 | 191.2 | 237.9 | 178.2 | 0.86 | 0.83 |
| | DIR2 | - | 138.1 | 132.0 | 0.85 | 0.84 |
| | DIR3 | - | 276.4 | 177.7 | 0.88 | 0.82 |
| | Mean | | | | 0.86 | 0.83 |
| Case2 | DIR1 | 463.7 | 392.4 | 365.2 | 0.89 | 0.53 |
| | DIR2 | - | 434.6 | 121.0 | 0.92 | 0.54 |
| | DIR3 | - | 370.3 | 350.6 | 0.90 | 0.50 |
| | Mean | | | | 0.86 | 0.52 |
| Case3 | DIR1 | 231.7 | 411.3 | 223.6 | 0.89 | 0.79 |
| | DIR2 | - | 540.3 | 386.0 | 0.59 | 0.48 |
| | DIR3 | - | 213.9 | 229.4 | 0.93 | 0.82 |
| | Mean | | | | 0.80 | 0.70 |
| Case4 | DIR1 | 337.7 | 204.5 | 196.0 | 0.90 | 0.57 |
| | DIR2 | - | 184.7 | 171.5 | 0.91 | 0.60 |
| | DIR3 | - | 313.5 | 302.1 | 0.93 | 0.72 |
| | Mean | | | | 0.91 | 0.63 |
| Case5 | DIR1 | 155.9 | 143.0 | 134.2 | 0.89 | 0.77 |
| | DIR2 | - | 156.2 | 141.1 | 0.91 | 0.83 |
| | DIR3 | - | 207.9 | 148.8 | 0.80 | 0.70 |
| | Mean | | | | | 0.77 |
| Total | Mean ±SD | | | | 0.87 ± 0.09 | 0.69± 0.14 p <0.05 |

**Table 4 Dose-volume histogram (DVH) parameters**

| | | Cumulative DVH parameter | Simple DVH parameter addition |
|---|---|---|---|
| HR-CTV D90 | Case 1 | 76.4 | 79.0 |
| | Case 2 | 84.3 | 82.9 |
| | Case 3 | 79.4 | 82.5 |
| | Case 4 | 82.1 | 85.6 |
| | Case 5 | 84.9 | 85.5 |
| | Mean ± SD | 81.4 ± 3.5 | 83.1 ± 2.7 p = 0.424 |
| Rectum D2cc | Case 1 | 67.8 | 72.2 |
| | Case 2 | 58.0 | 58.2 |
| | Case 3 | 57.9 | 62.1 |
| | Case 4 | 74.9 | 74.1 |
| | Case 5 | 69.7 | 69.4 |
| | Mean ± SD | 65.4± 8.3 | 67.2 ± 6.8 p = 0.719 |
| Bladder D2cc | Case 1 | 65.9 | 74.2 |
| | Case 2 | 85.2 | 91.4 |
| | Case 3 | 80.2 | 84.7 |
| | Case 4 | 104.2 | 102.9 |
| | Case 5 | 78.4 | 79.7 |
| | Mean ± SD | 83.6 ± 11.7 | 86.6 ± 11.1 p = 0.687 |

of HRCTV cannot be reduced by pre-imaging preparation. These positional and volumetric changes may have influenced the accuracy of image fusion in DIR. Consequently, the fusion uncertainty may have resulted in the lower D90 of HR-CTV in Cases 1, 3, 4, and 5, and the higher D2cc of the rectum and bladder in Case 4. These results suggest that DIR is limited in its capacity to evaluate cumulative DVH parameters for the HR-CTV, rectum, and the bladder. However, the differences in D90 for HR-CTV and D2cc for the rectum and bladder did not differ significantly between the two methods (Table 4), and dose distributions were illustrated fairly reasonably. Therefore, we surmise that assessment of the cumulative dose-volume relationships using DIR may provide beneficial information on radiotherapy for cervical cancer, despite its limitations. For example, when a midline block is inserted into the whole pelvic EBRT, it is difficult to estimate the cumulative dose-volume relationship for the target volumes and OARs by simple addition of DVH parameters. In this case, DIR may be the only way to illustrate cumulative dose distributions and calculate cumulative DVH parameters. Furthermore, DIR may also enable to estimate the dose contributions of brachytherapy to the parametrium or pelvic lymph node. Therefore, analysis of cumulative dose-volume relationships using DIR may provide more accurate information if intensity modulated radiotherapy for cervical cancer is performed.

## Conclusions

In conclusion, though there are some limitations in accuracy of DIR, DIR-based dose accumulation may be useful method for assessing cumulative dose-volume relationship in the combined radiotherapy for cervical cancer, especially when assessing dose of the combination of midline block EBRT and brachytherapy.

### Abbreviations

EBRT: External beam radiotherapy; ICBT: Intracavitary brachytherapy; DIR: Deformable image registration; CT: Computed tomography; HR-CTV: High-risk clinical target volume; DSC: Dice similarity index; EQD2: Equivalent dose in 2 Gy per fraction; MRI: Magnetic resonance imaging; OAR: Organ at risk; DVH: Dose-volume histogram.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

TA made substantial contributions to conception, design, acquisition of data, drafting and revising of the manuscript. TT, SM, TE, RH, KM, YK, NS and SK planned the treatments and contributed to the final draft of the manuscript. TO analyzed the data and contributed to the manuscript. All authors read and approved the final manuscript.

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