Int J Clin Oncol (2004) 9:491–497
DOI 10.1007/s10147-004-0433-1


ORIGINAL ARTICLE

**Minoru Suzuki · Kiyoshi Nakamatsu · Shuichi Kanamori**
**Kaoru Okajima · Masahiko Okumura**
**Yasumasa Nishimura**

# Comparison of outcomes between overlapping structure-based and non-overlapping structure-based optimization for simultaneous integrated boost IMRT for malignant gliomas

Received: September 22, 2003 / Accepted: June 28, 2004

**Abstract**
***Background.*** Intensity-modulated radiotherapy (IMRT) can deliver different doses to two target volumes with high conformity. The purpose of the present study was to compare outcomes provided by two different optimization methods, overlapping structure-based and non-overlapping structure-based methods, for simultaneous integrated boost (SIB)-IMRT for malignant gliomas.
***Methods.*** Treatment plans for three glioblastomas and one anaplastic astrocytoma were analyzed in the present study. The planning protocol was to deliver 70 Gy/28 fractions (fr) to the gross tumor volume (GTV) and 56 Gy/28 fr to the surrounding edema. Two different optimization methods were tested for optimizing dose distribution to the GTV and the surrounding edema. One method was the "including method", an overlapping structure-based (GTV and the clinical target volume [CTV]) optimization method. The other method was the "annulus method", a non-overlapping structure-based (GTV and the subtracted volume) optimization method. Dosimetric indexes derived from dose-volume histograms (DVHs) were used for the analysis.
***Results.*** There was no significant difference between the two methods in the mean doses of the target volumes and the doses delivered to the 5% or 95% target volumes ($D_{05}$ or $D_{95}$). The mean dose to the brain by the including method was significantly higher than that delivered by the annulus method ($P = 0.0001$). The $D_{05}$ of the brain showed no significant difference between the two methods.
***Conclusion.*** The two optimization methods provided comparable dose distributions within the target volumes and normal brain.

**Key words** Intensity-modulated radiotherapy · Simultaneous integrated boost · Malignant glioma · Inverse planning

## Introduction

Intensity-modulated radiotherapy (IMRT) has spread as a new radiotherapy technique for treating cancers at many sites; that is, head and neck cancers, prostate cancers, and gynecologic malignancies.[1–7] IMRT can deliver a conformal irradiation dose to the primary target, sparing organs at risk (OARs), including the spinal cord, lens, and parotid glands.[8,9] A simultaneous integrated boost (SIB) method, using the IMRT technique (SIB-IMRT), has been applied to accelerated fractionation therapy for head and neck cancers.[1–4] This fractionated schedule delivers a large fraction (2.12–2.4 Gy) to the gross tumor volume (GTV) while delivering a conventional fraction (1.8–2.0 Gy) to the clinical target volume (CTV) for lymph node areas for elective irradiation.

We started a pilot study for treating malignant gliomas with the SIB-IMRT in December 2000.[10] Our strategy is to treat the GTV and the surrounding edema with different fractions. In our protocol, the prescribed dose to the GTV and the surrounding edema is 70 Gy/28 fr (daily, 2.5 Gy) and 56 Gy/28 fr (daily, 2.0 Gy), respectively. SIB-IMRT has two advantages for the treatment of malignant gliomas. The first is that SIB-IMRT can shorten overall treatment time (OTT), which is preferable for treating tumors with rapid repopulation.[11,12] The second is that the dose gradient

M. Suzuki[1] (✉) · K. Nakamatsu · S. Kanamori · Y. Nishimura
Department of Radiology, Kinki University School of Medicine, Osaka, Japan

K. Okajima
Department of Radiology, Nara Hospital, Kinki University School of Medicine, Nara, Japan

M. Okumura
Department of Central Radiological Service, Kinki University School of Medicine, Osaka, Japan

*Present address:*
[1] Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Noda, Kumatori-cho, Osaka 590-0494, Japan
Tel. +81-724-51-2407; Fax +81-724-51-2627
e-mail: msuzuki@rri.kyoto-u.ac.jp

between the GTV and the surrounding edema may improve tumor control without increasing the late toxicity of brain necrosis. Because the surrounding edema is normal brain tissue at risk by microscopic invasion by malignant glioma cells, a conventional fraction size is preferable for reducing the late toxicity of brain necrosis. On the other hand, a large fraction size was reported to be effective for treating malignant gliomas. Tamura et al.[13] reported that patients with glioblastoma treated with hypofractionation (40 Gy/8 fr) showed a slightly longer survival time than those treated with conventional fractionation (60 Gy/30 fr).

In head and neck cancers, the CTV for lymphatic nodes is usually apart from the primary lesion. Therefore, in the inverse planning of SIB-IMRT for head and neck cancers, the GTV and the CTV for lymphatic nodes can be defined as two separate target volumes. On the other hand, in malignant glioma, the CTV is derived from the GTV expansion. Because the CTV for malignant glioma should be regarded as the GTV plus 2- or 3-cm margins,[14,15] the volume at risk of microscopic invasion by tumor cells (the CTV minus the GTV) is large, and can be treated as a separate target volume. The purpose of the present study was to compare outcomes between overlapping structure-based (GTV and the CTV) and non-overlapping structure-based (GTV and the subtracted volume) optimization methods in inverse planning for the treatment of malignant gliomas with SIB-IMRT.

## Patients and methods

### Analyzed cases

The treatment plans of four patients with malignant gliomas were analyzed in the present study. Three patients had glioblastoma and one patient had anaplastic astrocytoma. Table 1 summarizes the histology and location of the tumor and the target volume in each patient. All the tumors were located more than 2 cm apart from the normal critical structures.

### Target definition

Following the International Commission on Radiation Units and Measurements (ICRU) 50 recommendations,[16] the GTV and the CTV were delineated on axial computed tomography (CT) images. The GTV was defined by contrast-enhanced tumors on T1-weighted magnetic resonance imaging (MRI) or contrast-enhanced CT (CE-CT). The CTV was defined as the GTV plus a 2.0-cm margin to include surrounding edema, delineated as a high-intensity area on T2-weighted MRI or low density on CE-CT. The margin was modified so that it could be expanded to include the edema beyond 2 cm from the GTV and it could be shrunken to the anatomical defense, intracerebral fissure, or tentorium cerebelli, within 2 cm. The CTV-annulus (CTV-A) was defined as the volume outside the GTV, obtained by subtracting the GTV from the CTV (CTV minus the GTV). Figure 1 schematically shows each target volume defined by the two methods. In the present study, three planning target volumes (PTV), PTV-G, PTV-A and PTV-C, were defined. The PTV-G was the volume to which a 0.5-cm margin was added to the GTV. The PTV-C was the volume to which a 0.5-cm margin was added to the CTV. The PTV-A was the volume obtained by subtracting the PTV-G from the PTV-C. All the contours of the target volumes were delineated manually.

### IMRT planning

A commercial treatment-planning system, Cadplan Helios ver.6.01 (Varian Associates Palo Alto, CA, USA) was used in the present study. On the basis of the experience of treatment of malignant gliomas with SIB-IMRT at Kinki University, the IMRT beam arrangements consisted of five coplanar beams.[10] Five beams were equally spaced at 72° intervals at the following gantry angles: 20°, 92°, 164°, 236°, and 308°. The IMRT plans assumed that the treatments were to be done with a Clinac-600C accelerator (Varian Associates) equipped with 80 leaves, 40 per side, and a dynamic multileaf collimator. Beam energy of 4-MV X-rays was used.

In the inverse planning for optimizing the dose distribution to the PTV-G and the PTV-A, two different optimization methods were tested. One was the "including method", which uses overlapping volumes, the PTV-G and the PTV-C (the PTV-C includes the PTV-G), as the volumes for the optimization. The other method, the "annulus method", uses continuous target volumes, the PTV-G and the PTV-A (the PTV-A surrounds the PTV-G), as the volumes for the optimization.

In the present study, the prescribed doses to the PTV-G and the PTV-A were 70 Gy in 28 fractions (fr) and 56 Gy in

**Table 1.** Summary of the analyzed cases

| Case no. | Histology | Site of tumor | Volumme ($cm^3$) | | |
|---|---|---|---|---|---|
| | | | GTV | CTV | CTV-annulus |
| 1. | GBM | Right parietal | 63.4 | 261.6 | 172.2 |
| 2. | GBM | Right parietal | 55.4 | 205.8 | 139.2 |
| 3. | AA | Left temporal | 188 | 553 | 338.8 |
| 4. | GBM | Right parietal | 43.1 | 286.2 | 235.1 |

GTV, gross tumor volume; CTV, clinical target volume; GBM, glioblastoma; AA, anaplastic astrocytoma

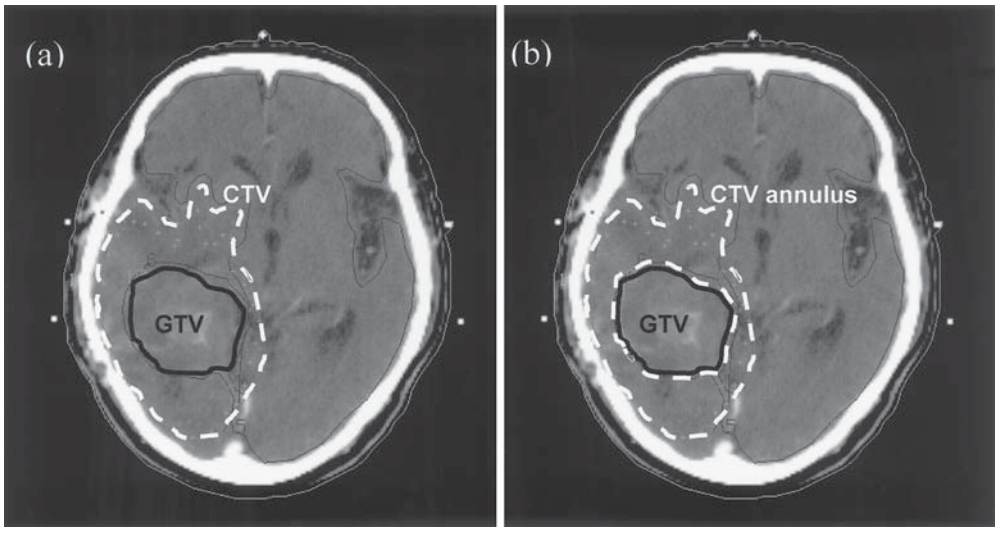


**Fig. 1a,b.** Target contouring by the including method (**a**) and the annulus method (**b**). Planning target volume (PTV)-G and PTV-C are delineated by *black solid* and *white dashed lines*, respectively. PTV-C includes PTV-G. The PTV-A is delineated with a *white dotted line*. PTV-A surrounds PTV-G. *GTV*, gross tumor volume; *CTV*, clinical target volume

28 fr, respectively. All treatment plans were normalized to deliver 70 Gy to 95% volume of the PTV-G. The following criteria were determined as the planning goals in the present study. The first was that the dose to 95% volume ($D_{95}$) of the PTV-A was greater than 56 Gy. The second was that the dose to 5% volume ($D_{05}$) of the PTV-G was 77 Gy, i.e., 110% of the prescribed dose to the PTV-G. The third was that the $D_{05}$ of the PTV-A was less than the prescribed dose to the PTV-G (70 Gy).

We fixed a set of user-defined parameters, which included the parameters for maximum and minimum doses for the PTV-G, the parameters for minimum doses for the PTV-A and the PTV-C, dose-volume parameters for the OARs, and penalties for the targets and the OARs. The parameters for maximum and minimum doses for the PTV-G were 71.4 Gy and 68.6 Gy (±2% of the prescribed dose to the PTV-G), respectively. The parameters for minimum doses for the PTV-A and the PTV-C were both 53.2 Gy (95% of the prescribed dose to the PTV-A).

Because the parameters for maximum doses for the PTV-A and the PTV-C were difficult to determine, the calculation for the treatment plan was run by changing the parameters for maximum doses of the PTV-A and the PTV-C at 2% increments, from 80% to 110% of the prescribed dose to the PTV-G (56 Gy–77 Gy). The parameters for appropriate maximum doses for the PTV-A and the PTV-C were determined from the calculated treatment plans to accomplish the planning goals. Table 2 shows the parameters for the targets and the OARs used in the present study.

**Table 2.** Parameters and penalties for targets and organs at risk

| | Dose parameters and penalties | |
|---|---|---|
| | Max (Gy)/Pen | Min (Gy)/Pen |
| Targets | | |
| PTV-G | 71.4/100 | 68.6/100 |
| PTV-A | 63.0–65.8/100 | 53.2/100 |
| PTV-C | 56.0–72.8/100 | 53.2/100 |
| OARs | | |
| Brain[a] | Max 54/80<br>$V_{33}$ 45/80<br>$V_{66}$ 40/80 | ND |
| Brain stem[a] | Max 54/80<br>$V_{33}$ 42/80<br>$V_{66}$ 38/80 | ND |
| Eye (retina) | 40/90 | ND |
| Optic nerve | | |
| Lens | 6/90 | ND |
| Pituitary gland | 30/90 | ND |

Max, maximum; min, minimum; pen, penalty; PTV, planning target volume; OARs, organs at risk; $V_{33}$, 33% of volume; $V_{66}$, 66% of volume; ND, not defined

[a] Dose-volume parameters were set for brain and brain stem

### Comparison of dose-volume analysis of treatment plans by two methods

For a comparison of the two methods, we evaluated the mean dose, $D_{05}$, and $D_{95}$ of the PTV-G and the PTV-A, and the difference between $D_{05}$ and $D_{95}$ for the PTV-G and the PTV-A. The $D_{05}$ was representative of the maximal target dose. The difference between $D_{05}$ and $D_{95}$ was considered to reflect the degree of dose homogeneity within the target. The mean dose and $D_{05}$ for normal brain were recorded. The mean doses and the differences between $D_{05}$ and $D_{95}$ for the PTV-G and the PTV-A by the two methods were compared by paired *t*-test. The mean dose and $D_{05}$ for normal brain by the two methods were also assessed with the paired *t*-test.

## Results

Figures 2–5 show the dose-volume histograms (DVHs) for the target volumes and normal brain in all patients. Table 3

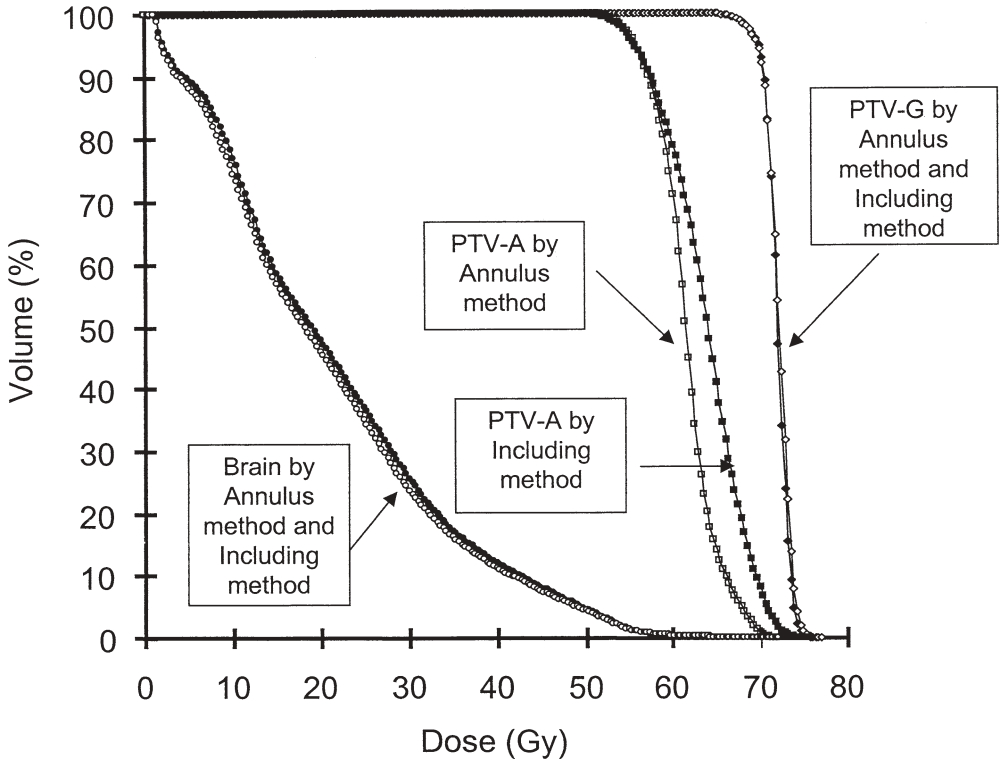


**Fig. 2.** Comparison of dose-volume histograms (DVHs) in case 1

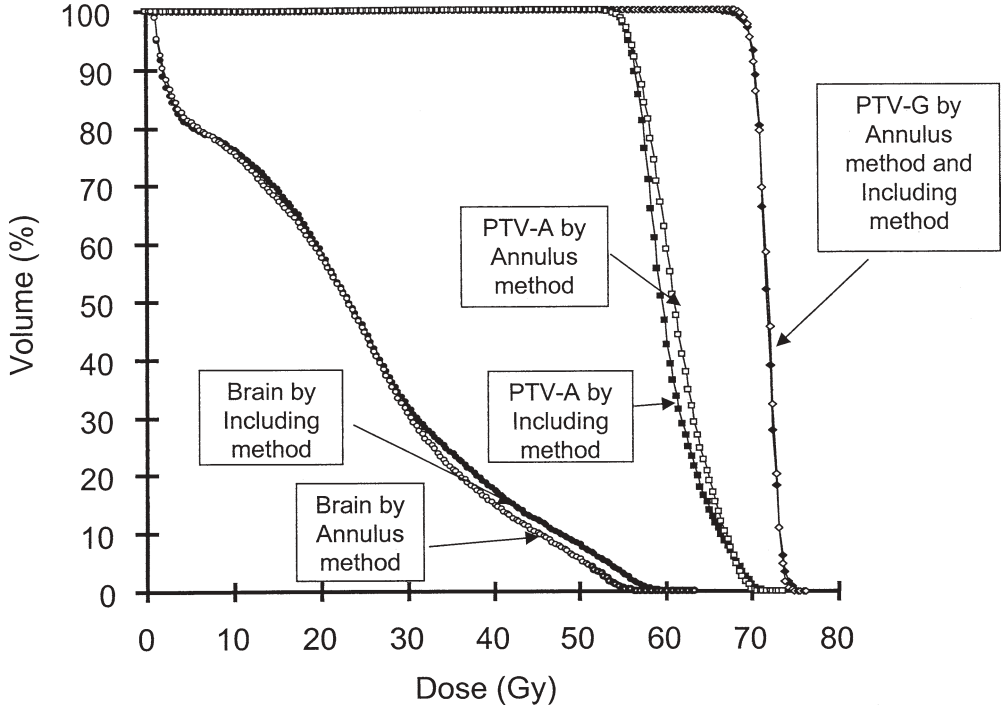


**Fig. 3.** Comparison of DVHs in case 2

summarizes various indexes for DVH analyses of all plans. There was no significant difference between the two methods in the mean doses ($P = 0.356$ and $P = 0.682$) or in the differences between the $D_{05}$ and $D_{95}$ ($P = 0.391$ and $P = 0.199$) of the PTV-G and the PTV-A. In case 1 (Fig. 2), the annulus method provided more homogeneous dose distribution than the including method. In all cases, the values of differences between the $D_{05}$ of the PTV-A by the including method were larger than those by the annulus method, although no significant difference was shown ($P = 0.199$). The mean dose to the brain delivered by the including method was significantly higher than that by the annulus method ($P = 0.0001$). The $D_{05}$ of the brain showed no significant difference between the two methods.

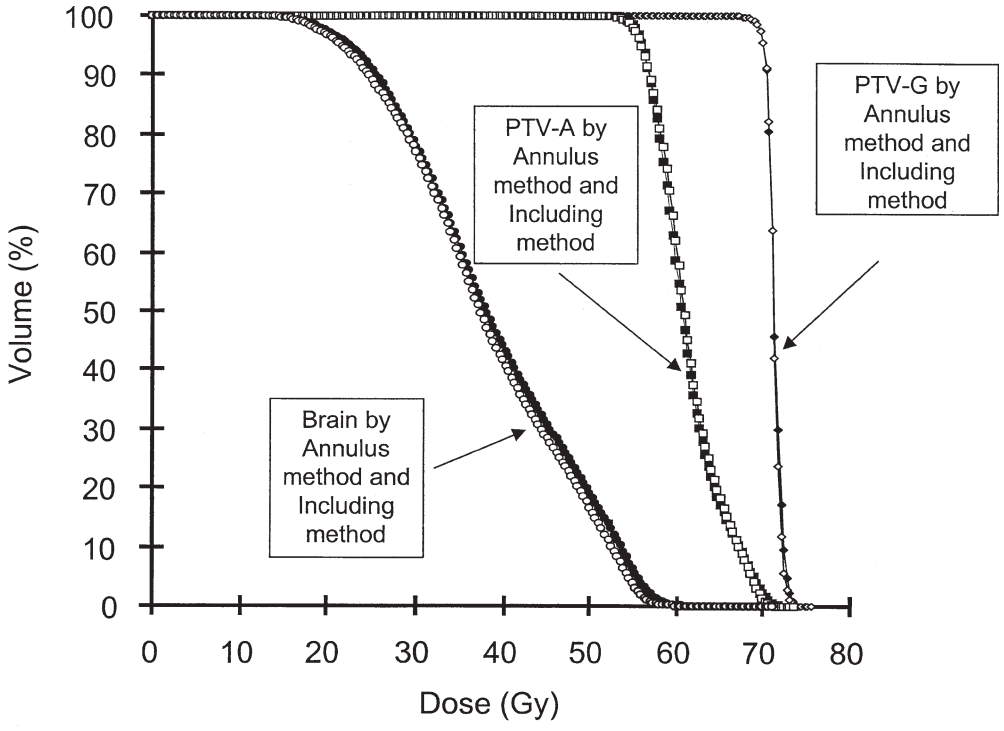


**Fig. 4.** Comparison of DVHs in case 3

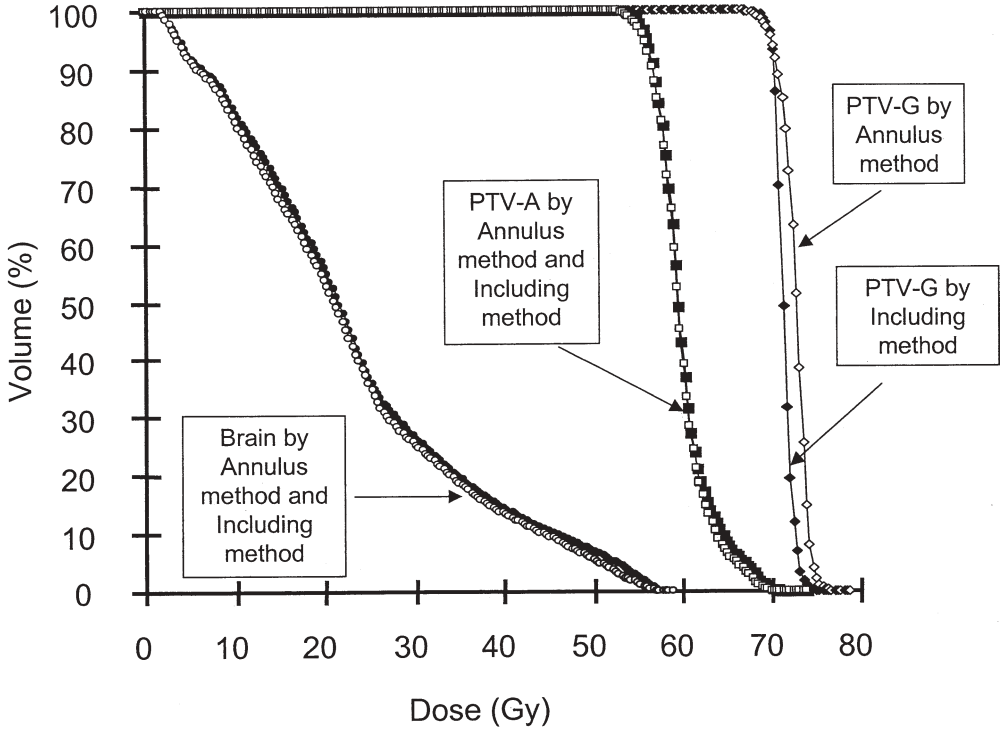


**Fig. 5.** Comparison of DVHs in case 4

## Discussion

SIB-IMRT has recently received attention as a new method for accelerated fractionation therapy. Several researchers have reported that SIB-IMRT is superior to three-dimensional (3D) conformal radiotherapy or two–phase IMRT (sequential-IMRT) in terms of conformity of dose distribution within the target volume and the sparing normal tissues. Mohan et al.[17] reported that the dose distributions provided by SIB-IMRT for head and neck cancers were more conformal than those with sequential-IMRT, and the doses to normal tissues were lower than those with sequential-IMRT. Dogan et al.[18] reported that SIB-IMRT for head and neck, lung, and prostate cancers could markedly reduce the doses to critical structures compared

**Table 3.** Dose-volume histogram analysis of the annulus method and including method

| Annulus method | | | | | | Including method | | | |
|---|---|---|---|---|---|---|---|---|---|
| Structure | Case no. | $D_{95}$ (Gy) | Mean (Gy) | $D_{05}$ (Gy) | $D_{05}$–$D_{95}$ (Gy) | $D_{95}$ (Gy) | Mean (Gy) | $D_{05}$ (Gy) | $D_{05}$–$D_{95}$ (Gy) |
| PTV-G | 1. | 70.0[a] | 72.0 | 74.0 | 4.0 | 70.0[a] | 71.8 | 74.0 | 4.0 |
| | 2. | 70.0[a] | 71.7 | 73.6 | 3.6 | 70.0[a] | 71.7 | 73.6 | 3.6 |
| | 3. | 70.0[a] | 71.1 | 72.6 | 2.6 | 70.0[a] | 71.2 | 72.8 | 2.8 |
| | 4. | 70.0[a] | 72.5 | 74.6 | 4.6 | 70.0[a] | 71.3 | 73.0 | 3.0 |
| PTV-A | 1. | 56.1 | 61.5 | 68.0 | 11.9 | 56.0 | 63.7 | 70.8 | 14.8 |
| | 2. | 56.1 | 61.3 | 68.2 | 12.1 | 56.0 | 60.4 | 68.2 | 12.2 |
| | 3. | 56.0 | 61.2 | 68.6 | 12.6 | 56.1 | 61.1 | 69.0 | 12.9 |
| | 4. | 56.0 | 59.8 | 66.0 | 10.0 | 56.1 | 59.8 | 67.0 | 10.9 |
| Brain | 1. | NA | 20.6 | 70.9 | NA | NA | 21.3 | 70.5 | NA |
| | 2. | NA | 22.9 | 59.0 | NA | NA | 23.7 | 62.0 | NA |
| | 3. | NA | 38.0 | 69.3 | NA | NA | 38.8 | 67.9 | NA |
| | 4. | NA | 22.6 | 57.8 | NA | NA | 23.3 | 58.5 | NA |

PTV, planning target volume; $D_{05}$, dose to 5% of volume; $D_{95}$, dose to 95% of volume; NA, not assessed
[a] The $D_{95}$ dose to the PTV-G is normalized to 70.0 Gy

with sequential-IMRT. In malignant glioma, Thilmann et al.[19] demonstrated that SIB-IMRT had some advantage over 3D conformal radiotherapy with regard to homogeneity of the CTV-A and reduction of the dose to the normal brain. Chan et al.[20] reported that SIB-IMRT could deliver a higher central tumor dose (~70 Gy to the GTV), while providing increased sparing of the uninvolved brain compared with 3D conformal radiotherapy. These dosimetric studies suggest that SIB-IMRT is appropriate for the treatment of malignancies at many sites, such as lung, prostate, or gynecologic cancers or brain tumors. Clinically, Floyd et al.[21] reported the results of a clinical trial for the treatment of malignant glioma with SIB-IMRT. Their treatment strategy was to deliver a total of 30 Gy, in 3-Gy fractions to the edema, with the simultaneous delivery of 50 Gy, in 5-Gy fractions, to the enhancing primary tumor. We started a pilot study for treating malignant gliomas, using SIB-IMRT, in December 2000,[10] and the dose-escalating phase I study is ongoing.

In the present study, the mean dose to the brain by the annulus method was significantly lower than that delivered by the including method, although the differences were meaningless from the clinical point of view. In case 1, the dose distribution within the PTV-A delivered by the annulus method was more homogeneous than that delivered by the including method, as shown in Fig. 2. Although the present study revealed that the two methods provided comparable dose distribution in the target volumes and normal brain, there is a possibility that one method provided more favorable dose distribution than the other one. Therefore, if one method cannot achieve the treatment goals, the other should be tried to obtain more suitable outcomes.

Theoretically (mathematically), the annuls method is better than the including method, but, in terms of achieving the goals set in the present study, the results for the two methods were comparable. However, if more difficult goals are set, such as 90 Gy to the PTV-G and 60 Gy to the PTV-A, the conclusion could be different. We would like to stress that whether the including method can achieve a result comparable to that for the annulus method would need to be determined case by case, and the results will differ from site to site and depending on the goals.

**Acknowledgments** This work was supported in part by a Grant-in-Aid for Scientific Research (14570887) from the Ministry of Education, Science, and Culture, of Japan. Portions of these data were presented at the 88th Scientific Meeting of the RSNA, December 1 to 6, 2002.

## References

1. Butler EB, Teh BS, Grant WH, et al. (1999) Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 45:21–32
2. Lee N, Xia P, Quivey JM, et al. (2002) Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12–22
3. Chao KS, Wippold FJ, Ozyigit G, et al. (2002) Determination and delineation of nodal target volumes for head and neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. Int J Radiat Oncol Biol Phys 53:1174–1184
4. Lee N, Xia P, Fischbein NJ, et al. (2003) Intensity-modulated radiation therapy for head-and neck cancer: the UCSF experience focusing on target volume delineation. Int J Radiat Oncol Biol Phys 57:49–60
5. Zelefsky MJ, Fuks Z, Hunt M, et al. (2002) High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 53:1111–1116
6. Mundt AJ, Lujan AE, Rotmensch J, et al. (2002) Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 52:1330–1337
7. Schefter TE, Kavanagh BD, Wu Q, et al. (2002) Technical considerations in the application of intensity-modulated radiotherapy as a concomitant integrated boost for locally advanced cervix cancer. Med Dosim 27:177–184
8. Hunt M, Hsiung C, Spirou S, et al. (2002) Evaluation of concave dose distributions created using an inverse planning system. Int J Radiat Oncol Biol Phys 54:953–962
9. Vineberg KA, Eisbruch A, Coselmon MM, et al. (2002) Is uniform target dose possible in IMRT plans in the head and neck? Int J Radiat Oncol Biol Phys 52:1159–1172
10. Suzuki M, Nakamatsu K, Kanamori S, et al. (2003) Feasibility study of the simultaneous integrated boost (SIB) method for malignant gliomas using intensity modulated radiotherapy (IMRT). Jpn J Clin Oncol 33:271–277

11. Withers HR, Taylor JMG, Macejewski B (1988) The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27:131–146
12. Ang KK, Peters LJ, Weber R (1990) Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int J Radiat Oncol Biol Phys 19:1339–1345
13. Tamura M, Nakamura M, Kunimae H, et al. (1989) Large dose fraction radiotherapy in the treatment of glioblastoma. J Neuro-Oncol 7:113–119
14. Lee SW, Fraass BA, Marsh LH, et al. (1999) Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas; a quantitative dosimetric study. Int J Radiat Oncol Biol Phys 43:79–88
15. Nakagawa K, Aoki Y, Fujimaki T, et al. (1998) High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiform. Int J Radiat Oncol Biol Phys 40:1141–1149
16. International Commission on Radiation Units and Measurements (ICRU) (1993) Report number 50: prescribing, recording and reporting photon beam therapy. ICRU, Washington, DC
17. Mohan R, Wu Q, Manning M, et al. (2000) Radiobiological considerations in the design of fractionation strategies for intensity-modulated radiation therapy of head and neck cancers. Int J Radiat Oncol Biol Phys 46:619–630
18. Dogan N, King S, Emami B, et al. (2003) Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. Int J Radiat Oncol Biol Phys 57:1480–1491
19. Thilmann C, Zabel A, Grosser KH, et al. (2001) Intensity-modulated radiotherapy with an integrated boost to the macroscopic tumor volume in the treatment of high-grade gliomas. Int J Cancer 96:341–349
20. Chan MF, Schupak K, Burman C, et al. (2003) Comparison of intensity-modulated radiotherapy with three-dimensional conformal radiation therapy planning for glioblastoma multiform. Med Dosim 28:261–265
21. Floyd NS, Woo SY, The BS, et al. (2004) Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiform. Int J Radiat Biol Oncol Phys 58:721–726