INTRODUCTION

Conventional magnetic resonance (MR) imaging [e.g., contrast-enhanced T1-weighted (CE-T1) imaging with gadolinium and fluid attenuated inversion recovery imaging)] has been recommended for reliable delineation of intracranial tumors (1, 2). However, because high-grade gliomas often diffusely infiltrate surrounding normal brain tissues, morphology-based target delineation using conventional MR imaging and computed tomography (CT) can miss lesions that should be included in the treatment volumes (3-5). Enlarging clinical target volumes (CTVs) to encompass suspicious regions which are not visible on CT and CE-T1 images of high-grade gliomas can hinder dose optimization for local high-risk regions. Moreover, image-based target definition including the tumor bed is even more critical for residual tumors after incomplete surgical resection to ensure coverage of the neoplastic regions and prevent recurrence (6). Thus, various attempts have been made to improve the radiation treatment outcome of high-grade gliomas by integrating multi-modal imaging, beam intensity-modulated techniques, and other adjuvant therapies (7-10).

However, high-grade gliomas showed poor survival rates and frequent recurrence, even within the pre-irradiated gross tumor volume (GTV) receiving higher doses than marginal tumors (10). It CTV delineation considering physiological and histopathological characteristics of the tumor and dose optimization to high-risk regions that may be positively applied to create more effective treatment plans (11). One of the characteristics for high-grade gliomas is increase cellularity during tumor progression (12). Apparent diffusion coefficient (ADC) maps reconstructed from diffusion-weighted (DW) MR images can describe histopathological information...
about cellularity in high-grade gliomas (2), by providing a quan-
titative index of restricted water diffusion in intracellular spaces
relative to extracellular spaces (13). Enhanced regions of malig-
nant gliomas with compact cellularity on ADC maps (aCTVHR)
can be used to define high-risk CTV (14-16) and doses were
optimized to the aCTVHR.

In this study, we defined aCTVHR on the ADC maps by mak-
ing reference to the reported quantitative ADC criteria which
indicates malignancy level of high-grade gliomas. The benefits
of aCTVHR-targeted dose optimization were assessed in dose
distributions of an intensity-modulated radiation therapy (IMRT)
plan based on ADC values (IMRTADC) as compared with a con-
ventional IMRT (IMRTconventional) plan.

MATERIALS AND METHODS

Image acquisition
A patient was diagnosed with a high-grade glioma (grade III) in
the right anterior temporal lobe and basal ganglia of the brain.
After surgical resection of the tumor, ADC images of the cavity
showed a suspicious malignant lesion; therefore, adjuvant radia-
tion therapy was performed according to the National Com-
prehensive Cancer Network practice guidelines (17). To deter-
mine residual tumor volumes, we examined perfusion-weighted
MR spectroscopy, and DW images along with conventional
MR and CT images.

MR imaging and CT were performed using a 1.5-Tesla MR
unit (GE SIGNA system, GE Medical Systems, Milwaukee, WI,
USA) and a GE 9800 Quick System CT scanner (GE Medical
Systems), respectively. CE-T1 imaging used gadolinium as the
counter agent and a spin echo T1-weighted sequence with a
TE of 75 ms and a TR of 8,000 ms. To obtain reliable signal-to-ratio and con-
sider clinically practical application of ADC maps, commonly
applied b-value of 1,000 s/mm2 was used (18).

Incorporation of ADCs into the radiation treatment plan
ADC values were used to verify the severity of the residual ma-
lignant lesion and to differentiate the aCTVHR from the tumor
bed. Average, maximum, and minimum ADC values and ADC
ratios (rADCs) were calculated using MATLAB (version 7.10.0.499,
MathWorks, Natick, MA, USA). To reduce variability in the se-
lection of the boundaries of tumor regions, ADC values were
evaluated in the compact rectangular volumes of interest (VOIs)
covering all apices of the suspected regions closely surrounding
hypo-intense voxels on ADC maps. Then, volumetric averaged
ADC values were evaluated within the expanded VOIs (VOIs
with at least a 2-cm margin on each side). Because high-grade
gliomas often contain cystic or necrotic regions, we averaged the
ADC values from 3-5 regions of interest (ROIs, 2-3 mm2 each) in
the expanded VOIs. The rADC is obtained from the ADC of the
aCTVHR divided by the ADC of the volume in contralateral nor-
mal brain tissues.

The aCTVHR showing a lower ADC value than the averaged
ADC value was extracted via computational analysis and image
processing of ADC maps. The extracted aCTVHR was re-marked
on the ADC maps (pixel intensity equal to the maximum pixel
intensity of the original ADC map). The ADC values were also
confirmed by comparing with those reported for high-grade
gliomas in diagnostic studies.

Because quantitative analysis of ADC maps and extraction of
aCTVHR by applying the ADC criteria were not possible in com-
mercial planning system (Eclipse, version 7.3.1, Varian Medical
Systems, Palo Alto, CA, USA), two kinds of CT images were im-
ported into Eclipse: the original CT images and another CT im-
ages including the aCTVHR and the CE-T1 image-based CTV
(tCTV). To obtain the contours of the aCTVHR and tCTV on CT
images using more reliable image registration functions, two
sets of images (ADC map vs. CE-T1, CE-T1 vs. CT) were regis-
tered using BrainSCAN (version 5.31, BrainLab, Munich, Heim-
stetten, Germany). The overall procedure used to incorporate the
determined aCTVHR into radiation treatment plans is shown
in Fig. 1.

We also referred to the converted DW ratio to confirm vol-
umes with low diffusion levels on DW-MR images. The DW-ra-
tio maps were obtained by normalizing the original DW images
to the average diffusion intensity of corresponding contralateral
normal brain tissues.

Treatment plans
To evaluate dose distribution in the IMRTADC plan, the following
tumor volumes were contoured on each CT image: CE-T1-based
GTV (gCTV), ADC-based CTV (aCTVHR), and relative comple-
ment volume of aCTVHR in tCTV (sCTV) (Fig. 2). The tCTV is
gCTV plus a 2.0-cm margin (1.5 cm for microscopic spread and
0.5 cm for set-up uncertainty). The CTV margin adjacent to criti-
cal structures, such as the right optic nerve, optic chiasm, and
pituitary gland, was compromised to spare organs at risk (OARs).

The IMRTADC plan was optimized to deliver 60 Gy to the aCTVHR
via the simultaneous integrated boost (SIB) technique (2,
17, 19). Because the ADC maps indicated the differentiated
aCTVHR from the residual tumor, the tumor bed needed to re-
ceive the required dose of 50 Gy (16). However, because the
IMRTconventional plan was based only on conventional CE-T1 images,
which showed the tumor bed but not CTVHR at the specific posi-
tion, the tCTV received 60 Gy. The other plan parameters were
equally applied to both plans, and they are summarized in Ta-
table 1. To provide a conformal dose to CTVs, 5 coplanar fields
with different gantry angles (70°, 130°, 250°, 270°, and 310°) and
Evaluation of dose distributions

Dose distributions in the two plans were evaluated using biophysical indices for plan comparison and dose volume histograms (DVHs) for the aCTV_{HR} and the tCTV. The homogeneity and conformity of dose distributions in the CTV were analyzed using the statistically modified homogeneity index (s-index) and the conformity number (CN), respectively (20, 21). The s-index and CN were evaluated using the prescribed doses (59.4 Gy for the aCTV_{HR} and 50.4 Gy for the tCTV). Dosimetric effects were evaluated on the basis of the equivalent uniform dose (EUD) of the two plans according to a linear quadratic model for the tumor (22, 23) and a power law for the OARs (24). Tumor control probability (TCP) based on Poisson statistics was compared for the aCTV_{HR} in both plans (25). In addition, the EUD-based figure-of-merit (f-EUD) was calculated for comprehensive plan evaluation using the EUD value of each primary structure (24). The weighting factors and the relative importance in f-EUD were assumed to be 1 in this study. Formulas and radiobiological parameters to evaluate dose distributions and calculate biophysical values are summarized in Appendix A and B (26-28).

2 non-coplanar fields (60°/60° and 300°/300° for gantry/couch angles, respectively) were used.
Ethics statement

This study protocol was approved by the institutional review board (IRB) of Konkuk University Medical Center (IRB No. KUH 1200065). Informed consent was waived by the board.

RESULTS

Clinical target volumes in multimodal images and apparent diffusion coefficients

Conventional CT images did not clearly distinguish between the high-risk CTV and normal brain tissues (Fig. 3A). The resection cavity was enhanced by the contrast medium in the CE-T1 images (Fig. 3B), but the histopathological characteristics of the high-risk CTV were not apparent. In contrast, the DW images and ADC maps could reveal residual high-risk CTV as enhanced and suppressed regions, respectively (Fig. 3C, D). In the converted color map of the DW image, the diffusion values for the high-risk CTV were more than two-fold higher than those for normal brain tissues. Higher intensity regions appear red or orange in Fig. 3E.

The average ADC of the high-risk CTV was $(0.73 \pm 0.23) \times 10^{-3} \text{mm}^2/\text{s}$, and the average rADC was $(0.67 \pm 0.32) \times 10^{-3} \text{mm}^2/\text{s}$; both were less than $1 \times 10^{-3} \text{mm}^2/\text{s}$. The minimum ADC of the high-risk CTV was $0.37 \times 10^{-3} \text{mm}^2/\text{s}$, which is lower than the ADCs reported in medical diagnostic studies of high-grade gliomas $[(0.86 \pm 0.12) \times 10^{-3} \text{mm}^2/\text{s}$ and $(0.82 \pm 0.13) \times 10^{-3} \text{mm}^2/\text{s}$ for average ADC and rADC, respectively] (15, 29). The volumes with values lower than the average ADCs were defined as $aCTV_{HR}$ (Fig. 3F).

Plan evaluation

Dose distributions in two IMRT plans were evaluated using DVHs and various dosimetric metrics. The IMRT$_{ADC}$ plan, which focused on dose optimization for the $aCTV_{HR}$, produced a well-confined conformal dose distribution around the $aCTV_{HR}$ within the prescribed 60-Gy isodose surface (fluorescent green in Fig. 4A). Because dose conformity is mainly affected by the size of the total volume which received dose more than prescribed value ($V_{85}$) (area surrounded by fluorescent green line in Fig. 4B), the $aCTV_{HR}$-targeted dose distribution resulted in less irr-
MRI-assisted RT Planning for Target Volumes at High Risk

The IMRT<sub>ADC</sub> plan improved the dose conformity of the aCTV<sub>HR</sub> up to 15 times, compared to the IMRT<sub>conv</sub> plan (Table 2). In addition, the IMRT<sub>ADC</sub> plan showed superior dose uniformity of the aCTV<sub>HR</sub> by 7%, as indicated by a lower s-index in this plan compared with that of the IMRT<sub>conv</sub> plan.

Although the IMRT<sub>ADC</sub> plan slightly increased the EUD (61.42 Gy vs. 60.00 Gy in the IMRT<sub>ADC</sub> and IMRT<sub>conv</sub> plans, respectively) and the TCP (26.67 % vs. 24.01%, respectively), the differential DVHs of the aCTV<sub>HR</sub> were comparable in both plans (Fig. 5A).

The DVHs showed greater dose sparing of OARs in the IMRT<sub>ADC</sub> plan (Fig. 5B), owing to differences in dose optimization with and without focusing on the aCTV<sub>HR</sub>. The tailored dose delivery in the IMRT<sub>ADC</sub> plan reduced EUDs by up to 16% in the brain stem and right lens (Table 3) and by more than 10% in the right

| Plan          | EUD [Gy] | Lt. Optic nerve | Rt. Optic nerve | Lt. Chiasm | Rt. Chiasm | Lt. Brain stem | Rt. Brain stem | Lt. Pituitary gland | Rt. Pituitary gland | EUD* |
|---------------|----------|-----------------|-----------------|------------|------------|----------------|-----------------|---------------------|---------------------|-------|
| IMRT<sub>ADC</sub> | 1.09    | 3.40            | 17.87           | 36.09      | 35.56      | 35.95          | 17.97           | 36.09               | 35.56               | 30.17 | 0.14 |
| IMRT<sub>conv</sub> | 1.21    | 3.91            | 18.60           | 41.19      | 39.12      | 41.62          | 34.99           | 39.12               | 41.19               | 34.99 | 0.12 |

*EUD, EUD-based figure-of-merit to evaluate plan quality using EUDs for structures of interest.

Fig. 4. Comparison of the dose distributions in the IMRT<sub>conv</sub> plan and IMRT<sub>ADC</sub> plan. (A) Dose distribution in the IMRT<sub>ADC</sub> plan. Prescribed doses of 59.4 Gy and 50.4 Gy were optimized to the aCTV<sub>HR</sub> and relative complement volume of aCTV<sub>HR</sub> in tCTV (sCTV), respectively, using the simultaneous integrated boost technique. (B) Dose distribution in the IMRT<sub>conv</sub> plan. A dose of 59.4 Gy was prescribed to the tCTV.

Fig. 5. Comparison of the dose volume histograms (DVHs) in the IMRT<sub>conv</sub> and the IMRT<sub>ADC</sub> plans. (A) Differential DVHs for the residual clinical target volumes at high risk on the ADC maps. Horizontal axis: doses normalized to the prescribed dose (59.4 Gy). (B) Cumulative DVHs for organs at risk.

Table 2. Evaluation of dose distributions using homogeneity (s-index) and conformity indices (conformity number) for the target volumes, aCTV<sub>HR</sub> showing malignancy of high-grade gliomas on ADC maps and tCTV defined on CE-T1 images

| Volume | IMRT<sub>ADC</sub><sup>*</sup> | IMRT<sub>conv</sub><sup>†</sup> |
|--------|-------------------------------|-------------------------------|
| Homogeneity (s-index) | aCTV<sub>HR</sub> | 1.49 | 1.60 |
| tCTV<sup>‡</sup> | 3.26 | 10.48 |
| Conformity (CN) | aCTV<sub>HR</sub> | 0.48 | 0.352 |
| tCTV<sup>§</sup> | 0.94 | 0.71 |

*IMRT<sub>ADC</sub>, intensity-modulated radiation therapy (IMRT) plan optimized to aCTV<sub>HR</sub> and tCTV using simultaneous integrated boost; †IMRT<sub>conv</sub>, conventional IMRT plan using CE-T1 images for tCTV; ‡aCTV<sub>HR</sub>, clinical target volume at high risk defined on the ADC maps; §tCTV, expanded tGTV (gross tumor volume on CE-T1 images) with a 2-cm margin.
Combining DW images and ADC maps with conventional CT and CE-T1 images can bring advantages in cancer diagnosis and therapy. In some cases, especially those involving high-grade gliomas with a rim that is not enhanced by contrast agents on CE-T1 images, DW images and ADC maps can help delineate CTVs by detecting pathologically relevant tumor characteristics not seen on conventional morphological images (5). As the large CTV is located close to critical organs, determination of image-based anisotropic target margin becomes more important for reducing toxicity in normal tissues. When we adopt DW images into radiotherapy plans for such as determination of target margins and high-risk CTV mentioned above, more rigorous image analysis and multimodality image-based confirmation of target volumes can support reliable application of advanced functional MR images.

Moreover, because DW images can show physiological and pathological variations of tumor to evaluate treatment responses through rapid and noninvasive scanning (30), those can be considered as an appropriate and powerful tool for adaptive radiation treatment plans. Patients can be monitored without additional radiation exposure during fractionated radiation treatment.

As application of extra-cranial DW images for patients with breast, prostate, and liver cancers (31) and the advent of a LINAC hybrid machine gradually become widespread, the role of DW images or ADC maps to define CTV becomes more important (32). Image-based dose optimization, especially targeting to the high-risk CTV, may facilitate effective and delicate dose delivery using dose painting techniques (33).

In conclusion, the aCTV<sub>HR</sub> was determined via quantitative analysis of ADC maps of a residual high-grade glioma. The IMRT<sub>ADC</sub> plan in combination with DW images and ADC maps showed optimized dose distribution to the aCTV<sub>HR</sub> with dense cellularity. Incorporating ADC maps into radiation treatment plans for high-grade gliomas may help achieve biophysical dose optimization in local high-risk tumor volumes.

DISCUSSION

The authors have no conflicts of interest to disclose.

AUTHORS CONTRIBUTION

Conception and design of the study: Lee JW, Ahn KJ, Choe BY, Park JY. Coordination of the study: Hong S, Suh TS, Choe BY. Case selection, image acquisition and interpretation: Ahn KJ. Radiation treatment planning and analysis: Park JY, Lee JW, Park HJ, Hong S. Manuscript preparation: Park JY, Lee JW. Manuscript revision and editing: Suh TS, Lee JW, Ahn KJ, Choe BY, Hong S, Park HJ. Manuscript approval: all authors.

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APPENDIX A.

Dose homogeneity and conformity are evaluated with statistical model and conformity number, respectively, using following equations (1) and (2):

\[ s_{\text{index}} = \sqrt{\frac{\sum (D_i - D_p)^2}{V_T}} \times \frac{V_T}{V}, \quad (1) \]

\[ CN = \frac{V_{T,RI}}{V_T} \times \frac{V_{T,RI}}{V_{RI}}. \quad (2) \]

Equivalent uniform dose (EUD) for target volumes and organs at risk (OAR) are calculated using equations (3) and (4):

\[ \text{EUD}_{\text{target}} = \frac{1}{2} \beta \left[ -\alpha + \sqrt{\alpha^2 - 4\beta \ln \left( \sum_{i=1}^{N_c} e^{-a D_i - \beta D_i^2} \right)} \right], \quad (3) \]

\[ \text{EUD}_{\text{OAR}} = \left[ \sum_i (V_i D_i^a)^{\gamma \alpha} \right]^{1/\gamma}. \quad (4) \]

Tumor control probability (TCP) and EUD-based figure-of-merit (f-EUD) for principal structures are analyzed using equations, (5) and (6):

\[ \text{TCP} = \left( \frac{1}{2} \right)^{\sum_i \exp \left[ \frac{2\gamma a (D_i - D_p)}{\gamma^{1/2}} \right]}, \quad (5) \]

\[ f\text{-EUD} = 1 \left[ 1 + k \times \frac{\sum_{i=1}^{\alpha} \sum_{j=1}^{\alpha} \omega_i EUD_{OAR}^j}{\sum_{i=1}^{\alpha} \sum_{j=1}^{\alpha} \omega_i EUD_{\text{target}}^j} \right]. \quad (6) \]

The parameters used in the formula are described in the table below.

| Parameters          | Definition                                      |
|---------------------|-------------------------------------------------|
| \( D_i \)           | delivered dose to the \( i \)-th voxel          |
| \( V_i^a \)         | corresponding target volume of \( i \)-th voxel |
| \( D_p \)           | prescribed dose                                 |
| \( V_T \)           | total target volume                             |
| \( V_{RI} \)        | corresponding volume to the reference isodose   |
| \( V_{T,RI} \)      | target volume covered by the reference isodose  |
APPENDIX B.

Radiobiological parameters in the following table are used to estimate the equivalent uniform dose (EUD) and tumor control probability (TCP) for principal structures.

| Type          | Cancer cell/Organs | α/β* | $TCD_{50}/TD_{50}$ | $a^\gamma$ | $γ_{50}$ | End point     |
|---------------|--------------------|------|-------------------|-------------|----------|---------------|
| Target        | High grade glioma (Primary culture) | 10   | 72.7              | -10         | 1.5      | Local control |
| Normal tissues| Brain              | 3    | 60                | 5           | 3        | Necrosis      |
|               | Brainstem          | 65   | 7                 | 3           | 3        | Necrosis      |
|               | Optic Chiasm       | 65   | 25                | 3           | 3        | Blindness     |
|               | Lens               | 18   | 3                 | 1           | 1        | Cataract      |
|               | Optic Nerve        | 65   | 25                | 3           | 3        | Blindness     |
|               | Retina             | 65   | 15                | 2           | 2        | Blindness     |

*α/β*, linear and quadratic term in dose at linear quadratic model of cell survival curve; $TCD_{50}$, required dose for 50% control probability of tumor; $TD_{50}$, radiation dose that results in a 50% severe complication rate of normal tissues; $a$, biological model parameter to calculate equivalent uniform dose; $γ_{50}$, normalized slope at the 50% tumor control probability.