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A Prospective Study of Intensity-modulated Radiation Therapy Using a Standard Radiation Dose for High-grade Glioma

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Abstract. *Background/Aim: We evaluated the treatment outcomes of intensity-modulated radiation therapy (IMRT) using a standard radiation dose in patients with high-grade glioma (HGG). Patients and Methods: We conducted a prospective, single-institutional, single-arm trial. Patients aged 20-75 years with histologically proven HGG were enrolled. Surgical procedures and chemotherapy regimens were not regulated. The prescribed dose of postoperative IMRT was 60 Gy in 30 fractions over six weeks. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), completion rate of IMRT, and Grade 3 or higher non-hematological toxicity. Results: Between 2016 and 2019, 20 patients were enrolled. According to the World Health Organization 2016 Classification, glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma were present in nine, six, and five of the recruited patients, respectively. Gross total resection, partial resection, and biopsy were performed in four, nine, and seven patients, respectively. All patients received concurrent and adjuvant chemotherapy using temozolomide with or without bevacizumab. The completion rate of IMRT was 100%. The median follow-up period was 29 months (range=6-68 months). Median OS and PFS were 30 and 14 months, respectively. No patients experienced Grade 3 or higher non-hematological toxicity. The 2-year OS rates were 100%, 57%, and 33% in Radiation Therapy Oncology Group-Recursive Partitioning Analysis (RTOG-RPA) classes I/II, IV, and V, respectively (p=0.002; log-rank test). Conclusion: IMRT using the standard radiation dose in patients with HGG can be carried out safely. RTOG-RPA class appears to be useful to estimate patient prognoses.*

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By convention, high-grade glioma (HGG) is defined as including the World Health Organization's (WHO's) Grades 3 and 4 tumors such as anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and glioblastoma (GBM) (1). Standard treatment for HGG involves maximally safe surgical resection followed by chemoradiotherapy (2). Regarding postoperative chemoradiotherapy for HGG, the guideline by the National Comprehensive Cancer Network (NCCN) recommends a dose of 60 Gy in 2.0 Gy fractions, or 59.4 Gy in 1.8 Gy fractions (3).

With regard to the radiotherapy (RT) method, three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) have been used primarily. Compared to 3D-CRT, IMRT delivers reduced dose to the organ at risk (OAR), and accordingly is associated with reduced adverse reactions, through changing the radiation intensity across the treatment field (1). Furthermore, a study failed to provide evidence that IMRT is better than 3D-CRT in improving overall survival (OS) in adult patients with newly diagnosed GBM (4). In another report, although no significant difference in median survival was observed between IMRT and 3D-CRT, IMRT was associated with reduced neurological toxicities for patients with GBM (5).

Patients treated with IMRT for HGG have been increasing in our country, but prospective data for IMRT are still limited. Therefore, we conducted a prospective trial to evaluate the efficacy and safety of IMRT using the standard radiation dose of 60 Gy in 30 fractions for patients with HGG.

Table I. *Dose constraints*.

Structure	Metric	Optimal	Mandatory
PTV	$D_{95\%}$	100%	>98%
	D_{mean}	<104%	<105%
	D_{max}	<110%	<115%
Brain	V_{60Gy}	<25%	<33%
	V_{50Gy}	<33%	<67%
	V_{45Gy}	<67%	<100%
Brain without PTV	D_{max}	<60 Gy	<64.2 Gy
	V_{30Gy}	–	As low as reasonably achievable
Brainstem	D_{max}	<54 Gy	<59 Gy
	V_{55Gy}	0%	<10%
Optic structure	D_{max}	<50 Gy	<54 Gy
Eye	D_{max}	<40 Gy	<45 Gy
Lens	D_{max}	<6 Gy	<10 Gy
Inner ear at least one side	D_{max}	<45 Gy	<50 Gy
	D_{mean}	<35 Gy	<45 Gy
Middle ear at least one side	D_{max}	<45 Gy	<50 Gy
	D_{mean}	<35 Gy	<45 Gy
Hippocampus	$D_{40\%}$	–	As low as reasonably achievable
	$D_{50\%}$	–	As low as reasonably achievable
	V_{55Gy}	–	As low as reasonably achievable

PTV: Planning target volume; $D_{n\%}$: irradiated dose to n% of volume of the structure; V_{nGy}: percentage of volume of the structure at least irradiated n Gy.

Patients and Methods

Patients. This prospective, single-institution and single-arm trial (clinical trial registration number: UMIN000022502) was approved by our institutional ethics committee (approval number: H28-008). Patients with written informed consent were registered before postoperative IMRT.

Inclusion criteria were as follows: patients who 1) had histologically proven HGG, 2) had no tumor in the brainstem and optic nerve on preoperative magnetic resonance imaging (MRI), 3) had a planning target volume (PTV) for 60 Gy less than 1/3 of the brain volume, 4) were aged 20-75 years old, 5) had Eastern Cooperative Oncology Group performance statuses of 0-2, or 3 due to neurological signs caused by their tumors, and 6) provided written informed consent. Histology was diagnosed based on the World Health Organization (WHO) 2016 classification.

Exclusion criteria were as follows: patients who 1) had undergone prior RT for intracranial diseases, 2) had received prior treatment for HGG, 3) were women who were pregnant, possibly pregnant, or breast-feeding, 4) were women who wished to become pregnant during the treatment course, 5) had psychiatric diseases, and 6) were unsuitable for this study, as judged by physicians.

Treatment procedures. Surgical procedures and chemotherapy regimens were not regulated and performed at the discretion of physicians.

Computed tomography (CT) simulation was performed using a three-dimensional RT planning system. MRIs of contrast-enhanced T1-weighted images and fluid-attenuated inversion recovery images before and after surgery were superimposed to the planning CT images for target contouring. IMRT was delivered using a 4-10 MV photons from a linear accelerator with a technique of volumetric modulated arc therapy and simultaneous integrated boost.

Gross tumor volume (GTV) was defined as the residual tumor and surgical bed. Clinical target volume 1 (CTV1) was GTV plus 15 mm and edematous lesion. CTV2 was the edematous lesion plus 15 mm. If the edematous lesion was large, modified CTVs were permitted as follows: CTV1, GTV plus 15 mm; CTVe, the edematous lesion; and CTV2, the edematous lesion plus 15 mm. Reduced margins of the CTVs were allowed to obey the dose constraints (Table I). A PTV margin of 3-5 mm was added to the CTVs. Prescribed doses that normalized to 95% of the volume of the PTV were 60 Gy for PTV1 and 51 Gy for PTV2 in 30 fractions over six weeks. If the edematous lesion was large, 60 Gy for PTV1, 54 Gy for PTVe, and 48 Gy for PTV2 was delivered. As for the dose constraints (Table I), we were able to evaluate near-maximum doses such as $D_{2\%}$, D_{2cc}, D_{1cc}, $D_{0.5cc}$, or $D_{0.1cc}$, but used D_{max} as a strict constraint.

Follow-up, evaluation, and statistics. Patients were followed-up every 1-3 months after RT. MRIs were performed every 3-6 months. Tumor response was assessed based on criteria of the Response Assessment in Neuro-Oncology for HGG (6, 7). Adverse events were graded using the Common Terminology Criteria for Adverse Events v4.

The primary endpoint was OS. Secondary endpoints were progression-free survival (PFS), completion rate of IMRT, and Grade 3 or higher non-hematological toxicity events. OS was defined as the time from the date of registration to death due to any cause. PFS was defined as the time from the date of registration to progression or any cause of death. The Kaplan–Meier method was used to calculate the OS and PFS rates with the log-rank test in our statistical analysis. As a prognostic factor, Radiation Therapy Oncology Group-Recursive Partitioning Analysis (RTOG-RPA) class by Curran *et al*. (8) was used, because our data included not only GBM but also anaplastic tumors such as AA and AO. Nominal variables were analyzed using

Fisher's exact test. A *p*-value of <0.05 was considered to indicate statistical significance. Statistical analyses were performed with JMP Pro ver. 15 (SAS Institute, Cary, NC, USA).

The sample size was set as 20 patients without calculation, to prioritize the feasibility of patient accrual because the main purpose of this study was to estimate OS after IMRT using the standard radiation dose in patients with HGG.

Results

Between June 2016 and October 2019, 20 patients were enrolled. Patient and tumor characteristics are listed in Table II. At the time of registration, mental status was normal in all patients, and neurofunction was normal in 15 patients (75%). Median symptom time was two months (range=1-158 months). Of the nine patients with GBM, eight and one patient had isocitrate dehydrogenase (IDH) 1-wildtype (not otherwise specified) and IDH-mutant tumors, respectively. All patients with AA had IDH1-wildtype (not otherwise specified) tumors. All patients with AO had IDH-mutant and 1p/19q-codeleted tumors.

At the time of surgery, carmustine wafers were used in five patients (25%). Median interval from surgery to IMRT was three weeks (range=2-5 weeks). Overall treatment time of IMRT ranged from 42 to 46 days (median, 43 days). There was no treatment interruption of IMRT due to toxicity. All patients completed IMRT with a dose of 60 Gy in 30 fractions. The completion rate of IMRT was 100%. All patients received concurrent chemotherapy: temozolomide (TMZ) alone (9) in 18 patients (90%) and TMZ with bevacizumab (BEV) (10) in two patients (10%). All patients received adjuvant chemotherapy: TMZ alone (9) in 17 patients (85%), TMZ with BEV (10) in two patients (10%), and TMZ with tumor treating fields (11) in one patient (5%).

Median follow-up time was 29 months (range=6-68 months). Eventually, partial response, stable disease, and progressive disease (PD) were observed in two (10%), three (15%), and 15 (75%) patients, respectively. Of the 15 patients with PD, 12 patients experienced progression within the 95% isodose line; two patients who had GBM with 50% and 80% of Ki-67 experienced progression on the edge of the 95% isodose line within PTV2; and one patient who had GBM with 30% of Ki-67 outside PTV2 and the 95% isodose line. With the cut-off value of 30% for Ki-67 (12), PD occurred within the 95% isodose line and others in 10 (100%) and zero (0%) patients with Ki-67 <30%, and two (40%) and three (60%) patients with Ki-67≥30%, respectively (p=0.022). After PD, three, two, two, seven, and one patient were treated with surgery plus TMZ, surgery plus TMZ with BEV, TMZ alone, TMZ with BEV, and best supportive care, respectively.

In total, 11 and one patient died of HGG and cardiac disease, respectively. Median OS, 2-year OS rate, median PFS, and 2-year PFS rate were 30 months, 65%, 14 months, and 30%, respectively (Figure 1). The 2-year OS rates were 100%, 57%, and 33% in RTOG-RPA class I/II, IV, and V, respectively (p=0.002) (Figure 2).

Toxicity is listed in Table III. No patients experienced Grade 3 or higher non-hematological toxicity. Grade 1 central nervous system (CNS) necrosis was observed in two patients: one with a pathological diagnosis of PD and radiation necrosis after salvage surgery for clinical PD, and another with clinical diagnosis because an enhanced lesion vanished after continuation of TMZ alone without BEV. Grade 2 CNS necrosis was observed in two patients: one with pathological diagnosis of radiation necrosis after

Table II. *Patient and tumor characteristics*.

Characteristics			%
Sex	Male	10	50
	Female	10	50
Age (years)	Median	59	
	Range	31-73	
ECOG-PS	0	8	40
	1	6	30
	2	2	10
	3	4	20
KPS	Median	80	
	Range	50-100	
Laterality	Right	6	30
	Left	9	45
	Bilateral	5	25
Location	Frontal	8	40
	Temporal	4	20
	Parietal	1	5
	Occipital	1	5
	Corpus callosum	1	5
	Extending over multiple areas	5	25
Surgical procedure	Gross total resection	4	20
	Partial resection	9	45
	Biopsy	7	35
Histology[a]	Glioblastoma	9	45
	Anaplastic astrocytoma	6	30
	Anaplastic oligodendroglioma	5	25
RTOG-RPA class[b]	I	6	30
	II	1	5
	IV	7	35
	V	6	30
Ki-67 (%)	Median	17	
	Range	4-80	
PTV1 (cc)	Median	199	
	Range	74-393	
PTV2 (cc)	Median	508	
	Range	202-915	

ECOG-PS: Eastern Cooperative Oncology Group performance status; KPS: Karnofsky performance status; RTOG-RPA: Radiation Therapy Oncology Group-Recursive Partitioning Analysis; PTV: planning target volume. [a]According to the World Health Organization 2016 Classification. [b]According to an analysis by Curra*n et al*. (8) because our data included anaplastic tumor.

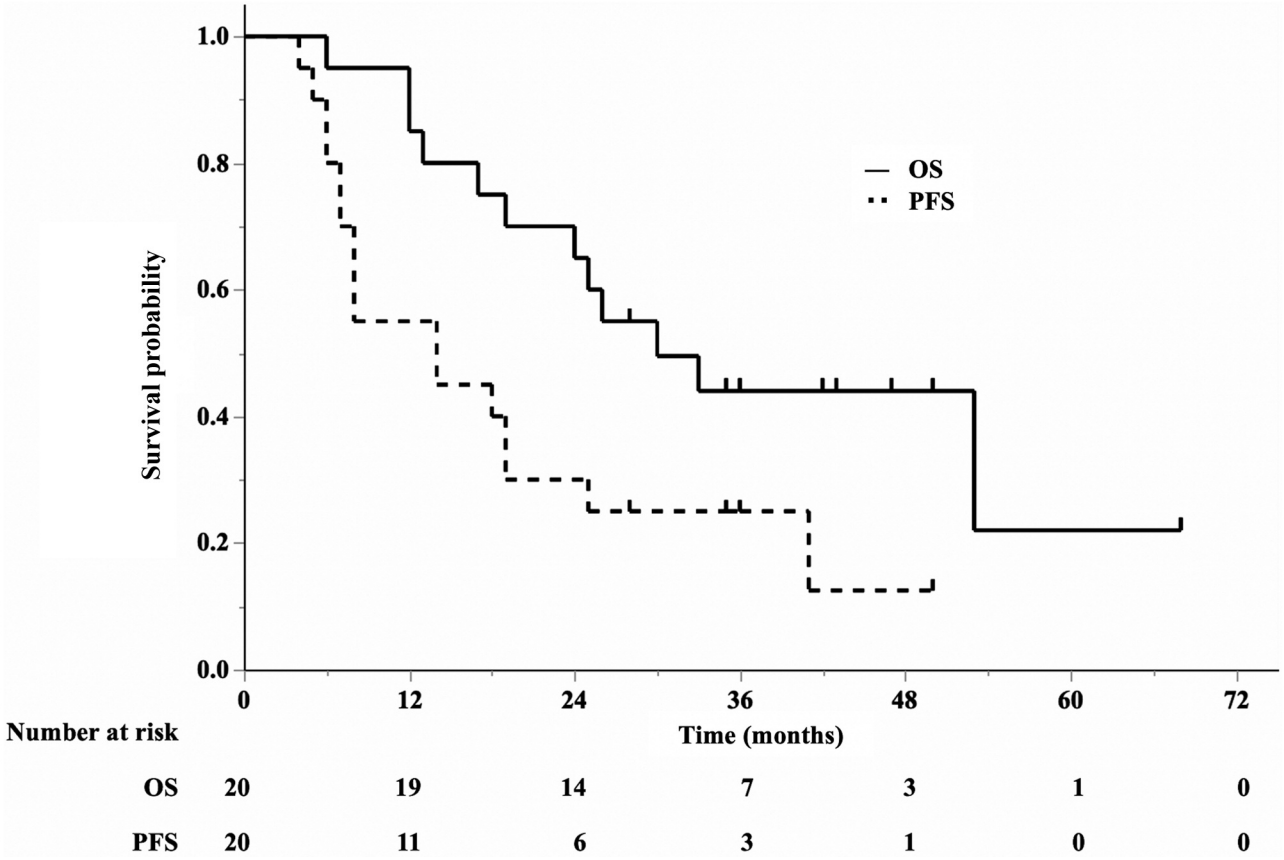

Figure 1. *Overall survival (OS) and progression-free survival (PFS). Black solid and broken lines indicate OS and PFS, respectively.*

salvage surgery for clinical PD, and another with a clinical diagnosis because an enhanced lesion was stable after temporary oral steroid treatment.

Discussion

In the TMZ era, large-scale randomized controlled trials of postoperative chemoradiotherapy were conducted on patients with GBM (9-11), whereas those for patients with whole HGG were limited. However, as described in the NCCN guideline, not only GBM but also whole HGG were treated with the same RT dose (3). In our clinical practice, we treat patients with HGG using the recommended standard RT dose. Therefore, we conducted this prospective trial to evaluate OS in current clinical practice using IMRT with the standard RT dose for HGG. Median OS and 2-year OS were 30 months and 65%, respectively.

For prognostic stratification of HGG, including GBM and anaplastic glioma, RTOG-RPA is used (8). The original literature on HGG showed that 2-year OS rates were 76%, 68%, 15%, and 6% in RTOG-RPA classes I, II, IV, and V, respectively (8). A recent retrospective study on HGG using IMRT with a median dose of 59.4 Gy in 30 fractions showed that 2-year OS rates were 82%, 32%, and 13% in patients with class I, IV, and V diseases, respectively (p<0.001) (13). In our prospective trial, 2-year OS rates were 100%, 57%, and 33% in class I/II, IV, and V patients, respectively (p=0.002). Our prospective results were comparable to those of the retrospective study (13). Moreover, the reproducibility of RTOG-RPA for HGG was confirmed in the IMRT era.

Although chemotherapy regimens were not regulated and were at the discretion of physicians, based on the current clinical practice in our institution, all patients received concurrent and adjuvant chemotherapy using TMZ with or without BEV. The completion rate of IMRT was 100%. Moreover, no patients experienced Grade 3 or higher non-hematological toxicity in both the acute and late phases. Thus, we can conclude that this trial was conducted safely.

As for the relationship between PD and Ki-67, one study reported that recurrence among GBM patients occurred within the 95% isodose line and others in 83% and 17% of patients with Ki-67 <30%, and 54% and 46% of those with Ki-67 ≥30%, respectively (p=0.014) (12). Our data were similar to these results: 100%, 0%, 40%, and 60%,

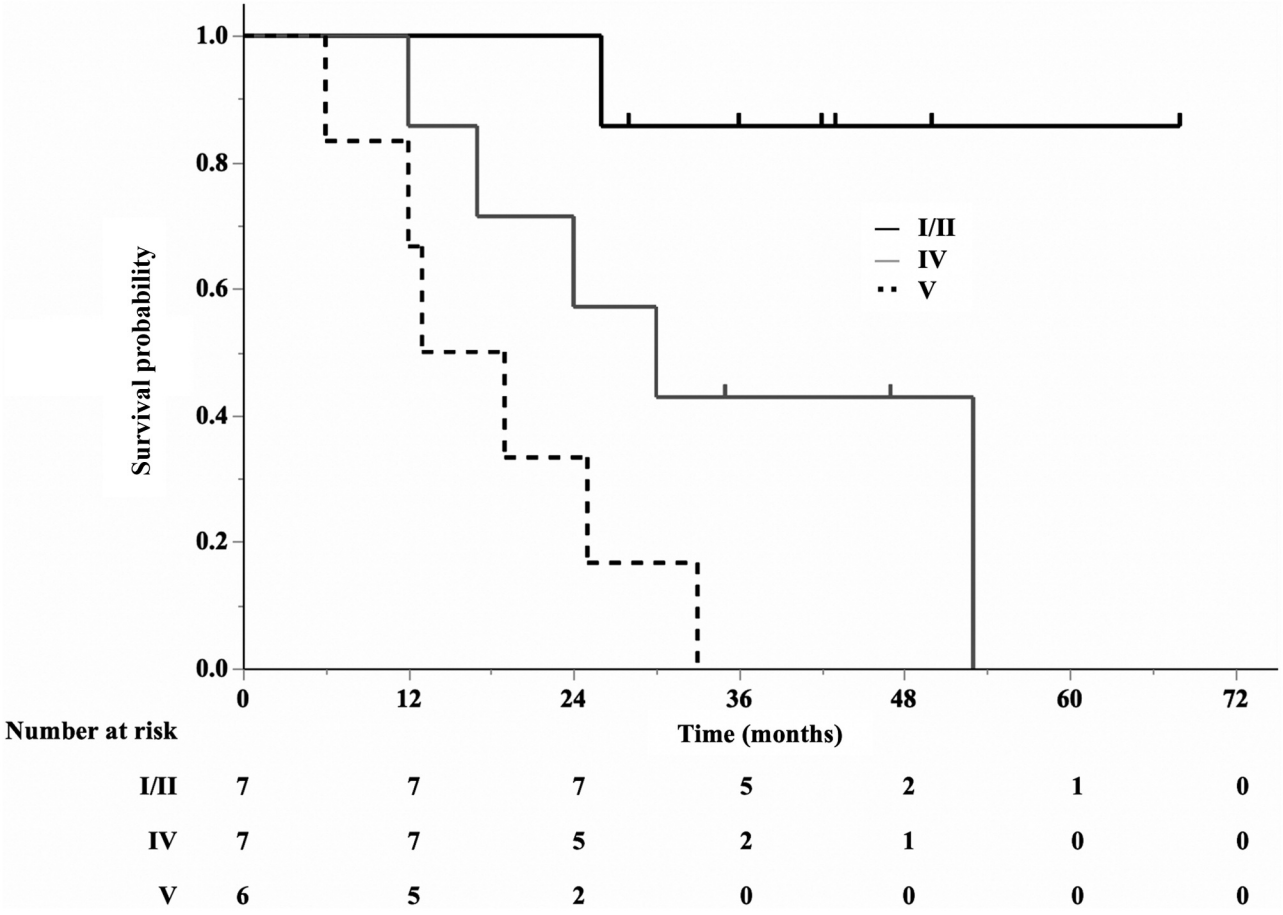

Figure 2. *Overall survival according to Radiation Therapy Oncology Group-Recursive Partitioning Analysis (RTOG-RPA). Black solid, gray solid, and black broken lines indicate RTOG-RPA class I/II, IV, and V, respectively.*

respectively (p=0.022). The cut-off value with 30% of Ki-67 had the reproducibility to distinguish the PD pattern of HGG including GBM.

Our study has some limitations. IDH2 was not evaluated, and IDH-mutant tumors may have been present among the IDH1-wildtype (not otherwise specified) tumors. However, the diagnosis of AO was correct because IDH-mutant and 1p/19q-codeletion was confirmed in all patients with AO. Moreover, the WHO 2021 classification was published in the follow-up phase of our study, and the fundamental diagnostic system is in the transition. However, the current NCCN guideline has not changed the recommended RT dose for HGG (3). Therefore, our results are still meaningful based on the current recommendation. The small number of subjects and the single-institution design of this study represent other potential limitations to its robustness.

In conclusion, IMRT using the standard radiation dose in patients with HGG can be carried out safely. RTOG-RPA classification appears to be useful for estimating the prognoses of these patients.

Conflicts of Interest

The Authors have no conflicts of interest regarding this study.

Authors' Contributions

This study was coordinated by ST and TS. Data was collected by ST, KM, DO, MA, TK, and TN. Collected data was analyzed by ST. This article was drafted by ST. Data interpretation and article revision were performed by all authors: ST, KM, DO, MA, TK, TN, and TS. All Authors approved the submitted article.

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Table III. *Toxicity.*

Acute toxicity within 12 weeks of completion of IMRT						
Hematological	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
WBC decreased	3	12	4	1	0	0
Neutrophil count decreased	19	1	0	0	0	0
Lymphocyte count decreased	2	7	6	5	0	0
Platelet count decreased	16	4	0	0	0	0
Anemia	9	8	3	0	0	0
Hypoalbuminemia	13	6	1	0	0	0
Non-hematological	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	4	14	2	0	0	0
Vomiting	18	1	1	0	0	0
Dermatitis radiation	4	16	0	0	0	0
Alopecia	0	1	19	0	0	0
Middle ear inflammation	18	2	0	0	0	0
Late toxicity after 12 weeks of completion of IMRT						
Non-hematological	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Middle ear inflammation	16	4	0	0	0	0
Cataract	20	0	0	0	0	0
CNS necrosis	16	2	2	0	0	0
Stroke	19	0	1	0	0	0
Hemangioma	19	1	0	0	0	0

IMRT: Intensity-modulated radiotherapy; WBC: white blood cell; CNS: central nervous system.

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