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Feasibility of image-guided robotic radiotherapy using three fractions for uveal melanoma

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ABSTRACT

Aims. A retrospective study was performed to demonstrate the feasibility and efficacy of 3-fraction image-guided robotic stereotactic radiotherapy (fSRT) for uveal melanoma.

Materials and methods. Six patients with medium-sized or large tumors, who declined enucleation, were enrolled. The gross tumor volume (GTV) ranged from 454 to 2185 mm^3. The total doses included 36 or 39 Gy in 3 fractions.

Results. Follow-up ranged from 19 to 40 months. In 5 patients, the tumor mass gradually underwent an average 24.5% size reduction. All 3 patients with a GTV <1000 mm^3 had a functional eye, while 3 patients with a GTV ≥1000 mm^3 did not have a functional eye. Radiation-induced complications occurred to some degree in all patients. However, complications that required enucleation were not detected.

Conclusion. We suggest that image-guided robotic radiotherapy using 3 fractions is a feasible and safe treatment option for patients with uveal melanoma. In cases of medium-sized and large tumors, fSRT could be used as an alternative treatment for cases ineligible for brachytherapy, but a longer follow-up and a larger number of patients are required to confirm the suitability of the method.

Introduction

Uveal melanoma is the most common primary ocular malignancy in adults[1]. In the United States, the incidence is 6.1 cases/million people per year for Caucasians and 0.5 per million person years for African-Americans[2]. The incidence of uveal melanoma is unknown in Korea and the disease is considered rare.

Medium-sized uveal melanomas are currently treated with eye-preserving radiotherapy[3-6]. No advantage of the use of enucleation for uveal melanomas of this size (<12 mm) could be demonstrated in multiple studies[7]. Eye conservation is achieved by means of several techniques, including proton[7-15] or other heavy charged particle therapies[6,8]; episcleral radionuclide plaque therapy is among the most commonly used therapies. Single session stereotactic radiosurgery (SRS) using frame-based gamma knife technology (Elekta AB, Stockholm, Sweden) has been used during the last decade to treat medium-sized to large tumors as an alternative to complete removal of the eye. Recently, with the advance of photon beam therapy techniques, hypofractionated stereotactic radiation therapy (fSRT) has been introduced[16]. Hypofractionated stereotactic radiation therapy is an emerging technology designed to improve tumor conformality, allowing precise treatment to reduce the tumor margin and allow for a radiobiological benefit of hypofractionation. Moreover, fSRT may be more convenient for patients as the technique typically uses a noninvasive frame for localization.

In a review of previously published studies for SRS and fSRT (Table 1)[9,11,13,14,17-25], dose, fraction number and prescription isodose line have been variable, and it has been difficult to determine proper treatment guidelines with the use of these modalities. Notably, in an effort to reduce the toxicity, dose de-escalation seems to be a re-

Key words: uveal melanoma, fractionated stereotactic radiotherapy, CyberKnife.

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Table 1 - Journal review of stereotactic radiosurgery, fractionated stereotactic radiotherapy and proton radiotherapy for uveal melanoma

	Study	Machine	Year	No. pts.	Volume (mm³) or diameter (mm)	Median F/U (range) (mo)	Dose (Gy) /fraction	Prescribed isodose line (%)	LC (%)	EP (%)	Secondary enucleation (%)
fSRT	Zehetmayer[17]	GK	2000	62	V 640 (100-3260)	28.3 (12-51)	45-70 /1-3	50	98	87	0 (D <8 mm) *vs* 27 (D >8 mm)
	Muller[18]	X-knife	2005	38	D 6.4 (2.2-11)	25 (mean) (10-36)	50 /5	80	100	97	3
	Dieckmann[19]	Linac	2007	158	V 329 (34-1950)	33.4 (3-85)	60 or 70 /5	80	98	86	13
	The present	CK		6	V 1706 (454-2185)	28 (19-40)	36 or 39 /3	76-80	84	84	15
SRS	Muacevic[20]	CK	2008	7	D 8.7-17.1	13 (6-22)	18-22 /1	65-75	100	100	0
	Marchini[21]	GK	1995	36	D 8-16	6 (1-30)	38-70 /1	45-90	97	NA	NA
	Mueller[22]	GK	2000	35	D 8.4-18.6	NA (10-20)	25 /1	50	97	94	3
	Langmann[23]	GK`	2002	31	V 10-910	NA (12-79)	30 or 45 /1(LD) *vs* 50 or 80 /1(HD)	55 (45~75)	85	72	NA
	Simonova[24]	GK	2002	75	V 640 (32-780)	32 (10-74)	31.4 /1 (20-76.5)	NA	87	81	5
	Cohen[25]	GK	2003	78	D 6.3 (2.3-13.4)	38 (1-120)	50 or 70 /1	50 or 90	95	90	NA
Proton	Fuss[13]	Cyclotron	2000	78	D 10	34 (6-102)	70.2 CGE /5	NA	95.8	75.3	15
	Höcht[11]	Cyclotron	2004	245	V 170 (10-1990)	18.4	60 /8	NA	96.4	92.6	NA
	Courdi[14]	Cyclotron	1999	538	D 14.6	NA	52 /4	NA	89	NA	NA
	Dendale[9]	Cyclotron	2006	1406	D 13 (2.5-24.4)	73 (24-142)	60 CGE /4	NA	96	NA	7.7

fSRT, fractionated stereotactic radiotherapy; F/U, follow-up; mo, months; SRS, stereotactic radiosurgery using single session; GK, gamma knife; CK, CyberKnife; LC, local control rate; EP, eye preserving rate; V, volume (range); D, largest diameter of tumor (range); LD, low dose; HD, high dose; CGE, cobalt gray equivalents; NA, not assessed.

cent trend in both SRS and fSRT. In this retrospective study, we used 36 Gy and 39 Gy in 3 fractions to a prescribed isodose line of 76-80%. This trial was also unique because treatment was administered with 3 fractions by a noninvasive method as well as with the utilization of an image-guided robotic delivery system equipped with a CyberKnife (Accuray, Sunnyvale, CA, USA). The CyberKnife uses multiple beams with more than 100 directions that allow tracking of the orbit contour during intrafraction. Accordingly, we reviewed 6 uveal melanoma patients treated with 3-fraction stereotactic radiation therapy, with a focus on ophthalmic complications and outcome.

Materials and methods

Patient and tumor characteristics

Inclusion criteria for this study included 1) a malignant choroidal melanoma detected by imaging; 2) a medium-sized or large tumor based on COMS criteria[26], and 3) declining enucleation. Patients were excluded from the study if they presented with evidence of extrascleral tumor extension, neovascular glaucoma (or any initial form of pretreatment) or metastasis. Because ocular plaque brachytherapy, considered the standard treatment for medium-sized uveal melanoma, was not available in Korea prior to 2004, this protocol was applied from April 2004 and was changed in 2007, when ocular brachytherapy became available in our hospital. The Multidisciplinary Tumor Board of the Korea Cancer Center Hospital approved this study. Informed consent was obtained from each patient or guardian after the nature of the procedure had been fully explained. A total of 6 patients with choroidal melanoma treated with the CyberKnife at the Korea Cancer Center Hospital were analyzed in this retrospective study. Diagnoses were based on the results of an ophthalmoscopic examination and ultrasonography. Physical examination, chest x-ray, blood liver function test and liver imaging study revealed no evidence of systemic metastasis. The patient characteristics are summarized in Table 2. The patients' ages ranged from 28 to 71 years and the male to female ratio was 3:3. The gross tumor volume (GTV) ranged from 454 to 2185 mm^3 (median, 1188 mm^3). The largest basal diameter and apical height are described in Table 2. Based on the COMS classification, tumor mass was classified as medium-sized in 4 patients and large in 2 patients. The visual acuity of the patients before fSRT ranged from 20/100 to 20/30 (Table 2). Four of the patients complained of mild periorbital discomfort and mild lid swelling, which was successfully managed with the administration of oral analgesics.

After fSRT treatment, follow-up examinations were performed 1 month after treatment and at 2-4-month intervals thereafter. An anterior segment slit lamp examination, indirect ophthalmoscopy, and ultrasonography were performed during the follow-up visits.

SBRT technique

After comfortably positioning each patient in the supine position on the CyberKnife treatment table, a custom Aquaplast (WFR/Aquaplast, Wyckoff, NJ, USA) mask was fabricated. A thin-slice (1.0 mm) high-resolu-

Table 2 - Demographic data of patients with uveal melanoma

Pt. no.	Sex /age (years)	Tumor location	Initial size (mm)*	Gross tumor volume (mm^3)	Initial VA	Dose (Gy) /fx	Final VA	Final size (mm)*	HR (%)	Prescribed isodose line (%)	Complication (months)[§]	F/U (months)
1	F/71	Post	15.0×4.8	454	20/60	39/3	HM	14.1×4.7	2.1	80	Vitreous hemorrhage (30)	29
2	M/54	Equator	11.6×7.1	733	20/50	36/3	20/50	8.7×5.1	28.2	77	Maculopathy (10)	24
3	M/53	Post	12.9×4.3	888	20/50	39/3	20/30	7.5×2.9	32.6	76	Cataract (39), maculopathy (16)	40
4	M/31	Equator	13.7×10.7	1487	20/100	39/3	NLP	14.5×9.2	14.0	79	Maculopathy (7)	19
5[#]	F/56	pph	13.5×8.8	1706	20/30	36/3	NLP	15.9×10.4	18.2	78	Temporary retinal detachment (1)	24
6	F/28	Equator	15.6×13.3	2185	20/30	39/3	NLP	13.0×7.2	45.9	80	Temporary retinal detachment (2), glaucoma (7), cataract (10), vitreous hemorrhage (19)	25

VA, visual acuity; fx, fraction number; HR, height reduction, initial height – final height / initial height; F/U, follow-up in months calculated from the start of SBRT to last follow-up; HM, hand movement; NLP, no light perception; pph, peripheral.
*Size is described as the largest basal diameter × apical height.
[§]The period from fSRT to detection of complication.
[#]This patient underwent an enucleation because of progression of the tumor.

tion computed tomographic (CT) scan was obtained after intravenous contrast administration. A network transferred the acquired images to the CyberKnife treatment planning workstation. Tumor volumes and critical structures were delineated manually on axial images with simultaneous overlay of the outlines on coronal and sagittal reconstruction images. Reconstructed images where the perspective was through the cranial base facilitated the accurate delineation of the eyes and the ipsilateral and contralateral optic nerves (Figure 1).

The total SRT doses and fractions were administered with 39 Gy/3 fractions in 4 patients and with 36 Gy/3 fractions in 2 patients on 3 consecutive days depending on the size and location of the tumor. The planned target volume (PTV) included the GTV plus a 2-mm margin. Radiation doses were prescribed to the 76-80% isodose line of the maximum dose covering the PTV (Figure 1). The median of the maximum doses in the optic nerve was 20.5 Gy (range, 9-40 Gy) and the maximal lens dose had a median of 14.2 Gy (range, 2.5-27 Gy).

Survival, response and toxicity assessments

Evaluations were performed at each follow-up to determine tumor size and visual acuity and to detect new lesions and complications such as retinopathy, cataracts, neovascular glaucoma or vitreous hemorrhage. During the follow-up period, the basal tumor diameter and tumor thickness were measured by ultrasonography. The follow-up period was calculated from the commencement of fSRT and median values are reported.

Results

Follow-up ranged from 19 to 40 months (median time, 28 months). None of the patients showed distant metastasis and no patients died during the follow-up period. During follow-up, 1 patient underwent an enucleation 6 months after irradiation because of tumor growth. The pathology result on the enucleated eye confirmed the presence of a residual mass on the sclera. In the other 5 patients the tumor mass shrank with an average 24.5% size reduction (range, 2.1-45.9%) determined at the final visit (Table 2). Functional visual acuity was achieved in 3 patients. All 3 patients with a PTV <1000 mm^3 (initial height less than 8 mm) had a functional eye while the 3 patients with a PTV ≥1000 mm^3 did not have a functional eye (Table 2).

Radiation-induced complications occurred to some degree in all patients (Table 2). Two cataracts, 2 retinal detachments, 2 cases of vitreous hemorrhage, 2 cases of maculopathy and 1 case of neovascular glaucoma were observed. No complications that required enucleation were seen during follow-up. There was no evidence of metastatic disease during the follow-up period.

Discussion

Different kinds of therapeutic options exist for the treatment of uveal melanoma. Eye conservation is achieved by several techniques, with proton or other heavy charged particle therapies; episcleral radionuclide

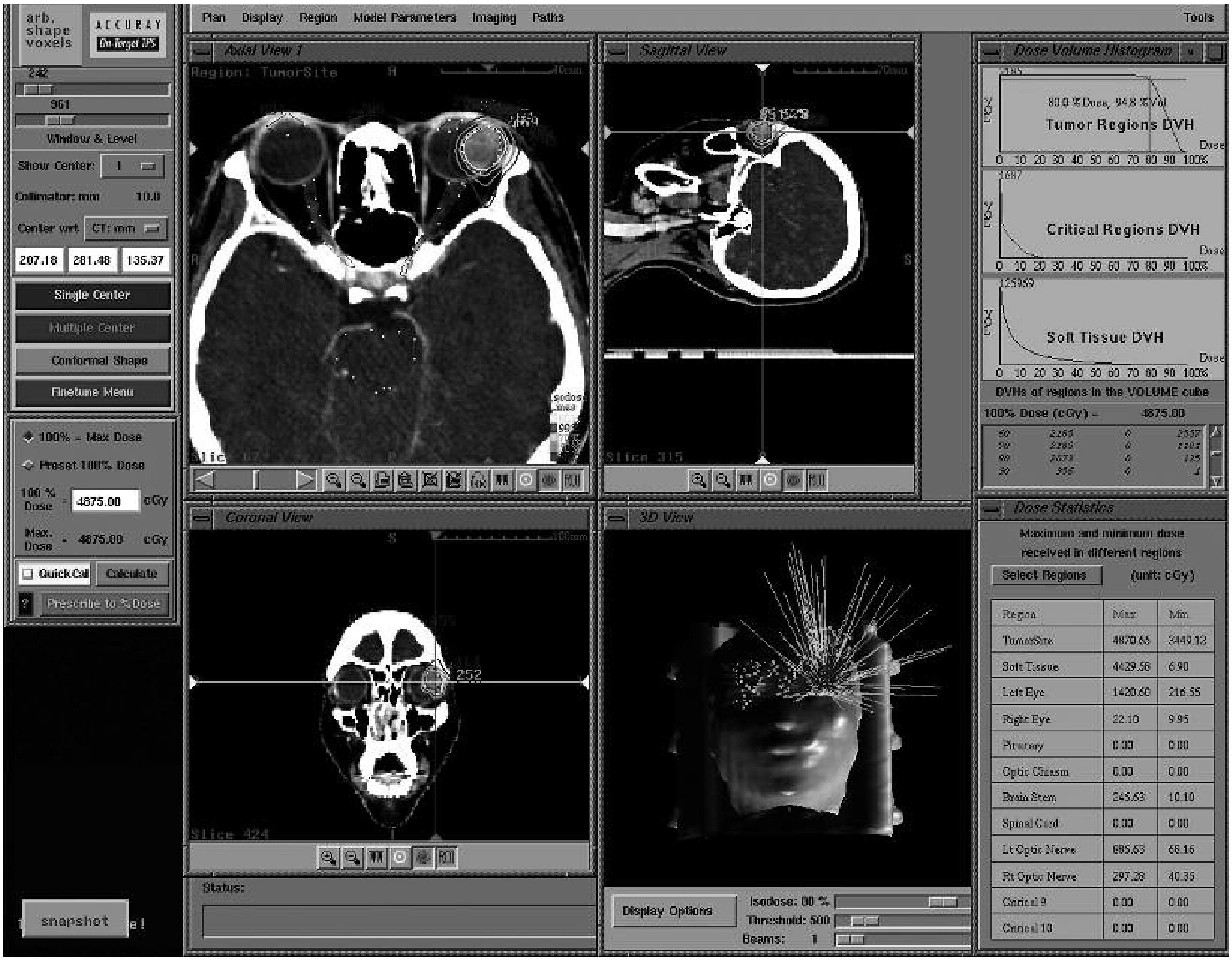

Figure 1 - Tumor volumes and critical structures including the lenses of both eyes, the ipsilateral and contralateral optic nerves, and the brainstem were delineated manually on axial images with simultaneous overlay of the outlines on coronal and sagittal reconstructions.

plaque therapy is among the most commonly used. The most suitable modality depends on the size and the location of the tumor. Stereotactic radiation therapy has proved to be a good alternative for medium-sized and large tumors[21-23,27]. Hypofractionated fSRT, if demonstrated safe and similarly effective, could be an alternative to brachytherapy because it is entirely noninvasive and also deliverable on an outpatient basis, with no requirement for anesthesia. Contraindications for fSRT are relatively rare as compared to other therapies. Especially for large uveal melanoma it has been previously suggested that the fSRT modality is more favorable than the SRS modality[27]. However, whereas there are some reports describing the use of SRS, there have been few studies that have described the efficacy or safety of fSRT. The present report provides rare information about optimal dosing and patient selection. In this study, we treated medium-sized and large uveal melanomas and prescribed 39 Gy or 36 Gy in 3 fractions to an isodose line of 76-80%. With the limitation of a small number of patients, no local failure was observed with a dose of 39 Gy while 1 local failure occurred among 2 patients who received a dose of 36 Gy. The administration of a lower dose (36 Gy) and a large tumor (1706 mm^3) possibly contributed to the local recurrence.

In trials to reduce complications while maintaining excellent local control, optimal dose and fraction number have not yet been defined. Langmann *et al.*[23] compared the results of the use of gamma knife SRS in patients with uveal melanomas who underwent high-dose (mean dose, 52.1 Gy) and low-dose irradiation (mean dose, 42.1 Gy). Neovascular glaucoma developed in 9% of the patients receiving a low dose and in 48% of the patients receiving a high dose, while the same rate of tumor regression between patients that received either a high or a low dose was achieved.

Another study included a large number of patients with uveal melanomas treated with an fSRT dose of 60 or 70 Gy in 5 fractions and excellent outcomes were reported. However, 21 (13%) of 158 patients developed severe complications and underwent enucleation. The investigators suggested conducting clinical trials with a reduced dose and number of fractions in the future. Mueller *et al.*[22] and Muacevic *et al.*[20] used a low dose of 18-22 Gy or 25 Gy in a single fraction to the tumor, respectively. Fortunately, a success rate of eye preservation of 98-100% was reported with less than 3% secondary enucleation in both series, even though there was the limitation of a short follow-up period (Table 1). In the present study, we attempted to reduce the rate of complications and used 36 Gy and 39 Gy. These doses can be converted to a biological effective dose by use of the linear quadratic model to 81 Gy and 90 Gy, respectively. The doses used in the Muacevic *et al.*[20] and Mueller *et al.*[22] studies ranged from 50 Gy to 88 Gy for the biological effective dose. In particular, 25 Gy in a single fraction as used in the study by Mueller and colleagues is similar to one of the doses employed in the present study. All of the patients showed some degree of complications in the present study, while enucleation due to a complication was not observed. The rate of complications did not decrease, even though we used relatively lower doses and 3 fractions instead of 1. The reason for the lack of a decline in the complication rate is not clear. Reduction of the margin through eyeball fixation using local anesthesia or a reduction of the prescribed isodose line, for example from 80% to 50%, would be a possible way to diminish the complication rate.

Final visual acuity after fSRT is likely to be related to tumor volume (GTV ≥1000 mm^3 *vs* GTV <1000 mm^3) in this study. These results are consistent with findings in a study by Zehetmayer and colleagues[17]. These investigators found that 27% of patients with a tumor diameter >8 mm underwent secondary enucleation while the eye could be conserved in patients with a smaller tumor (diameter ≤8 mm) and the patients had better visual acuity (Table 1).

In conclusion, this retrospective study has shown that a relatively lower dose of 36 to 39 Gy in 3 fractions using image-guided robotic radiation therapy can be administered to patients noninvasively and safely. In cases of medium-sized and large tumor, fSRT could be used as an alternative treatment for cases ineligible for brachytherapy, but a longer follow-up and a larger number of patients are necessary to confirm these findings.

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