FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR CHOROIDAL MELANOMA

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Purpose/Objectives : Although choroidal melanoma is a relatively rare disease in Taiwan, this study aimed to investigate the feasibility of using linear accelerator based hypofractionated stereotactic radiotherapy (SRT) for choroidal melanoma.

Materials and Methods : From 2009 to 2012, 6 patients with choroidal melanoma were treated for a total dose of 50 Gy in 5 fractions with SRT. All patients underwent image studies (CT or MRI) and ophthalmologic examination, including visual acuity, funduscopy and ultrasound, before and regularly after treatment. In this study, three patients had medium-sized tumors (tumor height ≦10 mm and tumor base ≦16 mm) and the other three had large-sized tumors (tumor height >10 mm or tumor base >16 mm).

Results : With a median follow-up duration of 29 months, the 3-year local control, distant metastasis free and overall survival were all 100%. One patient had enucleation due to the development of radiation-induced neovascular glaucoma after 25 months. In addition, one patient developed a cataract after 24 months and received an intraocular lens implant. Among the four patients with pre-treatment visual acuity >0.1(VA), VA was preserved in 3 patients.

Conclusions : Our study supports the theory that hypofractionated SRT with 50Gy applied in five fractions seems to be sufficient to obtain good tumor control. More efforts should be made to reduce the radiation-induced neovascular glaucoma and preserve visual acuity.

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Key words: *Choroidal melanoma, Stereotactic radiotherapy, Visual acuity preservation*

INTRODUCTION

Uveal melanoma is a common ocular malignancy in adults. Based on the Surveillance, Epidemiology, and End Results (SEER) report, its annual incidence is as high as 6 new patients per million people [14, 34, 37] in the United States. In Taiwan, the incidence of uveal melanoma is less than one new patient per million people [47]. Choroidal melanomas account for 85-90% of all uveal melanomas, and others are ciliary body (8-10%) and iris (1-3%) melanomas. Although approximately 50 percent of patients will develop metastases after treatment, local control is the primary goal of the treatment for choroidal melanomas [38].

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Primary treatment can involve enucleation; however, this is now reserved for patients with large-sized choroidal melanoma or other secondary problems. Eye-preservation radiotherapies, including brachytherapy, photon and charged particle therapy have showed equally success as enucleation in local control, distant metastasis control and overall survival. [17, 18, 21, 35].

The ability to treat choroidal melanomas with a linear accelerator (LINAC) offers new possibilities. In the past decade, LINAC based hypofractionated stereotactic radiotherapy (SRT) has been investigated for choroidal melanoma as an alternative option [9, 11]. Although choroidal melanoma is a relatively rare disease in Taiwan, this study presents the clinical results of the hypofractionated SRT regarding local tumor control and side effects at our hospital.

PATIENTS AND METHODS

Between January 2009 and December 2012, 6 consecutive patients with choroidal melanoma were treated with LINAC based hypofractionated SRT at Chang Gung Memorial Hospital at Linkou in Taiwan. All patients underwent comprehensive ophthalmologic examinations including best-corrected visual acuity (VA), tonometry, and funduscopy. The basal dimensions and height of the tumor were measured using both magnetic resonance (MR) imaging and ultrasound. According to the Collaborative Ocular Melanoma Study classification of choroidal melanoma, tumors were classified as nevus (tumor height <1 mm and tumor base ≦5 mm), small (tumor height ≦3mm and tumor base ≦16 mm), medium (tumor height ≦10 mm and tumor base ≦16 mm), or large (tumor height >10 mm or tumor base >16 mm). In addition, chest and abdominal CTs were done to exclude metastatic disease.

When doing computed tomography (CT) simulation and treatment, the patient's head was immobilized with a thermoplastic mask. To help fix the position of the eyes, a light source was integrated into the mask system. The light source was 30 cm above the middle of the eyes. The patients were told to fixate their gaze on the light during image acquisition (CT simulation) and during SRT. At the same time, the positions of the pupil and eyelid were closely monitored by the surveillance camera system [8].

Contouring the gross target volume (GTV) on 1.25-mm slice thickness of the CT image was performed on the Novalis iPlan® system (BrainLAB, Feldkirchen, Germany) with the aid of contrast medium MR images. The planning target volume (PTV) was derived from the GTV with 2-3 mm margins using computer-automated 3D margin expansion. All treatments were delivered by image-guided radiotherapy via matching kilovoltage orthogonal X-ray image with digital reconstructed radiographs from the planning CT. All patients were treated with five fractions of 10 Gy at 95% isodose (total dose 50 Gy) to encompass the PTV within a week. The maximal tolerate dose was 4 Gy per fraction in the optic nerve [32] and no constraint of lens. The high risk of developing cataracts was carefully explained to patients before treatment. The delivery time of each beam in treatment plans was designed to be less than 30 seconds to minimize the discomfort of fixating the gaze on the light source. Patients were allowed to close their eyes between each beam delivery. The radiation therapist maintained communication with patients, prompting them at the start and finish of beam delivery during the SRT treatment.

Patients were followed-up with image studies at 3-month intervals for the first year, and 6-month intervals thereafter. Assessments of visual acuity, ultrasound scans, and CT or MRI were done at each follow-up visit. Time of overall survival (OS) and local tumor

control were measured from the start date of radiotherapy. Local tumor control was defined as no increase in tumor volume by any image modalities. All analyses were performed on SAS, version 4.2 (SAS institute Inc., Cary, NC).

RESULT

The characteristics of the six patients are summarized in Table 1. Patients' ages ranged from 34 to 78 years with a median of 47 years. Three patients had medium-sized tumors and the other three had large lesions. The medians of tumor height and basal diameter were 9.3 mm and 13.4 mm, respectively. Three patients were noted by funduscopy to have retinal detachment. Two of the three patients had very poor VA (< 0.1) before radiotherapy. Two patients were noted to have senile cataracts on the first ophthalmologic examinations.

Patients tolerated hypofractionated SRT well without treatment interruption. Median follow-up time for these six patients was 29 months (24-49 months). All patients were still alive without evidence of tumor progression. Therefore, the three-year overall survival and local control rates were 100%. Although the choroidal melanoma is slow to respond to SRT, the median reductions of tumor height and basal diameter were 3.9 mm and 4.0 mm and median of each reduction ratio was 44% and 30% at the last individual follow-up. One patient had complete response by image studies after 48 months (Fig. 1).

Visual acuity is the major concern for both physicians and patients with choroidal melanoma. The two patients with pre-treatment visual acuity <0.1 had no improvement after SRT. Two patients had decreased visual acuity (0.9 and 0.8) to <0.1 13, 30 months after radiotherapy. The cause of loss of visual acuity in one 34-year-old patient was the early development of cataracts 24 months after treatment.

Table 1. Patient and tumor characteristics

	Gender	Age (Y)	Follow up (mo)	Location	COMS classification	Ciliary body invasion	Pre-Tx VA	Distance to optic nerve (mm)	Pre-Tx retinal detachment	Post-Tx VA	Post-Tx AEs
Patient 1	female	43.5	29.5	Lateral lower	Large	No	<0.1	>5	Yes	<0.1	Neovascular glaucoma
Patient 2	male	69.0	29.2	Medial upper	Medium	No	0.4	2	Yes	0.3	
Patient 3	female	34.2	46.4	Medial lower	Medium	No	0.8	>5	No	0.2	Cataract formation/ neovascular glaucoma
Patient 4	female	49.4	48.9	Medial upper	Medium	No	0.4	<1	No	0.2	
Patient 5	female	44.0	24.6	Lateral lower	Large	No	0.9	>5	Yes	<0.1	Neovascular glaucoma/ enucleation
Patient 6	male	78.1	24.4	Medial upper	Large	Yes	<0.1	<1	No	<0.1	Neovascular glaucoma

Abbreviation: VA, visual acuity; COMS, collaborative melanoma study; Tx, treatment

* Small: height 1.0~3.0 mm & diameter 5.0~16.0 mm; medium, height 3.1~8.0 mm & diameter ≤ 16.0 mm; large, height >8.0 mm or diameter >16.0 mmFig. 1 Initial pre-treatment and series follow-up CT images of 49 year-old female choroidal melanoma patient a) pre-treatment CT image, tumor 4.0 * 11.2 mm; b) 1.5-year follow-up CT image, tumor 3.7 * 9.5 mm; c) 2.5-year follow-up CT image, tumor 3.4 * 9.5 mm; d) 3.5-year follow-up image, complete response

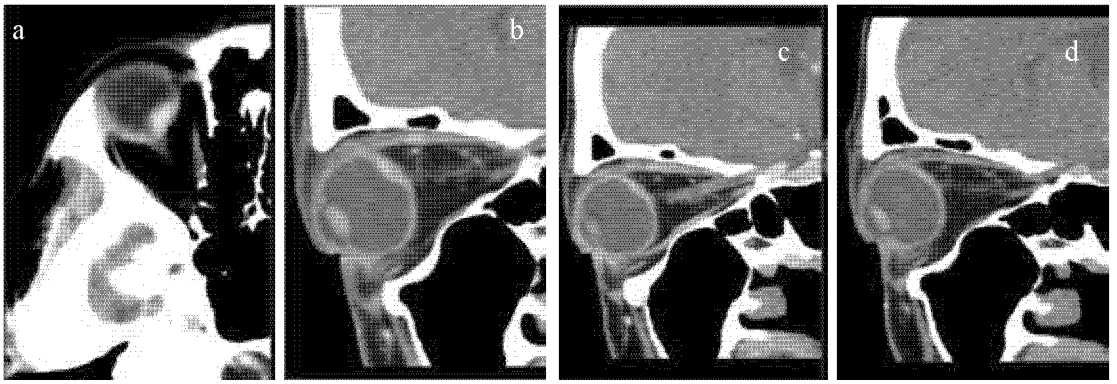

Fig 1. Initial pre-treatment and series follow-up CT images of 49 year-old female choroidal melanoma patient a) pre-treatment CT image, tumor 4.0 * 11.2mm; b) 1.5-year follow-up CT image, tumor 3.7 * 9.5mm; c) 2.5-year follow-up CT image, tumor 3.4 * 9.5mm; d) 3.5-year follow-up image, complete response.

The minimal dose to lens was 3.7 Gy. Her visual acuity recovered after an intraocular lens implant. Overall, 75% patients with initial normal vision had a visual acuity of more than 0.1 after 3 years. The other patient suffered from severe neovascular glaucoma. Even though this was treated with Bevacizumab (Avastin®) injections twice, the neovascular glaucoma still progressed and she had enucleation 24 months after SRT. In fact, four (67%) of the irradiated eyes developed neovascular glaucoma, which was noted one year after SRT. The main management was topical atropine, topical steroid or both. In addition, four patients had transient blepharoconjunctivitis, which subsided after conservative treatment. At the same time, no specific skin reaction was found in medical records.

DISCUSSION

Since proton therapy and radioplaque treatment are not available in Taiwan until now, most patients with choroidal melanoma were treated with enucleation [23]. Although there are a limited number of cases, this study provides evidence that LINAC based hypofractionated SRT is feasible for patients with choroidal melanoma. The local control rate is good and the complication-induced enucleation rate is acceptable when compared to treatment only by enucleation.

Local control is the main goal of treatment for patients with local choroidal melanoma. Once the local tumor recurred, the distant metastatic rate significantly increases and the survival duration after developing metastatic disease is only 7 months [5, 10]. Radioplaque brachytherapy is the most common conservative treatment used in the management of choroidal melanomas followed by charged-particle radiotherapy. The efficacy of the plaque brachytherapy for medium-sized tumors was established by a COMS-conducted randomized trial, which demonstrated that there was no difference in mortality between plaque brachytherapy and enucleation [20]. In the I-125 brachytherapy group, rates of melanoma-associated deaths at 5 and 10 years were 10% and 18%, respectively, and in the enucleation groups were 11% and 17%, respectively. The recurrence rate following Ru-106 brachytherapy ranged from 3% to 16% [39]. However, an invasive surgical procedure is required to open the conjunctiva and suture the metal plaque [19, 20, 25, 41]. For large-sized choroidal melanoma and lesions located close to the optic disc, there are often technical difficulties for plaque insertion and adequate dose coverage.

Proton-beam therapy has the advantage of delivering a homogenous dose to the entire tumor, no matter where the tumor is located. The sharp fall of radiation dose of the proton beam, the Bragg peak phenomenon, allows sparing of normal surrounding tissues. The usual prescribed dose is 60-70 cobalt gray equivalent (CGE) in 4 to 5 fractions [44]. Proton-beam therapy achieved good results with 95% local tumor control [4, 15]. The costs and few available sites around the world limit access to this effective modality.

SRT for choroidal melanoma can be performed utilizing a gamma knife or a linear accelerator. In 1990s, Logani et al. and Marchini et al. started to use the precise small irradiation field of gamma knife to treat choroidal melanoma [24, 26]. The local control rates by gamma knife radiosurgery ranged from 83% to 93% with a wide dose range (30 Gy to 70 Gy) [29, 33]. Tokuuye et al. and Buatti et al. introduced the feasibility of LINAC-based SRT for the treatment of choroidal melanoma [2, 40]. Several studies showed the 5-year local control rates from 86% to 100% and metastasis free survival rates from 75% to 85% [1, 11, 22, 31, 32, 42, 45, 46]. At the same time, the non-invasive stereotactic technique of eye fixation was introduced by Dieckmann et al. and showed over 90% center shift < 1 mm [8]. In our study, local control and overall survival rates were both 100%. In a large series with LINAC-based SRT, 212 patients were treated with five fractions of radiotherapy using three different total doses (50, 60, and 70Gy) [11]. With a median follow-up of 64 months, 5-year and 10-year local control rates were 95.9% and 92.6%. However, the proportions for eye retention were 78.6% after 5 years and 72.6% after 10 years of follow-up.

There was no high level evidence of treatment related complications when comparing LINAC-based SRT and brachytherapy or charged particles. Only one randomized trial was established in 1993 comparing the helium ion and iodine 125 brachytherapy [6]. Char et al. found that the charged particle group had less local recurrence and more treatment complications of the anterior segment such as cataracts. However, the meta-analysis of 27 studies in 2013 also confirmed a similar result of lower local recurrence using charged particle therapy but a different result of less retinopathy and cataract formations [44]. A possible factor in fewer complications with charged particle therapy might be the selection of beam paths to avoid traversing the lens and keeping the lens dose < 10% of prescribed dose. Another factor could be a lower uniform dose distribution with relatively lower dose delivered to small region of retina.

One of our six patients had enucleation due to the development of neovascular glaucoma, which occurred in two-thirds of the six patients after SRT. This observation is consistent with other reports using SRT [11, 29, 46]. In fact, neovascular glaucoma and other complications, such as corneal ulcers, were the major reasons (65-75%) for performing enucleation after the treatment of choroidal melanoma. Neovascular glaucoma results from the radiation-induced ischemic vascular event, which provokes the process of neovascularization. The new blood vessels obstruct the trabecular meshwork in the anterior chamber angle and lead to the development of glaucoma. Neovascular glaucoma is a potentially devastating glaucoma. Early diagnosis of the disease, followed by immediate and aggressive treatment, is imperative. Gragoudas et al. reported a low enucleation rate (10%) at five-year follow up after proton therapy [16]. Neovascular glaucoma was still the most common complication leading to enucleation, responsible for less than one half of post-treatment enucleations [13, 16]. Multiple parameters may have a role in the development and/or progression of neovascular glaucoma including tumor size.

location and radiation dose distribution. Kavita et al. reported that the specific characteristic of Bragg peak in proton therapy might spare lens, ciliary body, optic disc and optic nerve to reduce the risk of serious complications [28].

Visual preservation is a significant issue for quality of life for patients with choroidal melanoma [27]. Tumors in proximity to the macula and the optic disc have a worse visual prognosis than tumors sited in the periphery of the choroid (> 5 mm) [9]. Other factors, such as history of diabetes, initial poor visual acuity, initial retinal detachment, posterior-located tumor, post-treatment cataracts and post-treatment retinopathy, can affect the final visual capacity [7, 32, 36, 42]. While decreasing the total dose from 70 to 50 Gy, no prominent visual preservation was observed [12, 16]. Various modalities of radiotherapy seem to have different effects on the preservation of visual acuity. The results of gamma knife radiosurgery showed that the 5-year retention rate of visual acuity was 14% [42]. In patients receiving hypofractionated SRT, 19.8% and 8.8% of patients had a visual acuity above 0.1 after 3 years and 5 years, respectively [11]. Three of our four patients with an initial visual acuity of better than 0.1 ketp their vision after SRT. The patient with loss of visual acuity was due to severe repeated neovascular glaucoma. For patients treated with proton therapy, the 5-year rate of vision loss was 52%. However, this rate was as high as 68% for patients with tumors close to the optic nerve [4, 30].

Preserving a comfortable, cosmetically acceptable, and functioning eye with useful vision and minimizing the risk of metastasis continue to be the major concerns in the management of choroidal melanoma. Although this retrospective study with very limited patient numbers cannot provide solid evidence for the treatment of choroidal melanoma, our results support the theory that hypofractionated SRT with 50 Gy applied in five fractions seems to be sufficient to obtain good tumor control. However, results with more patients and a longer follow up period have to studied carefully before definitive conclusions can be drawn. More can be done to reduce radiation-induced neovascular glaucoma. Possibilities include: the use of anti-vascular endothelial growth factor (anti-VEGF) drugs [43]; surgical intervention of the scar endoresection after treatment [3]; preservation of visual acuity by reducing radiation dose to lens, optic nerve and retina. The advantages of proton therapy should help to overcome these obstacles.

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立體定位寡分次光子放射治療對脈絡膜黑色素瘤之結果分析

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目標：雖然脈絡膜黑色素瘤是最常見的眼睛原發惡性腫瘤，但是在台灣仍是較為罕見的疾病。在本研究中，我們希望能夠了解使用立體定位寡分次光子放射治療對於此疾病的治療效果。
材料與方法：從 2009 到 2012 年，共有 6 位脈絡膜黑色素瘤的病患拒絕接受眼球摘除手術並且使用直線加速器接受立體定位放射線體外照射治療。總劑量為 50 Gy 並分為 5 次進行。所有的病患於放射治療前以及治療後追蹤皆需要接受眼科詳細的檢查，包括：視力以及眼底鏡檢查。此外，電腦斷層也會在治療後用於追蹤腫瘤的治療效果反應。
結果：在本研究中，一共三位病患有中型的腫瘤，另外三位擁有大型的腫瘤。腫瘤高度的中位數為 9.3 mm，底部直徑中位數為 13.4 mm，以及體積中位數為 0.94 立方公分。追蹤時間中位數為 29 個月，三年的局部控制、遠端轉移控制以及整體存活率皆為 100%。有一位病患在接受治療的 25 個月後，因為治療後產生的新生血管型青光眼而接受眼球摘除手術。在四位治療前視力大於 0.1 的病患中，有三位仍然能夠在治療後保留視力。其中有一位34歲的病患於接受治療 24 個月後，發生了白內障的情況影響視力，並且在接受了人工水晶體置換手術後恢復了部分的視力。
結論：此研究顯示總劑量為 50 Gy 分為 5 次的立體定位寡分次光子放射線治療對於脈絡膜黑色素瘤有著良好的局部控制率。保留視力以及減少放射治療引起的新生血管型青光眼是我們仍舊需要在未來努力的目標。
[放射治療與腫瘤學 2014; 21(3): 191-199]

關鍵詞：立體定位放射治療、脈絡膜黑色素瘤、視力保留