Clinical research

Prevention and treatment of the toxic tumour syndrome following primary proton beam therapy of choroidal melanomas

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Abstract

Introduction: The aim of this study was to evaluate the efficacy and safety of endoresection for choroidal melanoma to prevent and treat the toxic tumour syndrome (TTS).

Material and methods: Thirteen patients who underwent primary proton beam therapy (PBRT) for choroidal melanoma followed by endoresection were evaluated. Main outcome measures were functional and anatomical results, surgical complications, rate of local recurrence, presence or absence of metastatic spread.

Results: The median time of the follow-up period was 61.6 months. Six patients with clinical signs of TTS and seven with large tumours to prevent TTS underwent endoresection. Tumour thickness was 5.8 to 9.3 mm (mean: 7.6), the basal diameters were 10.6 to 15.0 mm (mean: 13.4). Preoperative best corrected visual acuity (BCVA) was 6/7.5 to counting fingers and the final BCVA was 6/15 to no light perception, and was better in those treated to prevent TTS (p = 0.01). The most universal early postoperative complication was bleeding from the scleral bed. The most common late postoperative complications were epiretinal membrane formation (30.8%), cystoid macular oedema (23.1%) and silicone oil-induced glaucoma (15.4%). Two (15.4%) patients developed phthisis bulbi, neither developed local recurrence. One patient developed liver metastases.

Conclusions: Endoresection for choroidal melanoma is a safe and effective procedure with a high rate of local tumour control. The procedure appears to be useful in the prophylaxis and treatment of TTS after PBRT of choroidal melanoma.

Key words: choroidal melanoma, endoresection, pars plana vitrectomy, toxic tumour syndrome.

Introduction

Choroidal melanoma is the most common primary intraocular malignancy in adults with an incidence of 5–6 cases per million of the population per year [1]. For decades tumour was treated with enucleation, until the Collaborative Ocular Melanoma Study demonstrated that survival rates did not differ significantly between enucleation and I^{125}

brachytherapy [2]. Currently the main therapeutic options for choroidal melanoma that allow preservation of the globe include radiotherapy, which may be associated with severe ocular morbidity [1, 3]. Visual loss can occur as a result of damage to the optic nerve, retina, fovea, and lens or from exudation from the irradiated tumour, causing macular oedema, serous retinal detachment (RD) and neovascular glaucoma [1, 3]. The latter complications are the result of the "toxic tumour syndrome" (TTS), which is related to the released proinflammatory cytokines from the irradiated ischemic tumour mass [4–7]. TTS correlates mainly with tumour bulk. Resection of a tumour in eyes with serous RD and/or neovascular glaucoma following irradiation, may lead to resolution of these complications by removing the source of toxic inflammatory mediators [8, 9]. Endoresection may also play a role as adjunctive treatment in large choroidal melanomas following irradiation to prevent the development of TTS [10, 11].

To our knowledge, there are a few publications concerning the endoresection as a prevention of TTS following the choroidal melanoma irradiation [8, 9]. Most reports present the results of endoresection in eyes with established TTS or analyse the results of endoresection as a primary method of treatment with or without adjuvant brachytherapy [5, 9, 12–20].

The aim of this study was to present the efficacy, safety and outcomes of the endoresection of choroidal melanomas in the prevention and treatment of TTS after proton beam radiotherapy (PBRT).

Material and methods

The study comprised 13 eyes of 13 patients with choroidal melanoma treated primarily with PBRT. Inclusion criteria were: posterior or equatorial tumour localization, base diameter of ≤ 15.0 mm, tumour thickness ≥ 8.0 mm or less when clinical signs of TTS were present. The TTS was diagnosed when bullous serous RD involving the macula and/or macular oedema and/or neovascular glaucoma were present. Preoperative examination included Snellen best corrected-visual acuity (BCVA), slit-lamp biomicroscopy and ophthalmoscopy. Tumour dimensions were measured with ultrasonography. The tumour thickness was measured from the internal scleral surface to its apex (Quantel Medical, ABSolu, France). Optical coherence tomography (OCT, Topcon 3D OCT 2000, Japan) was performed to assess the morphology of macula. Screening for metastatic disease in all cases involved serum biochemistry, liver function tests, ultrasonography of the liver and chest X-ray. The endpoints of the study were the functional and anatomical results as well as the presence or absence of local and systemic complications.

The endoresection of the tumour was performed as previously described in the literature [12, 17]. Phacoemulsification of a cataract or a clear lens with a foldable intraocular lens implantation was performed in order to obtain better access to the vitreous base during subsequent vitrectomy. Then a three-port transconjunctival microincisional 23-gauge vitrectomy was fashioned. The surgery started with preservative-free triamcinolone guided posterior vitreous detachment. Extensive vitrectomy with indentation was performed and endodiathermy was applied beyond the tumour margins to close ambient vessels as well as retinal vessels at its base to decrease the risk of bleeding during tumour removal. Systemic hypotension (systolic blood pressure ≤ 90 mm Hg) was induced during tumour excision. In addition, the intraocular pressure (IOP) was increased for approximately 30 min to no more than 60 mm Hg to temporarily occlude the choroidal circulation so as to reduce bleeding from choroidal vessels and to decrease the risk of neoplastic haematogenous dissemination. Tumour cell dissemination was also prevented using high suction (600 mm Hg) and high flow (35–40 ml/min) rates. The cut rate was 200–300/min. Excision was started at the apex of the tumour and carried down to the sclera. The overlying retina was removed together with the tumour mass. After tumour removal, the infusion pressure was lowered until bleeding commenced, so that bleeding points could be recognized and treated by endodiathermy. The scleral bed was then treated by endodiathermy and/or endolaser photocoagulation (532 nm) with high power 200–300 mW to destroy any residual tumour cells. The retina was reattached by fluid-air exchange and all subretinal fluid was drained with a flute needle. Two or three rows of confluent endolaser were applied to the edges of the retinectomy as well as around the surgically-induced coloboma. Silicone oil (5000 cSt) was then injected in. At the end of surgery the retina was flat in all cases.

In all cases vitreous specimens were sent for histopathological evaluation.

Follow-up examination was performed on the first post-operative day and then after 1 month, 3 months, and subsequently every 6 months. Screening for metastatic spread was carried out every 6 months.

Statistical analysis

Statistical analysis was performed using StatSoft, Inc. (2015) Statistica (data analysis software system), version 12.7. The Fisher's exact test was used to assess the association between endoresection and the prevention or treatment of the TTS. The analysis included also the incidence of early and late postoperative complications, tu-

mour characteristics and visual outcomes. The significance level was taken as $p < 0.05$.

Results

Among 13 patients there were 6 men and 7 women with a mean age of 50.8 years (range: 28–73 years; standard deviation = 26.4 years). The follow-up time ranged from 34 to 84 months (the median: 61.6 months). The mean tumour thickness was 7.6 mm (range: 5.8–9.3 mm; standard deviation = 2.8 mm) and the mean base diameter was 13.4 mm (range: 10.6–15.0 mm; standard deviation = 2.1 mm). In 10 (84.6%) patients the tumours were posterior and in 2 (15.4%) they were equatorial. In all cases the endoresection was performed after PBRT. In each case, a total dose of 60 cGy (4 × 15 cGy) irradiation was applied. The time interval between PBRT and endoresection ranged from 3 to 9 weeks (mean: 5.6 weeks). In 7 patients with large choroidal melanomas, surgery was performed as prophylaxis for TTS and in 6 cases as treatment for established TTS which was characterized with the presence of serous bullous RD located in the lower quadrants of the fundus (3–7 clock hours), involving the macula in all cases. Additionally diffuse macular oedema with central retinal thickness (CRT) ranged from 312.5 to 383.6 µm was present in 4 cases and in two others, neovascular glaucoma was diagnosed. Tumours undergoing endoresection for TTS prophylaxis were thicker (8.3 vs. 6.6 mm, $p = 0.01$) and were located further from the fovea (5.6 vs. 2.8 mm, $p = 0.001$) than those treated for established TTS. None of the patients had metastatic disease prior to surgery. The detailed clinical characteristics of the patients and tumours are shown in Table I.

Before endoresection, the BCVA of 6/60 or better was present in 5 of patients treated to prevent TTS and in 4 of those who underwent surgery because of fully developed TTS. The final BCVA was significantly worse as compared to the preoperative levels in both groups and ranged from 6/15 to no light perception. However patients who underwent surgery for prophylaxis had better BCVA at the end of a follow-up as compared to those patients with fully established TTS. These differences were statistically significant ($p = 0.01$). No intraoperative complications occurred in any of the patients. The universal early postoperative complication (≤ 30 days) was bleeding from the margins of the resected choroid. Other early postoperative complications included: transient corneal oedema in 3 eyes, fibrous exudate in the anterior chamber in 4, transient ocular hypertension in 3, and endophthalmitis in one eye. In the last patient, an aqueous humour microbiological analysis showed *Bacillus species*. The patient was treated with intravitreal injections of vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml). Late postoperative complications (> 30 days) were: epiretinal membrane formation in 4 patients, cystoid macular oedema in 3, silicone oil-induced glaucoma in 2 and severe proliferative vitreoretinopathy (PVR) with rhegmatogenous RD (RRD) in one eye filled with silicone oil.

Silicone oil was removed 5–8 months after endoresection. The main complication after silicone oil removal was RRD with PVR in 3 eyes. These 3 cases, as well as another one with developed PVR and RRD in the eye filled with silicone oil, were reoperated and pars plana vitrectomy with a secondary silicone oil endotamponade was performed. The procedure was successful in three of these four complicated cases.

At last follow-up, all patients retained the eye, however, two eyes became phthisical. The phthisis occurred in one eye with endophthalmitis and in one eye with large surgically-induced choroidal coloboma (baseline tumour diameter 15.0 mm). Seven eyes showed flat retina after silicone oil removal and four had still endotamponade after the reoperation with silicone oil reinjection. In the latter eyes, the retina was flat under silicone oil except of one case in which the peripheral retinal break in atrophic retina was diagnosed (Table I).

Histological examination showed evidence of malignancy in all cases (Table I).

During the follow-up period, none of the patients developed choroidal, conjunctival or orbital recurrences. Metastatic disease was detected in one patient with a 15.2 mm diameter epithelioid cell melanoma. Metastatic disease occurred 37 months after endoresection but no deaths were recorded by the end of the study.

Statistical analysis

The statistical analysis showed no correlations between tumour thickness, localization, TTS, and postoperative complications. However, there was a significant correlation between the development of PVR with RRD and the diameter of the tumours' base: if it was ≤ 14.0 mm, the risk of PVR was smaller as compared to tumour base diameters of > 14.0 mm ($p = 0.01$).

Discussion

Vitreoretinal surgery has played an important role in the surgical management of choroidal melanoma since Peyman and Cohen described *ab interno* resection of uveal melanoma in 1986 [21]. Later Damato *et al*. reported his results and introduced the term *endoresection* [12].

Endoresection may be performed as a primary surgery or as a salvage procedure after

Table I. Characteristics of patients and summary of the results

Case no.	Sex	Age	Tumour largest base [mm]	Tumour thickness [mm]	Tumour localization	Indication for endoresection	Time from PBR to endo-resection [weeks]	Histo-pathologic cell type	Preop BCVA	Final BCVA	Anatomical success	Early Post-op. compli-cations	Late postop. complica-tions	Secondary procedures	F/U time [month])
1	M	56	12.6	8.1	Superotem-poral, 5.8 mm from the fovea	Prophylaxis of TTS	4	Spindle B	6/20	LP	Yes	Bleeding Elevated IOP FE in AC TCE	ERM PRN	SO removal	84
2	M	73	15.0	6.7	Juxtapapillary (3 clock h)	Serous RD RI	8	Epithelioid	CF	CF	Yes	Bleeding FE in AC TCE	SOG	SO removal	83 (liver metastasis)
3	F	63	14.4	5.8	Inferotemporal 2.0 mm from the fovea	Serous RD	9	Spindle B	6/60	CF	Yes	Bleeding TCE	ERM PRN CME	SO removal	74
4	M	58	15.0	7.9	Superonasal	Prophylaxis of TTS	4	Epithelioid	6/100	NLP	No	Bleeding FE in AC	PVR + RRD Phthisis	SO removal Repeated PPV with SO reinjection	73
5	F	57	14.6	6.8	Temporal, 2.1 mm from the fovea	Serous RD	8	Mixed	6/60	NLP	No	Bleeding Endophthal-mitis	Phthisis	IVI of antibiotics	69
6	F	54	13.2	9.3	Inferotempo-ral, 5.3 mm from the fovea	Prophylaxis of TTS	3	Spindle B	6/60	HM	Yes	Bleeding FE in AC	ERM, PVR + RRD, CME	SO removal	68
7	M	32	14.2	7.9	Nasal	Prophylaxis of TTS	4	Necrotic	6/7.5	6/15	Yes (S.O.)	Bleeding Elevated IOP FE in AC TCE	ERM PVR + RRD after SO removal	Repeated PPV with SO reinjection	64
8	M	51	14.8	8.4	Juxtapapillary (5 clock h)	Prophylaxis of TTS	4	Mixed	6/7.5	6/30	Yes (S.O.)	Bleeding TCE	PRN PVR + RRD after SO removal	Repeated PPV with SO reinjection	63
9	F	28	13.5	7.5	Temporal, involving the macula	Serous RD NG	9	Spindle B	CF	HM	Yes (S.O.)	Bleeding Elevated IOP	PVR + RRD after SO removal	Repeated PPV with SO reinjection	62

Table I. Cont.

Case no.	Sex	Age	Tumour largest base [mm]	Tumour thickness [mm]	Tumour localization	Indication for endoresection	Time from PBR to endoresection [weeks]	Histopathologic cell type	Preop BCVA	Final BCVA	Anatomical success	Early Post-op. complications	Late postop. complications	Secondary procedures	F/U time [month])
10	F	55	11.3	9.1	Inferonasal	Prophylaxis of TTS	6	Spindle B	6/10	6/20	Yes	Bleeding	SOG	SO removal	61
11	F	51	10.6	7.9	Juxtapapillary (3 clock h)	Prophylaxis of TTS	5	Mixed	CF	LP	Yes	Bleeding	–	SO removal	52
12	F	32	13.2	6.4	Superior	Serous RD	7	Mixed	6/30	6/24	Yes	Bleeding	PRN, CME	SO removal	34
13	M	36	13.8	8.2	Juxtapapillary (5 clock h)	Serous RD	7	Spindle B	6/30	CF	Yes	Bleeding	PRN	SO removal	34

RD – retinal detachment, RI – rubeosis iridis, NG – neovascular glaucoma, BCVA – best corrected visual acuity, NLP – no light perception, LP – light perception, CF – counting fingers, HM – hand movements, SO – silicone oil, FE in AC – fibrous exudate in anterior chamber, TCE – transient corneal oedema, ERM – epiretinal membrane, PVR – proliferative vitreoretinopathy, ERM – epiretinal membrane, CME – cystoid macular oedema, PRN – post radiation neuropathy, SOG – silicone oil glaucoma, IVI – intravitreal injection, F/U – follow-up.

brachytherapy or PBRT, however, it may be associated with severe ocular complications [13, 15, 17]. Indications for primary endoresection include: large tumours (thickness > 8 mm), patients with only one useful eye, and to prevent the TTS [10, 22–25]. Endoresection may also be an option to treat tumours near to the optic nerve head as radiotherapy carries a significant risk of optic neuropathy [12, 13, 15, 26]. Primary endoresection also enables assessment of prognosis by the examination of vitreous specimens using histopathological, cytogenetic tests [12, 17]. Secondary endoresection is indicated as a prophylaxis of the TTS, a serious complication of radiotherapy, and in tumour recurrence after primary radiotherapy [12]. Thus, based on the literature, it appears that removal of a choroidal melanoma may spare the eye some severe complications of radiation such as retinopathy and optic neuropathy and that these benefits may occur even when the tumour is treated with plaque brachytherapy or proton beam irradiation [25].

Endoresection can be performed irrespective of tumour dimensions, but there is an increased risk of local complications when the base exceeds 15 mm [5, 12, 16, 21, 23, 24]. Biewald *et al.* performed the endoresection in tumours with a base diameter up to 20 mm and the most common observed complications were: phthisis, local recurrence, opaque media with loss of fundus visibility and severe vitreous haemorrhage [27]. In our material, the biggest tumour's base diameter was noted in two cases and achieved 15.0 mm. In one of them phthisis bulbi occurred during a follow-up and the eye was enucleated.

Among analysed patients the most common early postoperative complication was bleeding from the margins of the resected choroid. This complication has also been reported by others and was observed in 4.8–100% of cases [12, 14, 17, 21]. This problem may be related to inadequate silicone-oil fill of the treated eye [28]. Transient ocular hypertension, corneal oedema and fibrous exudate in the anterior chamber were less frequent and the same observation was described by others [8, 14]. In our 4 patients the latter complication was probably associated with the cataract surgery (phacoemulsification) rather than with endoresection of the tumour itself. Two of these eyes required iris retractors during the surgery, which may increase the risk of fibrous exudate formation. One patient developed early post-operative endophthalmitis. Damato *et al.* also reported one similar case of endophthalmitis among 52 patients who underwent endoresection for choroidal melanoma [12]. In our study, the phthisis occurred in one eye with large surgically-induced choroidal coloboma and retinotomy. This rare complication

was also observed by others [12, 17]. To prevent this severe complication in eyes when a large coloboma is expected to cause postoperative hypotony and phthisis it is indicated to create a small retinotomy, less than 7 mm in diameter [28].

In the analysed group of patients, the most serious late postsurgical complication was RRD with PVR in one eye filled with silicone oil, which was associated with the presence of peripheral retinal break in atrophic retina. After silicone oil removal, the most common complication was retinal detachment, which occurred in 30.8% of treated eyes. In previous studies this complication was reported in 9.4% to 32.6% of eyes after silicone oil removal [12, 13, 17, 22, 25]. In our material the causes of retinal detachment after silicone oil removal were holes in retina within laser scars at the margins of coloboma (in 2 eyes) and peripheral retinal break in degenerative, atrophic retina (1 eye).

The majority of our patients undergoing endoresection showed deterioration of vision as compared with preoperative examination. Kertes *et al.* reported BCVA of 6/60 or better in 31.2% of cases, which is comparable to our results [13]. By contrast Karkhaneh *et al.* reported an incidence of BCVA of 6/60 only in 13.4% of cases [19]. These differences in the final BCVA may be associated with lower preoperative BCVA and the fact that most tumours were close to the macula. In our patients the worse postsurgical BCVA occurred in those who underwent endoresection for fully blown TTS. This may be also associated with the unfavourable localization of choroidal melanomas in these patients. Tumour location is therefore important in determining the postoperative visual outcome. In our study, other causes of visual loss after tumour endoresection were development of PVR with RRD, phthisis bulbi and these observations are also in accordance with the literature [13, 14, 19, 29].

The use of vitrectomy techniques for tumour biopsy, tumour removal by endoresection, and of the treatment of post-radiation complications is expanding rapidly. However despite many reports the place of this procedure remains controversial. A potential problem is the intraoperative dissemination of tumour cells that can lead to local recurrences, extraocular extension or increased risk of distant metastasis. Based on the literature, depending on the follow-up period, the risk of local dissemination of tumour cells may range up to 19% of patients [13, 15, 17, 25, 26, 30, 31]. In our study, we have not observed any local recurrences during a follow-up period. In order to reduce the incidence of local tumour cell seeding, a combined approach has been developed, which includes pre- or postoperative irradiation [11, 12, 25, 27]. Other measures to minimize this risk include photocoagulation or endodiathermy to the bed of the surgically-induced choroidal coloboma to destroy any residual tumour cells which may be responsible for future recurrences [29]. It is also advisable to apply cryotherapy to the scleral ports at the end of the surgery to prevent any seeding of residual tumour cells [5, 12, 17, 22].

According to the literature, the metastatic disease in patients undergoing endoresection for choroidal melanoma was observed in 1.9–15.5% of cases after a mean follow-up of 41–102.5 months [12, 13, 17, 21, 30]. However it is unclear whether metastatic disease is of the iatrogenic origin or is associated with the presence of circulating malignant cells which seeded liver before surgery [20, 32, 33]. Damato *et al.*, who observed metastatic disease only in one among 52 patients 41 months postoperatively, stated that endoresection did not increase the rate of metastases [12]. It cannot be excluded that patients may have micrometastatic lesions that escape detection before the surgical treatment is initiated [33, 34]. In this study among the analysed group of patients, liver metastatic disease occurred in one patient with a tumour base of 15.2 mm 37 months after endoresection.

In conclusion, treatment of choroidal melanoma with brachytherapy or PBRT may be associated with problems arising from the treatment itself and from TTS caused by regression of the treated tumour. Endoresection is challenging and carries a guarded visual prognosis. Some patients may require multiple vitreoretinal procedures to achieve anatomical success. However, endoresection is a safe and effective procedure with a high rate of local tumour control and a low rate of a metastatic disease used for both prevention and treatment of TTS after PBRT of choroidal melanomas.

Conflict of interest

The authors declare no conflict of interest.

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