PROTON BEAM RADIOTHERAPY LONG TERM COMPLICATIONS

AND LOCAL CONTROL OF CHOROIDAL MELANOMAS

Mariana Augusto Gonçalves

Faculty of Medicine, University of Coimbra, Portugal

mi.ag.90@gmail.com

Abstract:

Purpose: to analyse long term complications and systemic control of Choroidal Melanomas after proton beam radiotherapy.

Material and Methods: This is a retrospective, noncomparative, consecutive case series. A total of 23 patients, 24 different tumors, between 1994 and 2013 were diagnosed with Choroidal Melanoma and submitted to a follow up in Coimbra's University Hospital Center, after receiving treatment in Hôpital Ophtalmique Jules Gonin, Lausanne, with proton beam radiotherapy. Clinical and procedural data were obtained from the file from Lausanne and the clinical file of each patient from Coimbra's hospital. Data were analysed in April 2013. The age of patients, when diagnosed, ranged from 23 to 88 years, from which 15 (61.5%) were men and 9 (37.5%) were women. Largest tumor diameter ranged from 12 to 22.8 mm and tumor height from 3.1 to 10.7 mm. Median follow up time was 92.5 months (8 years and 9 months).

Results: The overall eye retention rate at 5 and 10 years after the treatment was 91.31% and 87% respectively, and remained the same after 15 years. In total 3 eyes had to be enucleated.

In order of frequency, the complications evaluated were loss of visual function, cataracts, radiation retinopathy, macular edema, retinal detachment, secondary enucleation, tumor systemic dissemination, ocular hypertension, neurovascular glaucoma, tambolus rings extrusion, ocular nerve neuropathy and ocular globe atrophy. There were no recurrences. The number of cases with metastasis was 3, being always the liver the first place affected.

The number and severity of complications were related to age, to limbus diameter, distance between cornea and posterior lent of the eye, distance between the tumor and the macula, length of the margin established and the percentage of the maximal dose of radiation captured by the macula and the lens. There was no relation with the tumor size.

Discussion: The proton beam radiotherapy shows to be a viable technique on the local control of choroidal melanomas, allowing a conservative treatment even for less favourable tumors (with a large length and/or located less than 3mm from the fovea and/or optic nerve). Nevertheless, it can't always prevent the systemic dissemination of the disease, the secondary need of enucleation and a big rate of complications associated.

Conclusion: The optimization of the treatment for this condition has been allowing the preservation of the eye, with a very positive survival rate and a progressively reducing number of long-term complications.

Introduction

Uveal melanomas are tumours developed from the melanocytes of the uveal tract. It is the most common primary intraocular cancer in adults[1], with an incidence of ~7 per million per year, being more common in Caucasians than other human populations. The role of sunlight is uncertain[2]. Tumours can involve the iris, the ciliary body and, most commonly, the choroid[2].

Less radical procedures compared with enucleation, which was the standard treatment until about the 70's[1], are available, including: transpupillary thermotherapy, local resection (endoresection or transscleral local resection) or, a more recent and emerging nowadays technique: radiotherapy.

The vision loss, the poor cosmetic outcome and the risk of tumour spread, caused by manipulation of the eye during surgery, have made irradiation therapy a popular alternative to enucleation[1]. Two major modalities are performed: placing radioactive plaques formed by, most commonly, iodine-125 or ruthenium-106, sutured on the sclera, over the base of the tumour, called brachytherapy or irradiating the tumour from outside with charged particles (using protons or helium). In charged particles treatment planning, the edges of the tumour are delineated by four tantalum rings sutured to the sclera[3]. Radiotherapy with proton beam became widely used and was the object of our study. With it, it has been possible to achieve local tumour control, preserving more often the eye and the visual function, without jeopardizing survival rates[4].

Proton beam radiotherapy emerged as an alternative to enucleation for large tumours and brachytherapy for small tumours, especially those who were close to the optic disc (parapapillary if close to, and peripapillary if contiguous to the optic disc) or to the macula, iris and ciliary body. There are two main theoretical advantages of proton therapy to brachytherapy: in brachytherapy, non-affected ocular structures such as the macula, the optic

disc and the optic nerve, may receive part of the dose delivered to the tumour apex, while that with proton therapy, the edge is much sharper, and the distribution of the radiation is much more homogeneous. The second advantage is that the radiation exposure to the surgeon's hands occurring during the fixation of episcleral plaques, doesn't happen with proton beam radiotherapy[5].

However, this kind of treatment cannot assure the strict systemic control of tumour dissemination. Also, collateral damage to healthy intraocular tissues can cause complications over the time[6], either specifically associated with the lesion of the tissues that receive high doses of radiation, either attending the lack of tumour growing control. A third kind of lesion has to be distinguished, concerning the effects that occur in tumoral and vascular endothelial cells, resulting in tumour shrinkage, ischemia, infarction, exudation, and fibrosis, which lead to exudative maculopathy, serous retinal detachment, rubeosis, and neovascular glaucoma (the so called, 'toxic tumour syndrome')[7].

Between the ones specifically associated with the treatment, we give special attention to radiation-induced retinopathy, optic neuropathy, cataract and secondary enucleation, and related to the dissemination control: metastatic dissemination and death.

The earliest and most common finding is retinopathy and cataracts. Macular oedema includes intra-retinal haemorrhages, cotton-wool spots, microaneurysms, lipid exudation, retinal neovascularization, retinal pigment epithelium changes and vitreous haemorrhage. Sub retinal neovascularization, central vein occlusion and central retinal artery occlusion are less frequent findings[8].

A huge investment in research has been developed around the choroidal melanoma ability to metastasize. Because the tumour is never actually excised, local tumour growing control can fail and metastasis can occur years after the treatment, tacking a big role in

survival rates. It disseminates mainly by haematogenous way, being the liver the most common place affected[11,12].

Despite the accuracy of the technique allowing sparing the healthy tissue surrounding the target volume, some eyes had to be enucleated after treatment because of complication, like ocular globe atrophy or local tumour control failure.

To help knowing better the pros and cons, we decided to evaluate long-term results of proton beam irradiation therapy, by the information of respective follow-up, according to complications, visual outcome and survival, sharing our experience with this growing technique.

Material and methods

We evaluated 23 patients who were diagnosed and followed at the Ocular Oncology Unit of Centro Hospitalar e Universitário de Coimbra, between November 1993 to April 2013. These patients were submitted to proton beam radiotherapy in Hôpital Ophtalmique Jules Gonin, Lausanne, from January 1994 to August 2012.

Diagnose of choroidal melanoma was established through a clinical examination using indirect ophthalmoscopy and ultrasonography. According to the COMS[9,10], these two methods present a diagnostic precision of 99.7%. The treatment was provided in an average 6 months after the diagnosis, more often between 2 and 3 months. Radiation planning was done with an interactive three-dimensional computer system to define the beam aperture and range modulation needed to adequately encompass the tumour and a 1.5mm margin, included to allow for motion during treatment, setup error and possible microscopic extension[3]. Patients received a 60 CGE total dose divided in 4 equal fractions in 2 to 4 days.

Follow up examinations were performed every 3 months in the first year, 6 months in the first five years after receiving the treatment, and then every year. In each and every

examination, all the complications and visual acuity were properly evaluated and registered, as also a hepatic ultrasonography or CT and blood tests with liver function tests.

The variables analysed in this study were:

1) Related to the patient: age, sex, visual acuity before and after treatment and complications after the therapy;

2) Related to the eye: eye affected, globe diameter, eye length, horizontal diameter of the eye, length thickness, globe volume, limbos diameter, eye vertical diameter, distance between cornea and posterior face of the lens;

3) Related to the tumour: tumour type, localization, TNM classification, tumour major large, tumour thickness, distance to the disc, distance to macula, volume, anterior margin of the tumor, position according to the equator and involvement of ciliary body;

4) Related to the treatment: time between diagnosis and treatment provided, dose received by different structures (such as retina, globe surface, globe and lent volume, lent periphery, ciliary body, optic disc, macula, optic nerve length, tumour surface and cornea surface) and percentage of irradiation received by the papilla, the macula, the lens and around it.

The statistical analysis, which adjusts for variable follow up time (5, 10 and 15 years after), provides an epidemiologic study of the affected population of the tumour characteristics, the treatment details, the rates of complications and the possible relation between these variables.

Results

The epidemiologic and tumor characteristics are presented in Table 1.

None of the patients had bilateral tumours but one patient had two different tumours in the same eye.

Table 1 - Epidemiologic and tumour characteristics' data.

Mean age	64.5
No. male	15 (62.5%)
No. left eye	18 (75%)
No. of pre-treated vision worse than +1	12 (52%)
Median tumour max diameter	16.33
Median height	7.42
Median distance to the disk	2.86
Median distance to the macula	2.88
Median volume	959
Ciliary body affected	13 (54.2%)
Median follow up	92.5 months

In order of frequency, the complications evaluated were (Table 2): loss of visual function (mean of 0.661LogMar), cataracts in 50% of the patients, radiation induced retinopathy in 25%, macular oedema in 16.7%, retinal detachment and secondary enucleation in 12.5%, ocular hypertension, neovascular glaucoma and tantalum rings extrusion in 8.3%, metastasis in 4 patients (8.3%) being the liver the first place, followed by the lungs and radial proximal diaphysis (only in one patient), ocular nerve neuropathy and ocular globe atrophy in 4.2%, and 0% of recurrences.

Table 2 - Complications, by general frequency order, according to time of follow up.

Complications	Years after the treatment and cumulative percentage			
	5 years	10 years	15 years	Cumulative frequency
Cataracts	8 (33.3%)	2 (8.3%)	2 (8.3%)	12 (50%)
Radiation induced retinopathy	6 (25%)	0	0	6 (25%)
Macular oedema	3 (12.5%)	1 (4.2%)	0	4 (16.7%)
Secondary enucleation	2 (8.3%)	1 (4.2%)	0	3 (12.5%)
Retinal detachment	3 (12.5%)	0	0	3 (12.5%)
Ocular hypertension	2 (8.3%)	0	0	2 (8.3%)
Neurovascular glaucoma	2 (8.3%)	0	0	2 (8.3%)
Tantalum rings extrusion	1 (4.2%)	1 (4.2%)	0	2 (8.3%)
Hepatic metastasis	1 (4,2%)	0	2 (8,3%)	3 (12,5%)
Extra hepatic metastases	0	0	1 (4,2%)	1 (4,2%)
Ocular nerve neuropathy	1 (4,2%)	0	0	1 (4,2%)
Ocular globe atrophy	1 (4,2%)	0	0	1 (4,2%)
Recurrences	0	0	0	0 (0%)

The earliest and most common finding was cataracts, which was present in 50% of patients overall, 33.3% by the end of 5 years, and 41.6% by the end of 10. Retinopathy, present in 25% of the cases, was developed always in the first 5 years after the irradiation. The overall eye retention rate at 5 and 10 years was 87.5% and 83.3% respectively and kept the same after 15 years. In total, 3 eyes had to be enucleated, including the eye with two tumours.

Variables related to the patient

Age was significantly influent in the appearance of macular oedema in the first 5 years (P = 0.032) and 10 years (P = 0.048) after the treatment, being this complication more prevalent in patients with more age (median of 62 vs 78 years old and 62 vs 75 years old,

respectively). Age was found to be significantly different between the group of patients that developed ocular hypertension (P = 0.037) and didn't, but it happened only in one case. About the influence of age in the development of cataracts, there was no significant difference in the first 5 years, but there was at the end of 10 years (P = 0.03) and 15 years (P = 0.001), being older patients more affected (median of 53 vs 70 and 46.5 vs 72.5 respectively).

Eye related

Limbos diameter was found to be significantly different between patients that developed cataracts (P = 0.014) being the patients with smaller diameter more vulnerable (median 12 vs 11.5). Distance between cornea and posterior lens was found to be significantly different between patients that did and didn't developed ocular hypertension (P = 0.02 at 5, 10 and 15 years after) but there was only one case. Also, secondary enucleation (in the first 5 years (P = 0.012; median 7.2 vs 7.5) and after that (P = 0.006) being the smaller distance more affected.

Tumor related

Distance between the tumour and the macula was found to be statistically different between patients that did and didn't developed cataracts in the first 5 (P = 0.035) (median 2.85 vs 0.5) and 10 years (P = 0.013) (median 3.95 vs 0.5), being the ones closer to the macula the ones more affected, but not after 15 years.

Treatment-related

A higher length of the anterior margin of the field of irradiation was found to be correlated (P = 0.036) with the development of macular oedema in the first 5 years after treatment (median 3.9 vs 8.1). Radiation maculopathy, which includes a big variety of

findings such as macular oedema, intraretinal haemorrhages and microvascular changes[8] was the third most frequent.

Two dose related lesions were found to be significant for the need of secondary enucleation:

1. A higher 90% maximal dose to the macula was found to be correlated with secondary enucleation after 10 years (P = 0.046) and also 15 years (P = 0.046). All the patients enucleated had received 90% of the maximal dose of radiation of 100% of the area of the macula (Table 3).

2. Higher % of the total dose captured by the area around the lens was found to be correlated with secondary enucleation after 5 years (P = 0.048).

Table 3 - Number of patients enucleated according to % of macular area affected

% of Macular area affected	No of patients receiving the dose	No of patients enucleated
100	12	3
50-<100	4	0
0-<50	8	0

Outcomes before treatment from patients preserving good rates of vision despite the tumor, were replaced by worst outcomes after the treatment, according to the last evaluation of each patient (Fig. 1). Even though, 4 patients improved their vision, one being in the second year after his treatment, and the other three preserving it for 5, 8 and 18 years already.
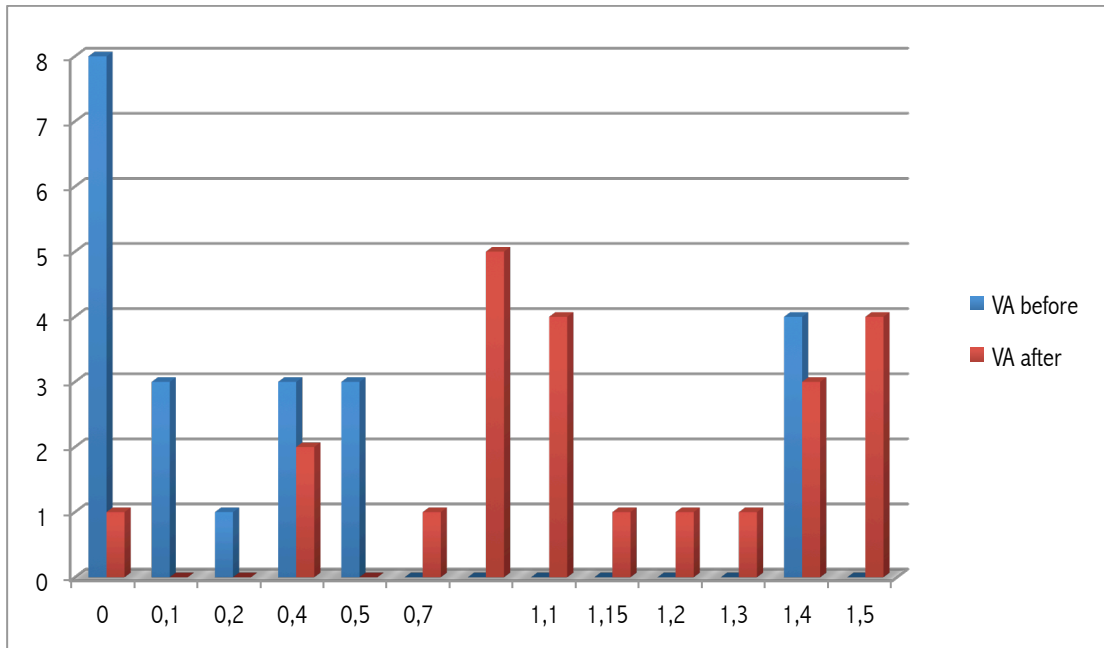
Figure 1 - Distribution of visual acuity before and after treatment.

In Table 4 we presents by colours the patients that preserved or improved (in blue) their visual acuity, against the ones who got worst outcomes after the treatment (in red). As we can see, the major part of the patients didn't preserve their visual function.

Table 4 - Progression of visual outcome, from baseline visual acuity, to the least documented. Blue cells represent patients who maintained or improved their visual acuity. Red cells represent the ones who lowered their outcomes.

Post irradiation Visual Acuities – No of eyes (%)					
Pre-treatment Visual acuities	-0,3 – 0,2 (>5 -10)	0,3-0,9 (>1 - 5)	1-1,15 (CF - 1)	1,3 – 1,5 (HM, LP, NLP)	Total
-0,3 – 0,2 (>5 -10)	1	1	6	4	12
0,3-0,9 (>1 - 5)		2	2	3	7
1-1,15 (CF - 1)					
1,3 – 1,5 (HM, LP, NLP)			3	1	4
Total	1	3	11	8	23

Discussion

Enucleation is inevitable for the treatment of extremely large tumours, according with criteria's defined by general guidelines[14], which have become less and less frequent as the improvement of health care access develops. Nevertheless, more and more tumours with large size are being treated with this therapy, with an acceptable rate of eye preservation and survival rate. In a Scottish study[15] with 147 patients with medium or large tumour size, 5-year eye retention rate was 71.3% and disease-specific survival rate was 87.7%.

Another big study[22] with 886 patients, treated between June 1991 and December 2007, presented excellent rates of ocular conservation: 91.1% at 5 years and 87.3% at 10 years.

As new treatment methods emerged, it became important sharing experiences from different techniques, so that better indications can be provided to choose the most case-to-case adjusted treatment for each patient.

Our study reveals that cataracts and retinopathy are common complications after proton beam irradiation of choroidal melanomas. Previous studies have shown that is a leading cause of visual loss in this group of patients[8]. Age was found to be significant influent in many complications. Despite we had no data, it has been described also as an important factor in survival[12].

Against data from other studies, Dendale *et al*[21] described a substantial significance (P < 0.0003) such as Egger *et al*[20] (P = 0.0318), gender wasn't found to be significant in local tumor control rate or complications. Even though other authors refer that the severest complication, usually the responsible for secondary enucleation, is neovascular glaucoma mainly encountered after irradiation of large to extra-large tumors[16, 22], we observed a low rate of neovascular glaucoma (only two patients, one being submitted to enucleation), not being able to establish a relation between these two. Mishra *et al*[19] established a relevant influence between >30% of ciliary body receiving ≥50% of the dose and the % of different structures

such as optic disk, lens and optic nerve disc receiving to ≥50% Dose (<100% vs 100%) (P = 0.0007), % of lens treated to ≥90% Dose (0 vs >0%-30% vs >30%) (P = .01), and optic nerve length treated to ≥90% Dose (≤1 mm vs >1 mm) (P = 0.02) as independent risk factors to NVG, but none of them revealed in our study.

Our outcomes in preserving the visual function aren't so cheerful as the ones in Guyer et al[8], or Fuss et al[23] with useful visual acuity in 49.1% of surviving patients (inferior to 1logmar or 0.10 decimal) once our visual acuity was 0.66logmar worst comparing to the beginning of the treatment, but their values were given for a follow up of one year, or a median follow up of 34 months, respectively, while our median time of follow up was 92.5 months.

In Caujolle et al[22] study, prognostic factors for poor visual acuity results were proximity of tumor to the optic disc or to the macula, very low initial visual acuity, and macular and retinal areas receiving 50% of the total dose. Against other many different studies[8,12,19,23], no specific relation was found between the visual loss and any of the characteristics of the tumor.

Two major points that support the success of this technique are: eye preservation, concerning cosmetic, and survival rate[4], both were well achieved.

Eye preservation rate

In the first year after treatment, no patient needed to be secondarily enucleated and after at least 5 years of follow up, 87.5% of the patients preserved their eye, which show the viability of eye preservation with this technique[17]. A higher % of the total dose captured around the lens was found to be correlated with secondary enucleation after 5 years (P = 0.048) (median 0 vs 12) (but not in more long-term results) but there was only dose's data about one of the cases, which doesn't allow to present medians. Against the findings of

14

Egger *et al*[5], that found the strongest correlation for eye preservation with lower tumor height, but also with bigger distance to optic disc and higher baseline visual acuity, or Caujolle *et al*[22] who says that the main prognostic factor for enucleation is large tumoral volume, it wasn't found any statistically difference between the characteristics of the tumor and the preservation of the globe.

Survival rate

By the date of the data collection, all the patients were alive, being the longest follow up of 230 months (this one without metastasis or need of enucleation), which is a very positive indicator.

Local control

No patients had recurrences. In different studies, local recurrence was found to be an important survival factor[12,22]. Caujolle *et al*[22] describes a lower overall survival in patients with local recurrence: 46.4% vs 79.9% at 10 years.

Systemic control

Several studies leaded by *Gragoudas et al*[11], having the bigger one 780 eyes evaluated, revealed a rate of metastasis of 8% in a population followed for a median of 2.2 years. In our study, the metastasis rate in the first 5 years was 4.3% and the final rate of metastatic disease was 13% being the liver the first place of dissemination (only one patient with established metastasis in the bone - proximal radial diaphysis - and in lungs). Even though considerably higher, the time of follow up was also four times the first one (8.75 years).

Another study from 2008 revealed a 10.7% rate of metastases, from 121 patients, being the liver also the most common place[17]. Our rate of metastasis in 15 years was 12.5%, very close to many other positive results in overall survival[5,19,22,23].

It wasn't found any statistical difference between the characteristics of the tumor and the appearance of metastasis which we could interpret according with the small sample that we had (only three cases developed metastatic disease) or to the small period of follow up of many recently diagnosed patients, who represent 25% of our sample (follow up inferior to 34 months). Because of its dose distribution, charged-particle irradiation can be used to treat larger tumors and tumors closer to the fovea or optic disc than plaque brachytherapy.

Even though this isn't a comparative study with brachytherapy, once only recently this treatment is available in our Centre, studies have to be made in order to compare it with proton beam radiotherapy. Good outcomes have been reported about complications rate, defending that they can be reduced associating other techniques such as intraoperative ecography[24,25] , and also about visual function preservation: a 2008 study shows that visual acuity was improved or stabled in 86% of patients[26].

Adding to this, an important comparative study[27] reveals that despite a local tumor regrowth rate by 4 years was higher with brachytherapy than with helium ion particles, (13.3% versus 0%; P < 0.001) the rates of metastasis, death from metastasis, and overall mortality was very similar in both arms.

As so, we could wonder if the big rate of complications shouldn't be an important point when choosing the treatment for more favorable tumors.

Conclusion

The perfect dose distribution, such as the major role of the dose needed, is essential to preserve the visual function. The Bragg peak, a characteristic of heavy charged particles such as protons, allows a much more homogenous and precise dose distribution when comparing with brachytherapy [9]. This last one delivers not only a high dose to the base of the tumor but also quite substantial doses to the surrounding healthy tissues. The sharp target of proton beam therapy reduces the amount of radiation delivered to adjacent structures, critical to preserve visual function such as the macula and the optic nerve. It allows also the perfect definition of a secure margin of normal tissue around the lesion, which is included for adequate coverage of the melanoma borders. The superior dose distribution by protons allows them to treat larger tumors because the target is more precise and so, smaller, there's not radiations misspend, and the eye can tolerate higher doses[18].

Nevertheless, regarding the big rate of complications associated, studies need to be made to evaluate if brachytherapy shouldn't be the chosen therapy in more favourable tumors.

Limitations of this study were the fact that it's a retrospective study and the rates estimated can be less precise than a prospective one.

References

[1] Koutsandrea C, Moschos MM, Dimissianos M, Georgopoulos G, Ladas I, Apostolopoulos M. Metastasis rates and sites after treatment for choroidal melanoma by proton beam irradiation or by enucleation. Cli Ophthalmol. 2008;2(4):989-95.

[2] Damato B. Progress in the management of patients with uveal melanoma. The 2012 Ashton Lecture. Eye (Lond). 2012;26(9):1157-72.

[3] Gunderson LL, Tepper JE, senior editors. Clinical Radiation Oncology. 3rd ed. Elsevier, Philadelphia; 2012.

[4] Young LH, Gragoudas ES. Macular uveal melanoma treated with proton beam irradiation. 10-year follow-up observation with histopathologic correlation. Retina. 1994;14:43-6.

[5] Egger E, Zografos L, Schalenbourg A, Beati D, Böhringer T, Chamot L, Goitein G. Eye retention after proton beam radiotherapy for uveal melanoma. Int J Radiat Oncol Biol Phys. 2003;55(4):867-80.

[6] Damato B, Kacperek A, Errington D, and Heimann H. Proton beam radiotherapy of uveal melanoma. Saudi J Ophthalmol. 2013;27(3):151-7.

[7] Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. Eye (Lond). 2013;27(2):163-71.

[8] Guyer DR, Mukai S, Egan KM, Seddon JM, Walsh SM, Gragoudas ES. Radiation maculopathy after proton beam irradiation for choroidal melanoma. Ophthalmol. 1992;99(8):1278-85.

[9] Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. Arch Ophthalmol.1990;108(9):1268-73.

[10] Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS report no. 6. Am J Ophthalmol. 1998;125(6):745-66.

[11] Gragoudas ES, Seddon JM, Egan KM, Glynn RJ, Goitein M, Munzenrider J, Verhey L, Urie M, Koheler, A. Metastases from Uveal Melanoma after Proton Beam Irradiation. Ophthalmology. 1988;95(7):992-9.

[12] Gragoudas ES. Proton Beam Irradiation of Uveal Melanomas: The First 30 Years The Weisenfeld Lecture. Invest Ophthalmol Vis Sci. 2006;47(11):4666-73.

[13] AJCC Cancer Staging Handbook, 7th ed. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (Eds.) Springer; 2010.

[14] The American Brachytherapy Society - Ophthalmic Oncology Task Force: The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy. 2014 Jan-Feb;13(1):1-14

[15] Macdonald EC, Cauchi P, Kemp EG. Proton beam therapy for the treatment of uveal melanoma in Scotland. Br J Ophthalmol. 2011;95(12):1691-95.

[16] Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, Cassoux N, Dendale R, Mazal A, Delacroix S, Sastre X, Plancher C, Asselain B. Treatment of uveal melanoma by accelerated proton beam. Dev Ophthalmol. 2012;49:41-57.

[17] Koutsandrea C, Moschos M, Dimissianos M, Georgopoulos G, Ladas J, Apostolopoulos M. Metastasis rates and sites after treatment for choroidal melanoma by proton beam irradiation or by enucleation. Clin Ophthalmol. 2008;2(4):989-95.

[18] Gragoudas ES, Goitein M, Seddon J, Verhey L, Munzenrider J, Urie M, Suit HD, Blitzer P, Johnson KN, Koehler A. Preliminary results of proton beam irradiation of macular and paramacular melanomas. Br J Ophthalmol. 1984;68(7):479-85.

[19] Mishra KK, Daftari IK, Weinberg V, Cole T, Quivey JM, Castro JR, Phillips TL, Char DH. Risk factors for neovascular glaucoma after proton beam therapy of uveal melanoma: a detailed analysis of tumor and dose-volume parameters. Int J Radiat Oncol Biol Phys. 2013;87(2):330-6.

[20] Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L, Goitein G. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. Int J Radiat Oncol Biol Phys. 2001;51(1):138-47.

[21] Dendale R, Lumbroso-Le Rouic L, Noel G, Feuvret L, Levy C, Delacroix S, Meyer A, Nauraye C, Mazal A, Mammar H, Garcia P, D'Hermies F, Frau E, Plancher C, Asselain B, Schlienger P, Mazeron JJ, Desjardins L. Proton beam radiotherapy for uveal melanoma: results of Curie Institut-Orsay proton therapy center (ICPO). Int J Radiat Oncol Biol Phys. 2006;65(3):780-7.

[22] Caujolle JP, Mammar H, Chamorey E, Pinon F, Herault J, Gastaud P. Proton beam radiotherapy for uveal melanomas at nice teaching hospital: 16 years' experience. Int J Radiat Oncol Biol Phys. 2010;78(1):98-103.

[23] Fuss M, Loredo LN, Blacharski PA, Grove RI, Slater JD. Proton radiation therapy for medium and large choroidal melanoma: preservation of the eye and its functionality. Int J Radiat Oncol Biol Phys. 2001;49:1053-9.

[24] Al Mahmoud T, Mansour M, Deschenes J. Intra-operative echographic localization for radio active ophtalmic plaques in choroidal melanoma. Ann NY Acad Sci. 2008;1138: 10-14

[25] Tarlan B, Kiratli H. Current Treatment of Choroidal Melanoma. Expert Rev Ophtalmol. 2012;7(2):189-95

[26] Finger PT. Radiation retinopathy is treatable with antivascular endothelial growth factor bevacizumab (Avastin). Int J Radiat Oncoly Biol Phys. 2008;70(4): 974-7

[27] Char DH, Quivey JM, Castro JR, Kroll S, Philips T. Helium ions versus iodine 125 brachytherapy in the management of uveal melanoma. A prospective, randomized, dynamically balanced trial. Ophthalmol. 1993;100(10):1547-54.