LITERATURE REVIEW

Efficacy and Safety Outcome Comparison of Endoresection and Proton Beam Therapy as Primary Treatment for Choroidal Melanoma

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ABSTRACT

Objective: To evaluate and compare the efficacy and safety between endoresection and proton beam radiotherapy, as primary treatment in choroidal melanoma.
Methods: Articles that were published from 2008 to 2018 were collected from multiple sources including Pubmed, Clinical Key, and Ophthalmology Advance. All study that comply with the inclusion and exclusion criteria were categorized based on level of evidence Oxford Center for Evidence-based Medicine Levels of Evidence. Primary outcome is secondary enucleation. Secondary outcomes are metastasis, recurrence, death, visual outcomes, and complication.
Result: Twelve articles were eligible to be reviewed. Mean secondary enucleation, metastasis, and death rate is lower in endoresection group (6.29% vs 12.94%; 8.00% vs 20.85%; 6.86% vs 20.43) while recurrence rate is lower in proton beam group (4.78% vs 6.86%). The most common complication that observed is retinal detachment. Other complications that were reported includes cataract formation, radiation retinopathy, neovascular glaucoma, vitreous hemorrhage, elevated intraocular pressure (IOP), iris neovascularization, and optic neuropathy.
Conclusion: Endoresection as primary treatment for choroidal melanoma shows better efficacy compared to proton beam therapy, regarding the ability to preserve the eyeball. The safety between endoresection and proton beam therapy, both therapy shows similar result.

Keywords: Choroidal melanoma, therapy, enucleation, endoresection, proton beam therapy

Choroidal melanoma is considered as the most common form of uveal melanoma and found in 80%-90% of all uveal melanoma cases. Uveal melanoma itself is found in 85% of all melanoma of the eye.[1,2] Collaborative Ocular Melanoma Study reported the cumulative rates of metastases in 5 and 10 years after treatment were 25% and 34%, with liver, lung and bone as the common sites of metastasis.[3]

Enucleation is gold standard therapy for choroidal melanoma. In 1987, however, Zimmerman et al mention his doubt on the benefit of enucleation and suggest that it may promote metastasis.[4] Currently, several treatments are widely being studied as primary treatment include endoresection and proton beam radiation therapy because they still preserve patient's eye.[5,6] Endoresection have been described in several studies as an alternative globe preserving therapy for choroidal melanoma with good outcomes and less risk of metastasis.[5,7,8] Proton beam radiotherapy (PBRT) was first developed in Boston and

is now performed in several centers worldwide.[9] This therapy has some advantages with respect to brachytherapy. Proton beam radiotherapy allows for a homogenous dose distribution within the whole tumor volume. It also has a good local tumor control in patients considered unsuitable for other forms of conservative treatment.[4] The aim of this literature review is to evaluate and compare the efficacy and safety between endoresection and proton beam radiotherapy, as primary treatment in choroidal melanoma.

METHODS

Literature search was conducted using following database: PubMed/MEDLINE, clinicalkey.com and ophtalmologyadvance.com. Keywords "choroidal melanoma", "endoresection", and "proton beam therapy" were used. Inclusion criteria were all interventional or observational studies that reported the efficacy of treatment, recurrence rate, metastasis rate, and death with or without safety between endoresection and proton beam therapy as primary treatment for choroidal melanoma. Studies not written in English, animal subject, single case report, inaccessible journal and non-ophthalmology journal were excluded.

The data was divided into subjects mean age of the patients, gender, laterality, mean basal tumor diameter, mean tumor thickness, tumor size, and outcomes. Outcome of this review include secondary enucleation, metastasis, recurrence, death, final visual acuity, tumor location, and complications. All of these data are presented in table form using Microsoft Excel (Microsoft Corp, Washington DC).

RESULT

Keywords were entered through Pubmed, Clinical Key, and Ophthalmology Advance. There were 198 articles found related to keywords. After selection process and detailed evaluation, 12 articles were eligible to be reviewed in this study. Those studies were published between year 2008 and 2018. Five studies analyzed endoresection as their outcome and five studies analyzed proton beam therapy as their outcome. All the studies reviewed in this study have evidence level IV. The characteristics of the reviewed studies were summarized in Table 1.

Table 2 showed the baseline characteristics between studies. In endoresection group, patients age ranges from the youngest 53 years old[10] to 64.2 years old.[15] Most of the study reveals male as dominating gender in choroidal melanoma. Mean follow up time in all studies ranges from 48 months[12] to 102.5 months.[13]

Table 3 showed efficacy among treatment compared to enucleation as gold standard. Secondary enucleation in endoresection group ranges from 4%-12.2%, while secondary enucleation in proton beam therapy group ranges from 6%-19.5%. The recurrence rate in endoresection group ranges from 3% to 18.2%, while in proton beam therapy group the recurrence rate ranges between 1.7%-14%. Study by Caminal et al[12] in endoresection group reported the lowest death rate (3.7%), while study by Mosci et al[4] in proton beam therapy group reported highest death rate (38%) in this review.

The most common complication that observed is retinal detachment and the second one is cataract formation. Retinal detachment reported in three of five endoresection study[18,21-22] and five of seven proton beam therapy study.[3,19,23-24,26] The rate of retinal detachment reported between 3.1%-62.8%.

Table 1. Articles summary

No	Author	Years	Study Design	Evidence Level	Treatment Type	Sample Number
1	Rice et al[20]	2013	Retrospective	4	Endoresection	22
2	Caminal et al[12]	2013	Case Control	4	Endoresection	27
3	Konstantinidis et al[21]	2013	Retrospective	4	Endoresection	71
4	Vidoris et al[18]	2017	Retrospective	4	Endoresection	14
5	Garcia-Arumi et al[22]	2015	Case Series	4	Endoresection	41
6	Mosci et al[9]	2012	Case Control	4	Proton Beam Therapy Enucleation	70 62
7	Konstantinidis et al[23]	2014	Retrospective	4	Proton Beam Therapy	63
8	Koutsandrea et al[3]	2008	Retrospective	4	Proton Beam Therapy Enucleation	121 31
9	Patel et al[24]	2018	Retrospective	4	Proton Beam Therapy	351
10	Bensoussan et al[19]	2016	Retrospective	4	Proton Beam Therapy	492
11	Riechardt et al[25]	2014	Retrospective	4	Proton Beam Therapy	147
12	Tran et al[26]	2011	Retrospective	4	Proton Beam Therapy	59

Table 2. Baseline characteristics of each group

No	Author	Mean Age (Years)	Gender (M/F)	Mean Follow Up (Months)	Laterality (R/L)	Mean Tumor Diameter (mm)	Mean Tumor Thickness (mm)	Classification*
1	Rice et al[20]	53	13/9	n/a	12/10	11.2	7.3	Medium
2	Caminal et al[12]	n/a	13/14	59.37	14/13	n/a	n/a	n/a
3	Konstantinidis et al[21]	n/a	41/30	n/a	41/30	9.5	4.4	Medium
4	Vidoris et al[18]	50.3	5/8	48	7/6	11.2	6.05	Medium
5	Garcia-Arumi et al[22]	53.6	27/14	102.5	n/a	9.9	9.8	Medium
6	Mosci et al[9]	62.7	43/27	53.4	35/35	15.2	9.8	Medium
7	Konstantinidis et al[23]	n/a	39/24	n/a	35/28	11.8	3.6	Medium
8	Koutsandrea et al[3]	64.2	53/68	n/a	57/64	n/a	7.3	Medium
9	Patel et al[24]	58.09	194/157	68.7	n/a	12.8	4.9	Medium
10	Bensoussan et al[19]	62.4	258/234	61.9	238/174	14.91	8.77	Medium
11	Riechardt et al[25]	57	n/a	78	n/a	11	3.7	Medium
12	Tran et al[26]	n/a	39/10	n/a	27/32	11.4	3.5	Medium

*COMS classification; n/a= Not Available

Table 3. Efficacy between Endoresection, Proton Beam Therapy, and Enucleation

No.	Author	Treatment type	Secondary enucleation	Metastasis (%)	Reccurence (%)	Death (%)	Visual Acuity (%)	
							≥6/60	< 6/60
1	Rice et al[20]	Endoresection	4.6	4	18.2	4	59.1	40.9
2	Caminal et al[12]	Endoresection	11.1	3.7	7.4	3.7	66.7	33.3
3	Konstantinidis et al[21]	Endoresection	4	9	3	11.3	n/a	
4	Vidoris et al[18]	Endoresection	0	7.1	n/a	7.1	84.6	15.4
5	Garcia-Arumi et al[22]	Endoresection	12.2	7.3	12.2	4.8	48.8	51.2
6	Mosci et al[9]	Proton Beam Therapy	12.9	n/a	14	38	32	68
7	Konstantinidis et al[23]	Proton Beam Therapy	6.3	n/a	3.2	23.8	n.a	
8	Koutsandrea et al[3]	Proton Beam Therapy	n/a	10.7	n/a	n/a	n/a	
9	Patel et al[24]	Proton Beam Therapy	6	19.9	1.7	19.9	n/a	
10	Bensoussan et al[19]	Proton Beam Therapy	19.5	25	n/a	n/a	19.8	80.2
11	Riechardt et al[25]	Proton Beam Therapy	9.5	15.6	6.1	17	n/a	
12	Tran et al[26]	Proton Beam Therapy	8.6	25.4	8.5	12	76	24

*n/a : Not Available

DISCUSSION

Choroidal melanoma characteristically presents as tumor in choroid that develop from melanoma. Collaborative Ocular Melanoma Study reported the mean age at diagnosis of choroidal melanoma is mid 50s.[20] In this review, the mean age were 58.9 years old with range between 19-89 years old. Choroidal melanoma have a poor prognosis after metastasis of the disease.[15] Conservative treatment such as brachytherapy, endoresection, or proton beam therapy are just some of the therapy that are being studied to increase patient's quality of life and preserve patient's eyeball.[18,20]

In this literature review, we found that mean secondary enucleation rate in endoresection group is lower than in proton beam therapy group (6.29% vs 12.94%). Indication for secondary enucleation in endoresection group is local recurrence while in proton beam therapy group is complication post therapy and local recurrence.[7,12,19] Tran et al[19] suggest that secondary enucleation rate related to tumor size ($p < 0.001$) and can be reduced by administrating intravitreal bevacizumab. Bensoussan et al[17] who reported highest secondary enucleation rate, has second largest mean tumor diameter. This finding may support that tumor size is contribute in developing secondary enucleation.[17]

From the local recurrence, ranges in local recurrence group between endoresection and proton beam therapy is similar even though mean local recurrence in proton beam therapy group is lower than in endoresection (4.78% vs 8.07%). Consideration of the local recurrence in endoresection is that it may cause intraoperative dissemination of tumor cells.[12] Local recurrence that occur in endoresection group may be affect by endoresection technique.[7,11]Local control

rate of proton beam therapy is reported in some of the studies. In previous studies, proton beam therapy show a good local control rates (90.5%-99%).[21–23] This review shows good outcome in terms of local control in proton beam therapy and is corresponding to previous study.

This review reported that metastasis and death rate endoresection group is lower than in others group. Caminal et al[7] reported that metastasis rate in endoresection compared to other conservative therapy is lower in his study, even though it is not statistically significant. Mean metastasis rate in proton beam group in our review is 20.85%, almost three times higher than in endoresection group (8%). Study by Bensoussan et al[17], in proton beam group, have the largest sample number compare to other study. The metastasis rate in his study is the second highest compare to all study. Using multivariate analysis, Bensoussan et al[17] reported the risk factor for metastasis are juxtapapillary location, extrascleral extension, and cilliary body extension. Mean mortality rate in endoresection is the lowest compare to proton beam therapy group (6.86% vs 20.43%). This trend may be affected with the fact that some patient that has metastasis, also deceased during follow up time.[7,10–12,16,19] Most of the death in the study occur due to metastasis.

Retinal detachment is the most common complication found in this review. In endoresection group, retinal detachment may occurs after the removal of silicone oil.[13] Previous studies reported retinal detachment ranged from 9.4%-32.6% in endoresection,[8,24] while this review reported retinal detachment rate between 14.3%-28.9%. Cataract formation is only found in two endoresection group because other studies performed lens extraction before performing endoresection. [7,12] Cataract formation in this group may be influenced by silicone oil that induced secondary cataract.

The limitations of this literature review are the lack of high level evidence that available regarding the efficacy and safety of treatment options and no statistical analysis performed in this literature review. In addition, enucleation is the only treatment option that available to treat choroidal melanoma in Cipto Mangunkusumo Hospital.

CONCLUSION

Endoresection as primary treatment for choroidal melanoma shows better efficacy compared to proton beam therapy, regarding the ability to preserve the eyeball. The safety between endoresection and proton beam therapy, both therapy shows similar result. These results however are not supported by statistical analysis. Further studies with better level of evidence are still needed to compare the efficacy and safety between endoresection and proton beam therapy as primary treatment for choroidal melanoma.

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