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Complications from Plaque versus Proton Beam Therapy for Choroidal Melanoma: A Qualitative Systematic Review

Victoria L. Tseng[1,2], Anne L. Coleman[1,2], Zuo-Feng Zhang[2], Tara A. McCannel[1]

[1]Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[2]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA
Email: young@jsei.ucla.edu

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Abstract

Plaque brachytherapy has been a mainstay of treatment for choroidal melanoma to achieve intraocular tumor control. The most common radioisotopes used for treating smaller sized tumors are Iodine-125 in North America and Ruthenium-106 in Europe. Proton beam radiotherapy is available at a few centers and may also be used to achieve local tumor control. Both plaque and proton beam therapy are known to be associated with a range of complications that may affect visual outcome and quality of life. These include radiation retinopathy, optic neuropathy, neovascular glaucoma and local treatment failure, requiring enucleation. While differences in the rates of these complications have not been well established in the literature for patients treated with plaque versus proton beam therapy for choroidal melanoma, certain geographic regions prefer one treatment modality over the other. The purpose of this qualitative systematic review was to compare and contrast reported complications that developed with plaque and proton beam therapy for the treatment of choroidal melanoma in studies published over a ten-year period. Reported rates suggest that patients with proton beam therapy had potentially higher rates of complications, including vision loss, enucleation, and neovascular glaucoma compared to those with plaque therapy. The rates of optic neuropathy, radiation retinopathy, and cataract formation were widely variable for the two treatment modalities and rates of metastasis and metastasis-free survival appeared similar with both treatments. The most common reported predictors of ocular complications following both types of therapy were tumor distance from the optic nerve, tumor thickness, and radiation dose, suggesting that inherent tumor characteristics play a role in visual prognosis.

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Keywords

Choroidal Melanoma, Uveal Melanoma, Plaque Therapy, Brachytherapy, Proton Therapy, Treatment Complications, Metastasis, Enucleation

1. Introduction

Choroidal melanoma, also known as posterior uveal melanoma, arises from melanocytes within the choroid. It is the most common primary intraocular tumor of adults and the second most common type of malignant melanoma after cutaneous melanoma. Despite advances in its diagnosis and treatment, the incidence of choroidal melanoma in the United States has remained unchanged since the 1970s, with a slight male predominance and peak incidence in the fifth to sixth decades of life [1]-[3]. Thirty to fifty percent of patients succumb to metastatic disease within ten years of diagnosis, with worse prognosis associated with the clinical factors of older age, greater tumor size, and ciliary body location; the histological factors of epithelioid cellular morphology and presence of vascular loops; and with the molecular finding of loss of chromosome 3 within the tumor tissue [4] [5].

In 2001, the Collaborative Ocular Melanoma Study (COMS) reported no difference in mortality 12 years following treatment with iodine-125 brachytherapy versus enucleation for medium sized tumors [6]. Since then, brachytherapy has been a globe-sparing treatment of choice, while enucleation may be recommended for large tumors. Proton beam radiotherapy is another globe-sparing treatment alternative for both medium and large choroidal melanoma [7].

Both plaque and proton beam therapy are known to be associated with a range of ocular complications including cataract formation, radiation retinopathy, optic neuropathy and neovascular glaucoma; however, the differences in the side effect profiles of the two treatment modalities have not been well explored [8] [9]. Additionally, varying rates of distant metastasis have been reported with the two treatments without an obvious benefit of one treatment over the other for long-term survival [10]-[26]. However, there are some geographic treatment pattern preferences for one treatment modality over the other despite a lack of convincing data in the published literature. To this end, the purpose of this review was to compare ocular complications for patients receiving plaque and proton beam radiotherapy for choroidal melanoma.

2. Search Strategy

A literature search was performed for this qualitative systematic review [27] using the following keywords on PubMed [28]: “side effects AND choroidal melanoma AND plaque therapy”, “visual outcomes AND choroidal melanoma AND plaque therapy”, “visual acuity AND choroidal melanoma AND plaque therapy”, “eye preservation AND choroidal melanoma AND plaque therapy”, “optic neuropathy AND choroidal melanoma AND plaque therapy”, “retinopathy AND choroidal melanoma AND plaque therapy”, “neovascular glaucoma AND choroidal melanoma AND plaque therapy”, “cataract AND choroidal melanoma AND plaque therapy”, and “metastasis AND choroidal melanoma AND plaque therapy”. For studies examining complications from proton beam therapy, we used the same search terms but replaced “plaque therapy” with “proton beam therapy” in each search term. Our inclusion criteria were 1) study published in the English language, 2) examination of at least a subset of patients treated initially with plaque therapy or proton beam therapy without initial adjunct treatments, and 3) examination of at least one of visual acuity, eye preservation, optic neuropathy, radiation retinopathy, neovascular glaucoma, cataract, and distant metastasis as an outcome following treatment for choroidal melanoma, and 4) publication over a ten-year period between January 1, 2005 and December 31, 2014. These inclusion criteria were selected based on the desire to examine ocular complications directly related to plaque or proton beam therapy in a recent time period when both treatment modalities were used frequently.

From each study, the following information was extracted: sample size, tumor type, duration of follow-up, rates of each outcome (visual acuity worse than 20/200, enucleation, optic neuropathy, radiation retinopathy, neovascular glaucoma, cataract, and distant metastasis), and baseline predictors of each outcome. Due to significant heterogeneity across studies with regard to tumor characteristics, radioisotope used, duration of follow-up, and study population, weighted averages of each complication were not calculated.

3. Results

3.1. Overview of Included Studies

The search strategy yielded 556 studies between 2005 and 2014, of which 29 were included in this review with the earliest published in 2005 and the latest in 2010. These included 22 studies of plaque therapy and 7 studies of proton beam therapy for choroidal melanoma. For studies of plaque therapy, sample sizes ranged from 24 to 650 patients and duration of follow-up ranged from an average of 23 to 60 months. For studies of proton beam therapy, sample sizes ranged from 18 to 349 patients and duration of follow-up ranged from an average of 28 to 78 months.

3.2. Visual Acuity

Studies examining visual acuity following plaque therapy for choroidal melanoma are outlined in **Table 1** and **Table 2**. Visual acuity can be temporarily or permanently compromised following treatment for choroidal melanoma for a variety of reasons including radiation-induced damage to the anterior segment, retina, and optic nerve. Of the 15 included studies [10]-[20] [29]-[31] that examined visual acuity as an outcome following plaque therapy, sample sizes ranged from 24 to 650 patients and follow-up ranged from a mean of 23 months to five years. In five of six studies that examined the proportion of patients with visual acuity better than 20/40, less than 50% of patients were able to preserve visual acuity equal to or better than 20/40 at last follow-up. Fourteen studies examined the proportion of patients with visual acuity equal to or better than 20/200 with a wide range of proportions reported (23% - 94.4%). Factors shown to be associated with poor long term visual acuity following plaque therapy in multivariate models included radiation dose and tumor location [13] [30] [32], with two studies [13] [32] demonstrating that tumor location near the optic nerve predicted poor long term visual function.

There were seven studies [9] [23]-[26] [34] included in this review that examined visual acuity as an outcome following proton beam therapy. The sample size in these studies ranged from 18 to 147 patients, and follow-up ranged from a median of 28 to 78 months. Compared to studies of plaque therapy, there were more studies that focused on large tumors and tumors close to the optic nerve. Most studies did not examine preservation of visual acuity equal to or better than 20/40 as an outcome, with only one study [23] reporting that 44.8% of patients had visual acuity equal to or better than 20/40 at five years following the initiation of treatment. Presumably, most studies only focused on preservation of visual acuity equal to or better than 20/200 as a long term outcome because proton beam therapy was associated with more visual loss compared to plaque therapy; the majority of studies [9] [24] [25] [33] [34] included in this review found that less than 50% of patients were able to preserve visual acuity equal or greater than 20/200 at the end of follow-up after proton beam therapy. The only study that examined predictors of poor visual acuity following proton beam therapy [27] found that initial degree of ocular involvement, tumor height, and initial visual acuity were predictive of poor visual acuity following therapy.

3.3. Eye Preservation

Studies examining eye preservation following plaque and proton beam therapy for choroidal melanoma are outlined in **Table 3** and **Table 4**. Secondary enucleation for choroidal melanoma is most often performed for tumor recurrence or treatment toxicity [33]. While enucleation may achieve local tumor control and provide symptomatic relief, it may also be associated with cosmetic side effects and potential detriment to quality of life [34]. There were 13 studies [10]-[14] [16]-[18] [20] [29]-[32] included in this review that examined eye preservation following plaque therapy for choroidal melanoma. Sample sizes ranged from 24 to 650 patients and mean follow-up ranged from 23 months to five years. The majority of studies of plaque therapy reported less than 10% enucleation rates for tumor recurrence [10] [11] [13] [17] [18] [20] [31], while enucleation rates for treatment toxicity ranged from 1.6% [13] to 14.2% [11]. The only study that examined predictors of enucleation [32] following plaque therapy found that plaque size, tumor recurrence, neovascular glaucoma, and nonproliferative retinopathy were predictive of requiring enucleation.

There were seven included studies [9] [23]-[26] [34] [35] that examined eye preservation following proton beam therapy for choroidal melanoma. Sample sizes ranged from 21 to 349 patients and follow-up time ranged from a mean of 28 months to a median of 78 months. While most studies reported similar secondary enucleation rates when compared to studies of plaque therapy, three studies [9] [24] [35] reported cumulative enucleation

Table 1. Visual acuity outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with VA ≥20/40 at End of Follow-Up	Number (%) with VA ≥20/200 at End of Follow-Up	Alternate Measure of VA	Predictors of Poor VA after Treatment
Bergman *et al.* 2005 [29]	579 eyes	Choroidal and ciliary body melanomas	3 and 5 years	64/171 (37.2%)	67/171 (39.2%)	--	--
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	--	38% non-enucleated eyes	--	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	--	23%	--	--
Finger *et al.* 2010 [30]	384 patients	Uveal melanomas treated with Palladium-103	Mean 47.2 months	--	--	Low and medium foveal doses: End median VA 20/25-20/30; High foveal dose: End median VA 20/80	Foveal dose of radiation
Gunduz *et al.* 2010 [12]	24 patients	Choroidal melanoma treated with ruthenium brachytherapy alone	--	3/21 (14.2%)	10/21 (47.6%)	--	--
Verschueren *et al.* 2010 [13]	430 patients	Choroidal melanoma	Median 50 months	--	283/430 (65.8%)	--	Central tumors, juxtapapillary tumors
Karlovits *et al.* 2011 [14]	35 patients	Choroidal melanoma treated with iodine brachytherapy	Median 45 months	--	32% of patients with 3 or more years of follow-up	--	--
Newman *et al.* 2011 [15]	50 patients	Subfoveal choroidal melanomas with ≥6 months of follow-up	Median 54 months	18/50 (36.0%)	25/50 (50.0%)	--	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	12/22 (55%)	17/22 (77%)	--	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	29/82 (35.4%)	35/82 (42.7%)	--	--
Caminal *et al.* 2013 [18]	54 patients	Choroidal melanoma treated with iodine brachytherapy	Mean 59.47 months	--	19/54 (35.2%)	--	--
Marconi *et al.* 2013 [31]	94 patients	Choroidal melanoma treated with ruthenium brachytherapy	Median 39 months	30%	56%	--	--
Semenova *et al.* 2013 [19]	72 patients	Small choroidal melanomas	Mean 54 months	--	68/72 (94.4%)	--	--
Sagoo *et al.* 2014 [32]	650 eyes	Juxtapapillary choroidal melanoma	Median 40 months	--	46% at 5 years, 13% at 10 years	--	Papillopathy, radiation cataract
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months		25/47 (53%)	--	--

Table 2. Visual acuity outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with VA ≥20/40 at End of Follow-Up	Number (%) with VA ≥20/200 at End of Follow-Up	Alternate Measure of VA	Predictors of Poor VA after Treatment
Damato *et al.* 2005 [23]	349 patients	Choroidal melanoma	Median 3.1 years	44.8% at 5 years	61.1% at 5 years	--	Ciliary body involvement, basal tumor dimension, retinal invasion, extraocular extension, tumor height, reduced initial VA
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	--	25% after 24 months	--	--
Kim *et al.* 2010 [33]	93 patients	Choroidal melanoma within 1 - 2 disc diameters of optic nerve and at least 2 disc diameters from fovea	Mean 5.5 years	--	23% at 5 years	--	--
Mosci *et al.* 2012 [24]	72 patients	T3 and T4 choroidal melanomas	Mean 53.4 months	--	7/22 (32%) at 5 years	--	--
Tran *et al.* 2012 [25]	59 patients	Peripapillary choroidal melanoma	Median 63 months	--	17% at 5 years	--	--
Riechardt *et al.* 2014 [34]	147 patients	Peripapillary choroidal melanoma	Mean 78 months	--	14%	--	--
Schonfeld *et al.* 2014 [26]	18 patients	Choroidal melanoma in intermediate zone of fundus	Median 77.2 months	--	66.7%	--	--

Table 3. Eye preservation outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) Requiring Enucleation for Tumor Recurrence by End of Follow-Up	Number (%) Requiring Enucleation for Treatment Side Effects by End of Follow-Up	Total Number (%) Requiring Enucleation	Predictors of Requiring Enucleation after Treatment
Bergman *et al.* 2005 [29]	579 eyes	Choroidal and ciliary body melanomas	3 and 5 years	60/579 (10.4%) at 3 years	17/579 (2.9%) at 3 years	106 patients enucleated total with cumulative incidence 16.8%	--
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	3/37 (8.1%)	4/37 (10.8%)	7/37 (18.9%)	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	7/141 (5.0%)	20/141 (14.2%)	27/141 (19.1%)	--
Finger *et al.* 2010 [30]	384 patients	Uveal melanomas treated with palladium-103 brachytherapy	Mean 47.2 months	--	--	11/384 (2.9%) within 3 years	--
Gunduz *et al.* 2010 [12]	24 patients	Choroidal melanoma treated with ruthenium brachytherapy alone	--	--	--	2/15 (13.3%) for tumors ≤5 mm, 1/9 (11.1%) for tumors >5 mm to <8 mm	--
Verschueren *et al.* 2010 [13]	430 patients	Choroidal melanoma	Median 50 months	10/430 (2.3%)	7/430 (1.6%)	17 (4.4%)	--

Continued

Karlovits *et al.* 2011 [14]	35 patients	Choroidal melanoma treated with iodine brachytherapy	Median 45 months	--	--	6%	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	--	--	0 (0.0%)	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	2/82 (2.4%)	--	--	--
Caminal *et al.* 2013 [18]	54 patients	Choroidal melanoma treated with iodine brachytherapy	Mean 59.47 months	1/54 (1.9%)	6/54 (11.1%)	7/54 (13.0%)	--
Marconi *et al.* 2013 [31]	94 patients	Choroidal melanoma treated with ruthenium brachytherapy	Median 39 months	4/94 (4.3%)	4/94 (4.3%)		--
Sagoo *et al.* 2014 [32]	650 eyes	Juxtapapillary choroidal melanoma	Median 40 months	--	--	16% at 5 years	Plaque size, tumor recurrence, neovascular glaucoma, absence of nonproliferative retinopathy
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	3/47 (6.4%)	2/47 (4.3%)	--	--

Table 4. Eye preservation outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) Requiring Enucleation for Tumor Recurrence by End of Follow-Up	Number (%) Requiring Enucleation for Treatment Side Effects by End of Follow-Up	Total Number (%) Requiring Enucleation	Predictors of Requiring Enucleation after Treatment
Damato *et al.* 2005 [23]	349 patients	Choroidal melanoma	Median 3.1 years	8/349 (2.3%)	17/349 (4.9%)	25/349 (7.2%); 1.6% at 1 year, 4.0% at 2 years, 9.4% at 5 years	--
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	4/21 (19.0%)	6/21 (28.6%)	10/21 (47.6%)	--
Macdonald *et al.* 2011 [35]	147 patients	Uveal melanoma	Mean 4.4 years	48% of enucleations for suspected recurrence	52% of enucleations for complications from proton therapy	22.4% of patients received enucleation	--
Mosci *et al.* 2012 [24]	72 patients	T3 and T4 choroidal melanomas	Mean 53.4 months	--	--	26% of patients received enucleation over 5 years	--
Tran *et al.* 2012 [25]	59 patients	Peripapillary choroidal melanoma	Median 63 months	4/59 (6.8%)	8/59 (13.6%)	12/59 (20%)	--
Riechardt *et al.* 2014 [34]	147 patients	Peripapillary choroidal melanoma	Mean 78 months	6/147 (4.1%)	8/147 (5.4%)	9.5% enucleated at 5 years, 10.7% enucleated at 10 years	--
Schonfeld *et al.* 2014 [26]	18 patients	Choroidal melanoma in intermediate zone of fundus	Median 77.2 months	--	--	1/18 (5.6%)	--

rates greater than 20%, which was noticeably higher than rates reported in studies of plaque therapy. One study [9] was limited to extra-large and ciliochoroidal tumors and another [24] to stage T3 and T4 tumors, which might explain the higher rates of enucleation reported in these studies. There were no included studies that examined multivariate predictors of secondary enucleation following proton beam therapy.

3.4. Optic Neuropathy

Studies examining optic neuropathy following plaque and proton beam therapy for choroidal melanoma are outlined in **Table 5** and **Table 6**. Optic neuropathy following radiation is thought to be secondary to demyelination and neuronal degeneration following glial and endothelial cell injury from radiation, and most often leads to irreversible vision loss over time [8] [36] [37]. There were ten studies [10]-[13] [16] [17] [19] [20] [32] [38] included in this review that examined optic neuropathy following plaque therapy, with sample sizes ranging from 24 to 650 patients and follow-up time ranging from a mean of 23 months to 56 months. Rates of radiation optic neuropathy ranged from 1.6% to 62.5%, with the highest rates being in studies of choroidal melanoma within 1.5 mm of the optic disc [24] and juxtapapillary choroidal melanoma [32]. In the two studies that examined multivariate predictors of optic neuropathy [19] [32], plaque size and subfoveal or juxtapapillary tumor location were found to be predictive of optic neuropathy following plaque therapy.

There were three studies reviewed [9] [33] [34] that examined optic neuropathy following proton beam therapy for choroidal melanoma. Sample sizes ranged from 21 to 384 patients and follow-up time ranged from a median of 28 months to a mean of 78 months. Similar to the studies of neuropathy following plaque therapy, the two studies of optic neuropathy following proton beam therapy, which focused on peripapillary tumors [33] [34], found high rates of neuropathy following treatment (89.6% and 67.7%), and proximity of the tumor to the optic disc was found to be predictive of radiation optic neuropathy in one of these studies [33].

Table 5. Optic neuropathy outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Optic Neuropathy at End of Follow-Up	Predictors of Optic Neuropathy after Treatment
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	9/37 (24.3%)	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	57/141 (40.4%)	--
Gunduz *et al.* 2010 [12]	24 patients	Choroidal melanoma treated with ruthenium brachytherapy alone	--	1/24 (4.1%)	--
Verschueren *et al.* 2010 [13]	430 patients	Choroidal melanoma	Median 50 months	7/430 (1.6%)	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	15/24 (62.5%)	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	12/82 (14.6%)	--
Krema *et al.* 2013 [38]	30 patients	Posterior tumor margin 0 - 2.5 mm from optic disc	--	40%	--
Semenova *et al.* 2013 [19]	72 patients	Small choroidal melanomas	Mean 54 months	15/72 (20.8%)	Subfoveal or juxtapapillary tumor location
Sagoo *et al.* 2014 [32]	650 eyes	Juxtapapillary choroidal melanoma	Median 40 months	61% at 5 years	Plaque size
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	24/47 (51%)	--

Table 6. Optic neuropathy outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Optic Neuropathy at End of Follow-Up	Predictors of Optic Neuropathy after Treatment
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	2/21 (9.5%)	--
Kim *et al.* 2010 [33]	93 patients	Choroidal melanoma within 1 - 2 disc diameters of optic nerve and at least 2 disc diameters from fovea	Mean 5.5 years	63/93 (67.7%)	Proximity to optic disc
Riechardt *et al.* 2014 [34]	147 patients	Peripapillary choroidal melanoma	Mean 78 months	89.6% at 5 years	--

3.5. Radiation Retinopathy

Studies examining radiation retinopathy following plaque and proton beam therapy for choroidal melanoma are outlined in **Table 7** and **Table 8**. Radiation retinopathy is characterized by retinal hemorrhage, exudation, edema, ischemia and neovascularization of the retina. These abnormalities may lead to permanent visual loss [39] [40]. There were 13 included studies [10] [11] [13] [15]-[17] [19] [20] [30] [32] [38] [41] [42] that examined radiation retinopathy following plaque therapy, with sample sizes ranging from 24 to 3841 patients and follow-up time ranging from 23 to 56 months. Rates of maculopathy ranged from 8% to 56%, with the highest rates reported in studies of tumors near the optic disc [16] [32]. Similarly, there was a wide range of retinopathy reported (3.6% - 66%), but higher rates were reported in studies of tumors near the optic disc (60% - 66%) [32] [38] and in large or subfoveal tumors (56% - 66%) [15] [20]. Tumor location was the only predictive factor reported in more than one study [30] [42].

There were two included studies [9] [34] that examined radiation retinopathy following proton beam therapy. While these studies differed greatly in sample size and follow-up time, the study that focused on juxtapapillary tumors [34] also found a high rate of retinopathy (90.3%) following proton beam therapy, similar to the studies of juxtapapillary tumors treated with plaque therapy. The other study [9], which focused on large tumors, found a low rate of retinopathy compared to the studies of retinopathy following plaque therapy, suggesting that tumor size may not be related to the development of retinopathy for patients receiving proton beam therapy.

3.6. Neovascular Glaucoma

Studies examining neovascular glaucoma after plaque and proton beam therapy for choroidal melanoma are outlined in **Table 9** and **Table 10**. Neovascularization of the retina and the iris is frequently a result of retinal ischemia from radiation retinopathy, leading to elevated intraocular pressure and permanent visual field loss from glaucoma [43]. There were seven studies [10] [11] [16] [20] [31] [32] [38] that examined neovascular glaucoma following plaque therapy for choroidal melanoma. Sample sizes ranged from 24 to 650 patients and follow-up time ranged from a mean of 23 months to 56 months. Rates of neovascular glaucoma in small and medium tumors were low (0.0% - 3%) [16] [31], while studies of tumors near the optic nerve and large tumors reported slightly higher rates (8% - 17%) [10] [11] [20] [32] [38]. One study found that tumor thickness was predictive of neovascular glaucoma [32].

There were three studies of neovascular glaucoma following proton beam therapy for choroidal melanoma [9] [25] [26], with sample sizes ranging from 18 to 59 patients and follow-up time ranging from a median of 28 to 77.2 months. While reported rates of neovascular glaucoma were higher in all of these studies (23% - 38.1%) compared to those of neovascular glaucoma following plaque therapy, two of these studies focused on large tumors and those near the optic nerve. The one study [9] that examined predictors of neovascular glaucoma after proton beam therapy also found that tumor thickness and proximity to the optic nerve were predictive of neovascular glaucoma.

3.7. Cataract

Studies examining cataract formation following plaque and proton beam therapy for choroidal melanoma are

Table 7. Radiation retinopathy outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Radiation Retinopathy at End of Follow-Up	Predictors of Radiation Retinopathy after Treatment
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	7/37 (18.9%) with proliferative retinopathy	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	61 (43.3%) patients with nonproliferative retinopathy, 26 patients (18.4%) progressed to proliferative retinopathy by the end of follow-up	--
Correa *et al.* 2009 [41]	120 patients	Choroidal melanoma treated with iodine-125 brachytherapy	--	7.5% with retinopathy	--
Bianciotto *et al.* 2010 [42]	3841 patients	Choroidal melanoma	--	138/3841 (3.6%) with proliferative retinopathy	Young age, diabetes mellitus, shorter tumor distance to optic disc
Finger *et al.* 2010 [30]	384 patients	Uveal melanomas treated with Palladium-103	Mean 47.2 months	Maculopathy in 8% of patients with anterior tumor and 41% of patients with posterior tumor	Posterior location, tumor height > 6.0 mm
Verschueren *et al.* 2010 [13]	430 patients	Choroidal melanoma	Median 50 months	56/430 (13.0%) with retinopathy; 65/430 (15.1%) with maculopathy	--
Newman *et al.* 2011 [15]	50 patients	Subfoveal choroidal melanomas with ≥6 months of follow-up	Median 54 months	28/50 (56%) with retinopathy; Stage 1: None; Stage 2: 14%; Stage 3: 54%; Stage 4: 32%	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	9/24 (37.5%) with maculopathy	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	31/82 (37.8%) with retinopathy	--
Krema *et al.* 2013 [38]	30 patients	Posterior tumor margin 0 - 2.5 mm from optic disc	--	60% with retinopathy	--
Semenova *et al.* 2013 [19]	72 patients	Small choroidal melanomas	Mean 54 months	31/72 (43.1%) with maculopathy	--
Sagoo *et al.* 2014 [32]	650 eyes	Juxtapapillary choroidal melanoma	Median 40 months	Nonproliferative retinopathy at 5 years: 66%; Proliferative retinopathy at 5 years: 24%; Maculopathy at 5 years: 56%	Nonproliferative: Hypertension; Proliferative: Mean tumor thickness; Maculopathy: Visual acuity > 20/60 at presentation
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	31/47 (66%) with retinopathy	--

Table 8. Radiation retinopathy outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Radiation Retinopathy at End of Follow-Up	Predictors of Radiation Retinopathy after Treatment
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	2/21 (9.5%)	--
Riechardt *et al.* 2014 [34]	147 patients	Peripapillary choroidal melanoma	Mean 78 months	90.3% at 5 years	--

Table 9. Neovascular glaucoma outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Neovascular Glaucoma at End of Follow-Up	Predictors of Neovascular Glaucoma after Treatment
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	5/37 (13.5%)	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	24/141 (17.0%)	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	0/24 (0.0%)	--
Krema *et al.* 2013 [38]	30 patients	Posterior tumor margin 0 - 2.5 mm from optic disc		8%	--
Marconi *et al.* 2013 [31]	94 patients	Choroidal melanoma treated with ruthenium brachytherapy	Median 39 months	3% with secondary glaucoma	--
Sagoo *et al.* 2014 [32]	650 eyes	Juxtapapillary choroidal melanoma	Median 40 months	15% at 5 years	Mean tumor thickness
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	8/47 (17%) with secondary glaucoma	--

Table 10. Neovascular glaucoma outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Neovascular Glaucoma at End of Follow-Up	Predictors of Neovascular Glaucoma after Treatment
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	8/21 (38.1%)	Proximity to optic nerve, tumor thickness
Tran *et al.* 2012 [25]	59 patients	Peripapillary choroidal melanoma	Median 63 months	31% at 5 years	--
Schonfeld *et al.* 2014 [26]	18 patients	Choroidal melanoma in intermediate zone of fundus	Median 77.2 months	4/17 (23.5%) with secondary glaucoma	--

outlined in **Table 11** and **Table 12**. Cataract formation is a well-known complication resulting from radiation-induced opacification of the lens [44]. There were 12 studies [10]-[12] [15]-[17] [20] [31] [38] [41] [44] [45] included that examined cataract development following plaque therapy for choroidal melanoma. Sample sizes ranged from 24 to 532 patients and follow-up time ranged from a mean of 23 months to five years. There was a range of reported cataract development rates from 5.5% to 68%. The highest rate was reported in patients with

Table 11. Cataract outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Cataract at End of Follow-Up	Predictors of Cataract after Treatment
Collaborative Ocular Melanoma Study Group 2007 [46]	532 patients	Choroidal melanoma randomized to iodine-125 brachytherapy	5 years	362/568 (68%) with cataract at 5 years, 49 (9%) with cataract surgery	Radiation dose
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	10/37 (27.0%)	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	66/141 (46.8%)	--
Correa *et al.* 2009 [43]	120 patients	Choroidal melanoma treated with iodine-125 brachytherapy	--	31.6%	--
Gunduz *et al.* 2010 [12]	24 patients	Choroidal melanoma treated with ruthenium brachytherapy alone	--	2/24 (8.3%)	--
Finger *et al.* 2011 [47]	208 phakic patients	Uveal melanoma treated with palladium 103	Mean 39.8 months	76/282 (27.0%)	Age, higher radiation dose
Newman *et al.* 2011 [15]	50 patients	Subfoveal choroidal melanomas with ≥6 months of follow-up	Median 54 months	22% of 46 patients	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	1/18 (5.5%)	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	26/82 (31.7%)	--
Marconi *et al.* 2013 [31]	94 patients	Choroidal melanoma treated with ruthenium brachytherapy	Median 39 months	16%	--
Krema *et al.* 2013 [38]	30 patients	Posterior tumor margin 0 - 2.5 mm from optic disc		62%	--
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	16/47 (36%)	--

Table 12. Cataract outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Cataract at End of Follow-Up	Predictors of Cataract after Treatment
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	6/21 (28.6%)	Tumor far from fovea
Riechardt *et al.* 2014 [34]	147 patients	Peripapillary choroidal melanoma	Mean 78 months	31% with new cataract after 5 years	--

choroidal melanoma randomized to iodine-125 brachytherapy in the COMS [44]; the high rate may be explained by the larger sample size, or more accurate documentation of outcomes due to the study being a randomized trial. Another study that reported similar rates by Krema *et al.* [38] focused on posterior tumors near the optic disc. Of the two studies that examined predictors of cataract formation following plaque therapy [44] [45], both found that radiation dose was predictive of cataract formation following treatment.

There were two studies [9] [34] that examined cataract formation following proton beam therapy for choroidal

melanoma. While the two studies had very different sample sizes and duration of follow-up and focused on different tumor types, both found similar rates of cataract development following proton beam therapy (28.6% and 31%). One of the studies [9] found that tumor distance from the fovea was predictive of cataract development following proton beam therapy, and the other study did not examine predictors of cataract development.

3.8. Distant Metastasis

Studies examining distant metastasis from choroidal melanoma following plaque and proton therapy are outlined in **Table 13** and **Table 14**. Distant metastasis from choroidal melanoma is associated with a poor prognosis with a median survival time of less than one year following metastasis [48]. The most common site of metastasis is the liver, with other sites being lung, bone, and skin [49]. There were 13 included studies [10]-[22] that examined the development of distant metastasis following treatment of choroidal melanoma with plaque therapy. Sample sizes ranged from 24 to 650 patients, and follow-up time ranged from a median of 17.3 months to a mean of 59.47 months. Rates of metastasis ranged from 0.0% to 31.9%, with the highest rates reported in a study of large tumors [20] and in the study with the longest duration of follow-up [18]. Of the studies that reported the time to development of metastasis [13] [14] [17], the average time ranged from 30.4 months [13] to 58 months [14]. Three studies [13] [17] [18] reported rates of metastasis-free survival, with all reported rates greater than 75%. The only study [22] to examine predictors of metastasis found that higher intraocular pressure and greater tumor base were predictive of distant metastasis following plaque therapy.

There were five studies [9] [23]-[26] that examined the development of metastasis following proton therapy for choroidal melanoma. Sample sizes ranged from 21 - 349 patients, and duration of follow-up ranged from a median of 28 months to 77.2 months. Rates of metastasis were similar to those reported after plaque therapy, ranging from 5.6% to 25.4%. The only study [25] that examined time to metastasis reported a median of 38 months to metastasis, and the studies [24] [25] that examined metastasis-free survival reported survival rates of 72% to 82% at five years. Tumor dimension was the only factor reported to be related to metastasis development in more than one study [9] [23].

4. Summary and Limitations

This review described the rates of a variety of complications following treatment with plaque versus proton beam therapy for patients with choroidal melanoma. In our descriptive comparisons of the rates of complications following the two different treatment modalities, patients with proton beam therapy have potentially higher rates of vision loss, enucleation, and neovascular glaucoma after treatment when compared to patients with plaque therapy. Reported rates of optic neuropathy, radiation retinopathy, and cataract formation were widely variable for the two treatment modalities, with no consistent differences that could be ascertained when trying to compare the two types of therapy. Reported rates of metastasis and metastasis-free survival appeared similar in studies of plaque versus proton beam therapy, though comparisons were limited by study population, tumor type, and duration of follow-up. The most common reported predictors of ocular complications following both types of therapy were tumor distance from the optic nerve, tumor thickness, and radiation dose, suggesting that inherent tumor characteristics play a role in visual prognosis.

This review was limited mainly by differences in study design, patient inclusion criteria, and the limited number of studies available. There were wide ranges of sample sizes and follow-up times which made it inherently difficult to compare complication rates across studies for both types of treatment. Additionally, several studies focused on specific tumor types such as large tumors or those near the optic nerve, which may have affected the complication rates reported in those studies. Finally, several studies included in this review only examined visual complications as a secondary outcome and did not provide comprehensive information regarding these complications. For further understanding of the side effects of plaque and proton beam therapy for choroidal melanoma, an aggregate registry of ocular and systemic complications of choroidal melanoma treatment would be beneficial.

In conclusion, both plaque and proton beam therapy are associated with a wide range of potentially devastating complications for patients with choroidal melanoma, and proton beam therapy may be associated with higher rates of vision loss, enucleation, and neovascular glaucoma. In addition to the development of treatments that prolong remission and survival, further studies are needed to compare outcomes and quality of life in patients receiving plaque versus proton beam therapy for choroidal melanoma.

Table 13. Distant metastasis outcomes following plaque therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Distant Metastasis at End of Follow-Up	Mean Time to Metastasis	Percentage with Metastasis-Free Survival	Predictors of Distant Metastasis after Treatment
Sagoo *et al.* 2007 [10]	37 patients	Circumpapillary choroidal melanoma	Mean 52 months, median 46 months	1/37 (4%)	--	--	--
Sagoo *et al.* 2008 [11]	141 patients	Juxtapapillary choroidal melanoma overhanging optic disc	Mean 56 months	15 patients (13%)	--	--	--
Gunduz *et al.* 2010 [12]	24 patients	Choroidal melanoma treated with ruthenium brachytherapy alone	--	2/24 (8.3%)	--	--	--
Verschueren *et al.* 2010 [13]	430 patients	Choroidal melanoma	Median 50 months	51/430 (11.9%)	30.4 months (range 0 - 68.4 months)	76.5% at 5 years, 69.1% at 10 years	--
Karlovits *et al.* 2011 [14]	35 patients	Choroidal melanoma treated with iodine brachytherapy	Median 45 months	5/35 (14.3%)	Median 58 months	--	--
Newman *et al.* 2011 [15]	50 patients	Subfoveal choroidal melanomas with ≥6 months of follow-up	Median 54 months	2/50 (4%)	--	--	--
Sagoo *et al.* 2011 [22]	650 patients	Juxtapapillary choroidal melanoma treated with plaque brachytherapy	--	11% at 5 years, 24% at 10 years	--	--	High intraocular pressure, greater tumor base
Chang *et al.* 2012 [21]	150 patients	Choroidal melanoma treated with iodine brachytherapy	Mean 21.5 months, median 17.3 months	9/150 (6.0%)	--	--	--
Finger *et al.* 2012 [16]	24 patients	Choroidal melanomas within 1.5 mm of optic disc treated with slotted radiotherapy	Mean 23 months	0/24 (0.0%)	--	--	--
Berry *et al.* 2013 [17]	82 patients	Medium sized choroidal melanomas	Median 46.8 months	9/82 (10.9%)	41.0 months (standard deviation [SD] = 34.7 months)	89% at 60 months	--
Caminal *et al.* 2013 [18]	54 patients	Choroidal melanoma treated with iodine brachytherapy	Mean 59.47 months	11/54 (20.4%)	--	84.2% at 5 years	--
Semenova *et al.* 2013 [19]	72 patients	Small choroidal melanomas	Mean 54 months	0/72 (0.0%)	--	--	--
Semenova *et al.* 2014 [20]	47 patients	T3 or T4 sized choroidal melanomas treated with palladium brachytherapy	Median 47 months	15/47 (31.9%)	--	--	--

Table 14. Distant metastasis outcomes following proton beam therapy for choroidal melanoma.

Study	Sample Size	Tumor Type	Duration of Follow-Up	Number (%) with Distant Metastasis at End of Follow-Up	Mean Time to Metastasis	Percentage with Metastasis-Free Survival	Predictors of Distant Metastasis after Treatment
Damato *et al.* 2005 [23]	349 patients	Choroidal melanoma	Median 3.1 years	2.5% died from metastasis at 2 years, 10.0% at 5 years, 14.1% at 8 years	--	--	Longest basal tumor dimension, tumor height, extraocular tumor extension
Conway *et al.* 2006 [9]	21 patients	Extra large choroidal or ciliochoroidal melanomas	Median 28 months	3/21 (14.3%)	--	--	Characteristics of patients with metastasis (no multivariate modeling performed): Mean age 80.7 years, maximum basal tumor diameter 21 - 24.4 mm
Mosci *et al.* 2012 [24]	72 patients	T3 and T4 choroidal melanomas	Mean 53.4 months		--	72% at 5 years	--
Tran *et al.* 2012 [25]	59 patients	Peripapillary choroidal melanoma	Median 63 months	15/59 (25.4%)	Median 38 months	82% at 5 years	--
Schonfeld *et al.* 2014 [26]	18 patients	Choroidal melanoma in intermediate zone of fundus treated with proton beam therapy only	Median 77.2 months	1/18 patients (5.6%) died from metastasis	--	--	--

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