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Pars Plana Vitrectomy Associated with or Following Plaque Brachytherapy for Choroidal Melanoma

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1. Introduction

There are underlying concerns regarding the safety of vitrectomy surgery in eyes with intraocular malignancy. These concerns are associated with vitrectomy, both with or without plaque brachytherapy for choroidal melanoma. These include the possibility of local tumor dissemination, extension of malignant cells to the ocular surface and orbit, and remote metastasis. The purpose of this chapter is to discuss the safety and efficacy of employing pars plana vitrectomy in the setting of choroidal melanoma, whether concurrent with treatment or post radiation treatment.

Uveal melanomas are the most common primary intraocular malignancy and, besides the skin, the uvea is the area most commonly affected by melanoma. The incidence of ocular melanoma in the United States is approximately six cases per one million population each year with a median age of onset of 55 years. [1,2] Distant metastasis peaks two to three years after enucleation with uveal melanomas, and patients with remote metastasis seldom survive longer than one year. [3]

Currently, treatments for remote metastasis include immunotherapy, hepatic chemoembolization, as well as experimental treatment modalities. Unfortunately, survival has not dramatically increased with any of the current treatment modalities for metastatic choroidal melanoma. Many factors have been suggested as being of prognostic value including larger tumor size, anterior tumor margin, cellular pleomorphism, extrascleral extension, and genetics including monosomy 3 and genetic expression profiling. These will be discussed in later paragraphs.

The indications for pars plana vitrectomy (PPV) have increased exponentially since its inception in the 1970s. Traditionally, 20-gauge PPV has caused delayed wound healing, re-

quirement of sclerotomy sutures, postoperative astigmatism, and patient discomfort. Recently, small gauge PPV has been introduced. The 25-gauge transconjunctival sutureless PPV system enables sutureless three-port PPV without the need for conjunctival peritomies, decreases mean operative times, reduces post surgical patient discomfort, and decreases surgically-induced trauma at sclerotomy sites. [4] Decreased traumatic conjunctival and scleral manipulation with less postop inflammation, as well as less induced astigmatism, allows for more rapid postoperative visual recovery. The self-sealing nature of the incisions in sutureless PPV, however, does pose potential concerns for the possibility of vitreous incarceration, postoperative endophthalmitis, and hypotony. [5-7]

Posterior uveal melanomas can cause visual disturbances secondary to vitreous hemorrhage, exudative retinal detachments, and radiation-related complications. Treatment consisted of enucleation prior to the Collaborative Ocular Melanoma Study (COMS), which found that at twelve years, there were no significant differences in survival between enucleation and plaque brachytherapy with regards to medium size choroidal melanomas. [8] Radiation has resulted in a new set of complications, some of which are amenable to the use of vitrectomy surgery in the setting of a treated choroidal melanoma. This chapter will discuss the safety and efficacy of vitrectomy regarding diagnosis and biopsy, endoresection, and radiation-induced complications.

2. Pars plana vitrectomy for diagnostic biopsy as well as molecular genetic testing

The diagnosis of posterior choroidal melanoma is often made clinically, as well as aided by ancillary testing, such as ultrasonography, optical coherence tomography, transillumination, and angiography. Choroidal melanoma rarely requires a biopsy to make the diagnosis. With the advent of cytogenetic and molecular genetic studies, there has been a recent effort to obtain fresh tumor tissue. Early cytogenetic studies suggested that certain chromosomes (chromosome 3, 6, and 8) abnormalities were associated with a higher likelihood for metastatic disease. In the early 1990s, it was recognized that a chromosomal 3 alteration was closely associated with metastatic disease. The most important was monosomy 3 (loss of one copy of chromosome 3), which is closely associated with metastatic disease. [9,10]

Other chromosomal changes have been associated with metastatic disease including loss of 1p and 8p as well as gain of 8q, loss of 6q, and gain of 6p. These have been linked statistically to metastatic death in choroidal melanoma. [11]

This cytogenetic information has become increasingly accessible to physicians, and the risk of misinterpreting this information has also increased. Cytogenetic analysis for choroidal melanoma was first performed with standard karyotyping, in which direct visualization was used and chromosomal abnormalities identified by morphologic changes and chromosome banding pattern and size. However, this technique required the need for a highly trained cytogeneticist, led to sampling error due to analysis of only a few tumor cells, and had an inability to detect small changes. There are other techniques that rely on direct analy-

sis of chromosomes including spectral karyotyping (SKY), fluorescence in situ hybridization (FISH), and comparative genomic hybridization (CGH).

The above techniques were superior to clinical and histopathologic variables alone in predicting which patients will develop metastatic disease. However, these techniques had limitations including false positives and negatives, a high rate of failure due to the amount of tissue required, the variability of technique from center to center, and intratumoral heterogeneity. Perhaps the most limiting factor in the accuracy of monosomy 3 analysis is due to heterogeneity. A single choroidal melanoma can be comprised of a mixture of cells, some of which contain one copy of chromosome 3 and others that contain the normal two copies. Sampling one portion of the tumor can often produce the wrong test result.

Recently, thousands of genes could be monitored simultaneously for micro-RNA (mRNA) expression. [12] With the advent of newer software, massive amounts of data could be analyzed and multidimensional analysis could provide new heights of biologic information that were previously unobtainable. This was seen in cancer, where gene expression profiling (GEP) revealed many types of cancer that were thought to be uniform based on their common tissue source, but were instead composed of multiple subtypes of molecularly distinct cancers. This was the case with choroidal melanoma. GEP has helped to simplify our molecular understanding of choroidal melanoma. Rather than many different molecular subtypes, there are only two major choroidal melanoma subtypes, class 1 and class 2. GEP is extremely accurate for predicting patient metastatic rates. Class 1 tumors have a very low risk and class 2 have a very high risk of metastatic disease. [12]

The superiority of GEP over monosomy 3 has been verified by multiple groups. [12] In the past, the major disadvantage of GEP was the expense and limited availability. [13] However, once the value of GEP became clear, considerable effort was devoted to optimizing it for application and use. With regards to choroidal melanoma, GEP evaluates 15 different genetic abnormalities resulting in a class 1 or class 2 classification. This small number of genes has allowed a commercially available, relatively inexpensive assay. This is a polymerase chain reaction based assay, which requires a much smaller biopsy sample and has a very low failure rate. With this technology, we can now identify uveal melanoma patients who are likely to develop metastatic disease. But the question remains, what is the role of vitrectomy with regards to biopsying choroidal melanoma?

Obtaining cells for analysis requires a fine-needle aspiration biopsy (FNAB). Techniques for performing biopsy may be transvitreal or transscleral. Newer techniques even involve the use of small gauge vitrectomy. Transscleral biopsy involves the use of a 27- or 30-gauge needle that is inserted tangentially through the sclera at the base of the tumor. Traditionally following transscleral biopsy, a radioactive plaque is then placed. Transvitreal biopsy may also be performed with a 25- or 27-gauge needle via a pars plana approach. The needle is inserted into the tumor and tumor cells are aspirated. [14] Paul Finger, M.D. was a pioneer in introducing the 25-gauge vitrector to biopsy ocular melanomas. He first used the technique to aspirate cells from an iris melanoma. [13] More recently with the advent of sutureless vitrectomy, newer techniques include performing a 25-gauge vitrectomy followed by inserting a

25- or 27-gauge needle through the 25-gauge cannula and into the center of the tumor, followed by aspiration of tumor cells. [15]

Potential complications of biopsy include vitreous hemorrhage, retinal detachment, and the potential for intraocular or extraocular tumor dissemination. In a series of 500 fine needle biopsy procedures, there were no cases of local recurrence or intraocular dissemination. [16] However, follow up was only three years. There were no cases of extrascleral extension due to FNAB. In another publication by Shields et al, they focused on the outcome of each patient after FNAB. [17] Each patient was treated with plaque brachytherapy at the time of FNAB, and there were no enucleations as all biopsy specimens were obtained by needle sampling. There were no complications in this study as well. Twenty-five-gauge PPV using the vitrector to obtain cells has also resulted in no intraocular dissemination or increased metastasis to date. [13,15]

Most recently, investigators at the Jules Stein Eye Institute performed an Institutional Review Board approved retrospective study to evaluate local and systemic outcomes in patients undergoing FNAB at the time of plaque surgery for choroidal melanoma. Included were all patients with choroidal melanoma treated with Iodine-125 brachytherapy and intraoperative transscleral FNAB from 2005 to 2010. [18] The study included 170 consecutive patients. The technique used for FNAB involved transscleral approach using a 30-gauge needle. They found no cases of treatment failure and there were no cases of orbital dissemination. Metastatic disease developed in 14 of the 170 patients. The metastatic rate in their study was similar to the metastatic rate in the COMS. The COMS did not include FNAB of tumors. In this study, when compared with the largest multicenter prospective study ever performed in ocular oncology, performing FNAB did not increase the risk of developing metastatic disease from choroidal melanoma.

3. Pars plana vitrectomy for treatment of choroidal melanoma using endoresection

Removal of a tumor using an internal approach (endoresection) was first investigated for posterior choroidal melanomas in the 1980s, primarily for small juxtapapillary melanomas that were not amenable to other forms of treatment including brachytherapy at that time. Endoresection has never gained widespread popularity. However, studies have investigated the use of endoresection as an alternative to plaque brachytherapy to avoid radiation related complications such as radiation retinopathy, optic neuropathy, and retinal ischemia. Surgical techniques vary dependent upon surgeon, however the basic principles remain. A three-port PPV is performed with posterior hyaloid dissection. Diathermy or endolaser is used around the periphery of the tumor, followed by creation of a retinotomy. The vitreous cutter is used to excise the tumor to bare sclera. Photocoagulation is then used followed by gas or silicone oil tamponade to flatten the retina. This surgical technique has many complications including retinal detachment, proliferative vitreoretinopathy, severe bleeding, and cataract. The results for local tumor control and metastasis have been favorable, with complications

ranging from 2% to 9.4%. [19-22] A very large risk and potential drawback has been the question of whether this procedure results in liberating active tumor causing a potential increase in orbital recurrence and metastatic disease. This question will be answered by the studies cited below.

Kertes et al, in the *British Journal of Ophthalmology*, followed 32 consecutive patients that were treated with endoresection. The patient's choroidal melanoma was pathologically confirmed and all patients were followed for a mean of 40.1 months. At the time, this was the longest follow up and largest series reporting on endoresection for posterior uveal melanoma. [19] The authors found that only three patients developed distant metastasis and died of malignant melanoma. In one case, distant metastasis developed in association with an intraocular recurrence. The most common complications the authors encountered were vitreous hemorrhage in 37.5% of patients, cataract in eight of 32 eyes, and three cases of retinal detachment. With an average of almost three and one-half years follow up, the authors concluded that their results, with regards to metastatic disease, were no worse than patients treated with plaque brachytherapy. They stated that their experience did not support the contention that surgical manipulation of malignant choroidal melanoma promotes metastasis. Furthermore, endoresection is a reasonable and safe alternative to the management of posterior uveal melanoma. Approximately 50% of uveal melanomas occur less than 3mm from the optic nerve or fovea, and the authors felt that their technique was particularly well suited to the treatment of choroidal melanomas that are in close proximity to the optic nerve and fovea.

Damato and associates, in a 1998 *British Journal of Ophthalmology* article, reported on 52 patients undergoing endoresection for choroidal melanoma. Their technique involved vitrectomy, retinal incision, hemostasis by raising intraocular pressure and by moderate hypotensive anesthesia, endoresection using the vitrector, endodiathermy, endolaser, and fluid-air exchange to reattach the retina. [20] They used adjunctive ruthenium plaque radiotherapy in selected cases. Their patients had a mean tumor thickness of 3.9 mm. Most of the choroidal melanomas extended to within two disc diameters of the optic nerve. Follow up was a median of 20 months. The main complications included retinal detachment in 16 of 52 patients and cataract in 25 of 52 patients. Twenty-three of the 52 patients had 20/200 or better vision postoperatively. No patients developed local tumor recurrence. Only one of the 52 patients undergoing endoresection developed metastatic disease, 41 months postoperatively. The authors concluded that endoresection did not increase the rate of metastatic disease.

Garcia-Arumi and associates reported on 25 consecutive patients undergoing vitreoretinal surgery with endoresection for high posterior choroidal melanomas. [21] The tumor thickness ranged from 9.1 mm to 12.8 mm. The authors employed standard endoresection technique, but did use a 120-degree anterior retinotomy prior to endoresecting the melanoma and reattaching the retina. The postoperative complications included cataract in 40%, retinal detachment in 16%, epiretinal macular proliferation in 8%, and submacular hemorrhage in 4%. The final visual acuity postoperatively ranged from hand motion to 20/30, with a mean of 20/100. Remarkably, no tumors recurred, and there was no evidence of metastatic disease in follow up, which ranged from 12 to 72 months. The authors state that the reason for having

such a low rate of retinal detachment was due to modifying their technique, including trimming the vitreous base, examining the peripheral retina carefully for breaks, and avoiding high infusion pressure. These authors also concluded that endoresection was efficacious and did not increase the rate of metastatic disease.

Most recently, Karkhaneh and associates reported on 20 patients undergoing endoresection for medium size posterior choroidal melanoma. [22] Tumor thickness ranged from 5.5 mm to 11 mm. Preoperative visual acuity ranged from hand motion to 20/40, while postoperative visual acuity ranged from no light perception to 20/30. The authors stated that for tumors with thickness less than 9 mm in their study, they could have been treated with radiotherapy, but endoresection of the tumor may be an alternative approach in some parts of the world where radiotherapy is not readily available. Of the authors' patients, 6.7% had 20/40 or better vision at three years, while 73% had 20/200 or less. Only one in 20 patients died of metastatic disease in a mean follow up of 89.5 months. This is the longest follow up of all case series of patients undergoing endoresection for choroidal melanoma. This rate of metastatic disease is certainly lower than the metastatic rate seen in the COMS.

In contrast to enucleation, endoresection of posterior choroidal melanoma is designed to preserve vision and maintain a cosmetically acceptable eye. In contrast to brachytherapy, endoresection has fewer long-term complications such as radiation optic neuropathy or radiation retinopathy. Immediate complications of endoresection can be severe, including vitreous hemorrhage, retinal detachment, cataract, and proliferative vitreoretinopathy. [19-22] The primary goal of endoresection is to eradicate the tumor while preserving vision. However, the question of cutting into a malignant tumor and liberating cells, some of which may lead to local tumor recurrence or orbital tumor recurrence and/or distant metastasis, needed to be answered. There is no current evidence that endoresection of posterior choroidal melanoma is different from enucleation or brachytherapy with regard to patient survival and metastatic disease, seen in the above detailed literature. [19-22]

4. Pars plana vitrectomy for exudative retinal detachment secondary to choroidal melanoma

Exudative retinal detachment is the most common etiology of vision loss from untreated, recently diagnosed choroidal melanoma. Historically, management has been conservative, as the exudative retinal detachment will often resolve following brachytherapy for choroidal melanoma. However, large exudative retinal detachments secondary to choroidal melanoma often will not resolve and can lead to irreversible vision loss from photoreceptor damage during the several months needed for post brachytherapy resolution. The consistency of subretinal fluid associated with exudative retinal detachment from choroidal melanoma is found to be more viscous compared to subretinal fluid in rhegmatogenous retinal detachments, which can explain the longer duration of reabsorption leading to limited visual recovery. [23]

Gibran and Kapoor reported on six consecutive patients with choroidal melanoma and secondary exudative retinal detachment that underwent radiation therapy, transretinal biopsy with the 25-gauge vitrector, and surgical treatment of the exudative retinal detachment, including vitrectomy and drainage of subretinal fluid with retinal tamponade. [23] All patients had a successful reattachment of the retina with significant restoration of vision. There were no recurrences of exudative retinal detachment. Five of the six patients had 20/40 or better vision postoperatively. More importantly, there were no cases of extrascleral extension or metastatic disease.

5. Pars plana vitrectomy for complications after brachytherapy for choroidal melanoma

Posterior choroidal melanoma treated by brachytherapy can often result in decreased visual acuity due to retinal detachment, vitreous hemorrhage, radiation retinopathy, radiation optic neuropathy, radiation macular ischemia, epimacular proliferation, vitreous debris, and cataract. Potential indications for vitrectomy following melanoma brachytherapy include exudative retinal detachment, tractional and rhegmatogenous retinal detachment, vitreous hemorrhage, vitreous debris, and epimacular proliferation.

There is controversy regarding surgical treatment of eyes harboring a melanoma, whether treated or untreated, and whether there are viable tumor cells that may increase intraocular recurrence, extraocular recurrence, and metastatic disease. This question will be answered by the articles discussed below, as well as our data at Retina Consultants of Alabama/The University of Alabama at Birmingham School of Medicine, Department of Ophthalmology.

Foster and associates reported on nine patients undergoing 20-gauge PPV in eyes containing a treated posterior uveal melanoma. [24] In their series, vitrectomy was performed for vitreous hemorrhage in five patients, macular pucker in two patients, macular hole in one patient, and rhegmatogenous retinal detachment in one patient. Vitrectomy was performed at a mean 24.7 months after melanoma radiation treatment. Dispersion of tumor cells during vitrectomy was not observed in any patient. One patient had melanoma cells detected in the vitreous aspirate. This patient had intratumoral and vitreous hemorrhage before plaque brachytherapy, underwent combined cataract extraction and vitrectomy, and developed intraocular tumor dissemination 56 months after vitrectomy. No other patients developed intraocular tumor dissemination. None of the nine patients developed systemic metastatic disease.

More recently, Bansal et al reported on the author's experience with vitrectomy for vitreous hemorrhage in eyes with posterior choroidal melanoma. [25] They reviewed the medical records of 47 patients who underwent vitrectomy for vitreous hemorrhage following Iodine-125 brachytherapy for posterior choroidal melanoma. The primary outcome of their analysis included rates of intraocular tumor dissemination, extrascleral extension, local tumor recurrence, and systemic metastasis. The average time to develop vitreous hemorrhage was 22 months following brachytherapy. With a mean follow up of five years, only four of

the 47 patients (8%) developed metastatic disease, and no cases had intraocular tumor dissemination or extraocular extension.

In 2012, Sisk and Murray reported on combined phacoemulsification and sutureless vitrectomy for complex vitreoretinal diseases. [26] In their retrospective review of 114 eyes that had vitrectomy and cataract extraction, 72 of these eyes had a diagnosis of melanoma post radiation treatment. The authors' primary outcome measures were visual acuity and perioperative complications. They did not report on tumor recurrence or metastatic disease.

We at Retina Consultants of Alabama/The University of Alabama at Birmingham School of Medicine, Department of Ophthalmology reviewed the medical records of 155 consecutive patients with choroidal melanoma treated with Iodine-125 brachytherapy. [15] We identified 20 patients that subsequently underwent 25-gauge PPV following brachytherapy. The average age was 64. The etiology for 25-gauge PPV was epimacular proliferation in one patient, vitreous debris in two patients, rhegmatogenous retinal detachment in three patients, exudative retinal detachment in one patient, and vitreous hemorrhage in 13 patients. The average interval from plaque brachytherapy to 25-gauge vitrectomy was 59 months (range 16 to 98 months). Patients were followed after their 25-gauge PPV an average of 36 months (range nine to 100 months). We found one of 20 patients to have local intraocular recurrence. One patient subsequently was enucleated for a blind painful eye secondary to neovascular glaucoma. Sixteen of the 20 patients had improvement in vision following PPV. Most importantly, no systemic metastatic disease was reported in any of the 20 patients at their last visit, which was a mean of 36 months following their 25-gauge PPV.

In summary, the reports by Foster et al, [24] Bansal et al, [25] and Mason and Mullins [15] reveal the safety of performing vitrectomy in patients who have been treated with brachytherapy for choroidal melanoma. The combined reports by Foster and Mason found zero of 29 patients developed metastatic disease following vitrectomy, while Bansal found only four of 47 patients to have developed metastatic disease following vitrectomy in patients with treated choroidal melanoma. This meta-analysis certainly reveals a much lower incidence of metastatic disease than previous reports, including the COMS (which did not include PPV following brachytherapy). [8] Our current findings based on the above literature, are the following: sutureless vitrectomy may be performed safely in patients having post brachytherapy complications, sutureless vitrectomy does not increase the rate of metastatic disease, and, patients may take comfort that vitrectomy following brachytherapy for choroidal melanoma may result in an increase in vision with no threat of increasing metastatic disease.

6. Conclusion

With the advent of globe salvaging techniques regarding management of choroidal melanoma, ocular oncologists face challenges in the care of these patients. Tumor biopsy is gaining widespread acceptance to obtain tissue for genetic analyses, allowing for more precise determination of metastatic disease prognosis. The use of vitrectomy with regards to tumor biopsy, endoresection, and post radiation complications has expanded rapidly.

Fortunately, all literature to date has shown PPV to be very efficacious and safe in the setting of a patient with choroidal melanoma. Furthermore, there has been no increased rate of metastasis of choroidal melanoma when vitrectomy has been employed prior to or following treatment of the tumor.

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