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REVIEW

Brachytherapy for patients with uveal melanoma: historical perspectives and future treatment directions

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Beatrice Y Brewington[1]
Yusra F Shao[2]
Fredrick H Davidorf[1]
Colleen M Cebulla[1]

[1]Havener Eye Institute, Department of Ophthalmology and Visual Science, Ohio State University, [2]Medical Student Research Program, The Ohio State University College of Medicine, Columbus, OH, USA

Abstract: Surgical management with enucleation was the primary treatment for uveal melanoma (UM) for over 100 years. The Collaborative Ocular Melanoma Study confirmed in 2001 that globe-preserving episcleral brachytherapy for UM was safe and effective, demonstrating no survival difference with enucleation. Today, brachytherapy is the most common form of radiotherapy for UM. We review the history of brachytherapy in the treatment of UM and the evolution of the procedure to incorporate fine-needle-aspiration biopsy techniques with DNA- and RNA-based genetic prognostic testing.

Keywords: brachytherapy, uveal melanoma, UM, fine-needle-aspiration biopsy, genetic prognostic testing, molecular markers

Introduction

In the early 1900s, patients often presented with large, symptomatic uveal melanoma (UM), for which the primary course of treatment was enucleation. Many of these cases resulted in mortality due to metastasis to the liver and other sites, even after enucleation had been performed.[1,2] The increase in metastasis after enucleation for UM led to a concept called the "Zimmerman hypothesis", popularized during the 1970s.[3,4] Zimmerman et al proposed that a spike in intraocular pressure at the time of cutting the optic nerve could cause dissemination of tumor cells through the vortex veins into the systemic circulation, leading to liver metastasis.[3] A method for freezing the melanoma at the time of cutting the optic nerve in order to prevent dissemination developed by Fraunfelder et al was utilized for years at several centers.[5] The method was referred to as "no-touch enucleation", and represented continued efforts to minimize surgical trauma at the time of globe removal. Eventually, researchers came to realize that metastatic disease was more complex and had likely occurred microscopically months or years before melanoma diagnosis and enucleation.[6,7] Metastasis represents the biologic process of cancer. This led to a challenge of the Zimmerman hypothesis and alleviated the concern over the negative effects of enucleation. For reviews of this subject, see Singh et al and Shields and Shields.[7,8]

The 1970s were also a period where the desire for globe-conserving treatments that could prevent further metastasis but also preserve visual function led to the development of alternative modalities such as xenon-arc photocoagulation, argon-laser photocoagulation, transpupillary thermotherapy, proton-beam irradiation, and brachytherapy. Of all these treatment approaches, brachytherapy has become the most widely utilized conservative treatment for UM. Therefore, we focus our discussion on the history of

Correspondence: Colleen M Cebulla
Havener Eye Institute, The Ohio State University, Wexner Medical Center, Columbus, OH 43210, USA
Tel +1 614 652 2600
Email colleen.cebulla@osumc.edu

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brachytherapy in the treatment of UM, the use of fine-needle-aspiration biopsy (FNAB) as an adjunct procedure at the time of brachytherapy, and genetic prognostic information that can be obtained with the help of FNAB.

The history of brachytherapy

Bechrakis et al reported that the first successful treatment of UM by brachytherapy was performed by Deutschmann in Hamburg in 1915.[9] Hungerford reported that the first successful radiotherapy treatment of melanoma was by Moore on February 18, 1929 at Saint Bartholomew's hospital in London.[10] Moore inserted a radon seed into a melanoma in the eye. In 1948, this was a technique that Stallard was exploring for the treatment of retinoblastoma. Stallard and his physicist George Innes began inserting radon seeds into wax, positioning them on the surface of the eye, and later removing them.

Radon

In the late 1960s, William Havener, an ophthalmologist at The Ohio State University with a special interest in UM, worked with Frank Batley, a radiation oncologist, to develop a ring plaque that utilized radon seeds. In 1970, Newman et al published the first paper on the treatment of posterior UM using radon seeds encapsulated in gold.[11] They reported their results after treating five patients with conservative management. These techniques employed radon gas encapsulated in gold as the radiation source. Radon gas, a decay product of radium, was selected because of its availability and ease of dosage calculations.[11] Dose calculations were based on the rules outlined by Paterson and Parker.[12] The gold seeds filled with radon gas were uniformly distributed around the circumference of a circular mold of polyethylene tubing. Each plaque was sized to deliver 6,000–8,000 R.[11] Gold seeds permitted the γ-rays from radon-decay products to penetrate the tumor while limiting the α- and β-rays that could cause local tissue necrosis.[11] The tubing was then sutured to bare sclera overlying the tumor, and the Tenon's capsule and conjunctiva were then closed in two layers. Given the short half-life of radon (3.8 days), the device was typically not removed as long as it was tolerated by the patient.[11] While radon use was initially used for brachytherapy, Stallard simultaneously explored the use of cobalt 60 (^{60}Co).

Cobalt 60

Stallard's technique evolved to the development of a ^{60}Co radioactive scleral plaque. The technique revolutionized treatment and allowed vision to be preserved in patients with retinoblastoma.[13] By 1966, Stallard was ready to report his results after treating over 100 cases of UM.[14] A total of 99 of his patients were treated with ^{60}Co-loaded circular, crescentic, or semicircular applicators that were sutured to the sclera over the neoplasm with a 1 mm margin. Most of the patients received a radiation dose of 20,000–40,000 R at the tumor base over 7–14 days.[14] The optimal dose was still under trial. However, it was reported that a number of the tumors had been reduced to a flat, pigment-stippled scar. Cruess et al reported in 1984 that the "average" UM treated with ^{60}CO-plaque therapy did not completely regress to a flat, depigmented scar, leaving concern that the remaining tumor may be viable and capable of metastasizing.[15] In addition, ^{60}Co plaques are high in energy and cannot be shielded effectively on their external surface.[10] The result of this was significant radiation side effects on adjacent retina, choroid, optic nerve, lens, eyelids, and lacrimal apparatus. By 1985, cobalt plaques were no longer regularly used in London. Additional isotopes were subsequently explored for use during low-energy brachytherapy, including ruthenium 106 (^{106}Ru) in Europe and iodine 125 (^{125}I) in the US.

Ruthenium 106

β-Radiation with ^{106}Ru is currently the most commonly used radioisotope for brachytherapy in Europe. ^{106}Ru was introduced by Peter Lommatzsch in the 1960s.[16] It is a β-emitter, which allows it to be shielded and allows for limited depth of penetration. ^{106}Ru applicators are manufactured commercially. ^{106}Ru brachytherapy for UM provides excellent local control with low tumor-recurrence rates for tumors <7 mm in height.[16–21] The limited range of penetration causes less damage to the eye, with better preservation of vision. ^{106}Ru can be combined with other treatments, such as transpupillary thermotherapy or γ-emitting isotopes, such as ^{125}I or ^{60}Co.[16] However, some caution is suggested when adopting ^{106}Ru use in UM treatment centers familiar with ^{125}I: high recurrence rates have been reported in applying Collaborative Ocular Melanoma Study (COMS) ^{125}I-treatment plans to ^{106}Ru plaques for UM brachytherapy.[22]

Iodine 125

^{125}I with γ-radiation is the most commonly used brachytherapy isotope in the US. In 1987, Packer examined the advantages of using gold ^{125}I plaques in the treatment of posterior UM.[23] The plaques were 4–6 mm larger than the estimated base diameter.[24] Improvements in plaque design included recessing the ^{125}I seeds and modifications to reduce stray radiation. These modifications were utilized in the design of

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the COMS plaque, which utilized an apex dose of 85 Gy in the trial.[25] Custom-made plaques designed to specific tumor specifications are most often utilized in the US. Eye Physics plaques are descendants of the plaque designs used at the University of Southern California from 1980 to 2010. These plaques were originally prototyped for ^{192}Ir seeds, and in the late 1980s were retired in favor of prototypes intended for ^{125}I seeds. Eye Physics plaques compare favorably with COMS plaques in terms of adverse effects of radiation, metastasis, and local tumor recurrence.[26] Nag et al demonstrated that a custom-made plaque can control medium-sized UM and that a 1 mm, rather than 2 mm, margin used in COMS is sufficient.[27] The custom-made Nag plaque for ^{125}I therapy compares favorably to the COMS plaque.[28] COMS and other recent trials have demonstrated that ^{125}I brachytherapy provides survival rates that are equal to enucleation.[29,30] The 5-year local recurrence rate in the COMS was 10.3%, and even lower rates have been achieved.[10,31] There are side effects associated with brachytherapy as a result of radiation delivered to adjacent structures. Almost 50% of patients develop radiation retinopathy. Other complications include optic atrophy, cystoid macular edema, cataracts, vitreous hemorrhage, central retinal vein occlusion, secondary glaucoma, and scleral necrosis.[32]

Palladium 103

COMS established ^{125}I as the most common and widely used radionuclide for treatment of UM in 1985. Palladium 103 (^{103}Pd) seeds became available for the treatment of cancer 4 years later.[33] ^{103}PD emits lower-energy photons (21 KeV) than ^{125}I, which would potentially shift energy away from normal ocular structures.[34,35] In 2009, Finger et al looked at outcomes in 400 patients with UM treated with ^{103}Pd-plaque therapy. Patients were given a mean apical radiation dose of 73.3 Gy.[36] The study found that for an equivalent apex dose, ^{103}Pd-treated UM tissue received more radiation than ^{125}I-treated UM. However, ^{103}Pd photons are more rapidly absorbed by the vitreous, and thus decrease the risk of macular retinopathy. The study reported favorable visual acuity and local control when compared with ^{125}I and ^{106}Ru.[36] The cost of ^{125}I and ^{103}Pd plaques is roughly the same for insured patients in the US. For self-pay patients, a ^{103}Pd seed is more expensive than an equivalent ^{125}I seed, although fewer ^{103}Pd seeds are typically required in each plaque.[36,37]

Patient selection

Over the years, many controversies developed regarding such variables as treatment modality, tumor size and location, and radioisotopes. To address some of these controversies, the COMS group performed a nationwide, multi-institutional, randomized prospective clinical trial to compare the efficacy of enucleation vs ^{125}I plaques for medium-sized UM. The results provided guidelines for episcleral plaque use. However, there were no standardized procedures. Therefore, the American Brachytherapy Society formed a panel to issue brachytherapy-use guidelines for the treatment of UM.[38] Prior to treatment, a metastatic workup, physical exam, and ophthalmic exam (including ophthalmoscopy, ultrasound, and fundus photography) should be conducted.

Uveal tumors were typically classified on the basis of thickness – small ($\leq$3 mm), medium (>3 mm), or large (>8 mm) – with prognosis being a direct correlate with size.[39] The American Joint Commission on Cancer (AJCC) released the seventh edition of cancer-staging criteria for UM in 2010, which represents the universal standard for staging using clinical, pathologic, and genetic criteria. The current edition of the AJCC staging manual uses the TNM model for anatomical staging.[40] The "T category" is based on tumor basal dimension and thickness, and is divided into four increasing sizes: T1, T2, T3, and T4. It is also classified by extent of ciliary body involvement and extrascleral extension. "Node" refers to nodal involvement, with N0 (lymph-node metastasis absent) and N1 (lymph-node metastasis present). "Metastasis" refers to distant metastasis consisting of MX (cannot be assessed), M0 (distant metastasis absent), and M1 (distant metastasis present). The AJCC criteria were adopted by the American Brachytherapy Society and utilized for consensus in staging and treatment of UM.

In general, small T1 UMs are difficult to distinguish from atypical choroidal nevi. Therefore, although treatment is typically offered to patients with these tumors based on several high-risk characteristics to maximize early treatment, it is also common practice to offer close, serial observation for growth prior to treatment.[41–44] Medium-sized T2 UMs and large (T3 and T4) melanomas require treatment.[38] In 2003, Nag et al outlined several considerations for patients who may potentially be treated by plaque brachytherapy.[38] Our group's modifications of these considerations are listed in Table 1.

Currently, it is common practice to consider brachytherapy for tumors with unbulky extrascleral extension, but the patient is informed of the higher rate of recurrence.[39] A case using excision of a bulky extrascleral extension combined with brachytherapy has been reported, with good results through 30-month follow-up.[45] With large tumors, patients are also more likely to experience side effects, including

Table 1 Considerations for uveal melanoma-plaque brachytherapy candidates

Good candidates
• Small tumor with documented growth
• Medium tumor size
• Large tumor (visual outcomes may be compromised)
Candidates with additional counseling recommendations (higher rates of visual compromise, tumor recurrence, loss of eye)
• Large tumor
• Peripapillary tumor
• Extrascleral extension
Poor candidates
• Extensive circumpapillary/peripapillary location involvement (slotted plaque may increase treatment options)[49]
• Bulky extrascleral extension
• Ring melanoma
• Tumor involvement of more than half the ciliary body
• Very large tumor (exceeds diameter limits of brachytherapy)
• Blind, painful eyes

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recurrence, severe vision loss, scleral necrosis, and blind painful eye requiring enucleation.[46] Patients with peripapillary tumors overhanging the nerve may be treated with brachytherapy, but the recurrence rate is higher.[47] For those patients with more than four clock hours of peripapillary tumor, a deeply notched[48] or particularly a slotted plaque with an 8 mm-wide slot to accommodate the retrobulbar optic nerve[49] may be considered; however, proton-beam therapy or enucleation may be preferable modalities if there is circumferential involvement with peripapillary tumor.[50,51] See the publication from the American Brachytherapy Society for more discussion.[52]

FNAB and prognostic testing in uveal melanomas undergoing brachytherapy

FNAB is a method of obtaining tumor samples in vivo. It is used for the diagnosis of a wide range of tumors, including thyroid and liver, and has been extended to the diagnosis of ocular tumors.[53,54] In UM, it is used for prognostic evaluation of tumors undergoing brachytherapy. Prognostic testing uses biomarkers to risk-stratify patients for likelihood of developing disease and disease progression. In the case of UM, it is used to identify patients at high risk of developing metastatic disease to facilitate closer follow-up for detection and treatment of metastasis and enrollment in clinical trials.[55] Currently, patients receiving brachytherapy undergo FNAB at the time of brachytherapy surgery or very shortly before treatment.[56,57] Samples are sent for prognostic testing, including cytopathologic and DNA- or RNA-based tests. According to a study in the UK, almost all patients (97%) with UM choose to undergo cytogenetic prognostic testing with hopes of early detection and better treatment of metastasis.[58]

Prognostic testing

Traditionally, histopathologic features like histologic cell type, tumor size, periodic acid–Schiff vascular mimicry patterns, and ciliary body involvement were used for prognosis at the time of UM enucleation. However, several studies have identified DNA- and RNA-based changes as prognostic features with improved ability to predict outcome than traditional measures.[56,59–62] The prognostic ability of traditional factors, such as largest tumor diameter, is improved by factoring in cytogenetic features of tumors and genetic analysis, and predicts prognosis with greater accuracy than traditional predictive factors.[59,62]

DNA: chromosome analysis

The most basic somatic tumor DNA change associated with UM prognosis is chromosomal copy-number aberration, where monosomy of chromosome 3 and gain of 8q are predictors of poor prognosis (Table 2).[63,64] Monosomy 3 and 8q gain are also found in metastatic UM lesions.[65,66] Patients with monosomy 3 have significantly worse relapse-free and overall survival.[63] Tumors with >33% of cells positive for monosomy 3 have a greater risk of metastatic death than those with 1%–33% of cells positive for monosomy 3.[67] Research suggests that there is no significant difference in prognosis in tumors with disomy 3 compared with partial change in chromosome 3.[68] However, isodisomy of chromosome 3 (loss of one copy of chromosome 3 with duplication of the other) has a poor prognosis, similar to monosomy 3.[69] Chromosome 3 and 8 abnormalities correlate with traditional factors of poor prognosis, such as largest-tumor basal diameter and ciliary body involvement.[59,70] Gain of chromosome 6p correlates

Table 2 Summary of molecular markers of metastasis in uveal melanoma

Molecular markers of decreased risk of metastasis
– Gain of chromosome 6p
– *EIF1AX* gene mutation
– GEP class 1A
Molecular markers of intermediate risk of metastasis
– *SF3B1* gene mutation
– GEP class 1B
Molecular markers of high risk of metastasis
– Monosomy of chromosome 3 and gain of 8q
– *BAP1* gene mutation
– GEP class 2

Abbreviation: GEP, gene-expression profile.

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with improved survival, and in patients with 8q gain, lack of 6p gain is correlated with worse prognosis (Table 2).[71]

Chromosome 3 and 8 changes have been detected with assays ranging from karyotype, fluorescence in situ hybridization (FISH) assay, microsatellite analysis, single-nucleotide-polymorphism analysis, comparative genomic hybridization (CGH), and multiplex ligation-dependent probe amplification (MLPA).[63,69,71–73] While most assays are beneficial for prognostication in most cases, CGH and FISH assays will miss cases of isodisomy 3.[69]

Chromosomal analysis of UM FNAB or formalin-fixed, paraffin-embedded specimens is clinically available.[74] MLPA is used to assess abnormalities in copy numbers of chromosomes 1p, 3, 6, and 8. Microsatellite analysis is used to assess copy loss and isodisomy of chromosome 3. If findings are negative for monosomy 3 or gain of 8q, *GNAQ*/*GNA11* mutations, which are common in UM, are evaluated to assess for presence of tumors within the FNAB sample to limit false-negative results. Mutations in *SF3B1* and *EIF1AX* are evaluated in disomy 3 specimens. A validated online prognosticator tool has been developed that incorporates data on monosomy 3 information, as well as AJCC staging and pathologic characteristics,[75] and is discussed further in the following section.

DNA: gene analysis

A gene hunt was undertaken on chromosome 3 to identify the gene responsible for poor prognosis in monosomy 3 patients. Somatic mutation in the *BAP1* gene was found in 84% of early-metastasizing (class 2) tumors.[76] Subsequently, germ-line mutation in *BAP1* has been shown to be part of a cancer syndrome leading to UM, cutaneous melanoma, renal cell carcinoma, and other cancers.[77–81] UM patients with germ-line *BAP1* mutations have significantly larger tumor diameters and a higher rate of ciliary body involvement.[82] The rate of germ-line *BAP1* mutation is significantly higher in metastatic UM compared to nonmetastatic UM.[82] The rate of germ-line *BAP1* mutation is estimated to be 22% in patients with familial UM compared to 1.6%–4% of nonfamilial UM.[82–85] In patients with a family history of *BAP1*-related tumors, the rate of germ-line *BAP1* mutation can range up to 50%.[83] Germ-line mutations may be evaluated with DNA from peripheral blood or cheek swabs.

Other mutations have been found to have prognostic significance. As such, *SF3B1* mutation is associated with intermediate risk of metastasis and *EIF1AX* mutation with lowest risk of metastasis (Table 2).[86–89] In patients with disomy 3, *SF3B1* mutation is associated with late development of metastasis.[86] While these gene mutations have significant prognostic value, there is currently no prognostic tool available for calculating risk of metastasis based on individual gene mutations.

RNA: gene-expression-profile testing

RNA-based gene-expression profiling (GEP) classifies UM into distinct classes: class 1A (lower risk), class 1B (intermediate risk), and class 2 (high risk) (Table 2).[62,90–92] Such molecular classification is strongly predictive of metastatic death and better describes the survival difference between low- and high-risk classes compared to traditional prognostic factors. A polymerase chain reaction-based assay of 15 genes is clinically available to risk stratify UMs into low- and high-risk categories, and the predictive validity of this assay has been tested in prospective clinical trials.[55,91,93] It is recommended that high-risk patients by GEP classification receive strict monitoring and referrals for relevant clinical trials (Table 2).[55] In addition, testing of PRAME expression is available, and tumor positivity for PRAME is a poor prognostic feature that may have potential as a future therapeutic target.[94,95]

Reappraisal of traditional prognostic factors

It must be noted that genetic features are not the only predictors of metastasis. Certain clinicopathologic factors add to the risk of metastasis in tumors with high-risk genetic characteristics. For instance, class 2 UMs with longest basal tumor diameter of <12 mm have a better prognosis than larger class 2 UMs.[96,97] In patients with chromosome 3 and 8q abnormality, epithelioid histology, high mitotic rate, and closed loops correlate with worse survival, and these pathologic predictors have a cumulative effect on survival.[71] Liverpool UM Prognosticator Online (LUMPO) is an online risk calculator that has been developed and validated to predict metastatic risk and survival time based on clinical, pathological, and genetic data.[75,98] Calculations integrate the variables age, sex, largest tumor diameter, anterior margins, extraocular extension, tumor-cell type, presence of closed loops, mitotic count, and chromosome 3 status.[98] Future versions of LUMPO will likely integrate information from newly elucidated gene mutations, such as those in *BAP1*, *SF3B1*, and *EIF1AX*, to provide more accurate prognostic estimation.[75]

Adequacy and validity of FNAB samples for prognostic testing

FNAB is successful in yielding sufficient samples for chromosome 3 analysis by FISH in 81.2% of cases and

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microsatellite assay in 75% of transscleral and 97% of transvitreal cases.[99,100] Larger tumors, increased tumor height, and increased tumor distance from the fovea are significantly correlated with increased FNAB yield for FISH analysis, while tumor thickness is correlated with successful yield for CGH testing.[101,102] Similarly, a transscleral approach has been reported to be adequate for FISH in 53% of UMs <3 mm height and 91% of UMs >5 mm height.[103] FNAB samples allow successful GEP testing in 94%–100% of cases.[57,91,104] Amplification is a factor in GEP testing that promotes successful analysis on small RNA samples obtained from FNAB.[93]

Validity of prognostic testing on FNAB samples has also been studied. UM has known heterogeneity in the tumor, and whether FNAB could adequately capture representative prognostic information was initially questioned.[105] Naus et al demonstrated good reliability of FISH from FNAB sampling compared with enucleation specimens.[106] However, variability in monosomy 3 status does exist within the same tumor,[107,108] and variations in chromosomal copy number between the intraocular and extraocular portions of UM tumors have been reported.[109] Similarly, the rate of discordance in GEP from two FNAB sample sites has been reported at 11.3%.[110] However, prospective clinical trials have validated the prognostic ability of GEP on FNAB samples.[91] Interestingly, Klufas et al found discordance between high-risk results from FISH and MLPA compared with GEP; 19.3% of class 1 UMs also had monosomy 3 on MLPA testing.[57] Although the results of FNAB testing are excellent for prognostication, a negative test does not exclude the chance of a higher-risk tumor with absolute certainty.

Some authors have suggested that obtaining FNABs from two sample sites may increase the validity of GEP results.[110] However, there is a concern that the blood liberated from the first biopsy could affect the GEP results of the second biopsy, leading to inaccurate results. We currently do not advocate taking a second biopsy for GEP testing. Further work on the impact of tumor heterogeneity and discordance between GEP and MLPA results and patient outcomes would be useful.

FNAB approach and timing with brachytherapy

The development of DNA- and RNA-based testing has allowed for in vivo prognostic testing and use of FNAB at the time of brachytherapy. Adequate RNA and DNA can be obtained from FNAB samples for chromosomal analysis and GEP to classify tumors into high- and low-risk categories.[56,68,99,101,102,104,111–113] FNAB can be performed with a transscleral or transvitreal approach depending on tumor thickness and location, and instrumentation can include use of 25–30 G needles, including custom needles, or 25–27 G vitrectors attached to flexible tubing connected to a syringe.[56,101,102,104,111,112,114–116] Direct pressure with a sterile Q-tip is applied to elevate the pressure and achieve hemostasis. Intravitreal injection or vitrectomy infusion of balanced salt solution may also be used to pressurize the eye.

Frequently, an FNAB pass for cytological analysis is also taken at the time of biopsy for prognostic testing. When obtaining GEP testing, we recommend using the first pass of the FNAB for molecular prognostic testing, since hemorrhage liberated during the biopsy will dilute the tumor GEP profile of the tumor with RNA from the blood. The success rate of GEP on FNAB samples is significantly higher than cytopathologic analysis, since cytopathology for prognostic cell-type analysis requires larger samples.[104] However, cytopathology remains useful in the management of UM, since it confirms the cells undergoing testing. Importantly, genetic tests do not discriminate melanoma from other types of cancer: nonmelanoma lesions of the choroid will be classified as class 1 or 2 by GEP testing.[117] Cytopathology or other DNA-based testing, such as *GNAQ*/*GNA11* sequencing, can help confirm the diagnosis of melanoma in uncertain cases.[117]

Proper timing of FNAB for genetic prognostic testing with the brachytherapy procedure is critical, since radiation can alter tumor RNA and DNA and potentially affect the result of the prognostic test. Currently, RNA-based prognostic testing has been validated only for use prior to or during brachytherapy insertion.[91] It is not known if accurate results can be obtained at the time of brachytherapy plaque removal. A case series has reported three cases of successful GEP testing after radiation therapy; however, GEP results before radiation were not available for comparison.[118] A report of 15 patients described successful chromosome analysis by CGH after radiation.[119] However, chromosome status before radiation is only available for five cases for comparison of accuracy of results.[119] Karyotype and FISH analysis have been shown to be unsuccessful after radiotherapy.[120]

Procedural safety and complications

The safety of UM FNAB has been established by several studies. Such complications as persistent hemorrhage (0–4.1%) and retinal detachment (0–1.8%) are rare, and no cases of endophthalmitis have been reported (Table 3).[100–103,115] Cumulative rates of metastatic disease have not increased.[103] However, histopathologic tumor seeding along the biopsy

Table 3 Reported rates of complications of FNAB

Complications of FNAB	Reported complication rates	References
Persistent hemorrhage	0–4.1%	101–103, 115
Retinal detachment	0–1%	101–103, 115
Local recurrence of uveal melanoma	0–0.2%	100–103, 123
Endophthalmitis	0	100–103, 115

Abbreviation: FNAB, fine-needle-aspiration biopsy.

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tract, and rarely cases of extraocular extension of UM after FNAB, has been reported.[101,121–125] Contamination of the needle tract on histopathology has been demonstrated in up to 4% of transvitreal biopsies, causing concern for the possibility of local recurrence, since the needle-entry site is outside the field of radiation.[101] Glasgow et al demonstrated a greater number of tumor cells in the aspirate tract from the direct transscleral approach compared with the indirect transvitreal approach.[121] As a precaution to prevent local recurrence from tumor seeding during FNAB, we recommend keeping the biopsy site dry and treating the needle tract with cryotherapy when using a transvitreal approach. When using a transscleral approach for FNAB during brachytherapy, we recommend that the biopsy site be kept dry and the conjunctiva well retracted. We place a sterile Q-tip over the needle tract as the needle is removed, holding pressure for several seconds. The Q-tip is removed from the field. We secure the preplaced plaque sutures immediately after the FNAB pass is completed, in order to initiate rapid radiation treatment to the site.

Local FNAB-related recurrence is rare. In one series, local recurrence after UM FNAB occurred in one of 408 cases (0.2%) with a transscleral approach and one of 929 (0.1%) with a transvitreal approach (Table 3).[123] Many large and small series at multiple centers have reported no local tumor recurrence after FNAB.[100–103] These low rates are in contrast to open biopsy techniques and invasive procedures in eyes with unrecognized UMs, which have a relatively high rate of recurrence or extraocular extension.[115,124,126]

Conclusion

Brachytherapy has now become a standard of care as an eye-preserving treatment modality for UM. Now, genetic testing via FNAB has allowed for prognostication for patients with ocular melanoma receiving globe-sparing brachytherapy in clinical practice. Despite the improving treatment and understanding of primary UM, survival from metastatic disease remains low. Advancements in ocular screening and understanding of the genetic basis of UM will promote early detection and the development of targeted therapies that may significantly improve the prognosis of UM.

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Disclosure

The authors report no conflicts of interest in this work.

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