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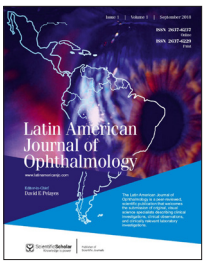

Neuro-ophthalmology/Oncology *Original Article*

Diagnostic algorithm in small pigmented choroid tumors (less than 3 mm thick)

David Eduardo Pelayes[1], Anibal Martin Folgar[1], Pablo Chiaradia[2], Jorge Oscar Zarate[1]

[1]Department of Oftalmologia, Universidad Maimonides, [2]Department of Ophthalmology, University of Buenos Aires.

***Corresponding author:**
David Eduardo Pelayes,
Department of Ophthalmology,
University of Buenos Aires.

anibalmartinfolgar@gmail.com

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ABSTRACT

Objectives: The aim of this paper is to present a diagnostic algorithm for a controversial topic in ophthalmic oncology, small pigmented choroidal tumors (<3 mm thick).

Material and Methods: Nineteen consecutive patients with a clinical diagnosis of small choroidal pigmented tumors were included in the study. The group of patients studied consisted of 9 patients (47.36%) female and 10 patients (52.64%) male, the age range was 14–68 years. All cases were ophthalmologically evaluated, including best-corrected visual acuity, anterior and posterior segment biomicroscopy, intraocular pressure, binocular indirect ophthalmoscopy, and as additional complementary examinations, ocular ultrasound was performed, which in 100% of the cases was inconclusive, optical coherence tomography, autofluorescence, and angiography in selected cases according to location and symptomatology. In 13 patients (68.50%), transvitreous puncture was performed with or without vitrectomy. Trans-scleral puncture was performed in 6 patients (31.50%), located at the equator (4 patients) and ciliary body (2 patients). Post-surgical follow-up was performed within the first 3 weeks after the procedure and then controlled every 3 months within the 1st year. The material obtained by fine-needle aspiration (FNA) was placed in non-hemolytic preservative liquid. Hematoxylin and eosin, Pas, Masson's trichrome, and immunohistochemistry (HMB 45, MELAN A, PROT. S-100 base) were performed.

Results: The yield of cytologic material was 100% in the sampled patients. The most frequent complication was subretinal hemorrhage in three patients with transvitreous access and two patients with trans-scleral access, in all cases, there was a favorable evolution without requiring further action. In three patients, there were mild vitreous hemorrhages that resolved spontaneously, all of them had undergone transvitreous access.

Conclusion: In TPPC of less, we propose a diagnostic algorithm with FNA to obtain cytological sample which allows not only the diagnosis of certainty to indicate treatment but also to determine cytological and molecular prognostic factors that allow classifying melanoma of high or low grade and potentially in case of metastatic disease to indicate systemic treatments. We believe that it is essential to diagnose this type of lesions in which a diagnosis of certainty is required. The alternative is the observation that we consider potentially dangerous in these cases.

Keywords: Melanoma, Small, Pigmented, Biopsy, Needle

INTRODUCTION

In general clinical oncology, the treatment of malignant tumors requires histologic confirmation to indicate treatment, but in intraocular tumors, such as uveal melanoma (UM), the treatment decision is based on clinical examination and complementary tests, especially ultrasound, which due to its low mean echogenicity allows the confirmation together with the clinical

features of the diagnosis of UM in the vast majority of cases.[1,2] Unfortunately, this is not proven for small choroidal pigmented tumors (SCPT), that is, those with a thickness <3 mm and a basal diameter <10 mm [Figure 1] in which the sensitivity and specificity of ultrasound are limited by the thickness of the tumors.[3]

PTPCs are treated only if their appearance or growth suggests malignancy. Several studies have identified risk factors for growth [Figure 1][4-9] and metastasis.[8,9] These include in particular tumor thickness greater than 2 mm, the presence of subretinal fluid, symptoms, orange pigment, and tumor margin within 3 mm of the optic disc margin, giving rise to TFSOM ("'To Find Small Ocular Melanoma"').[7-9]

The current treatment of PCPT (which includes atypical nevi and small melanomas), especially those without risk factors and those with foveolar location, since their treatment seriously compromises vision, is periodic observation until growth,[8-10] but this conduct has the potential risk of generating metastasis in cases of melanomas, for which reason observation is a controversial issue.[11,12] Moreover, this behavior is in contradiction with the practice of clinical oncology, which considers earlier diagnosis and treatment as a mandatory first step to improve patient survival.[13,14]

The only way to confirm the diagnosis of SCLC is to obtain cellular material from the lesion by biopsy or fine needle aspiration puncture (FNA), the latter is a technique for obtaining cytological samples of neoplasms that were described more than 100 years ago. Although it was widely applied to different tumors, the first report of an aspiration puncture in a solid intraocular tumor was made by Jakobiec *et al*., 1979.[15]

Initially, it was thought that the technique resulted in seeding of tumor cells in the needle tract or was associated with significant intraocular complications. These problems limited its use; however, it is currently known to be a safe technique and in more than 200,000 systemic cases using a diameter of 25 G or less, no tumor seeding is detected.[16]

Another point to consider is that despite improvements in local treatment of UM, prevention and treatment of metastatic disease remains unresolved and almost 50% of patients develop liver metastases. The current model suggests that tumor cells have already spread at the time of diagnosis and remain dormant until favorable conditions exist. Therefore, tumor sampling procedures at the time of diagnosis/treatment of the primary tumor can now be performed not only to confirm the diagnosis of MU but also to obtain a tissue sample for prognostication and to assess the risk of producing metastases. In addition, several studies are underway to identify genes specific to MU tumorogenesis, leading to various targeted therapeutic strategies. Genetic information may also influence the timing of surveillance and risk of metastasis in patients with MU.[17-19]

Despite the widespread use of biopsies in general surgical practice, in ophthalmic oncology, the indications and contraindications for tumor biopsy are still under debate.

We present the algorithm to treat TPPC (less than 3 mm thick) based on cell processing techniques, instruments, and techniques specifically developed to obtain material and minimize risk in TPPC.

MATERIAL AND METHODS

In the present prospective study, 19 consecutive patients with clinical diagnosis of SCPT were included. Epidemiologically 9 patients (47.36%) were female and 10 patients (52.64 %) were male, the age range was 14–68 years [Figure 2].

The sample was approved by the Ethics Committee of the University of Buenos Aires and Maimonides University and with signed informed consent of the patients for the cytopathological analysis of cells obtained by aspiration.

All cases were ophthalmologically evaluated by recording best-corrected visual acuity, anterior and posterior segment biomicroscopy, intraocular pressure, binocular indirect ophthalmoscopy, and as additional complementary examinations, ocular ultrasound was performed, which was inconclusive in 100% of cases, optical coherence tomography, autofluorescence, and angiography in selected cases according to location and symptomatology.

The selection criterion of the anatomical access route for the punctures was given by the location of the tumor [Figure 3]. In 13 patients (68.50%), the puncture was performed through the transvitreous route and vitrectomy was chosen

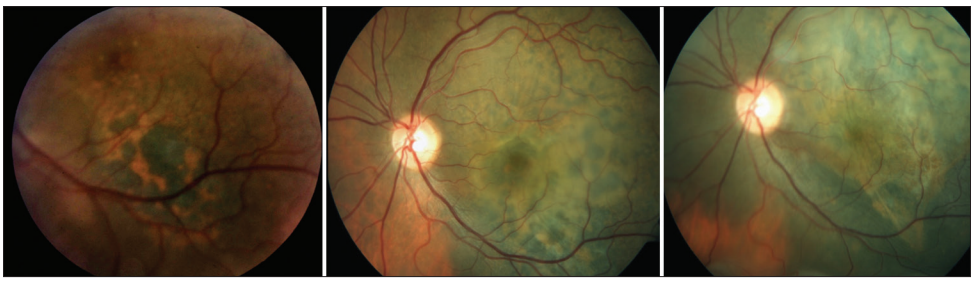

Figure 1: Observation in TPPC after 19 months the patient developed diffuse flat melanoma. Patient dies of liver metastases.

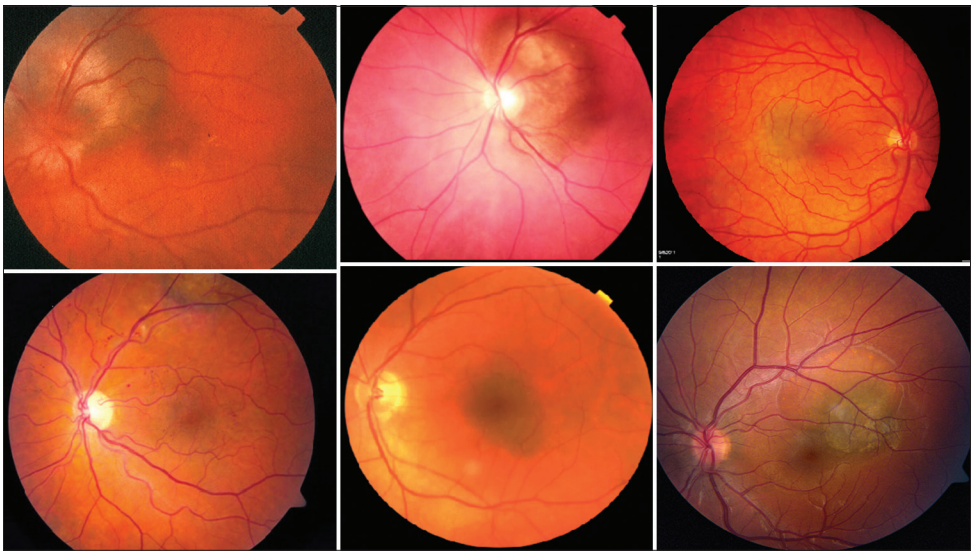

Figure 2: Color retinography images corresponding to clinical cases N°: 2, 5, 7, 19, 12, and 3.

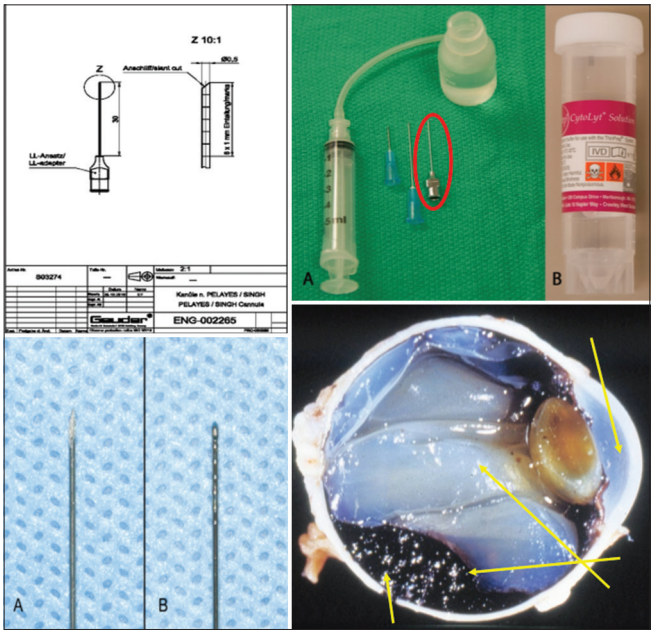

Figure 3: Note the PAFF needle design used in trans-scleral puncture. The needle is millimeter and allows to know how long the tumor penetrated, and the angle and cut changes compared to the 25 G needle. The upper right image shows a diagram of the needle developed in the patent. In the upper right image, A shows a syringe and a set of cannulas (in red the needle to puncture) and in B, the tube with the liquid to preserve the sample. In the lower right box, a conventional needle is compared in A and the one developed by the authors in B, which is calibrated, changes the angle and length of the entry perforation. The lower right box shows the different approaches according to the location of the tumor.

if the patient presented vitreous opacity. The location of the vitrectomy was in the macular area (eight patients) and parapapillary (five patients).

In 6 patients (31.50%), the puncture was performed through the trans-scleral route, the location was in the equator (four patients) and ciliary body and choroid (two patients).

Post-surgical follow-up was performed in weeks 1, 2, and 3 after the procedure and then controlled at 2, 5, and 8 months within the 1st year, all cases presented have at least 1 year of follow-up.

As for the FNA technique (FNA puncture), a calibrated 25G needle (Geuder, Heidelberg, Germany) is used, with millimetric markings and an external orifice of 0.5 mm, which allows a penetration of the tissue. This allows a more controlled tissue penetration for trans-scleral or clear cornea [Figure 3][20,21] or a biopsy needle with millimetric scale and transparent base for transvitreous route introduced by 25G trocar (Alcon, Fort Worth, TX, USA) at 3.5 mm from the limbus, once the lesion is located [Figure 4].[22]

The material obtained by FNA was placed in non-hemolytic preservative fluid (general purpose non-hemolytic cell preservative fluid – 05NG000014), which provides immediate fixation, maintenance of cell morphology, and stability of the necessary spreads for complementary staining. The material obtained with this methodology, which basically consists of the following steps: Cytoconcentration in two stages, filtering, disintegration by vortex, sealing and staining, with which thin spreads are obtained, constituting a circle of 13 mm in diameter on the slide with an average cell concentration of 60,000 cells/mm^2 [Figure 5].[23] H and E, Pas, Masson's trichrome, and immunohistochemistry were performed using in these cases: Monoclonal vimentin (mouse IgG Biogenex), monoclonal pan cytokeratin (mouse IgG Biogenex), monoclonal mammary antigen (mouse IgG Biogenex), monoclonal HMB-45 melanoma (mouse

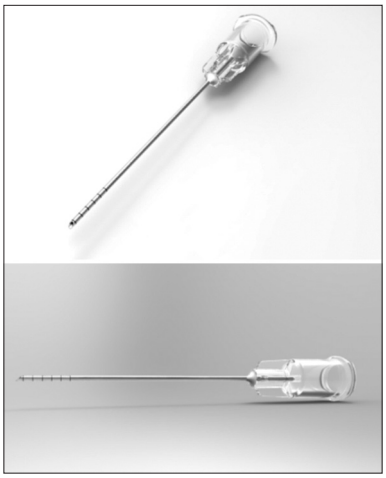

Figure 4: Cannula to perform FNAB through the transvitreous route, adapts to the vitrectome tube. It has a transparent base that allows you to see the material obtained and the needle is sent with the complete material for analysis.

Figure 5: Monolayer liquid-based cytology with AutoCyte.

IgG Biogenex), MELAN-A (mouse IgG Biogenex), and monoclonal protein S (mouse IgG Biogenex).

RESULTS

We obtained a cytologic yield of 100% of patients, in all cases, malignancy was proved in cytology with usual smears and basic IHC was positive in all cases which always included at least Melan A, Protein S 100, and cytokeratin which confirm the diagnosis of melanoma [Figures 6 and 7].

The transvitreous approach (13 patients) did not differ if the technique was with or without previous vitrectomy.

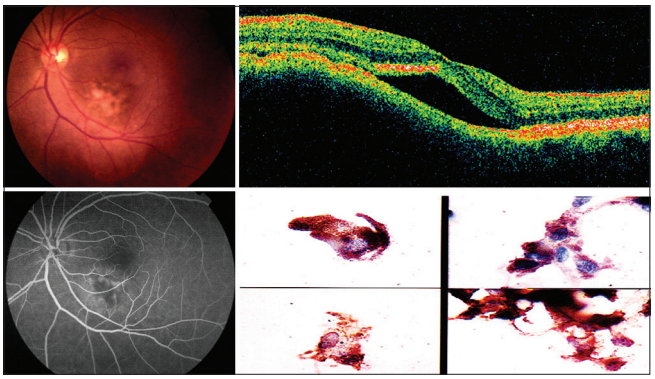

Figure 6: Clinical case belonging to patient No. 11. Macular TPPC is observed, and subretinal fluid in OCT, we can also observe melanoma cells obtained by FNA.

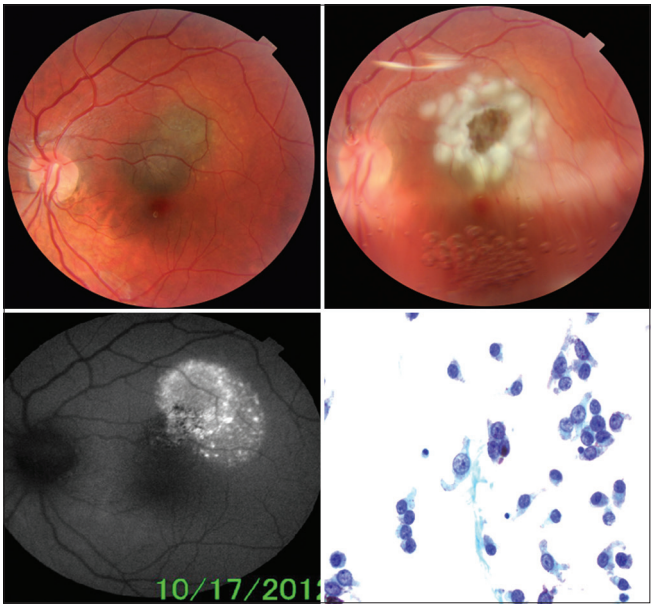

Figure 7: Clinical Case No. 10, a 14-year-old female patient with macular PCPD. A fine-needle aspiration puncture is proposed through the transvitreous route accompanied by vitrectomy and placement of tamponade with silicone oil. The cytological diagnosis of choroidal melanoma is confirmed.

The locations of the tumor in the transvitreous route were; five patients parapapillary and eight patients macular. The decision to perform vitrectomy was based on the presence of vitreous opacities. By trans-scleral route (six patients), a cytological diagnosis of the lesion was obtained in 100% of the cases. The locations were four patients in the equator, and two patients with choroidal ciliary location.

The most frequent complication was subretinal hemorrhage in three patients with transvitreous access, and two patients with trans-scleral access, in all cases, there was a favorable evolution without requiring further action.

Three patients presented mild vitreous hemorrhages that resolved spontaneously, all of them were in the transvitreous approach.

The treatment performed with a diagnosis of certainty was 18 patients with brachytherapy with I 125, one patient had a cytological diagnosis, but no treatment was performed.

DISCUSSION

The first publication for the detection of circulating tumor cells corresponds to Ashworth in 1869,[24] one of the greatest advances for the detection of these cells is the use of FNA. Although Paget was the first to use aspirated samples of mammary tumors for their microscopic examination in 1853, other authors carried out isolated experiences in this respect, it was Mannheim, a disciple of Hirschfeld, who proposed the use of a thin needle of 1 mm in diameter for the aspiration of tumors, publishing his results in 1931, quoted by Koss *et al*.[25] However, the methodology undoubtedly took effect in 1926, at the Memorial Hospital for Cancer and Associated Diseases in New York (today Memorial-Sloan Kettering Cancer Center). The technique was performed by Hayes Martin and Bradley Coley (surgeons) with the technical assistance of Edward Ellis. They were followed by multiple contributions. Aspiration biopsy, as performed at Memorial-Sloan-Keteering, had a great disadvantage: Thick, poorly prepared biopsy specimens. Subsequently, in the European school, especially in Holland and Sweden, they used thin and comprehensible hematologic-type biopsies.[25]

FNA was used in multiple presentations for the diagnosis of intraocular tumors.[26-31] Several systems are currently trying to achieve better thin and monolayer cytologic smears, among them, the one used in this communication known as liquid cytology in monolayer (Autocyte Prep)[26-32] with the use of preserving liquid and eliminating all artifacts. The results obtained in these cases, as well as in others, we have performed in vitrectomies, show it to be highly satisfactory. The use of FNA for cytologic diagnosis of intraocular lesions was limited with classical processing techniques due to the scarce positive results obtained and the eventual complications of the methods used for the diagnosis of intraocular lesions. However, with liquid-based techniques,[32,33] the positive results improve, which changes the cost-benefit ratio of the procedures to collect the cellular sample, especially when the material is scarce; on the other hand, the routine use of immunohistochemistry allows not only the diagnosis but also to establish prognostic factors of the tumor that allows more adequate therapeutic decisions to be made. Part of the specimen (as in gynecological cytological studies) is fixed according to the AutoCyte technique, which allows single-cell grouping in a single layer. The preparation is fixed on glass, with electrical conduction applied to the preparation, the cells take a spatial arrangement that allows their adequate study.

Several studies have shown that FNA has a diagnostic accuracy rate of more than 90%.[34-37] Char observed that FNA is accurate in both diagnosis and cytologic typing of UMs, Shields *et al*.[26] reported similar results, with 26 of 27 (96%) patients diagnosed with FNA with UM later shown to have melanoma on enucleation.

Regarding the clinical presentation of PTPCs, those of anterior location are usually biopsied using a trans-scleral approach, while posterior tumors and small tumors are best reached using a transvitreous approach in cases of iris through clear cornea. The most complex group to diagnose is formed by pigmented lesions smaller than 3 mm in height, which are in a "kind of limbo" in terms of diagnosis and still do not provide the diagnostic basis that is required for any oncologic entity, with the risk of life that late diagnosis and therapy imply for the patient. However, the techniques used to obtain the specimen are still not based on limbo¨ in terms of diagnosis and do not provide the diagnostic basis that is required for any oncological entity, with the risk to the patient's life that late diagnosis and therapy imply.

Augsburger J[3] alerted about the risk of the expectant attitude in PPCT that according to their clinical characteristics were suspicious of being small melanomas and the conduct was only to observe and determine their treatment according to the clinical evolution, especially their growth, which is particularly dangerous in melanomas since in this stage of growth they usually produce more metastases[38] there is no conclusive scientific evidence that such conduct is beneficial for a patient, in fact it is not usually recommended by most ophthalmologic oncologists. The other pillar of clinical diagnosis, ultrasound, does not provide conclusive data in lesions less than 3 mm thick, especially the low mean echogenicity that is typical of melanoma.[39-43]

In addition, other studies note that, based on their size, it could be inferred that the smallest choroidal melanomas that metastasize range from 1.7 to 2.5 mm in thickness and 5.0 to 8.0 mm in basal major diameter (LBD).[39-44]

Theoretical calculations based on tumor doubling times have suggested that UMs as 3 mm in LBD could already metastasize.[40-42] However, the size at which melanoma would have the ability to metastasize remains unknown.

The COMS defined a small melanoma as 1–3 mm thick and 5–16 mm LBD; tumors smaller than this were considered probable nevi.[40] More recently, the European Ophthalmic Oncology Group with a study that included 15 centers determined that some choroidal melanomas are indeed smaller than 5 mm in basal length diameter, but also that tumors as small as this can spread, this study considered that at that time, the tumor cells had already divided

22 times over approximately 9 years and that clinical metastases would be diagnosed on average 5 years later. The vast majority of choroidal melanomas are diagnosed and treated when they are much larger than 3 mm in diameter, this study cannot say what proportion of them actually metastasize later but a high percentage would already be metastatic.[43] Based on previous evidence taken together, they indicate that the most likely cutoff of 3.0 mm before which a choroidal melanoma would not yet have the ability to metastasize.[40,45-48]

Given the evidence, the only way to reach a diagnosis of certainty in this type of lesions is to obtain cytologic material, but biopsy of an intraocular malignant tumor remains a controversy because of the theoretical risk of tumor dissemination due to the invasive procedure, the small size and posterior location of the lesions increase the risk of insufficient sampling and ocular complications.[49,50]

In addition, other studies note that, depending on their size, they could spread, this study considers that at that time, the tumor cells had already divided 22 times during approximately 9 years and that clinical metastases would be diagnosed on average 5 years later. The vast majority of choroidal melanomas are diagnosed and treated when they are much larger than 3 mm in diameter, this study cannot say what proportion of them actually metastasize later but a high percentage would already be metastatic.[47] Based on previous evidence taken together, they indicate that the most likely cutoff of 3.0 mm before which a choroidal melanoma would not yet have the ability to metastasize.[43-48]

Recently the emergence of new treatments in metastatic cases that require characterization of the genetic and molecular profile of melanoma in order to participate in these protocols and personalized therapies that require this profile of the tumor and not only the size, location.[51-53] Current prognostic tests are based on DNA or RNA extraction from tumor samples, FISH, CGH, MLPA, FISH, CGH.[51-57]

Several potential risks can be associated with intraocular tumor biopsy, including hemorrhage, retinal detachment, cataract and endophthalmitis, as well as extraocular dissemination or tumor seeding. The main potential risk when performing a UM biopsy is tumor dissemination. Mechanical rupture of intratumoral blood vessels during the biopsy procedure carries a theoretical risk of intravascular dissemination of tumor cells;[16] however, it is well known that the metastatic potential of tumor cells is not related to mechanical dissemination, but to the biological characteristics of the tumor.[41] However, local dissemination can theoretically occur by passive dragging of tumor cells along the needle body into the vitreous body and scleral wall or by active migration of tumor cells through the lesion produced by the biopsy needle.[58]

It is of great importance to minimize the risk of seeding, since local recurrence has a higher risk of metastatic disease.[59] Minimally invasive transvitreous FNA is characterized by several features that can theoretically decrease the risk of local seeding. The intact vitreous body decreases flow within the eye and thus potentially reduces intraocular spread of tumor cells. A histopathologic examination of the needle tracts revealed a lower number of tumor cells seeded after transvitreous biopsies compared with trans-scleral biopsies.[58-60] However, because of the location of the trans-scleral biopsy site generally within the radiation field, as opposed to the transvitreous entry site, the trans-scleral approach at the time of brachytherapy appears to be the safest approach. A case of seeding within the vitreous body after transvitreous biopsy has been described in a clinical study, but the clinical significance of tumor cells seeding into the vitreous body is doubtful,[61] in fact, spontaneous migration of tumor cells into the vitreous body in eyes of previously untreated patients does not seem to be associated with a poor prognosis.[62]

Access through the pars plana allows surveillance for tumor cell spillage and late local recurrence at the biopsy entry point. In addition, scleral ports probably reduce the risk of tumor spread into the sclera.[56] However, the risk of scleral spread is not completely eliminated, as demonstrated by case reports of extraocular recurrence at the scleral port entry site after transvitreous biopsy.[63,64] The vitrectomy system allows sufficient biopsy material to be obtained with a single pass compared to trans-scleral biopsies, which usually require several passes, increasing the number of tumor cells seeded mainly if multiple needle trajectories are performed.[16] Nevertheless, UM FNA is generally accepted as a safe procedure.[41,54-58]

In a prospective case series, Singh *et al*. described the results in 150 eyes that had UM FNA, including 71 eyes that had a partial-thickness scleral flap at the time of trans-scleral biopsy and plaque placement.[61] They reported no tumor recurrence at 37 months follow-up;[41] however, some rare cases of extra-scleral tumor extension after FNA have been described in the literature.[7,56]

Different precautions have been suggested to limit this occurrence, including the use of a small bore instrument (25 or 27 G), performing a peritomy over the biopsy site, maintaining a dry field during biopsy with minimal use of infusion, releasing negative pressure before removing the needle, using a trans-scleral cannula to create a protected needle tract, and applying cryotherapy to sclerotomies.[22,38,54] Subsequent application of radiotherapy may further reduce the risk by sterilizing tumor cells seeded within the eye, even if late sampling, at a prolonged interval after radiotherapy, may affect the results of genetic testing.[65-71] Siegel *et al*. evaluated three eyes with UM that had FNA using a lamellar

scleral flap at the time of plaque brachytherapy placement and subsequently developed scleral thinning over the flap site,[72] then, two eyes developed melanocytic proliferation over the scleral flap site. The third patient showed scleral thinning and evidence of tumor growth on ultrasound, with extraocular tumor extension confirmed on histopathology. The authors concluded that patients with scleral flaps created for MU biopsy are at risk for scleral thinning and extra-scleral extension of tumor recurrence through the flap.

Given the potential for confounding the clinical picture, the authors recommend caution when using a lamellar scleral flap during trans-scleral biopsy. Shields *et al*. evaluated the safety of FNA in 140 patients. Complications were minimal and there were no cases of extra-scleral tumor extensions.[18]

More recently, Bagger *et al*.[73] followed 1637 patients with MU for a total of 3.9 and 8.4 thousand person-years of observation for patients undergoing trans vitreous biopsy (TVRC, FNAB, or Essen forceps biopsy) and without performing biopsies, respectively, and found no significant increase in all-cause mortality and melanoma-specific mortality among patients undergoing biopsy compared to patients without biopsy. These findings are in agreement with previous case series of intraocular biopsy in MU where excess mortality has not been reported.[72]

In the population-based study by Bagger *et al*.,[73] patients who had vitreous hemorrhage on the 1st day after surgery spontaneously disappeared and in 5 patients (5.9%) underwent vitrectomy due to persistent vitreous hemorrhage. Other groups have reported similar frequencies using transvitreous FNA with or without vitrectomy, whereas transvitreous FNA appears to cause lower rates of vitreous hemorrhage.[22,60,74-81]

The risks are even lower in FNA obtained through the trans-scleral approach which appears to be safer than transvitreous biopsy in terms of vitreous hemorrhages, probably due to limited manipulation of tumor tissue and vessels. A more infrequent complication of ocular tumor biopsy is rhegmatogenous retinal detachment, with a slightly higher incidence after transvitreous biopsy than in transvitreous FNA.[30,78-80]

Even in cases with exudative retinal detachment already present at the time of sampling, the procedure does not appear to worsen the detachment.[30,77]

Associated retinal tears tend to seal spontaneously, perhaps due to the buckle effect of the tumor mass. In some cases, laser treatment may be necessary.[78-80] No significant cases of endophthalmitis have been reported after tumor biopsy, probably due to the sterilizing action of radiation.[73] We believe that it is fundamental to reduce maneuvers and complications to have precise control of which measure of the needle penetrates the retina and the choroidal tumor so we developed instrumentation for these cases in trans-scleral through Singh *et al*., Pelayes *et al*.[20,21] and more recently in 2017 for transvitreous through with or without vitrectomy.[22]

In relation to systemic adjuvant therapies may theoretically be more effective in the treatment of microscopic than macroscopic tumor metastases, where multiple mechanisms of resistance generally develop, where tumor genetic and molecular factors may become appropriate targets for individualized therapies and stratified enrollment in clinical trials. Indeed, the most significant achievements have been made in terms of prognosis, as chromosomal alterations in UM have been shown to be highly predictive of metastatic risk.

Accurate prognosis allows individualized follow-up and systemic surveillance, effective patient counseling, and optimization of healthcare resources. In this context, prognostic biopsies take on a different significance than cytologic biopsies, requiring a personalized approach.[81] Based on current medical evidence, we propose the following diagnostic algorithm.

We believe that it is important to point out some weaknesses of the work, the limited number of patients, although these tumors frequently arrive at the office with a large size, with thicknesses where ultrasound provides diagnostic information. In addition, chromosomal and genetic studies were performed only in isolated cases, in which the major limitation was the cost of the procedures. Long-term complications were not evaluated due to the limited follow-up, so a multicenter study has been designed to obtain results in a larger population and in a longer term.

CONCLUSION

There is no way to know with diagnostic certainty by clinical, ultrasound, and other diagnostic methods in cases of PTPC in this type of tissue we are, if not performed by FNA or biopsy, the latter usually has more complications and technical limitations, especially the location of the tumor, to evaluate cells with neoplastic characteristics. The development of new devices, such as transparent needles that allow adequate visualization during active aspiration with the vitrectome has been considered an important tool to do the the procedure. The cytological management of the sample, which is scarce, is the fixation with new liquid-based substances, which makes cell collection more efficient and has been a key diagnostic tool.

This procedure, which comes from gynecology, makes it possible for the cells to be grouped together when little material is taken, facilitating their observation, without the damage caused by formalin.

FNA is a procedure widely used in ocular oncology for prognosis and cytological diagnosis. The procedure is considered relatively safe and with minimal adverse effects. Establishing the conduct of biopsy taking, assuming the risks of any interventional process aims not only to take care of visual health but also an even more powerful end, saving the life of a patient with a life-threatening oncologic disease.

Procedures to obtain tumor cells are commonly performed not only to confirm the diagnosis of UM but also to obtain a tissue sample for prognosis, which can help to assess the risk of producing patient-specific metastasis, this is currently so, but in case of lesions less than 3 mm thick, we do not believe to have another way of diagnosis except waiting for the growth of the lesion with the risks involved in such conduct. On the other hand, the genetic information obtained may also influence the timing of surveillance and the type of therapeutic alternatives in metastatic cases.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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