(27)

Uveal melanoma – is a biopsy safe and justified?

Czerniak naczyniówki – czy biopsja jest bezpieczna i uzasadniona?

Anna Bogdali, Anna Markiewicz, Joanna Kowal, Magdalena Dębicka-Kumela, Bożena Romanowska-Dixon

Department of Ophthalmology of the Jagiellonian University Medical College in Cracow
Head: Professor Bożena Romanowska-Dixon, PhD, MD

Summary: Uveal melanoma can be typically diagnosed based on clinical presentation and the A and B mode ultrasound. In some atypical intraocular tumours or for prognostic purposes intraoperative biopsy may be performed. Uveal melanoma biopsy is not safe in 100% and can cause complications (vitreous hemorrhage, retinal detachment and endophthalmitis). Like all biopsies, a biopsy in uveal melanoma biopsy may show limited cellularity and can yield insufficient tissue specimen for histology, cytology and genetic testing. This is most likely in small tumours, below 3 mm in thickness. Another limitation of biopsy-based prognosis is the issue of intratumoural heterogeneity. As a biopsy allows for only a small sample to be removed from the tumour, it is possible to receive false negative results. The most devastating complication of uveal melanoma biopsy is the extraocular spread of the tumour.

The study is a review of the current opinions and findings on the role of biopsy in uveal melanoma.

Key words: uvela melanoma, biopsy, monosomy 3.

Streszczenie: Diagnostyka czerniaka błony naczyniowej może być wykonana za pomocą różnych metod. Najczęściej do postawienia rozpoznania wystarczą standardowe metody diagnostyczne (badania dna oka oraz ultrasonografii w projekcji A i B). W niektórych przypadkach nietypowych guzów lub w celach prognostycznych konieczne staje się wykonanie biopsji guza wewnątrzgałkowego. Przeprowadzając biopsję, należy pamiętać o tym, że nie jest to metoda 100-procentowo bezpieczna i może zagrażać powikłaniami takimi jak krwawienie do ciała szklistego, odwarstwienie siatkówki i zapalenie wnętrza gałki ocznej. Podobnie jak w przypadku biopsji innych narządów, również pobierając materiał z czerniaka błony naczyniowej, należy się liczyć z pobraniem niewystarczającej ilości materiału do badań histopatologicznych, cytologicznych lub genetycznych. Ma to miejsce zwłaszcza w przypadku guzów o grubości mniejszej niż 3,0 mm. Wykonując biopsję, należy również wziąć pod uwagę niejednorodność tkanki guza – jeśli zostanie pobrana niewłaściwa tkanka, wynik będzie fałszywie ujemny. Największym niebezpieczeństwem związanym z wykonywaniem biopsji guzów wewnątrzgałkowych podejrzanych o czerniaka błony naczyniowej jest możliwość rozsiewu komórek nowotworowych.

Celem pracy jest przedstawienie aktualnych poglądów na temat biopsji czerniaka błony naczyniowej.

Słowa kluczowe: czerniak błony naczyniowej, biopsja, monosomia chromosomu 3.

Uveal melanoma is the most common primary ocular malignancy in adults. Typically, uveal melanoma can be diagnosed with non-invasive methods (dilated fundus exam, A- and B-mode ultrasound). In selected cases of atypical presentations, a biopsy becomes necessary (1–5).

Despite effective treatment methods available nowadays, there is always a risk of systemic metastases. The 25-year cumulative mortality associated with uveal melanoma is about 52% for medium-size tumours (1, 6, 7). Most researchers confirm the presence of melanoma micrometastases at the time of diagnosis. Micrometastases can remain as stand-alone sequelae of melanoma or precede systemic, most commonly liver, metastases (1). The following are known as factors predisposing to systemic metastases: larger diameter of a tumour base, tumour location in the cilliary body, epithelioid cell type melanoma, extraocular extension of melanoma, its vascular closed-loop system, chromosomal abnormalities and recurrence (8). Histopathology, cytogenetic, and gene expression patterns can facilitate prediction of systemic metastases (1, 9–13).

Uveal melanoma biopsy is performed for prognostic purposes, in order to detect chromosomal abnormalities associated with the high risk of metastases (most commonly chromosome 3 monosomy), for diagnostic purposes (usually in 1–2% of diagnosed intraocular tumours), and in patients, who refuse therapy for uveal melanoma without prior histopathological verification (1–5, 14). If a biopsy is considered, it is necessary to analyze its likely prognostic and diagnostic outcomes as well as the risk of tumour cell spread, complications, and potential false negative result. In posteriorly located tumours, a biopsy is performed using transvitreal approach through the pars plana, while in patients with cilliary body and anterior choroidal tumours, it is performed by transscleral approach (1, 4, 10). The fine-needle aspiration biopsy (FNAB) is the most frequently used biopsy technique in uveal melanomas (4, 10, 14, 15).

In uveal melanoma, chromosomal abnormalities detected during the prognostic biopsy correlate with the risk of metastases. The alterations most commonly affect chromosome 3, 6q, 8p, 11q,13, and 1p (11, 16–22). The detection of mo-

nosomy 3 found in almost 50% of uveal melanoma patients is of the highest prognostic value (1, 16–24). It is associated with the high risk of metastases-related death. Survival analyses in the monosomy 3 patients showed 50–70% mortality in this group in the four-year period since the beginning of therapy (12, 13). Complete monosomy 3 is linked to worse survival prognosis, as compared to the partial monosomy 3 or disomy for chromosome 3 (20). Similarly, gain of chromosomal region 8q, loss of 6q, loss of 1q and lack of BAP1 expression correlate with less favourable prognosis. However, gain of chromosome 6p and EIF1AX expression are associated with better prognosis (11, 17, 18, 25–27).

Another means to assess the risk of metastatic disease in patients with uveal melanoma is gene expression profiling (GEP), which simultaneously measures the expression of several (about 12) tumour genes (1, 9–11, 18). The risk of systemic metastases is low in GEP class 1 tumours and high in GEP class 2 tumours (1, 9–11). The five-year risk of developing systemic metastases is only 2% in class 1A tumours, 21% in class 1B tumours, reaching 72% in GEP class 2 tumours (28). However, the detection of monosomy 3, which occurs in about 10% of GEP class 1 tumours is linked to an increased risk of systemic metastases (1).

The results of a prognostic biopsy in patients with uveal melanoma are used for care planning, including diagnostic imaging to detect systemic metastases. In patients with low risk of systemic metastases, abdominal ultrasound and CT should be performed at least once a year, whereas in high risk patients, liver function assays are recommended every 3, 4 up to 6 months, and imaging tests every 3–6 months (9).

According to the literature, 66–97% of biopsies yield positive result, confirming uveal melanoma (2, 3, 5, 7, 15, 29). The numeric discrepancy can be attributed to the insufficient biopsy aspirates as well as cytogenetic and histological heterogeneity of the tumour (1, 4, 10, 15, 29–33). Insufficient biopsy samples for cytological examination were obtained through pars plana vitrectomy in 3–29% of patients and by transscleral approach in 29–44% of cases (3, 7, 10, 30).

Cumulative 5-year probability of death from metastasis was 14.1 % for patients whose biopsy aspirates were insufficient for cytology-based classification versus 22.4 % for patients whose biopsy aspirates were sufficient for cytology-based classification (10). When assessed in terms of GEP classification, though, it was 8% in cases where biopsy samples were insufficient for GEP classification or in GEP class 1 tumours, as compared to 45% in GEP class 2 tumours (10). It should be noted that for cytology evaluation, bigger tumour tissue samples are required, as compared to GEP classification purposes (2, 10).

Some researchers attempted to relate biopsy feasibility (obtaining positive result) to tumour size. Augsburger et al., Cohen et al., and Chang et al. reported a correlation between a positive result of a biopsy and tumour thickness in 37.5–64.7% of tumours thinner than 3.0 mm, in 75–92% of tumours 3.0–5.0 mm thick, and in 90–100% for tumour thicker than 5.0 mm (2, 3).

Another issue significantly affecting biopsy findings is tumour heterogeneity. Percentage distribution of spindle and epithelioid cells in tumour zones differs. Similarly, the percentage of chromosomal abnormalities, i.e. chromosome 3 monosomy or disomy, may vary (1, 7, 32). Higher rates of monosomy 3 are more likely to occur in large-size tumours (31). The survival prognosis is worse in the patients with detected 33% of monosomy 3 cells (31). Tumour heterogeneity for monosomy of chromosome 3 affects 14–18% of patients with uveal melanoma (1). Thus, it is possible to collect biopsy aspirates from the tumour zone without chromosomal abnormalities, which normally indicate high risk of systemic metastases.

The question should be asked about the most appropriate tumour site for drawing representative biopsy sample. Killgaard J. et al. demonstrated in their research a 58–59% chance for obtaining most representative samples from the central portions of tumours. The chance for obtaining representative samples from the periphery, top or tumour base was only 43–57% (34). It is therefore reasonable to aspirate more than 1 sample (usually 2–12 samples) during a single biopsy (1, 7).

The obtained biopsy result can be false negative. However, even a negative result cannot completely exclude the presence tumour cells (4, 33). Ideally, an experienced pathologist should be present in the treatment room to immediately asses the quantity and quality of the obtained aspirate, so as to ensure the reliability of a biopsy (4).

When referring the patient for biopsy it is always necessary to consider its potential complications. These may include vitreous hemorrhage which occurs in 21–46% of patients, more commonly when 22G needles are used for aspiration. Usually, vitreous hemorrhage spontaneously resolves after some time (1, 3, 4, 7, 15). Retinal detachment occurring more frequently during pars plana vitrectomy biopsy may lead in some cases to retinal holes just above the lesion. The risk of retinal detachment is lower in small-size posterior tumours with a small amount of subretinal fluid. It increases in large-size tumours, containing more subretinal fluid. Retinal detachment is a rare complication of a biopsy performed through the transscleral approach, and the rates are even lower for the large-size tumours (4). Another very rare complication of a biopsy is uveitis. There are only two reports of uveitis as a complication of biopsy. Cohen et al. reported 2 cases of uveitis in a series of 83 performed biopsies, and Faulkner-Jones et al. reported 1 case in their series of 33 performed biopsies (4, 6).

The most serious biopsy complication in uveal melanoma is intraoperative extraocular tumour spread, which may present either as extraocular extension or as systemic metastasis. The extraocular tumour spread may occur along the aspiration track at the site of sclerectomy (3, 4, 6, 15). The risk of tumour spread is lower when a patient receives brachytherapy. It is also less likely in biopsies performed during the pars plana vitrectomy (3, 4).

In 2013, four cases of extraocular spread of uveal melanoma to the orbit were reported as a complication of a biopsy. In three of these patients, more than one biopsy was performed and 1 patient did not receive brachytherapy (35). The majority of patients undergoing biopsy (83–159) did not develop extraocular recurrence of uveal melanoma (3, 4, 10, 15).

The risk of tumour spread during FNAB is scarce, but cannot be eliminated (4). Until now, there has been no report of systemic metastases as a complication of a biopsy. It is believed that 25–27G may lower the risk of tumour spread in patients with uveal melanoma (4, 6).

ISSN 0023-2157 Index 362646

FNAB of uveal melanoma is becoming one of the main prognostic examinations. Despite all advantages of a biopsy, its limitations (tumour heterogeneity, obtaining non-representative sample) and complications should be always considered on a case basis.

References:

1. Aronow ME, Biscotti CV, Chan C, Singh AD: *The Role of Biopsy in the Assessment of Uveal Melanoma. Its value can vary according to the methodology used and the diagnostic criteria applied*. Retinal Physician. 2012 June; Vol.: 9, Issue: 13–17.
2. Chang MY, McCannel TA: *Comparison of uveal melanoma cytopathologic sample retrieval in trans-scleral versus vitrectomy--assisted transvitreal fine needle aspiration biopsy*. Br J Ophthalmol. 2014; 0: 1–5.
3. Cohen VML, Dinakaran S, Parsons MA, Rennie IG: *Transvitreal fine needle aspiration biopsy: the influence of intraocular lesion size on diagnostic biopsy result*. Eye. 2001; 15: 143–147.
4. Eide N, Walaas L: *Fine-needle aspiration biopsy and other biopsies in suspected intraocular malignant disease: a review*. Acta Ophthalmol. 2009; 87(6): 588–601.
5. Seregard S, All-Ericsson C, Hjelmqvist L, Berglin L, Kvanta A: *Diagnostic incisional biopsies in clinically indeterminate choroidal tumours*. Eye. 2013; 27(2): 115–118.
6. McCannel TA, Chang MY, Burgess BL: *Multi-year follow-up of fine-needle aspiration biopsy in choroidal melanoma*. Ophthalmology. 2012; 119(3): 606–610.
7. Young TA, Burgess BL, Rao NP, Glasgow BJ, Straatsma BR: *Transscleral fine-needle aspiration biopsy of macular choroidal melanoma*. Am J Ophthalmol. 2008; 145(2): 297–302.
8. Damato B, Duke C, Coupland SE, Hiscitt P, Smith PA, Campbell I, et al.: *Cytogenetics of uveal melanoma*. Ophthalmology. 2007; 114: 1925–1931.
9. Aaberg TM, Cook RW, Oeschlager K, Maetzold D, Kumar Rao P, Mason III JO: *Current clinical practice: differential management of uveal melanoma in the era of molecular tumour analyses.* Clinical Ophthalmology. 2014; 8: 2449–2460.
10. Correa ZM, Augsburger JJ: *Sufficiency of FNAB aspirates of posterior uveal melanoma for cytologic versus GEP classification in 159 patients, and relative prognostic significance of these classifications*. Graefes Arch Clin Exp Ophthalmol. 2014; 252(1): 131–135.
11. Onken M, Worley L, Ehlers J, Harbour W: *Gen exspression profiling in uveal melanoma reveals two molecular classes and predicts metastasic death*. Cancer Research. 2004; 15, 64: 7205––7209.
12. Tschentscher F, Husing J, Holter T, Kruse E, Dresen I, Jockel K, et al.: *Tumour classification based on gene expression profiling shows that uveal melanomas with and without monosomy 3 represent two distinct entities*. Cancer Research. 2003; 15, 63: 2578–2584.
13. Young TA, Rao NP, Glasgow BJ, Moral JN, Straatsma BR: *Fluorescent in situ hybridization for monosomy 3 via 30-gauge fine needle aspitarion biopsy of choroidal melanoma in vivo*. Ophthalmology. 2007; 114: 142–146.
14. McCannel TA: *Fine-needle aspiration biopsy in the management of choroidal melanoma*. Curr Opin Ophthalmol. 2013; 24(3): 262–266.
15. Bagger M, Tebering JF, Kiilgaard JF: *The ocular consequences and applicability of minimally invasive 25-gauge transvitreal retinochoroidal biopsy*. Ophthalmology. 2013; 120(12): 2565––2572.
16. Abdel-Rahman MH, Cebulla CM, Verma V, Christopher BN, Carson WE 3rd, Olencki T, et al.: *Monosomy 3 status of uveal melanoma metastases in associated with rapidly progressive tumours and short survival*. Exp Eye Res. 2012 Jul; 100: 26–31.
17. Van den Bosch T, van Beek JGM, Vaarwater J, Verdijk R, Naus NC, Paridaens D, et al.: *Higer percentage of Fish-determined monosomy 3 and 8q amplification in uveal melanoma cells relate to poor patient prognosis*. Incest Ophthalmol Vis Sci. 2012; 53(6): 2668–2674.
18. Coupland SE, Lake SL, Zeschnig M, Damato BE: *Molecular pathology of uveal melanoma*. Eye. 2013; 27(2): 230–242.
19. Dopierala J, Damato BE, Lake SL, Taktak AF, Cuopland SE: *Genetic heterogenity in uveal melanoma assessed by multiplex ligation dependent probe amplification*. Incest Ophthalmol Vis Sci. 2010; 51(10): 4898–4905.
20. Shield CL, Ganguly A, Bianciotto CG, Turaka K, Tavallali A, Shields JA: *Prognosis of uveal melanoma in 500 cases using genetic testing of fine-needel aspiration biopsy specimens*. Ophthalmology. 2011; 118(2): 396–401.
21. Shields CL, Materin AM, Teixeira L, Mashayekhi A, Ganguly A, Shields JA: *Small choroidal melanoma with chromosom 3 monosomy on fine-needle aspiration biopsy.* Ophthalmology. 2007; 114: 1019–1924.
22. Smith JH, Padnick-Silver L, Newlin A, Rhodes K, Rubinstein WS: *Genetic study of familial uveal melanoma*. Opthalmology. 2007; 114: 774–779.
23. Damato B, Duke C, Coupland SE, Hiscitt P, Smith PA, Campbell I, et al.: *Cytogenetics of uveal melanoma*. Ophthalmology. 2007; 114: 1925–1931.
24. Isager P, Ehlers N, Overgaard J: *Prognostic factors for survival after enucleation for choroidaland ciliary body melanomas.* Acta Ophthalmol Scand. 2004; 82: 517–525.
25. Ewens K, Kanetsky P, Richards-Yutz J, Purrazzella J, Shields CL, Ganguly T, et al.: *Chromosom 3 status combined with BAP1 and EIF1AX mutation profiles are associated with metastasis in uveal melanoma*. Invest Ophthalmol Vis Sci. 2014; 26, 55(8): 5160–5167.
26. Field MG, Harbour JW: *Recent developments in prognostic and predictive testing in uveal melanoma*. Curr Opin Ophthalmol. 2014; 25(3): 234–239.
27. Kalirai H, Dodson A, Faqir S, Damato B, Coupland SE: *Lack of BAP1 protein expression in uveal melanoma is associated with increased metastatic risk and has utility in routine prognostic testing*. Br J Cancer. 2014 Sep 23; 111(7): 1373–1380.
28. *My uveal melanoma*: www.myuvealmelanoma.com, http://www.myuvealmelanoma.com/uveal-melanoma-testing/understandingthe-results/
29. Seregard S: *To biopsy or not to biopsy?* Acta Ophthalmol. 2009; 87: 586–587.
30. Augsburger JJ, Corrêa ZM, Trichopoulos N: *Prognostic implications of cytopathologic classification of melanocytic uveal tumours evaluated by fineneedle aspiration biopsy*. Arq Bras Oftalmol. 2013; 76(2): 72–79.

31. Chang MY, Rao NP, Burgess BL, Johnson BL, McCannel TA: *Heterogenity of monosomy 3 in fine needle aspiration biopsy of choroidal melanoma*. Mol Vis. 2013; 7, 19: 1892–1900.
32. Mensink HW, Vaarwater J, Kilic E, Naus NC, Mooy N, Luyten G, et al.: *Chromosom 3 intratumour heterogeneity in uveal melanoma*. Investigative Ophthalmology & Visual Sience. 2009; 50, 2: 500–504.
33. Sala-Puigdollers A, Rodríguez-de la Rúa E, Saornil MA, García-Álvarez C, García-Lagarto E, Ovelar Arribas Y: *Combined choroidal biopsy and cytology for diagnosis of intraocular tumour*. Arch Soc Esp Oftalmol. 2013 Sep; 88(9): 365–368.
34. Killgaard J, Bagger M, Tolstruo Andersen M, Heegaard S, Klarskov Andersen M: *Can we trust the biopsy for prognostication in patients with choroidal melanomas?* EVER – 2014 October 1–4.
35. Schefler AC, Gologorsky D, Marr BP, Shields CL, Zeolite I, Abramson DH: *Extraocular extension of uveal melanoma after fine-needle aspiration, vitrectomy, and open biopsy*. Jama Ophthalmol. 2013; 131(9): 1220–1224.

The paper was originally received 06.11.2015 (KO-00037-2015)/
Praca wpłynęła do Redakcji 06.11.2015 r. (KO-00037-2015)
Accepted for publication 22.04.2016/
Zakwalifikowano do druku 22.04.2016 r.

Reprint requests to (Adres do korespondencji):
dr n. med Anna Bogdali
Department of Ophthalmology
Jagiellonian University Medical College
Kopernika 38
31-501 Kraków
e-mail: annabogdali@poczta.onet.pl

ISSN 0023-2157 Index 362646