Beyond cytology:

Prognostic advances in uveal melanoma

On February 2, 2024, Christina Herrspiegel defended her thesis "From cytologic features to serum markers: advancing prognostication of uveal melanoma" at Karolinska Institutet. The PhD project was conducted at the Dept. of Clinical Neuroscience/Division of Eye and Vision, Karolinska Institutet and St. Erik Eye Hospital. The supervisors were Prof.Gustav Stålhammar, MD, PhD, FEBO,, Katarina Bartuma, MD, PhD, FEBO , and Prof. Stefan Seregard, MD, PhD, all from the Dept. of Clinical Neuroscience at Karolinska Institutet.

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Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, yet early prognostication remains limited to tumor size/location, or invasive biopsies. Metastatic spread occurs in nearly half of patients within a decade, often despite prompt local therapy, and carries a median survival of one year. This thesis addressed the urgent need for faster, less invasive, and more affordable prognostic tools to stratify patients by metastatic risk at the time of diagnosis.

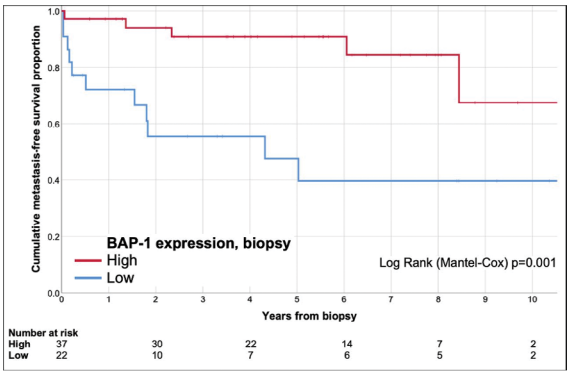

Figure 1. Kaplan-Meier curve. Patients with tumors who had low nuclear BAP-1 expression in transvitreal incisional biopsies (blue) had significantly shorter metastasis-free survival than patients with tumors who had high nuclear expression (red, log-rank p = 0.001). Reprinted with permission from Herrspiegel et al, Br J Ophthalmol 2021, under CC-BY-NC 4.0.

Digital Cytologic Analysis

Traditional cytology relies on pathologist inspection of tumor nuclei—an inherently time-consuming and variable process. In Paper I, over 10,000 nuclei from enucleated UM specimens underwent digital morphometric analysis for twelve shape/size variables. Automated quantification correlated strongly with BAP-1 expression, monosomy 3, gene expression class, and patient survival, with an average analysis time under 2.5 minutes per tumor. Digital cytometry thus provides an objective, rapid, and reproducible prognostic readout.

Future directions:

- Initiate prospective, biomarker-stratified clinical trials to evaluate adjuvant therapies for patients deemed high-risk by serUM-Px and TNC

Minimally Invasive Biopsies

Enucleation-free prognostication is critical for patients with smaller tumors or those prioritizing globe preservation. Paper II demonstrates that transvitreal incisional biopsies of posterior UM yield BAP-1 staining results concordant with enucleation specimens and predict metastasis-free survival (**Figure 1**). This finding paves the way for personalized metastatic risk assessment without sacrificing the eye.

Serum Biomarker Signature

Blood-based testing offers a completely non-invasive alternative. In Paper III, protein profiling identified candidate serum markers at diagnosis. Follow-up ELISAs pinpointed leptin and osteopontin as key predictors; their combined serUM-Px signature stratifies patients into low, intermediate, and high metastatic risk categories years before clinical spread, based on a single venous serum sample.

Tenascin C as a Novel Marker

Paper IV explored Tenascin C (TNC), an extracellular matrix protein linked to tumor progression. Peripheral blood and tumor RNA levels of TNC—measured decades after initial cohort sampling—showed that elevated TNC is associated with BAP-1 mutation, monosomy 3, epithelioid cytology, and increased cumulative incidence of metastasis-related death. TNC thus emerges as an additional prognostic biomarker amenable to both tissue and serum assays.

Conclusions

Collectively, these studies expand the UM prognostic toolbox along a spectrum—from ultra-rapid digital imaging to minimally invasive biopsies and blood-based tests—offering clinicians tailored, cost-effective risk stratification for diagnosis and facilitating patient counseling, trial inclusion, and targeted interventions.

Key points:

- High-throughput digital morphometry of tumor nuclei enables objective, rapid prognostic assessment correlating strongly with BAP-1 status, monosomy 3, gene expression class, and patient survival
- Transvitreal incisional biopsies for BAP-1 immunostaining yield results concordant with enucleation specimens and reliably predict metastasis-free survival, facilitating prognostication without enucleation
- A serum biomarker signature of leptin and osteopontin (serUM-Px) stratifies patients into low, intermediate, and high metastatic risk groups years before clinical spread based on a single blood sample
- Elevated Tenascin C levels in blood and tumor RNA is an emerging noninvasive prognostic marker

References

1. Herrspiegel C, et al. Digital morphometry of tumor nuclei correlates to BAP-1 status, monosomy 3, gene expression class and survival in uveal melanoma. *Exp Eye Res.* 2020;193:107987.
2. Herrspiegel C, et al. Nuclear expression of BAP-1 in transvitreal incisional biopsies and subsequent enucleation of eyes with posterior choroidal melanoma. *Br J Ophthalmol.* 2021;105(4):582-586.
3. Herrspiegel C, et al. A serum protein signature at the time of Uveal Melanoma diagnosis predicts long-term patient survival. *BMC Cancer.* 2023;23(1):277.
4. Herrspiegel C, et al. Prognostic implications of tenascin C in peripheral blood and primary tumours at the time of uveal melanoma diagnosis. *Can J Ophthalmol.* 2024;59(6):e749-e757.