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Assessment of the Relationship between Metabolic Activity of Uveal Melanoma in Positron Emission Tomography (PET) and Chromosome 3 Monosomy

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Submitted to the editorial board: April 19, 2025
Accepted for publication: May 16, 2026
Available on-line: August 5, 2026

The authors of the study declare that no conflict of interests exists in the compilation, subject and subsequent publication of this professional communication, and that it is not supported by any pharmaceuticals company. This study has not been printed or submitted for publication in any other professional periodical.



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SUMMARY

Introduction: Uveal melanoma is the most common primary malignant intraocular tumor in adults. A major prognostic factor is the cytogenetic profile of the tumor, particularly the presence of monosomy of chromosome 3, which is associated with an increased risk of developing distant metastases. The aim of this study was to determine whether there is a relationship between the metabolic activity of the tumor assessed by SUVmax (maximum standardized uptake value) in PET/CT or PET/MRI and the presence of monosomy 3 in the tumor cytogenetic profile.
Material and Methods: A total of 37 patients with uveal melanoma were included in this retrospective analysis. All patients underwent staging whole-body PET/CT or PET/MRI with calculation of SUVmax, followed by enucleation of the affected eye and cytogenetic examination of the tumor. All patients were examined and subsequently treated between 2009 and 2024 at the Department of Ophthalmology, University Hospital Plzeň.
Results: Monosomy 3 was detected in 21 patients. In this group, SUVmax values ranged from 2.7 to 14.5 (mean 6.6; median 6.5). Metastatic dissemination occurred within 5 years of diagnosis in 16 patients (76.2%), and in an additional four patients after a longer interval. Disomy 3 was present in 16 patients, with SUVmax values ranging from 1.1 to 8.0 (mean 3.4; median 3.4). Metastatic spread occurred in only one patient (6.3%). The difference in SUVmax values between the groups was highly statistically significant (p = 0.00012).
Conclusion: Higher SUVmax values were associated with the presence of monosomy 3 and an increased risk of metastatic progression. PET/CT and PET/MRI imaging may be beneficial not only for diagnosis and primary staging of metastatic disease, but also for indirect estimation of the tumor's genetic variant.
Key words: uveal melanoma, chromosome 3 monosomy, PET/CT, PET/MRI, SUVmax

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INTRODUCTION

Uveal melanoma represents the most common primary malignant intraocular tumor in the adult population (Figures 1, 2). The prognosis of this pathology is dependent to a substantial degree on genetic factors, of which the most significance is the loss of one of two chromosomes 3. This aberration occurs in approximately 50% of patients with uveal melanoma, and is closely associated with a high risk of metastatic spread, especially to the liver [1].

In addition to monosomy 3, an important role is also played by the gain of a long arm of chromosome 8 (8q), known as polysomy 8q, which is generally present in biologically aggressive tumors and is also associated with an unfavorable prognosis. The highest risk of occurrence of remote metastases is stated in patients with a combination of monosomy 3 and polysomy 8q [2].

In recent years there has been increased interest in the use of the hybrid imaging methods PET/CT and PET/MRI with 18F-fluorodeoxyglucose (18F-FDG) in the diagnosis and monitoring of patients with uveal melanoma. These methods enable quantification of the metabolic activity of the tumor with the aid of the parameter SUVmax (Standardized Uptake Value maximum), which can help predict the genetic profile of the tumor and the risk of metastases for the patient [3–5].

The aim of this study is to evaluate the relationship between the SUVmax values at the baseline staging PET/

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CT or PET/MRI examination and the presence of monosomy 3 in patients with uveal melanoma, and at the same time to assess their correlation with the progression of the pathology over the course of five-year observation.

MATERIAL AND METHOD

The retrospective study included 37 eyes of 37 patients with histologically confirmed uveal melanoma, within the age range of 30–84 years (mean 62,4; median 66 years). The cohort consisted of 26 men (70.3%) and 11 women (29.7%). These were patients in whom the ciliary body was affected (total 10 patients; 27.1%), and in whom the choroid was affected (total 27 patients; 72.9%). The cohort consisted of patients who had undergone enucleation at our center in the period of 2009–2024.



Figure 1. Fundus image demonstrating a choroidal melanoma in the macula

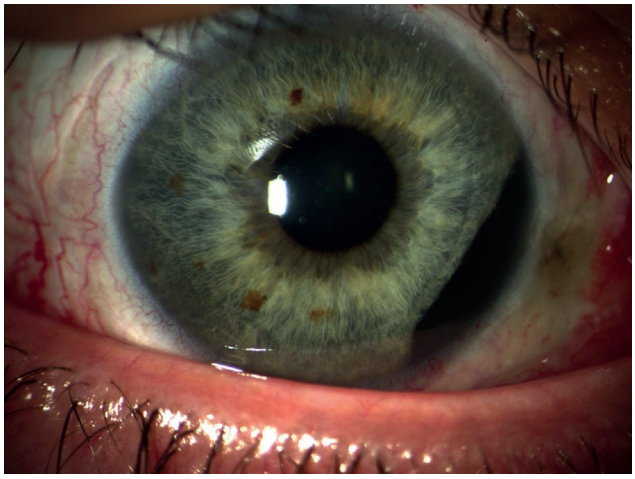


Figure 2. Image of the anterior segment showing ciliary body melanoma with invasion of the anterior chamber

All the patients underwent an examination using the hybrid methods PET/CT (14 patients, 37.8%) or PET/MRI (23 patients, 62.2%) following the application of 18F-FDG in a dose of 3–5 MBq/kg of body weight. Scanning of the patient was performed approximately 60 minutes after the application of the radiopharmaceutical. PET/CT combines the functional data obtained from PET with anatomical CT imaging, which at the same time serves for correcting damping of the signal. PET/MRI offers more detailed imaging of soft tissues and a lower radiation dose, which is an advantage especially for younger patients or in the case of repeated examinations (Figure 3). The SUVmax value was determined automatically for the individual patients using software based on the ratio of activity of the radiopharmaceutical in the selected area of the tumor to the mean activity in the whole body, in which the result was standardized to the administered dose and body weight of the patient.

Enucleation was indicated for all patients, performed under general anesthesia. This procedure involves the removal of the entire eyeball, while attempting to avoid damage to the ocular wall due to the risk of spread of tumor cells. During the procedure the rectus extraocular muscles are progressively ligated, and after removal of the eyeball are sutured over a pad inserted in the eye socket. The type of pad used depends on the individual center; at our center a porous polyethylene pad is used. The eye socket with the pad and extraocular muscles is subsequently covered over by the conjunctiva, and the wound is closed. In most cases it is possible to begin to use a temporary prosthesis three months after enucleation. The definitive prosthesis is produced after approximately six months, varying individually according to the patient's healing. After the procedure the eyeball is sent for a histological and genetic examination without fixation, together with a sample of the patient's peripheral blood.

The cytogenic analysis is performed using the method of fluorescence in situ hybridization (FISH) or new generation sequencing (NGS) on samples from the enucleated eyeballs. FISH enables the detection of specific chromosomal aberrations, in this case loss of chromosome 3, with the aid of fluorescently marked probes that bind to the target DNA sequences in interphase nuclei. The advantage of this method is fast and targeted detection, while the disadvantage is its limitation to the predefined genomic loci [6]. NGS enables a detailed analysis of the genetic profile of the tumor on the level of the entire genome or exome. This method provides comprehensive information about the presence of gains, losses and point mutations, but it requires high quality DNA and is more demanding in terms of bioinformatic processing and interpretation of the results [7].

The patients included in the study had been observed for at least 24 months, the longest observed patient has been in our care for 177 months (the mean observation period is 85.9 months). In patients with progression

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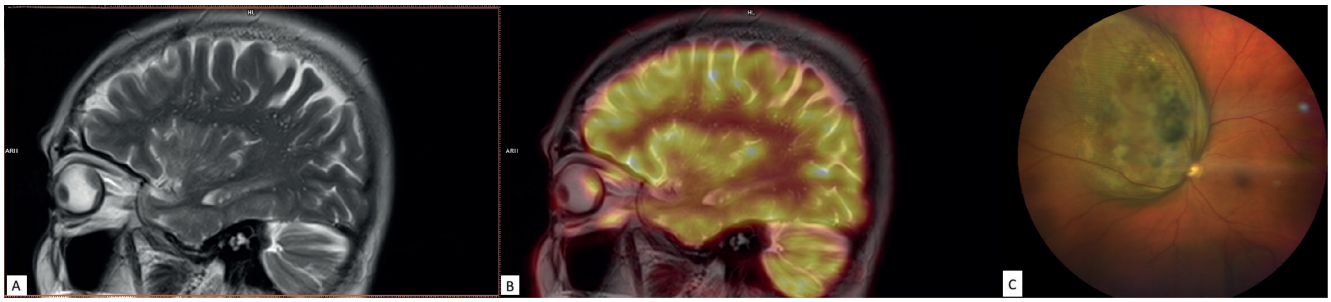


Figure 3. Images of a female patient with choroidal melanoma of the left eye (SUVmax = 14.1). (**A**) Magnetic resonance imaging. (**B**) Positron emission tomography showing increased uptake of ^{18}F-fluorodeoxyglucose within the lesion. (**C**) Fundus photograph demonstrating a large melanoma located at the posterior pole of the left eye
SUV max - Standardized Uptake Value maximum

of the tumor, the average period from determination of the diagnosis to the identification of metastatic spread was 27.6 months (in our cohort this concerned a range of 1–108 months). In the first 10 years after determination of the diagnosis, the patients underwent regular follow-up examinations at six-monthly intervals, and afterwards at yearly intervals for the remainder of their lives. The statistical analysis was conducted with the aid of a non-parametric Mann-Whitney U test in order to compare the SUVmax values between the groups with chromosome 3 monosomy and without chromosome 3 monosomy. The level of statistical significance was set at $p < 0.05$.

RESULTS

Out of the total number of 37 patients, chromosome 3 monosomy was determined in 21 patients (56.8%, group 1), while chromosome 3 disomy was confirmed in 16 patients (43.2%, group 2).

In group 1, the SUVmax values were within the range of 2.7 to 14.5 (mean 6.6; median 6.5). Group 1 consisted of 14 choroidal melanomas (66.7%) and 7 ciliary body melanomas (33.3%). In 16 patients (76.2%) progression of the tumor was determined within five years of the primary diagnosis, in another four patients within ten years (Fig. 4).

In group 2, the SUVmax values were determined within the range of 1.1 to 8.0 (mean 3.4; median 3.4); progression occurred in only one patient (6.3%), whose SUVmax value was 8.0. This group consisted of 13 cases of choroidal melanoma (81.3%) and 3 cases of ciliary body melanoma (18.7%).

The difference in the SUVmax values between the two groups was statistically highly significant (Mann-Whitney U test, $p = 0.00012$).

The mean height of the tumor was also greater in the group with chromosome 3 monosomy than in the group with chromosome 3 disomy (9.6 mm vs. 6.6 mm).

The results of our observation are presented in summary in Graph 1. In the graph the patients are divided into three groups according to the SUVmax value; group 1 with SUVmax values of up to 4, group 2 with SUVmax values of 4–8 and group 3 with SUVmax values over 8.

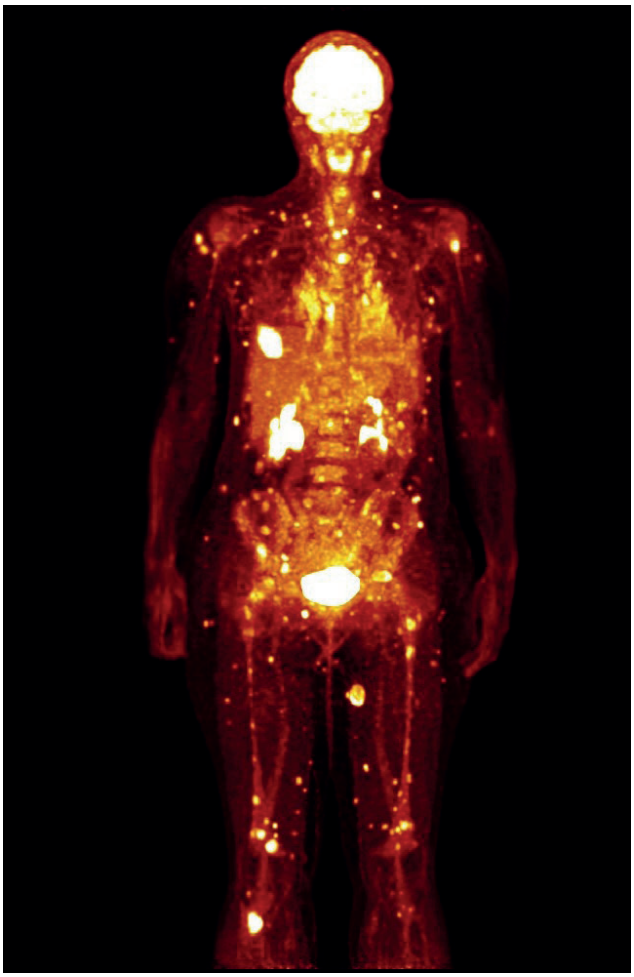
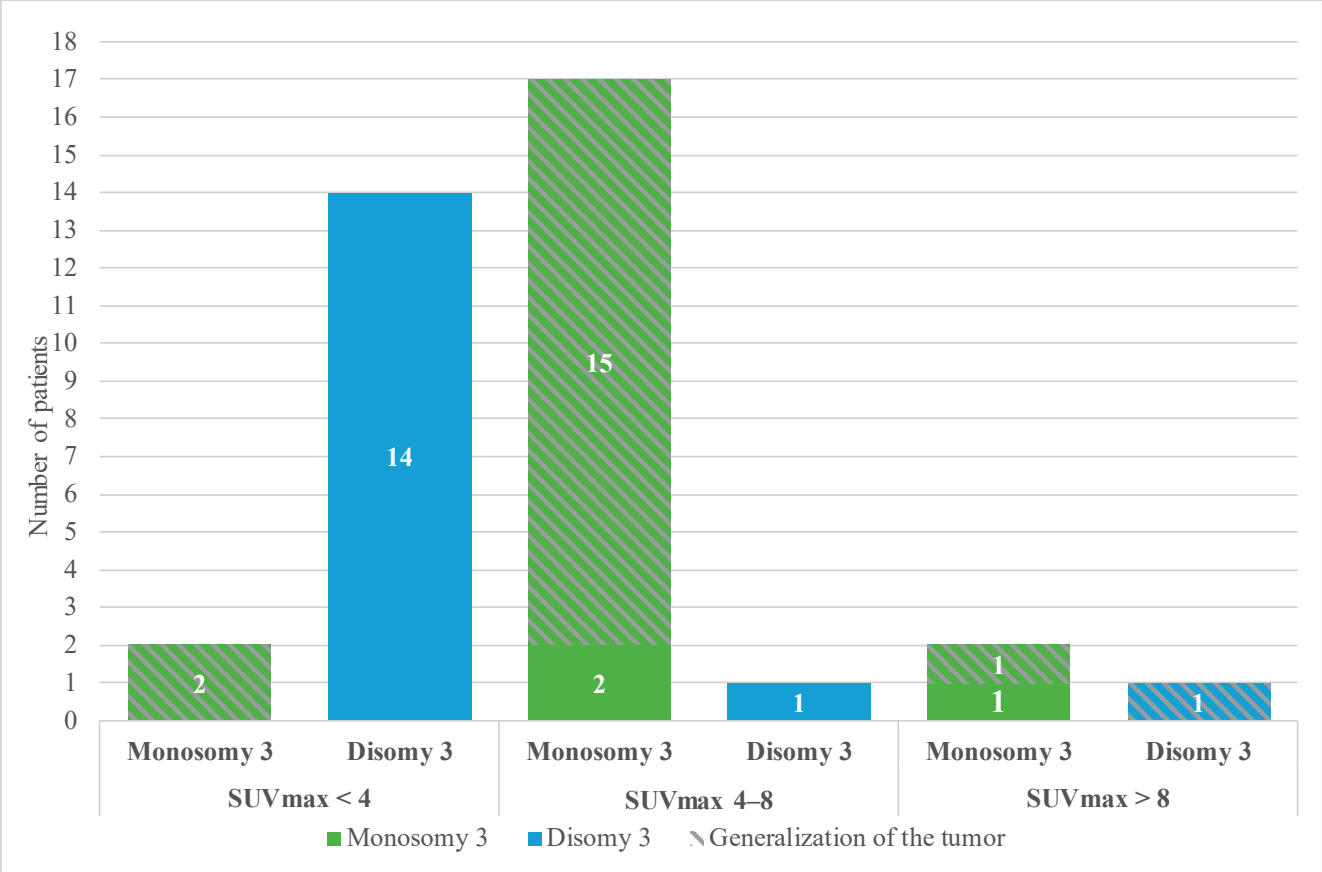


Figure 4. PET/MRI image of a female patient with metastatic spread of ciliary body melanoma. The patient had chromosome 3 monosomy, and the SUVmax value was 9.1
PET/MRI – positron emission tomography/magnetic resonance imaging
SUVmax – maximum standardized uptake value

The patients in each group are further divided according to the results of the genetic examination into a group with chromosome 3 monosomy and with chromosome 3 disomy. The numbers of patients with progression of the tumor in each group are indicated by cross-hatching.

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Graph1. Summary chart of the study results
SUV max – Standardized Uptake Value maximum

DISCUSSION

The current literature confirms that genetic factors and metabolic activity of the tumor represent the principal prognostic indicators of uveal melanoma. In their review study, Papastefanou and Cohen summarize the current possibilities of staging and emphasize the importance of cytogenic markers, in particular of monosomy 3 and polysomy 8q, as well as the role played by imaging methods. Prescher et al. have demonstrated that monosomy 3 represents a strong independent prognostic factor for the occurrence of metastases and shorter survival time [9], while a combination of monosomy 3 and polysome 8q is associated with the worst prognosis [2].

The hybrid examination methods PET/CT and PET/MRI are used not only for the detection of metastases, but also as a means of estimating the biological aggressivity of the primary tumor [4]. A systematic meta-analysis conducted by Mirshahvalad et al. (2024) demonstrated high sensitivity and specificity of the 18F-FDG PET examination in detecting liver metastases, and at the same time confirmed that increased metabolic activity of the tumor correlates significantly with the shortest survival time of patients. Correspondingly, the authors recommend including PET/CT in a comprehensive examination in order to provide a more precise estimate of the risk [11]. Similarly, Solnik et al. (2022) emphasize the benefit of functional imaging and highlight the advantages of PET/MRI, which thanks to better contrast of soft tissues and the lower radiation dose may be more suitable especially for younger patients [12].

Our results are in accordance with these observations. The difference in the SUVmax values between the groups with chromosome 3 monosomy and chromosome 3 disomy in our cohort was statistically highly significant ($p = 0.00012$). The higher SUVmax value in primary uveal melanoma in our cohort was unequivocally linked with the presence of monosomy 3 and a higher risk of progression. The mean SUVmax value in patients with monosomy 3 was 6.6 as against 3.4 in patients with disomy 3, in which 76% of patients with monosomy 3 progressed within 5 years, in contrast with only 6% in the case of disomy 3. The results of our study are in accordance with the observations of the authors Papastefanou et al., who similarly demonstrated a positive relationship between metabolic activity of the tumor on PET/CT and the presence of monosomy 3. As many as 94% of tumors with monosomy 3 had an SUVmax value of > 2.5, and 80% a value of > 4, whereas in disomy 3 an SUVmax value of > 4 was recorded in only 57% of cases [8]. Review studies also confirm that PET/CT and PET/MRI can serve

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as indirect indicators of the biological aggressivity of a tumor and effectively supplement genetic stratification of the risk [4,11,12].

However, there are certain limitations of imaging methods Reddy et al. demonstrated that PET/CT has low sensitivity for the detection of small primary melanomas: no small tumor recorded an SUVmax value of > 2.5, whereas for larger tumors positivity was present in 75% of cases [10].

Tumor size represents a further known prognostic factor for uveal melanoma, and at the same time may influence SUVmax values. In our cohort the mean tumor height in the group with chromosome 3 monosomy was greater than in the group with chromosome 3 disomy (9.6 mm vs. 6.6 mm). The higher metabolic activity of tumors with monosomy 3 may therefore be due not only to a biologically more aggressive genetic profile, but partially also due to the larger volume of the tumor and easier detectability upon PET examination. In the case of smaller lesions, metabolic activity may be underestimated due to the influence of the partial-volume effect. SUVmax values may further be influenced by technical and operational factors, including the used modality of PET/CT versus PET/MRI, the method of reconstructing the image and the time between the application of 18F-FDG and the actual examination. However, both modalities use an identical PET principle based on detecting the accumulation of 18F-FDG, and provide comparable metabolic information. They differ above all in the anatomical component of the examination, the method of correcting damping of the signal and the quality of imaging of soft tissues. PET/MRI may be an advantage especially due to its low radiation dose and better imaging of orbital structures [14].

A certain limitation relating to our study is the relatively small number of patients (n = 37), although taking into account the low incidence of uveal melanoma and the fact that enucleation is no longer the primary method of treatment, this still represents a relatively high quality cohort. The retrospective, single-center character of the study nevertheless entails a risk of selection distortion and limits the generalizability of the results. We focused primarily on chromosome 3, which limits the possibility of more comprehensive genetic modelling of risk.

Genetic testing still remains the gold standard for determining the risk of uveal melanoma and its progression. However, our results indicate that quantification of metabolic activity (SUVmax) may be a practical and repeatable supplement to genetic analysis, especially in cases where it is not possible to perform a biopsy or the available material is limited. In accordance with the literature [3–5,11,12], we may assume that the combination of data obtained by the imaging methods (SUVmax) and the genetic indicators (monosomy 3, 8q) will lead to more precise prognostic models than the use of individual markers in isolation.

The above-discussed results of the study can subsequently be used for individualized follow-up care of patients after treatment of uveal melanoma. According to the Cancer Care Alberta guidelines (Weis et al., 2023), monitoring is divided according to the risk of progression, in which it is recommended to perform clinical examination and ultrasound of the liver at annual intervals for low-risk patients (tumor size ≤ 9 mm in height and/or ≤ 12 mm diameter, low-risk genetics), whereas for high-risk patients examination of the liver (alternating ultrasound and MRI) is indicated every six months [13]. In this respect our follow-up procedure is more intensive, since we perform six-monthly examinations of the abdomen (sonography, CT or MRI) on all patients, regardless of their risk profile. Annual examination of the lungs and laboratory tests correspond to annual clinical follow-up examinations recommended in the aforementioned guidelines. Like Weis et al., we continue with long-term observation for a minimum period of ten years, after which we perform follow-up examinations once per year. This uniform regime, not taking into account risk stratification, may be an advantage especially in situations where complete genetic data are not available, or where the genetic profile is imprecise or ambiguous.

CONCLUSION

Our results confirm that higher SUVmax values correlate significantly with the presence of monosomy 3 and an increased risk of progression of uveal melanoma. Quantification of metabolic activity may represent a practical and repeatable supplement to genetic testing, especially in cases where it is not possible to perform a biopsy or where the sample is limited. The hybrid methods PET/CT and PET/MRI are therefore beneficial not only in the staging and detection of metastases, but also in predicting the biological behavior of the tumor. In future, integration of metabolic and genetic markers could contribute to a more precise estimate of risk, and more targeted follow-up care of patients.

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