UNIVERSITY OF MEDICINE AND PHARMACY
"CAROL DAVILA", BUCHAREST

DOCTORAL STUDIES

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SUMMARY OF THE DOCTORAL THESIS

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DOCTORAL STUDENT:
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UVEAL MALIGNANT MELANOMA LABORATORY ASPECTS OF REDOX BALANCE AND TUMOR MARKERS

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Introduction

Uveal malignant melanoma (UMM) represents the most common primary intraocular tumor in adults and, at the same time, one of the most aggressive forms of ocular malignancy. Although its incidence is relatively low compared to that of cutaneous melanoma, the considerable impact on patients' quality of life and the generally poor prognosis highlight the necessity for comprehensive and systematic scientific investigation.

Melanoma is a relatively uncommon neoplasm arising from melanocytes, which are pigment-producing cells located in various anatomical sites, including the skin, mucous membranes (nasal, oropharyngeal, pulmonary, gastrointestinal, anal/rectal, and urinary tracts), and the ocular region (uvea, conjunctiva, eyelids, orbit). In rare cases, melanomas may originate from an unknown primary anatomical site [1].

In an analysis of 84,836 cases from the National Cancer Database, including patients diagnosed between 1985 and 1994, the distribution of melanoma cases by primary site was as follows: cutaneous melanomas accounted for 91%, ocular and adnexal melanomas for 5%, mucosal melanomas for 1%, and melanomas of unknown primary origin for 2% [2].

Among all ocular melanomas, approximately 83% arise within the uvea, 5% originate from the conjunctiva, and about 10% occur in other anatomical structures of the eyeball [3]. The choroid represents the most frequent site of uveal melanoma, forming—together with the ciliary body and iris—the uvea, the highly vascularized middle tunic of the eye.

In a large-scale study published by Shields et al. [2], which included 8,033 patients diagnosed with uveal melanoma, the tumor was localized to the iris in 285 patients (4%), to the ciliary body in 492 patients (6%), and to the choroid in 7,256 patients (90%) [2].

An analysis conducted through the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute, covering a period of more than 36 years (from 1973 to 2008) and including 4,070 patients with primary uveal melanoma, reported an age-adjusted mean annual incidence rate of 5.1 cases per one million individuals [4].

Uveal melanoma occurs most frequently in elderly individuals, with an incidence rate that increases progressively with age, reaching a peak around 70 years, followed by a plateau after the age of 75 years [4–7]. Uveal melanoma in children is exceedingly rare, while congenital uveal melanoma represents an extremely uncommon entity [7–9].

In population-based epidemiological studies, the age-adjusted incidence of uveal melanoma has been found to be higher in men than in women [4,5]. According to an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Program of the U.S. National Cancer Institute, the age-adjusted incidence rate of uveal melanoma was 5.8 cases per one million in men, compared with 4.4 cases per one million in women [4].

Although the etiology of uveal melanoma remains incompletely understood, several risk factors have been implicated in its development. Certain host susceptibility characteristics, such as fair skin, inability to tan, and light-colored eyes, have been shown to be significantly associated with an increased risk of uveal melanoma, with odds ratios of 1.80, 1.64, and 1.75, respectively [10].

Oculodermal melanocytosis, also known as Nevus of Ota, represents a significant risk factor for the development of uveal melanoma [11,12]. This condition is characterized by abnormal congenital hyperpigmentation involving the V1/V2 branches within the distribution of the trigeminal nerve, and it may affect the periocular skin, orbit, uvea, sclera, and conjunctiva, as well as other structures such as the palate, meninges, and tympanic membrane [11,12].

A choroidal nevus is a relatively common finding in the general population, with an estimated prevalence of approximately 5% among individuals in the United States [13]. Based on the concept that all ocular melanomas originate from a preexisting intraocular nevus, the rate of malignant transformation of a choroidal nevus into melanoma has been reported to be 1 in 8,845, increasing to 1 in 3,664 among elderly individuals aged 80 to 84 years [14].

Exposure to ultraviolet (UV) sunlight has been clearly established as a major risk factor for cutaneous melanomas [15]. However, there remains an ongoing debate regarding whether ultraviolet light exposure may also represent a risk factor for uveal melanoma. Some authors support this hypothesis [16], whereas others have found insufficient evidence to substantiate such an association [17].

With respect to artificial light sources, blue light exposure has been proposed as a potential contributor to the oncogenic process and progression of uveal melanoma [18]. Furthermore, occupational cooking, which may involve chronic exposure to heat and light radiation, has been reported to be associated with an increased risk of developing uveal melanoma [19].

The motivation for selecting this research topic arises from the need to gain a deeper understanding of the biological and immunological mechanisms that influence the clinical

evolution of the disease, particularly given that overall survival remains modest despite significant therapeutic advances.

By correlating clinical parameters with biological, metabolic, and immunological markers, this study aims to elucidate the mechanisms underlying hepatic metastasis in uveal malignant melanoma and to provide an original contribution to the comprehension of prognostic determinants. Furthermore, it seeks to establish a foundation for the development of personalized therapeutic strategies tailored to the individual biological profile of affected patients.

The working hypothesis of this doctoral research is based on the premise that specific biological, metabolic, and immunological markers play a crucial role in the evolution, prognosis, and therapeutic management of uveal malignant melanoma. The identification and correlation of these markers may enable the early prediction of metastatic recurrence, particularly in the liver—the primary target organ in metastatic uveal melanoma—and support the development of prognostic and therapeutic response prediction models.

At present, there remain significant knowledge gaps regarding the identification of predictive biomarkers and effective therapeutic targets. The novelty of this research lies in the systematic correlation of clinical parameters with biological and immunological markers, aiming to construct predictive models that could contribute to risk stratification and the personalization of treatment.

The relevance and timeliness of this topic are reinforced by the fact that, internationally, immunotherapy and research into the tumor microenvironment have become leading priorities in oncology, including in the field of uveal melanoma.

The clinical evolution of uveal malignant melanoma is not determined solely by morphological features or tumor dimensions, but rather represents the outcome of a complex interplay between the tumor's biological profile (including serum markers, molecular expression, and cytogenetic alterations) and the host's immunological and metabolic status—encompassing the inflammatory response, regulatory T cells, tumor-associated macrophages, and immunosuppressive factors within the tumor microenvironment.

It is assumed that serum biomarkers, the molecular expression of specific genes, and the immunological characteristics of the tumor microenvironment may serve as objective tools for a more accurate classification of patients and a more precise assessment of tumor disease status.

The main objectives pursued within this research can be systematized as follows:

1. The first objective of the study is to identify specific tumor biomarkers associated with uveal malignant melanoma (UMM) that are commonly expressed at the hepatic level and can be correlated with hepatic metastasis, given that the liver represents the primary site of metastasis in uveal malignant melanoma.

2. The second objective is to identify specific proteins that can be quantitatively or qualitatively differentiated from those of the primary tumor, in order to demonstrate the hepatic tropism of uveal malignant melanoma, acknowledging the liver as the principal metastatic target organ in the course of metastatic disease.

3. The third objective concerns the role of the redox balance in the clinical evolution of patients with uveal malignant melanoma (UMM), aiming to demonstrate the metabolic reprogramming capacity of this neoplasm in relation to metastatic disease and to identify potential therapeutic targets within redox-associated pathways.

The thesis is structured into two major parts:

- a general section, which presents the current state of knowledge regarding uveal malignant melanoma (UMM), and
- a personal (original research) section, which encompasses the author's original investigations.

The obtained results include the description of correlations between clinical characteristics and biological markers, the identification of immunological factors associated with prognosis, as well as the exploration of potential therapeutic directions.

The original research section comprises two distinct studies. The first study focuses on the role of redox balance in the treatment of uveal malignant melanoma through enucleation and radiotherapy, while the second study investigates serum sialic acid levels and their potential utility as a tumor biomarker for assessing disease progression and determining whether elevated serum levels may predict tumor recurrence or metastatic spread.

In the first study, the post-treatment responses of total antioxidants, albumin thiols, and lipid peroxides were analyzed following enucleation or radiotherapy in patients with uveal melanoma, with the aim of evaluating the sustained adaptive response of the organism to oxidative stress. The findings indicated that serum antioxidant levels remained elevated both before and after treatment, persisting until the end of the follow-up period.

In the second study, which analyzed serum sialic acid levels in patients with uveal melanoma and their temporal dynamics, the results—consistent with data reported in the

scientific literature—demonstrated that sialic acid exhibits high sensitivity but low specificity in the monitoring of patients with uveal malignant melanoma.

1.General Research Methodology

1.1. Study Design and Patient Informed Consent

The research was conducted as a retrospective clinical study spanning a five-year period (2019–2024) and included patients who presented for the treatment of uveal malignant melanoma (UMM) at the "Prof. Dr. Alexandru Trestioreanu Oncology Institute Bucharest".

The study design involved two distinct patient cohorts, corresponding to the two methodological approaches used to assess the tumor biomarker classes analyzed in this research:

1. Evaluation of redox balance–related tumor markers (including lipid peroxides, albumin thiols, and total antioxidants), and
2. Assessment of sialic acid as a tumor biomarker.

From both an ethical and methodological perspective, the study was carefully designed to avoid any interference with clinical practice, therapeutic decisions, or other aspects that could influence the ethical integrity of medical care. Patients evaluated by the institute's medical team were informed of the opportunity to participate in the study. Those who expressed willingness to participate received comprehensive information regarding the study objectives and procedures, after which written informed consent was obtained. Participation in the research did not in any way alter or interfere with the appropriate management of uveal malignant melanoma cases, including surgical, radiotherapeutic, or chemotherapeutic decisions, nor with the doctor–patient relationship within the clinical context.

Patients were also informed that they could withdraw from the study at any time without any consequences to their treatment. The post-therapeutic follow-up intervals used in the research adhered to the standard recommendations of the Oncology Institute, depending on the treatment modality administered (surgery, radiotherapy, or chemotherapy).

Participants were advised and encouraged to maintain regular contact with the medical staff—to return for evaluation in case of any symptomatic manifestations, regardless of the scheduled follow-up intervals, and to attend routine follow-up visits every

six months. These evaluations aimed to monitor both the ocular evolution of the neoplasm and the systemic status of the patient, in order to identify any potential metastatic spread.

1.2. Inclusion Criteria

The study included patients who met the following criteria:

- Patients who presented to the "Prof. Dr. Alexandru Trestioreanu Oncology Institute Bucharest" with a clinically and paraclinically confirmed diagnosis of uveal malignant melanoma (UMM).
- Eastern Cooperative Oncology Group (ECOG) performance status score between 0 and 2.
- Minimum age: 18 years.
- Maximum age: 70 years.
- Provision of written informed consent prior to inclusion in the study.
- Compliance with regular clinical follow-up visits, including biological sample collection and paraclinical examinations every six months, or whenever additional evaluations were deemed necessary.

1.3. Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

- Age outside the range of 18 to 70 years.
- Severely impaired clinical status, with evidence of widespread metastatic disease.
- Concurrent administration of complex oncological treatments other than those specified within the study protocol.
- Withdrawal of written informed consent or a personal decision to discontinue or decline participation at any stage of the study.
- Failure to attend regular postoperative or post-radiation follow-up visits, or noncompliance with scheduled biological sample collection and clinical evaluations.

1.4 Methods used:

1.4.1. The method used for redox balance–specific tumor markers

Following the written expression of informed consent, venous blood samples were collected from all participants. Serum was obtained by centrifugation of whole blood samples, and the resulting material was used for the determination of the biochemical parameters analyzed in this study.

- ✓ Lipid Peroxidation Index

The lipid peroxidation index was evaluated by measuring the serum concentration of malondialdehyde (MDA), the final degradation product of lipid hydroperoxides. MDA levels were determined by reaction with 2-thiobarbituric acid (TBA) according to the Carbonneau method [20].

Although lipid peroxidation in biological samples can be assessed by various physical and chemical methods [20], the procedure based on MDA quantification—formed through the cleavage of endoperoxides during the final stage of polyunsaturated fatty acid oxidation—is currently the simplest and most widely used approach.

MDA, a weak, unstable, and highly reactive acid, reacts with TBA under boiling conditions in a trichloroacetic acid (TCA) medium, yielding a red chromogen with a maximum absorbance at 532 nm.

By examining the specific extinction at 532 nm of the carbonyl compounds resulting from oxidative degradation of lipid hydroperoxides, it can be reliably inferred that the absorbance corresponds to the TBA–MDA complex. The method is based on the formation of a red adduct (MDA–TBA_2), which exhibits a characteristic absorption maximum at 532 nm.

The solutions used included:

- Thiobarbituric acid (TBA) (Sigma) – 0.7% in 50% acetic acid;
- Trichloroacetic acid (TCA) (Sigma) – 20%;
- Acetic acid–sodium acetate buffer, 50 mmol, pH 7.

All reagents were of analytical grade, supplied by Merck and Sigma, and specifically intended for clinical research use. Ultrapure water was obtained using a Millipore Milli-Q Biocel filtration system. Spectrophotometric readings were performed using a Specord 210 spectrophotometer (Analytik Jena).

Determination of Albumin Thiol Groups

The albumin thiol (–SH) groups were determined using the Albini method with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), also known as Ellman's reagent [21].

Thiol groups play a significant role in the plasma antioxidant defense system, acting to inhibit oxidative propagation by neutralizing alkoxyl (RO•) and hydroxyl (OH•) radicals, converting them into alcohol and water, respectively:

$$\text{protein–SH} + \text{RO}\bullet \rightarrow \text{protein–S}\bullet + \text{ROH}$$

$$\text{protein–SH} + \text{HO}\bullet \rightarrow \text{protein–S}\bullet + H_2O$$

The resulting thiyl radicals subsequently interact to form bisulfide bonds:

$$\text{protein–S}\bullet + \text{protein–S}\bullet \rightarrow \text{protein–S–S–protein}$$

Through this self-oxidation process, thiol groups act as protective agents against highly toxic free radicals. However, the formation of new disulfide bridges may lead to protein instability and functional alterations.

The determination of plasma thiol groups was based on the spectrophotometric measurement of the colored complex formed at 412 nm as a result of the reaction between the SH groups and DTNB at room temperature.

A decrease in thiol group concentration correlates directly with a reduction in plasma antioxidant barrier efficiency.

Reagents were freshly prepared using chemicals supplied by Merck. The phosphate buffer solution (pH 8.0) was prepared according to standard protocols, and the Ellman reagent was obtained by dissolving 4% DTNB in 100 mL of buffer solution, under gentle heating.

✓ Ferric Reducing Ability of Serum (FRAS) [22]

The FRAS assay measures the ferric reducing ability of serum, reflecting the total antioxidant capacity of non-enzymatic antioxidants present in biological fluids. This method is particularly useful for assessing the resistance index to oxidative damage.

The reaction is based on the reduction of the ferric (Fe^{3+})–2,4,6-tripyridyl-s-triazine (TPTZ) complex to a ferrous (Fe^{2+}) form, resulting in the formation of an intense blue chromophore with a maximum absorbance at 593 nm.

Under acidic conditions (pH 3.6), antioxidants in the sample reduce the Fe^{3+}–TPTZ complex to Fe^{2+}–TPTZ, and the intensity of the resulting color is directly proportional to the reducing power of the plasma antioxidants. In this method, an excess of Fe^{3+} ions is used, making the antioxidant concentration in the sample the limiting factor of the reaction and, consequently, of the color intensity.

Reagents used:

- Acetate buffer, 300 mM (pH 3.6)
- 2,4,6-tripyridyl-s-triazine (TPTZ), 10 mM
- Ferric chloride ($FeCl_3$), 20 mM, prepared in distilled water
- Ferrous sulfate, 1 mM, used to prepare a series of standard solutions for the calibration curve

The FRAP reagent was prepared by mixing 200 mL acetate buffer (pH 3.6), the TPTZ solution, the $FeCl_3 \cdot 6H_2O$ solution, and distilled water.

For each analysis, 30 µL of serum sample was added to 900 µL of FRAP reagent and 90 µL of distilled water. The absorbance was measured at 593 nm, against a reagent blank in which the sample was replaced by distilled water.

1.4.2. Method Used for the Determination of Sialic Acid

Following the written expression of informed consent, venous blood samples were collected from each participant. Serum was obtained by centrifugation of whole blood, and the resulting samples were used to determine the biochemical parameters described in this study.

The quantification of sialic acid was adapted from the method of Kattermann and Kriegel (1981). This technique is based on the oxidation of sialic acid with periodic acid, leading to the formation of β-formylpyruvic acid, which subsequently reacts with two molecules of thiobarbituric acid (TBA) to produce a pink chromophore. The resulting complex exhibits a maximum absorbance at a wavelength of 549 nm (λ = 549 nm).

Reagents

- Standard: *N-acetylneuraminic acid* 1 mmol/L (Merck, Germany)
- Solution A: 0.2 mol/L *sodium metaperiodate* (Merck); 9 mol/L *orthophosphoric acid* (Merck)
- Solution B: 1.54 mol/L *sodium arsenite* (Merck); 0.5 mol/L *sodium sulfate* (Merck); 0.05 mol/L *sulfuric acid* (Merck)
- Solution C: 0.037 mol/L *2-thiobarbituric acid* (Merck); 0.5 mol/L *sodium sulfate* (Merck)

Working Procedure

- Pipette 0.05 mL of each sample into individual test tubes, then add 0.95 mL of 0.1 N sulfuric acid.
- Hydrolyze 0.05 mL of serum with 0.95 mL of 0.1 N sulfuric acid for 1 hour at 80°C.
- Pipette 20 µL of the standard solution, and add 220 µL of 0.1 N sulfuric acid.
- Pipette 240 µL of the hydrolyzed samples.
- Add 100 µL of Solution A.
- Incubate for 20 minutes at room temperature.
- Add 200 µL of Solution B.
- Mix gently until the brown coloration disappears.
- Add 1 mL of Solution C.
- Boil the mixture for 15 minutes.

- Extract the final colored complex using 1.6 mL of cyclohexanone.
- Centrifuge for 10 minutes at 1200 × g.
- Collect the supernatant.
- Measure the absorbance at 549 nm using a Specord M40 UV–VIS spectrophotometer.

Calculation of Results

$$A_{549\,nm\ (\text{sample})}/A_{549\,nm\ (\text{standard})} \times 83.3 = \mu mol/L\ NANA$$

where

NANA = N-Acetylneuraminic Acid (sialic acid).

To obtain the final result, the calculated value is multiplied by the sample dilution factor and expressed in millimoles (mM).

2. Data Collection and Statistical Analysis

For the purpose of statistical analysis, data were collected from both written and digital patient records within the "Prof. Dr. Alexandru Trestioreanu Oncology Institute Bucharest", and compiled into an anonymized electronic database using Microsoft Excel (Excel 365, versions 2310–2311).

The parameters collected for the analyzed patient cohort included:

- Patient sex
- Operated eye (right or left)
- Type of therapeutic procedure (radiotherapy or enucleation)
- Serum lipid peroxides, expressed in micromoles (μmol) per 100 milliliters (mL)
- Total albumin thiol groups, measured in millimoles per Liter (mmol/L)
- Total antioxidant levels, expressed in millimoles per Liter (mmol/L)
- Serum sialic acid concentration, expressed in millimoles per liter (mmol/L)

For statistical processing and analysis, the following software packages were employed:

- Minitab® 20 (Minitab Ltd., Coventry, United Kingdom)
- SPSS Statistics version 29 (subscription-based version, International Business Machines Corporation—IBM, Endicott, New York, USA)

These programs were used to perform the statistical evaluation, data organization, and interpretation of the study results.

3. Study I – The effect of oncological treatment on the redox balance in patients with uveal malignant melanoma

In the human body, normal cells primarily rely on oxidative phosphorylation (OXPHOS) to produce energy in the form of adenosine triphosphate (ATP). In contrast, cancer cells develop a distinct metabolic phenotype characterized by increased aerobic glycolysis, a phenomenon known as the “Warburg effect” [23,24].

This metabolic reprogramming enables tumor cells to preferentially convert glucose to lactate, even in the presence of oxygen—a process that is less efficient in terms of ATP production but is believed to be crucial for generating biosynthetic intermediates necessary to sustain rapid cell proliferation and growth [25–27].

Aerobic glycolysis accounts for approximately 56%–63% of total ATP production in most cancer cells [28]. Tumor cells increase their glucose uptake capacity from the surrounding environment and intensify lactic acid secretion to meet their enhanced energy and metabolic demands [25,28].

In addition to aerobic glycolysis, tumor cells exhibit alterations in multiple other metabolic pathways, including amino acid metabolism, fatty acid metabolism, and Krebs cycle modulation, as well as redox homeostasis disruption. Furthermore, an upregulated glutamine metabolism provides an additional source of nitrogen and carbon, supporting tumor cell growth and survival [29].

In uveal malignant melanoma (UMM), significant alterations in oxidative stress parameters have been observed. These modifications may be induced both by the presence of the primary tumor and by the effects of therapeutic interventions, such as enucleation or radiotherapy.

For this reason, particular emphasis in the present study is placed on the determination of specific biochemical parameters and on the evaluation of changes in their values following radical surgical treatment (enucleation) or conservative therapy (radiotherapy).

3.1. Aim of the Study

This retrospective study aims to analyze the systemic impact of oxidative stress and redox balance, as well as the treatment-related dynamics in patients with uveal malignant melanoma (UMM). Although several studies — such as those conducted by Han [30], Longhitano [31], Onken [32], and Chattopadhyay [33] — have addressed aspects of metabolic reprogramming, the tumor microenvironment, and the distinct biological

behavior of UMM compared to cutaneous melanoma, current knowledge still reveals a lack of data regarding the systemic effects on oxidative and redox homeostasis in this malignancy [34].

The present study was therefore designed to monitor redox balance by measuring serum levels of lipid peroxidation markers, total albumin thiol groups, and total antioxidant capacity in patients treated for uveal malignant melanoma by either stereotactic radiotherapy or enucleation [34].

Patients were followed for a two-year period, with serum samples collected before and after treatment, as well as at subsequent six-month intervals, in accordance with established therapeutic protocols. The therapeutic decision — specifically, the choice between radiotherapy and enucleation — was made by the oncology board for each patient, based on tumor parameters, ocular involvement, visual function, and individual clinical characteristics, and was entirely independent of the study design.

The study population consisted of 39 patients, including 17 women and 21 men, who underwent treatment for uveal malignant melanoma (UMM) either by stereotactic radiosurgery (21 patients: 11 women and 10 men) or by surgical enucleation (18 patients: 6 women and 12 men).

The study spanned a two-year follow-up period, with clinical evaluations and biological sample collection scheduled at 6, 12, 18, and 24 months post-treatment.

Out of the total cohort of 39 patients,

- 39 patients (100%) attended the 6-month follow-up,
- 22 patients (56.41%) attended the 12-month follow-up,
- 10 patients (25.64%) attended the 18-month follow-up, and
- 6 patients (15.38%) attended the 24-month follow-up.

The mean time to loss of follow-up was 11.85 months (standard deviation, SD = 6.527).

Loss to follow-up was attributed to factors such as poor general health, death, limited access to the medical center, or the patient's personal decision to discontinue participation in subsequent evaluations.

3.2. Results and Discussion

The results obtained for serum antioxidant levels indicate that serum antioxidant concentrations remained elevated both before and after treatment, persisting throughout the 24-month follow-up period. This finding suggests a sustained adaptive response of the

organism to oxidative stress induced both by the disease itself and by the therapeutic interventions applied.

When comparing the two treatment modalities, radiotherapy maintained higher antioxidant levels, confirming a less disruptive impact on serum antioxidant homeostasis compared to enucleation. The differences were statistically significant in both female and male subgroups, supporting the hypothesis that radiotherapy either stimulates or preserves the antioxidant system more effectively than surgical removal.

Moreover, sex-related differences were also observed: following enucleation, female patients exhibited higher antioxidant levels, whereas after radiotherapy, male patients showed statistically higher values. These results suggest that physiological redox defense mechanisms are influenced not only by the type of treatment but also potentially by hormonal and metabolic characteristics specific to each sex.

Lipid peroxides were found to be elevated above normal values during most stages of the study, confirming the presence of a persistent systemic oxidative stress. Although a general decreasing trend was observed after 12–18 months, the levels did not return to baseline by the end of the 24-month follow-up.

When comparing the two therapeutic approaches, patients who underwent enucleation generally exhibited higher lipid peroxide levels, suggesting that the surgical procedure induces a more intense oxidative stress, likely due to direct tissue trauma and postoperative inflammation. However, these differences were not statistically significant, which may reflect both individual variability and the relatively small sample size of the study cohort.

The influence of sex appeared to be more evident for lipid peroxide levels: in the enucleation group, male–female differences were not statistically relevant, whereas in the radiotherapy group, male patients showed significantly higher values ($p = 0.0055$), with a pronounced peak at 18 months. This discrepancy could be explained by an intrinsically lower antioxidant capacity in males, a phenomenon also reported in other oxidative stress–related pathologies.

Regarding albumin thiols, their evolution varied according to the treatment type. Following enucleation, thiol levels remained stable or slightly increased, reaching a maximum at 18 months and remaining above the reference limit at 24 months. This finding suggests that although enucleation induces acute oxidative stress, the organism is capable of restoring and stabilizing the protein redox balance relatively quickly.

In contrast, after radiotherapy, a progressive decline in albumin thiol levels was observed, falling below the lower limit of normal at 24 months. This pattern may indicate that repeated exposure to radiation can induce a chronic oxidative imbalance, which is more difficult to compensate for through physiological antioxidant mechanisms.

The difference between the two treatment modalities was found to be statistically significant (p = 0.036). From a sex-based perspective, female patients treated by enucleation exhibited significantly higher values compared to those treated by radiotherapy, whereas among male patients, only a non-significant trend was observed between the two therapeutic approaches. These findings suggest that women may derive a greater metabolic benefit from surgical intervention, while men appear to be better protected by radiotherapy, supporting the hypothesis that sex plays a determining role in the biological response to treatment.

In summary, when comparing the two therapeutic strategies — enucleation and radiotherapy — the results indicate that radiotherapy more effectively preserves antioxidant levels, but is associated with a progressive decline in albumin thiols and higher lipid peroxide levels, particularly in male patients. Conversely, enucleation is linked to a more pronounced increase in lipid peroxides but a better preservation of albumin thiols, suggesting a more favorable long-term redox recovery.

With regard to sex-related differences, the two treatments appear to elicit divergent adaptive responses: female patients seem to benefit more from enucleation in terms of albumin thiol preservation, while male patients appear to respond more favorably to radiotherapy with respect to serum antioxidant levels.

3.3. Clinical and Research Implications

Based on the findings of this study, the following conclusions can be drawn:

- Personalized Treatment: The choice of therapeutic modality should take into account not only oncological criteria, but also the oxidative profile and sex-specific characteristics of the patient.
- Long-Term Monitoring: The serum levels of antioxidants, lipid peroxides, and albumin thiols have proven to be relevant biomarkers for the long-term monitoring of redox balance following treatment.
- Use of Adjuvant Strategies: The results support the potential use of antioxidant supplementation or sex- and treatment-specific redox-supportive therapies as adjunct strategies to conventional oncologic management.

• Foundation for Future Research: The statistically significant differences observed between therapeutic procedures and patient sex open new avenues for investigating the hormonal, metabolic, and genetic factors that modulate the oxidative response in post-oncologic recovery.

3.4. Conclusions

In conclusion, enucleation and radiotherapy exert distinct impacts on systemic redox homeostasis, and patient sex emerges as a key determinant of the biological response to treatment. These findings underscore the need for a personalized oncological management approach, integrating oxidative stress biomarkers into both clinical evaluation and long-term patient follow-up.

4. Study II – Sialic Acid as a tumor biomarker in uveal malignant melanoma

This retrospective study aimed to monitor sialic acid levels as a tumor biomarker and to assess their correlation with survival rates in patients diagnosed with uveal malignant melanoma (UMM).

The determination of sialic acid has been employed in other malignancies as well, serving as a biochemical marker for disease progression and patient survival [35]. However, its specificity is relatively low, since elevated levels of sialic acid–rich glycoproteins may also occur in inflammatory diseases [35].

Patients were followed over a two-year period, with serum sample collection performed before and after treatment, and subsequently at six-month intervals, in accordance with the established therapeutic protocols. The choice of treatment modality—radiotherapy or enucleation—was made by the oncology board for each patient based on individual clinical parameters, independently of this study [35].

Serum sialic acid levels were measured every six months. The first measurement was conducted before treatment (Determination 1), the second six months after treatment (Determination 2), the third after one year (Determination 3), and so on. In total, 99 initial measurements (Determination 1) were recorded, followed by 44 at 6 months, 29 at 12 months, 12 at 18 months, 7 at 24 months, 4 at Determination 6, 3 at Determination 7, and 2 at Determination 8. The longest follow-up included two patients assessed three and a half years after treatment initiation.

The analysis of serum sialic acid levels in patients with uveal melanoma revealed several significant findings regarding the temporal dynamics of this biomarker. Consistent with previously published data, sialic acid demonstrated high sensitivity but low specificity in monitoring disease evolution in uveal malignant melanoma.

4.1. Results and Discussion

The results of the present study showed a significant post-treatment increase in serum sialic acid levels, with statistical differences observed at 6-month, 12-month, and 24-month evaluations. This increase cannot be attributed solely to tumor progression or metastasis, but must also be interpreted in the context of post-therapeutic inflammatory processes and treatment-induced oxidative stress, both of which may lead to transient elevations in serum concentrations. These findings confirm the hypothesis that sialic acid is a sensitive yet nonspecific biomarker, influenced by multiple pathophysiological mechanisms.

From a data distribution perspective, the pre-treatment and 6-month measurements showed significant deviation from normal distribution, reflecting population heterogeneity and variable immediate post-treatment responses. In contrast, beginning with the 12-month measurement, the data distribution approached a Gaussian model, suggesting biological response homogenization and stabilization of sialic acid levels over the medium to long term.

Another relevant finding was the progressive decline in maximum sialic acid values during follow-up, indicating a reduction in extreme variability and, consequently, better control of metabolic and tumor status within the studied cohort. This trend may be interpreted as an indirect indicator of disease regression or lack of tumor progression in a subset of patients.

A sex-stratified analysis revealed higher values and greater variability among male patients compared to female patients, with the largest difference observed at the 2-year follow-up. This finding aligns with some reports in the literature describing sex-related differences in glycoprotein and lipid metabolism, but may also reflect individual factors such as lifestyle, comorbidities, and hormonal status.

4.2. Conclusions

In the context of uveal melanoma, the interpretation of sialic acid levels must be approached with caution. Although elevated values may precede tumor recurrence or metastasis, they can also be influenced by post-therapeutic inflammation. Therefore, the

use of sialic acid as a single biomarker is not recommended; rather, it should be considered a complementary parameter, integrated into a panel of biochemical and imaging investigations, to enable a more accurate and comprehensive monitoring of patient evolution.

5. Conclusions and personal contributions

The present thesis, dedicated to the analysis of the correlation between the clinical evolution of uveal melanoma and its biological and immunological parameters, with a particular focus on hepatic metastasis, represents a personal contribution to the understanding of this rare but highly aggressive malignancy, characterized by its poor prognosis and the significant challenges in diagnosis and treatment.

The chosen topic is not only highly relevant but also methodologically complex, bearing both theoretical and practical implications, as it addresses one of the most severe ophthalmologic malignancies with a high metastatic potential.

The conclusions formulated in this work are grounded in the current scientific literature, but are further strengthened by original findings obtained through clinical, imaging, and immunological studies, all integrated within a multidisciplinary framework aimed at improving the understanding and management of uveal malignant melanoma.

The main objective of this research was to conduct a comprehensive analysis of the correlations between the clinical characteristics of uveal melanoma and its biological and metabolic markers, with the dual purpose of identifying prognostic factors and improving patient stratification, as well as exploring why the liver represents the principal site of metastasis and whether a correlation exists between these biological markers and hepatic dissemination.

Within this work, epidemiological aspects, risk factors, clinical and paraclinical characteristics, and modern diagnostic methods (ultrasound, OCT, angiography, MRI, histopathology) were investigated and integrated into a comprehensive analytical framework. Particular emphasis was placed on serum biomarkers and on redox and metabolic alterations, domains that remain relatively underexplored in the Romanian scientific literature.

The conducted research confirmed that the clinical course of uveal melanoma depends not only on tumor size and location, but also on its molecular and immunological profile. The study demonstrated that:

- Oxidative stress and redox imbalance significantly influence disease progression and therapeutic response.
- Biological markers, such as sialic acid, may hold prognostic value in the monitoring and follow-up of uveal melanoma patients.

These findings underscore the importance of a comprehensive and multidisciplinary assessment, which should not be limited to imaging or histopathological data, but should also incorporate serum biomarkers along with immunological, genetic, and metabolic analyses to achieve a more precise understanding of disease behavior and prognosis.

The most significant aspect of this doctoral thesis lies in its original contribution to the field. This contribution is reflected on several levels:

1. Clinical and paraclinical integration; I actively participated in the examination, diagnosis, and follow-up of patients with uveal melanoma, rigorously documenting their clinical evolution and correlating clinical findings with imaging and biological data. This integrative approach ensured a comprehensive understanding of disease behavior in a real-world clinical context.

2. Analysis of biomarkers and redox parameters is an original component of the research involved the investigation of oxidative imbalances and the prognostic role of sialic acid. The findings demonstrated that these parameters can serve as valuable tools for patient stratification and may help guide therapeutic decision-making, representing a novel perspective in the management of uveal melanoma.

3. Published articles and research dissemination; the results of this study have been published in high-impact scientific journals between 2021 and 2024, underscoring both the originality and scientific relevance of the research, and contributing to the broader understanding of oxidative and immunometabolic mechanisms in uveal melanoma.

Thus, this thesis represents not only a comprehensive synthesis of the existing literature, but also a concrete and original contribution, supported by the author's own documented studies, which may serve as a foundation for future research and further development in this field.

The originality of this thesis lies in its integrated and multidimensional approach to uveal melanoma, combining clinical, imaging, molecular, and metabolic perspectives. Through this comprehensive vision, it has been demonstrated that prognosis cannot be determined based on a single parameter, but rather requires a complex, multifactorial evaluation algorithm.

The practical value of this research is significant: the conclusions support the development of more rigorous monitoring protocols, the identification of patients at high metastatic risk, and the personalization of therapeutic strategies. Furthermore, the results may serve as a foundation for future clinical studies aimed at validating the identified predictive biomarkers.

The applied dimension of this work further reinforces its originality. The obtained data can be used to improve diagnostic protocols and to establish more effective follow-up schemes. For instance, patients showing elevated expression of biomarkers associated with high metastatic potential could benefit from closer monitoring, including periodic hepatic imaging assessments, considering the hepatic tropism of metastases in uveal malignant melanoma.

It should be noted that the number of patients included in this analysis was limited, an inherent characteristic of a rare pathology, which underscores the need for validation of the conclusions through larger, multicentric studies. Future research should extend to the genetic profile of patients and their response to modern immunotherapies, an area in which uveal melanoma remains a major therapeutic challenge. Continued investigation of redox biomarkers and the role of sialic acid could also provide novel therapeutic directions.

Beyond its practical implications, this thesis offers new perspectives for future research. A potential direction would be the integration of metabolic and molecular markers into prognostic assessment models, enabling a comprehensive classification of patients. Moreover, the results obtained open the possibility for validation in larger cohorts and multicenter studies, with the aim of reinforcing these findings and ensuring their broader clinical applicability.

The doctoral research presented herein provides a genuine personal contribution to the understanding of the biological and metabolic mechanisms involved in the evolution of uveal melanoma. By integrating clinical data with biomarker analysis and establishing relevant correlations, this work demonstrates the importance of a multidisciplinary approach in both the diagnosis and treatment of this malignancy. The results represent a significant step forward in elucidating the pathophysiology of this rare disease and may serve as a solid foundation for future research and for the optimization of clinical management in affected patients.

The analytical methods employed in this study were developed and implemented within the institute’s own laboratory, without reliance on commercial reagent kits, which would have entailed substantial costs. This approach not only enabled the adaptation of

methods to the specific objectives of the research but also provided a considerable economic advantage. The in-house preparation of reagents and chemical solutions contributed to reducing costs and enhancing accessibility of biochemical investigations, while maintaining high standards of accuracy and reproducibility.

The overall conclusion emerging from this study is that uveal malignant melanoma must be approached from a multidimensional perspective. Both prognosis and patient management should not rely solely on clinical or anatomical criteria, but must also integrate a broad spectrum of biological markers and oxidative stress parameters. This complex and integrated vision represents a cornerstone of precision medicine, in which therapeutic strategies and follow-up protocols are tailored to the individual characteristics of each patient.

Thus, this thesis brings an original contribution to the scientific literature through the following key aspects:

- Integration of clinical, biological, and redox balance data within a unified analytical framework;
- Identification of novel correlations between biological markers, oxidative stress indicators, and clinical evolution;
- Highlighting of the fundamental differences between uveal melanoma and cutaneous melanoma in terms of biology, progression, and systemic behavior;
- Proposing new directions for the development of personalized medicine in ocular oncology.

In conclusion, the present research represents a valuable and original scientific contribution, with major theoretical and practical implications, opening new perspectives for the diagnosis, monitoring, and treatment of patients with uveal melanoma.

An essential observation emerging from this thesis is that traditional classification systems—particularly the TNM classification and anatomical–clinical staging—retain their descriptive and orientative value in current medical practice, yet they are no longer sufficient for accurate risk stratification or reliable prognostic prediction. These findings underscore the necessity of incorporating molecular, metabolic, and immunological parameters into future classification and prognostic models for uveal melanoma.

Tumor size, local extension, and the presence of regional or distant metastases are indeed important prognostic indicators; however, the evolutionary heterogeneity of uveal melanoma clearly demonstrates that patients within the same clinical stage may follow entirely different disease trajectories.

At present, laboratory and genetic data have surpassed clinical classifications in terms of predictive value. The Cancer Genome Atlas (TCGA) Project has successfully redefined uveal melanoma by identifying its characteristic molecular profiles. The presence of chromosome 3 monosomy, 8q gain, and 6q loss represent essential genetic alterations that determine the true prognosis of the patient, possessing a much higher predictive power than tumor size or anatomical location. Consequently, patients exhibiting monosomy 3 and 8q gain face a high risk of hepatic metastasis, even when the primary tumor appears relatively small or clinically "favorable."

Cytogenetics and the TCGA classification have introduced the concept of genetic subgroups with distinct prognostic significance, enabling a personalized approach to disease management. For example, uveal melanomas with chromosome 3 disomy and chromosomal gain at 6p display a significantly better prognosis and are categorized as low-risk tumors, regardless of their TNM stage. This observation highlights that clinical and anatomical data remain useful for descriptive purposes but are insufficient for accurate prognostic prediction.

From this perspective, clinical and anatomical classifications have become subordinate to molecular and genetic frameworks. While TNM staging remains necessary for standardized clinical communication and basic therapeutic decision-making, the true prognostic value and the pathway toward personalized therapy stem from the analysis of the tumor's genetic profile. The integration of molecular and cytogenetic data into clinical practice represents a major direction in modern ocular oncology, and the research presented in this thesis reinforces the concept that a multimodal approach, with emphasis on biomarkers and cytogenetics, provides the most accurate reflection of disease evolution.

Although the main objective of this thesis was to correlate biological parameters and oxidative stress markers with the clinical evolution of uveal malignant melanoma and to demonstrate the hepatic tropism of systemic metastasis in relation to these biological and redox balance markers, the findings presented suggest that the metabolic component also plays a crucial role in this ocular malignancy with major systemic implications.

From this perspective, just as there is a TNM classification for tumors and, more recently, a TCGA classification based on cytogenetic subgroups, there should also exist a metabolic classification or metabolic map that accounts for both tumor status and its capacity for systemic metastasis.

Such a metabolic classification system should be developed not only for uveal malignant melanoma, but for all tumor types, since without metabolic reprogramming, tumors would be unable to survive, proliferate, and achieve systemic dissemination.

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List of published works:

2021:

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