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Correlation of Tumor Regression Patterns of Choroidal Melanoma to Prognosis

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Original Article

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Abstract

Introduction: Nowadays, episcleral brachytherapy is the leading treatment for medium and some large choroidal melanomas as it spares the eye and, in a subset of patients, a useful vision. Thus far, a great amount of studies have demonstrated the correlation between initial dimensions and its regression rate with prognosis, but available data concerning regression patterns as a closer surrogate for determining prognosis, is still scarce.

Aim: To characterize correlation between initial dimensional parameters with survival rates and to assess regression patterns of thickness, largest basal diameter and cross-sectional area, following iodine-125 plaque brachytherapy in order to establish potential surrogate markers that correlate with the same outcomes.

Material and methods: We retrospectively analyzed 101 patients with choroidal melanoma who were treated, between 2013 and 2019, with iodine-125 brachytherapy at Centro Hospitalar e Universitário de Coimbra. Regression patterns were assessed through standardized B-scan ultrasonography.

Results: A first assessment of initial dimensional parameters allowed us to identify a statistically significant correlation between initial largest basal diameter ≤11.72 mm, a higher metastasis free-survival (p=0.050) and a higher enucleation free-survival (p=0.080), whereas initial largest basal diameter >11.72 mm was positively correlated with a higher overall survival and cancer specific survival (p=0.047). Furthermore, initial thickness >6.13mm had a statistically significant correlation with a higher overall survival and cancer specific survival (p=0.015). Regarding to regression patterns for thickness, patients were classified into four groups according to observed regression behavior: exponential regression (76.4%), linear regression (7.9%), no regression (5.6%) and zig-zag pattern (10.1%). The corresponding percentages for cross-sectional area were 73.0%, 13.5%, 4.5% and 9.0%. Linear regression pattern group for thickness demonstrated a statistically significant correlation with higher locoregional progression free-survival (p=0.016) and higher overall survival and cancer specific survival (p=0.011).

Conclusions: Initial largest basal diameter and thickness demonstrated to be consistent prognostic factors of tumor prognosis and linear regression pattern for thickness can potentially be associated with several favorable prognostic outcomes.

Keywords: Choroidal melanoma, brachytherapy, tumor regression, prognosis, ultrasound.

Resumo

Introdução: Atualmente, a braquiterapia episcleral constitui o tratamento de eleição em tumores de tamanho médio e alguns de tamanho grande, pois poupa o globo ocular e, num subgrupo de doentes, uma visão útil. Até aos dias de hoje, uma grande quantidade de estudos avaliaram a correlação entre a dimensão inicial e o padrão de regressão com o prognóstico. No entanto, a informação disponível sobre os padrões de regressão na avaliação do prognóstico continua a ser insuficiente.

Objetivo: Correlacionar as dimensões iniciais, a taxa de sobrevivência e determinar os padrões de regressão da espessura, do maior diâmetro basal e da área de superfície, após braquiterapia com iodo-125, a fim de estabelecer potenciais fatores prognósticos.

Materiais e métodos: Analisámos retrospetivamente um grupo de 101 doentes com melanoma da coroideia, tratados no Centro Hospitalar e Universitário de Coimbra, entre 2013 e 2019, com braquiterapia com iodo 125. Os padrões de regressão foram avaliados através de ecografia em modo B padronizada.

Resultados: Inicialmente avaliámos os vários parâmetros dimensionais iniciais e pudemos identificar uma correlação estatisticamente significativa entre um maior diâmetro basal ≤11,72 mm, uma taxa de sobrevivência livre de metastização superior (p=0,050) e uma taxa de sobrevivência livre de enucleação superior (p=0,080), enquanto que um maior diâmetro basal >11,72 mm foi positivamente correlacionado com uma taxa de sobrevivência global e uma taxa de sobrevivência específica de doença superiores (p=0,047). Adicionalmente, a presença de uma espessura inicial >6,13mm apresentou uma correlação estatisticamente significativa com uma maior sobrevivência global e uma sobrevivência específica de doença (p=0,015). Relativamente aos padrões de regressão relativos à espessura, os doentes foram classificados em quatro grupos: regressão exponencial (76,4%), regressão linear (7,9%), sem regressão (5,6%) e padrão zig-zag (10,1%). As percentagens correspondentes para a área de superfície tumoral foram 73,0%, 13,5%, 4,5% e 9,0%. O grupo com um padrão de regressão linear para a espessura demonstrou ter uma correlação estatisticamente significativa com uma maior sobrevivência livre de progressão locorregional (p=0,016), uma maior sobrevivência global e uma sobrevivência específica de doença (p=0,011).

Conclusões: O maior diâmetro basal e a espessura iniciais demonstraram ser fatores consistentes para o prognóstico destes tumores, e o padrão de regressão linear da espessura pode ser associado a um prognóstico favorável.

Palavras-chave: Melanoma da coroideia, braquiterapia, regressão tumoral, prognóstico, ecografia.

Abbreviations

AJCC - American Joint Committee on Cancer
CHUC - Centro Hospitalar e Universitário de Coimbra
COMS - Collaborative Ocular Melanoma Study
CSS - Cancer Specific Survival
EBT - Episcleral Brachytherapy
EFS - Enucleation Free-Survival
LRPFS - Locoregional Progression Free-Survival
MFS - Metastasis Free-Survival
SD - Standard Deviation
SPSS - Statistical Package for the Social Sciences
OS - Overall Survival

Introduction

Melanomas of the ocular and adnexal structures comprise 3 to 5% of all melanomas and, within these, choroidal melanoma has been established as the most common primary intraocular malignancy in adults, accounting for 85% of all ocular melanomas.[1-6]

In general, uveal melanoma is more commonly seen in an older age group, resulting in a median age diagnosis of 61.4 years.[4] Differences in gender had also been identified and previous studies have shown that there was an overall significantly higher age specific incidence in men aged more than 45 years, when compared with women in the same age range.[3]

Several risk factors have been indicated, such as UV light exposure which includes occupational setting, race, skin phototype and genetic predisposition, but up to now, it hasn't been found a consistent correlation.[3,7]

Despite being a relatively rare disease, 10-year mortality rate remains closer to 50% and, in the presence of metastatic disease, choroidal melanoma can be potentially fatal after 6 to 12 months.[8-10] Regarding long-term prognosis of uveal melanomas, choroidal melanoma has been associated with a worse prognosis in comparison with iris melanoma. On the other hand, the inverse situation is presented when the comparison is made with ciliary body melanoma.[3,5,6]

Nowadays, it is known that the diagnosis of this entity is best achieved through clinical examination, which includes indirect ophthalmoscopy complemented by ultrasonography.

Based on the previous landmark article conducted by Zimmerman, McLean and Foster, enucleation was positively correlated with a transient rise in post-treatment mortality.[11] This was associated with the decreased levels of angiostatin, previously produced by the tumor cells, leading to the growth of micrometastases. Zimmerman, McLean and Foster's theory propelled the improvement of alternative therapies such as episcleral brachytherapy. However, current evidence in literature remains contradictory and hasn't attributed a consistent rise in mortality rate immediately after enucleation.[11]

Multicenter randomized clinical trials from the Collaborative Ocular Melanoma Study (COMS) group have shown repeated evidence of no significant difference in survival, local tumor control and metastasis prevention between patients with medium sized tumors, treated with primary enucleation or episcleral brachytherapy (EBT) with a standard dose of 85 Gy.[12-14]

Overall, the chosen method of treatment has not influenced the prognosis in a large scale and, nowadays, EBT is the leading treatment modality for medium and

some large melanomas, as it spares the eye and, in a subset of patients, the useful vision, when compared to enucleation.[15-17]

EBT presents a 5 year local tumor control rate of 89.7% and a metastatic disease-free survival rate of 90%.[18] This modality allows us to deliver a highly concentrate radiation dose to the tumor with less radiation of the surrounding tissues. Despite this, EBT is not an innocuous modality and radiation induced complications are responsible for a significant morbility rate.[19-21]

Several prognostic factors have been pointed out, including clinical, cytologic, histopathologic, cytogenetic and molecular genetic features.[3,22,23]

Previous literature emphasizes not only that magnitude of radiation-induced tumor shrinkage reflects, to some extent, the intrinsic radiosensitivity of tumoral cells, but also that rapidly proliferating cells are often more sensitive to radiation.[24] Nevertheless, tumors that proliferate rapidly and shrink immediately after irradiation are often more resistant to a cure by EBT. Other factors such as kinetics of tumors cells death, tumor stroma influence and host reaction against residual tumor are also important in the evaluation of regression.[25]

Given that a prognostic biopsy sample is not obtained in every patient submitted to irradiation, choroidal melanoma regression patterns, assessed through B-scan ultrasound follow-up, have been explored as a potential surrogate marker. Research in this subject is scarce and, although most studies agree that tumor regression is a prognostic factor to take into consideration, some contradictory results have been obtained in previous studies.[26]

To evaluate choroidal melanoma regression, several clinical features were taken into account and initial tumor thickness and size were consistently established as relevant parameters to long-term prognosis.[21,23,27-30]

Most studies agree that initially large uveal melanomas regressed faster and in a greater proportion than smaller ones. Moreover, rapid initial regression, mainly in the first 6 to 12 months after radiation, was also associated with higher mortality from metastatic disease[24,25,31,32], but these results have not been consistent.[26,33,34]

Taking into account that uveal melanomas come in a wide variety of shapes, such as flat, oval, dome, mushroom, lobulated and irregular, the regression or progression of the tumor may be associated with a change in shape. For this reason, it is not certain that measurement of tumor thickness would accurately reflect the tumor volume regression.[35]

In addition, some studies have shown that the regression pattern of an individual uveal melanoma may differ widely, from more or less rapid decrease, through no change or even increase in thickness. Moreover, authors of the same studies found out

that regression of tumor thickness differed substantially from that of cross-sectional area and speculated that this last parameter could possibly be used as a closer surrogate for tumor volume.[23,35]

The aims of this study were not only to evaluate the correlation between initial dimensional parameters with overall and cancer specific survival, tumor progression, enucleation rate and emergence of metastatic disease, but also to assess regression patterns of thickness, largest basal diameter and cross-sectional area of choroidal melanomas treated after irradiation, in order to establish potential surrogate markers that correlate with the same outcomes.

Material and Methods

Study design and Eligibility criteria

This is a retrospective case series review with a set of 101 patients with choroidal melanoma who were treated with primary iodine-125 EBT at Centro de Referência de Onco-Oftalmologia, Centro Hospitalar e Universitário de Coimbra (CHUC), between September 2013 and October 2019 (inclusion ratio of 95% of all uveal melanomas).

Eligible for this study were all consecutive patients with the diagnosis of choroidal melanoma without ciliary body and iris extension submitted to episcleral brachytherapy, which were measured at the time of diagnosis and at least twice during follow-up. Patients were reviewed in the Onco-Ophthalmology Reference Center, clinically and by ultrasonography, during the first 5 years after starting irradiation. These follow up visits were scheduled to months 1, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60.

Exclusion criteria included patients with iris and primary ciliary body melanomas, tumors measured using other equipment and patients submitted to previous silicone oil tamponade, as it hampered evaluation by ultrasound.

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of Centro Hospitalar e Universitário de Coimbra (CHUC).

Ultrasonography

Tumor measurements were collected with the 20-MHz probe of Aviso^{TM} ultrasound platform (Quantel Medical^{TM}, France). The magnetic 20 MHz probe for posterior pole has a transducer frequency of 20 MHz, an angle of exploration of 50°, with a 24 to 26 mm focus, an axial resolution of 100μm and a lateral resolution of 250μm.

In order to achieve the purpose of this study, tumor largest basal diameter, thickness and cross sectional area from stored scans were re-measured, by consensus of two investigators. A mouse driven cursor was used to manually mark the inner scleral surface of the tumor and its apex, perpendicular to the largest basal diameter, to measure the linear distance between these points and, posteriorly, to delineate the tumor area. Representative digitized scans were stored at the time of each diagnostic and follow-up visit.

Brachytherapy

The choice of this treatment modality was, to a great extent, dependent of the fellow eye's status, tumor location, likelihood of lowering radiation damage to the optic nerve and retina by plaque design and seed positioning, as well as the preference of patient.

Iodine-125 radioactive plaques (COMS standard plaques, Trachsel Dental Studio, Inc., Minnesota, USA and BEBIG GmbH, Berlin, Germany and ROPES plaques, Radiation Oncology Physics and Engineering Services, Australia) loaded with radioactive seeds were sutured adjacent to the sclera and remained implanted for a variable period of time, depending on previous dosimetric studies. These plaques were placed and removed under general anesthesia by a multidisciplinary team.

Iodine-125 radioactive plaques were used to treat tumors up to 13 mm thick (median 6.13; IQR 3.6), and with a largest basal diameter up to 18.7 mm (median 11.72 mm; IQR 3.8), based on COMS classification system and guidelines from the American Brachytherapy Society.[16] Maximum plaque size was limited to 20 mm, thus conditioning the selection of patients and presenting one of the more considerable limitations of this therapy towards larger tumors.

We generally intended to deliver an isodose of 85 Gy to the tumor apex during a maximum period of 10 days. Throughout the course of treatment, patients were hospitalized in a controlled environment with several safety measures.

Statistical Analysis

To perform statistical analysis, the investigators used IBM® SPSS Statistics Software version 26.

Regarding descriptive statistics, skewed continuous variables were presented as median and range, as opposed to normally distributed variables, reported as mean and standard deviation (SD) with a 95% confidence interval, after testing variables for normality with Kolmogorov-Smirnov test. Absolute and relative frequencies with were presented for the categorical variables.

Regression of tumor thickness, basal diameter and cross-sectional area through time was evaluated for each patient and patterns were categorized as "exponential regression", "linear regression", "no regression" or “zig zag pattern”.

For the group of patients with exponential regression, data adjustment was achieved by using Prism GraphPad, based on the following equation:

$$y = (1 - y_0) \times e^{-\frac{ln2}{T_{\frac{1}{2}}}} + y_0$$

For exponential regression, all follow-up measures were normalized for the initial value:

$$y = \frac{measure\ for\ month\ X}{initial\ measure}$$

Plateau (y_0) corresponds to the value at which stability is achieved after a decreasing period. $T_{\frac{1}{2}}$ represents the time needs to achieve the half size between the initial measure and the plateau.

Adjustment through graphic representation in combination with coefficient determination were used to reclassify patterns that were not included in the exponential regression pattern.

For inferential analysis, Kaplan–Meier estimates were obtained for the following outcomes: Metastasis-Free Survival (MFS), Locoregional Progression-Free Survival (LRPFS), Enucleation-Free Survival (EFS), Overall Survival (OS) and Cancer Specific Survival (CSS). Log-rank test was performed to compare survivals between groups.

A type I error of 0.05 was considered for all comparisons.

Results

Demographic and Clinical Characteristics

A total of 101 patients (40 males, 61 females) have been included in this study. Patient's age ranged between 26 and 87 years old, with the mean age of 59.5 ± 1.3 years old. Of the total 101 patients, 54 patients had the right eye affected whereas 47 had the left eye affected. Demographic characteristics are summarized in Table 1.

Table 1. Baseline demographics.

Age at diagnosis (years)		
Mean	59.5	
Minimum	24	
Maximum	85	
Gender		
	n	**%**
Male	40	39.6
Female	61	60.4
Affected Eye		
	n	**%**
Right	54	53.5
Left	47	46.5

Regarding to the location of the tumor, the majority, represented by 53 cases, were located temporally (52.5%), followed by 26 tumors on nasal division (25.7%), 4 with a peripapillary location (4%), 3 tumors covering macula region (3%), 7 located inferiorly (6.9%) and 8 located superiorly (7.9%).

Episcleral braquitherapy treatment period varied between 4 to 10 days, with a median treatment duration of 6 days.

The median initial largest basal diameter, thickness and cross-sectional area of the tumor were 11.72 mm (IQR 3.8), 6.13 mm (IQR 3.6) and 41.6mm^2 (IQR 34.7), respectively.

Tumor features and clinical information are presented in Table 2.

Table 2. Tumor characteristics and clinical variables.

Median tumor thickness (mm)	6.13 mm	
Minimum	2.8 mm	
Maximum	13.0 mm	
Median largest basal diameter (mm)	11.72 mm	
Minimum	6.9 mm	
Maximum	18.7 mm	
Median cross-sectional area (mm^2)	41.6 mm^2	
Minimum	12.0 mm^2	
Maximum	132.0 mm^2	
Location		
	n	**%**
Temporal	53	52.5
Nasal	26	25.7
Peripapillary	4	4.0
Macular	3	3.0
Inferior	7	6.9
Superior	8	7.9
EBT duration (days)		
Median	6	
Minimum	4	
Maximum	10	
Plaque design		
	n	**%**
COMS 12 mm	17	16.8
COMS 14 mm	23	22.8
ROPES notched 15 mm	22	21.8
COMS 16 mm	17	16.8
COMS 18 mm	19	18.8
COMS 20 mm	3	3.0

According to the classification of American Joint Committee on Cancer (AJCC) for uveal melanoma[33] 14 (13.9%) of the 101 choroidal melanomas represented size T1a; 47 (46.5%) were T2a; 1 (1.0%) was T2b; 38 (37.6%) were T3a; and 1 (1.0%) was T4a. Following the same classification, 14 patients were categorized as stage I (referring to T1a, N0, M0), 47 were categorized as stage IIA (referring to T1b-d or T2a, N0, M0), 39 were categorized as stage IIB (referring to T2b or T3a, N0, M0) and 1 was categorized as stage IIIA (referring to T2c-d or T3b-c or T4a N0, M0).

The staging classification is summarized in Table 3.

Table 3. Staging classification.

TNM			
T			**n**
	T1	Tumor base ≤ 9 mm with thickness ≤ 6mm Tumor base 9.1-12 mm with thickness ≤ 3 mm	
		T1a*	14
	T2	Tumor base ≤ 9 mm with thickness 6.1-9 mm Tumor base 9.1-12 mm with thickness 3,1-9 mm Tumor base 12.1-15 mm with thickness ≤ 6mm Tumor base 15.1-18 mm with thickness ≤ 3mm	
		T2a*	47
		T2b**	1
	T3	Tumor base 3.1-9 mm with thickness 9.1-12 mm Tumor base 9.1-12 mm with thickness 9.1-15 mm Tumor base 12.1-15 mm with thickness 6.1-15mm Tumor base 15.1-18 mm with thickness 3.1-12 mm	
		T3a*	38
	T4	Tumor base 12.1-15 mm with thickness > 15 mm Tumor base 15.1-18 mm with thickness > 19 mm Tumor base > 18 mm with any thickness	
		T4a*	1
N			
	N0	No regional lymph node involvement	101
M			
	M0	No distant metastasis by clinical classification	101

STAGE GROUP	**n**	**%**
I	14	13.9
IIA	47	46.5
IIB	39	38.6
IIIA	1	1.0

* without ciliary body involvement and extraocular extension
** with ciliary body involvement

Side-Effects

Despite the advantages already mentioned, episcleral braquitherapy is not a treatment modality without side-effects. During clinical evaluation conducted in the follow-up visits, with a median follow-up of 27 months (range, 2-65), several side-effects secondary to radiation exposure were detected and recorded. Corresponding frequencies of all cases mentioned are described in Table 4.

Table 4. Side-effects secondary to radiation exposure.

Side effects		
	n	**%**
Cataract	42	41.6
Central retinal vein occlusion	1	1.0
Hemovitreal hemorrhage	23	22.8
Intratumoral hemorrhage	19	18.8
Iridocyclitis	1	1.0
Macular edema	12	11.9
Neovascular glaucoma	20	19.8
Optic neuropathy	9	8.9
Peripapillary detachment	2	2.0
Phthisis bulbi	1	1.0
Radiation retinopathy	40	39.6
Retinal detachment	25	24.8
Rubeosis iridis	9	8.9
Superficial punctate keratitis	12	11.9

Four of the total patients were submitted to panretinal photocoagulation to prevent progression of radiation retinopathy. Forty patients were treated with intravitreal bevacizumab injections, with a maximum number of nine injections, and two patients underwent treatment with dexamethasone intravitreal implant (Ozurdex®) for cystoid macular edema.

Regression Patterns

Regression patterns associated to longitudinal evolution of thickness, largest basal diameter and cross-sectional area, evaluated during each follow up visit, were based on values obtained by resorting to ultrasonography.

Throughout the evaluation we were able to divide patients into four categories of regression patterns: exponential regression, linear regression, no regression and zig-zag pattern. From this analysis, we excluded 12 patients who had only three acceptable follow-up measurements and could not be accurately integrated into any group, as the regression curve required more than three measurements of each parameter.

Considering the four categories mentioned previously, 89 of the total patients were classified according to following graphics (Fig.1).

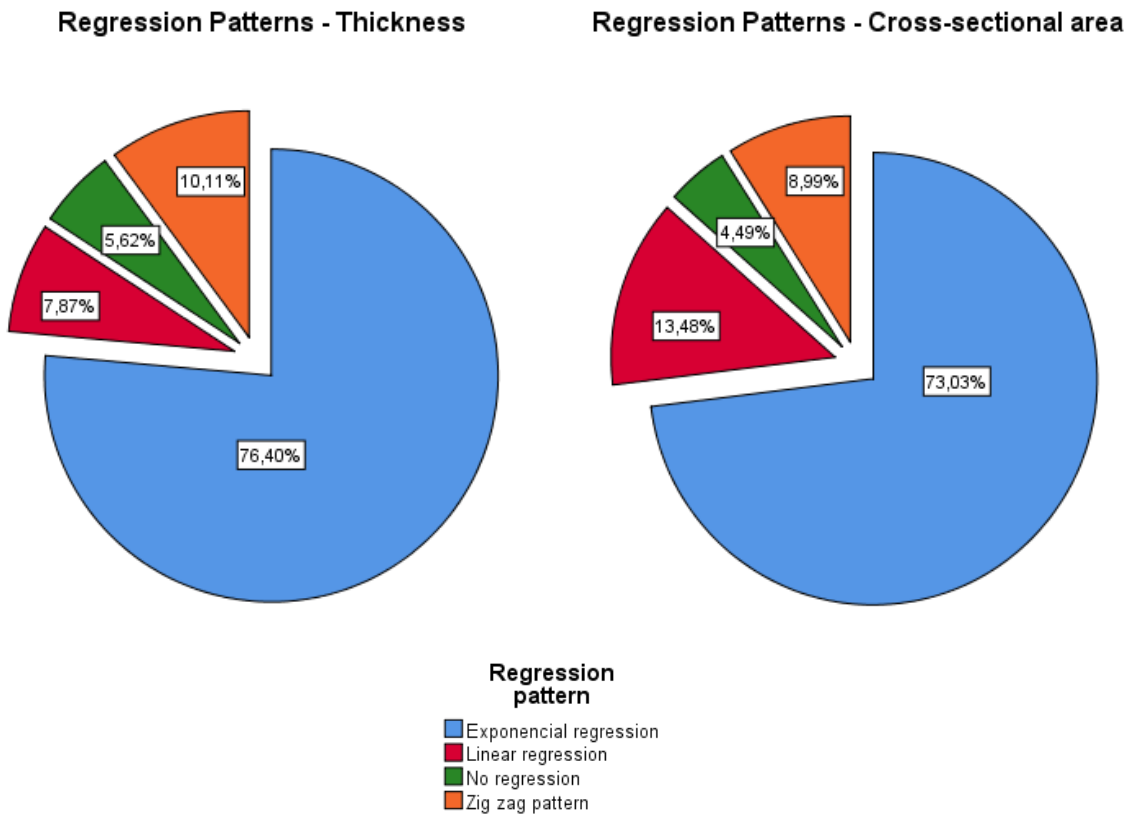

Figure 1. Regression patterns according to category for thickness and cross-sectional area.

Regarding the largest basal diameter, after evaluation of each adjustment graphic representation we were able to detect a substantial temporal variability of data in most cases, hampering the possibility of a correct categorization of patterns in this parameter.

In the exponential regression group for thickness, data adjustment equation led us to a plateau (y_0) with a range between 0 and 0.90 and a median value of 0.46. $T_{\frac{1}{2}}$ ranged between 0.42 and 32.27 months and the median value was 3.06 months.

In the cross-sectional area, the plateau (y_0) ranged between 0 and 0.94, with a median value of 0.389, and $T_{\frac{1}{2}}$ ranged between 0.3 and 19.72 months, with a median value was 2.50 months.

Survival Rates

By the end of October 2019, metastatic disease was detected in 12 patients and a local recurrence was identified in 5 patients that underwent enucleation.

Two and five year rates of MFS were 89.6% and 81.6%, respectively, whereas two, five and eight year rates of LRPFS were 94.6%, 80.4% and 67.1%, respectively. EFS rates was 99.0% at two years, 97.6% at five years and 84% at 8 years (Fig. 2, 3 and 4).

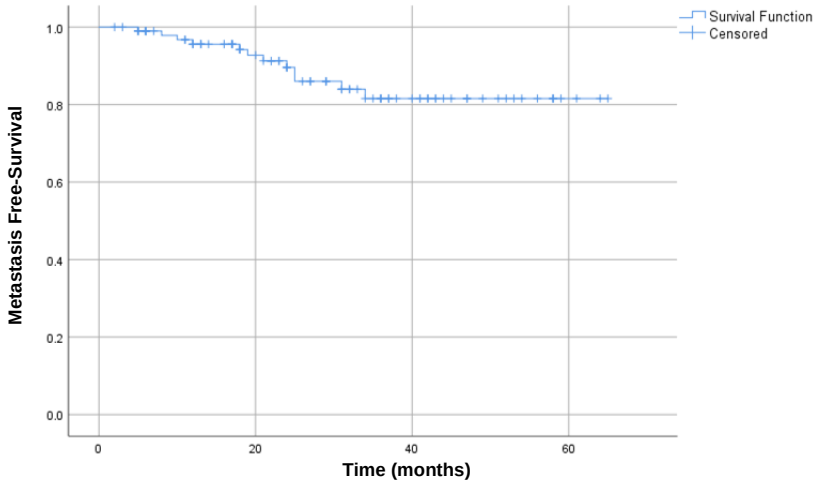

Figure 2. Metastasis Free-Survival (MFS).

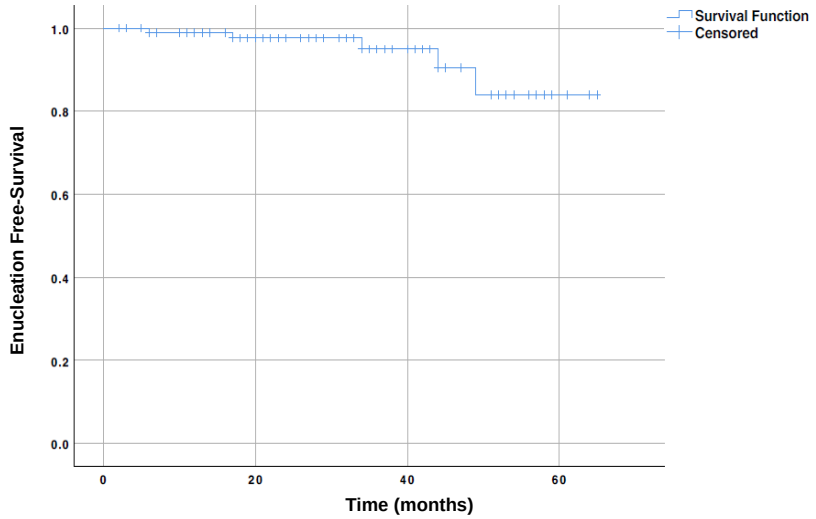

Figure 3. Enucleation Free-Survival (EFS).

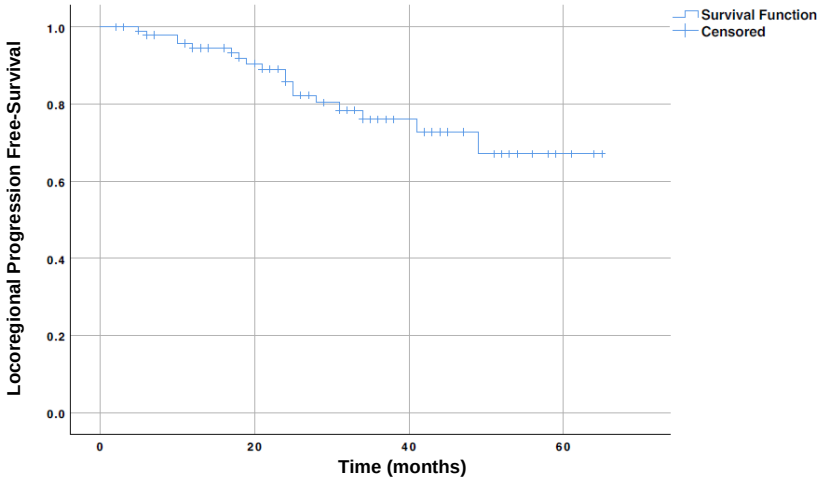

Figure 4. Locoregional Progression Free-Survival (LRPFS).

Regarding to OS and CSS, the two and five year rates 96.5% and 88.8% were obtained, respectively, for both outcomes (Fig. 5).

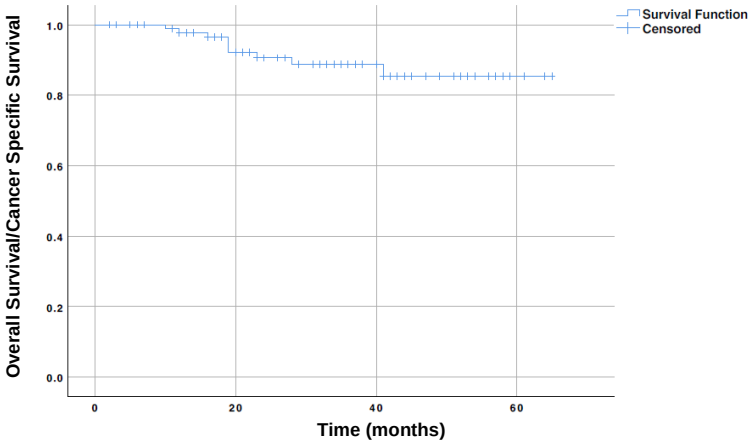

Figure 5. Overall Survival (OS) and Cancer Specific Survival (CSS).

Correlation between Survival Rates and Initial Dimensional Parameters

To evaluate the impact of initial thickness, largest basal diameter and cross-sectional area, we have established two groups for each parameter based on the median value as cut-off, determining a group of 51 patients with a parameter's value less than or equal to the median and a group of 50 patients with a parameter's value higher than the median. Furthermore, the same outcomes mentioned previously were obtain for each group and parameter.

Beginning with results for Largest Basal Diameter parameter, we have found a significant difference between the two established groups concerning MFS, EFS, OS and CSS with a p-value of 0.050, 0.008 and 0.047, respectively. As it was stated before, OS and CSS are the same since no patients died of other causes. On the other hand, there was not a significant difference between groups concerning LRPFS (p=0.588).

Through the assessment of results concerning to the two groups of Thickness parameter, we were able to find a significant difference in OS and CSS (p=0.015), contrarily to the remaining survival parameters.

Regarding to Cross-sectional Area parameter, there was not a significant difference between the two groups, in any of the survival rates. Survival rates at two and five years, according to each parameter are displayed on Tables 5 and 6.

Table 5. Metastasis Free-Survival and Locoregional Progression Free-Survival for each dimensional parameter.

	MFS			LRPFS		
	2 year rate (%)	5 year rate (%)	p	2 year rate (%)	5 year rate (%)	p
Largest Basal Diameter						
≤ 11.72 mm	94.1	94.1	**0.050**	89.3	60.3	0.588
> 11.72 mm	79.8	72.8		82.9	82.9	
Thickness						
≤ 6.13 mm	92.8	84.0	0.810	90.7	77.7	0.936
> 6.13 mm	84.6	81.2		79.9	62.5	
Cross-sectional Area						
≤ 41.6 mm^2	95.4	95.4	0.099	93.3	85.5	0.132
> 41.6 mm^2	80.8	74.3		76.4	58.7	

MFS = Metastasis Free-Survival; LRPFS = Locoregional Progression Free-Survival

Table 6. Enucleation Free-Survival, Overall Survival and Cancer Specific Survival for each dimensional parameter.

	EFS			OS/CSS		
	2 year rate (%)	5 year rate (%)	p	2 year rate (%)	5 year rate (%)	p
Largest Basal Diameter						
≤ 11.72 mm	94.9	62.7	**0.008**	97.1	97.1	**0.047**
> 11.72 mm	100.0	100.0		82.6	77.1	
Thickness						
≤ 6.13 mm	97.8	97.8	0.438	91.7	70.7	**0.015**
> 6.13 mm	94.2	77.8		94.9	94.9	
Cross-sectional Area						
≤ 41.6 mm^2	97.8	89.7	0.811	94.7	91.1	0.779
> 41.6 mm^2	97.9	82.2		87.7	83.1	

EFS = Enucleation Free-Survival; OS = Overall Survival; CSS = Cancer Specific Survival

Correlation between Survival Rates and Regression Patterns

Through further statistical analysis, we were able to divide patients from the exponential regression group into two subsets, according to median value of $T_{\frac{1}{2}}$ and plateau, regarding thickness and cross-sectional area.

In respect to thickness and corresponding $T_{\frac{1}{2}}$, 26 patients took 2.06 months or less to reach 50% of the total decrease in thickness, whereas 42 patients took more than 2.06 months. When the plateau was evaluated, both groups contemplated a total of 34 patients, considering that half of them had a plateau less than or equal to 0.46 and the other half had a plateau superior to 0.46.

Concerning to cross-sectional area and $T_{\frac{1}{2}}$, 33 patients took 2.31 months or less to reach 50% of the total decrease in thickness, whereas 32 patients took more than 2.31 months. In the evaluation of plateau, 33 patients had a plateau less than or equal to 0.389 and 31 had a plateau superior to 0.389.

Subsequently, we have tested the potential correlation between these groups, according to the survival rates mentioned previously.

Regarding to thickness, patients with $T_{\frac{1}{2}}$ less than or equal to 2.06 months had a 2-year MFS, LRPFS and EFS rates of 70.1%, 70.1% and 66.7%, respectively. Similarly to previous, findings OS and CSS rates were coincident, exhibiting a 2-year rate of 96.2%. On the other hand, patients with $T_{\frac{1}{2}}$ superior to 2.06 months had 2-year MFS, LRPFS and EFS rates of 87.8%, 84.2 and 95.0%, respectively, as the 2-year rate OS and CSS was 90.8%.

Concerning the plateau, patients with less than or equal to 0,46 had a 2-year MFS, LRPFS and EFS rates of 85.5%, 80.9% and 94.1%, respectively. OS and CSS rates were also coincident, exhibiting a 2-year rate of 86.3%. Patients with a plateau superior to 0.46 had a 2-year MFS, LRPFS and EFS rates of 79.1%, 79.1% and 100.0%, respectively, as the 2-year rate OS and CSS was 100.0%.

Our analysis demonstrated that there was not a significant difference between groups in any of the survival rates (Tables 7 and 8).

Table 7. Metastasis Free-Survival and Locoregional Progression Free-Survival according to thickness's $T_{\frac{1}{2}}$ and plateau.

THICKNESS				
	MFS 2 year rate (%)	**p**	**LRPFS** 2 year rate (%)	**p**
$\boldsymbol{T_{\frac{1}{2}}}$				
≤ 2.06 months	72.3	0.080	70.1	0.061
> 2.06 months	91.7		84.2	
Plateau				
≤ 0.46	85.5	0.804	80.9	0.764
> 0.46	79.1		79.1	

MFS = Metastasis Free-Survival; LRPFS = Locoregional Progression Free-Survival

Table 8. Enucleation Free-Survival, Overall Survival and Cancer Specific Survival according to thickness's $T_{\frac{1}{2}}$ and plateau.

THICKNESS				
	EFS 2 year rate (%)	**p**	**OS/CSS** 2 year rate (%)	**p**
$\boldsymbol{T_{\frac{1}{2}}}$				
≤ 2.06 months	100.0	0.569	88.9	0.309
> 2.06 months	94.4		96.2	
Plateau				
≤ 0.46	94.1	0.233	86.3	0.061
> 0.46	100.0		100.0	

EFS = Enucleation Free-Survival; OS = Overall Survival; CSS = Cancer Specific Survival

In regard to cross-sectional area's data, patients with $T_{\frac{1}{2}}$ less than or equal to 2.31 months exhibited a 2-year MFS, LRPFS and EFS rates of 70.2%, 67.6% and 96.4%, respectively. OS and CSS rates were coincident, displaying a 2-year rate of 83.3%. Furthermore, patients with $T_{\frac{1}{2}}$ superior to 2.31 months had a 2-year MFS, LRPFS and EFS rates of 90.8%, 85.9 and 93.8%, respectively, as the 2-year rate OS and CSS was 92.9%.

Concerning the plateau, patients with less than or equal to 0.389 had a 2-year MFS, LRPFS and EFS rates of 82.9%, 77.9% and 93.8%, respectively. OS and CSS rates were also coincident, exhibiting a 2-year rate of 90.0%. Patients with a plateau superior to 0.389 had 2-year a MFS, LRPFS and EFS rates of 80.4%, 77.2% and 96.0%, respectively, as the 2-year rate OS and CSS was 91.4%.

Similarly to previous data demonstrated for thickness, there was not a significant difference between groups in any of the survival rates (Tables 9 and 10).

Table 9. Metastasis Free-Survival and Locoregional Progression Free-Survival according to cross-sectional area's $T_{\frac{1}{2}}$ and plateau.

CROSS-SECTIONAL AREA				
	MFS 2 year rate (%)	**p**	**LRPFS** 2 year rate (%)	**p**
$\boldsymbol{T_{\frac{1}{2}}}$				
≤ 2.31 months	70.3	0.157	67.7	0.261
> 2.31 months	87.0		82.3	
Plateau				
≤ 0.389	82.9	0.581	77.9	0.819
> 0.389	76.6		73.5	

MFS = Metastasis Free-Survival; LRPFS = Locoregional Progression Free-Survival

Table 10. Enucleation Free-Survival, Overall Survival and Cancer Specific Survival according to cross-sectional area's $T_{\frac{1}{2}}$ and plateau.

CROSS-SECTIONAL AREA				
	EFS 2 year rate (%)	**p**	**OS/CSS** 2 year rate (%)	**p**
$\boldsymbol{T_{\frac{1}{2}}}$				
≤ 2.313 months	96.4	0.732	83.6	0.400
> 2.313 months	93.8		92.9	
Plateau				
≤ 0.389	93.8	0.634	90.0	0.769
> 0.389	96.0		91.7	

EFS = Enucleation Free-Survival; OS = Overall Survival; CSS = Cancer Specific Survival

When correlating the established regression patterns with the same survival rates, the distribution of patients into the four groups was not equitable.

Regarding to thickness, the exponential regression group comprehended a total of 68 patients (76.4%), while the linear regression group, the no regression group and the zig zag pattern group were constituted by 7 (7.9%), 5 (5.6%) and 9 (10.1%) patients, respectively.

Similarly, the distribution concerning to cross-sectional area displays a total of 65 patients (73.0%) in the exponencial regression group, 12 patients (13.5%) in the linear regression group, 4 patients (4.5%) in the no regression group and lastly 8 patients (9.0%) in the zig-zag pattern group.

Concerning to thickness, we were able to observe, in the exponential regression group, a 5-year MFS, LRPFS and EFS rates of 82.5%, 72.7% and 88.5%, respectively. OS and CSS rates were coincident, displaying a 5-year rate of 92.5%. Regarding to linear regression group we obtained a 5-year MFS, LRPFS and EFS rates of 100.0%, 85.7% and 87.5%, respectively, while OS and CSS rates displayed a 5-year rate of 92.5%. Furthermore, in the no regression group we observed a 5-year MFS, LRPFS and EFS rates of 80.0%, 40.0% and 75.0%, respectively, as OS and CSS rates displayed a 5-year rate of 40%. Lastly, the zig-zag pattern group exhibited a 5-year MFS, LRPFS and EFS rates of 64.8%, 32.4% and 50.0%, respectively, as OS and CSS rates displayed a 5-year rate of 64.8%. We found statistically significant differences between the four groups when we evaluated LRPFS was evaluated (p=0.016), as well as regarding to OS and CSS (p=0.011).

Survival rates according to regression patterns for thickness are displayed on Tables 11 and 12 and its corresponding graphic representations are demonstrated on Fig. 6, 7, 8 and 9.

Table 11. Metastasis Free-Survival, Locoregional Progression Free-Survival according to regression patterns for thickness.

THICKNESS				
	MFS 5 year rate (%)	**p**	**LRPFS** 5 year rate (%)	**p**
Exponential regression	82.5	0.312	72.7	**0.016**
Linear regression	100.0		85.7	
No regression	80.0		40.0	
Zig-zag pattern	64.8		32.4	

MFS = Metastasis Free-Survival; LRPFS = Locoregional Progression Free-Survival

Table 12. Enucleation Free-Survival, Overall Survival and Cancer Specific Survival according to regression patterns for thickness.

THICKNESS				
	EFS 5 year rate (%)	**p**	**OS/CSS** 5 year rate (%)	**p**
Exponential regression	88.5	0.079	92.5	**0.011**
Linear regression	85.7		100.0	
No regression	75.0		40.0	
Zig-zag pattern	50.0		64.8	

EFS = Enucleation Free-Survival; OS = Overall Survival; CSS = Cancer Specific Survival

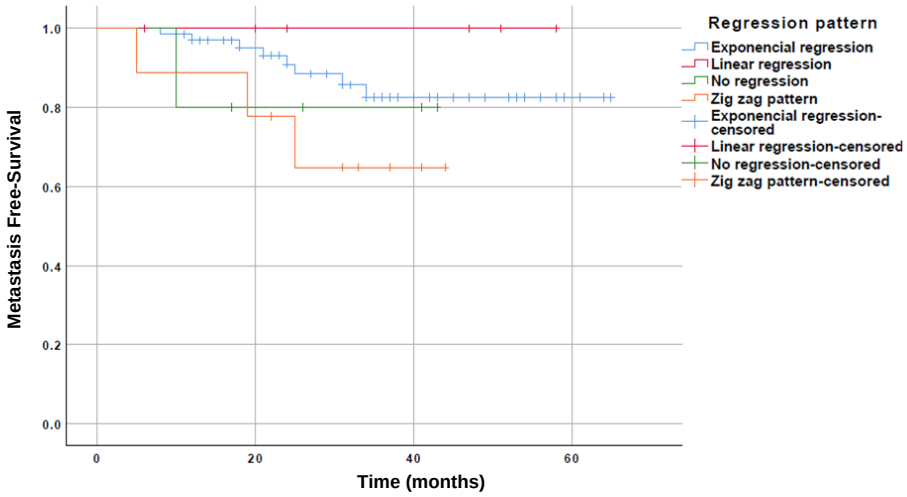

Figure 6. Metastasis Free-Survival (MFS) according to regression patterns for thickness.

Concerning to cross-sectional area, we were able to observe, in the exponential regression group, a 5-year MFS, LRPFS and EFS rates of 78.8, 68.0% and 86.9%, respectively. OS and CSS rates were coincident, displaying a 5-year rate of 88.5%. In the linear regression group we obtained a 5-year MFS, LRPFS and EFS rates of 87.5%, 80.2% and 91.7%, respectively, as OS and CSS rates displayed a 5-year rate of 87.5%. On the other hand, the no regression group exhibited a 5-year MFS, LRPFS and EFS rates of 75.0%, 37.5% and 100.0%, respectively, while OS and CSS rates displayed a 5-year rate of 37.5%.

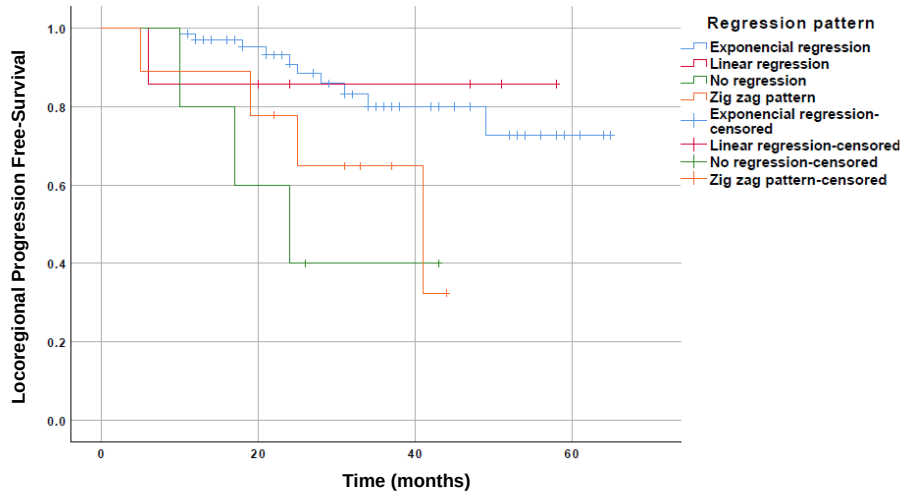

Figure 7. Locoregional Progression Free-Survival (LRPFS) according to regression patterns for thickness.

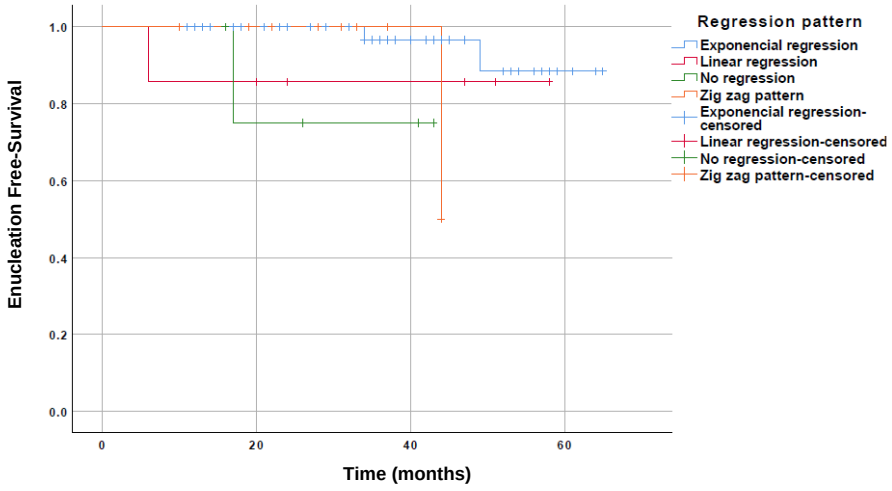

Figure 8. Enucleation Free-Survival (EFS) according to regression patterns for thickness.

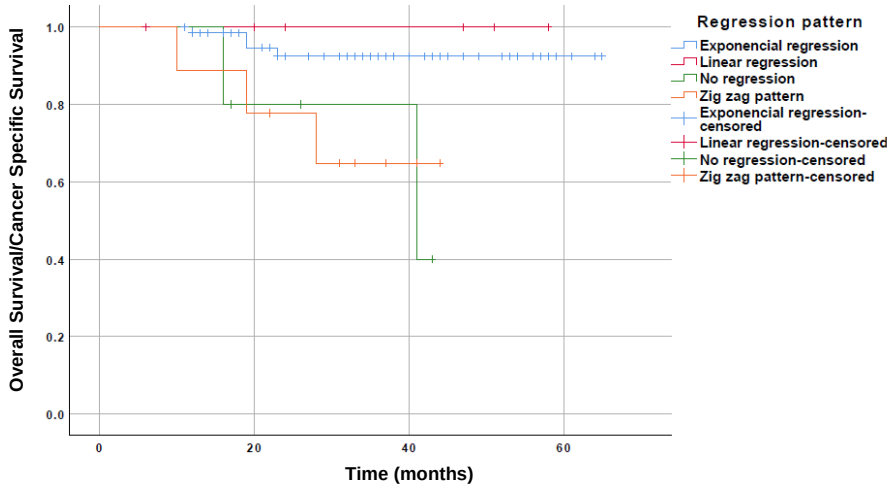

Figure 9. Overall Survival (OS) and Cancer Specific Survival (CSS) according to regression patterns for thickness.

Lastly, the zig-zag pattern group exhibited a 5-year MFS, LRPFS and EFS rates of 64.8%, 0.0% and 100.0%, respectively, as OS and CSS rates displayed a 5-year rate of 100.0%. There were no statistically significant differences between the four regression pattern groups in any of the survival rates.

Survival rates according to regression patterns for cross-sectional area are displayed on Tables 13 and 14 and its corresponding graphic representations are demonstrated on Fig. 10, 11, 12 and 13.

Table 13. Metastasis Free-Survival, Locoregional Progression Free-Survival according to regression patterns cross-sectional area.

CROSS-SECTIONAL AREA				
	MFS 5 year rate (%)	**p**	**LRPFS** 5 year rate (%)	**p**
Exponential regression	78.8	0.312	68.0	0.345
Linear regression	87.5		80.2	
No regression	75.0		37.5	
Zig-zag pattern	64.8		0.0	

MFS = Metastasis Free-Survival; LRPFS = Locoregional Progression Free-Survival

Table 14. Enucleation Free-Survival, Overall Survival and Cancer Specific Survival according to regression patterns for cross-sectional area.

CROSS-SECTIONAL AREA				
	EFS 5 year rate (%)	**p**	**OS/CSS** 5 year rate (%)	**p**
Exponential regression	86.9	0.571	88.5	0.092
Linear regression	91.7		87.5	
No regression	100.0		37.5	
Zig-zag pattern	100.0		100.0	

EFS = Enucleation Free-Survival; OS = Overall Survival; CSS = Cancer Specific Survival

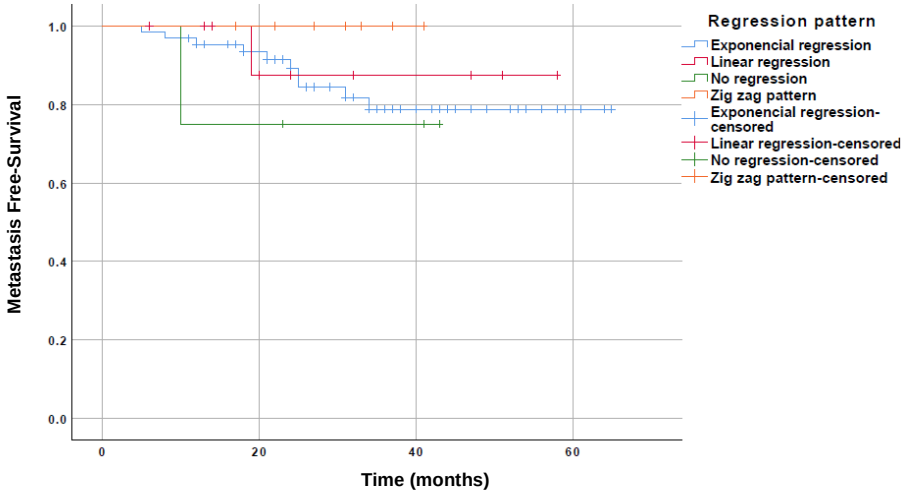

Figure 10. Metastasis Free-Survival (MFS) according to regression patterns for cross-sectional area.

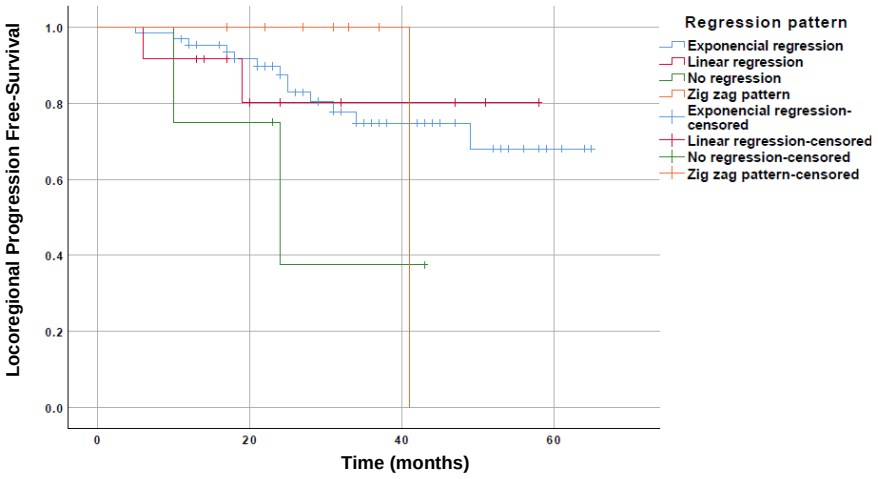

Figure 11. Locoregional Progression Free-Survival (LRPFS) according to regression patterns for cross-sectional area.

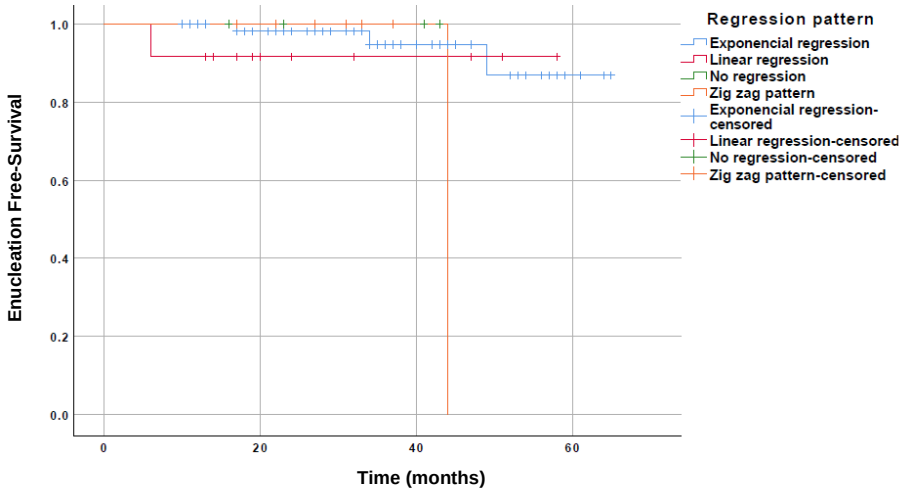

Figure 12. Enucleation Free-Survival (EFS) according to regression patterns for cross-sectional area.

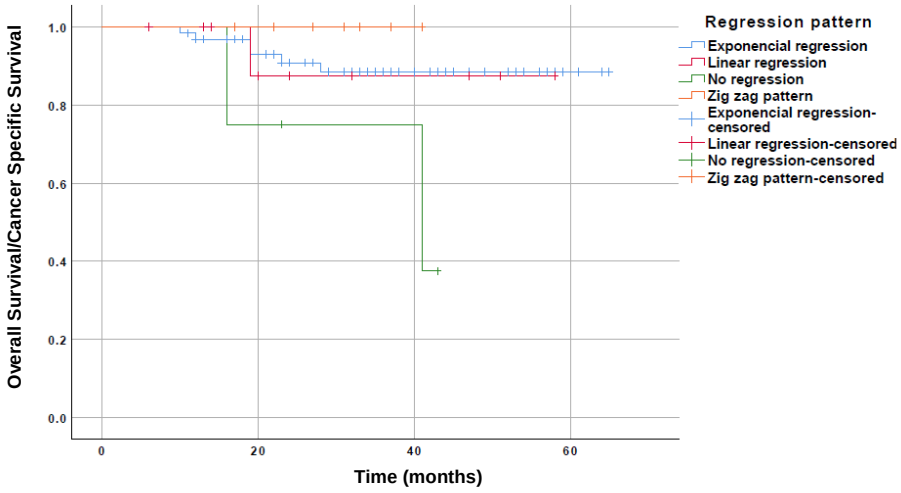

Figure 13. Overall Survival (OS) and Cancer Specific Survival (CSS) according to regression patterns for cross-sectional area.

Discussion and Conclusion

The present study assessed ultrasonographically measured initial dimensions and their evolution in choroidal melanomas treated with episcleral brachytherapy, in order to establish distinctive tumor regression patterns. After this initial assessment, it was searched a correlation between the initial dimensional parameters and regression patterns with survival rates.

In a review of images from 330 choroidal melanomas irradiated from 2000 to 2008, Rashid *et al*.[23] concluded that not only the regression of choroidal melanoma was largely associated with several treatment parameters and clinical characteristics, most of which were shown to reflect initial tumor size, but also that this parameter had a significant correlation to metastasis rate, local tumor recurrence and death.

On the other hand, a review that included 111 patients performed by Krohn *et al*.[27] demonstrated that, in their multivariate analyses, the large basal tumor diameter was the only significant predictive factor for metastatic disease. Moreover, in a retrospective study involving 213 patients conducted by Rouberol *et al*.[37], largest basal diameter, along with Bruch membrane rupture, was also stated as a predictive factor of recurrence.

Thus far, earlier series did not consider initial cross-sectional area as an important prognostic factor and this study aimed to evaluate the hypotheses of initial cross-sectional area as a parameter that could be correlated with prognosis.

To study the impact of initial dimensional parameters that comprehended initial thickness, largest basal diameter and cross-sectional area, patients were divided in two equitable groups based on median value of each parameter and survival rates were evaluated for each group. Hence, it was found that a smaller initial largest basal diameter (≤11.72mm) was significantly correlated to higher metastasis free-survival, overall survival and cancer specific survival. Unexpectedly, a statistical significant correlation between a higher initial basal diameter (>11.72 mm) with a higher enucleation free-survival was also found. However, due to the fact only 5 events of enucleation were found throughout the study, this last assumption may not be positively related to a strong clinical inference of our result. Similarly, we were able to determine a significant correlation between a higher initial thickness (>6.13 mm) and a higher overall survival and cancer specific-survival, but the number of deaths by general causes, coincident with deaths cancer-related, was also small, thus this statistical significant difference may not be clinically significant.

Concerning to cross-sectional area, a significant correlation between higher or smaller initial cross-sectional area and survival rates was not found. Therefore, initial cross-sectional value does not seem to correlate with choroidal melanoma prognosis.

The controversy concerning the prognostic value of tumor regression rate has been persistent for more than 3 decades. According to previous literature, most studies agree that regression rate of choroidal melanomas after brachytherapy stands as a relevant prognosis factor and the majority of authors defend that faster tumoral shrinking is associated with adverse survival rates.[24,25,31,32] In an earlier study carried out by Demirci *et al*.[25], the authors separated patients according to several categories of tumor thickness and were able to find that not only uveal melanomas with higher initial thickness presented a steeper and more reduction in tumor thickness following radioactive I-125 plaque, but there was also a significant difference in the decrease of the tumor thickness between melanomas that developed metastatic disease and those that remain without metastatic evolution. Moreover, in a review of 147 cases with choroidal melanoma submitted to radioactive ruthenium-106 plaque performed by Kaiserman *et al*.[31], they found that the initial tumor thickness regression rate was significantly higher in patients who developed metastatic disease (6% per month), comparing to patients who did not (4% per month).

Similarly, Glynn *et al*.[32] determined variation of tumor thickness following proton-beam radiotherapy in 700 patients with uveal melanoma and found that tumors that presented a rapid regression were significantly more likely to present with metastatic disease within 2 years of treatment, while tumors associated with a slower regression exhibited a higher probability of metastasis after 2 years of treatment.

On the other hand, a review of 100 cases of uveal melanoma treated with cobalt-60 plaque brachytherapy published in 1984 by Cruess *et al*.[33] did not obtain a significant difference in tumor regression between the patients who developed metastasis and those who remained systemically well. Likewise, a more recent work carried out by Novak-Andrejcic *et al*.[34] in 2003 did not find a significant difference in the extent and rate of the tumor regression in groups of deceased and successfully treated. More recently, in 2018, a study conducted by Pépin *et al*.[26] that involved 128 patients with medium-sized tumors treated with iodine-125 brachytherapy also stated that regression rate at 6 and 12 months after iodine-125 brachytherapy was not associated with a higher metastatic rate.

When we proceeded to analyze the possibility of correlation between tumors with rapid regression opposed to tumors with slower regression, there was no statistical significance in the survival rates, in both thickness and cross-sectional area's groups. Although there is no established regression velocity for both thickness and cross-

sectional area to consider one as a fast regressive tumor, the temporal period employed in our analysis may have been too limited. Regardless, it is important to highlight the fact that previously mentioned studies that found a significant difference used a different isotope. In 2018 Rashid *et al*.[23] demonstrated that the use of ruthenium-106 isotope, as opposed to iodine-125 isotope, independently contributed to a faster regression of tumor thickness.

Several studies attempted to define different regression patterns.[35,38] Rashid *et al*.[35] performed a review of 330 patients where they categorized regression patterns, regarding thickness and cross-sectional area, according to decrease (D), stable (S), increase (I) and other. Posteriorly, main subpatterns were established, generating the categories of decrease-stable (DS) and zig zag.

This study is, to our knowledge, the first to distinguish regression patterns for thickness and cross-sectional area into four groups: exponential regression, linear regression, no regression and zig-zig pattern. In the evaluation of regression patterns regarding largest basal diameter, we found a significant variability of data that prevented us from establishing cohesive patterns and, therefore, utilizing this parameter in our assessment. A possible explanation for this variability may rely on inaccurate measurements, as the approach by ultrasound evaluation is often associated to human error.

Regarding thickness, we were able to observe that there was a statically significant correlation between the linear regression group with a higher locoregional progression free-survival, overall survival and cancer specific survival, whereas the zig-zag pattern group was associated with a lower locoregional progression free-survival, overall survival and cancer specific survival. We have not found a significant correlation between the four regression patterns and metastatic free-survival or enucleation free-survival. Contrarily to the finding by Rashid *et al*.[35] referring to cross-sectional area, it seems that there is no evidence of a significant correlation between regression patterns found for this parameter and survival rates. Nevertheless, it is important to highlight the fact that distribution of patients through the four regression patterns was not equitable, considering that the exponential regression group included a higher proportion of patients not only regarding thickness, but also cross-sectional area.

As mentioned in a previous study by Maschi *et al*. [39], there's a proven risk of early pseudoprogression during the first months post-treatment, which can be explained by a maintained enlargement of the tumor, resulting in retinal detachment or bleeding, which can cause an appearance of growth. According to this, and also taking into account the several similar side-effects associated with braquitherapy that we also recorded in our

patients, the zig zag pattern may derive from several events of intra-tumoral hemorrhage or necrosis, therefore not reflecting accurately the regression of tumor.

One of the main limitation of this study was the inevitable measurement bias and intra-observer variability associated to ultrasonography, despite the fact that all ultrasonographic digitalized scans were re-evaluated and new measurements were obtained. Rashid *et al*.[23] also demonstrated that the location and shape of tumors were also significant factors that could lead to a more difficult standardization of readings. Furthermore, more studies are needed to process a similar evaluation, taking shape and location as possible confounders.

Moreover, our study was based on a retrospective design, in a single institution, involving a relatively small sample size that should be extended in further studies. Consequent to our sample size, the absolute number of studied events such as enucleation, metastatic disease, tumor's progression and tumor-related death was small, which stands as a limitation to the power of statistical analysis in the evaluation of significant correlations and subsequent clinical inference. Moreover, as the program to treat choroidal melanomas began in September 2013, there has been a gradual inclusion of patients, which resulted in a discrepancy of follow-up time between patients, ranging from two to sixty-five months. Although most of our patients maintained a reasonable attendance to follow-up visits and allowed a prospective collection of data, there were also limitations associated to missing data and loss of follow-up.

In summary, initial largest basal diameter and thickness demonstrated to be proven prognostic factors of tumor prognosis and linear regression pattern of thickness appeared to have a positive correlation with several outcomes.

Nowadays, cytogenetic abnormalities have been progressively indicated as major prognostic factors.[40-43] Further studies should be performed, taking into account the gene expression profile and its relation with the regression patterns, as it would provide a better understanding of the uveal melanoma pathophysiology.

Acknowlegments

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