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Tumor Regression Patterns after Iodine-125 Brachytherapy for Choroidal Melanoma

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Abstract

Uveal melanoma is the most common primary intraocular malignancy in adults. The main treatment modality is episcleral brachytherapy (EBT) for medium and some large melanomas, as it spares the eye and the vision, when compared to enucleation. Research about uveal melanoma regression patterns is scarce, but most studies agree that tumor regression is a prognostic factor to take into consideration.

The present study consists in a prospective case series mainly aimed to stablish regression patterns and to verify if they had any influence on the survival rates and complications. The study sample included a total of 100 patients treated in Centro Hospitalar e Universitário de Coimbra with 125-Iodine brachytherapy.

The patients were divided into three distinctive groups according to the regression behaviour of the tumor: exponential regression (66%), linear regression (19%) and no regression (5%). The results have shown that the three groups are associated with different survival rates (p=0.004 for Disease-Free Survival and p=0.009 for Overall Survival and Cancer Specific Survival) and that the no regression group has the worst prognosis, whereas the exponential regression group is linked to better survival rates. Moreover, we stablish statistically significant correlations between tumor regression and some of the treatment side-effects such as intra-tumoral fibrosis (OR=0.129; 95% CI: 0.026-0.641; p=0.005) and superficial punctate keratitis (OR=0.202; 95% CI: 0.039-1.036; p=0.039) which are related with faster tumor regression velocity, and also cotton wool spots which are associated with stabilized tumor thicknesses in lower values (OR=0.090; 95% CI: 0.011-0.749; p=0.008).

In conclusion, the uveal melanoma regression patterns defined in this study have a prognostic value and impact in the survival rates. However, further studies are needed to better understand the implications of these finding, as it is a complex topic in which little research has been done.

Keywords: Melanoma, Uveal Neoplasms, Brachytherapy, Prognosis, Regression Analysis, Disease Progression, Disease Free-Survival.

Resumo

O melanoma da úvea é o tumor intraocular primário maligno mais comum nos adultos. A principal modalidade de tratamento para melanomas de tamanho médio e alguns de tamanho grande é a braquiterapia episcleral, já que poupa o globo ocular e a visão, quando comparada com a enucleação. Os estudos realizados sobre os padrões de regressão do melanoma da úvea são escassos, embora a maioria concorde que a regressão tumoral é um fator prognóstico a ter em consideração.

O presente estudo consiste numa série prospetiva em que o principal objetivo foi estabelecer padrões de regressão e verificar a existência de influência sobre as taxas de sobrevivência. A amostra populacional incluiu um total de 100 doentes tratados no Centro Hospitalar e Universitário de Coimbra com braquiterapia com iodo-125.

Os doentes foram divididos em três grupos distintos de acordo com o comportamento de regressão tumoral: diminuição exponencial (66%), diminuição linear (19%) e sem diminuição (5%). Os resultados mostraram que os três grupos estão associados a diferentes taxas de sobrevivência (p=0,004 para Sobrevivência Livre de Doença e p=0,009 para Sobrevivência Global e Sobrevivência Específica de Cancro) e que o grupo sem diminuição está associado a pior prognóstico, enquanto o grupo da diminuição exponencial se relaciona com melhores taxas de sobrevivência. Adicionalmente, estabelecemos correlações estatisticamente significativas entre a regressão tumoral e alguns efeitos secundários do tratamento tais como a fibrose intra-tumoral (OR=0,129; 95% CI: 0,026-0,641); p=0,005) e a queratite superficial ponteada (OR=0,202; 95% CI: 0,039-1,036; p=0,039), que se relacionam com uma maior velocidade de regressão tumoral, e ainda a presença de manchas algodonosas que se encontra associada a uma estabilização da espessura tumoral em valores mais baixos (OR=0,090; 95% CI: 0,011-0,749; p=0,008).

Conclui-se que os padrões de regressão do melanoma da úvea definidos neste estudo têm valor prognóstico, bem como impacto nas taxas de sobrevivência. Ainda assim, estudos futuros são necessários para uma melhor compreensão das implicações destes resultados, dado que se trata de um tema complexo em que pouca investigação tem sido realizada.

Palavras-chave: Melanoma, Úvea, Braquiterapia, Análise de Regressão, Prognóstico, Progressão de Doença, Intervalo Livre de Doença.

Introduction

Uveal melanoma is the most common primary intraocular tumor in adults[1] and accounts for 3-5% of all melanoma and 85% of all ocular melanoma cases. The majority of cases are originated from choroidal melanocytes (85-90%) with the remaining arising from the iris and ciliary body.[2] The incidence of choroidal melanoma is variable depending on age, race, sex and latitude.[3] It is greater in non-Hispanic whites (6.02 per million), as well as in men (30% greater than females).[4,5] The median age of diagnosis is 61,4 years.[6] In Europe, incidence diverges with latitude from two per million in the Southern countries to eight per million in the Northern countries.[7]

At the moment, episcleral brachytherapy (EBT) is the leading radiation treatment modality for medium and some large melanomas, as it spares the eye and vision, when compared to enucleation.[8,9] The role of EBT was stablished in part by two-multicenter randomized clinical trials from the Collaborative Ocular Melanoma Study (COMS) group. The study for medium melanomas revealed no significant difference at 5 and 12 years between groups randomized to enucleation or EBT. Similarly, the trial for large melanomas showed comparable 5 and 10-year cumulative tumor-related mortality rates, meaning there is no advantage in pre-enucleation irradiation[10–13]. EBT presents 5-year local control rates of 89, 5% and 5-years treatment failures of 10,3%.[13]

As the distance between the source of radiation and the tumor is reduced, EBT allows a local high-dose irradiation of the tumor with little damage of the surrounding tissues[14], inducing tumor regression, which can be evaluated as a change in tumor thickness and cross-sectional area measured by B-scan ultrasonography.[13] The tumor regression depends on the radiosensitivity of tumor cells and the clearance rate of dead tumor cells, as well as the dynamic balance between different tumor components.[15]

The studies about the regression patterns of choroidal melanoma after radiotherapy are scarce. With one exception[16], all agree that tumor regression rate is an important factor in the prognosis for patients with treated choroidal melanomas.[15,17,20] Tumors with higher initial thickness show a greater and faster reduction after treatment and are more associated with metastatic disease.[15,17–21] However, time after treatment should also be taken into consideration as one study shows that at 2 years after treatment the tumors with a slow annual decline are the ones most likely to metastasize.[17] Moreover, another study shows that although in initial phases the regression curve is steeper for thicker tumors and flatter for less thick tumors, it has a propensity to become similar for tumors with different thicknesses as time passes by.[15]

Recent studies have focused on relating regression patterns with gene expression profile (GEP), although with contradictory results. Some argue that tumors with monosomy 3 or class 1 GEP are bigger and tend to have a faster and greater regression[22–25] whereas other studies found that class 2 tumors have higher tumor related mortality or even that there is no correlation between GEP and the regression rate.[26–31] The contradictory results likely reflect a variable case mix regarding the size and other characteristics of the tumor and different methods of irradiation, which include both brachytherapy with iodine and ruthenium and proton beam therapy.

More recent studies have identified different regression patterns: D (decrease; progressive decrease in thickness by at least 15% after brachytherapy), S (stable; less than 15% change in thickness), I (increase; progressive increase in thickness by at least 15%), and zigzag (alternating measurements).[32-33]

The aims of the present study were to analyze regression of tumor thickness of choroidal melanomas and the pattern of regression after EBT and to correlate them with tumor characteristics, survival rate and EBT side-effects.

Material and Methods

Study design and eligibility criteria

This is a prospective case series of patients with choroidal melanoma treated with primary Iodine-125 EBT at Centro de Referência de Onco-Oftalmologia, Centro Hospitalar e Universitário de Coimbra (CHUC), between September 2013 and November 2018. Eligible for this study were all consecutive patients who had a choroidal melanoma without ciliary body and iris extension that was measured at diagnosis and at least twice during follow-up with the 20-MHz probe of Aviso^{TM} ultrasound platform (Quantel MedicalTM, France). We excluded patients with iris and primary ciliary body melanomas, which were measured using other equipment, and tumor eyes that had silicone oil tamponade at the time of diagnosis. Additionally, patients lost to follow-up were excluded. A total of 100 patients and tumors were thus enrolled in this study (inclusion ratio, 95% of all uveal melanomas). The study was approved by the Institutional Review Board of CHUC and followed the tenets of the Declaration of Helsinki.

Brachytherapy

Iodine-125 radioactive plaques (COMS standard plaques, Trachsel Dental Studio, Inc., Minnesota, USA, and BEBIG GmbH, Berlin, Germany) were used to treat tumors up to 10 mm thick (median, 2.75; range, 1.0–10; 3 tumors were over 10 mm), based on the COMS classification system and the guidelines from the American Brachytherapy Society[9]. We generally aimed to deliver a dose of 85 Gy to the tumor apex with in a maximum of 8 days. The median delivered apical dose was 85 Gy (range, 49–164). The corresponding median delivered dose rates to tumor apex were 68 cGy/h (range, 14–350). The corresponding median treatment durations were 119 hours (range, 27–467).

Ultrasonography

The 20-MHz probe of Aviso S^{TM} ultrasound platform (Quantel Medical*TM,* France) was used in all tumor measurements. 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 and axial resolution of 100 µm and a lateral resolution of 250 µm. One specialist in ocular ultrasonography and one ocular oncologist measured the thickness of the tumor from the inner surface of the sclera to tumor apex and the largest basal diameter (LBD). Thickness was measured from two meridians, along the LBD and perpendicular to it. Representative digitized scans were prospectively stored at the time of each diagnostic and follow-up visit. Patients were reviewed in the Onco-Ophthalmology Reference Center clinically and by

ultrasonography during the first 3 years after irradiation (at 1, 3, 6, 9, 12, 18, 24, 30, and 36 months).

For the purpose of this study, tumor thickness and largest basal diameter from stored scans were re-measured by consensus of two investigators. We used a mouse-driven cursor 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.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22. Descriptive statistics for continuous variables was reported as mean ± standard error or median and range, depending on the normality of the distribution, tested using Kolmogorov-Smirnov test.

Regression of tumor thickness through time was assessed for each patient and the pattern was ranked as "exponential regression", "linear regression" or "no regression". For the exponential regression group, data adjustment was performed using Prism GraphPad using the following equation:

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

The plateau (y_0) corresponds to the value in which the tumor thickness achieved a state of stabilisation after decreasing. $T_{1/2}$ is defined as the time that tumor thickness takes to reduce half of its total decrease.

When the determination coefficient was less than 0.9, the regression pattern was reclassified either as "linear regression" or "no regression", depending on the evolution of tumor thickness.

For inferential statistics on survival Kaplan-Meyer estimates were determined for Disease-Free Survival, Overall Survival and Cancer Specific Survival. Log-rank test was used for comparing survivals between groups.

All comparisons were performed at a significance level of 0.05.

Results

Demographic and Clinical Characteristics

Of the 100 patients included in this study, 42 were male and 58 were female. All had ages between 26 and 87 years old, with the median age of 62.5 years old. Most of the tumors were in the right eye (54%) and 53 had a temporal location whereas 26 had a nasal location.

Regarding pre-treatment dimensions, mean basal diameter was 11.59±2.8 mm and mean thickness was 6.46±0.23 mm. The BTE duration was between 4 and 10 days, being the median duration 6 days.

The demographic and clinical characteristics are summarized in Table I.

Table I. Demographic and Clinical Characteristics.

Demographic Variables		
Gender	n	%
Male	42	42
Female	58	58
Age (years)		
Median	62.5	
Minimum	26	
Maximum	87	
Involved Eye	n	%
Right	54	54
Left	46	46
Clinical Variables		
Tumor Location	n	%
Temporal	53	53
Nasal	26	26
Superior	8	8
Inferior	7	7
Macular	3	3
Peripapilar	3	3
Thickness (mm)	6.46 ± 0.23	
Largest Basal Diameter (mm)	11,59 ± 2.8	
BTE duration (days)		
Median	6	
Minimum	4	
Maximum	10	

According to the American Joint Committee on Cancer (AJCC) classification of the uveal melanoma,[34] regarding the size and extent of the main tumor (T), a total of 46 patients had an uveal melanoma classified as T2a (tumor size category 2 without ciliary body involvement and extraocular extention) and 39 had a T3a uveal melanoma (tumor size category 3 without ciliary body involvement and extraocular extention). These two are the most frequent T subclassifications. All tumors had no regional lymph node involvement (N0) and no distant metastasis by clinical classification (M0). Accordingly, a total of 45 patients were classified as stage group IIA (T1b-d or T2a, N0, MO) and 40 patients were classified as stage group IIB (T2b or T3a, N0, M0).

The staging classification is summarised in Table II.

Table II. Staging according to AJCC.

TNM	n	(%)
T		
T1a	11	11
T1b	2	2
T2a	46	46
T2b	1	1
T3a	39	39
T4a	1	1
N		
N0	100	100
M		
M0	100	100
Stage Group		
I	12	12
IIA	45	45
IIB	40	40
IIIA	3	3

Side-Effects

During the follow-up, several patients experienced the development of radiation side-effects. All the side-effects and the corresponding frequencies are described in Table III.

Table III. Iodine-125 BTE side-effects.

Side Effects	n (100)
Cataract	44
Underwent surgery	14
Radiation retinopathy	42
Cotton wool spots	15
Vascular hyalinization	16
Peritumoral exudation	19
Exudative retinal detachment	9
Radiation-induced neuropathy	2
Superficial Punctate Keratitis	13
Vitreous hemorrhage	12
Neovascular glaucoma	12
Tumor necrosis syndrome	2
Intra-tumoral fibrosis	26
Phtisis bulbi	1

Regression Patterns

The tumor regression patterns were based on evaluation of tumor thickness by ultrasonography. We were able to separate patients into three distinct groups of regression patterns: exponential regression (66%), linear regression (19%) and no regression (5%), which means that the tumor thickness was stable through time. There were 10 patients that could not be integrated in any of the groups because the data adjustment necessary to build the regression curves required 4 or more measurements of the tumor thickness.

Regarding the exponential regression group and its data adjustment equation, the plateau (y_0) range was between 0 and 0.839 mm and the median value was 0.486 mm. $T_{1/2}$ ranged between 0.2 and 56.740 months and the median value was 3.016 months.

Survival Rates

By the end of February 2019, local or systemic progression of the disease occurred in 19 patients and 10 of these patients have died of confirmed or suspected melanoma metastasis.

The 2-year rate of Disease-Free Survival (DFS) was 82.6% (Fig. 1), whereas the Overall Survival (OS) and the Cancer Specific Survival (CSS) were both 89.5% (Fig. 2 and 3).

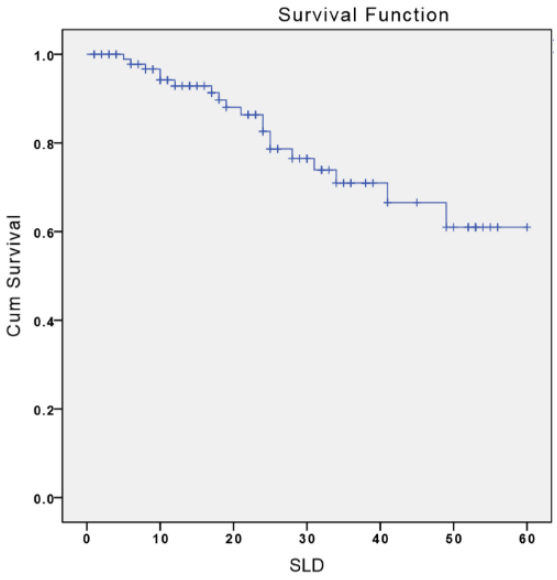

Fig. 1. Disease-Free Survival.

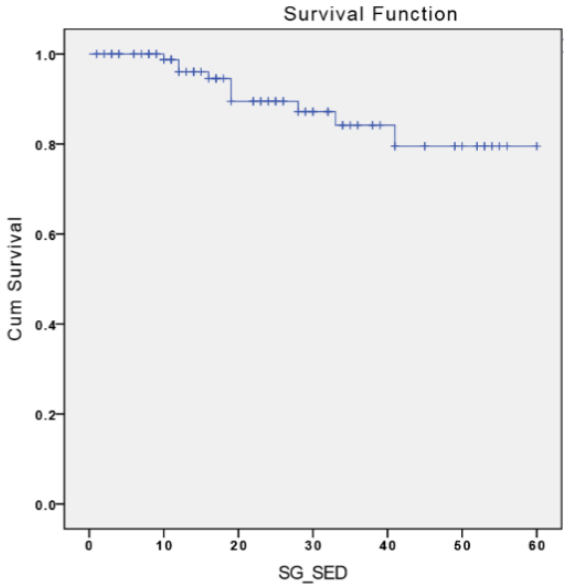

Fig. 2. Overall Survival.

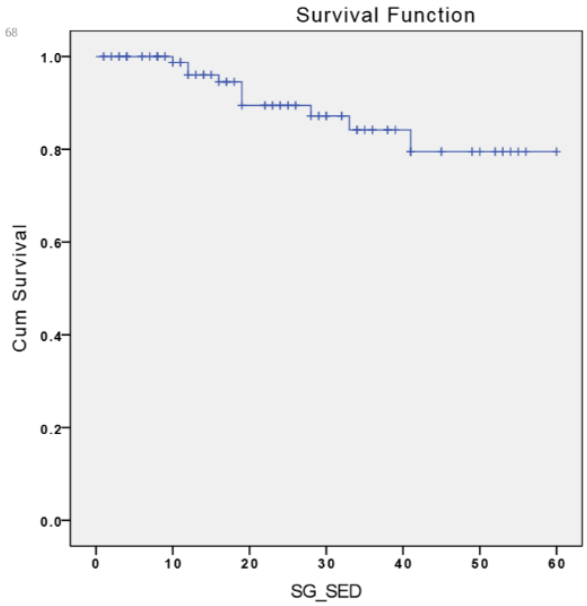

Fig. 3. Cancer Specific Survival.

Correlation between Regression Patterns, Survival Rates and Side-Effects

When correlating the established regression patterns with the occurrence of local or systemic progression of the disease, the distribution of the patients by the three groups was not even. The exponential regression group comprehended a total of 10 patients (15.2%), while the linear regression group included 6 patients (31.6%). The no regression group had 3 patients (60.0%). As a result, the three groups are associated with different DFS rates (Fig. 4) and these correlations were statistically significant (p=0.004). The exponential regression group had a 2-year rate of 90.4%, in comparison to the linear regression group which had a 69.7% rate and to the no declining group, with a 2-year rate of 30%.

Concerning the OS and the CSS rates (Fig. 5 and 6), there was also a statistically significant difference between the groups (p=0.009). There were 5 patients from the exponential regression group (7.6%) that died, whereas the linear regression group registered 2 deaths (10.5%) and there were 3 deaths within the patients of the no regression group (60.0%). Therefore, the OS and CSS 2-year rate for each group were respectively: 91.9%, 93.8% and 60%. All the deaths were due to metastatic disease, thus the OS and the CSS 2-year rate have both the same value for each group. The correlations between the regression patterns and survival rates are described in Table IV.

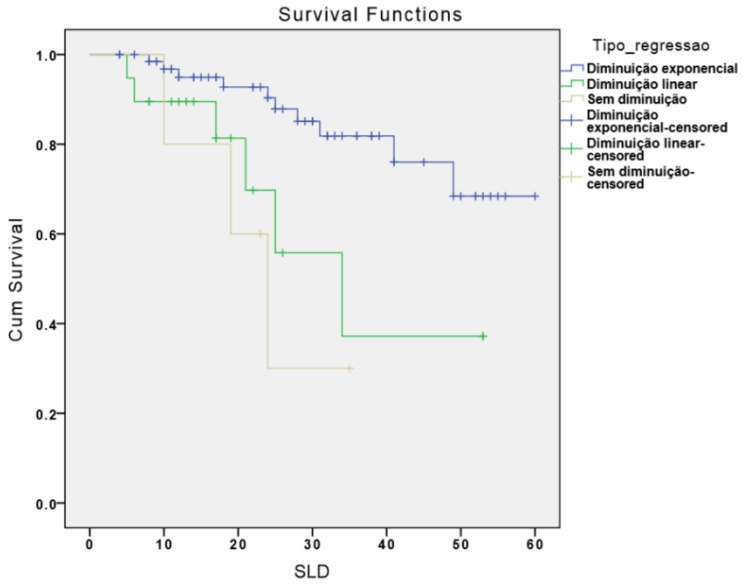

Fig. 4. Disease-Free Survival according to the regression patterns.

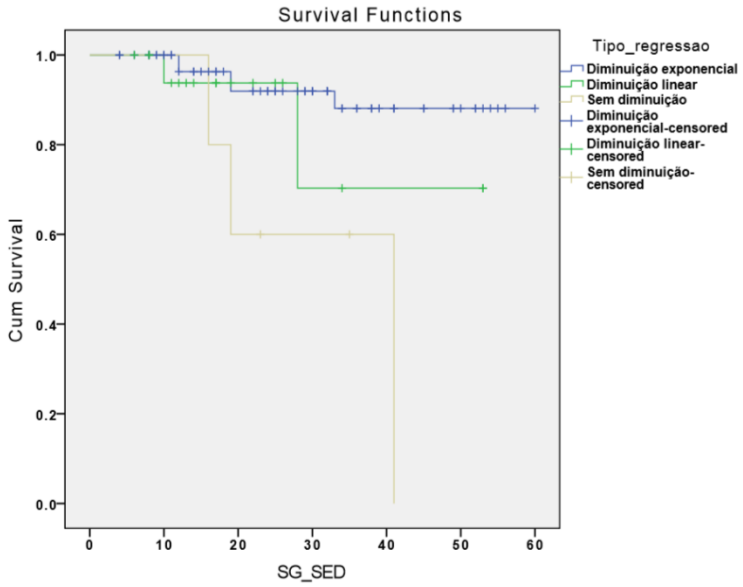

Fig. 5. Overall Survival according to the regression patterns.

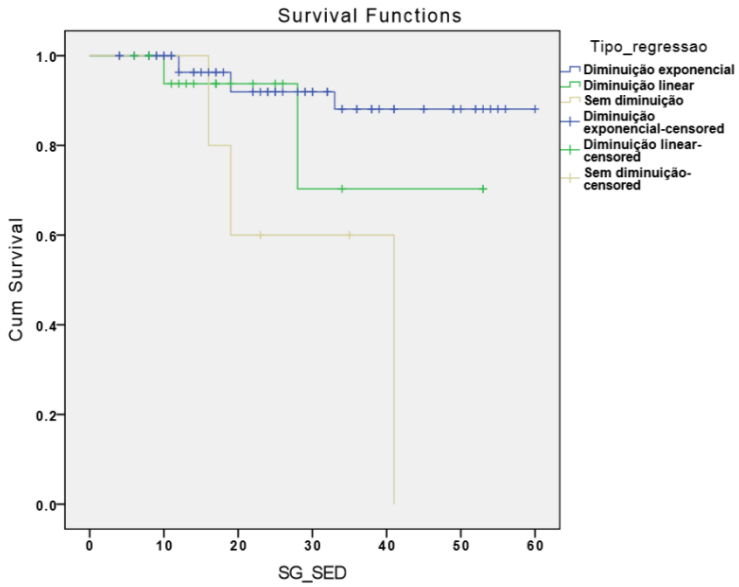

Fig. 6. Cancer Specific Survival according to the regression patterns.

Table IV. Correlation between regression patterns and survival rates.

Regression Patterns	**Disease Progression (%)**	**Disease-Free Survival 2-year rate (%)**	**Death by Metastatic Disease (%)**	**Overall Survival and Cancer Specific Survival 2-year rate (%)**	**p**
Exponential Regression	15.2	90.4	7.6	91.9	**0.004**
Linear Regression	31.6	69.7	10.5	93.8	**0.009**
No Regression	60	30	60	60	**0.009**

For statistical analysis, we divided the patients from the exponential regression group regarding the $T_{1/2}$ and the plateau. 33 patients took 3 months or less to achieve half of the total decrease in tumor thickness, whereas the other half took more than 3 months. Concerning the plateau, 36 patients had a plateau inferior to 0.5 mm and 30 had a plateau superior or equal to 0.5 mm. The division parameters are described in Table V.

Table V. Exponential regression group division according to $T_{1/2}$ and plateau.

Variables	n
$T_{1/2}$	
≤3 months	33
>3 months	33
Plateau	
<0.5 mm	36
≥0.5 mm	30

Subsequently, we tested for correlations between this group and the survival rates. The patients with $T_{1/2}$ equal or inferior to 3 months had a 2-year DFS rate of 86.8% and a 2-year OS and CSS rate of 91.7% in contrast with patients with $T_{1/2}$ superior to 3 months, which had 2-year rates of 92.9% and 92.3%, respectively.

On the other hand, patients with a plateau inferior to 0.5 mm had a 2-year DFS rate of 90.6% and a 2-year OS and CSS rate of 87.1% when compared to patients with a plateau equal or superior to 0.5 mm, that had 2-year rates of 89.9% and 82.3%, respectively. Our analysis has found no statistically significant correlations (Table VI).

Table VI. Correlation between the exponential regression group and the survival rates.

Exponential regression group	2-years Rate (%)	p
Disease-Free survival		
$T_{1/2}$		
≤3 months	86.8%	0.101
>3 months	92.9%	
Plateau		
<0.5 mm	90.6%	0.619
≥0.5 mm	89.9%	
Overall and Cancer Specific Survival		
$T_{1/2}$		
≤3 months	91.7%	0.968
>3 months	92.3%	
Plateau		
<0.5 mm	87.1%	0.094
≥0.5 mm	82.3%	

Furthermore, the correlation between patients with the exponential regression pattern and treatment side-effects, as well as clinical characteristics, was also tested. The vast majority of the correlations were not statistically significant. Nevertheless, the analysis

suggests that patients show a faster tumor regression if they develop intra-tumoral fibrosis (OR=0.129; 95% CI: 0.026-0.641; p=0.005) or superficial punctate keratitis (OR=0.202; 95% CI: 0.039-1.036); p=0.039). Additionally, patients with cotton wool spots reached a lower plateau (OR=0.090; 95% CI: 0.011-0.749, p=0.008). These correlations are described in Table VII and Table VIII.

Table 7. Significant correlations between the $T_{1/2}$ and side-effects.

Side-Effects	**$T_{1/2}$**		**p**	**OR (95%IC)**
	≤3 months n (%)	**>3 months n (%)**		
Intra-tumoral fibrosis				
Yes	11 (84.6%)	2 (15.4%)	**0.005**	0.129 (0.026-0.641)
No	22 (41.5%)	31 (58.5%)		
Superficial Punctate Keratitis				
Yes	8 (80.0%)	2 (20.0%)	**0.039**	0.202 (0.039-1.036)
No	25 (44.6%)	31 (55.4%)		

Table 8. Significant correlation between the plateau and side-effects.

Side-Effects	**Plateau**		**p**	**OR (95%IC)**
	<0.5 mm n (%)	**≥0.5 mm n (%)**		
Cotton Wool Spots				
Yes	10 (90.9%)	1 (9.1%)	**0.008**	0.090 (0011-0749)
No	26 (47.3%)	29 (52.7%)		

Discussion

In this study, we established distinctive melanoma regression patterns after Iodine-125 BTE and searched for correlations with survival rates and treatment side-effects.

Some studies have already made an attempt to define different regression patterns. Abramson *et al.*[19] divided the patients according to the decrease (type D), increase (type I) or stabilisation (type S) of the tumor thickness after treatment and showed that an increase or stabilisation after treatment are related with worse survival rates when compared to a decrease (34% patients alive with type I and 88% alive with type D at 48 months). Rashid *et al*.[34] followed the same categorization but added subpatterns that consisted of combinations of the main patterns, including a zigzag pattern defined as alternating measurements with little evidence of a trend.

This study is, to our knowledge, the first to separate the tumor regression patterns into exponential regression, linear regression and no regression. We did not found the zigzag pattern as it may derive from inaccurate measurements due to ultrasound probe definition or different probe orientation. In previous studies a 10-MHz probe was used. We used a high definition probe, the 20-MHz probe of Aviso^{TM} ultrasound platform (Quantel Medical^{TM}, France), much more accurate in tumor mesurements. A possible explanation for the zigzag pattern could also be intra-tumoral edema, bleeding or necrosis. The location or shape of the tumor are other factors that makes it difficult to get the readings always from the same meridian.[33]

Our results show that, even in the decreasing group used by the two mentioned studies, there is a difference in the survival rates depending on the decrease being linear or exponential. We also confirmed Abramson *et al.* results that patients with tumors that do not experience regression have worse prognosis. Additionally, and similarly to Rashid *et al.*, we came to the conclusion that an exponential decay function, which is often used in the studies to model tumor regression,[15,18,22] was applicable to most but not all tumors.[33]

According to the literature, most authors agree that uveal melanoma regression after brachytherapy has prognostic value and affirm that faster shrinking tumors are associated with a higher prevalence of systemic progression and, consequently, with lower survival rates.[15,18,20–22] Augsburger *et al.* reported that the percentage of change in tumor thickness at 12 months after treatment has prognostic value and that rapid regression is a useful clinical parameter for assessing the patient's risk of death from metastatic disease as it is related with an unfavourable prognosis.[20] Similarly, Glynn *et al.* described that rapid declining tumors are more likely to metastasize within the first two years of proton beam radiotherapy whereas slow declining tumor present higher risk for metastatic disease after the first two years.

Additionally, large initial diameter, ciliary body involvement and old age were all related to risk of metastatic disease in the first two years of treatment.[18] Likewise, Guthoff *et al.* correlated a faster decrease in tumor thickness with a worse prognosis. Nonetheless, emphasis was put on the fact this result was only a statistical statement and should not lead to premature prognosis observations.[21] Kaiserman *et al.* found that tumor thickness regression rate in the first three months had a prognostic value, albeit small.[22] Demirci *et al.* stated thickness and regression rate as significant parameters for the development of metastatic disease and found that tumor regression follows a downward sloping curve with a steeper curve for thicker tumors and flatter one for less thick tumors, even though these curves become similar over time.[15] However, some studies have yielded contradictory results.[16,17]

In our study, unexpectedly, when comparing tumors with rapid regression against tumors with a slower regression, we found no statistical significance in the survival rates which is supported by a minority of the studies.[16,17] As there is not a defined thickness regression velocity to consider one as a fast regressive tumor, the time interval used in our analysis to distinguish this parameter (3 months) may have been too limited. It was already mentioned that Kaiserman *et al.* found prognostic value, although small, in the regression rate of the first three months after treatment with Ruthenium-106. However, the study had more patients (n=147) and a greater percentage of death by metastatic disease (around 20%). Another important factor to take into consideration is the isotype used for the treatment. A recent study[33] reported differences in the regression rate according to the isotype used and associates Ruthenium-106 with a faster regression when compared to I-125, the isotype used in our study.

In our study, there was no clinical characteristic that were predictive of tumor regression over time. In 2015, another study reported no clinical correlations as well, although it has described an association between tumor location at presentation and tumor thickness, with tumors superiorly located being on average a millimetre thicker when compared to those located in the nasal quadrant.[15] Nevertheless, we stablish correlations between tumor regression and some of the treatment side-effects. Our results showed that intra-tumoral fibrosis as well as superficial punctate keratitis are related with higher tumor decreasing velocity. Additionally, the presence of cotton wool spots is associated with tumor thicknesses that stabilize in lower values. There are no other studies, to our knowledge, that have explored correlations between these entities. Consequently, our findings should be considered preliminary and be confirmed with further studies.

The present study has several limitations. First, sample size should be extended and further studies are needed to create an appropriately powered sample size. Second, it is a

single institution study with a short follow-up time. Although our patients maintained a reasonably good follow-up, there are limitations inherent to missing data. Additionally, as the program to treat uveal melanoma started in September 2013, the patients have been subjected to treatment gradually since then. As a result, all patients have discrepant follow-up times that range from a year to five years. Third, the absolute number of events, such as presence of metastatic disease, tumor-related deaths or side-effects, was small, which serves as a limitation to the power of exploratory analysis for potential statistically significant correlations. Forth, tumor measurements imprecisions may occur, as they are susceptible to human error, although all ultrasonographic digitalized scans have been reviewed and new measurements obtained. Lastly, the gene expression profile, which may contribute to the existence of different regression patterns and different responses to the treatment[23–26], was not evaluated.

Conclusions

The categorization of the tumor regression into three distinctive patterns (exponential regression, linear regression and no regression) was shown to have an impact in the prognosis and survival rates of the patients. Moreover, tumor regression pattern may predict some treatment side-effects.

The literature about regression patterns is scarce and the majority of the studies are dated from more than fifteen years ago. It is of the most importance to conduct more studies in this area, in order to validate our results. Additionally, a deeper knowledge about the gene expression profile and its relation with the regression patterns would allow a better understanding of the uveal melanoma physiopathology and ultimately lead to the development of new treatments.

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