Changes in Ultrasound Findings in Posterior Uveal Melanoma after Ruthenium 106 Brachytherapy

Igor Kaiserman, MD, MPA, Irene Anteby, MD, Itay Chowers, MD, Eytan Z. Blumenthal, MD, Iris Kliers BMedSc, Jacob Pe'er, MD

Purpose: To analyze the postbrachytherapy ultrasonographic dynamics of uveal melanoma tumor height and internal reflectivity.

Design: Prospective, comparative, observational case series.

Participants: One hundred forty-seven patients (147 eyes) with posterior uveal melanoma having a mean age of 61 years (range, 29–97 years) who were treated with Ruthenium 106 brachytherapy.

Methods: Patients were followed-up with ultrasonography using both A and B modes of standardized echography every 6.7 ± 0.3 months (mean ± standard error of the mean) for a total of 1001 ultrasound examinations. On average, each patient was examined 5.8 times (range, 3–17 times). The echographic parameters included tumor base size, height, internal reflectivity, regularity, vascularity, and extra-scleral extension. To compare the response of tumors of different sizes, each tumor was standardized to its initial size at brachytherapy.

Main Outcome Measures: The dynamics of the tumor height and internal reflectivity.

Results: At the time of brachytherapy, the mean height of the tumors was 5.2 mm (range, 2.2–11.8 mm). After brachytherapy, 142 tumors (96.6%) responded by a decrease in height. The decrease in height was at an initial rate of approximately 3% per month. Most of the tumors did not regress entirely; rather, their height stabilized on a constant value (on average 61% of the initial height) after approximately 18 to 24 months. The decrease in height after brachytherapy was best fitted by the sum of a first order exponential decay and a constant ($h = 61 + 35*e^{-0.12t}$, in which t = time in months). The half-life of the decay was 5.8 months. Large tumors (>8 mm) had a faster initial decrease in height, and stabilized on a lower percentage of their initial height (50%) compared with small tumors (70%). Thus, the half-life of the height exponential decay was 5.3 months for small tumors (2–4 mm) and 3.3 months for the large tumors (>8 mm). Internal reflectivity increased from a mean of 40% before therapy to 70% after 2 years. The dynamics of the reflectivity were best fitted with the function: $f = 45 + 24(1\text{-}e^{-0.09t})$. Larger tumors, which initially had lower internal reflectivity, presented with a slower increase in internal reflectivity ($t_{½} = 8.7$ months) compared with smaller tumors ($t_{1/2} = 5$ months).

Conclusions: The postbrachytherapy ultrasonographic dynamics of uveal melanomas resemble a function composed of the sum of a constant and a first order exponent, suggesting the possible existence of two components (cell populations), one unaffected by brachytherapy and the other a radiosensitive population that reacts to brachytherapy in an exponential decay. An exponential decay can imply that the postbrachytherapy death of each tumor cell is a stochastic Markovian process that is independent of the death of other tumor cells.
Ophthalmology 2002;109:1137–1141 © 2002 by the American Academy of Ophthalmology.

Melanoma of the uvea is the most common primary intraocular malignancy in adults. Uveal melanomas metastasize relatively late; the 5-, 10- and 15-year survival rates based on tumor-related mortality are reported to be 72%, 59%, and 53%, respectively,[1,2] compared with age-matched controls. For patients with uveal melanoma, there is no curative therapy if metastases have developed. The survival after clinical diagnosis of hepatic metastasis is poor.[3,4] To lower melanoma-related mortality, it is essential to prevent or eradicate metastatic disease.

Whereas enucleation was the original treatment for uveal melanoma, Zimmerman et al[5] suggested that it can cause dissemination of tumor emboli. This led to a shift toward more conservative treatments intended to preserve the eye. These treatments, such as brachytherapy[6] and external proton beam irradiation,[7] aim to destroy the tumor by irradiation.[8] However, it was shown that postirradiation, most tumors shrink but do not disappear. Moreover, some studies have shown that viable-appearing cells are found in the

Originally received: January 9, 2001.
Accepted: October 12, 2001. Manuscript no. 210015.

Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel.

Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, April 30–May 5, 2000.

Reprint requests to Igor Kaiserman, MD, MPA, Department of Ophthalmology, Hadassah University Hospital, P.O.B. 12000, IL-91120 Jerusalem, Israel. E-mail: Igork@cc.huji.ac.il.

ISSN 0161-6420/02/$–see front matter
PII S0161-6420(02)01054-0

tumor's remnant. Histopathologic examination of 42 enucleated tumors that were previously irradiated showed regressive features in all tumors, but only 5 melanomas were completely necrotic, and viable-appearing tumor cells were present in all of the remaining 37 irradiated tumors.[9] Using proliferation markers such as PC-10 monoclonal antibodies[10] and Ki-67 (Mib-1),[11,12] cell proliferation was shown to exist in areas that were undertreated and in recurrent tumors. The proliferative activity was shown to correlate well with more aggressive metastatic tumors[10,13] and other prognostic variables, such as mitotic index and histologic largest tumor diameter.[12] Thus, the existence of viable, sometimes proliferating, cells in almost all tumors postirradiation, although they have not been proven to be of metastatic potential, warrants long-term ultrasonic follow-up to detect and treat regrowth.

Grange et al[14] analyzed the rate of tumor regression in 127 uveal melanomas treated with Ru^{106} brachytherapy and divided them into two groups: radio-sensitive tumors and radio-resistant ones. Correlation between radio-sensitivity and tumor cell type was obtained with intraoperative fine needle aspiration biopsy and showed a prevalence of the epithelioid type in the radio-sensitive group.

In the present study, we looked at the postbrachytherapy ultrasonographic changes of tumor height and internal reflectivity to understand better the effects of brachytherapy on uveal melanoma.

Materials and Methods

One hundred forty-seven consecutive patients who had uveal malignant melanoma and were treated with Ru^{106} brachytherapy were included in the study. The patients included 80 females and 67 males. The standard dose of irradiation was 10,000 cGy to the apex of the tumor. In higher tumors (7.5–8.0 mm height) in which this dose of irradiation could not be applied, the tumor base was irradiated with a maximum dose of 100,000 cGy were irradiated to the tumor base. In general, tumors higher than 8 mm were not treated by brachytherapy. However, in this study, we did include patients with tumors higher than 8 mm who refused any other treatment and insisted on brachytherapy despite the physician's reservations.

The patients were followed by clinical and echographic means using both standardized A scans and B scans (B-Scan "S"; Biovision, Paris, France) before and after brachytherapy. Follow-up was scheduled 3 months after brachytherapy and every 6 months thereafter. The echographic examination included measurement of tumor height (A scan), base diameter (B scan), internal reflectivity (A scan after calibration to "tissue sensitivity" as defined by standardized echography, in which the retina's reflectivity is 100% and the amplification curve is S-shaped),[15] regularity (A scan), vascularity (A scan) and extra-scleral extension (A and B scans). To compare tumors of different sizes, all tumors were standardized to their size at brachytherapy.

For the temporal dynamics analysis, the tumor data (height and internal reflectivity) were grouped into 3-month groups, and the mean and standard deviation of each group were calculated. The postbrachytherapy height and internal reflectivity data were fitted with polynomial, hyperbolic, logarithmic, and first and second order exponential equations using the least-square fitting method (Sigmaplot, Version 6, SPSS Inc., Chicago, IL). The best fitting equation was chosen using the goodness-of-fit analysis.

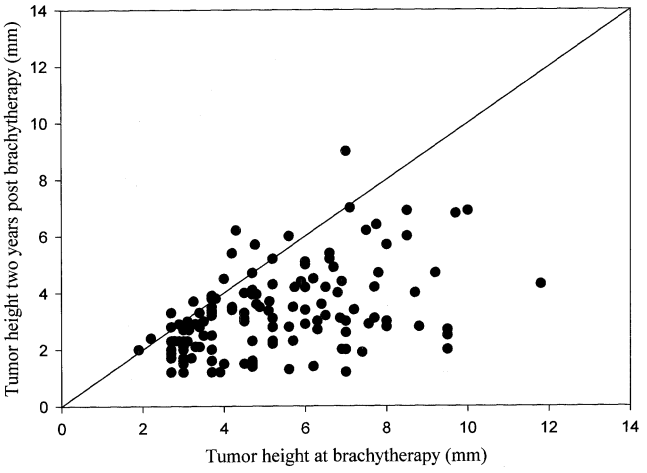

Figure 1. The correlation between tumor height at brachytherapy and 2 years postbrachytherapy. At 2 years, the tumors were significantly smaller.

The melanomas were classified into three groups according to tumor height before therapy: (1) small tumors (2–4 mm); (2) medium tumors (4–8 mm); and (3) large tumors (>8 mm). The postbrachytherapy dynamics of height and internal reflectivity were compared among the three groups using the *t* test and analysis of variance statistics.

Results

One hundred forty-seven patients with a mean age of 61 years (range, 29–97 years) were included in the study (57 with small tumors, 66 with medium tumors, and 24 with large tumors). The postsurgical follow-up included A and B ultrasonography and an ophthalmologic examination 3 months after surgery and every 6.6 ± 0.3 months (mean ± standard error of the mean) thereafter for a total of 1001 ultrasonography examinations. Each patient was examined on average 5.6 times (range, 3–17 times).

Before brachytherapy, the mean tumor height was 5.2 mm (range, 2.2–11.8 mm). After brachytherapy, 142 tumors (96.6%) responded by a decrease in height. Figure 1 presents the distribution of tumor height at brachytherapy (mean height, 5.2 mm) and 2 years postbrachytherapy (mean height, 3.3 mm). At 2 years, the tumors were significantly smaller (paired *t* test; $t = 9.9$; $P < 0.001$).

Figure 2 shows the decrease in tumor height postbrachytherapy. The height decreased at an initial rate of approximately 3% per month, and stabilized on a constant value (61%) after approximately 24 months. We fitted the dynamics of the height (h) decrease with various mathematical functions. The function that fitted best was the sum of a first order exponential decay and a constant ($h = 61 + 35*e^{-0.12t}$ in which t = time in months). The half-life of this decay is 5.8 months.

Figure 3 shows the postbrachytherapy dynamics of small tumors (2–4 mm) versus large tumors (>8 mm). The larger tumors showed a faster initial decrease in height and they stabilized on a lower percentage of their initial height. Thus, the half-life of the height decay was 5.3 months for small tumors ($h = 70+27*e^{-0.13t}$ in which t = time in months) and 3.3 months for the large tumors ($h = 50 + 47*e^{-0.21t}$ in which t = time in months). The small tumors stabilized on 70% of their initial height, whereas the large tumors stabilized on 50%.

Figure 4 shows the distribution of the tumor internal reflectivity

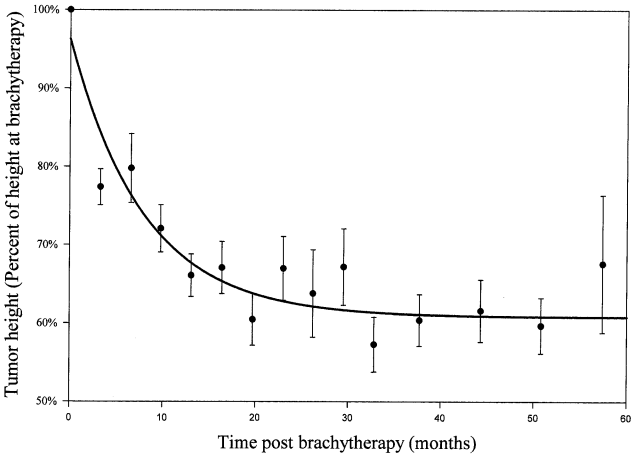

Figure 2. Postbrachytherapy dynamics of the mean (± standard error of the mean) tumor height. The line represents the function: height = 61 + $35*e^{-0.12t}$ in which t = time in months.

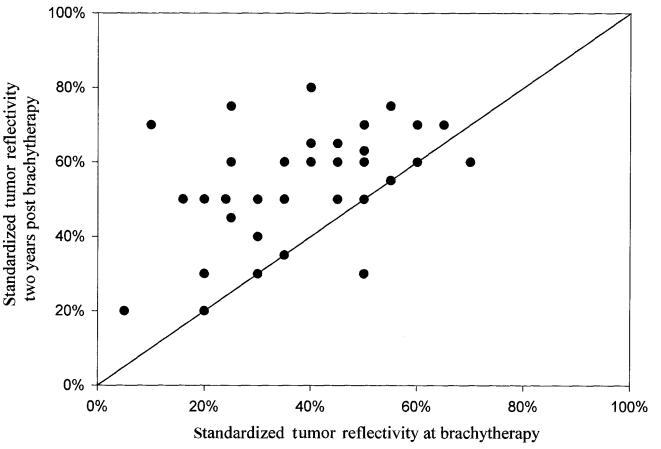

Figure 4. The correlation between tumor internal reflectivity at brachytherapy and 2 years postbrachytherapy. At 2 years, the tumors were significantly more reflective.

at brachytherapy (mean internal reflectivity, 40%) and 2 years postbrachytherapy (mean internal reflectivity, 70%). At 2 years, the tumors were significantly more reflective (paired *t* test, t = 7.8; $P < 0.001$).

Figure 5 shows the increase in tumor internal reflectivity postbrachytherapy. We fitted the dynamics of the internal reflectivity (R) with various mathematical functions. The function that fitted best was the sum of a first order exponential rise and a constant: $R = 45 + 24(1\text{-}e^{-0.09t}$ in which t = time in months). The half life of this rise is 7.7 months.

Figure 6 shows that smaller tumors, which initially had a significantly higher internal reflectivity (*t* test; $P = 0.03$) than large tumors, also had a faster initial rise in internal reflectivity ($t_{1/2}$ = 5 months) compared with the larger tumors ($t_{1/2}$ = 8.7 months). All tumors stabilized on a similar final internal reflectivity (about 70%).

Because we noted a significant difference between smaller and larger tumors in regard to their postbrachytherapy height and internal reflectivity changes, we looked at the mean radiation dose to the tumor base –1 mm from the radioactive plaque. In general, all tumors were planed to receive 10,000 cGy to the apex, without exceeding 100,000 cGy to the base. Whereas the small tumors (2–4 mm) received a mean radiation dose of 30,580 ± 7590cGy (mean ± standard deviation) to their base, the medium tumors (4–8 mm) received a mean dose of 64,228 ± 11,325 cGy, and the large tumors (>8 mm) received a mean dose of 101,990 ± 7080 cGy. The difference among all three groups was statistically significant (analysis of variance; $P < 0.0001$). Calculating the midtumor radiation dose (linear calculation at midrange between the base and the apex), we noted that whereas the small tumors received a midtumor dose of 20,628 ± 3600 cGy, the medium tumors received 37,540 ± 8942 cGy, and the large tumors received 53,610 ± 3772 cGy. The difference among the three groups was again statistically significant (analysis of variance; $P < 0.0001$).

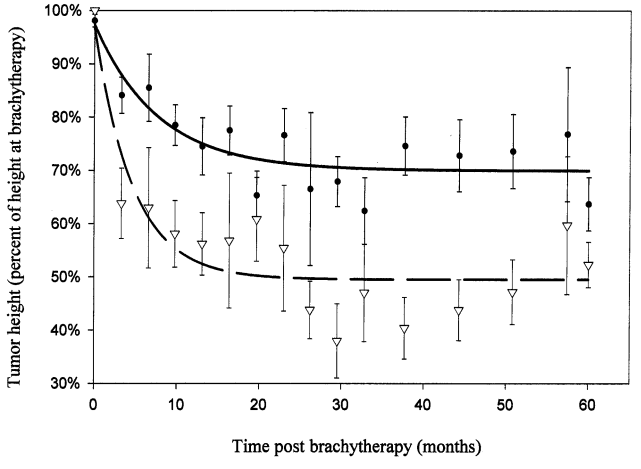

Figure 3. Postbrachytherapy dynamics of small (<4 mm, circles, solid line) versus large (>8 mm, triangles, dashed line) tumor height. The solid line represents the function: height = 70 + $27*e^{-0.13t}$ in which t = time in months, and the dashed line represents height = 50 + $47*e^{-0.21t}$.

Discussion

The present study confirms the well-known fact that postbrachytherapy uveal melanomas shrink in size and their

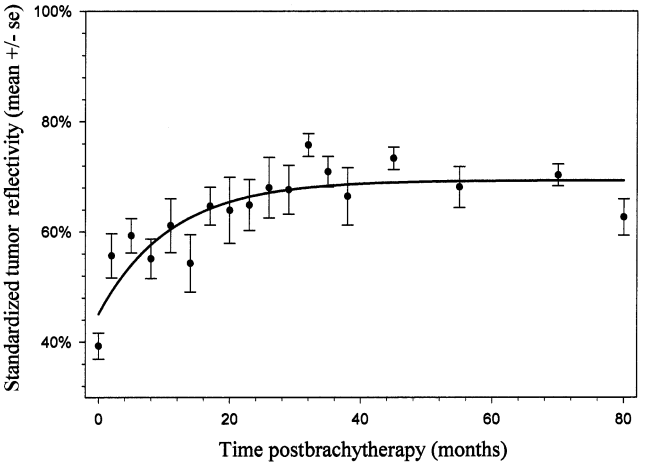

Figure 5. Postbrachytherapy dynamics of mean (± standard error of the mean) tumor internal reflectivity. The line represents the function: reflectivity = 45 + $24(1 - e^{-0.09t})$ in which t = time in months.

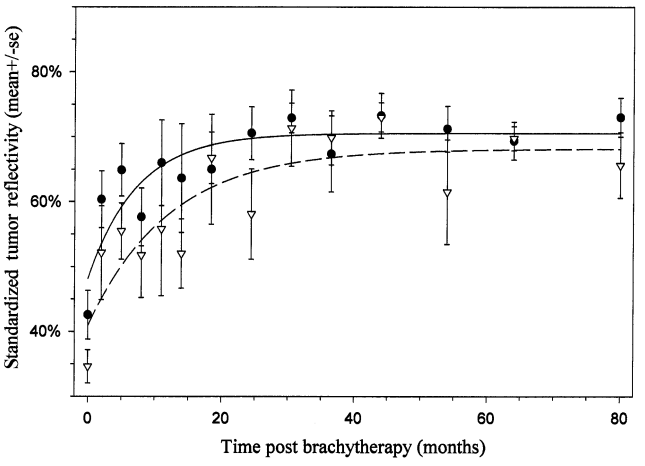

Figure 6. Postbrachytherapy dynamics of small (height, <4 mm, circles, solid line) versus large (height, >8 mm, triangles, dashed line) tumor internal reflectivity. The solid line represents the function: reflectivity = $48 + 22(1 - e^{-0.14t})$ in which t = time in months, and the dashed line represents the function reflectivity = $40 + 27(1 - e^{-0.08t})$.

internal reflectivity increases. Most tumors do not disappear entirely, and there is usually a residual mass, which in most cases does not change.[16] This mass has a histological composition of small spindle cells with a low proliferation index.[9–11]

We have shown that the larger, probably more aggressive, tumors are more radio-sensitive than the smaller tumors. Similarly, Grange et al[14] analyzed the speed of tumor regression in 127 uveal melanomas treated with brachytherapy and divided them into two groups: (1) radio-sensitive tumors with a residual volume < 50% in the following year, and (2) radio-resistant tumors. Correlation between radio sensitivity and tumor cell type was obtained with intraoperative fine needle aspiration biopsy and showed the prevalence of epithelioid type cells. The results of enucleation indicated the prevalence of spindle cell type inside the radio-resistant tumor group.

Because our treatment protocol requires delivering a radioactive dose of 10,000 cGy to the tumor's apex, the larger tumors received a significantly larger midtumor and base radiation dose. Thus, one might claim that the larger radiation dose was the cause of the faster decrease in height in the large tumors. However, because 97% of the tumors did not regrow during the follow-up period, we assume that almost all of our tumors received a more than sufficient dose of radiation to kill all the proliferating elements within the tumor. With such high radiation doses, we do not necessarily expect to see a dose dependence in tumor response to irradiation, unless there is an inherent difference among tumors in their radio-sensitivity.

We have also shown that the postbrachytherapy dynamics of uveal melanoma height and reflectivity resemble a function composed of the sum of a constant and a first order exponent. The fact that the dynamics of both tumor height and tumor internal reflectivity were best fitted by a similar mathematical function supports the assumption that this function reflects an inherent trait of these tumors. The mathematical analysis suggests the existence of two components (populations) in each tumor. One component is unaffected by irradiation (on average two-thirds of tumor height, which is about 30% of the volume), whereas the other is radio sensitive (about 70% of the volume) and as such shrinks after brachytherapy. The latter component, which may include both radio-sensitive tumor cells and radio-sensitive blood vessels, has lower internal reflectivity, whereas the residual radio-resistant component (tumor cells that might be accompanied by fibrotic tissue, necrotic tissue, inflammatory cells and macrophages) has higher internal reflectivity.

In larger tumors, the percentage of the radiation-sensitive component is higher, resulting in a larger postbrachytherapy decrease in tumor height (50% decrease in tumors >8 mm vs. 30% decrease in tumors <4 mm). Moreover, the radiation-sensitive cells in the larger tumors are probably more active, leading to a shorter exponential half-life (3.3 months in large tumors vs. 5.3 months in small ones). This difference in behavior is important in the evaluation of melanomas because rapid regression of a choroidal melanoma after brachytherapy is thought to be an unfavorable prognostic sign.[17]

Coleman et al[18] suggested that acoustic tissue typing (discriminant analysis of tumor ultrasonic power spectra) is correlated with tumor regression during the first 18 months after treatment. We have shown that large (fast-shrinking) tumors have a significantly lower initial internal reflectivity and a slower postbrachytherapy rise in internal reflectivity compared with small tumors. We postulate that the radiation-sensitive cell population shows lower internal reflectivity compared with the cells that are radio-resistant. After long-term follow-up, all tumors reach a similar internal reflectivity of approximately 70%. This suggests that the tumor remnant is composed homogeneously of radiation-resistant cells.

A mono-exponential decay is typical of populations that have a first-order decay pattern with a constant probability in time for an event to happen, independent of previous events (Markovian behavior), such as the decay of radioactive atoms. This can signify that the radiation-sensitive tumor cells do not die all at once at the time of brachytherapy but rather suffer an injury that causes the independent death of each cell at a later time, possibly the time when the cell goes into mitosis. Therefore, the postbrachytherapy death of each tumor cell is a stochastic Markovian process, which is independent of previous events (the death of other tumor cells).

In conclusion, we have shown that the postbrachytherapy dynamics of uveal melanoma height and internal reflectivity are exponential processes with time constants that depend on initial tumor size. The mathematical functions describing these processes may suggest the existence of two components in the tumor that differ in radiation sensitivity, ultrasonic reflectivity, and possibly, malignant potential.

References

1. Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. Arch Ophthalmol 1992;110:245–50.
2. Gamel JW, McLean IW, McCurdy JB. Biologic distinctions between cure and time to death in 2892 patients with intraocular melanoma. Cancer 1993;71:2299–305.
3. Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. Arch Ophthalmol 1983;101: 1894–9.
4. Kath R, Hayungs J, Bornfeld N, et al. Prognosis and treatment of disseminated uveal melanoma. Cancer 1993;72:2219–23.
5. Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells? Br J Ophthalmol 1978;62:420–5.
6. Packer S, Rotman M. Radiotherapy of choroidal melanoma with iodine 125. Int Ophthalmol Clin 1980;20:135–42.
7. Gragoudas ES, Goitein M, Verhey L, et al. Proton beam irradiation. An alternative to enucleation for intraocular melanomas. Ophthalmology 1980;87:571–81.
8. Rotman M, Long RS, Chan B, et al. Radiation therapy of choroidal melanoma. In: Hilaris BS, ed. Afterloading: 20 Years of Experience, 1955-1975. New York: Memorial Sloan-Kettering Cancer Center, 1975;133–9.
9. Seregard S, Lundell G, Lax I, et al. Tumour cell proliferation after failed ruthenium plaque radiotherapy for posterior uveal melanoma. Acta Ophthalmol Scand 1997;75:148–54.
10. Pe'er J, Gnessin H, Shargal Y, Livni N. PC-10 immunostaining of proliferating cell nuclear antigen in posterior uveal melanoma. Enucleation versus enucleation postirradiation groups. Ophthalmology 1994;101:56–62.
11. Schilling H, Sehu KW, Lee WR. A histologic study (including DNA quantification and Ki-67 labeling index) in uveal melanomas after brachytherapy with ruthenium plaques. Invest Ophthalmol Vis Sci 1997;38:2081–92.
12. Chiquet C, Grange JD, Ayzac L, et al. Effects of proton beam irradiation on uveal melanomas: a comparative study of Ki-67 expression in irradiated versus non-irradiated melanomas. Br J Ophthalmol 2000;84:98–102.
13. Seregard S, Oskarsson M, Spangberg B. PC-10 as a predictor of prognosis after antigen retrieval in posterior uveal melanoma. Invest Ophthalmol Vis Sci 1996;37:1451–8.
14. Grange JD, Thacoor S, Bievelez B, et al. Comparative study of the tumor regression rate of 127 uveal melanomas irradiated with 106 Ru/106 Rh. Attempted analysis of the correlations between per-operative cytology and histopathology of the enucleated eye and the tumoral regression on the one hand, and general prognosis on the other hand. Ophtalmologie 1990; 4:221–4.
15. Ossoinig KC. Standardized echography: basic principles, clinical applications, and results. Int Ophthalmol Clin 1979;19: 127–210.
16. Cruess AF, Augsburger JJ, Shields JA, et al. Regression of posterior uveal melanomas following cobalt-60 plaque radiotherapy. Ophthalmology 1984;91:1716–9.
17. Augsburger JJ, Gamel JW, Shields JA, et al. Post-irradiation regression of choroidal melanomas as a risk factor for death from metastatic disease. Ophthalmology 1987;94:1173–7.
18. Coleman DJ, Lizzi FL, Silverman RH, et al. Regression of uveal malignant melanomas following cobalt-60 plaque. Correlates between acoustic spectrum analysis and tumor regression. Retina 1985;5:73–8.