

Echographic findings in uveal melanomas treated with the Leksell gamma knife

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Abstract

Background/claims—Between June 1992 and July 1995, 29 uveal melanomas were treated radiosurgically with the Leksell gamma unit at the University of Graz. The aim of this retrospective study was to examine the pattern of regression and the extent and time period of the decrease in tumour size.

Methods—The Leksell gamma knife, model B, was used. Patients were divided into three groups according to marginal dose: group 1: eight patients with a marginal dose >50 Gy, group 2: 15 patients with a marginal dose = 50 Gy, and group 3: six patients with a marginal dose = 45 Gy. For the retrospective study two groups were examined: group A, tumours <5 mm and group B, tumours ≥5 mm.

Results—No significant correlation was found between tumour regression and the marginal dose. Tumour shrinkage depends on the pretreatment height. In the group of eight patients with an initial tumour prominence of less than 5 mm, no prominence was found after therapy. In the group of patients with an original tumour prominence of 5 mm and more, only two tumours formed a flat scar while a residual prominence was found in 18 patients. Increase in reflectivity combined with a decrease in size appears to be a good criterion for the effectiveness of the treatment. In five patients with tumours showing low reflectivity, over a longer period of time metastases were found. An enucleation was performed in two patients because of uncertain tumour regression and in one patient as a result of an increase in tumour size.

Conclusion—The pattern of echographic reflectivity and decrease in size is similar to brachytherapy and is one of the most important diagnostic variables for evaluation of tumour regression. An increase in reflectivity as well as a decrease in tumour size in the first 6-8 months can be considered a therapeutic success.

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Ever since cobalt-125, ruthenium-106 applicators, and teletherapy (proton, helium ions)¹⁻⁵ have been used for local treatment of uveal melanomas, echographic examinations have become increasingly important as follow up and evaluation of effectiveness. So far, studies on reflectivity patterns, decrease in tumour size, and sound attenuation have been published in connection with brachytherapy with

ruthenium-106, iodine-125, and cobalt-125.⁶⁻¹³ Experience with radiosurgical treatment of uveal melanoma has been reported by Chinela *et al*,¹⁴ Langmann *et al*,¹⁵ Marchini *et al*,¹⁶ Rennie *et al*,¹⁷ Zambrano *et al*,¹⁸ and Zehetmayer *et al*.¹⁹ Uveal melanomas have been treated radiosurgically with the Leksell gamma unit at the University of Graz since 1992. There have been several reports on echographic behaviour, internal reflectivity, and tumour regression.^{8-11 13}

Echographic follow up controls (A and B echography) were performed on all treated tumours to determine the effectiveness of treatment. The purpose of this study was to evaluate our experience with the dynamics of tumour regression and reflectivity patterns and to compare them with ruthenium-106 brachytherapy.

Patients

Between June 1992 and July 1996, 29 consecutively selected uveal melanomas were treated with the Leksell gamma unit at the University Eye Clinic, Graz. Besides routine biomicroscopy, tonometry, photodocumentation, and fluorescein angiography examinations, echographic examinations were performed preoperatively and 1 week, 6 weeks, 3 months, 6 months, 12 months, and finally at half year intervals postoperatively. The shortest interval was 1 year, the longest 4 years. The oldest patient was 90 years old and the youngest was 33 years old (average age 63 years). The smallest tumour was 2.67 mm high and the largest was 11.1 mm (Table 1).

Patients were divided into three groups according to treatment: group 1 with a marginal dose more than 50 Gy, group 2 with a marginal dose of 50 Gy, and group 3 with a marginal dose smaller than 50 Gy (Table 2).

All patients were treated with the Leksell gamma knife (LGK), Model B, manufactured by Elekta Instruments AB, Stockholm, Sweden. The LGK is a neurosurgical instrument. The LGK γ radiation is emitted from 201 cobalt sources (cobalt-60) localised in a hemisphere around the patient's head. The beams from all 201 sources converge to a focus point and, depending on the exposure time, an appropriate dose of radiation can be applied to the lesion. Radiosurgical treatment of uveal melanomas has been described in detail by Langmann *et al*.¹⁵ Firstly, a retrobulbar block was performed, using 5 ml anaesthetic drug. The eye was fixed with four sutures and the stereotactic frame was attached to the patient's head. All rectus muscles were fixed with sutures to the stereotactic frame. With the

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Table 1 Patient characteristics

No	Age (years)	Date of treatment	Height (mm)		Base of the tumour	Reflection (%)		Dose (Gy)
			Preop	Postop		Preop	Postop	
1	69	2/6/92	6.5	3.6	16.6 × 6.5	10	80	50
2	72	5/10/92	8.9	4.0	12.9 × 10.4	40	90	50
3	66	10/11/92	3.0	scar	15.0 × 12.0	20	90	60
4	31	10/12/92	7.9	3.72	7.2 × 14.5	20	80	40
5	61	11/12/92	6.6	2.6	7.3 × 6.4	20	80	60
6	53	17/12/92	4.0	scar	3.5 × 4.0	40	90	60
7	82	26/1/93	10.1	3.14	20.9 × 15.3	20	80	50
8	72	9/5/93	7.0	3.72	16.8 × 14.8	20	90	50
9	68	2/7/93	4.0	scar	4.3 × 8.2	20	90	70
10	62	2/9/93	5.0	scar	11.6 × 15.6	40	90	80
11	77	21/10/93	7.0	7.3 enucleation	16.8 × 15.0	70	70	60
12	74	30/11/93	3.5	scar	10.3	20	90	70
13	63	21/1/94	4.6	scar	10.0 × 11.0	40	90	50
14	65	11/2/94	5.2	3.5	12.6 × 9.8	20	70	50
15	32	1/3/94	2.9	scar		20	80	50
16	65	10/3/94	8.0	3.7		20	80	50
17	61	8/7/94	3.4	scar	11.0 × 13.0	50	90	50
18	51	6/10/94	5.5	2.8	12.3 × 7.8	30	90	45
19	46	18/10/94	10.8	4.8	9.8 × 8.6	20	90	50
20	51	8/11/94	9.4	applicator		50	70	50
21	50	21/11/94	8.6	8.0 enucleation	6.8 × 6.5	20	40	50
22	43	25/11/94	8.1	7.6 enucleation	7.7 × 16.8	20	40	50
23	47	21/12/94	9.8	5.2	15.1 × 21.4	20	90	50
24	98	22/12/94	11.1	5.35	12.6 × 15.4	60	80	50
25	71	8/3/95	5.9	scar	12.2 × 15.4	20	90	45
26	67	13/3/95	7.9	4.8		20	80	45
27	67	6/4/95	8.7	3.5	7.1 × 1.25	20	80	45
28	64	31/7/95	10.8	5.67		20	80	45
29	51	3/8/95	2.67	scar	5.9 × 5.7	20	90	45

stereotactic frame the patient's head was fixated at the magnetic resonance table with a special adapter to ensure that the axis system of the frame and the axis system of the magnetic resonance were concordant. The coordinates were determined by magnetic resonance and recorded. Treatment planning volume was defined as the gross tumour volume plus a safety margin of 1 mm around the tumour.

Echographic examinations were performed with Biovision A and B scan (Biovision, Clermont-Ferrand, France) and Ultrascan Digital A and B, Cooper Vision (California, USA) units. Standardised A-scan and B-scan echography was performed on all patients; the A-scan was performed in contact mode and the B-scan was done in immersion technique.

The following variables were used to characterise the tumours echographically:

- (1) Maximum tumour size in mm preoperatively, and 1 week, 6 weeks, 3 months, 6 months, 1 year, and every 6 months postoperatively.
- (2) Changes in reflectivity in percentages (pre- and postoperative values).
- (3) Half life of the tumour (time of tumour shrinkage to half its height).

Results

We divided our patients into three groups according to the marginal dose (Table 2) and two groups according to the tumour size—group A: tumours smaller than 5 mm and group B: tumours of 5 mm in height and more. We did not follow the TNM classification

because we treated tumours greater than 5 mm in height. The TNM classification grades T3 grade at 5 mm in height with an extension of 15 mm in diameter. We divided the tumours into smaller than 5 mm and 5 mm and larger, so that the extent of treatment with ruthenium-106 on the melanoma should not exceed 5 mm in height and 15 mm in diameter. Tumours smaller than 5 mm in height (average 4.6 mm) regressed completely in 8/8 cases to form a scar. Tumours above 5 mm in height (average

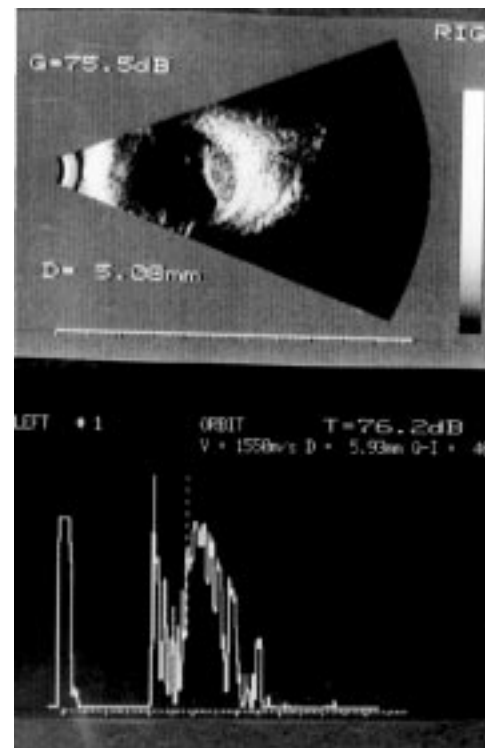


Figure 1 A 71 year old man. A-scan 5.9 mm solid tumour, low internal reflectivity, B-scan 5.1 × 12.2 mm.

Table 2 Tumour thickness, marginal dose, and follow up time (mean(SD))

	Thickness (mm)	Marginal dose (Gy)	Follow up (months)	No of patients
Group 1	4.4 (1.3)	65.7 (7.9)	33.1 (14.2)	8
Group 2	7.7 (2.5)	50	28.3 (9.7)	15
Group 3	8.2 (1.8)	44.4 (1.7)	20.0 (11)	6

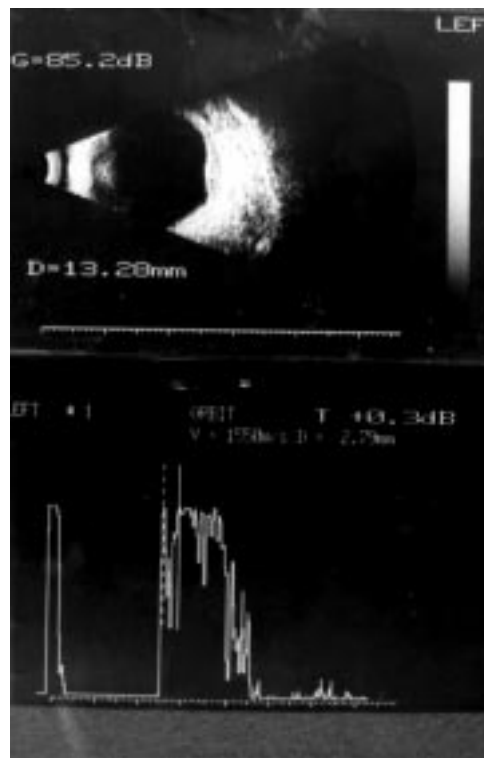


Figure 2 Same patient as in Figure 1, 12 months after stereotactic surgery. A scan 2.8 mm high prominence with high internal reflectivity.

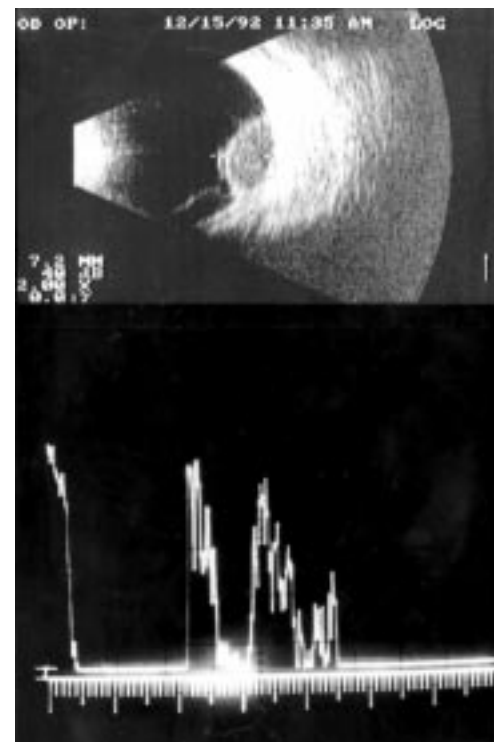


Figure 4 Same patient as in Figure 3, 4 months after stereotactic surgery. Tumour with low internal reflectivity and a height of 7.9 mm prominence.



Figure 3 A 35 year old man with a solid tumour of 7.9 mm prominence with low internal reflectivity.

7.0 mm) regressed completely in 2/20 (10%) cases but showed a residual prominence in 15/20 patients which was between 3 and 6.5 mm depending on pretreatment height. One patient (no 20) who had been treated primarily with a ruthenium applicator and then under-

went additional stereotactic treatment owing to lack of tumour regression after 1.5 years was excluded from this study. Enucleation was performed on three patients—on one eye because of an echographically assessed increase in tumour size (12 months postoperatively, preoperative 7.0 mm; postoperative 7.3 mm) and two eyes because of uncertain tumour regression—that is, no significant decrease in tumour height or increase in internal reflectivity (11 and 14 months, preoperative 8.6 and 8.0 mm; postoperative 8.0 and 7.6 mm). Histological examination of the eyes revealed active melanoma cells besides tumour cell necrosis, an infiltration of the sclera, and tumour vessel damage. No mitotic characteristics were found in the enucleated eyes with uncertain tumour regression, whereas some mitotic characteristics were found in the eye enucleated because of an increase in tumour size. Metastases were found in one patient belonging to the group with tumours smaller than 5 mm and in three patients with primary tumours larger than 5 mm.

After analysing the data, the following conclusions could be drawn:

(1) In 11 cases, the tumours seemed to increase in size with an increase in serous retinal detachment 1 week after treatment. The echographically measured increase in size was between 0.4 and 0.7 mm. We believe this apparent tumour growth is due to an exudative and/or inflammatory response since it subsided within 2 weeks to 4 months.

(2) Tumour regression occurred at different times depending on the marginal dose. In patients in groups 1 and 2 treated with a marginal dose of 50 Gy or more, a significant

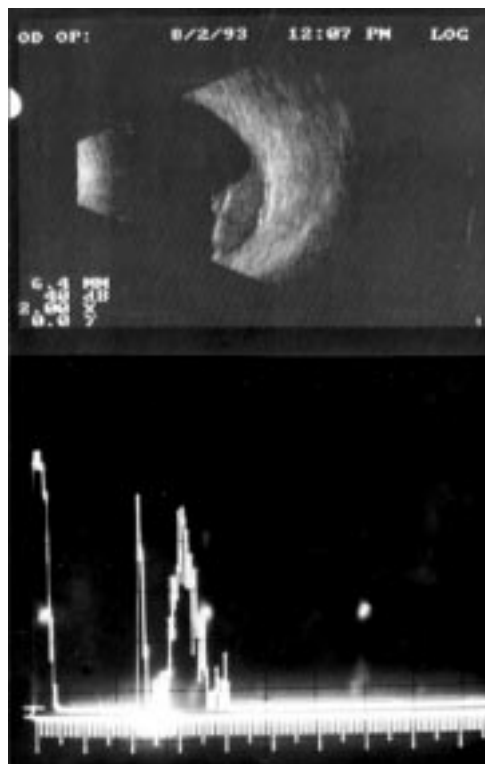


Figure 5 Same patient as in Figure 3, 12 months after stereotactic surgery. Tumour with height of 5.9 mm and low internal reflectivity. Metastases were found 28 months after treatment.

decrease in tumour size appeared after 3–6 months and in group 3 (smaller than 50 Gy marginal dose) after 5 to 7 months. The average tumour height after 1 year was 68.8% in group 1, 62.5% in group 2, and 56.9% in group 3 compared with pretreatment heights.

(3) The tendency to regress was found to depend on initial tumour height. In group A (eight patients) with a pretreatment tumour height of less than 5 mm, the tumours formed scars in all eight patients, while only two tumours formed scars in group B (20) patients with tumours above 5 mm (Figs 1–5).

(4) A difference was found in the reflectivity pattern between the groups. Group A showed a steady increase in internal reflectivity within the first 6 months, whereas in group B a steady increase in internal reflectivity appeared within the first 8–12 months. In six patients, the degree of reflectivity remained low up to 1 year without any increase in size.

(5) The tumour half life showed a dependence on pretreatment height. In the group of tumours less than 5 mm, the tumours were found echographically to have decreased in size by one half after a mean of 6 months (plus or minus 3 months) while tumours larger than 5 mm had a half life of 12 months (plus or minus 3 months)

Discussion

To our knowledge no previous reports have been published on the pattern of reflectivity of uveal melanomas after treatment with the Leksell gamma unit. Our goal was to compare our results with other reports about brachy-

therapy with ruthenium-106⁶⁻¹³ and teletherapy.

Eichler *et al*⁷ and Guthoff *et al*^{8,9} described typical patterns of reflectivity of uveal melanomas after brachytherapy with a marked reduction of tumour height and a simultaneous increase in the degree of reflectivity after 4 months. Relapses are characterised by an increase in prominence and a continuously low, or decrease in, reflectivity. Continuously low reflectivity is considered to be a bad prognostic sign. After evaluation of our data, radio-surgically treated melanomas were found to change in similar ways. A marked reduction in size and a steady increase in reflectivity usually occurred within 4–8 months in tumours smaller than 5 mm.

In group B, with tumours greater than 5 mm, the increase in internal reflectivity and marked tumour reduction were observed usually after 12 months and longer. It seems that small tumours react in the same way as when treated with brachytherapy, and large tumours as when treated with teletherapy as reported by Kindy-Degnan *et al*.¹ The pretreatment height of the tumour is a determining factor for its tendency to decrease. The initial tumour enlargement caused by inflammation or exudation can be observed more often in tumours greater than 5 mm than in smaller tumours and is probably due to the larger dose of irradiation. This initial enlargement is characterised by a low inner reflectivity and, in our experience, should not last longer than a maximum of 4 months. In our patients the enlargement reached a maximum after 3 weeks and stayed at a constant level for up to 3 months until finally the tumour began to decrease and the reflectivity slowly began to increase. The average enlargement was 0.4 mm (plus or minus 0.3 mm) depending on the pretreatment tumour height. Tumours above 8 mm showed an average increase of about 0.6 mm. Should the enlargement remain longer than 4 months combined with low inner reflectivity, indicating inadequate or no tumour regression, a strict follow up examination and steps for further treatment should be considered.

A marked decrease in tumour size combined with an increase in inner reflectivity is considered to be a good prognostic sign. The appearance of a measurable decrease in size depends on the pretreatment tumour height. Tumours smaller than 5 mm had a half life averaging 6 months (minimum 4 months, maximum 1 year). A complete regression occurred after an average of 18 months (minimum 1 year, maximum 2 years). Tumours larger than 5 mm had a half life averaging 18 months (minimum 6 months, maximum 2 years) and complete regression was observed in two cases after 1 year. Guthoff *et al*⁹ correlates the speed of regression with the prognosis for survival. Tumours with a rapid rate of regression were found to have a significantly higher risk for metastasis than tumours with a slow rate of regression. According to Guthoff *et al*,^{8,9} the rate of regression as well as the tumour size should be considered as individual prognostic

factors since a rapid radiogenic decrease in volume indicates a poor prognosis for survival.

We could not observe a correlation between rapid regression and a higher risk for metastasis, since only one patient presented with rapid tumour regression (pretreatment tumour height: 6 mm, half life: 2 months, complete regression after 1 year), and this patient has so far remained free of metastases. We did find a correlation between a long standing low reflectivity and the risk for metastasis. Reflectivity remained low for over 1 year in all patients with metastases and unsatisfactory tumour regression. This finding is in agreement with reports by Kissinger *et al.*,¹⁰ Eichler *et al.*,⁷ and Guthoff *et al.*^{8,9} who also consider low reflectivity to be a bad prognostic sign.

Metastasis or lack of tumour regression was compared with respect to the marginal dose. In the group with marginal doses higher than 50 Gy, three patients presented with metastases, and in the groups with doses equal to and smaller than 50 Gy, one patient presented with metastases in each group. Because of our small groups and the short post-treatment observation period (minimum 18 months, maximum 57 months) further larger studies are required to reach significant conclusions.

Evidence indicates that adequate tumour regression can be expected with a marginal dose smaller than 50 Gy.

The authors compared gamma knife therapy of uveal melanomas mainly with brachytherapy. This is because we do not have experience with teletherapy—proton beam and helium ions. When we compared our two groups (<5 mm and 5 mm and higher) we consider that tumour behaviour after gamma knife therapy is similar to teletherapy in group B. Small uveal melanomas will often regress to a flat chorioretinal scar, whereas large tumours regress partially, because of their height.

In summary, the echographic behaviour of uveal melanomas after gamma knife therapy is comparable with that after brachytherapy in small tumours and similar, with regard to time of regression and increase of internal reflectivity, to teletherapy in large tumours. Differences between the groups were observed—at the start of regression and with the increase in reflectivity which depended on the pretreatment height.

No marked increase in reflectivity within 6 months or no substantial decrease in the tumour height within 6 months should be considered a warning signal calling for further diagnostic and therapeutic steps.

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