Rate of Resolution of Exudative Retinal Detachment After Plaque Radiotherapy for Uveal Melanoma

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Objectives: To determine the clinical relevance of exudative retinal detachment (ERD) and the rate of ERD resolution after plaque radiotherapy of posterior uveal melanomas.

Methods: Retrospective, nonrandomized study of 135 consecutive patients with posterior uveal melanoma treated by iodine 125 plaque radiotherapy. Extent of ERD and tumor thickness were assessed before radiotherapy and at postoperative follow-up visits. Local tumor control was assessed at each follow-up visit.

Results: An ERD was present in 71 patients (53%) and was a risk factor for local treatment failure ($P=.03$). The ERD resolved after radiotherapy in 59 (83%) of the 71 patients. The ERD resolved within 1 year in 64 patients (90%) (mean time to resolution, 5.6 months). The rate of ERD resolution correlated with the rate of decrease in tumor thickness ($P=.004$). The ERD did not resolve and the tumor thickness continued to increase in 5 patients, who required further intervention. A recurrent retinal detachment developed in 5 patients, who were diagnosed as having rhegmatogenous retinal detachment (3 patients) and lipid exudation secondary to tumor vasculopathy (2 patients). Two patients with local tumor recurrence did not develop a recurrent ERD. Local tumor control was achieved in 130 patients (96%).

Conclusions: An ERD may be a risk factor for local failure after plaque radiotherapy for uveal melanoma. If an ERD does not resolve within 9 to 12 months of radiotherapy and the tumor is not regressing, treatment failure should be suspected. A recurrent ERD does not necessarily represent local tumor recurrence.

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PLAQUE RADIOThERAPY is one of the most common treatments for posterior uveal melanoma and has associated survival rates that are comparable to those for enucleation for medium-sized tumors. PLAQUE RADIOThERAPY is often the first clinical sign of irradiation response, and failure of the ERD to resolve has been interpreted as a sign of tumor unresponsiveness. However, it is not known how long it may take for an ERD to resolve before local treatment failure should be suspected. In addition, a coexistent rhegmatogenous retinal detachment or a persistent ERD due to an irradiation-induced inflammatory reaction can be mistaken for tumor unresponsiveness. Most irradiated tumors exhibit a slow but steady reduction in thickness during the first 2 to 3 years after treatment, and this tumor regression has been used as a gauge of therapeutic response. However, in some irradiated tumors, the tumor size may remain unchanged (or even increase) for a short time before regression occurs, possibly owing to tumor edema resulting from acute radiation vascular injury, inflamma-
tion, and necrosis. It remains unclear how long it may take for the tumor thickness to begin decreasing before local treatment failure should be suspected.

Local tumor recurrence, which is most commonly detected within the first 2 to 3 years after plaque therapy, can take the form of a flat marginal extension, a nodule protruding from the tumor surface, or a diffuse regrowth of the tumor. However, it remains unclear whether recurrent ERD is a common sign of local tumor recurrence.

In this study, we analyzed 135 patients who underwent iodine 125 ($^{125}$I) plaque radiotherapy for posterior uveal melanoma. The clinical course of ERD and tumor thickness were evaluated over time and correlated with local tumor control. We conclude that these variables are useful clinical indicators of tumor response to plaque radiotherapy, and we suggest guidelines for clinical monitoring of postradiotherapy tumor regression based on the rates of decrease in these variables.

### METHODS

Patients treated with $^{125}$I plaque radiotherapy for posterior uveal melanoma were identified via a computer-based search of the Barnes Retina Institute medical records. The Washington University institutional review board approved this study. We identified 135 patients meeting inclusion criteria who were initially evaluated between May 1, 1992, and June 30, 2001. Detailed clinical notes and detailed fundus drawings were available for most patients. Exclusion criteria included use of radioisotopes other than $^{125}$I, inadequate clinical information, uncertainty regarding the clinical diagnosis, and media opacity (eg, cataract or vitreous hemorrhage) that prevented ophthalmologic assessment of retinal detachment.

Posterior uveal melanoma was diagnosed on the basis of an elevated mass involving the choroid or ciliary body with ophthalmologic and ultrasonographic features typical of melanoma. Preoperative data recorded and evaluated for statistically associated inclusion criteria included patient age, sex, race (all patients were white), involved eye, visual acuity, systemic status, tumor basal dimensions (determined by fundus photographs and indirect ophthalmologic examination), tumor thickness (determined by A-scan ultrasonography), tumor pigmentation (light, medium, or dark), presence of collar-button configuration, tumor location (posterior or anterior to equator), proximity to the optic nerve and lobe, and size of the initial ERD (determined by indirect ophthalmoscopic examination). Exudative retinal detachment was characterized by (1) detachment of the retina by serous subretinal fluid extending beyond the tumor margins, (2) the presence of shifting fluid on patient repositioning, and (3) the absence of retinal breaks that would suggest a rhegmatogenous cause. For shallow detachments, ultrasonography was used to corroborate statistical estimates of ERD size. The percentage of detached retina was estimated by morphometric measurements from detailed fundus drawings.

All tumors were treated with $^{125}$I plaque radiotherapy using standard Collaborative Ocular Melanoma Study–style plaques prescribed to deliver 8300 rad (83 Gy) to the tumor apex in 4 to 5 days. Postoperative follow-up visits were typically performed at 3, 6, 9, 12, 16, 20, 24, 30, and 36 months, and at least annually thereafter. Some patients with atypical treatment response were followed up more frequently. Documentation at each follow-up visit included visual acuity, tumor basal diameter, tumor thickness by A-scan ultrasonography, size of the ERD, additional treatments (eg, laser therapy, thermotherapy, and enucleation), and reason for treatment (eg, unresponsiveness or local recurrence). Tumor responsiveness was defined as resolution of the ERD and a demonstrable decrease in tumor thickness (usually >10%, depending on the length of follow-up). Local recurrence was defined as regrowth of a previously responsive tumor by at least 1 mm in either the horizontal or vertical dimension, as measured by fundus photographs or A-scan ultrasonography, respectively.

Rates of decrease in tumor thickness and ERD size were assessed using the recorded tumor thickness and ERD size at each follow-up visit. The follow-up times (in months) at which tumor thickness decreased to below 90%, 75%, and 50% of the initial measurement were noted. Likewise, the follow-up times to 25%, 50%, 75%, and complete resolution (defined as no more than a thin layer of subretinal fluid overlying the tumor) of the ERD were documented for each patient.

Statistical analysis was performed using SPSS computer software (SPSS Inc, Chicago, Ill). Pearson correlation coefficients were calculated to analyze the relationship among continuous, quantitative initial clinical variables (pretreatment tumor thickness, largest basal diameter, ERD size, and patient age) and between continuous, quantitative initial variables and outcome variables (rates of decrease in tumor thickness and ERD size). Probability values were obtained from the corresponding 2-tailed $t$ test value. Two-tailed $t$ tests were used to analyze the relationship between dichotomous initial variables (tumor location, presence of ERD, and diagnosis of diabetes mellitus and hypertension) and continuous initial and outcome variables. The $t$ tests were also used to analyze the relationship between dichotomous outcome variables (tumor regression, persistence, or recurrence) and continuous variables. The threshold of significance was set at $P < .05$.

### RESULTS

A total of 135 patients with posterior uveal melanoma treated with $^{125}$I plaque radiotherapy were included in the study (Table). The patient group comprised 76 men and 59 women, with a mean age of 60 years (range, 26-88 years). The melanoma was located in the right eye in 66 patients and in the left eye in 69 patients. Sixty tumors (44%) were predominantly anterior to the equator, and 75 (56%) were posterior. The pretreatment mean largest basal tumor diameter was 11 mm (median, 11 mm; range, 3-20 mm), and the mean tumor thickness was 5.1 mm (median, 4.3 mm; range, 1.9-12.9 mm). Mean follow-up was 27 months (median, 24 months; range, 3-103 months).
TUMORS WITHOUT A PRETREATMENT ERD

Sixty-four (47%) of the 135 patients did not have an associated ERD before treatment. In this subgroup, tumor location was anterior to the equator in 24 patients (38%) and posterior in 40 (62%). The pretreatment mean largest basal tumor diameter was 12 mm (median, 11 mm; range, 5-20 mm), and the mean tumor thickness was 4.9 mm (median, 4.0 mm; range, 2.5-12.1 mm). Sixteen patients (25%) without an initial ERD developed one after radiotherapy, and all of these detachments resolved without further treatment. In all 64 patients without an initial ERD, the tumor regressed satisfactorily without further treatment and without local tumor recurrence at mean follow-up of 31 months (median, 28 months; range, 3-103 months).

TUMORS WITH A PRETREATMENT ERD

Seventy-one (53%) of the 135 patients had an ERD at the time of plaque surgery. In this subgroup, tumor location was anterior to the equator in 36 patients (51%) and posterior in 35 (49%). The mean largest basal diameter was 12 mm (median, 11 mm; range, 3-20 mm), and the mean tumor thickness was 5.3 mm (median, 4.7 mm; range, 1.9-12.9 mm). The mean percentage of the retina detached at the time of plaque placement was 22% (median, 15%; range, 5%-70%). Among patients with an initial ERD, the size of the ERD was statistically significantly associated with larger basal tumor diameter and greater tumor thickness (P<.001 for both). However, the presence of an ERD was not associated with any tumor characteristics or systemic features that were evaluated.

RESOLUTION OF ERD

Decreasing Tumor Thickness

In 56 (79%) of the 71 patients with an initial ERD, plaque radiotherapy resulted in complete resolution of pretreatment ERD and a decrease in tumor thickness without additional treatment. None of these patients developed local tumor recurrence at last follow-up. The mean time to 25% ERD reduction was 3.9 months (median, 3.2 months; range, 0.5-13.0 months), to 50% ERD reduction was 4.7 months (median, 3.3 months; range, 0.5-19.0 months), and to complete ERD resolution was 5.6 months (median, 3.5 months; range, 0.75-19.3 months). Fifty-eight patients (80%) with a pretreatment n=56) or posttreatment (n=16) ERD experienced a substantial (>25%) reduction in ERD size within 4 months of radiotherapy (Figure 1). Complete ERD resolution was achieved in 59 patients (83%) by approximately 9 months and in 64 (90%) by approximately 1 year after radiotherapy.

Larger initial ERD size was associated with longer time to ERD resolution (P<.001), and the rate of ERD resolution correlated with the rate of decrease in tumor thickness (P=0.04). However, no other patient or tumor characteristics were associated with ERD resolution or the rate of ERD resolution.

In 6 (8%) of the 71 patients with an initial ERD, tumor thickness continued to increase at the 3-month postoperative visit despite prompt ERD resolution. Four of these patients were observed closely without further treatment, and the tumor thickness began to decrease spontaneously 6 to 15 months after therapy. In 1 patient, transpupillary thermotherapy (TTT) was performed 12 months after radiotherapy, with subsequent rapid tumor shrinkage and local tumor control through 18 months of follow-up. In another patient, enucleation was performed, and pathological examination findings demonstrated abundant residual tumor cells consistent with tumor unresponsiveness to radiotherapy.

Recurrent Retinal Detachment

In 5 (7%) of the 71 patients with an initial ERD, the ERD resolved but a recurrent ERD later developed. Three patients had prompt resolution of ERD 3, 8, and 17 months after radiotherapy, but they subsequently developed recurrent ERD 6, 16, and 20 months after radiotherapy, respectively, in association with retinal breaks, consistent with rhegmatogenous retinal detachment. In addition, proliferative vitreoretinopathy was present in 2 of these patients, who had undergone recent panretinal photocoagulation for proliferative radiation retinopathy. In the patient without proliferative vitreoretinopathy, the retina was successfully reattached using a nondrainage scleral buckling procedure, and the tumor remained regressed through the last follow-up visit. The other 2 eyes were enucleated, and pathological examination revealed no evidence of local tumor recurrence.

In 2 other patients, the ERD resolved and tumor thickness was decreasing 3 and 6 months after radiotherapy, but a recurrent ERD developed 6 and 9 months after radiotherapy, respectively, associated with massive subretinal lipid exudation and intratumoral hemorrhage (Figure 2). Radiation retinopathy and papillopa-
thy were not noted in either case. The ERD did not resolve in both patients, and 1 patient underwent enucleation for irradiation complications; pathological examination findings showed no evidence of local tumor recurrence.

**Local Tumor Recurrence**

In 2 (3%) of the 71 patients with an initial ERD, the ERD resolved but local tumor recurrence was diagnosed (based on an increase in apical tumor thickness of >1 mm) 24 and 26 months after radiotherapy. Neither of these tumors developed a recurrent ERD. One of these patients underwent enucleation, and pathological examination demonstrated focal areas of abundant viable tumor cells consistent with local tumor recurrence. The other patient died of an undetermined cause before enucleation.

**PERSISTENCE OF ERD**

In 7 (10%) of the 71 patients with an initial ERD, the ERD remained unchanged or increased at the second postoperative visit (at approximately 6 months). In 2 of these patients, tumor thickness was stable or decreasing, and there was evidence of irradiation-induced tumor inflammation characterized by an inflammatory exudate over the tumor surface and perivascular sheathing (Figure 3). Both patients were observed closely without further treatment. The ERD began to decrease 7 and 9 months after radiotherapy and resolved completely at 19 and 12 months, respectively, accompanied by tumor shrinkage.

In the other 5 patients, the persistent ERD was accompanied by increasing tumor thickness, suggesting tumor unresponsiveness (Figure 4). Two of these tumors were treated with TTT 7 months after radiotherapy, which was followed by rapid resolution of the ERD, decreased tumor thickness, and continued local control at last follow-up, 34 and 16 months after radiotherapy. In 3 patients, enucleation was performed or recommended (1 patient refused treatment and was lost to follow-up). Pathological examination was available in 2 patients and showed abundant tumor cells with minimal irradiation-induced changes, consistent with unresponsiveness to radio-
therapy. Tumors in which ERD or tumor thickness did not respond to plaque therapy had a lower mean initial tumor thickness (4.3 mm) than all other tumors (5.2 mm) ($P=0.055$).

**LOCAL CONTROL RATES**

Overall, local tumor control was achieved in 130 (96%) of 135 patients treated with $^{125}$I plaque radiotherapy, 3 of which required supplemental TTT for irradiation unresponsiveness. All 5 patients with local treatment failure had an initial ERD ($P=0.03$). Of the 71 patients with an initial ERD, ERD resolution occurred in 65 (92%), and local tumor control was achieved in 66 (93%) at the last follow-up visit (mean, 23 months; median, 20 months; range, 4-78 months). Enucleation was performed (or recommended) for irradiation complications in 8 patients (5 with an initial ERD), tumor persistence in 3 (all with an initial ERD), and local tumor recurrence in 2 (both with an initial ERD). The association between an initial ERD and enucleation did not reach statistical significance ($P=0.06$).

**COMMENT**

We analyzed the changes in ERD and tumor thickness after $^{125}$I plaque radiotherapy in 135 posterior uveal melanomas. Approximately half of the tumors had an ERD before treatment, and the presence of an ERD was associated with local treatment failure. About one quarter of the tumors without an initial ERD developed an ERD after treatment. The ERD resolved in 59 patients (83%) within approximately 9 months and in 64 patients (90%) within approximately 1 year of radiotherapy. Resolution of ERD correlated strongly with decreasing tumor thickness and local tumor control. In a small subset of tumors, the ERD and thickness did not respond in a typical manner because of tumor unresponsiveness (presumably resulting from intrinsic tumor radioresistance), rhegmatogenous retinal detachment, irradiation-induced lipid exudation, or local tumor recurrence. We conclude that the rates of decrease in ERD and tumor thickness are useful indicators of tumor responsiveness and can be useful guides for postoperative management (Figure 5).

Of the 64 patients without a pretreatment ERD (47% of all patients), local tumor control was achieved without further treatment in all cases. Sixteen of these tumors (25%) developed a transient ERD after plaque therapy that subsequently resolved without further treatment, similar to previous observations. Fifty-nine tumors (83%) with a pretreatment ERD underwent prompt resolution of the ERD after treatment. Patients with a pretreatment ERD were at higher risk for local treatment failure than were those without an ERD. However, this finding should be interpreted with caution owing to the small number of patients. The size of the ERD was associated with larger tumor diameter and thickness. This finding is consistent with previous observations by Kivela and colleagues, who found ERD to be associated with tumor size and microvascular loops and networks, suggesting that tumor vascularity may play a role in the development of ERD. These investigators did not find a significant association between ERD and survival.

Serial evaluation of the ERD and tumor thickness were useful in monitoring tumor response to treatment. Based on our findings, one might expect approximately 90% of patients to have a substantial ($\geq 25\%$) reduction in ERD by the 6-month postoperative visit (Figure 1). Complete ERD resolution may be observed in 80% of pa-

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Figure 5. Postoperative management guidelines for uveal melanomas treated with plaque radiotherapy, based on the change in exudative retinal detachment (ERD) size and tumor thickness. The first checkpoint in the algorithm (boldfaced) occurs at the 3- to 6-month postoperative visits. Subsequent events may occur at any time. The indicated management steps are only general suggestions; other clinical factors must also be considered for each individual patient. TTT indicates transpupillary thermotherapy.
patients by 9 months and in 90% by 1 year after radiotherapy. In cases in which the ERD does not decrease within 6 to 9 months, tumor thickness is useful in determining whether the tumor is responding to radiotherapy. If the thickness is decreasing despite a persistent ERD at 6 to 9 months, the tumor may eventually respond to radiotherapy. If the thickness is increasing at 6 to 9 months, however, one must be concerned about the possibility of local treatment failure. One should also take into account that a larger initial ERD may take longer to resolve. Beyond 9 to 12 months, if neither the tumor size nor the ERD is decreasing, further treatment may be necessary. We initially used adjuvant TTT whenever possible, because this modality usually induces rapid ERD resolution and tumor shrinkage. If the tumor is not amenable to TTT (owing to large size, anterior location, or a large overlying ERD), we generally recommended enucleation. In both patients who underwent enucleation owing to persistent ERD and increasing tumor thickness, histopathologic examination findings revealed abundant tumor cells, suggesting intrinsic tumor radioresistance. Some tumors continue to increase in size for a few months after radiotherapy even though the ERD is decreasing. Our findings suggest that most of these tumors will eventually respond to radiotherapy without further intervention. Transient increases in ERD or tumor thickness after radiotherapy may be due to acute irradiation edema associated with tumor vasculopathy, inflammation, and necrosis. The presence of perivascular sheathing and an inflammatory exudate overlying the tumor may help distinguish an exuberant inflammatory response from local treatment failure (Figure 3).

The role of TTT in the management of uveal melanoma still remains controversial. However, we observed a strong synergistic effect between TTT and plaque radiotherapy, similar to initial observations by Oosterhuis and colleagues. These findings suggest that TTT may have an important role as an adjunct to plaque radiotherapy not only in tumors that are unresponsive to radiotherapy but also as a prophylactic measure in tumors at higher risk for local failure (eg, juxtapapillary tumors). A prospective, randomized study would be required to address this question.

Three patients developed a recurrent retinal detachment after resolution of the initial ERD that proved to be rhegmatogenous in origin. Tumor thickness was decreasing in all 3 cases, with no evidence of local recurrence. Two of these patients had undergone recent panretinal photocoagulation. However, the small number of patients does not permit us to determine whether there is a causal relationship between laser treatment and retinal detachment. If a rhegmatogenous retinal detachment is suspected in an eye containing a melanoma, careful indirect ophthalmoscopy with scleral depression should be performed. If the tear is responsible for the retinal detachment, it may be repaired by pneumatic retinopexy or scleral buckling surgery, as in our patient. Vitrectomy or external drainage of subretinal fluid should be approached with extreme caution if there is any uncertainty about the viability of the tumor owing to the theoretical risk of disseminating tumor cells out of the eye.

Two patients developed a recurrent ERD that seemed to be caused by exuberant subretinal lipid exudation, which was associated with chronic retinal detachment and poor visual outcome (Figure 2). Neither patient had clinically evident irradiation retinopathy or papillopathy. Instead, the emanation of lipid directly from the tumor, the associated intratumoral hemorrhages, and the short time course (6-9 months) suggest that this clinical presentation may be due to irradiation-induced tumor vasculopathy.

Only 2 patients (1.5%) in our study developed bona fide local tumor recurrence, and neither had a recurrent ERD. These results suggest that in the absence of verified tumor regrowth, a recurrent ERD does not necessarily signify local tumor recurrence. A persistent or recurrent ERD must be distinguished from separation of atrophic retina from the regressing tumor. This finding occurs commonly as a chronic change after plaque radiotherapy and can be identified by slitlamp biomicroscopy. The thin, atrophic neurosensory retina becomes separated from the underlying tumor, which has a regressed, inactive appearance. The retinal separation usually does not extend beyond the tumor margins, and the subretinal space may contain gray-white debris.

Tumors in which the ERD did not resolve after plaque radiotherapy tended to be thinner than responsive tumors, although this association did not achieve statistical significance (P = .055). This finding is consistent with those of previous studies linking thinner tumors to a higher local failure rate. One possible explanation for this observation is that thinner tumors receive less radiation (the dosimetric treatment depth is determined by the tumor thickness) and tend to be located more posteriorly, where plaque tilting away from the sclera is more likely to occur. This combination of factors may increase the risk of undertreatment of the tumor. Other possible factors include intrinsic radioresistance in thinner tumors, inadvertent dosimetric miscalculations (none were detected in our study), and poor plaque placement. In an attempt to circumvent some of these potential factors, we routinely use ultrasound at plaque insertion to aid in plaque localization and to detect plaque tilting. Further studies are ongoing to determine whether these steps contribute to improved local control rates.

Limitations in our study design must be taken into account when interpreting the results. Because most tumors responded satisfactorily to plaque radiotherapy, the number of patients with atypical responses was small, which could lead to statistically significant associations that occurred by chance. The nonrandomized study design does not allow us to determine whether the secondary interventions used in tumors that did not respond to radiotherapy altered the local or systemic outcomes. The relatively short length of follow-up precludes an analysis of survival and may not identify some patients who will eventually develop local treatment failure.

In conclusion, we found that posterior uveal melanomas with an associated ERD may be at higher risk for local treatment failure after plaque radiotherapy. The rates of decrease in ERD size and tumor thickness after plaque radiotherapy are useful clinical indicators of tumor re-
gression and can be used to establish clinical guidelines for postoperative management.

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CONGRATULATIONS TO THE WINNER OF OUR JULY QUIZ, JOSH LITWIN, MD. THE CORRECT ANSWER TO OUR JULY CHALLENGE WAS BACTERIAL KERATITIS. FOR A COMPLETE DISCUSSION OF THIS CASE, SEE THE CLINICOPATHOLOGIC REPORTS, CASE REPORTS, AND SMALL CASE SERIES SECTION IN THE AUGUST ARCHIVES (CHO BJ, LEE YB. INFECTIOUS KERATITIS MANIFESTING AS A WHITE PLAQUE ON THE CORNEA. ARCH OPHTHALMOL. 2002;120:1091-1093).

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I believe that medicine is at a crossroads between “what is in the best interest of the patient?” and “follow the money.” The medical profession currently has mutual trust through a social contract between the physician and the patient. I am involved in teaching ethics in the Department of Ophthalmology at Washington University, St Louis, Mo, and we follow the American Academy of Ophthalmology’s book *The Ethical Ophthalmologist: A Primer*, which I highly recommend. Residents are very interested in this subject.

I strongly believe that the graduate student in medicine can be taught ethics and can learn ethical behavior in a structured curriculum. More important, teaching ethics fosters discussions of issues and leads to the practical resolution of many dilemmas. However, I am not aware of any scientific or social studies that prove that “teaching and learning” ethics can modify behavior. We are human; “Our characters are the result of our conduct.”

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**Correction**

**Error in Figure.** In the Clinical Sciences feature titled “Rate of Resolution of Exudative Retinal Detachment After Plaque Radiotherapy for Uveal Melanoma,” published in the November issue of the ARCHIVES (2002;120:1463-1469), data in Figure 5 were accidentally transposed. The fourth row down reading across should have read “Decreasing,” “Increasing,” “Increasing,” “Decreasing.” Figure 5 is reprinted correctly herein.

![Figure 5](https://archopht.jamanetwork.com/)

**Figure 5.** Postoperative management guidelines for uveal melanomas treated with plaque radiotherapy, based on the change in exudative retinal detachment (ERD) size and tumor thickness. The first checkpoint in the algorithm (boldfaced) occurs at the 3- to 6-month postoperative visits. Subsequent events may occur at any time. The indicated management steps are only general suggestions; other clinical factors must also be considered for each individual patient. TTT indicates transpupillary thermotherapy.