



Nina Mikhailenko. *May in Prague*. Oil on canvas, 16" × 20".

*Alternative methods to enucleation are being investigated to improve survival, vision, and quality of life for patients with choroidal melanoma.*

# Choroidal Melanoma: Natural History and Management Options

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**Background:** Choroidal melanoma is the most common primary malignancy of the eye. Enucleation has been the mainstay of treatment, but new and more effective options have recently been proposed as eye- and vision-sparing alternatives.

**Methods:** We reviewed the medical literature for trials and case reports involving the evolution, current uses, and limitations of alternatives to enucleation for treating choroidal melanoma.

**Results:** Options to treat choroidal melanomas depend on the location and size of the tumor and goals of therapy. Local control with plaque radiotherapy has provided overall survival comparable to enucleation. Transscleral resection may leave behind potentially viable melanoma cells following surgery; adjuvant brachytherapy is recommended to irradiate remaining tumor cells. Elevating tissue temperature potentiates the effect of ionizing radiation, thus reducing the dose of radiation needed to treat uveal melanoma. Transpupillary thermotherapy has been effective only in select circumstances, and long-term results have shown poorer local control rates and similar visual outcomes compared with other conservative treatment methods.

**Conclusions:** Treatment therapies for choroidal melanoma warrant further study. Currently, enucleation remains as effective as the eye- and vision-sparing approaches.

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Abbreviations used in this paper: COMS = Collaborative Ocular Melanoma Study; TTT = transpupillary thermotherapy.

## Introduction

Choroidal melanoma is the most common primary malignancy of the eye,<sup>1</sup> with an estimated incidence in the United States of 6 to 7 cases per million people.<sup>2,3</sup> Enucleation was historically the mainstay of treatment. However, because of the devastating consequences of removing an eye that still may be capable of useful vision, more effective and more conservative therapies to diagnose and treat the tumors are being investigated. Alternative treatment modalities that have been proposed in recent years include observation, microsurgical resection, photocoagu-

lation, plaque or charged-particle radiotherapy, and thermotherapy.<sup>4</sup> This review article examines the evolution, current use, limitations, and future of these modalities, particularly transpupillary thermotherapy (TTT).

## Natural History and Metastasis

Much effort has been directed at determining which choroidal lesions are dangerous and therefore need to be treated. Because the treatment is severe and life altering, it would be beneficial to know which lesions are nevi and which lesions are melanomas. The upper limit of normal for benign choroidal nevi is approximately 5 mm in diameter and 1 mm in thickness, and the mortality risk from such a lesion is essentially zero.<sup>5</sup> Choroidal melanomas are routinely classified as small (<10 mm in diameter and <3 mm in height), medium (10 to 15 mm in diameter and 3 to 5 mm in height), or large (>15 mm in diameter and >5 mm in height).<sup>6,7</sup> Multiple studies, including the Collaborative Ocular Melanoma Study (COMS), have specified tumor size as the strongest indicator of metastasis and therefore survival.<sup>8,9</sup> Ten-year survival rates for uveal melanomas have been published as 81.2% for small melanomas, 60.0% for medium melanomas, and 34.8% for large uveal melanomas.<sup>10</sup> The COMS additionally identified older patient age as a baseline covariate that affected the prognosis for survival.<sup>8</sup>

Ocular melanomas metastasize hematogenously primarily to the liver but also to lung, bone, kidney, and brain.<sup>9,11</sup> Zakka et al<sup>11</sup> reported only 75% of ocular melanomas had metastasized at the time of death compared with 96% of nonocular melanomas. Although ocular melanomas are not as aggressive as cutaneous melanomas, they carry a substantial risk of metastasis. In a long-term study of patients treated for uveal melanoma by enucleation in Finland between 1962 and 1981, 61% of patients eventually died as a result of the disease.<sup>12</sup> Mortality related to uveal melanoma was 31% by 5 years, 45% by 15 years, 49% by 25 years, and 52% by 35 years. Among patients who died of uveal melanoma, 62%, 90%, 98%, and 100% died within 5, 15, 25, and 35 years, respectively. Once metastasis occurs, survival is less than 7 months.<sup>13</sup> Therefore, it is important to identify cancerous lesions and begin treatment before metastasis occurs.

Accuracy in diagnosing choroidal melanomas has improved in recent years as a result of more experience, a better understanding of risk factors, and improved diagnostic equipment such as ultrasound. Thirty years ago, published studies from the Armed Forces Institute of Pathology indicated that approximately 20% of eyes enucleated for melanoma in fact had benign lesions.<sup>14</sup> Follow-up reports described a decline in misdiagnosis rate from 12.5% to 1.4% from 1970 to 1980,<sup>15</sup> which was attributed to improved accuracy in diagnoses made outside of major academic centers. Most recently, the COMS,

involving more than 50 centers in the United States and Canada, reported a misdiagnosis rate of 0.48%, the lowest rate ever reported.<sup>16</sup>

In a retrospective review of 1,329 small melanocytic choroidal tumors, Shields et al<sup>17</sup> found that documented growth of a lesion carried a 3.2 relative risk of metastasis. They also reported that 18% of identified lesions in the study demonstrated growth in a median time of 25 months, and 3% metastasized in a median time of 51 months. This conclusion is supported by Diener-West et al,<sup>18</sup> who performed a meta-analysis and found that detection of a small tumor has a more favorable prognosis than detection of a medium or large tumor, as evidenced by estimated 5-year mortality rates following enucleation of 16%, 32%, and 53% for small, medium, and large tumors, respectively. This indicates that observation of a choroidal lesion is risky, given the fact that growth may decrease survival. However, estimates indicate that it takes 7 years for a small melanoma to grow into a large melanoma and an additional 4 years before metastasis occurs.<sup>6,10</sup> At this rate of growth, there is ample time to initiate treatment. An alternate model published by Eskelin et al<sup>19</sup> estimated that micrometastases could develop as early as 5 years prior to the treatment of the primary tumor, which presumably occurs when suspicious characteristics first appear. At this estimated time of micrometastasis, the primary tumor size would be theoretically only 7 mm<sup>3</sup>, or approximately 3 mm in diameter and 1.5 mm in height at the time of metastasis.<sup>20</sup> Therefore, much effort has been devoted to better predict which lesions are likely to grow so that treatment may be initiated prior to metastasis.

Shields et al<sup>17</sup> found increased tumor thickness (>1 mm), location touching the optic disc, visual symptoms, presence of orange pigment, and subretinal fluid as factors predictive of future growth (Fig 1). The risk of tumor growth is 4% if none of these factors are present and more than 50% if three factors are present.<sup>21</sup> McLean<sup>22</sup> argued that observing tumors less than 1 mm in height in order to document growth increased the metastasis rate by only 1% (11% for tumors less than 1 mm in thickness vs 12% for tumors thicker than 1 mm). He concluded that there is little benefit to early treatment prior to clinically documenting growth.

In 1979, Zimmerman and colleagues<sup>6,23</sup> proposed that enucleation of a globe with choroidal melanoma may actually decrease survival, noting the rise in the mortality rate in the years following enucleation from a baseline of 1% per year to a peak of 8% per year during the second year following enucleation. The rate subsequently returned to its baseline level of 1% per year over the next 3 to 5 years. The authors suggested two possible explanations: overwhelming tumor dissemination during surgery and a lowering of the host's immunologic defense. Their report served as the impetus for development of the no-touch surgical technique,<sup>24-26</sup> but conclusive evidence linking tumor dissemination and subsequent development of

metastasis to a transient rise in intraocular pressure was not forthcoming. Furthermore, data from the COMS published in 1998 demonstrated that no survival advantage was gained by pre-enucleation radiation in more than 1,000 patients with large choroidal melanomas. This result suggests that metastasis occurs prior to enucleation.<sup>8</sup>

Other investigators proposed that uveal melanomas metastasize during a time of growth that coincides with the time they become clinically visible. This would be in keeping with the work of Eskelin et al<sup>19,20</sup> and supports the second hypothesis of Zimmerman and McLean,<sup>23</sup> ie, that removal of the eye alters the immune system and thus allows existing micrometastases to grow unchallenged.

## Treatment of Choroidal Melanomas

There are multiple therapeutic options for treating choroidal melanomas. Enucleation was the only treatment option available for uveal melanoma for most of the last century.<sup>27</sup> However, in recent decades, with the emergence of more conservative treatment options that attempt to spare the affected eye and retain vision, the enucleation rate has substantially declined, but enucleation remains a common treatment for large tumors or in cases where there is no hope of regaining vision.

## Radiotherapy

Radiation is one such alternative treatment method now in widespread use for the treatment of choroidal melanomas. Various materials for delivering radiation have been investigated, beginning with radon in the 1930s by Moore.<sup>28</sup> Iodine-125 is currently the most commonly used isotope for plaque radiotherapy of choroidal melanomas,<sup>29,30</sup> although cobalt-60, ruthenium-106, iridium-192, strontium-90, and palladium-103 have also been

used. Modern techniques for plaque brachytherapy involve suturing a shielded plaque containing seeds of the radioactive isotope to the sclera. This remains in place for a specified number of days in order to deliver the proper dose of radiation (Fig 2). Most melanomas are treated with a calculated apex dose of 70 to 85 Gy.<sup>31</sup>

The COMS included more than 1,300 patients with medium-sized choroidal melanomas and randomized them to treatment with either enucleation or iodine-125 plaque radiotherapy. When the results were first published, 81% of patients had 5 years of follow-up, and 32% had 10 or more years. Five-year unadjusted survival rates for the two therapies were comparable, at slightly better than 80% for both.<sup>32</sup> The COMS and other recent trials have shown that iodine-125 brachytherapy provides survival rates equal to enucleation for both medium<sup>27</sup> and large<sup>33,34</sup> choroidal melanomas, providing reliable data when alternative treatment methods are discussed with patients.

Local control with plaque radiotherapy has been excellent, providing overall survival comparable to enucleation as shown by the COMS.<sup>8</sup> Wilson and Hungerford<sup>35</sup> noted the 5-year local recurrence rate was 4.2% with iodine-125. Tumors with larger basal diameters are more likely to recur.<sup>35,36</sup> Karlsson et al<sup>36</sup> found that patients with local tumor recurrence, which are likely to occur at the tumor margin, were at greater risk of life-threatening distant metastasis, having a 5-year survival rate of 58% compared with 82% for those without local recurrence. However, while local control of choroidal melanomas obtained with radioactive plaques has been reported at more than 90%, many treated eyes develop complications secondary to radiation delivered to adjacent structures.<sup>37</sup> Radiation retinopathy has been identified in up to 43% of patients treated with plaque radiotherapy.<sup>38</sup> Other reported complications include optic atrophy, cystoid macular edema, cataracts, vitreous hemorrhage, secondary glaucoma, central retinal vein occlusion, and scleral necrosis.<sup>37,39</sup> Secondary strabismus has also

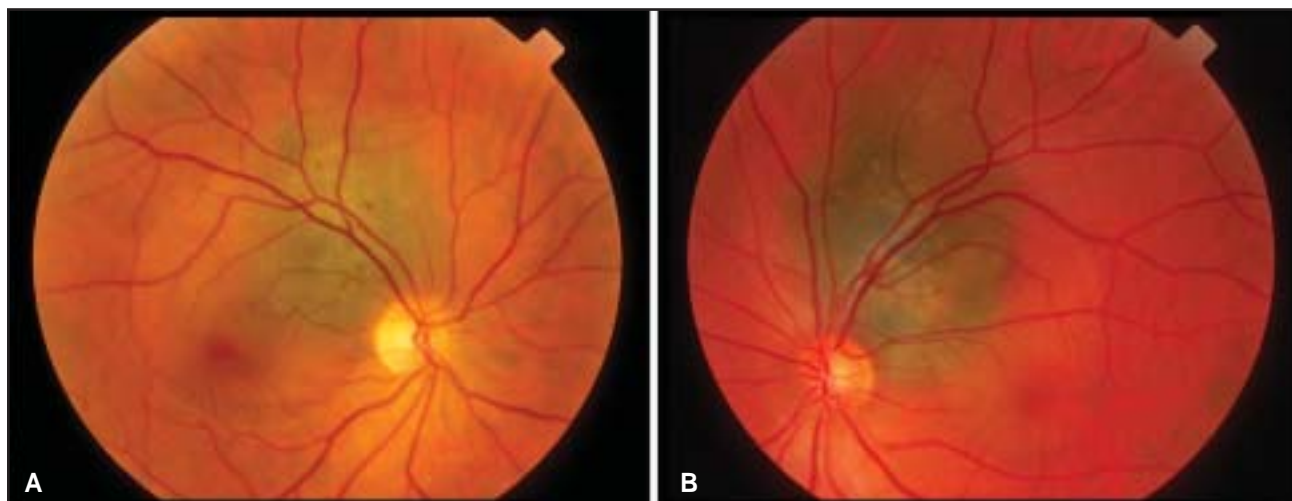


Fig 1A-B. — Small pigmented choroidal tumors with orange pigment and subretinal fluid characteristic of choroidal malignant melanomas.

occurred in 5% of patients as a result of moving extraocular muscles in order to properly place the plaque.<sup>39</sup>

An alternative method of delivering radiation to an ocular tumor uses charged particles, either protons or helium ions. Tantalum clips are fixed to the episcleral surface around the base of the tumor, and charged particles are then directed toward the tumor from an anterior approach. Advantages of charged particle therapy include a uniform dose distribution throughout the treatment zone and a predictable area of treatment, since protons travel in a straight line and stop after a certain distance based on the initial energy imparted.<sup>40</sup> The highly collimated beam of radiation includes a 1-mm tumor margin, a 0.5-mm margin for patient movement, and a 1-mm margin for the penumbral effect.<sup>41</sup> Seventy percent of the maximum radiation dose is delivered by the entrance beam as it travels through the eye before reaching the tumor. Therefore, anterior complications including epiphora, lash loss, and neovascular glaucoma occur more frequently with charged particles than with radiation delivered posteriorly.<sup>39</sup> Gragoudas et al<sup>42</sup> reported that radiation macu-

lopathy occurred in approximately 75% of tumors within 1 disc diameter of the fovea and in 40% of tumors greater than 1 disc diameter from the fovea treated with proton-beam radiotherapy.

Wilson and Hungerford<sup>35</sup> found local recurrence of 5.2% with proton-beam radiotherapy. Metastatic death rates of 12.8% at 5 years and 20.7% at 10 years have been reported following proton-beam irradiation.<sup>43</sup>

## Transscleral Resection

Local transscleral resection has largely been abandoned in favor of more successful treatment methods. In 1986, Foulds and Damato<sup>44</sup> recommended local resection for tumors 10 to 15 mm in diameter after finding that most of the failures in their series involved tumors larger than 15 mm in diameter. They reported a 19% incidence of retinal detachment as a result of the surgery, with only 41% of these responding well to repair. However, 81.1% of the eyes in the COMS showed local invasion of the sclera,

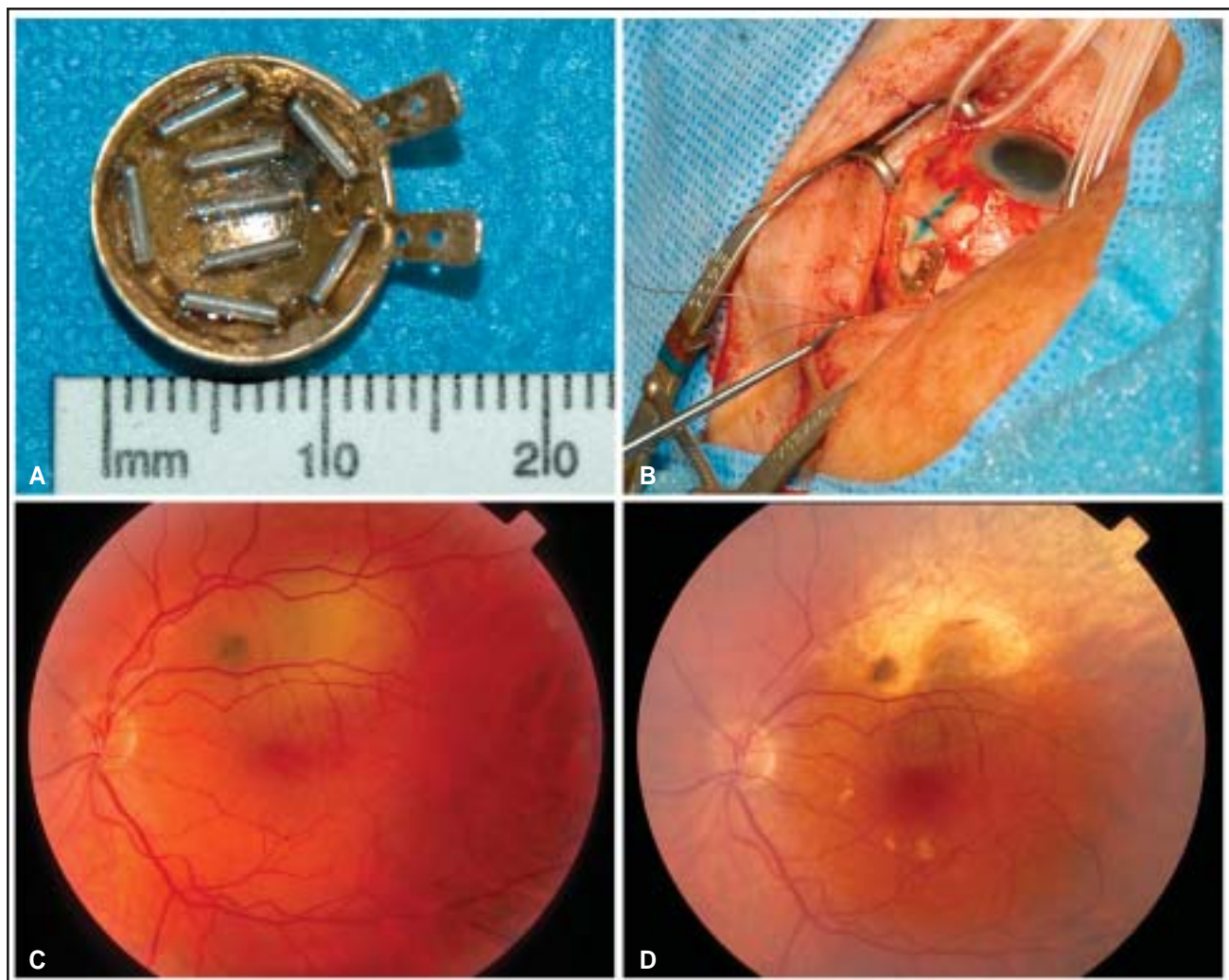


Fig 2A-D. — (A) Iodine-125 radioactive plaque. (B) Radioactive plaque, placed surgically on sclera. (C) Choroidal malignant melanoma before treatment with iodine-125 radioactive plaque. (D) Choroidal malignant melanoma after treatment with iodine-125 radioactive plaque.



Fig 3A-C. — Choroidal malignant melanoma before (A), immediately after (B), and 24 months after (C) treatment with transpupillary thermotherapy.

which the authors stated argued against the advisability of scleral resection as a treatment for choroidal melanoma due to the fact that potentially viable melanoma cells are likely to remain following surgery.<sup>45</sup> Proponents of transscleral resection now recommend adjuvant brachytherapy to irradiate any remaining tumor cells.<sup>46</sup>

## Elevation of Tissue Temperature

Many methods have been used to elevate tissue temperature in order to potentiate the effect of ionizing radiation. The addition of heat could allow for reduction in the dose of radiation required to treat a uveal melanoma by 50% or more, thereby reducing the incidence of radiation complications.<sup>41</sup> Several methods have been used to heat choroidal tumors. Finger et al<sup>47</sup> used a microwave heat delivery system in a clinical trial of 18 patients in 1989. Lasers have also been used to photocoagulate tumor cells at temperatures of more than 60°C.

## Transpupillary Thermotherapy

Investigators from the Netherlands investigated the use of lasers at subphotocoagulation levels (45°C to 60°C) to obtain tumor cell necrosis by hyperthermia.<sup>48</sup> Their experiments conducted on Greene melanomas in Syrian golden hamsters first revealed that using a xenon photocoagulator to produce near-infrared radiation in the 780- to 880-nm range could produce tumor cell necrosis by cell membrane damage, protein denaturation, chromosomal damage, and breakdown of mitochondria<sup>49,50</sup> up to a depth of 6 mm.<sup>51</sup> They named this technique *transpupillary thermotherapy* (TTT). These investigators then used xenon arc photocoagulation or diode laser prior to enucleation on 7 human patients with choroidal melanomas. The four tumors treated with the red-filtered light of the xenon arc photocoagulator showed no distinct melanocyte necrosis in contrast to the results previously found in animal models. However, the tumors treated with the diode laser at 810 nm showed tumor cell necrosis of varying depths up to 3.9 mm. Oosterhuis et al<sup>50</sup> published

the first study on the use of TTT as primary treatment for uveal melanoma in 1995. Tumor necrosis developed within days, and reduction in tumor height was clinically visible within months in 11 of 12 eyes compared with up to 1 year for brachytherapy. The authors concluded that TTT is useful as a complementary modality to brachytherapy.

### Treatment Procedure

TTT uses a diode laser to deliver a beam of infrared radiation through a dilated pupil into an intraocular tumor in order to induce tumor cell necrosis.<sup>52</sup> The entire surface of the tumor is covered with overlapping treatment areas extending 1.5 mm over the edge of the tumor into normal tissue.<sup>29</sup> Pigment in the tumor is responsible for absorbing energy and creating the heat that destroys the tumor cells, overlying pigment epithelium, and retina. The heat from TTT leaves a light gray uptake over the tumor at the end of each 60-second treatment<sup>51</sup> that is sharply demarcated from normal choroid around the tumor even though both areas are included in the treatment zone<sup>53,54</sup> (Fig 3). It is important to note that the appearance of a white coagulation lesion early during the application of TTT increases the amount of laser light reflected and thus decreases the amount transmitted into the tumor.<sup>50,55</sup>

### Advantages and Disadvantages

Advantages of TTT include immediate necrosis with quickly evident clinical regression, precision of treatment, and ease of treatment on an outpatient basis with local anesthesia.<sup>52</sup> TTT causes less choroidal damage than plaque radiotherapy.<sup>55</sup> However, TTT still leads to immediate profound visual field defects corresponding to the treated areas secondary to photoreceptor and nerve fiber layer destruction.<sup>54</sup> Since TTT destroys nerve fibers within this area, the defects will extend from this area to the area innervated by the fibers passing through the treated area. Moreover, the defect may be markedly larger than the treated area if the tumor is located very close to the optic disc. Subretinal fluid may be produced or increased following treatment but resolves within a few weeks.<sup>50</sup> Shields et al<sup>56</sup> found that vascular obstruction occurred in 23% and retinal traction in 20% following an average of three treatment sessions. TTT cannot be performed if the

pupil cannot be dilated to allow passage of the beam, if the tumor is peripheral enough that the edges are not visible, if opacities prevent a clear view, or if there is more than 3 mm of subretinal fluid.<sup>29</sup>

Initial results with TTT seemed promising. Shields et al<sup>57</sup> found that at an average follow-up of 1.7 months, tumor thickness was reduced 27% in heavily pigmented melanomas and 15% in amelanotic lesions. Stoffelns<sup>55</sup> reported that 75% of melanomas regressed to a flat chorioretinal scar after treatment with TTT (range 2 to 7 months, mean 2.9 months). However, in the same series, only 10% had complete destruction of the choriocapillaris, and 10 of 15 eyes with flat scars still had patent choroidal vessels.

Long-term results of TTT have been disappointing, however, with poorer local control rates and visual outcomes that are similar to other conservative treatment methods (Fig 4). Failure to achieve local control of choroidal melanomas is associated with a 4-fold increased rate of melanoma-associated death.<sup>58</sup>

Several reasons may explain why melanoma cells may escape destruction during TTT. Viable melanoma cells

have been found beneath treated areas of attenuated retina and choroid.<sup>59</sup> Analysis of choroidal vasculature following TTT revealed 100% occlusion of the choriocapillaris but only 24% occlusion of medium and large choroidal vessels. Similar analysis of choroidal circulation following iodine-125 plaque brachytherapy revealed complete occlusion of all vessels, including large choroidal vessels.<sup>60</sup> The ability of these patent vessels to act as a heat-sink during TTT may explain the survival of tumor cells near the vessels.<sup>51</sup> Harbour et al<sup>61</sup> reported a 29% local treatment failure and retinal complications in 76% of patients treated with primary TTT. They also noted no improved visual outcome vs plaque radiotherapy in a case-matched comparison of the two treatment modalities. The mean final visual acuity was 20/64 for the TTT group and 20/70 for the plaque radiotherapy group, a posttreatment decrease of 2.9 lines and 3.1 lines, respectively. Failures included growth of pigmented tumor tissue laterally at the margins of the treated tumor despite flattening and replacement of tissue with scar tissue.<sup>61,62</sup> Shields et al<sup>52</sup> found two characteristics as factors predictive of tumor



Fig 4A-D. — Small choroidal malignant melanomas successfully treated with transpupillary thermotherapy, shown before (A, C) and after (B, D) treatment.

recurrence: tumor that abuts or overhangs the optic disc and an increase in the required number of thermotherapy treatment sessions to more than three.

Melanoma cells near vessels can survive TTT, and those that have invaded the sclera may not be destroyed by TTT.<sup>54,63</sup> Zaldivar et al<sup>62</sup> reported melanoma cells found in emissary canals in all of the eyes they examined after failed TTT. It is not uncommon for melanoma cells to invade the sclera, as reported by Robertson et al<sup>64</sup> (27%) and Donders<sup>65</sup> (80%). COMS data showed that 55.7% of eyes had intrascleral invasion. However, the study likely underestimates the percentage of tumors that spread into the sclera since extrascleral extension was an exclusion criterion for the study.<sup>45</sup> Extrascleral extension can be difficult to detect prior to treatment, as Zaldivar et al<sup>62</sup> reported that in 5 eyes that histologically demonstrated extranodal extension, only 1 was detected by ultrasonography prior to enucleation. In other cases, the tumor cells appear to be resistant to treatment, especially if amelanotic.<sup>55</sup> Fifty percent of the tumors in the COMS had no or minimal pigmentation.<sup>45</sup> Oosterhuis et al<sup>66</sup> reported 15% more energy was required to treat amelanotic lesions than pigmented melanomas. However, the tumor reduction was 33% greater at 3 months. The effect of TTT on amelanotic melanomas can be improved by the injection of indocyanine green 30 minutes prior to treatment, as the dye will increase the absorption of infrared light in the tumor.<sup>29</sup>

Although TTT has largely failed as primary treatment for every choroidal melanoma, there may be selected instances where it can be of benefit. TTT has been used successfully in select cases where plaque brachytherapy has failed.<sup>67</sup> TTT has also been combined with plaque radiotherapy in a technique called *sandwich therapy*, as TTT is maximally effective at the apex of the tumor and brachytherapy is maximally effective at the base.<sup>65</sup> Moreover, TTT may show benefit in the treatment of hemangiomas and small retinoblastomas in addition to uveal melanomas.

## The Future of Choroidal Melanoma Treatment

The management of choroidal melanoma continues to evolve toward treatment of smaller tumors, achieving improved survival and less vision loss. TTT is currently under investigation for use in the treatment of occult and classic neovascularization in age-related macular degeneration.<sup>29</sup> Transscleral thermotherapy, which heats the sclera sufficiently to destroy intrascleral tumor cells without damaging scleral collagen, is also under investigation as a technique to replace plaque radiotherapy.<sup>29</sup> The results of these investigations may change the future role of TTT. For now, however, other techniques such as brachytherapy are more efficacious and enucleation provides the same survival prognosis as these conservative methods.

## References

1. Seregard S. Posterior uveal melanoma: the Swedish perspective. *Acta Ophthalmol Scand.* 1996;74:315-329.
2. Wilkes SR, Robertson DM, Kurland LT, et al. Incidence of uveal malignant melanoma in the resident population of Rochester and Olmsted County, Minnesota. *Am J Ophthalmol.* 1979;87:639-641.
3. Wilkes S, Kurland L, Campbell RJ, et al. Incidence of uveal malignant melanoma. *Am J Ophthalmol.* 1979;88:629-630.
4. De Potter P, Shields CL, Shields JA. New treatment modalities for uveal melanoma. *Curr Opin Ophthalmol.* 1996;7:27-32.
5. Augsburger JJ. Is observation really appropriate for small choroidal melanomas? *Trans Am Ophthalmol Soc.* 1993;91:147-168.
6. Zimmerman LE, McLean IW, Foster WD. Statistical analysis of follow-up data concerning uveal melanomas, and the influence of enucleation. *Ophthalmology.* 1980;87:557-564.
7. Shields JA, Shields CL, Donoso LA. Management of posterior uveal melanoma. *Surv Ophthalmol.* 1991;36:161-195.
8. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma II: initial mortality findings. COMS report No. 10. *Am J Ophthalmol.* 1998;125:779-796.
9. Mooy CM, De Jong PT. Prognostic parameters in uveal melanoma: a review. *Surv Ophthalmol.* 1996;41:215-228.
10. McLean IW, Foster WD, Zimmerman LE, et al. Inferred natural history of uveal melanoma. *Invest Ophthalmol Vis Sci.* 1980;19:760-770.
11. Zakka KA, Foos RY, Omphroy CA, et al. Malignant melanoma: analysis of an autopsy population. *Ophthalmology.* 1980;87:549-556.
12. Kujala E, Makitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci.* 2003;44:4651-4659.
13. Kath R, Hayungs J, Bornfeld N, et al. Prognosis and treatment of disseminated uveal melanoma. *Cancer.* 1993;72:2219-2223.
14. Shields JA. Lesions simulating malignant melanoma of the posterior uvea. *Arch Ophthalmol.* 1973;89:466-471.
15. Chang M, Zimmerman LE, McLean I. The persisting pseudomeganoma problem. *Arch Ophthalmol.* 1984;102:726-727.
16. Collaborative Ocular Melanoma Study Group. Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report No. 1. *Arch Ophthalmol.* 1990;108:1268-1273. Erratum in: *Arch Ophthalmol.* 1990;108:1708.
17. Shields CL, Shields JA, Kiratli H, et al. Risk factors for growth and metastasis of small choroidal melanocytic lesions. *Ophthalmology.* 1995;102:1351-1361.
18. Diener-West M, Hawkins BS, Markowitz JA, et al. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol.* 1992;110:245-250.
19. Eskelin S, Pyrhonen S, Summanen P. Tumor doubling times in metastatic malignant melanoma of the uvea: tumor progression before and after treatment. *Ophthalmology.* 2000;107:1443-1449.
20. Eskelin S, Kivelä T. Uveal melanoma: implications of tumor doubling time. Author's reply. *Ophthalmology.* 2001;108:830-831.
21. Shields CL, Cater J, Shields JA, et al. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol.* 2000;118:360-364.
22. McLean IW. Discussion of "risk factors for growth and metastasis of small choroidal melanocytic lesions." *Ophthalmology.* 1995;102:1361.
23. Zimmerman LE, McLean IW. An evaluation of enucleation in the management of uveal melanomas. *Am J Ophthalmol.* 1979;87:741-760.
24. Fraunfelder FT, Boozman FW, Wilson RS, et al. No-touch technique for intraocular malignant melanomas. *Arch Ophthalmol.* 1977;95:1616-1620.
25. Wilson RS, Fraunfelder FT. "No-touch" cryosurgical technique: a minimal trauma technique for eyes harboring intraocular malignancy. *Ophthalmology.* 1978;85:1170-1175.

26. McCubbin JA, Spratt JS. The value of no-touch isolation technique for the resection of cancer: the eye as a model. *Arch Surg.* 1980; 115:224-228.
27. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma I: characteristics of patients enrolled and not enrolled. COMS report No. 9. *Am J Ophthalmol.* 1998;125:767-778.
28. Moore RE. Choroidal sarcoma treated by intraocular insertion of radon seeds. *Br J Ophthalmol.* 1930;14:145-152
29. Journée-de Korver JG, Keunen JEE. Thermotherapy in the management of choroidal melanoma. *Prog Retin Eye Res.* 2002;21:303-317.
30. Shields CL, Cater J, Shields JA. Combined plaque radiotherapy and transpupillary thermotherapy for choroidal melanoma: tumor control and treatment complications in 270 consecutive patients. *Arch Ophthalmol.* 2002;120:933-940.
31. Nath R, Anderson LL, Luxton G, et al. Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No 43. American Association of Physicists in Medicine. *Med Phys.* 1995;22:209-234.
32. The Collaborative Ocular Melanoma Study (COMS) randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS report No. 18. *Arch Ophthalmol.* 2001;119:969-982.
33. Puusaari I, Heikkonen J, Summanen P, et al. Iodine brachytherapy as an alternative to enucleation for large uveal melanomas. *Ophthalmology.* 2003;110:2223-2234.
34. Wilson MW, Alejandro KC, Cantrell JE, et al. 125-I episcleral plaque brachytherapy in the management of large melanomas of the ciliary body and/or of the choroid. Scientific Poster 76, 2002. Presented at the Joint Meeting American Academy of Ophthalmology and Pan-American Association of Ophthalmology. Oct 20-23, 2002; Orlando, FL.
35. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology.* 1999;106:1579-1587.
36. Karlsson UL, Augsburger JJ, Shields JA, et al. Recurrence of posterior uveal melanoma after 60Co episcleral plaque therapy. *Ophthalmology.* 1989;96:382-388.
37. Lommatzsch PK, Kirsch IH. 106Ru/106Rh plaque radiotherapy for malignant melanomas of the choroid: with follow-up results more than 5 years. *Doc Ophthalmol.* 1988;68:225-238.
38. Gunduz K, Shields CL, Shields JA, et al. Radiation retinopathy following plaque radiotherapy of posterior uveal melanoma. *Arch Ophthalmol.* 1999;117:609-614.
39. CharDH, Castro JR, Quivey JM, et al. Uveal melanoma radiation: 125I brachytherapy versus helium ion irradiation. *Ophthalmology.* 1989;96:1708-1715.
40. Gragoudas ES, Goitein M, Verhey L, et al. Proton beam irradiation: an alternative to enucleation for intraocular melanomas. *Ophthalmology.* 1980;87:571-581.
41. Finger PT. Radiation therapy for choroidal melanoma. *Surv Ophthalmol.* 1997;42:215-232.
42. Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol.* 2000;118:773-778.
43. Li W, Gragoudas ES, Egan KM. Tumor basal area and metastatic death after proton beam irradiation for choroidal melanoma. *Arch Ophthalmol.* 2003;121:68-72.
44. Foulds WS, Damato BE. Alternatives to enucleation in the management of choroidal melanoma. *Aust N Z J Ophthalmol.* 1986;14: 19-27.
45. Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS report No. 6. *Am J Ophthalmol.* 1998;125:745-766.
46. Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. *Ophthalmology.* 2004;111:977-983.
47. Finger PT, Packer S, Paglione RW, et al. Thermoradiotherapy of choroidal melanoma: clinical experience. *Ophthalmology.* 1989; 96:1384-1388.
48. Journée-de Korver JG, Oosterhuis JA, Van Best JA, et al. Xenon arch photocoagulator used for transpupillary hyperthermia. *Doc Ophthalmol.* 1991;78:183-187.
49. Journée-de Korver JG, Oosterhuis JA, Kakebeeke-Kemme HM. Transpupillary thermotherapy (TTT) by infrared irradiation of choroidal melanoma. *Doc Ophthalmol.* 1992;82:185-191.
50. Oosterhuis JA, Journée-de Korver HG, Kakebeeke-Kemme HM, et al. Transpupillary thermotherapy in choroidal melanomas. *Arch Ophthalmol.* 1995;113:315-321.
51. Journée-de Korver JG, Verberg-van der Marel EH, Oosterhuis JA, et al. Tumorcidal effect of hyperthermia by near infrared irradiation on pigmented hamster melanoma. *Lasers Light Ophthalmol.* 1992;4:175-180.
52. Shields CL, Shields JA, Perez N, et al. Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations. *Ophthalmology.* 2002;109:225-234.
53. Robertson DM, Salomão DR. The effect of transpupillary thermotherapy on the human macula. *Arch Ophthalmol.* 2002;120: 652-656.
54. Robertson DM, Buettner H, Bennett SR. Transpupillary thermotherapy as primary treatment for small choroidal melanomas. *Arch Ophthalmol.* 1999;117:1512-1519.
55. Stoffelns BM. Primary transpupillary thermotherapy (TTT) for malignant choroidal melanoma. *Acta Ophthalmol Scand.* 2002; 80:25-31.
56. Shields CL, Shields JA, Cater J, et al. Transpupillary thermotherapy for choroidal melanoma: tumor control and visual results in 100 consecutive cases. *Ophthalmology.* 1998;105:581-590.
57. Shields CL, Shields JA, De Potter P, et al. Transpupillary thermotherapy in the management of choroidal melanoma. *Ophthalmology.* 1996;103:1642-1650.
58. Egan KM, Ryan LM, Gragoudas ES. Survival implications of enucleation after definitive radiotherapy for choroidal melanoma: an example of regression on time-dependent covariates. *Arch Ophthalmol.* 1998;116:366-370.
59. Finger PT, Lipka AC, Lipkowitz JL, et al. Failure of transpupillary thermotherapy (TTT) for choroidal melanoma: two cases with histopathological correlation. *Br J Ophthalmol.* 2000;84:1075-1076.
60. Midena E, Pilotto E, de Belvis V, et al. Choroidal vascular changes after transpupillary thermotherapy for choroidal melanoma. *Ophthalmology.* 2003;110:2216-2222.
61. Harbour JW, Meredith TA, Thompson PA, et al. Transpupillary thermotherapy versus plaque radiotherapy for suspected choroidal melanomas. *Ophthalmology.* 2003;110:2207-2215.
62. Zaldívar RA, Aaberg TM, Sternberg P Jr, et al. Clinicopathologic findings in choroidal melanomas after failed transpupillary thermotherapy. *Am J Ophthalmol.* 2003;135:657-663.
63. Journée-de Korver JG, Oosterhuis JA, de Wolff-Rouendaal D, et al. Histopathological findings in human choroidal melanomas after transpupillary thermotherapy. *Br J Ophthalmol.* 1997;81:234-239.
64. Robertson DM, Campbell RJ, Weaver DT. Residual intrascleral and intraretinal melanoma: a concern with lamellar sclerouvectomy for uveal melanoma. *Am J Ophthalmol.* 1991;112:590-593.
65. Donders PC. Malignant melanoma of the choroid. *Trans Ophthalmol Soc UK.* 1973;93:745-751.
66. Oosterhuis JA, Journée-de Korver HG, Keunen JE. Transpupillary thermotherapy: results in 50 patients with choroidal melanoma. *Arch Ophthalmol.* 1998;116:157-162.
67. Robertson DM. TTT as rescue treatment for choroidal melanoma not controlled with iodine-125 brachytherapy. *Ocul Immunol Inflamm.* 2002;10:247-252.