

# Transpupillary Thermotherapy

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[Instructions for Use](#)

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## Related Medical Management Guideline

- [Macular Degeneration Treatment Procedures](#)

## Coverage Rationale

Transpupillary thermotherapy is proven and medically necessary for treating the following:

- Choroidal melanomas
- Retinoblastoma

Transpupillary thermotherapy is unproven and not medically necessary for treating all other indications due to insufficient evidence of efficacy. These include but are not limited to:

- Choroidal neovascularization
- Macular degeneration

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
67299	Unlisted procedure, posterior segment
92499	Unlisted ophthalmological service or procedure

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## Description of Services

Transpupillary thermotherapy (TTT), also called diode laser hyperthermia is a method that utilizes diode laser to raise the temperature within the tumor tissue, causing heat induced sclerosis of vascular channels and eventually tumor regression and resolution of subretinal fluid. Transpupillary thermotherapy has been used to treat ocular tumors such as choroidal melanoma and retinoblastoma and has also been proposed for choroidal neovascularization, macular degeneration and other ocular

indications. Transpupillary thermotherapy differs from laser photocoagulation in that it uses a different type of laser and targets the tumor cells directly rather than the blood vessels supplying the tumor.

## Clinical Evidence

### Transpupillary Thermotherapy for Choroidal Melanomas

Mashayekhi et al. (2015) reported the long-term outcome of primary transpupillary thermotherapy (TTT) for 391 patients with choroidal melanoma in a retrospective review of medical records. Of 391 patients, 311 (80%) were treated from 1995 to 2000 and 80 (20%) from 2001 to 2012. Kaplan-Meier estimates for tumor recurrence in the 1995 to 2000 group were 29% at 5 years and 42% at 10 years, whereas estimates for tumor recurrence in the 2001-2012 group were 11% at 5 years and 15% at 10 years. Of 108 recurrent tumors 20 were controlled with additional TTT and 62 required plaque radiation (n = 60) or proton beam radiation (n = 2), with enucleation necessary in 26 patients. Tumor recurrence correlated with the number of high-risk tumor features: 10-year recurrence was 18% in those with 1 or 2 risk factors, 35% in those with 3 to 5 factors, and 55% in those with 6 or 7 factors. On multivariate analysis, features predictive of tumor recurrence were presence of symptoms, shorter distance between the tumor and the optic disc, subretinal fluid, thickness of residual tumor scar, and elevation of residual tumor scar. The only factor predictive of extraocular tumor extension was intraocular tumor recurrence after TTT treated with additional TTT. Presence of orange pigment before TTT, tumor recurrence, and extraocular tumor extension were predictive of distant metastasis. The authors concluded that this study shows a direct correlation between a larger number of high-risk tumor features and higher rates of tumor recurrence after primary TTT of (small) choroidal melanoma. The authors recommend that when possible, small choroidal melanomas with multiple risk factors should be treated with methods other than TTT. According to the authors, the impact of this new diagnostic and prognostic modality on case selection for primary TTT of small choroidal melanocytic tumors warrants further study.

Chojniak et al. (2011) evaluated the efficacy of TTT for the treatment of small choroidal melanomas. The study was a prospective nonrandomized study of TTT for small (thickness  $\leq 4.0$  mm and basal diameter  $\leq 12$  mm) pigmented choroidal melanomas presenting either growth or risk factors for growth and metastasis. Ophthalmoscopic aspect, tumor control, visual acuity and complications were evaluated. Twenty-seven patients were treated; mean age 61 years; mean tumor thickness before treatment was 2.7mm and base was 8.52mm. After a mean of three treatment sessions and 45-month follow-up, mean tumor thickness decreased significantly to 1.34 mm and mean tumor base to 5.48 mm. Complications were observed in 12 patients (44%) and included retinal vascular occlusion, optic disc atrophy, retinal traction, vitreous hemorrhage, rhegmatogenous retinal detachment, and maculopathy. Lesions touching the optic disc were associated with a significantly higher rate of disc atrophy after treatment (60% vs. 40%). Visual acuity remained the same in nine eyes (33%), improved in five (19%) and decreased during the first 6 months after treatment in 13 eyes (48%). Complete tumor control without recurrence was observed in 25 patients (93%). Recurrence at tumor margin was detected in two (7%). All eyes were preserved. One patient had tumor-related death. According to the investigators, TTT is an effective treatment in the management of selected small choroidal melanoma. Decrease in visual acuity occurred early after treatment, mainly as a complication of sub-foveal and perifoveal tumor treatment.

Pilotto et al. (2009) compared long-term choroidal vascular changes after iodine-125 brachytherapy (IBT) versus TTT used as primary treatment. A total of 95 small choroidal melanomas were randomized: 49 eyes with TTT and 46 eyes with IBT alone. Mean follow-up was 56.2 months. Tumor regressed in 45 (92%) TTT-treated vs. 45 (98%) IBT-treated eyes. Four TTT-treated and one IBT-treated tumor recurred. Closure of medium and large choroidal vessels was observed in 17 (35%) TTT-treated vs. 44 (96%) IBT-treated eyes. Choroidal vascular remodeling was detected in 20 (41%) TTT-treated and 16 (35%) IBT-treated eyes. Retinochoroidal anastomosis was present in 4 of the 37 (11%) TTT-treated eyes with patency of medium and large choroidal vessels, but never observed in the IBT-treated eyes, and was associated with tumor recurrence. Among IBT-treated eyes, segments of choroidal vascular wall ICG staining and choroidal aneurysmal changes were detected in 30 (65%) and 7 (15%), respectively. These changes were never detected in TTT-treated cases. The investigators concluded that the pattern of tumor choroidal vascular changes following IBT and TTT differs. TTT is less effective in closing all tumor vasculature. The role of long-term choroidal vascular remodeling observed after these two treatments needs longer follow-up.

Desjardins et al. (2006) conducted a randomized study to determine whether systematic TTT after proton beam radiotherapy could have a beneficial effect in 151 patients with uveal melanomas. One half of the patients received proton beam radiotherapy alone and the other half received the same dose of proton beam radiotherapy followed by TTT at 1, 6 and 12 months. The median follow-up was 38 months. The patients treated with TTT showed a greater reduction of tumor thickness,

less retinal detachment at the latest follow-up and a lower secondary enucleation rate. Further studies are needed to determine whether TTT could be beneficial to smaller tumors and to define its optimal dose.

## ***Clinical Practice Guidelines***

### **National Comprehensive Cancer Network (NCCN)**

NCCN guidelines for uveal melanoma state that TTT is recommended for small recurrences in patients who cannot undergo radiation therapy or surgery. (2021; updated 2022)

### **National Cancer Institute (NCI)**

The NCI states that TTT has important limitations that confine its use to very restricted circumstances. The limited ability of TTT to penetrate thick tumors with sufficient energy restricts its use to small melanomas or tumors of a size that some ophthalmologists recommend for follow-up without any initial therapy. When used as the primary therapy, there are relatively high rates of local recurrence and retinal vascular damage. Recurrence rates are particularly high when the tumor abuts the optic nerve and overhangs the optic disc. The NCI notes that for small choroidal melanomas, TTT has very limited use, but it can be used as a primary treatment or as an adjunctive method to plaque radiation therapy. The NCI also states that combined therapy, with ablative laser coagulation or TTT to supplement plaque treatment may be used for medium-sized choroidal melanomas. (NCI, Intraocular (Uveal) Melanoma, 2022)

### **Transpupillary Thermotherapy for Retinoblastomas**

Russo et al. (2021) conducted a prospective phase II study aimed to include children affected by bilateral intraocular macular/paramacular retinoblastoma. The protocol consisted of six cycles of a three-drug combination (vincristine, etoposide, carboplatin), and the addition of macula-sparing TTT to the third cycle. The primary endpoint was the local control rate without external beam radiotherapy (EBR) and/or enucleation. Nineteen patients (26 eyes) were included from July 2004 to November 2009. Thirteen eyes belonged to group V of the Reese-Ellsworth classification and 10 to group D of the International Intraocular Retinoblastoma Classification. Macular/paramacular tumors were treated with chemotherapy alone in nine eyes, and with chemotherapy associated with macula-sparing TTT in 17 eyes. Four eyes experienced macular relapse. At a median follow up of 77 months, 23 eyes (88.5%) were saved without EBR, two were enucleated and one received EBR. The median visual acuity of the 24 saved eyes was 20/50. No severe adverse effect was observed. The authors concluded 6 cycles of a three-drug combination associated with macula-sparing TTT achieved good tumor control, improved eye preservation rates without EBR, and decreased macular damage, often providing satisfactory visual results with long-term follow up. The study is however limited by lack of comparison group.

Shields et al. (2005) evaluated the effectiveness of chemoreduction alone and chemoreduction with thermotherapy for macular retinoblastoma in a prospective, nonrandomized, single-center observational study. There were 68 macular retinoblastomas in 62 eyes of 49 patients managed with chemoreduction. All patients received 6 cycles of intravenous chemoreduction using vincristine, etoposide, and carboplatin. The patients were then treated according to 1 of 2 approaches: chemoreduction alone with no adjuvant focal therapy (group A) or chemoreduction combined with adjuvant foveal-sparing thermotherapy to each macular retinoblastoma (group B). The main outcome measure was tumor recurrence. Of the 68 tumors, 28 were in group A and 40 were in group B. A comparison of both groups revealed that the tumors were similar with regard to clinical features. Following treatment, Kaplan-Meier estimates revealed that group A tumors showed recurrence in 25% by 1 year and 35% by 4 years whereas those in group B showed recurrence in 17% by 1 year and 17% by 4 years. By multivariate analysis, the most important factors predictive of tumor recurrence were smaller macular tumor size (judged by percentage of the macula occupied by the tumor), absence of subretinal or vitreous seeds, and unilateral disease. Tumors most destined for recurrence are small tumors. According to the investigators, treatment of macular retinoblastoma with chemoreduction plus adjuvant foveal-sparing thermotherapy provides tumor control of 83% by 4 years, and this is slightly more favorable than chemoreduction alone, which provides control of 65% by 4 years.

Abramson and Scheffler (2004) evaluated 91 retinoblastoma tumors in 24 patients with TTT as the primary treatment modality. In this case series, the outcome measures included local tumor recurrence and failure of TTT, requiring the use of salvage therapies. The mean follow-up from the time of the first TTT treatment was 21 months. Tumors were defined as cured when no regrowth had been observed for six months after treatment. A total of 84 tumors (92%) were cured with TTT alone and seven tumors (8%) required salvage treatments. All seven tumors requiring salvage treatment were cured without enucleation. The

mean number of treatment sessions required for cure was 1.7, with 64% of the tumors requiring only one session. According to the investigators, retinoblastoma tumors less than 1.5 DD in base diameter can be successfully treated with TTT alone.

Shields et al. (1999) reported on the results of TTT in 188 retinoblastomas in 80 eyes of 58 patients in a prospective study. Smaller tumors were managed by thermotherapy alone; larger tumors were managed by chemoreduction, followed by tumor consolidation with thermotherapy. Complete tumor regression was achieved in 161 tumors (85.6%). A total of 27 tumors (14.4%) developed recurrence. The investigators concluded that thermotherapy is effective for relatively small retinoblastomas without associated vitreous or subretinal seeds. Such tumors are generally best managed by chemoreduction, followed by plaque brachytherapy or external beam irradiation. However, supplemental thermotherapy can often be employed in such cases if vitreal or subretinal seeds have resolved following irradiation. The study also concluded that larger tumors require more intense treatment than smaller tumors and are at greater risk of ocular complications, such as focal iris atrophy and focal paraxial lens opacity.

## ***Clinical Practice Guidelines***

### **National Cancer Institute (NCI)**

According to the NCI, laser therapy may be used as primary therapy for small retinoblastoma tumors or in combination with chemotherapy for larger retinoblastoma tumors. Traditional photocoagulation (argon laser), in which the laser was applied around the tumor, has given way to thermotherapy (diode laser). Thermotherapy is delivered directly to the tumor surface via infrared wavelengths of light. The NCI includes thermotherapy as a treatment option for unilateral and bilateral intraocular retinoblastomas and progressive or recurrent intraocular retinoblastomas. (NCI, Retinoblastoma, 2022)

### **Transpupillary Thermotherapy for Choroidal Neovascularization (CNV) Associated With Age-Related Macular Degeneration (AMD)**

Results of studies evaluating the use of TTT for the prevention or control of choroidal neovascularization lesions in individuals with age-related macular degeneration (AMD) do not provide sufficient evidence to conclude that TTT improves loss of vision due to AMD.

In a 24-month, double-masked, randomized, active-controlled clinical trial, Söderberg et al. (2012) compared the effect of combined low-dose TTT and intravitreal ranibizumab with sham TTT and intravitreal ranibizumab in patients with neovascular AMD. A total of 100 patients were randomly assigned (1:1) to receive intravitreal ranibizumab and sham TTT or intravitreal ranibizumab and low-dose TTT. Patients in the TTT group required fewer treatments with ranibizumab compared to those in the sham TTT group. The mean number of ranibizumab injections was 8.0 in the sham TTT group versus 6.3 in the TTT group over two years. There was no statistically significant difference in best corrected visual acuity (BCVA), central retinal thickness (CRT) or lesion area between the treatment groups at the final examination. The results of the intent-to-treat population (92 patients) were similar to the per-protocol (PP) population. The authors concluded that treatment with low-dose TTT significantly reduced the number of intravitreal injections of ranibizumab over 24 months. According to the authors, these results suggest that low-dose TTT can serve as an adjuvant in combination with intravitreal ranibizumab for neovascular AMD. Further research with a larger number of patients is needed to confirm these results and further assess the impact on vision outcomes.

In a prospective, interventional, comparative case series, Nowak et al. (2012) compared the efficacy of verteporfin photodynamic therapy (PDT), intravitreal injections of bevacizumab (IVB), and TTT in patients with neovascular AMD. The study included 426 eyes of 426 consecutive patients presenting with neovascular AMD. Patients presented with sub-foveal CNV predominantly classic, minimally classic, and occult with no classic component; lesion size less than 5000  $\mu\text{m}$  in the greatest linear dimension, and the area of hemorrhages  $\leq 1/3$  were randomized to receive either PDT (group I) or IVB (group II) in a 1:1 ratio. Other patients with CNV were included into the group III and received TTT. One hundred eyes were treated with PDT. Mean baseline logMAR BCVA was 0.62 and final visual acuity decreased to 0.74; 104 eyes were treated with IVB. Mean baseline BCVA was 0.82 and final visual acuity increased to 0.79; 222 patients were treated with TTT. Mean baseline BCVA was 1.10 and final visual acuity decreased to 1.15. Among all eyes the average number of treatment sessions was 2.34. The authors concluded that IVB injections had the best efficacy in the improvement of final BCVA. However, both IVB and TTT demonstrated good stabilization of vision. The lack of a control group limits the validity of the results of this study.

Mitamura et al. (2009) compared the therapeutic efficacy of photodynamic therapy (PDT) to that of TTT for polypoidal choroidal vasculopathy (PCV) a form of choroidal neovascularization. PDT or TTT was performed on 46 eyes of 46 patients with PCV; 19

eyes were treated with TTT (TTT group) and 27 eyes with PDT (PDT group). Best-corrected visual acuity (BCVA) was significantly better and the fovea was significantly thinner in the PDT group than in the TTT group after treatment.

## Clinical Practice Guidelines

### National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (NICE) concluded that clinical evidence on the safety and efficacy of TTT for AMD was inadequate for TTT to be used without special arrangement for consent and for audit or research. (NICE, 2004; updated 2018)

### Transpupillary Thermotherapy for Other Conditions

Based on limited studies, small sample sizes, and weak study designs, there is insufficient evidence to conclude that TTT is safe and/or effective for treating other conditions.

Hajjaj et al. (2022) conducted a systematic review to summarize published evidence on efficacy and safety of different interventions for Von Hippel-Lindau patients with peripheral retinal hemangioblastomas (RH) and to provide treatment recommendations for specialists. Twenty-seven articles were included in this review describing nine different treatment options for peripheral RH: laser photocoagulation (n = 230), cryotherapy (n = 50), plaque radiotherapy (n = 27), vitreoretinal surgery (n = 88), photodynamic therapy (PDT; n = 14), transpupillary thermotherapy (TTT; n = 10), external beam radiotherapy (n = 3), systemic treatment (n = 7) and intravitreal anti-VEGF (n = 2). Complete tumor eradication was achieved in 86.7% (95% CI: 83.5-89.9%) of all eyes. For the different treatments, this was after laser photocoagulation 89.9% (86.1-93.7%), cryotherapy 70.2% (57.0-83.4%), plaque radiotherapy 96.3% (89.1-100.0%), vitreoretinal surgery (100.0%), PDT 64.3% (38.3-90.3%) and TTT 80.0% (53.8-100.0%). No complete tumor eradication was achieved after systemic therapy, external beam radiotherapy or intravitreal anti-VEGF. Photodynamic therapy and vitreoretinal surgery showed the highest complication rate after treatment compared to the other treatments (OR 10.5 [95% CI: 2.9-38.4]) and (OR 5.9 [95% CI: 3.4-9.9]), respectively. Cases that had pretherapeutic complications showed a higher treatment-related complication rate (OR 14.8 [95% CI: 7.3-30.0]) than cases without complications before treatment. These findings suggest that laser photocoagulation is the safest and most effective treatment method for peripheral RH up to 1.5 mm in diameter. Vitreoretinal surgery has the highest success rate for complete tumor eradication and may be the most suitable treatment option in the presence of pretherapeutic complications and for larger tumors.

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Ophthalmic lasers are regulated by the FDA as Class II devices and many lasers have been approved via the 510(k)-approval process. Ophthalmic diode laser systems that have received 510(k) marketing clearance for transpupillary thermotherapy include but are not limited to:

- IRIS Medical IQ 810 laser photocoagulator (IRIDEX Corp.) 510(k) approval (K040209) received 1/30/2004. Refer to the following website for more information: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf4/K040209.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf4/K040209.pdf).
- Nidek DC - 3000 laser diode photocoagulator (Nidek, Inc.) 510(k) (K903639) approval received 08/13/1990. Refer to the following website for more information: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/K013760.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/K013760.pdf).

(Accessed January 3, 2023)

A listing of all devices in the same product classification as those above (product code HQF and GEX) is available on the following FDA website <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed January 3, 2023)

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## Guideline History/Revision Information

Date	Summary of Changes
04/01/2023	<b>Supporting Information</b> <ul style="list-style-type: none"><li>Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, and <i>References</i> sections to reflect the most current information</li><li>Archived previous policy version MMG139.L</li></ul>

## Instructions for Use

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state

mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.