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ORIGINAL ARTICLE

Transpupillary thermotherapy for choroidal melanomas: A systematic review and meta-analysis.

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ABSTRACT… Objective: To evaluates the efficacy and safety of transpupillary thermotherapy (TTT) for the management of choroidal melanaomas. **Study Design:** Systematic review and meta-analysis. **Setting:** Review of published international literature on transpupillary thermotherapy (TTT) for choroidal melanomas. **Period:** All available studies from database inception to January 2025. **Methods:** This study was registered in PROSPERO (ID: CRD420251141671). A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Scopus, and Cochrane Library. Inclusion criteria were treatment-naïve small choroidal melanomas (<4.5 mm thickness, <12 mm basal diameter) treated with TTT and reporting at least one of the outcomes: tumor control, globe salvage, adverse effects, or metastasis. Studies with >12 patients and ≥12 months follow-up were included. Data were extracted independently by two reviewers, and risk of bias was assessed using RoB 2 and JBI tools. Pooled estimates were calculated using a random-effects model. **Results:** Eighteen studies comprising 1,296 eyes were included. Tumor thickness ranged from 0.78 mm to 4.5 mm, with a base diameter <12 mm, representing data on small-sized choroidal melanomas. Meta-analysis demonstrated a pooled tumor control rate of 0.81 (95% CI: 0.73-0.88). Globe salvage rate was 0.94 (95% CI: 0.91-0.96). The pooled adverse effects rate was 0.37 (95% CI: 0.22-0.54), while metastasis rate was 0.04 (95% CI: 0.02–0.06). Notable adverse effects included macular edema, epiretinal membrane, optic disc atrophy, retinal vein occlusion, vitreous hemorrhage, and serous retinal detachment. **Conclusion:** Transpupillary thermotherapy appears to be an effective treatment option for small-sized choroidal melanomas, with generally favorable tumor control and globe salvage outcomes. Adverse effects are more frequently reported in tumors involving the macula or peripapillary region. Overall, TTT provides outcomes comparable, to other treatment modalities.

Key words: Choroidal Neoplasms, Transpupillary Thermotherapy, Melanoma, Treatment Outcome.

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INTRODUCTION

Choroidal melanoma is the most common primary intraocular malignancy in adults, arising from melanocytes within the uveal tract. It occurs most frequently in the choroid (90%), followed by the ciliary body (5–8%) and the iris (3–5%). The incidence of uveal melanoma varies considerably across regions, with higher rates reported in Europe, North America, and Oceania (3–10 cases per million annually) compared with markedly lower rates in Asian populations (<1 case per million).[1,2]

Management of small choroidal melanomas remains a subject of debate. Observation is often recommended for lesions lacking high-risk features, as proposed by Shields and colleagues, while the Collaborative Ocular Melanoma Study (COMS) demonstrated that even small tumors can metastasize, with 5-year and 8-year all-cause mortality rates of ~6% and ~15%, respectively.[3,4] The liver is the most frequent site of dissemination.[5] These findings highlight the clinical dilemma between monitoring indeterminate lesions and initiating early intervention to reduce metastatic risk.

Various treatment modalities have been employed for small choroidal melanomas, including laser photocoagulation, photodynamic therapy, plaque brachytherapy, proton beam radiotherapy, local tumor resection, and enucleation.[6] Among these, transpupillary thermotherapy (TTT), first described by Oosterhuis et al. in 1995[7], emerged as a minimally invasive, globe-preserving alternative. TTT delivers an 810-nm diode laser beam (2–3 mm spot size) through a contact lens to cover the tumor and a surrounding margin.

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The induced hyperthermia (45–60 °C) penetrates up to 4 mm, leading to vascular occlusion, protein denaturation, and subsequent tumor necrosis, making it particularly suitable for small posteriorly located lesions.[8] Transpupillary thermotherapy (TTT) is mainly used as an adjunct to radiotherapy or used for medium-risk nevi and uncertain lesions due to its high recurrence rates. It is best suited for small uveal melanomas (<3.0 mm height, <16.0 mm basal diameter). When used as a primary treatment, TTT has a recurrence rate up to 29%, higher than with plaque brachytherapy.[9]

Despite its advantages, the efficacy and safety profile of TTT remain controversial, with variable outcomes reported in terms of tumor control, recurrence, visual prognosis, and ocular complications. Given these uncertainties, a systematic evaluation of the available literature is warranted. This meta-analysis aims to assess the effectiveness and safety of transpupillary thermotherapy in the management of choroidal melanoma, with emphasis on tumor control, visual outcomes, and treatment-related complications.

METHODS

This study is registered under PROSPERO ID CRD420251141671. A comprehensive literature review was conducted without any time limitation. The databases searched were PubMed/MEDLINE, Embase, Scopus and Cochrane Library. Literature research was conducted using both MeSH terms and keywords, including "transpupillary thermotherapy," "choroidal neoplasms," and "melanoma," within each category using the Boolean operator OR to ensure inclusiveness. Forward and backward citation tracking was also performed.

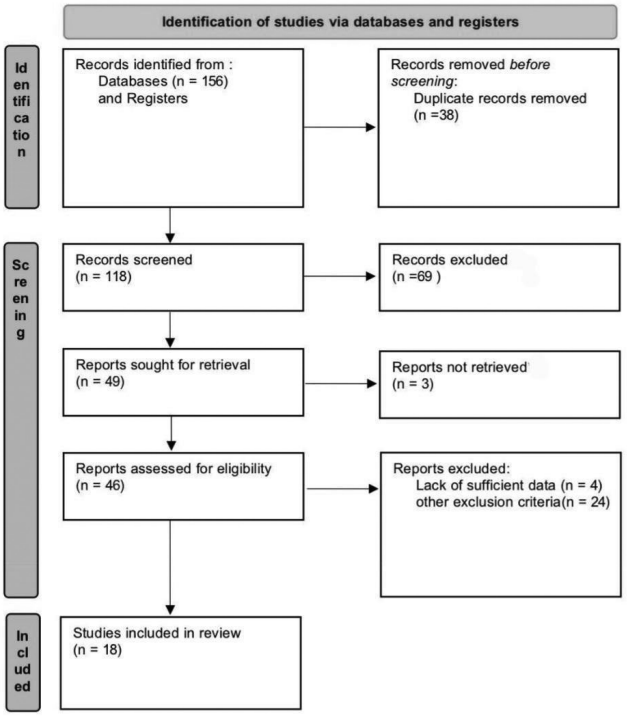
Each study was independently evaluated by two reviewers, and disagreements were resolved by consensus. Our outcome measures were tumor control, adverse effects, metastasis rate, and globe salvage rate. These outcomes were presented in tabulated form against each study.

Inclusion criteria included treatment-naive choroidal melanomas treated with transpupillary thermotherapy with at least one of the desired outcomes reported. All types of studies were included, provided they had more than 12 patients and at least one year of follow-up. Exclusion criteria included non-English studies for which translation was not available, case reports, and animal studies.

We followed the PRISMA checklist when reporting our review.(10) The study selection flowchart is shown in Figure-1.

FIGURE-1

Prisma flow diagram



Eighteen studies were independently reviewed by two reviewers. Among these, one was a randomized controlled trial (RCT) and one was a non-randomized controlled trial (non-RCT). For the non-RCT, only one arm was considered, and this study, along with other case series, was critically appraised using the Joanna Briggs Institute (JBI) tool.[11] The Risk of Bias 2 (RoB 2) tool was applied to the RCT, which showed an overall low risk of bias. The JBI appraisal indicated that most studies clearly defined participant inclusion; however, several studies were flagged with unclear or partial responses across domains such as demographic reporting and clinical information clarity. Collectively, these results suggest that while some studies demonstrate robust methodology with low risk of bias, others

TABLE-I

Summary of outcomes across various studies. summary of outcomes across included studies

Study (Author, Year)	Study Design	Comparator	Sample Size (eyes)	Mean Follow-up (months)	Main Adverse Events (grouped)	Adverse Effects(n)	Globe Salvage (n)	Tumor Control (n)	Recurrence (n)	Metastasis (n)
Spire et al., 2006(13)	Non-randomized prospective interventional case series	None	18	-	-	-	15	8	8	-
Stoffelns et al., 2011(14)	Non-randomized interventional case series	None	26	-	Macular pucker, macular edema, CNV, iris atrophy; 2 deaths from liver metastasis	16	26	16	6	2
Robertson et al., 1999(15)	Non-randomized interventional case series	None	20	-	Visual field loss, retinal detachment, vascular occlusion, macular edema, epiretinal membrane	-	20	18	1	0
Shields et al., 2002(16)	Non comparative interventional case series	None	256	-	-	-	253	232	24	2
Pan et al., 2008(17)	Prospective interventional case series	None	20	46.1	Vitreous hemorrhage, epiretinal membrane, retinal detachment	3	19	11	3	0
Chojniak et al., 2011(18)	Prospective non-randomized study	None	27	45	Retinal vascular events, optic atrophy, retinal traction/ detachment, vitreous hemorrhage	12	27	25	2	1
Godfrey et al.,1999(19)	Interventional Case series	None	14	16	Retinal hemorrhage, vascular occlusion, retinal traction, serous detachment, vitreitis, pain	-	13	10	-	0
Gündüz et al., 2011(20)	Observational cohort	None	24	22.7	Vitreous hemorrhage, cataract, synechiae, epiretinal membrane, vascular occlusion, glaucoma, retinal detachment	12	21	21	3	1
Win et al., 2006(21)	Non comparative interventional Case series	None	40	42	Vitreous hemorrhage, cataract, synechiae, iris atrophy, epiretinal membrane, vascular occlusion, glaucoma, retinal detachment	20	38	31	5	0
Parrozzani et al., 2009(22)	Prospective non-randomized	None	77	48.7	Macular pucker, macular edema, vascular occlusion, glaucoma, vitreous hemorrhage	20	75	68	9	4
Stoffelns et al.,2002(23)(	Prospective Interventional case series series	None	20	10	Macular edema, synechiae, pigment dispersion, retinal edema, pain	-	20	15	0	0
Mashayekhi et al., 2014(24)	Retrospective chart review	None	391	-	-	-	365	283	108	-
Harbour et al.,2003(25) (25)	Retrospective case-matched comparative study(only TTT arm has been considered)	Plaque brachytherapy	21	33	Retinal complications (not specified)	16	21	15	-	0
De Potter et al., 2003(26)	Randomized controlled trial	TTT with ICG	30	30	-	-	30	28	2	-
Yarovoy et al., 2010(27)	Retrospective case series	None	78	32.8	-	-	76	51	10	0
Forte et al., 2008 (28)	Retrospective case series	None	50	38	Decrease in vision, cystoid macular edema	6	-	49	0	-
Shields et al., 1998(29)	Prospective non-randomized analysis	None	100	14	Vision loss (subfoveal treatment, traction, vascular occlusion, disc edema, ischemia)	42	96	94	2	0
Numenko, 2020(30)	Retrospective analysis	None	84	-	Retinopathy, retinal hemorrhage, hemophthalmia, enucleation for relapse/complications	12	72	79(51 tumor resorption,28 tumor stabilization)	41	5

exhibit uncertainties in reporting and methodological transparency. These limitations should be taken into account when interpreting the pooled results of the meta-analysis.

Grade assessment was performed for all four outcomes. Overall, the certainty of the evidence was low. The evidence base primarily consisted of observational case series with variable risk of bias and substantial heterogeneity in the reporting of tumor control and adverse effects. The methodological quality of this systematic review and meta-analysis was rigorously evaluated using the AMSTAR-2 tool.[12] The review demonstrated good methodological rigor, supported by a comprehensive search strategy, a pre-registered protocol, and a detailed assessment of risk of bias and heterogeneity.

RESULTS

We performed meta-analyses for proportions using the metaprop function from the meta package in R (version 4.4.2). For each outcome (metastasis, adverse effects, globe salvage, and tumor control), study-specific event rates and sample sizes were extracted. Proportions were pooled using the logit transformation (PLOGIT) with the inverse variance method. A random-effects model was applied in all analyses, with between-study variance (τ^2) estimated using the Hartung–Knapp adjustment to provide more robust confidence intervals. To account for zero-event studies, a continuity correction of 0.5 was applied to all cells. Results are presented as pooled proportions with 95% confidence intervals (CI), alongside 95% prediction intervals (PI) to reflect the expected range of effects in future studies. Statistical heterogeneity was quantified using the I^2 statistic, τ^2, and Cochran's Q test. Forest plots were generated for each outcome to visualize study-level estimates, pooled effects, and heterogeneity measures.

Tumor control, the pooled random-effects rate was 81.3% (95% CI: 72.7–87.6%), but with considerable heterogeneity (I^2 = 82.9%, τ^2 = 0.71, Q = 99.6, $p < 0.001$). Prediction intervals for tumor control were wide (40.7% to 96.5%), indicating variability in outcomes across future settings.

FIGURE-2

Forest plot showing pooled tumor control rates after transpupillary thermotherapy for choroidal melanoma (18 studies; 1,296 eyes).

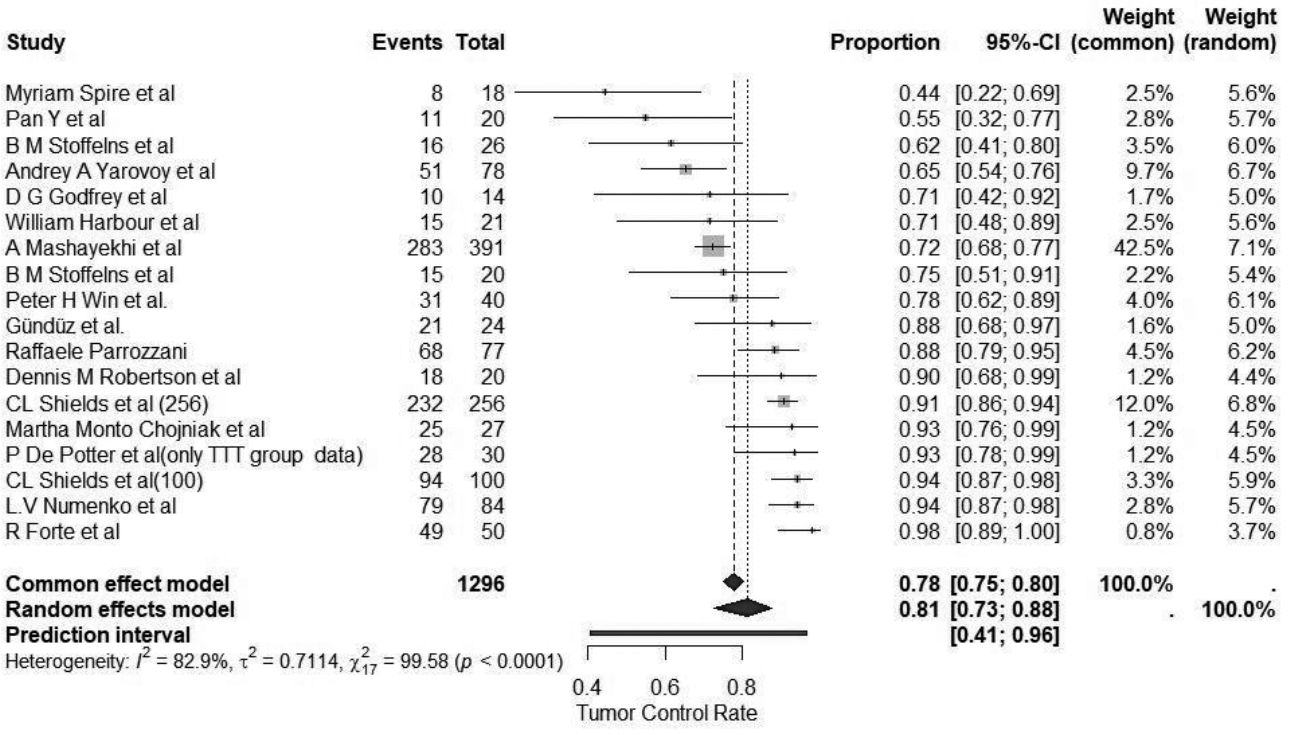


FIGURE-3

Forest plot of globe salvage following transpupillary thermotherapy (17 studies).

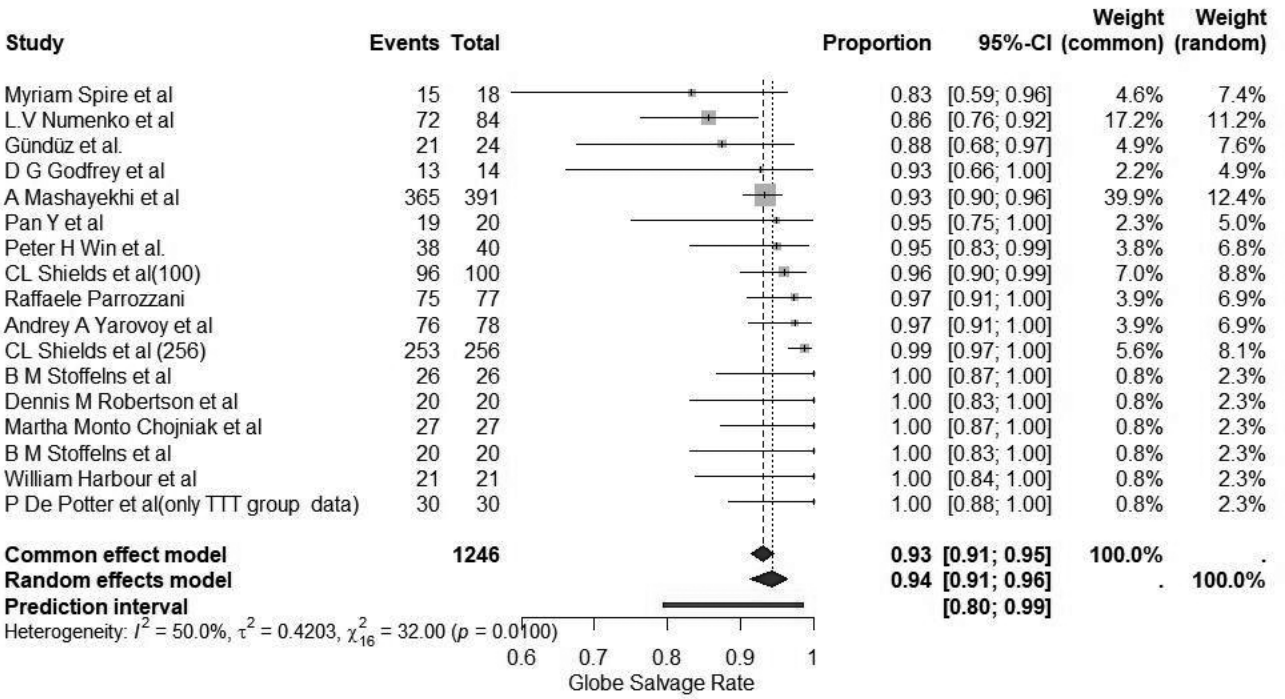
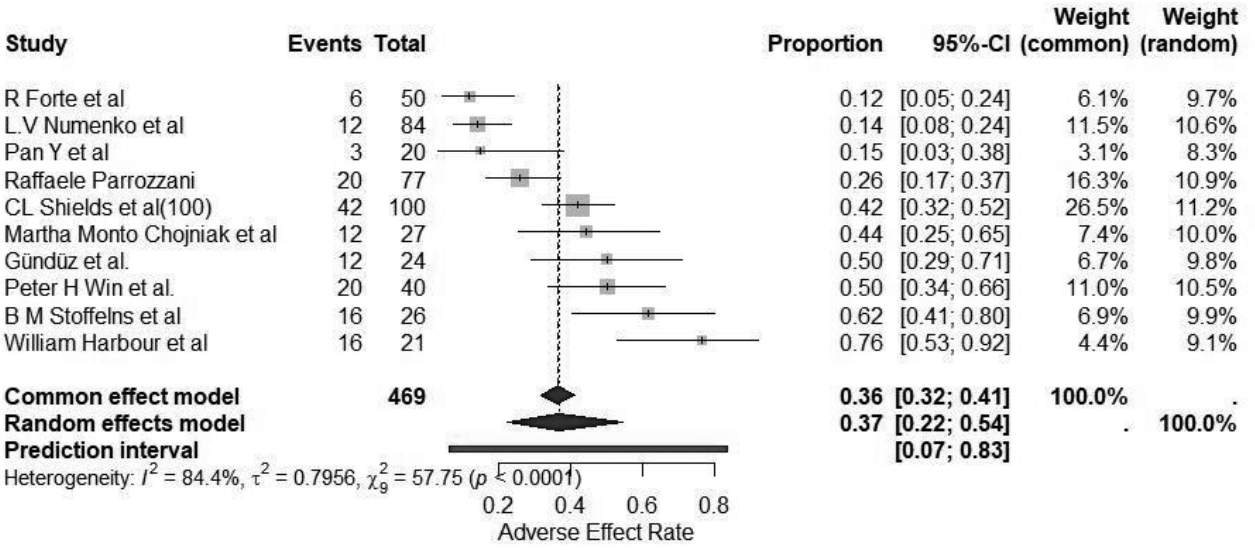


FIGURE-4

Forest plot of adverse effects following transpupillary thermotherapy (10 studies).

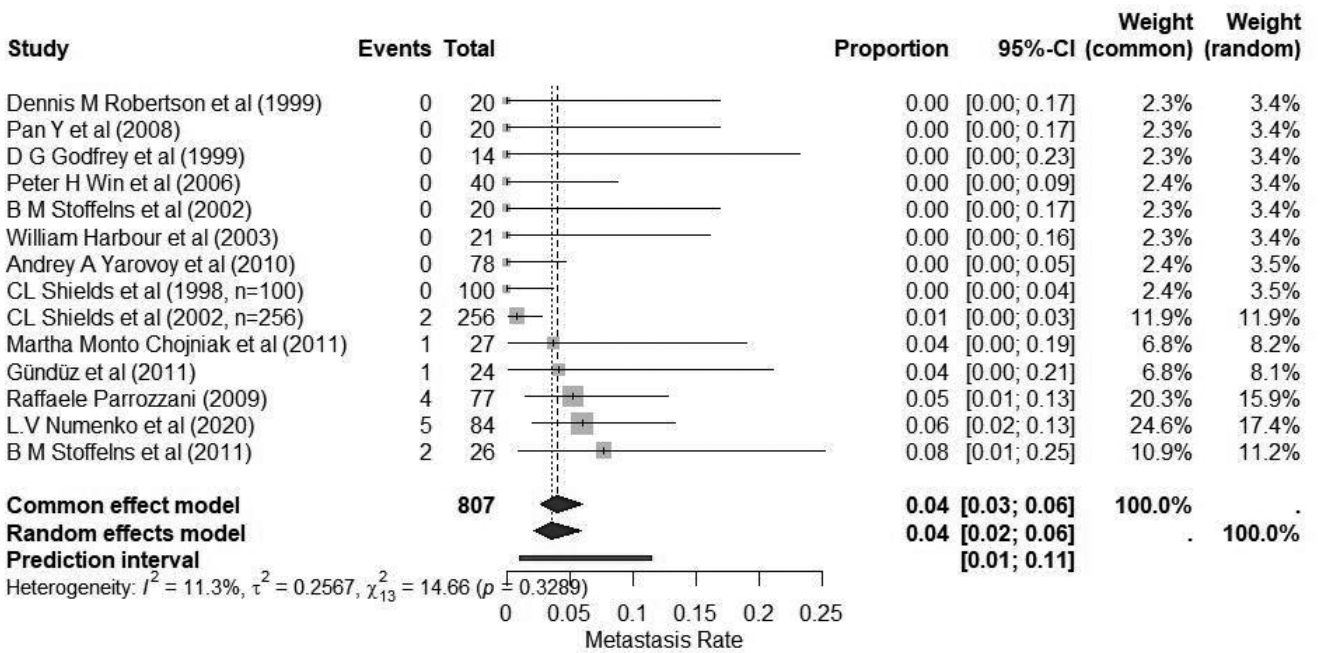


Globe salvage was highly consistent across studies, with a pooled random-effects estimate of 94.4% (95% CI: 91.4–96.4%), though moderate heterogeneity was observed (I^2 = 50.0%, τ^2 = 0.42, Q = 32.0, p = 0.01). Subgroup analysis based on tumor follow-up duration (greater than or less than 24 months) reduced heterogeneity to I^2 = 0%, τ^2 = 0, p = 0.7163. Therefore, meta-regression was not performed.

For adverse effects, the random-effects model estimated a pooled rate of 37.0% (95% CI: 22.5–

FIGURE-5

Forest plot of metastasis rates after transpupillary thermotherapy (14 studies).



54.4%), with wide prediction intervals (6.5% to 83.2%) reflecting substantial heterogeneity (I^2 = 84.4%, τ^2 = 0.80, Q = 57.8, p < 0.001). Though subgroup analysis and meta-regression could not explain heterogeneity. Meta-Regression with study year showed a negative coefficient (-0.07), suggesting a trend towards lower complication rates in more recent studies, although this did not reach statistical significance (p=0.20)

For metastasis, the pooled random-effects proportion under the logit transformation was 4% (95% CI: 2.0-6%), with a prediction interval ranging from 1.0% to 11.4%. Heterogeneity was low (I^2 = 11.3%, τ^2 = 0.25, Q = 14.6, p = 0.33), suggesting consistency in metastasis rates across various studies.

Subgroup analyses indicated that tumors ≥3 mm had a tumor control rate of 78%, and adverse effects of 39, with heterogeneity varying across outcomes. Tumor control was comparable across tumor locations (~76–77%) despite high heterogeneity. Analyses by follow-up duration showed stable tumor control (~85%) but a slight increase in adverse effects over time. None of these factors accounted for the observed between-study heterogeneity.

Meta-regression further demonstrated that sample size, publication year, and follow-up duration were not significant sources of heterogeneity for tumor control rate.

Publication bias assessment suggested possible bias for metastasis (Egger's test, p = 0.022); however, trim-and-fill analysis imputed six missing studies, and the adjusted effect remained significant and stable. No evidence of publication bias was found for tumor control, globe salvage, or adverse effects.

Sensitivity analyses, including leave-one-out and cumulative approaches, confirmed the robustness of the pooled estimates, indicating that the results were not driven by any single study.

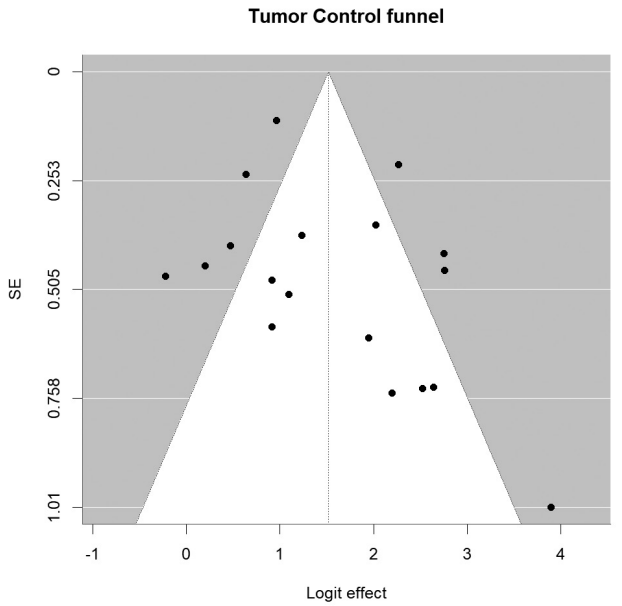
DISCUSSION

This systematic review and meta-analysis included 18 studies encompassing a total of 1,296 eyes. Among these, only one randomized controlled trial was identified, while another comparative study contributed a single treatment arm and was therefore analyzed as a case series. The remaining

studies were also case series. The mean follow-up duration across studies ranged from 10 to 48.7 months, offering moderate-term outcome data. Tumor characteristics were generally consistent, with initial thickness ranging from 0.78 mm to 4.5 mm and basal diameters less than 12 mm.

FIGURE-6

Funnel plot for studies reporting tumor control with transpupillary thermotherapy. The distribution of effect sizes appears relatively symmetrical around the pooled estimate, suggesting no strong evidence of publication bias.



Commonly reported adverse effects included macular scarring, vitreous hemorrhage, epiretinal membrane formation, retinal vascular obstruction, serous retinal detachment.[13,16,22,24,28,30] and optic disc atrophy 60% in parapapillary tumors.[18] Many of these were vision-threatening, particularly when involving the macula or optic disc. Despite this, metastasis rates remained low, with a pooled estimate of 4% (95% CI: 2–6%) during the available follow-up period. However, several studies noted that the follow-up duration might be insufficient to detect late-onset metastatic events.[15,23]

Despite heterogeneity in study designs and outcome reporting, the available evidence suggests that transpupillary thermotherapy (TTT) can offer satisfactory tumor control and excellent globe preservation in carefully selected cases of small choroidal melanoma. A recent review on photodynamic therapy (PDT) reported an overall tumor response rate of 80% (range: 58–100%) with a mean follow-up of 50 months. Both TTT and PDT therefore appear to provide comparable efficacy in terms of tumor regression. However, PDT outcomes were noted to be influenced by tumor pigmentation, with better responses observed in non-pigmented lesions[31], whereas TTT has been more extensively used in pigmented tumors.

The pooled tumor control rate achieved with TTT in our analysis was 81.3%, closely aligning with the 84% weighted mean control rate reported in a recent meta-analysis of Ru-106 brachytherapy involving nearly 4,000 patients. In the Karimi et al. meta-analysis of Ru-106, vision-threatening complications such as cataract formation, radiation retinopathy, and optic neuropathy were well documented. For instance, the Naples series reported that up to 63% of eyes developed some form of radiation-related complication. However, these studies did not provide pooled estimates for final visual acuity thresholds or the proportion of eyes experiencing severe vision loss.[32,33] In contrast, our TTT meta-analysis showed a somewhat lower overall adverse event rate of 37%, although a significant proportion of these involved the macula or optic disc with well-established potential to severely impact vision.

While TTT achieved a pooled tumor control rate slightly lower than the 89% three-year control rate reported with CyberKnife stereotactic radiosurgery, it offered notably higher rates of globe preservation 95% compared to 84% at three years and 79% at five years with CyberKnife.[34] Recurrence rates also varied, with CyberKnife demonstrating a pooled recurrence of 23%, compared to 17% for TTT.

Proton beam therapy (PBT) has also demonstrated favorable outcomes, with meta-analysis data indicating tumor control rates exceeding 90% at 1–5 years and approximately 88% at 10 years. (35) While TTT provides acceptable tumor control in carefully selected small choroidal melanomas, direct comparative data between these modalities remains limited. Further research specifically targeting small tumors and stratifying outcomes by location is warranted to validate these findings.

TTT is most commonly utilized for tumors located posterior to the equator, particularly those within the posterior pole. It remains a viable option for lesions near critical visual structures such as the optic disc and fovea, although central vision loss remains a frequent limitation. Juxtapapillary tumors, especially those abutting or overhanging the optic nerve head, are associated with increased risks of treatment failure and complications compared to non-juxtapapillary lesions.[16,22] Several prognostic factors have been identified for treatment failure, including the need for more than three treatment sessions, tumor thickness greater than 3 mm, basal diameter exceeding 10.2 mm, elevated systolic vascular velocity (>11.2 cm/s), presence of subretinal fluid, and the amelanotic tumor subtype (16)(27)(29).

LIMITATIONS

This meta-analysis has several limitations. The included studies were predominantly non-randomized and observational, introducing potential selection and reporting biases. Variability in treatment techniques and outcome definitions further complicates cross-study comparisons. Additionally, the lack of individual patient data precluded more nuanced subgroup analyses, such as by tumor genetics or baseline visual acuity.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

TTT remains a valuable tool in the ophthalmologist's arsenal for managing select choroidal melanomas. Future studies should aim to standardize treatment protocols and reporting criteria to facilitate more robust comparisons. Prospective randomized trials comparing TTT with other focal therapies especially in the era of genetic prognostication would help refine patient selection and optimize therapeutic outcomes.

CONCLUSION

This systematic review and meta-analysis demonstrates that transpupillary thermotherapy achieves satisfactory tumor control (81.6%) and excellent globe salvage (94.4%) in small choroidal melanomas, with relatively low metastatic risk during available follow-up. Comparisons with other modalities suggest that TTT offers a favorable safety profile and good rates of eye preservation, though tumor control may be somewhat lower than with proton beam therapy or stereotactic radiosurgery. Variability in treatment protocols, particularly regarding the number of sessions remains a major limitation. Overall, TTT remains a valuable, eye-preserving option for carefully selected posterior choroidal melanomas, but standardized treatment protocols and prospective comparative trials are needed to better define its role alongside modern therapies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Anahita Jamil:** Concept, design, writing.
2	**Romaisa Kiran Baloch:** Data extraction.
3	**Anaam Rahman:** Interpretation.