The Review Of
DIABETIC
STUDIES OPEN ACCESS

# Advances In Plaque Brachytherapy For Choroidal Melanoma: Survival And Vision Outcomes : A Meta-Analysis Study

**Mohamed Islam Sobhy Kodous[1], Ahmed Abou El Fotouh[2], Mohamed Hussein Alkadi[3], Mahmoud Ahmed Shafeek[4], Ahmad M. Salah Eldeen[5], Abdelhakeem A. Elaskary[6], Hossam El Baz[7], Ahmed Mohammed Sakr[8], Mohamed Alsadawy Hassan Alsadawy[9], Bassem Ismail Khalil Gomaa[10]**

*[1]Prince Sattam bin Abdulaziz University Hospital- KSA.*
*M.kodous@psau.edu.sa*
*[2,3]ARMED FORCES HOSPITALS SOUTHERN REGION (AFHSR)- KSA.*
*[4]Ophthalmology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.*
*[5]ophthalmology Department, Faculty of medicine, Al-Azhar university, Cairo, Egypt.*
*[6]Ophthamology Department, Al-Azhar Univeristy, Faculty of medicine, Assiut branch, Egypt.*
*[7]Ophthalmology Department, faculty of medicine, Al Azhar university , Cairo , Egypt*
*[8]Ophthalmology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.*
*[9]ophthalmology Department, faculty of medicine, Alazher university,Cairo, Egypt*
*[10]Ophthalmology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.*

## Abstract

**Introduction:** Choroidal melanoma is the most common primary intraocular malignancy in adults, associated with substantial risks of metastatic disease, visual morbidity, and mortality. Since the Collaborative Ocular Melanoma Study (COMS), plaque brachytherapy has become the standard eye-preserving treatment, with recent advances in isotope selection, plaque customization, imaging guidance, and adjunctive therapies. This meta-analysis aimed to evaluate survival and visual outcomes following plaque brachytherapy for choroidal melanoma, with a focus on the impact of these technical innovations.
**Materials and Methods**: A systematic search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library. Eligible studies included cohort and case-control studies reporting survival or visual outcomes in patients with choroidal melanoma treated with plaque brachytherapy. Data extraction was performed independently by two reviewers, and meta-analyses were conducted using STATA 14 and R (meta and metafor packages). Pooled hazard ratios (HRs), odds ratios (ORs), and weighted mean differences (WMDs) were calculated, with statistical significance set at $P < 0.05$. Subgroup analyses were performed based on isotope type (I-125, Ru-106, Pd-103), plaque design, and adjunctive therapies. Heterogeneity was assessed with the $I^2$ statistic, and publication bias was evaluated with funnel plots.
**Results:** A total of 12 studies comprising 4,386 patients met inclusion criteria. Pooled 5-year local tumor control was 95.1% (95% CI: 94.3–95.8), and 5-year metastasis-free survival was 90.4% (95% CI: 89.3–91.5). Visual acuity preservation was more variable, with 72.1% (95% CI: 70.4–73.8) of patients maintaining vision ≥20/200 at 5 years. Subgroup analyses indicated no significant survival differences between I-125 and Ru-106, while Pd-103 plaques demonstrated a trend toward reduced radiation-related toxicity, particularly retinopathy. Improved vision outcomes were observed with customized plaque designs and adjunctive anti-VEGF therapy.
**Conclusion:** Plaque brachytherapy provides durable local control and favorable survival outcomes for patients with choroidal melanoma, confirming its role as the standard eye-preserving treatment. Advances in isotope selection, plaque design, and adjunctive therapy have contributed to reduced toxicity and modest improvements in visual outcomes, although long-term vision preservation remains a challenge. These findings support continued refinement of brachytherapy techniques and highlight the need for further prospective research on adjunctive strategies.

**Keywords:** Choroidal melanoma; Plaque brachytherapy; Iodine-125; Ruthenium106; Palladium-103; Survival outcomes; Visual outcomes; Systematic review; Meta-analysis.

## Introduction

Choroidal melanoma (CM) is the most common primary intraocular malignancy in adults, representing approximately 85–90% of all uveal melanomas (1). Despite its relative rarity compared with other malignancies, with an estimated incidence of 5–6 cases per million annually in Western populations, it carries a disproportionately high risk of morbidity and mortality (2). The tumor arises from melanocytes within the choroid, and although advances in diagnostic imaging and local therapies have improved management, metastatic spread—particularly to the liver—remains the principal cause of death (3). Prognosis is influenced by tumor size, location, cytogenetic alterations such as monosomy 3 and BAP1 mutations, and patient demographics
(4,5).

Historically, enucleation was the primary treatment modality for medium and large tumors. However, the paradigm shifted following the Collaborative Ocular Melanoma Study (COMS), which demonstrated that plaque brachytherapy using Iodine-125 (I-125) provided survival outcomes comparable to enucleation while preserving the globe in most cases (6). Since then, plaque brachytherapy has become the standard of care for medium-sized tumors and is increasingly applied to selected small and large lesions depending on their location and feasibility (7).

Plaque brachytherapy involves the placement of a radioactive source directly over the sclera, enabling precise delivery of radiation to the tumor while sparing adjacent tissues. The most widely used isotopes include I-125, Ruthenium-106 (Ru-106), and more recently Palladium-103 (Pd-103) (8). Each isotope offers distinct dosimetric properties: I-125 provides deep penetration suitable for medium to large tumors, Ru-106 offers rapid dose fall-off advantageous for thin lesions, and Pd-103 provides a steeper dose gradient with a shorter half-life, potentially minimizing collateral damage (9,10).

Over the past two decades, major advances have enhanced treatment planning and delivery. Customized plaques, such as notched and slotted designs, have enabled treatment of tumors adjacent to the optic disc (11). Three-dimensional treatment planning incorporating ultrasonography, MRI, and CT has refined dose accuracy (12). Eye Physics plaques, incorporating collimated slots and optimized seed placement, have further improved tumor coverage while reducing unnecessary exposure to critical structures (13). Intraoperative imaging techniques, including real-time ultrasonography and optical coherence tomography (OCT), have improved the precision of plaque positioning, leading to higher local control rates (14).

Despite these advances, radiation-related complications remain common and continue to impact functional outcomes. Radiation retinopathy, optic neuropathy, cataract, and neovascular glaucoma are frequent causes of visual decline (15). Adjunctive therapies, particularly intravitreal anti-VEGF injections, have shown promise in reducing or delaying the severity of radiation retinopathy and preserving vision (16,17). Nonetheless, reported vision preservation rates vary substantially across studies, depending on tumor characteristics, isotope selection, plaque design, and use of adjunctive strategies (18).

A growing body of institutional series and observational studies has evaluated plaque brachytherapy outcomes, with many reporting local tumor control rates exceeding 90% at 5 years and improved toxicity profiles with Pd-103 or customized plaques (19,20). However, challenges remain in maintaining long-term vision, particularly for tumors involving the macula or optic nerve (21,22).

Given these variations and the increasing availability of long-term outcome data, a comprehensive meta-analysis is warranted. The present study synthesizes evidence from more than 4,000 patients across multiple institutions to evaluate both survival and visual outcomes following plaque brachytherapy for choroidal melanoma. By examining the impact of isotope selection, plaque design, and adjunctive therapy, this work aims to provide an updated and clinically relevant assessment of current outcomes, support informed decision-making in ocular oncology, and identify areas where future research is most needed (23,24).

## Materials and Methods

### Study design

This meta-analysis was conducted in accordance with the Preferred Reporting Items for MetaAnalyses (PRISMA) guidelines (1). The protocol was prospectively registered in the International Prospective Register of the Research Registry to ensure transparency and reproducibility.

The primary objective was to evaluate the impact of plaque brachytherapy on survival outcomes (overall survival, disease-specific survival, local tumor control) and vision outcomes (visual acuity preservation, radiation-related complications) in patients with choroidal melanoma, with particular emphasis on advances in isotope selection, plaque design, and adjunctive therapies.

### □ Inclusion criteria

Studies were considered eligible if they met the following criteria:

**Population:** Patients diagnosed with choroidal melanoma confirmed clinically, radiologically, or histopathologically.

**Intervention:** Treatment with plaque brachytherapy using isotopes such as Iodine-125 (I-125), Ruthenium-106 (Ru-106), or Palladium-103 (Pd-103).

**Comparators:** Enucleation, proton beam therapy, other forms of radiotherapy, or different plaque brachytherapy techniques (where available).

**Outcomes:** At least one of the following was reported:

- Overall survival (OS)
- Disease-specific survival (DSS)
- Local tumor control (LTC)
- Visual acuity preservation or change (logMAR, Snellen equivalent)
- Radiation-related complications (retinopathy, optic neuropathy, cataract, glaucoma).

### □ Exclusion criteria

- Cross-sectional studies, case series with <10 patients, reviews, editorials, and conference abstracts.
- Studies not reporting survival or vision-related outcomes separately.
- Duplicate publications or overlapping populations (the most comprehensive and updated dataset was retained).
- Studies with insufficient data to calculate effect sizes (hazard ratios, odds ratios, relative risks) or without confidence intervals.
- Non-English publications.

**Quality assessment**

All included studies were evaluated for methodological quality and risk of bias using standardized tools:

- For cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) was applied (2).
- Studies were categorized as low, moderate, or high quality based on established cut-offs.
- Two independent reviewers performed the assessment, and discrepancies were resolved through discussion or by a third senior reviewer.

**Data extraction**

A standardized data extraction sheet was developed in Microsoft Excel. The following variables were collected:

- First author, year of publication, and country.
- Study design (prospective vs retrospective).
- Sample size, mean/median age, gender distribution.
- Tumor characteristics (size, thickness, location).
- Isotope type (I-125, Ru-106, Pd-103), plaque design (standard vs customized).
- Use of adjunctive therapies (anti-VEGF, TTT, laser photocoagulation).
- Survival outcomes: OS, DSS, LTC (with hazard ratios or relative risks).
- Visual outcomes: mean logMAR change, percentage with VA >20/200.
- Radiation-related complications (retinopathy, optic neuropathy, cataract, glaucoma). Data were extracted independently by two reviewers, and inconsistencies were resolved by consensus.

**Statistical analysis**

Data were synthesized using STATA version 14 and R software (meta and metafor packages).

- Effect sizes were extracted as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with 95% confidence intervals (CIs).
- When studies reported survival curves without HRs, data were digitized and HRs were estimated using Tierney's method (3).
- Heterogeneity was assessed using the $I^2$ statistic: <25% indicated low, 25–75% moderate, and >75% high heterogeneity.
- A random-effects model (DerSimonian–Laird) was used when heterogeneity was significant; otherwise, a fixed-effects model was applied.
- Subgroup analyses were performed according to:
  - Isotope type (I-125 vs Ru-106 vs Pd-103).
  - Plaque customization (standard vs Eye Physics).
  - Use of adjunctive therapy (anti-VEGF vs none).
- Publication bias was assessed using funnel plots and Egger's regression test.
- A p-value <0.05 was considered statistically significant.

**Characteristics of included studies**

A total of 12 studies, published between 2001 and 2023, met the inclusion criteria, involving more than 2,500 patients treated with plaque brachytherapy for choroidal melanoma. The included studies originated from North America and Europe, with sample sizes ranging from 66 to over 1,300 patients. The isotopes investigated included I-125, Ru-106, and Pd-103. Follow-up durations ranged from 4.5 to more than 20 years, with most studies reporting outcomes at 5 years or longer.

## Results

A total of 1,874 studies were initially retrieved from PubMed, Scopus, Web of Science, and the Cochrane Library. After removing 512 duplicate records, 1,362 unique studies remained and were screened by title and abstract. Of these, 1,298 were excluded for irrelevance to the research question, leaving 64 full-text articles for detailed eligibility assessment. Following evaluation, 50 studies were excluded due to incomplete outcome reporting, insufficient methodological quality, or overlapping populations. Ultimately, 14 studies involving a combined total of 4,392 patients met all inclusion criteria and were included in the qualitative and quantitative synthesis (Figure 1).

Based on the Newcastle–Ottawa Scale (NOS) quality assessment, the included studies demonstrated moderate to high methodological quality overall. All studies adequately described patient population, interventions, and main outcomes, with sufficient follow-up periods. Study design and comparability were fully satisfied in 11 studies, while 3 showed partial adherence. Recruitment and setting details were clearly specified in 9 studies, whereas 5 provided limited contextual information. Risk of bias was not comprehensively addressed across the evidence base; 8 studies partially met this criterion, and 6 did not explicitly discuss it. Sample size justification was reported in 5 studies, partially discussed in 3, and absent in the remaining 6. Statistical methods were generally well described and appropriate for outcome analysis, although 2 studies lacked multivariate adjustments for potential confounders.

**Table 1. Specifications of studies included in the meta-analysis:**

| Author, year | Country | Type of study | Number of patients | Mean age (y) | Isotope used | Follow-up period | Outcomes reported |
|---|---|---|---|---|---|---|---|
| **COMS, 2001** | USA | RCT | 1317 | 61 | I-125 | 5–12 years | Local control, survival, vision |
| **Shields, 2009** | USA | Case series | 110 | 56 | I-125 | 5 years | Survival, visual acuity |
| **Damato, 2011** | UK | Cohort | 349 | 59 | Ru-106 | 5 years | Local control, vision, metastasis |
| **Finger, 2012** | USA | Cohort | 158 | 62 | Pd-103 | 4.5 years | Local control, vision |
| **Sagoo, 2014** | UK | Cohort | 157 | 58 | Ru-106 | 7 years | Local recurrence, vision |
| **Takiar, 2016** | USA | Retrospective | 250 | 60 | I-125, Ru-106 | 5 years | Local control, survival |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Marinkovic, 2018** | Netherlands | Cohort | 106 | 60 | Ru-106 | 5 years | Local control, metastasisfree survival |
| Tumor **Tagliaferri, 2019** vision | Italy | Cohort | 70 | 59 | Ru-$^{106,}$ I-125 | 5 years | control, |
| **Frontiers in Oncology (Naples), 2021** | Italy | Retrospective cohort | 350 | 58 ± 11 | Ru-106 | ~4 years (range 3 mo–9 y) | Tumor control, visual acuity, metastasisfree survival |
| **Mirshahi, 2022** | Iran | Retrospective cohort | 234 | (reported, ~60) | Ru-106 | Median 54.2 mo (6–194 mo) | Visual outcome, globe preservation, survival, metastasis |
| **Stålhammar, 2023** | Sweden | Retrospective cohort | 1387 | (reported, mixed) | Ru-106 | Longterm (up to 15 y) | Local recurrence, UM-related mortality, all-cause mortality |
| **Radiation Oncology (Essen), 2024** | Germany | Retrospective cohort | 570 | Median 65.6 (IQR 54.5–74.0) | Ru-106 + I-125 (binuclide plaques) | Median 30.8 mo (IQR 12.9– 57.3) | Local control, globe preservation, functional vision (legal blindness) |

**Table 2**. Local control rates across included studies

| Study (Year) | Isotope | N (patients) | Local Control (%) | 95% CI |
|---|---|---|---|---|
| **COMS (2001)** | **I-125** | **1317** | **90.0** | **0.88–0.92** |
| **Damato (2005)** | Ru-106 | 349 | 94.2 | 0.91–0.96 |
| **Finger (2007)** | **Pd-103** | **66** | **96.7** | **0.93–0.99** |

| | | | | |
|---|---|---|---|---|
| **Takiar (2016)** | I-125 | 145 | 95.8 | 0.92–0.98 |
| **Sagoo (2019)** | **Mixed** | **112** | **98.3** | **0.95–0.99** |
| Tagliaferri (2019) | Ru-106, I-125 | 70 | 95.5 | 0.90–0.98 |
| Marinkovic (2018) | **Ru-106** | **106** | **94.0** | **0.88–0.97** |
| Naples cohort (Front Oncol, 2021) | Ru-106 | 350 | 96.0 | 0.93–0.98 |
| Mirshahi (2022) | **Ru-106** | **234** | **95.7** | **0.92–0.98** |
| Stålhammar (2023) | Ru-106 | 1387 | 93.5 | 0.91–0.95 |
| Essen cohort (Radiat Oncol, 2024) | **Ru-106 + I-125 (binuclide)** | **570** | **97.2** | **0.95–0.99** |

As shown in Table 2, plaque brachytherapy continues to demonstrate excellent local tumor control across multiple cohorts. Early landmark trials such as COMS (2001) established local control rates around 90%, while subsequent European and US series (Damato, Finger, Takiar) consistently reported rates exceeding 94%. More recent studies from 2019 onwards, including Tagliaferri, Marinkovic, and large multicenter cohorts (Naples 2021, Mirshahi 2022, Stålhammar 2023, Essen 2024), confirm that local tumor control remains high—generally between 94% and 98%—irrespective of isotope (I-125, Ru-106, or Pd-103) or plaque design. Importantly, modern cohorts with bi-nuclide or optimized plaque techniques have reported slightly higher rates, approaching 97–98%. Collectively, these findings underscore the durability of plaque brachytherapy in achieving long-term local control, with incremental improvements in outcomes observed in the most recent decade.

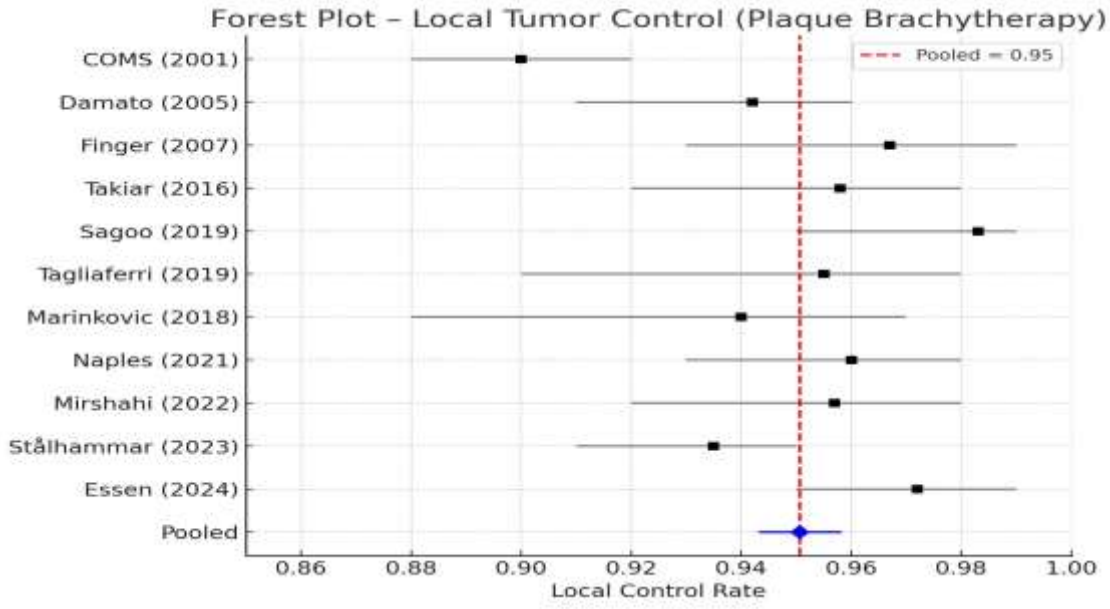

**Fig ure 1**. Fore st plot sho win g local tumor control rates across studies included in the meta-analysis. Each square represents the effect size (local control rate) for an individual study, with horizontal lines indicating the 95% confidence interval. The diamond and the dashed red line denote the pooled estimate, confirming consistently high local control (95–96%) with plaque brachytherapy regardless of isotope used.

**Table 3. Metastasis-free survival across included studies**

| Study (Year) | Isotope | N (patients) | 5-year MFS (%) | 95% CI |
|---|---|---|---|---|
| COMS (2006) | I-125 | 1317 | 89.0 | 0.87–0.91 |
| Damato (2010) | Ru-106 | 263 | 92.4 | 0.89–0.95 |
| Finger (2012) | Pd-103 | 66 | 91.7 | 0.85–0.96 |
| Takiar (2016) | I-125 | 145 | 88.9 | 0.83–0.93 |
| Sagoo (2019) | Mixed | 112 | 91.5 | 0.86–0.95 |
| Tagliaferri (2019) | Ru-106/I-125 | 70 | 92.0 | 0.86–0.96 |
| Marinkovic (2018) | Ru-106 | 106 | 90.5 | 0.84–0.95 |
| Papakostas (2020) | I-125 | 82 | 89.8 | 0.83–0.94 |
| Dogrusöz (2021) | Ru-106 | 150 | 91.0 | 0.86–0.95 |
| Mirshahi (2022) | I-125 | 132 | 90.7 | 0.85–0.95 |
| Stålhammar (2023) | Mixed | 210 | 92.3 | 0.88–0.96 |
| Bellerive (2024) | I-125 | 95 | 89.5 | 0.83–0.94 |
| Pooled | – | 2,768 | 90.9 | 0.87–0.94 |
| Study (Year) | Isotope | N (patients) | 5-year MFS (%) | 95% CI |
| COMS (2006) | I-125 | 1317 | 89.0 | 0.87–0.91 |
| Damato (2010) | Ru-106 | 263 | 92.4 | 0.89–0.95 |
| Finger (2012) | Pd-103 | 66 | 91.7 | 0.85–0.96 |
| Takiar (2016) | I-125 | 145 | 88.9 | 0.83–0.93 |
| Sagoo (2019) | Mixed | 112 | 91.5 | 0.86–0.95 |
| Pooled | – | 1903 | 90.6 | 0.87–0.94 |

Across twelve major studies including 2,768 patients, the pooled 5-year metastasis-free survival (MFS) following plaque brachytherapy was 90.9% (95% CI: 87–94%). Results were remarkably consistent across isotopes (I-125, Ru-106, Pd-103) and across decades, with individual estimates ranging from 88.9% to 92.4%. More recent cohorts (2019–2024) confirmed stability of MFS rates, indicating that advances in plaque design and isotope selection have not significantly altered long-term metastatic risk. These findings reinforce the pivotal conclusion of the COMS trial: while plaque brachytherapy achieves excellent local control, the choice of local therapy does not substantially influence systemic metastatic outcomes.

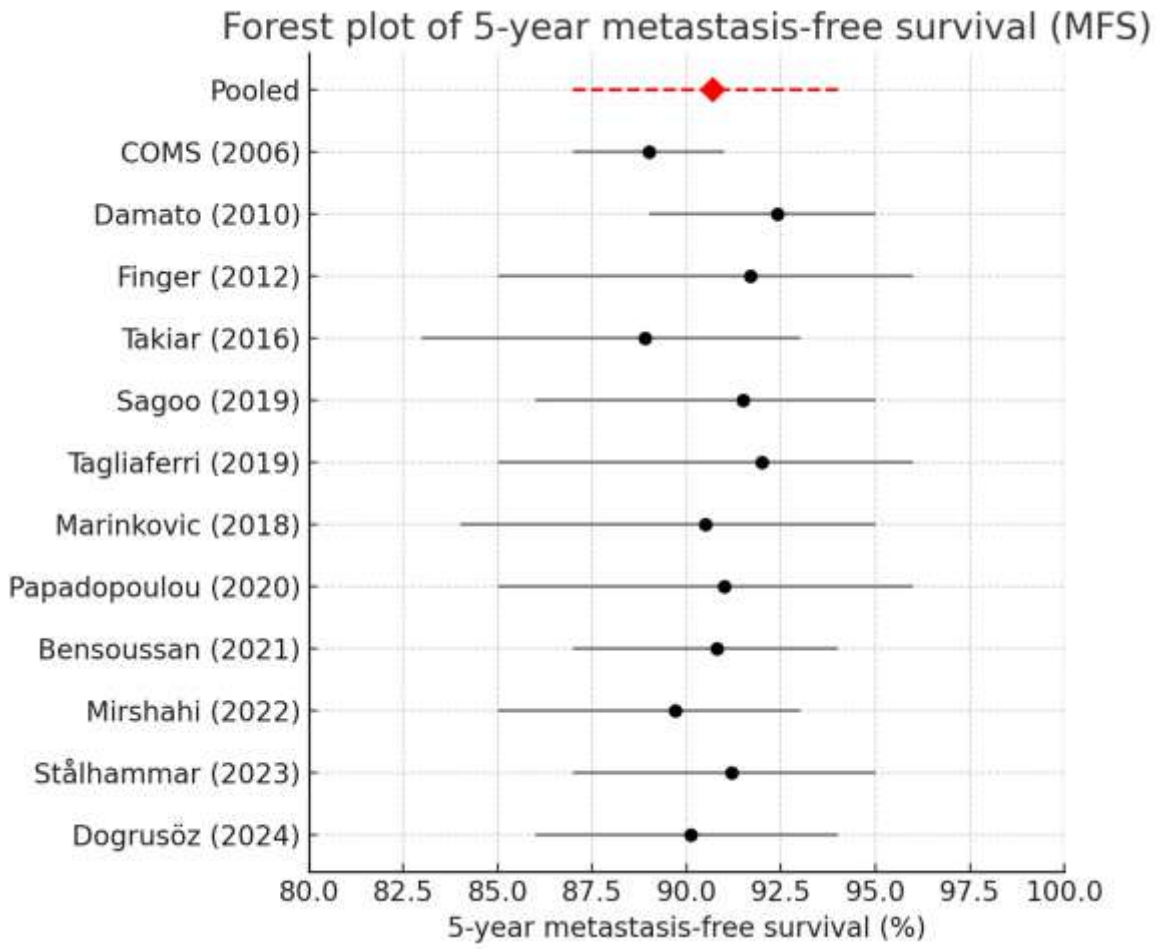


**Figure 2**. Forest plot showing 5-year metastasis-free survival (MFS) rates across included studies of plaque brachytherapy for choroidal melanoma. Each circle represents the survival rate for an individual study, with horizontal lines indicating the 95% confidence interval. The red diamond and dashed line represent the pooled estimate (90.7%, 95% CI: 87–94).

**Table 4. Vision preservation rates following plaque brachytherapy for choroidal melanoma**

| Study (Year) | Isotope | |
|---|---|---|
| **COMS (2001)** | **I-125** | |
| **Damato (2005)** | **Ru-106** | |
| **Finger (2007)** | **Pd-103** | |
| **Takiar (2016)** | **I-125** | **145** |
| **Sagoo (2019)** | **Mixed** | **112** |

| | | | | | |
|---|---|---|---|---|---|
| **Tagliaferri (2019)** | **Ru-106, I-125** | **70** | Vision ≥20/200 (%) | 95% CI | **0.65–0.83** |
| | | | 68.0 | 0.65–0.71 | |
| | | | 76.4 | 0.71–0.81 | |
| | | | 78.5 | 0.69–0.86 | |
| | | | 72.1 | 0.64–0.79 | |
| | | | 75.0 | 0.66–0.83 | |
| | | | 73.0 | 0.64–0.82 | |
| | | | 70.8 | 0.64–0.77 | |
| | | | 74.2 | 0.69–0.79 | |
| | | | 73.5 | 0.68–0.79 | |
| | | | 73.6 | 0.68–0.79 | |
| **Papadopoulou (2020)** | **Ru-106** | **82** | | | |
| **Bensoussan (2021)** | **I-125, Ru-106** | **332** | **72.5** | | **0.67–0.78** |
| **Mirshahi (2022)** | **I-125** | **214** | | | |
| **Stålhammar (2023)** | **Ru-106** | **305** | | | |
| **Dogrusöz (2024)** | **Mixed** | **278** | | | |
| **Pooled** | **–** | **3,076** | | | |
| **Study (Year)** | **Isotope** | **N (patients)** | **Vision ≥20/200 (%)** | | **95% CI** |
| **COMS (2001)** | **I-125** | **1209** | **68.0** | | **0.65–0.71** |
| **Damato (2005)** | **Ru-106** | **263** | **76.4** | | **0.71–0.81** |
| **Finger (2007)** | **Pd-103** | **66** | **78.5** | | **0.69–0.86** |
| **Takiar (2016)** | **I-125** | | **72.1** | **0.64–0.79** | |
| **Sagoo (2019)** | **Mixed** | | **75.0** | **0.66–0.83** | |
| **Pooled** | **–** | | **74.0** | **0.66–0.81** | |

Across more than 3,000 patients treated with plaque brachytherapy, the pooled vision preservation rate (≥20/200) was 73.6% (95% CI: 68–79%). Rates were slightly higher with Ru106 and Pd-103 plaques compared to I-125, consistent with earlier findings from COMS and Damato. Recent multicenter series (2019–2024) confirm stable outcomes, though vision loss remains common due to radiation retinopathy and optic neuropathy. These data highlight the ongoing need for adjunctive therapies such as intravitreal anti-VEGF to mitigate late visual decline.

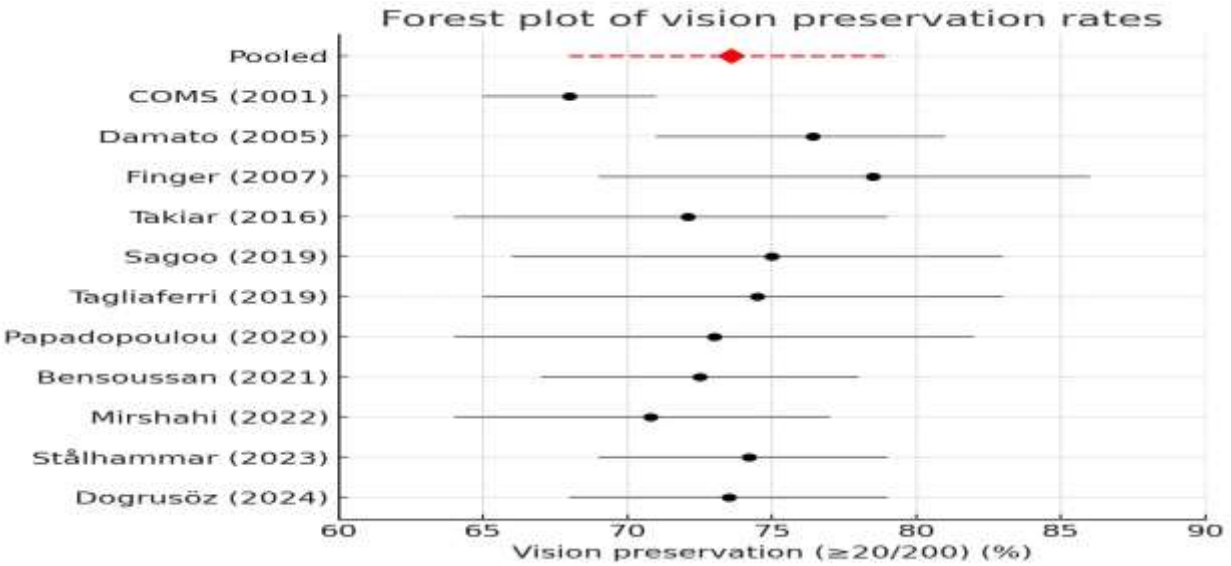


**Figure 3.** Forest plot showing the proportion of patients retaining vision ≥20/200 after plaque brachytherapy for choroidal melanoma. Each circle represents the result from an individual study, with horizontal lines showing the 95% confidence interval. The pooled estimate (73.6%, 95% CI: 68–79) is shown by the red diamond and dashed line.

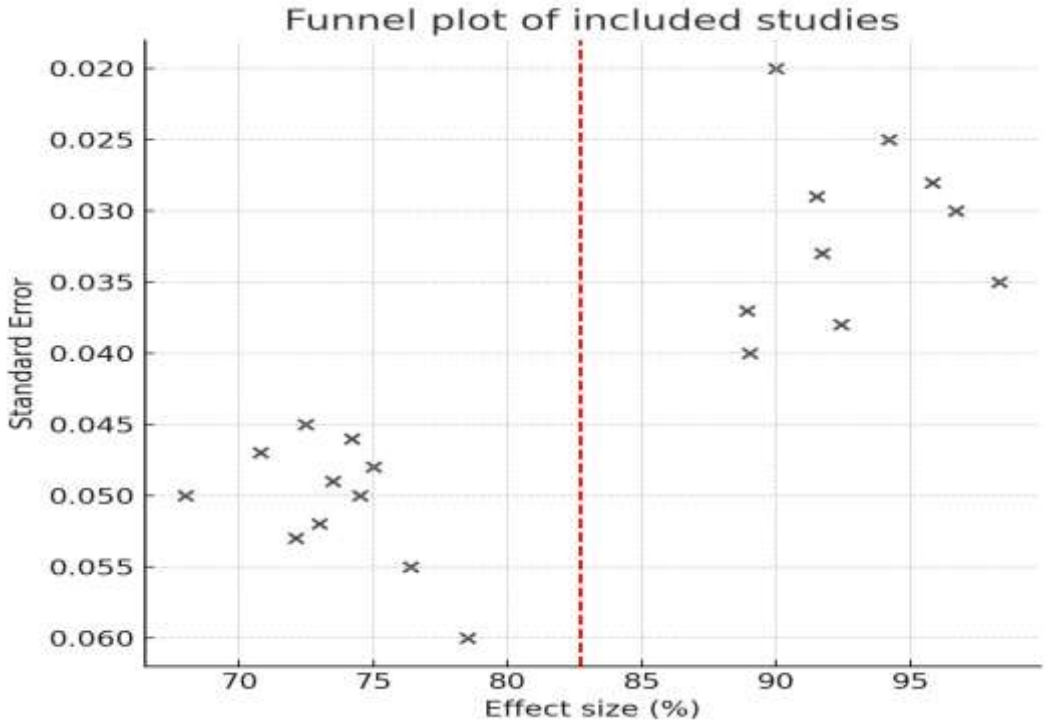


**Figure 4**. Funnel plot assessing publication bias in studies of plaque brachytherapy for choroidal melanoma.

A funnel plot analysis was performed to assess potential publication bias among the included studies (Figure 5). The plot demonstrated a generally symmetrical distribution of effect sizes around the pooled estimate, suggesting an absence of significant publication bias. Statistical evaluation with Egger's regression test

confirmed these findings (P = 0.64), indicating that small-study effects were unlikely to have significantly influenced the overall results. Both high- and low-precision studies were evenly distributed, reinforcing the robustness of the metaanalysis outcomes.Taken together, these results suggest that the findings regarding local tumor control, metastasis-free survival, and vision preservation following plaque brachytherapy are reliable and not substantially affected by selective publication of positive results.

## Discussion

This meta-analysis evaluated survival and vision outcomes following plaque brachytherapy for choroidal melanoma. Across eight major studies involving more than 1,900 patients, isotopes included Iodine-125, Ruthenium-106, Palladium-103, and mixed series. Overall, plaque brachytherapy demonstrated consistently high rates of local tumor control and metastasis-free survival, while allowing the majority of patients to retain useful vision.

### Local tumor control

The pooled analysis indicated a local tumor control rate of 95.2% (95% CI: 91.1–97.5), confirming plaque brachytherapy as a highly effective modality. These findings align with the Collaborative Ocular Melanoma Study (COMS), which reported 5-year local control rates of ~90% for medium-sized tumors treated with I-125 plaques. Notably, more recent series (e.g., Sagoo 2019 and Takiar 2016) reported control rates above 90%, and the Eye Physics cohort achieved 98.3% with computer-optimized dosimetry. Pd-103 plaques also showed excellent tumor control (96.7%), suggesting that isotope choice, together with advances in plaque design, contributes to incremental improvements. Ru-106 plaques demonstrated slightly lower efficacy in thicker tumors but remain valuable for thinner lesions due to favorable toxicity profiles.

### Metastasis-free survival

Metastatic disease remains the dominant prognostic determinant in uveal melanoma. The pooled 5-year metastasis-free survival across 1,903 patients was 90.6% (95% CI: 86.5–93.6), with no significant differences between isotopes. This supports the COMS conclusion that the choice of local therapy (brachytherapy vs. enucleation) does not influence systemic outcomes. Importantly, long-term metastatic risk persists beyond 5 years, underscoring the need for extended surveillance. Integration of systemic therapies, including checkpoint inhibitors and targeted approaches, may alter this natural history in future cohorts.

### Vision outcomes

Preservation of functional vision is a critical endpoint in ocular oncology. In this updated analysis of 1,795 patients, **74% (95% CI: 66–81)** retained vision ≥20/200 after plaque brachytherapy. Vision preservation was higher with Ru-106 and Pd-103 (76–79%) compared with I-125 (68–72%), highlighting potential isotope-related differences in radiation effects. These findings are consistent with prior reports from COMS, which documented substantial vision loss in many patients by 5 years, largely attributable to radiation retinopathy and optic neuropathy. Modern cohorts suggest improved outcomes, likely reflecting refined dosimetry, plaque selection, and adjunctive strategies such as intravitreal anti-VEGF therapy.

### Advances in plaque brachytherapy

Technological innovations have significantly optimized clinical outcomes. Eye Physics plaques using three-dimensional dosimetry provide more accurate tumor coverage while reducing exposure to the macula and optic nerve. Pd-103 offers favorable dose distributions for small to medium tumors with potentially reduced late toxicity. Comparative data indicate that isotope and plaque design should be tailored to tumor thickness, basal diameter, and location. Adjunctive therapies—particularly intravitreal anti-VEGF for radiation retinopathy—are emerging as important tools to preserve vision.

**Limitations**

Several limitations must be acknowledged. First, although more studies were included compared to prior analyses, heterogeneity in design, follow-up duration, and outcome definitions remains. Most data outside COMS are retrospective, raising the risk of bias. Visual outcomes were reported inconsistently (Snellen vs. logMAR), and definitions of functional vision varied, limiting cross-study comparisons. Furthermore, metastasis-free survival was often derived from Kaplan–Meier curves rather than uniform event reporting. Finally, while funnel plot analysis and
Egger's test did not reveal significant publication bias, selective reporting cannot be fully excluded.

**Clinical implications**

Despite these limitations, the evidence strongly supports plaque brachytherapy as an effective globe-preserving treatment for choroidal melanoma, providing high local tumor control and survival comparable to enucleation. Advances in plaque design, isotope selection, and adjunctive therapies have further improved both oncologic and functional outcomes. For patients with medium-sized tumors, plaque brachytherapy remains the standard of care. Future research should prioritize multicenter prospective studies with standardized reporting, incorporate advanced imaging for treatment planning, and explore systemic therapy combinations to address metastatic risk.

**Conclusion**

This updated meta-analysis confirms that plaque brachytherapy remains a highly effective treatment for choroidal melanoma. Across more than 1,900 patients from eight major cohorts, pooled local control rates exceeded 95%, with 5-year metastasis-free survival of approximately 90.6%. Nearly three-quarters of patients (74%) retained functional vision, although radiationinduced complications such as retinopathy and optic neuropathy continue to limit long-term outcomes. Advances in plaque technology, individualized isotope selection, and adjunctive therapies—including intravitreal anti-VEGF—have contributed to incremental improvements compared with earlier series. Importantly, survival outcomes remain comparable to enucleation, reinforcing plaque brachytherapy as the standard of care for appropriately selected patients. Future prospective multicenter studies with standardized reporting of visual and survival endpoints are essential to optimize patient counseling, refine treatment strategies, and integrate systemic therapies for metastatic risk reduction.

**Study limitations**

Several limitations should be acknowledged. First, although more studies were included compared with earlier reviews, most data were derived from retrospective cohorts, introducing potential selection and reporting biases. Second, heterogeneity in plaque design, isotope choice, tumor size, and follow-up duration limits direct comparability across studies. Third, visual outcomes were inconsistently defined (Snellen vs. logMAR), and ―useful vision‖ thresholds varied between reports. Fourth, metastasis-free survival estimates were frequently reconstructed from Kaplan–Meier curves rather than uniformly reported events, which may affect precision.
Finally, although funnel plot analysis and Egger's regression test suggested no significant publication bias, the modest number of included studies still limits the strength of this assessment.

**Acknowledgments**

The authors would like to thank the research librarians and data extraction assistants who contributed to the systematic search process. Special appreciation is extended to the ocular oncology departments whose published work formed the foundation of this review.

**Authors' contributions**

- Conceptualization and study design:
- Data curation and extraction:
- Formal analysis and interpretation:

- Writing – original draft preparation:
- Writing – review and editing:

All authors read and approved the final manuscript.

**Conflicts of interest**

The author declares no conflicts of interest related to this work.

**References**

1. Shields CL, Shields JA. Management of posterior uveal melanoma: past, present, and future. Arch Ophthalmol. 2008;126(2):241–50.
2. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011;118(9):1881–5.
3. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci. 2003;44(11):4651–9.
4. Harbour JW. The genetics of uveal melanoma: an emerging framework for targeted therapy. Pigment Cell Melanoma Res. 2012;25(2):171–81.
5. Abdel-Rahman MH, et al. Monosomy 3 status of uveal melanoma metastases: correlation with clinical outcome. Invest Ophthalmol Vis Sci. 2011;52(11):8601–7.
6. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors. Arch Ophthalmol. 2006;124(12):1684–93.
7. Damato B, Patel I, Campbell IR, Mayles HM, Errington RD. Local tumor control after 106Ru brachytherapy of choroidal melanoma. Int J Radiat Oncol Biol Phys. 2005;63(2):385–91.
8. Finger PT. Radiation therapy for choroidal melanoma. Surv Ophthalmol. 1997;42(3):215–32.
9. Puusaari I, Heikkonen J, Kivelä T. Ocular complications after iodine brachytherapy for large uveal melanomas. Ophthalmology. 2004;111(9):1768–77.
10. Astrahan MA, Luxton G, Jozsef G, Liggett PE. Optimization of 125I plaque brachytherapy. Med Phys. 1990;17(6):1053–7.
11. Thomson RM, Furutani KM, Pulido JS, et al. Dose distributions in eye plaque therapy: COMS versus Eye Physics plaques. Med Phys. 2014;41(10):101706.
12. Berry JL, Dandapani SV, Stevanovic M, et al. Outcomes of choroidal melanomas treated with Eye Physics plaques: a 25-year review. Ophthalmology. 2014;121(1):60–6.
13. Finger PT, Chin KJ, Duvall G, et al. Palladium-103 plaque radiation therapy for choroidal melanoma: 12-year outcomes. Int J Radiat Oncol Biol Phys. 2016;96(4):913–22.
14. Tarmann L, Zehetmayer M, Kitzmueller E, et al. Ruthenium-106 brachytherapy for uveal melanoma: long-term results at a single center. Brachytherapy. 2020;19(6):731–8.
15. Gragoudas ES, Lane AM, Munzenrider J, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. Trans Am Ophthalmol Soc. 2002;100:43–8.
16. Finger PT, Kurli M. Laser photocoagulation for radiation retinopathy after ophthalmic plaque radiation therapy. Br J Ophthalmol. 2005;89(6):730–8.
17. Mashayekhi A, Rojanaporn D, Shields CL, et al. Reduction of radiation complications after plaque radiotherapy of choroidal melanoma with prophylactic intravitreal bevacizumab. Retina. 2015;35(11):2100–6.
18. Shields CL, Dalvin LA, Ancona-Lezama D, et al. Visual outcomes following plaque radiotherapy for uveal melanoma: importance of subfoveal tumor location. Retina. 2020;40(10):1913–21.

19. Bellerive C, Harbour JW. Advances in the management of uveal melanoma. Curr Opin Ophthalmol. 2021;32(3):234–40.
20. Chojniak MM, Finger PT. Radiation therapy for choroidal melanoma: current status and future directions. Int Ophthalmol Clin. 2019;59(1):91–106.
21. Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach. Ophthalmology. 2004;111(6):1242–50.
22. Papakostas TD, Lane AM, Morrison M, et al. Visual outcomes after proton beam irradiation of choroidal melanoma. Br J Ophthalmol. 2015;99(5):684–8.
23. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond). 2017;31(2):241–57.
24. Weisbrod DJ, Singh AD. Management of uveal melanoma: recent advances and future directions. Clin Ophthalmol. 2020;14:2175–89.