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Retrospective protocol for a systematic review and meta-analysis of five-year local control after radiotherapy for choroidal melanoma

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ADMINISTRATIVE INFORMATION

Support - NR.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 August 2026 and was last updated on 2 August 2026.

INTRODUCTION

Review question / Objective Among adults with choroidal melanoma treated with eye-preserving radiotherapy, what are the absolute five-year local-control rates for each treatment modality, and what direct comparative effects have been reported within the same cohort? Eligible modalities include iodine-125 and ruthenium-106 plaque brachytherapy, proton beam radiotherapy, carbon-ion radiotherapy, historical helium-ion radiotherapy, photon stereotactic radiosurgery or fractionated stereotactic radiotherapy, and CyberKnife. The primary objective is to estimate local tumour control at exactly five years using only actuarial estimates with uncertainty reported by the original source. Secondary objectives are to synthesise endpoint-specific direct within-cohort comparisons and to reproduce the pooling conventions of previous reviews as a non-inferential sensitivity analysis. No treatment ranking or indirect comparison is planned.

Condition being studied Choroidal melanoma is the most common primary intraocular malignancy in adults. It carries a lifelong risk of haematogenous metastasis, predominantly to the liver. Eye-preserving radiotherapy is now widely used, including plaque brachytherapy, charged-particle radiotherapy, and stereotactic photon techniques. Although these modalities generally achieve high local control, their comparative effectiveness and toxicity remain uncertain because randomized head-to-head evidence is scarce and most available studies are retrospective, single-centre cohorts.

METHODS

Participant or population Adults with choroidal melanoma, or predominantly choroidal uveal melanoma cohorts, with at least one eligible radiotherapy arm containing 20 or more patients. Enucleation and combined-modality arms may be retained only as contextual comparators.

Intervention Eye-preserving radiotherapy with iodine-125 plaque, ruthenium-106 plaque, proton beam, carbon-ion, historical helium-ion, photon stereotactic radiosurgery or fractionated stereotactic radiotherapy, or CyberKnife.

Comparator Any other eligible radiotherapy modality evaluated within the same report or cohort. Modality-specific absolute five-year analyses do not require a comparator. Indirect comparisons between unrelated cohorts will not be used.

Study designs to be included Randomized trials, prospective or retrospective comparative cohorts, single-arm cohort studies, and case series with at least 20 participants in an eligible arm. Case reports, reviews, editorials, laboratory studies, and nonclinical reports will be excluded.

Eligibility criteria Reports will be eligible when they include adults with choroidal melanoma, or a predominantly choroidal uveal melanoma population, treated with one of the prespecified radiotherapy modalities and report at least one eligible clinical outcome between one and ten years. At least one eligible treatment arm must contain 20 or more patients. For the strict five-year synthesis, the outcome must be reported at exactly five years using a Kaplan-Meier, actuarial, or life-table estimator, and the source must report its uncertainty. Crude proportions, outcomes reported only at other horizons, unlabelled uncertainty, and estimates requiring reconstruction of event counts from a percentage and denominator will not enter the strict synthesis. Reports will be excluded when the population, intervention, design, or outcome is ineligible; radiotherapy is only adjuvant, neoadjuvant, or salvage; treatment modalities cannot be separated; no usable outcome is reported; or the report duplicates or substantially overlaps another included report. At the revision stage, eligibility was amended to exclude conference abstracts, posters, and non-English full-text publications. This amendment was applied before the final analysis freeze and is declared as a retrospective protocol amendment.

Information sources Information sources comprise Scopus, Embase, the Web of Science Core Collection, PubMed/MEDLINE through the NCBI E-utilities, Europe PMC, OpenAlex, and Crossref. Source PDFs and bibliographic records retained in the review archive will be used for eligibility assessment, extraction, source verification, and risk-of-bias appraisal. No trial registry or direct author-contact search is included in the documented review process.

Main outcome(s) The primary outcome is local tumour control at exactly five years. Eligible values must be reported by the original source as Kaplan-Meier, actuarial, or life-table estimates with source-reported uncertainty. Absolute results will be pooled by treatment modality as percentages on the complementary log-log scale using random-effects models, Hartung-Knapp confidence intervals, and 95% prediction intervals. Pooling requires at least three reports. Within-cohort comparative local-control effects will be expressed as hazard ratios for local failure, harmonized so that values above 1 indicate a greater hazard of the adverse outcome. Direct comparisons will be synthesized separately for each treatment pair, with no indirect estimate or treatment ranking.

Quality assessment / Risk of bias analysis Risk of bias is assessed at report level. Single-arm cohort studies are assessed with the Joanna Briggs Institute cohort checklist, case series with the Joanna Briggs Institute case-series checklist, and comparative non-randomized reports with ROBINS-I. Each item-level judgement is stored with a verbatim supporting source passage or an explicit indication that the source provides no information. No independent duplicate risk-of-bias assessment is claimed. Reports contributing to the inference-bearing within-cohort and strict five-year analyses are all assessed. Thirteen inference-bearing reports with a disputed initial instrument assignment will undergo source-level reassessment under the appropriate instrument before publication. Certainty of direct comparative evidence is evaluated using GRADE, beginning at high certainty for randomized evidence and low certainty for observational evidence.

Strategy of data synthesis Three analyses will be kept separate. First, comparative effects calculated within the same cohort will be transformed to the log-ratio scale with their standard errors, harmonized to the hazard of the adverse event, and pooled separately for each endpoint and treatment pair using random-effects meta-analysis. No indirect, mixed, or network estimate will be calculated. When a multi-arm report provides correlated contrasts without their covariance, one contrast will be retained using a deterministic prespecified rule. Second, exact five-year absolute outcomes will be pooled by modality on the complementary log-log scale. Between-report variance will be estimated using restricted maximum likelihood, confidence intervals using the Hartung-Knapp method, and 95% prediction

intervals will be reported. At least three reports are required for pooling. Third, a convention sensitivity analysis will reproduce the broader pooling rules of previous reviews, including mixed horizons and denominator-derived binomial variance. This third analysis will be reported only to assess the effect of analytic conventions and will not support clinical inference. Analyses will use R with the meta and metafor packages.

Subgroup analysis No formal subgroup analysis or meta-regression is planned because most direct comparisons contain only one report. Treatment modalities will remain separate, and all syntheses will be stratified by outcome, treatment modality, and direct treatment pair.

Sensitivity analysis Leave-one-report-out analyses will be performed for pooled cells containing at least four reports. Results under the strict five-year rule will be compared with results obtained using the previous reviews' broader pooling conventions. Estimates lacking source-reported uncertainty will be excluded from the strict synthesis. The effect of duplicate cohorts, alternative effect polarity, and correlated multi-arm contrasts will be audited through the cohort register and source-traced analysis tables.

Country(ies) involved Taiwan.

Keywords choroidal melanoma; uveal melanoma; radiotherapy; plaque brachytherapy; proton beam therapy; carbon-ion radiotherapy; stereotactic radiotherapy; local control; systematic review; meta-analysis.

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