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Adjuvant chemoradiotherapy with procarbazine, lomustine, and vincristine (PCV) or temozolomide for 1p/19q Co-deleted anaplastic oligodendroglioma: a systematic review and network meta-analysis

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Abstract

Introduction Anaplastic oligodendrogliomas are rare diffuse gliomas. Although radiotherapy (RT) combined with procarbazine, lomustine, and vincristine (PCV) has been the historical standard, temozolomide (TMZ) has been increasingly used.

Objective To compare the efficacy of RT combined with PCV versus RT combined with TMZ in adult with anaplastic oligodendroglioma.

Methods A systematic search of PubMed, Embase, and the Cochrane Library was conducted up to March 2025. Eligible studies included patients with 1p/19q-codeleted anaplastic oligodendroglioma treated with RT + PCV, RT + TMZ, or RT alone. Studies comparing RT alone to RT + PCV or RT + TMZ were used to create indirect comparisons, with RT as a common comparator. A frequentist network meta-analysis with a random-effects model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS). Risk of bias was assessed with RoB 2 and ROBINS-I. The protocol was registered in PROSPERO (CRD420251012169). No funding was received.

Results Eight studies comprising 2,416 patients were included. The network meta-analysis, compared with RT alone, RT + PCV significantly improved OS (HR: 0.617; 95% CI 0.465–0.819; $p = 0.0009$), and PFS (HR: 0.547; 95% CI 0.415–0.721; $p < 0.0001$), while RT + TMZ showed a trend toward improved OS (HR: 0.913; 95% CI 0.666–1.252; $p = 0.421$) and PFS (HR: 1.270; 95% CI 0.870–1.855; $p = 0.215$), without statistical significance. In the comparison between RT + PCV and RT + TMZ, RT + PCV demonstrated superior OS (HR: 0.676; 95% CI, 0.585–0.781; $p < 0.0001$) and better PFS (HR: 0.431;

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95% CI, 0.325–0.570; $p < 0.0001$). Limitations include the small number of randomized trials directly comparing key outcomes, and the fact that most studies predated current molecular diagnostic criteria, with toxicity data often reported in heterogeneous populations.

Conclusion In patients with anaplastic oligodendroglioma, RT combined with PCV provides superior survival outcomes compared to radiotherapy combined with TMZ.

Keywords Anaplastic oligodendroglioma, 1p/19q co-deletion, Radiotherapy, PCV, Temozolomide, Network meta-analysis

Introduction

Oligodendrogliomas are rare infiltrative gliomas that represent a distinct molecular and clinical subtype of adult diffuse gliomas. According to the CBTRUS 2024 report, the estimated annual incidence of anaplastic oligodendroglioma in the United States is approximately 251 new cases, with a total of 6,002 cases reported between 2001 and 2020 [1].

According to the 2021 World Health Organization (WHO) classification, the diagnosis of oligodendroglioma requires the presence of both an IDH mutation and 1p/19q co-deletion [2]. This integrated molecular definition reflects the biological nature of the disease as well as its prognostic and therapeutic implications. Nonetheless, several studies have defined oligodendroglioma solely by 1p/19q co-deletion [3], underscoring its strong prognostic value even in the absence of confirmed IDH mutation. This alternative approach is particularly relevant in retrospective cohorts and real-world datasets, where IDH testing may not have been consistently available or may have been performed using methods with limited sensitivity [4].

The standard treatment for anaplastic oligodendroglioma (WHO grade 3) consists of maximal safe surgical resection followed by radiotherapy (RT) in combination with chemotherapy. Two chemotherapy regimens are commonly employed with RT: the traditional PCV protocol (procarbazine, lomustine, and vincristine), supported by long-term survival data from randomized trials such as RTOG 9402 [5] and EORTC 26951 [6]; and temozolomide (TMZ), an oral alkylating agent widely used in gliomas, though with less direct evidence in this specific molecular subgroup.

Because no randomized controlled trials have directly compared RT + PCV and RT + TMZ in patients with molecularly defined 1p/19q co-deleted anaplastic oligodendrogliomas, we conducted a systematic review and network meta-analysis to evaluate the relative efficacy of these regimens. By integrating both direct and indirect comparisons, this study aims to address a critical gap in the literature and provide evidence to support therapeutic decision-making in this well-defined glioma population.

Methods

Eligibility criteria

We included studies that met all the following criteria: (1) randomized controlled trials (RCTs), prospective, or retrospective studies; (2) adjuvants treatment arms including radiotherapy (RT) in combination with either PCV (procarbazine, lomustine, vincristine) or temozolomide (TMZ); (3) reporting at least one of the predefined outcomes of interest: overall survival (OS) and progression-free survival (PFS).

We excluded studies assessing RT alone without a comparative chemoradiotherapy arm. However, RT was retained as a network node when it appeared alongside RT + PCV or RT + TMZ arms, serving as a common comparator. Therefore, "radiotherapy" was not included as a search term in the strategy to avoid irrelevant retrievals of RT-only trials.

Search strategy and data extraction

A systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials was conducted in March 2025, with no restriction on publication year. Only articles published in English were considered. The following search terms were used: ("Oligodendroglioma" OR "Oligodendroglial" OR "Oligodendroglial tumors") AND ("PCV protocol" OR "PCV regimen" OR "Procarbazine" OR "Lomustine" OR "CCNU" OR "Vincristine" OR "Temozolomide" OR "TMZ").

Two independent reviewers (MS and NR) screened and extracted the data. Discrepancies were resolved by a third reviewer (FG). The following information was extracted from eligible studies: study design, country, sample size, patient age, duration of follow-up, treatment regimen, and outcome measures.

In studies with multiple treatment arms, we extracted data only from the groups that matched the predefined comparisons of interest (RT + PCV or RT + TMZ or RT alone). Notably, in the CODEL trial, OS was analyzed by comparing RT alone to RT + TMZ, whereas PFS was analyzed by comparing RT alone to a grouped arm consisting of TMZ-containing regimens (TMZ alone and RT + TMZ), as reported by the study authors.

Population definition and molecular criteria

This meta-analysis focused on adult patients with anaplastic oligodendroglioma (WHO grade 3). Although the current WHO 2021 classification defines oligodendrogliomas as tumors harboring both 1p/19q co-deletion and IDH mutation [2], we adopted a broader inclusion criterion. This choice was made to ensure comparability across available evidence, as many pivotal trials predated routine IDH testing. Following the approach of Lamba et al., 2022 [3], tumors with confirmed 1p/19q co-deletion were presumed to correspond to oligodendrogliomas, even in the absence of confirmed IDH mutation.

Outcomes

The primary outcomes were: OS and PFS.

Quality assessment

The systematic review and meta-analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), CRD420251012169.

Two reviewers (NR and FG) independently assessed the risk of bias according to the study design. For RCTs, the Cochrane Risk of Bias tool version 2.0 (RoB 2) [8] was applied. For non-randomized studies (prospective or retrospective), the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions) [9] was used. Disagreements were resolved by consensus or by consulting a third reviewer (MS).

Statistical analysis

To compare the relative effectiveness of RT + PCV versus RT + TMZ, we performed a network meta-analysis (NMA) that integrated both direct and indirect comparisons across the included studies. This was performed under a frequentist framework using a random-effects model to account for between-study heterogeneity. The analysis included only treatment arms in which RT was administered in combination with PCV or TMZ, or RT alone compared with RT combined with one of these chemotherapies, with RT serving as the common comparator across trials.

Statistical analyses were performed using the R programming language. The netmeta package was used to perform network meta-analysis. Hazard ratios (HRs) and corresponding 95% confidence intervals were extracted when available or otherwise estimated from published survival data according to the methods described by Parmar et al. [10] and Tierney et al. [11]. The network structure was assessed for consistency using node-splitting methods. Treatment ranking probabilities were calculated for both OS and PFS. Net heat plots were generated separately using Python to enhance visual presentation of network consistency, without influencing the statistical results obtained in R.

Results

Study selection

A total of 3,272 records were identified from PubMed ($n = 549$), Embase ($n = 2{,}603$), and Cochrane ($n = 120$). After removing 1,282 duplicate entries, 1,990 records were screened by title and abstract, leading to the exclusion of 1,893 studies. Ninety-seven full-text articles were assessed for eligibility. Of these, 22 were excluded due to overlapping patient populations, and 67 were excluded for reasons such as non-comparable study populations, absence of 1p/19q co-deletion data, lack of relevant outcomes, inclusion of progression-only cohorts, or omission of RT in the treatment arms.

A total of seven studies provided data on OS endpoint and six for PFS. However, one of the publications, Lassman et al. (2022) [12], reported the long-term final results of two independent randomized phase III trials (RTOG 9402 and EORTC 26951) [5, 6], which were conducted separately but published together. These trials were treated as two distinct comparisons in network meta-analysis.

In total, eight studies were included in the final synthesis and network meta-analysis. Of these, seven provided data on OS and six on PFS. A detailed flow of study selection is illustrated in the PRISMA diagram shown in Fig. 1. Overall, 2,416 patients with 1p/19q-codeleted and IDH-mutant (or presumed IDH-mutant) oligodendrogliomas were included across the studies summarized in Table 1.

Network structure

The analysis included three treatment strategies: radiotherapy alone (RT), RT with procarbazine, lomustine, and vincristine (RT + PCV), and RT with temozolomide (RT + TMZ). The network was composed of three treatment nodes and three designs, forming a closed triangular structure that enabled both direct and indirect comparisons, with the network for OS shown in Fig. 2 and for PFS in Fig. 3. Although RT was not a comparator of primary interest, it was consistently used as a methodological anchor to link indirect comparisons between RT + PCV and RT + TMZ.

All analyses were performed using a frequentist graph-theoretical approach. HRs were synthesized under both common-effects and random-effects models. Between-study heterogeneity was assessed using τ^2, I^2, and Q statistics. Node-splitting methods were used to evaluate consistency, and treatment rankings were generated based on probabilistic simulations.

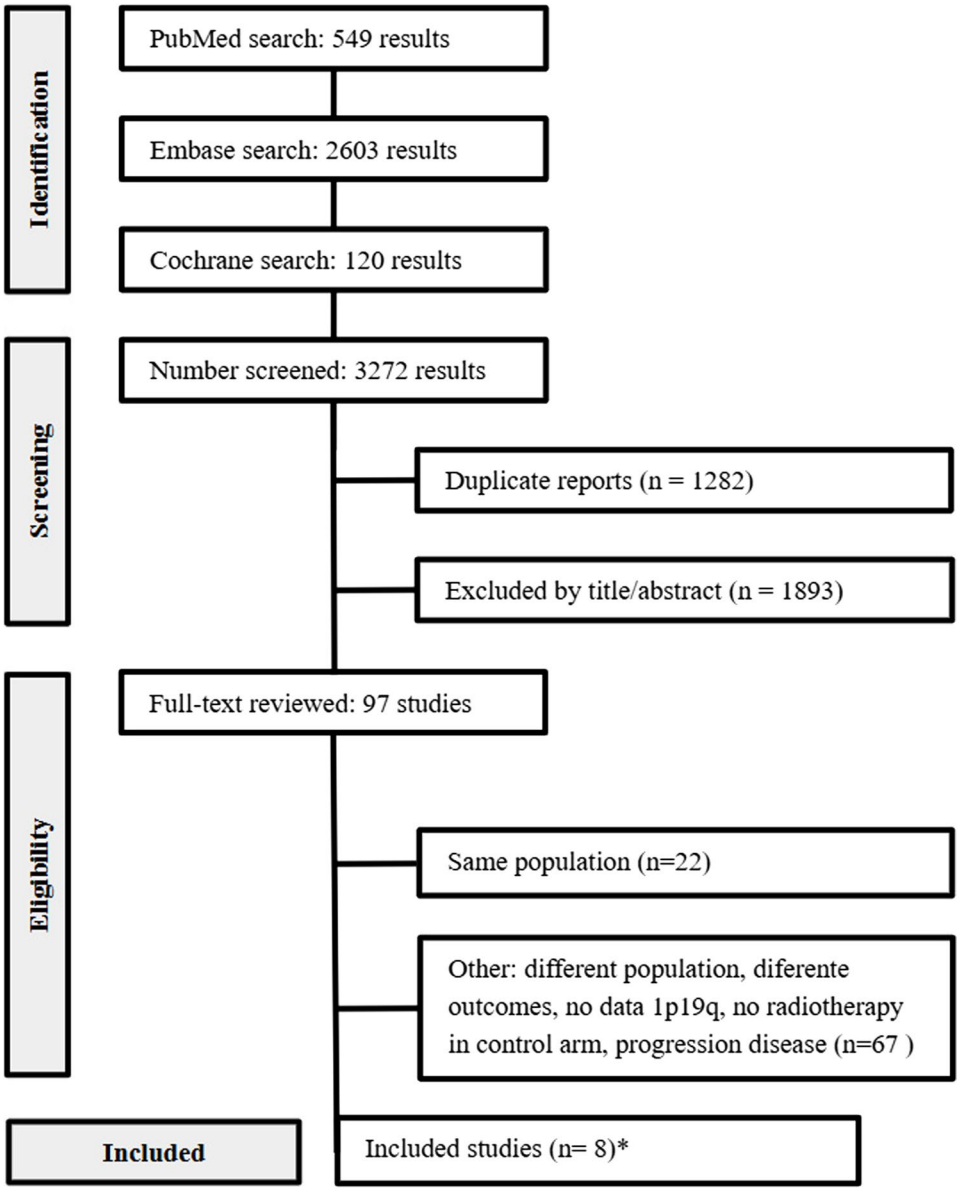

Fig. 1 PRISMA flow diagram of study identification, screening, eligibility, and inclusion

Overall survival (OS)

The network meta-analysis demonstrated a consistent and statistically significant survival benefit favoring RT + PCV over RT + TMZ, with similar results across random-effects and common-effects models (HR: 0.676; 95% CI, 0.585–0.781; $p < 0.0001$). The results are illustrated in Fig. 4.

When compared to radiotherapy alone, RT + PCV significantly reduced the risk of death (HR: 0.617; 95% CI 0.465–0.819; $p = 0.0009$), supporting its long-term survival benefit. In contrast, RT + TMZ did not show a statistically significant improvement over RT (HR: 0.913; 95% CI 0.666–1.252; $p = 0.421$).

Direct comparisons from four studies also favored RT + PCV over RT + TMZ (pooled HR: 0.679; 95% CI 0.587–0.785; $p < 0.001$), and low heterogeneity for this comparison (I^2 = 15.9%), consistent with indirect network estimates. There was no evidence of inconsistency across the network (Q_between = 0.44; $p = 0.506$).

Progression-Free survival (PFS)

In terms of PFS, RT + PCV was also associated with a significantly lower risk of progression or death compared to RT + TMZ. The random-effects network meta-analysis showed a statistically significant benefit favoring RT + PCV (HR: 0.431; 95% CI, 0.325–0.570; $p < 0.0001$), which was consistent in the common-effects model.

Table 1. Summary of included studies in the systematic review and network meta-analysis. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; RCT: randomized controlled trials, OS: overall survival, PFS: progression-free survival

Study	Treatment Groups	Total Patients (N)		Molecular Criteria	Median Age (Range)	RT Dose	Outcome
Lassman 2011	RT + PCV (n = 58), RT + TMZ (n = 66), and RT alone (n = 54)	178	Retrospective	1p/19q co-deleted	42 years (18–89)	NR	OS
Polivka 2016	RT + PCV (n = 7) and RT alone (n = 5)	12	Retrospective	1p/19q co-deleted	55.4 years (25–72)	54-60 Gy	OS, PFS
González-Aguilar 2018	RT + PCV (n = 21) and RT + TMZ (n = 27)	48	Retrospective	1p/19q co-deleted	43 years (19–66)	59.4 Gy in 33 fractions	OS, PFS
Jaeckle 2021 (CODEL)	RT alone (n = 12) and RT + TMZ/TMZ alone (n = 24)	36	RCT	1p/19q co-deleted	48.5 years (18–66)	59.4 Gy in 33 fractions	OS, PFS
Lassman 2022 (RTOG 9402)	RT + PCV (n = 58) and RT alone (n = 67)	125	RCT	1p/19q co-deleted	43 years (18–76)	59.4 Gy in 33 fractions	OS, PFS
Lassman 2022 (EORTC 26951)	RT + PCV (n = 43) and RT alone (n = 37)	80	RCT	1p/19q co-deleted	49 years (18–68)	59.4 Gy in 33 fractions	OS, PFS
Lamba 2022	RT + PCV (n = 182) and RT + TMZ (n = 1414)	1596	Retrospective	1p/19q co-deleted	48 years (*) (>18 years)	Median of 59.4 Gy (59.4-60.0 Gy) in 30 fractions (30-33)	OS
Rincón-Torroella 2024	RT + PCV (n = 19) and RT + TMZ (n = 17)	36	Retrospective	1p/19q co-deleted and IDH mutated	47.4 years (**) (adults)	Median of 59.4 Gy	PFS
Kacimi 2025 (POLA Cohort)	RT + PCV (n = 207) and RT + TMZ (n = 98)	305	Retrospective	1p/19q co-deleted and IDH mutated	49.5 years (*)(>18 years)	Median 59.4 Gy (RT+PCV) / 60 Gy (RT+TMZ)	OS, PFS

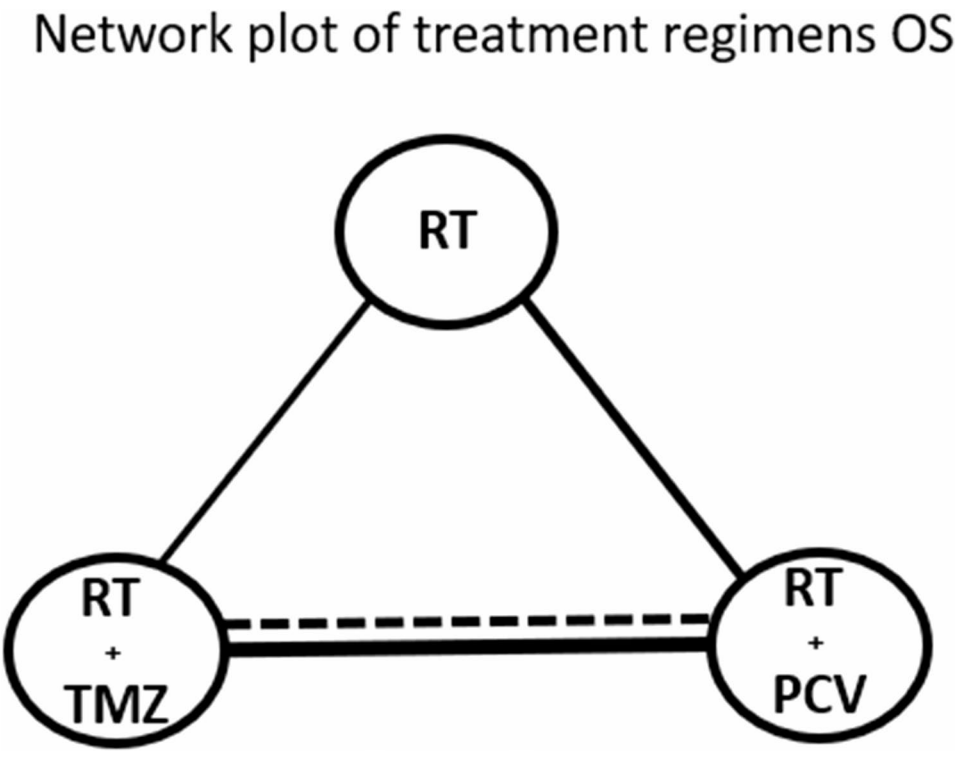

Fig. 2 Network plot of treatment regimens for OS. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; OS: overall survival

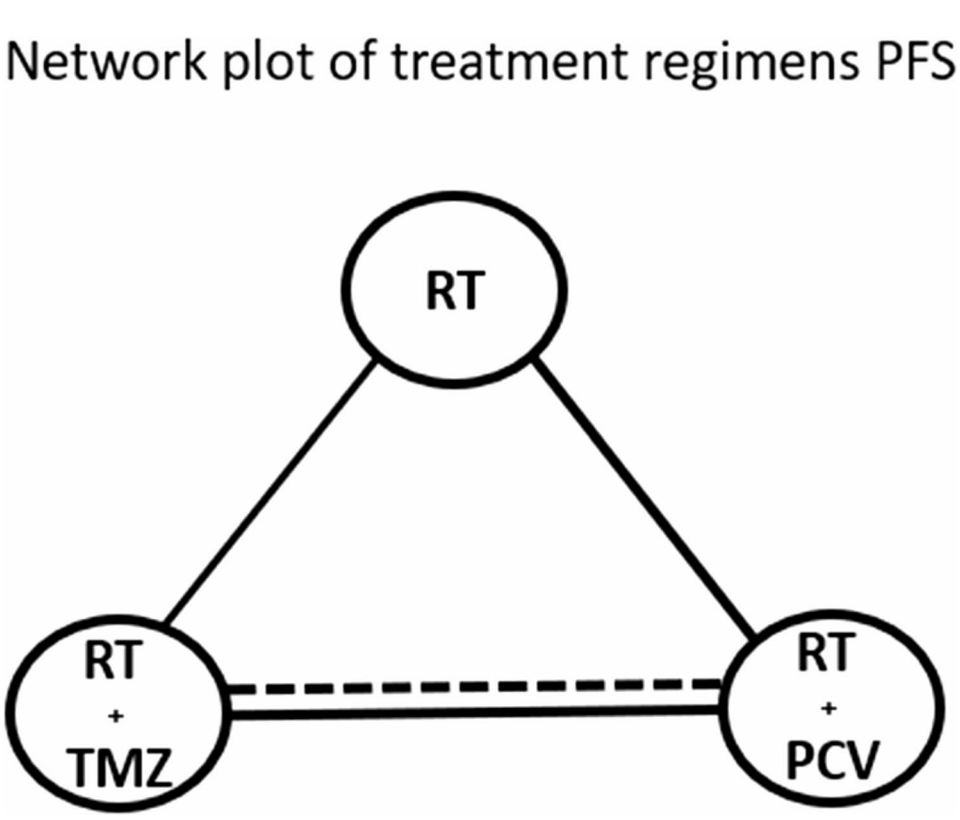

Fig. 3 Network plot of treatment regimens for PFS. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; PFS: progression-free survival

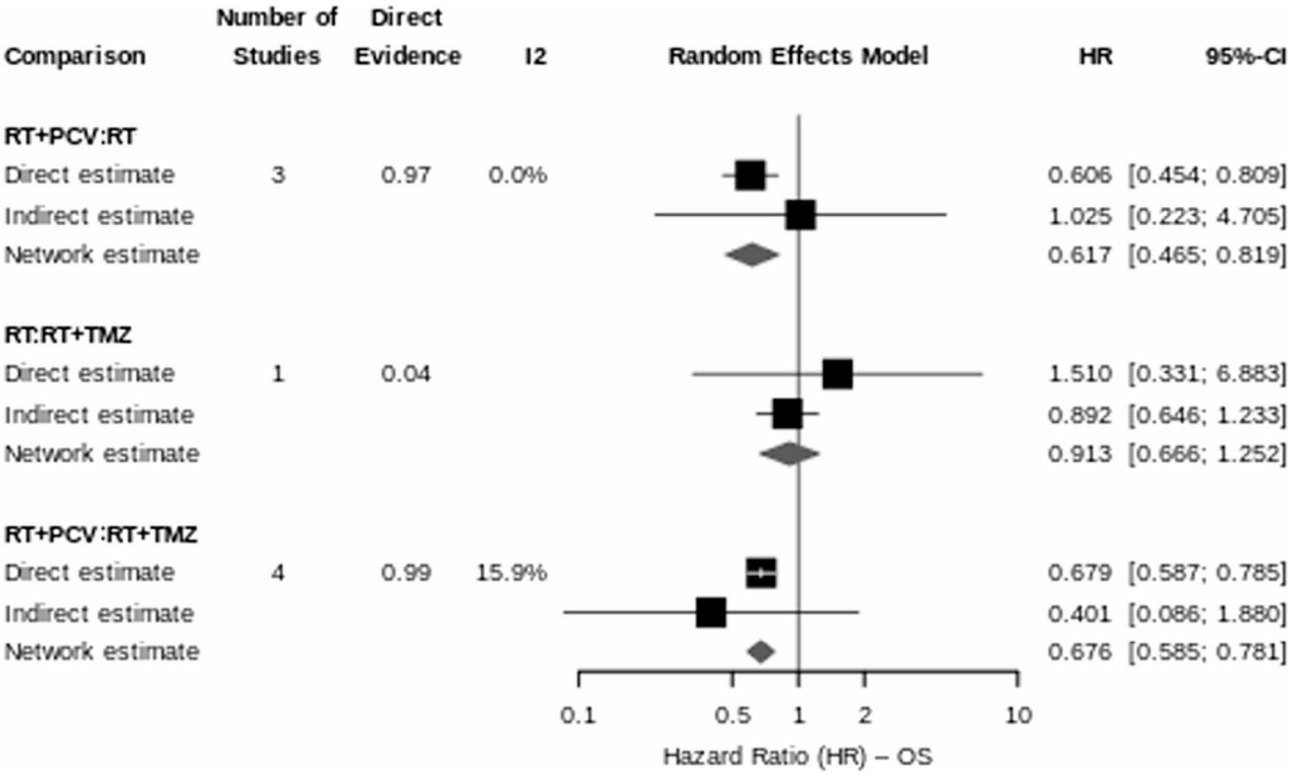

Fig. 4 Forest plot of the network meta-analysis for OS, showing direct, indirect, and network estimates for comparisons between RT, RT + TMZ, and RT + PCV. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; HR: hazard ratio; OS: overall survival

When compared to radiotherapy alone, RT + PCV significantly reduced the risk of progression (HR: 0.547; 95% CI 0.415–0.721; $p < 0.0001$), although moderate heterogeneity was observed in this direct comparison (I^2 = 40.6%). The results are illustrated in Fig. 5.

Conversely, RT + TMZ did not provide a statistically significant benefit over RT in terms of PFS (HR: 1.270; 95% CI 0.870–1.855; $p = 0.215$), underscoring the greater efficacy observed with the PCV-based regimen.

There was no evidence of network inconsistency (Q_between = 0.02; $p = 0.8818$), supporting the robustness of the treatment comparisons between RT + PCV and RT + TMZ. The consistency between direct and indirect estimates reinforces the observed advantage of RT + PCV in this molecularly defined patient population.

Treatment ranking, quality of evidence, and risk of bias assessment

In the treatment ranking analysis, RT + PCV demonstrated the highest probability of being the most effective regimen for both OS and PFS, as shown in Figs. 6 and 7, respectively. RT + TMZ had the lowest probability of ranking first across outcomes. This probabilistic ranking reinforces the superiority of PCV-based chemoradiotherapy in this molecular subgroup.

According to the GRADE assessment [13], the quality of evidence was rated as high for the comparisons of RT + PCV versus RT + TMZ and RT + PCV versus RT, supported by consistent estimates and narrow confidence intervals. The comparison between RT + TMZ and RT was rated as low due to imprecision and inconsistency across studies, due to the modifications of protocol design during the study.

Risk of bias was assessed for all included studies using appropriate tools according to study design. Among the RCTs, the CODEL trial [14] was rated as having high risk due to deviations from the intended intervention resulting from modifications in trial design during accrual. The two independent randomized trials reported in Lassman et al. (2022) (RTOG 9402 and EORTC 26951) were considered to have some concerns overall due to some concerns in one domain, as shown in Fig. 8.

Among the non-randomized studies, two were judged to have a moderate risk of bias, two a serious risk, and two a critical risk, according to the risk of bias table, as shown in Fig. 9. No studies were excluded based on risk of bias alone.

Consistency of the network and contribution of direct evidence across comparisons were evaluated through the net heat plot, as shown in Figs. 10 and 11, for OS and PFS, respectively.

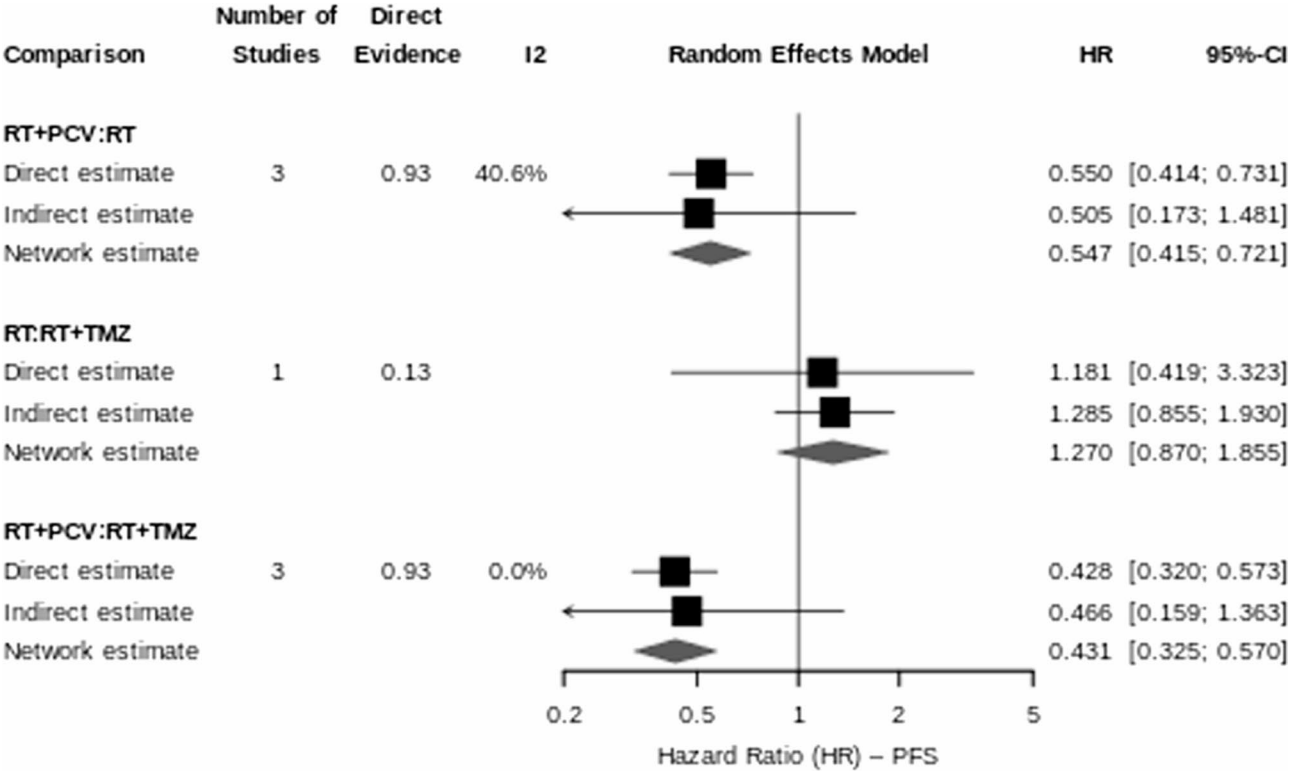

Fig. 5 Forest plot of the network meta-analysis for PFS, showing direct, indirect, and network estimates for comparisons between RT, RT + TMZ, and RT + PCV. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; HR: hazard ratio; PFS: progression-free survival

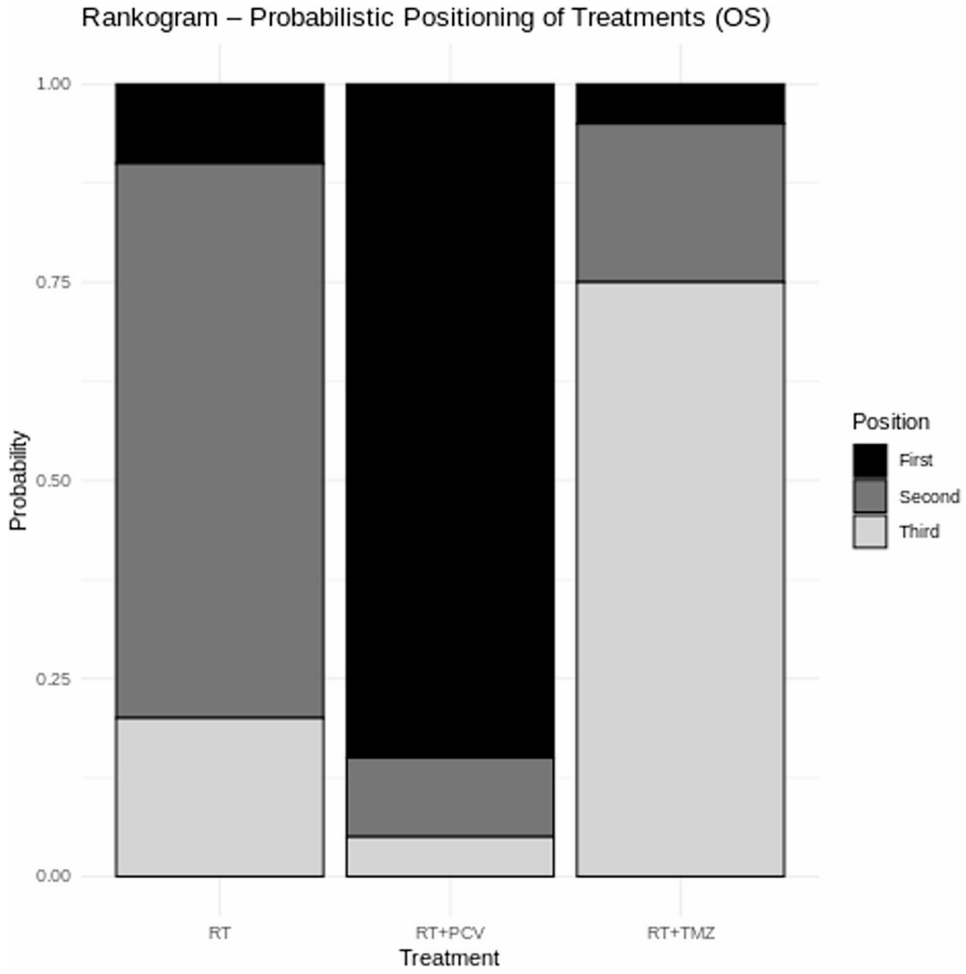

Fig. 6 Rankogram of probabilistic treatment ranking for OS. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; OS: overall survival

Discussion

Oligodendrogliomas are characterized by a molecular signature that is associated with improved treatment responsiveness and favorable prognosis. In these tumors, IDH mutations are invariably accompanied by 1p/19q co-deletion, defining a biologically and clinically distinct subtype of diffuse glioma [2, 15]. Their co-occurrence is linked to a more differentiated phenotype, reduced proliferative potential, and greater genomic stability, features that contribute to enhanced sensitivity to RT and alkylating chemotherapy. IDH mutations, through the accumulation of the oncometabolite 2-hydroxyglutarate, interfere with DNA repair and epigenetic regulation [5], whereas 1p/19q co-deletion leads to the loss of genes involved in apoptosis and cell cycle control, further amplifying chemosensitivity. These molecular characteristics provide a biological rationale for the favorable outcomes observed in this subgroup and underscore the importance of selecting an optimal chemotherapeutic partner for RT. While temozolomide (TMZ) offers the advantages of oral administration and a more manageable toxicity profile, the multi-agent PCV regimen combines distinct cytotoxic mechanisms that may more effectively utilize the genomic vulnerabilities inherent to these tumors.

Although several studies have evaluated chemoradiotherapy regimens in diffuse gliomas [3, 12, 16, 17], much of the available evidence comes from heterogeneous patient populations, in which molecularly defined oligodendrogliomas represented only a subgroup of the cases. When present, most cases were classified based only on 1p/19q co-deletion status, predating the adoption of the current WHO molecular diagnostic criteria, and consistently demonstrated distinct prognostic outcomes compared to non-codeleted tumors. The pivotal RTOG 9402 [5] and EORTC 26951 [6] trials established the benefit of adding PCV to radiotherapy, particularly among patients with 1p/19q co-deleted tumors, although these findings were derived from post hoc subgroup analyses without prospective molecular stratification. Although the NOA-04 trial [18] is often referenced in discussions of chemotherapeutic strategies, it focused on recurrent disease and was excluded from the present analysis. These

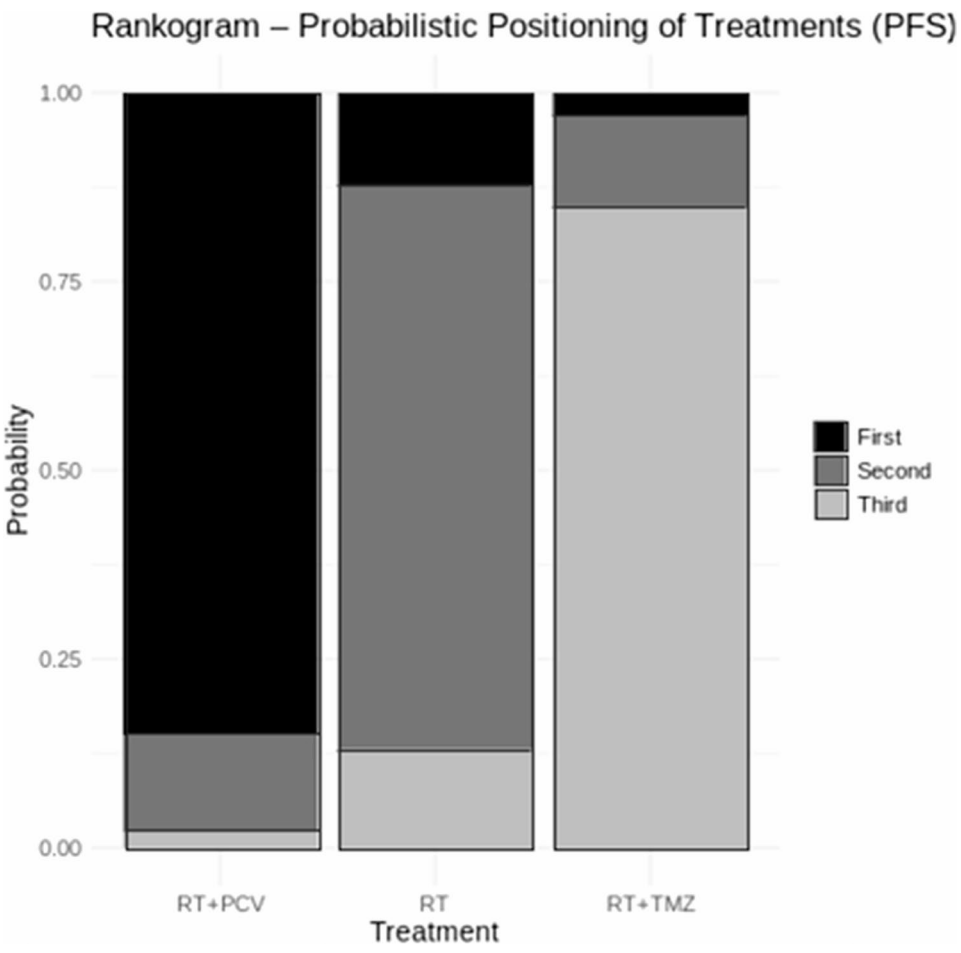

Fig. 7 Rankogram of probabilistic treatment ranking for PFS. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; PFS: progression-free survival

Study ID	D1	D2	D3	D4	D5	Overall
Lassman, 2022 (EORTC)	+	+	+	+	!	!
Lassman, 2022 (RTOG)	+	+	+	+	!	!
Jaeckle, 2021	+	+	+	-	+	-

Domains:

D1 - Randomization process

D2 - Deviations from the intended interventions

D3 - Missing outcome data

D4 - Measurement of the outcome

D5 - Selection of the reported result

\+ Low risk

! Some concerns

\- High risk

Fig. 8 Risk of bias assessment of randomized controlled trials included in the network meta-analysis, evaluated with the RoB 2 tool across five domains

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
Rincon-Toroella, 2025	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Gonzalez-Aguilar, 2018	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Lamba, 2022	Serious	Serious	Low	Low	Serious	Low	Low	Serious
Kacimi, 2025	Moderate	Serious	Low	Low	Serious	Low	Low	Serious
Polivka, 2016	Critical	Serious	Low	Low	Serious	Low	Low	Critical
Lassman, 2011	Critical	Serious	Low	Critical	Serious	Low	Low	Critical

Fig. 9 Risk of bias across domains for retrospective studies included in the network meta-analysis, evaluated with the ROBINS-I tool

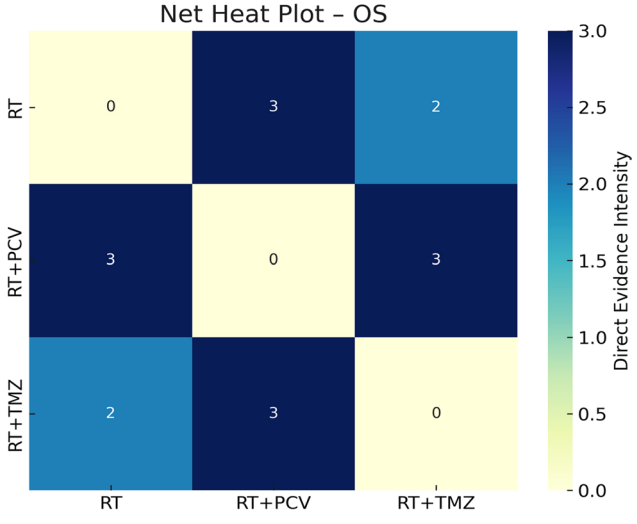

Fig. 10 Net heat plot of the network meta-analysis for OS, illustrating the contribution and intensity of direct evidence across treatment comparisons. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; OS: overall survival

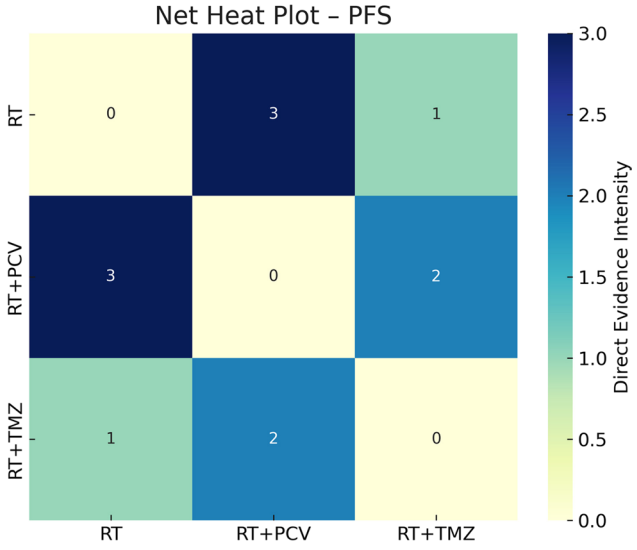

Fig. 11 Net heat plot of the network meta-analysis for PFS, illustrating the contribution and intensity of direct evidence across treatment comparisons. RT: radiotherapy; PCV: procarbazine, lomustine, and vincristine; TMZ: temozolomide; PFS: progression-free survival

limitations underscore the absence of high-quality, direct comparative data between RT + PCV and RT + TMZ [19, 20] in this distinct biological subgroup, highlighting the need for a NMA to integrate available evidence and clarify the optimal chemoradiotherapy strategy.

In this NMA, RT + PCV was associated with a 32% reduction in the risk of death and a 57% reduction in the risk of disease progression compared to RT + TMZ. Although the primary objective was to evaluate the relative efficacy of chemoradiotherapy regimens, RT + PCV also demonstrated a significant survival advantage over RT alone, confirming its role as a critical component of effective treatment presented in RCT [5, 6] and retrospective studies [21]. In contrast, RT + TMZ did not confer a statistically significant survival benefit compared to RT alone, a finding that agrees with the results of the CODEL trial [14], where TMZ-containing regimens failed to improve outcomes over RT. These observations reinforce the concept that TMZ, despite its favorable

toxicity profile, may offer insufficient therapeutic intensity for patients with 1p/19q co-deleted oligodendrogliomas, and that the multi-agent PCV regimen remains the most robust strategy to optimize long-term outcomes in this population.

Given the favorable biology of 1p/19q co-deleted anaplastic oligodendrogliomas, patients in this molecular subgroup often experience prolonged survival, with reported median OS exceeding 10 to 15 years in some cohorts [5, 6]. This long-term prognosis underscores the importance of optimizing initial treatment strategies to maximize durable disease control. The present findings, demonstrating the superiority of RT + PCV over RT + TMZ, highlight the need to carefully balance therapeutic efficacy against treatment-related toxicity when selecting chemoradiotherapy regimens. Although TMZ offers a more favorable toxicity profile, its lack of a significant survival advantage when combined with radiotherapy, as also observed in the CODEL trial [14], raises concerns about its adequacy as a frontline agent in this setting. In contrast, the durable survival benefit associated with PCV-based therapy, consistently observed across multiple studies [3, 16, 17] supports its continued use as the preferred chemotherapeutic partner to RT in molecularly defined oligodendrogliomas.

Although this network meta-analysis provides robust evidence regarding the comparative efficacy of RT + PCV and RT + TMZ in anaplastic oligodendrogliomas, it is important to acknowledge the limitations. Most of the studies included were conducted prior to the widespread adoption of molecular diagnostic criteria, and consequently, toxicity outcomes were generally reported for heterogeneous glioma populations without stratification by 1p/19q co-deletion status or histological grade. Only the CODEL trial [14] and the retrospective analysis by González-Aguilar et al. [16]. provided toxicity data specific to molecularly defined oligodendrogliomas. Furthermore, the rarity of anaplastic oligodendrogliomas resulted in relatively small sample sizes across studies, limiting the statistical power for subgroup analyses.

An additional limitation involves the retrospective cohort reported by Lamba et al. [3], which included patients diagnosed between 2010 and 2018 in the United States and may have inadvertently incorporated individuals who also participated in other clinical trials separately analyzed in this meta-analysis, introducing a potential duplication bias. Finally, the inclusion of presumed oligodendrogliomas defined by 1p/19q co-deletion without confirmed IDH mutation may not be fully aligned with the WHO 2021 classification. Nevertheless, molecular studies have shown that tumors with complete 1p/19q codeletion almost always harbor concurrent IDH mutations [22], supporting the biological plausibility of this assumption.

Nevertheless, the consistent survival benefit observed with RT + PCV across both OS and PFS, both with the absence of significant heterogeneity among studies, underscores the robustness and reliability of these findings. These results support PCV-based chemoradiotherapy as the most effective current approach for optimizing long-term outcomes in patients with molecularly defined anaplastic oligodendrogliomas, reinforcing the critical role of treatment intensity in this biologically favorable subgroup.

Conclusion

This network meta-analysis demonstrates that, in patients with molecularly defined anaplastic oligodendrogliomas, chemoradiotherapy with PCV is associated with superior OS and PFS compared to radiotherapy combined with temozolomide. By quantitatively synthesizing available evidence, this study reinforces and strengthens current recommendations favoring PCV-based chemoradiotherapy as the strategy most likely to optimize long-term outcomes in this biologically favorable subgroup. These findings support the continued use of PCV as the preferred chemoradiotherapy regimen when clinically feasible, while underscoring the need for future randomized trials to confirm these results.

Abbreviations

CBTRUS	Central Brain Tumor Registry of the United States
WHO	World Health Organization WHO
IDH	Isocitrate dehydrogenase
RT	Radiotherapy
PCV	Procarbazine lomustine and vincristine
TMZ	Temozolomide
RTOG	Radiation Therapy Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
RCTs	Randomized controlled trials
OS	Overall Survival
PFS	Progression-Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RoB 2	Cochrane Risk of Bias tool version 2.0
ROBINS-I	Risk of Bias in Non-randomized Studies of Intervention
NMA	Network meta-analysis
HR	Hazard ratio
GRADE assessment	Grading of Recommendations Assessment Development and Evaluation
DNA	deoxyribonucleic acid
CI	Confidence Interval
I^2	Inconsistency index
τ^2	Between-study variance

Authors' contributions

M.D.C.S., N.M.V.R., F.G., and F.A.G. contributed to study conception, data collection, and analysis. A.C.P.C., O.F., A.R.N.S.S., S.A.H., C.C., C.C.B., D.V.A., and C.F. contributed to manuscript review and provided input on important intellectual content. F.Y.M. provided critical revisions and guidance throughout the project. M.V.C.M. supervised the study. All authors reviewed and approved the final version of the manuscript.

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Data availability
All data analyzed in this study were obtained from previously published articles. The compiled dataset supporting the findings is available from the corresponding author upon reasonable request.

Declarations

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No applicable

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

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