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Three-dimensional conformal therapy vs. intensity modulated radiation therapy in GBM: survival, dosimetry, and side effects a systematic review and meta-analysis

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Background: Glioblastoma multiforme (GBM) is an aggressive brain tumor with a poor prognosis, often managed with radiotherapy. Two primary modalities, three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), differ in their precision and impact on survival, side effects, and OAR sparing. However, their comparative benefits remain unclear. This meta-analysis evaluates 3D-CRT and IMRT in GBM treatment, focusing on dosimetric parameters, toxicity, and OAR sparing, with an exploratory analysis of overall survival (OS).

Methods: A systematic review of 19 studies was conducted, comparing dosimetric and side effects, including planning target volume (PTV) doses (Dmean, Dmax, and Dmin), conformity and homogeneity indices, and OAR sparing.

Results: IMRT provided significant dosimetric advantages, with higher PTV Dmean (mean difference (MD) 1.26 Gy; 95% CI: 0.22–2.31; P = 0.02) and better conformity index (MD −0.21; 95% CI: −0.33 to −0.08; P = 0.001). IMRT significantly reduced doses to healthy brain (MD −1.08 Gy; 95% CI: −2.08 to −0.09; P = 0.03), brainstem (MD −0.66 Gy; 95% CI: −1.18 to −0.15; P = 0.01), optic chiasm (MD −4.93 Gy; 95% CI: −9.15 to −0.70; P = 0.02), right optic nerve (MD -5.82 Gy; 95% CI: −9.49 to −2.15; P = 0.002), and left optic nerve (MD −1.20 Gy; 95% CI: −1.77 to −0.63; P < 0.0001).

Conclusion: IMRT provides significant dosimetric benefits and potentially lower toxicity compared to 3D-CRT in GBM treatment. While an exploratory analysis suggests a possible OS benefit, this requires cautious interpretation due to study limitations. IMRT's precision supports its use in GBM treatment.

KEYWORDS

glioblastoma multiforme (GBM), intensity-modulated radiotherapy (IMRT), three-dimensional conformal radiotherapy (3D-CRT), overall survival (OS), organs at risk glioblastoma multiforme (GBM), dosimetry, toxicity, organs at risk

1 Introduction

One of the most aggressive cancers and the most prevalent malignant primary tumour of the brain and central nervous system, glioblastoma multiforme (GBM) accounts for 14.5% of all tumours of the central nervous system and 48.6% of malignant tumours of the central nervous system [1]. Despite significant advances in surgery, radiotherapy, and chemotherapy, the prognosis of patients with GBM remains poor, with a median overall survival (OS) of only 12–15 months after diagnosis [2–4]. Standard treatment for GBM includes maximal safe surgical resection followed by radiotherapy and concomitant chemotherapy, which has been shown to improve local tumor control and overall survival of patients [4].

Radiotherapy plays a crucial role in the management of GBM, with two main modalities being widely used: three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). While 3D-CRT has traditionally been used due to its ability to deliver doses that are consistent with tumor targets, [5], which improves target coverage while reducing the radiation dose to adjacent organs at risk (OARs), such as the optic chiasm, brainstem, and optic nerves [6]. The IMRT, on the other side, has the potential to offer better dose conformity and reduced toxicity compared to 3D-CRT, particularly in tumors located near critical structures [7].

Few comparative studies have examined the differences between 3D-CRT and IMRT in terms of dosimetric outcomes, clinical efficacy, and treatment-related toxicity. IMRT has been reported to reduce high-dose exposure to healthy brain tissue, resulting in improved dose homogeneity and conformity compared to 3D-CRT [7, 8]. Furthermore, IMRT has been shown to potentially reduce acute and late toxicities by minimizing unnecessary radiation exposure to OARs, which may contribute to improved patient quality of life [9–11]. A meta-analysis indicated that while 3D-CRT and IMRT provide comparable overall survival rates, IMRT demonstrated significant advantages in reducing toxicity and improving dosimetric parameters [12, 13].

The present meta-analysis aims to provide a comprehensive comparison between 3D-CRT and IMRT for the treatment of GBM by assessing key factors including overall survival (OS), dosimetric parameters, and radiation effects on organs at risk (OARs). Specific dosimetric parameters of interest include conformity index (CI), homogeneity index (HI), and dose delivered to critical OARs, such as the brainstem, optic chiasm, and optic nerves. Previous studies have highlighted the potential superiority of IMRT in achieving better dose conformity and reduced treatment toxicity compared with 3D-CRT, although survival results remain inconsistent across studies [12, 14, 15]. Given the infiltrative nature of GBM and its proximity to sensitive structures, it is essential to determine the optimal radiotherapy technique that balances effective tumor control with minimized adverse effects.

The aim for this meta-analysis is to address the ongoing debate regarding the clinical benefits of IMRT versus 3D CRT in the treatment of GBM. By synthesizing evidence from multiple studies, we aim to provide a clearer understanding of the relative efficacy of these two radiotherapy modalities, with the goal of informing clinical decision-making and optimizing treatment strategies for patients with newly diagnosed GBM [4].

2 Materials and methods

This study was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. No ethical approval nor patients' consent were needed in the study.

2.1 Search strategy

We conducted an extensive literature search in PubMed, Embase, and the Cochrane Library from their inception up to 15 October 2024, using the keywords "intensity modulation radiation therapy," "IMRT," "three-dimensional conformal radiotherapy," "3D-CRT," "glioblastoma," "glioma", specifically "("glioblastoma" or "Glioma" or "gbm" [All Fields]) AND ("3D-CRT" or "three dimensional conformal therapy" [All Fields]) and ("imrt" or "intensity modulated radiation therapy" [All Fields]). No language restrictions were applied. Additionally, a manual search was carried out by reviewing the references in the retrieved original articles to identify any further eligible studies.

2.2 Study selection and quality assessment

Only original studies were included. Studies were selected if they provided data on dosemetric parameters, organs at risk (OARs) or overall survival (OS) for patients treated with IMRT and 3D-CRT. We employed a paired design approach, where studies were included only if they provided comparative data for the interventions of interest (3DCRT and IMRT) within the same study population, except for OS and side effects. This paired design inherently controls for certain types of biases that traditional RoB tools assess in unpaired or independent study designs, as both interventions are assessed within the same experimental context and participant pool [16].

Of the 19 studies initially reviewed, only 5 studies were eligible for assessment using standard RoB tools. The remaining studies did not meet the RoB tool's specific criteria due to the paired design and limited independent data, which precluded meaningful application of the tool across all included studies. Using the RoB tool for only a subset of studies could lead to inconsistent bias assessment across the dataset, potentially impacting the validity of the pooled analysis.

Instead, to evaluate potential publication bias and ensure robustness, we opted to use funnel plots [17]. Funnel plots are well-suited for assessing bias in paired or comparative designs, especially when RoB assessment is impractical or inconsistent across studies. This approach allowed us to visually assess symmetry in the distribution of effect sizes, thereby identifying potential publication or reporting biases in our meta-analysis.

To summarise, the paired design of this study, combined with the limited applicability of the RoB tool across studies, led us to use funnel plots as a more appropriate and consistent method for evaluating potential bias in our meta-analysis. This approach ensured a fair and consistent assessment of all included studies, aligning with the paired nature of the data and maintaining methodological integrity [18].

3 Analysis

The statistical analysis for this meta- was conducted using Review Ma-ger (RevMan) version 5.4, a software tool widely used for systematic reviews and meta-analyses. The analysis included both dichotomous and continuous outcomes, covering survival outcomes OS, side effects and dose-related metrics such as homogeneity and conformity indices.

For dichotomous outcomes, Overall Survival (OS) and Side effects results were expressed as Odds Ratios (OR), each reported with 95% Confidence Intervals (CIs). ORs were preferred for outcomes with low event rates due to their ability to handle rare events [19]. The Mantel-Haenszel method was applied for pooling ORs, a standard approach for meta-a-lyses involving binary outcomes, especially for studies with varied event rates [16].

Overall survival (OS) was extracted from each included study. Studies reported OS (throughout the entire follow-up period), where either median survival time, 1-year or 2-year survival rates were reported, Kaplan-Meier survival curves used to extract the OS. Data was extracted using graphical data extraction software Plotdigitizer (https://plotdigitizer.com/app), to estimate survival probabilities over time. For consistency across studies, a pooled odds ratio (OR) for OS was calculated using a fixed effects model. The OR was used to quantify the relative likelihood of survival between the IMRT and 3DCRT groups throughout the entire follow-up period, providing a unified summary measure for comparing treatment efficacy. The extracted data were then reconstructed to estimate OR using the method outlined by [20, 21] and validated by [22]. This validated approach enables accurate extraction of time-to-event data from published Kaplan-Meier plots, allowing for reliable integration of survival outcomes into the meta-. Supplementary Figure 1A shows the points estimate extraction method.

For side effects, only two studies reported data on treatment-related side effects, with variations in the types, timing, and grades of toxicities reported. Specifically, Chen et al. [15] provided detailed data on both acute and late toxicities, for IMRT: two cases were reported of acute Grade I/II toxicities and three cases of late Grade I/II neurotoxicity related to white matter changes. Additionally, one patient experienced pseudoprogression. For 3DCRT, two cases of acute Grade I/II toxicities and three cases of late Grade I/II neurotoxicity. One patient developed acute Grade III neurotoxicity (altered consciousness), and six patients were diagnosed with pseudoprogression. The second study, Thibouw et. al [12] reported only acute toxicities across Grades 1, 2, 3, and 4 for both treatment modalities. Given this inconsistency in reporting, particularly the limited data on high-grade (Grade III/IV) and late toxicities, we adjusted our analysis approach to ensure robustness and clarity as Overall Symptoms: We first analyzed all reported toxicities together as an aggregate of symptoms, regardless of grade or timing, to provide a comprehensive overview of the side effect profile associated with each modality. And for Acute Grade 1/2 Toxicities: We then focused specifically on acute Grade 1/2 toxicities, as these were the most consistently reported across both studies and allowed for a more direct comparison. This approach excludes the single case of acute Grade III toxicity observed in the 3DCRT group in the first study, which could not be meaningfully compared given the small number of high-grade toxicity cases across the dataset.

By structuring the side effect analysis as both an overall symptom profile and a focused analysis of acute G1/2 toxicities, we ensure that our findings are consistent with the data available, minimize potential bias from isolated high-grade cases, and provide a clear comparison of the side effect profile for each treatment modality. This approach allows for a balanced interpretation while acknowledging the limitations of the reported data.

A fixed-effect model was applied when low heterogeneity was detected ($I^2 < 50\%$), assuming a common effect size across studies. In contrast, a random-effects model was used when heterogeneity was substantial ($I^2 > 50\%$) to account for between-study variability. The DerSimonian and Laird method was used to implement the random-effects model, which provides a weighted average of effect sizes while incorporating between-study variance [23]. Mean difference (MD) or Standardized mean difference (SMD) were used to measure the differences. Cochran's Q test, with a significance threshold of 0.1, was used as a complementary measure to detect heterogeneity [16]. Moreover, in analyses where high heterogeneity was observed, the variation was investigated by performing sensitivity.

To ensure consistency in measuring dose distribution quality across studies, we recalculated Homogeneity Index (HI) using standardized formulas, as studies varied in their calculation methods. The HI was calculated using [24, 25]:

$$\mathrm{HI} = \frac{Dmax}{Dperscribed}$$

where Dmax is the maximum dose within the target and Dprescribed is the prescribed dose for treatment. This equation, often used in radiation therapy research, provides a measure of dose uniformity, with lower HI values indicating greater homogeneity [26].

For Conformity Index (CI) several formulas were used across the studies, we tried to unify the measure into one formula, but several studies lack the needed data to calculate a unified CI value, so we have chosen only the studies who reported the CI as per this formula [27]:

$$\mathrm{CI} = \frac{V95\%\,PD}{VPTV}$$

where it's defined as the ratio of the volume included in the isodose line for 95% of the prescribed dose and the PTV volume where is the measure from 0 to 1 and the ideal is 1 which indicates that the high-dose region precisely conforms to the target volume without extending into surrounding tissues [13, 28]. However, due to variations in the dose distribution, some studies reported CI values greater than 1, which reflects dose spillage beyond the target.

To standardize these values across studies and facilitate comparison, we converted all CI values by calculating their absolute difference from 1 (Abs Diff from 1 = |CI−1|) [29, 30]. This transformation aligns all values such that those closest to 0 indicate better conformity to the ideal CI, while higher values represent greater deviation from the target conformity. This approach allowed us to analyze the pooled effect with a consistent interpretation, where values closer to 0 are considered optimal.

To assess the robustness of pooled estimates, sensitivity analyses were performed by systematically removing individual studies and recalculating the overall effect size. This approach allowed us to identify any studies exerting a disproportionate influence on the results.

Publication bias was evaluated using funnel plots for the primary outcomes. For outcomes with ten or more studies, Egger's test was applied to statistically assess funnel plot asymmetry, which would indicate the presence of publication bias if significant [17]. All analyses used a significance level of 0.05, with 95% CIs reported for all estimates. For Cochran's Q test, a significance threshold of 0.1 was applied to detect heterogeneity.

4 Results

4.1 Study selection

As demonstrated in Figure 1 (PRISMA). 217 studies were identified in the initial search, with 195 studies remaining after removing duplicates. 162 studies were excluded on title and abstract screening resulting in 33 articles for full-text screen. Of these articles, 19 were included [6, 7, 9, 12, 14, 15, 28, 31–39]; 9 were excluded as they were comparing PT and VMRT or IMAT, 1 was excluded as it was for paediatrics GBM, 2 reviews on the advancement in GBM radiotherapy, 1 was excluded as it clustered the patients into 4 groups based on the number of overlapped OAR, 1 was excluded as it's used 3DCRT and IMRT but the comparison was reported as OS based on acute severe lymphopenia, and 1 was excluded as it there was a mismatch between the comparison results reported in the results section with the results provided in the tables as well as mismatch with the results that were reported in the supplementary table, Figure 1. PRISMA checklist, Supplementary Material, was used to extract studies data, studies characteristics in Supplementary Table 1.

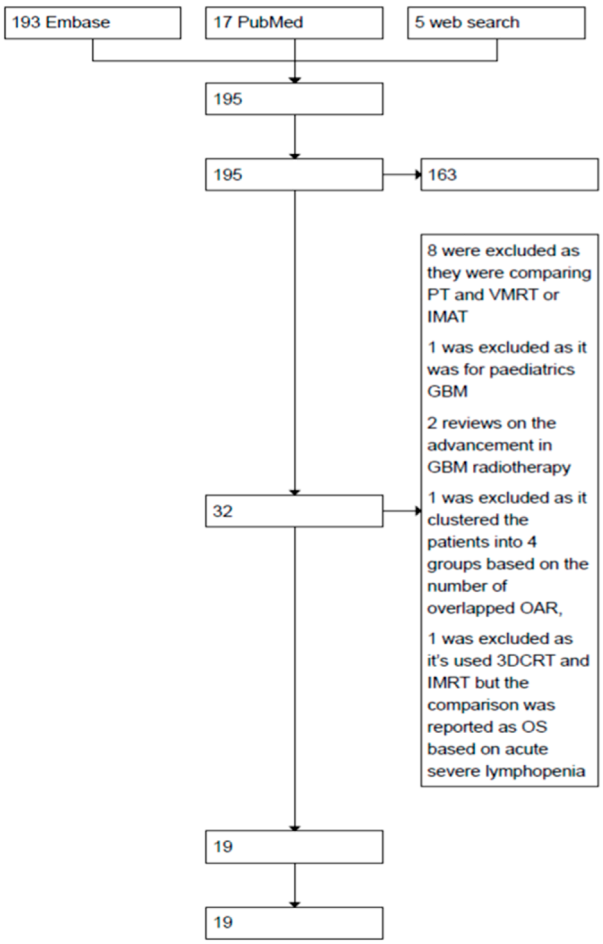

FIGURE 1
PRISMA chart for included studies.

4.2 OS

Five studies comparing overall survival (OS) with total of 556 patients were included, with 306 patients in the IMRT group and 250 in the 3DCRT group [12, 14, 15, 32, 36]. Characteristics of the included studies in Supplementary Table S2. The pooled odds ratio (OR) for OS, using a fixed-effects model, was 0.36 (95% CI: 0.19 to 0.70; P = 0.003), indicating a statistically significant difference favouring the IMRT. Figure 2A. However, this analysis is limited by retrospective designs, lack of adjustment for confounders (e.g., treatment era, temozolomide use), and reliance on unadjusted Kaplan-Meier data.

4.3 Dosimteric outcomes

Thirteen studies were included [6, 7, 9, 13, 28, 31, 33, 34, 37–40]. Nine included for PTV Dmean [7, 9, 13, 28, 31, 34, 37, 38, 40], one study [12] was excluded from PTV Dmean analysis since the reported results in the text mismatched with the values reported in the table, nine for PTVDmax [6, 9, 13, 31, 33, 37–40], eight for PTVDmin [6, 9, 13, 31, 33, 37, 39, 40], six for CI [6, 9, 12, 33, 34, 38] and eight for HI [6, 9, 13, 31, 33, 37, 38, 40] were analysed, Table 1. The pooled mean difference (MD) for PTV Dmean was 1.26 (95% CI: 0.22 to 2.31; P = 0.02), indicating a higher PTV Dmean for IMRT, Figure 2B. For conformity index (CI); the pooled mean difference (MD) was −0.21 (95% CI: −0.33 to −0.08; P = 0.001), indicating a higher conformity index for IMRT (ideal is 0 after conversion as described in the analysis section), Figure 2C. Dmax, Dmin, and HI did not show a significant difference between the two groups, P > 0.05. Supplementary Figures S2A–C, respectively.

4.4 OAR

Fourteen studies were included [6, 9, 13, 15, 28, 31, 33, 34, 37–42] in this analysis, Table 2.

4.4.1 Healthy brain

Eleven studies were included in for brain Dmean [6, 12, 13, 28, 31, 33, 34, 37, 40–42]. The pooled standardized mean difference (MD) for the whole brain Dmean between IMRT and 3DCRT was −1.08 (95% CI: −2.08 to −0.09; P = 0.03), indicating a lower Dmean to healthy brain for IMRT. Figure 2D.

4.4.2 Brainstem

Ten studies were included for the brainstem Dmean [6, 9, 15, 28, 33, 37–41] and nine for Dmax [6, 9, 15, 28, 33, 37–42].

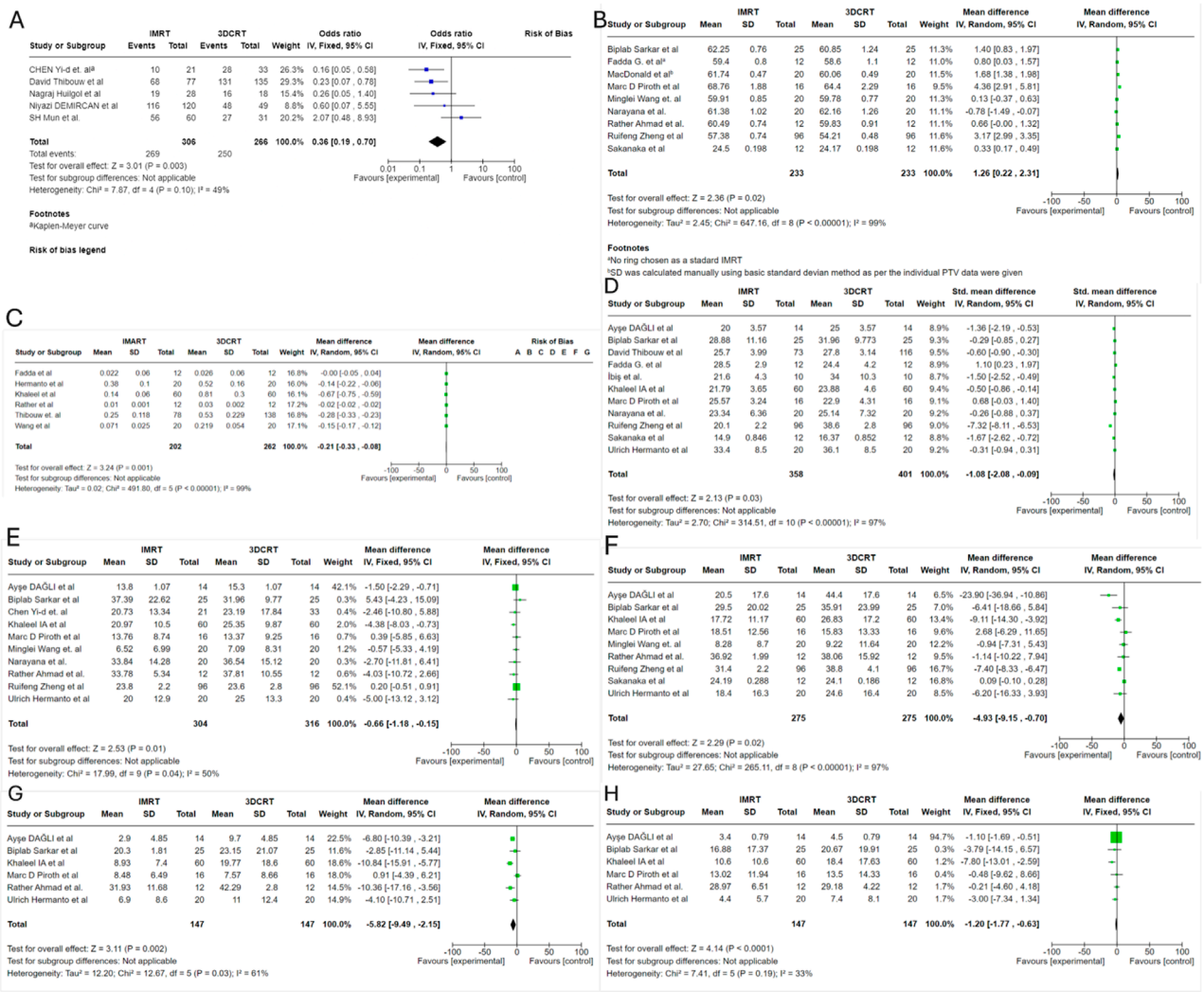

FIGURE 2
(A–H) forest plots; OS **(A)**, PTV Dmean **(B)**, CI **(C)**, healthy brain **(D)**, Brainstem Dmean **(E)**, Optic chiasm Dmean **(F)**, Right optic nerve Dmean **(G)**, and Lrft optic nerve **(H)**.

The pooled MD for brainstem Dmean −0.66 (95% CI: −1.18 to −0.15; P = 0.01) shows significant reduction with IMRT, Figure 2E. No significant difference in Dmax between IMRT and 3DCRT, P > 0.05, Supplementary Figure 2D.

4.4.3 Optic chiasm

Nine studies were included in the analysis for optic chiasm Dmean [6, 9, 13, 28, 31, 33, 37, 38, 41] and eleven studies for Dmax [6, 9, 13, 28, 33, 34, 37, 38, 40–42]. The pooled MD for optic chiasm Dmean was −4.93 (95% CI: −9.15 to −0.70; P = 0.02), indicating a significant reduction with IMRT, Figure 2F. No significant difference in Dmax between IMRT and 3DCRT, P > 0.05, Supplementary Figure 2E.

4.4.4 Right optic nerve

Six studies were included the right optic nerve Dmean [6, 9, 31, 33, 37, 41] and five for Dmax [6, 9, 33, 37, 41]. The pooled MD for right optic nerve Dmean was −5.82 (95% CI: −9.49 to −2.15; P = 0.002) indicating a significant reduction with IMRT, Figure 2G. No significant difference in Dmax between IMRT and 3DCRT, P > 0.05, Supplementary Figure 2F.

4.4.5 Left optic nerve

Six studies were included for the left optic nerve Dmean [6, 9, 31, 33, 37, 41] and five for Dmax [6, 9, 33, 37, 41]. The pooled MD for left optic nerve Dmean was −1.20 (95% CI: −1.77 to −0.63; P < 0.0001), indicating a significant reduction with IMRT, Figure 2H. No significant difference in Dmax between IMRT and 3DCRT, P > 0.05, Supplementary Figure 2G.

5 Side effects

Only two studies were found that compare both modalities directly [12, 15] with a total of 274 patients (175 for 3DCRT and

TABLE 1 Dosemtric outcomes.

Author and year	PTV Dmean (Gy)		PTV Dmin (Gy)		PTV Dmax (Gy)		Conformity index (CI)[d]		Homogeneity index (HI)[b]	
	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT
Hermanto et al., (2007)	-	-	46.0 ± 4.2	44.0 ± 2.4	63.1 ± 0.6	62.3 ± 0.9	1.52 ± 0.16	1.38 ± 0.10	1.262 ± 0.6	1.246 ± 0.9
Piroth et al., (2009)	64.40 ± 2.79	68.76 ± 1.88	57.39 ± 6.79	61.07 ± 3.31	73.94 ± 1.88	73.14 ± 0.98	-	-	1.015 ± 1.88	1.016 ± 0.98
Khaleel et al., (2018)	-	-	43.65 ± 6.20	39.11 ± 5.10	63.30 ± 1.04	61.72 ± 1.09	1.81 ± 0.3	1.14 ± 0.06	1.266 ± 1.04	1.234 ± 1.09
Rather et al. (2022)	59.83 ± 0.90	60.49 ± 0.74	51.86 ± 2.95	55.87 ± 1.81	63.96 ± 1.25	62.99 ± 0.67	0.97 ± 0.002	0.99 ± 0.001	1.066 ± 2.38	1.045 ± 2.29
Zayat et. al. (2014)	-	-	75 ± 16.99	77.31 ± 20.98	106.3 ± 2.38	107.9 ± 2.94	-	-	-	-
Wang et al. (2015)	59.78 ± 0.77	59.91 ± 0.85	-	-	65.06 ± 0.46	64.88 ± 0.66	1.219 ± 0.054	1.071 ± 0.025	1.301 ± 0.46	1.298 ± 0.66
Zheng et al. (2015)	54.21 ± 0.48	57.38 ± 0.74	-	-	-	-	-	-	-	-
Fadda et al. (2013)	58.6 ± 1.1	59.4 ± 0.8	-	-	-	-	0.74 ± 0.06	0.78 ± 0.06	-	-
Sarkar et al. (2011)	60.85 ± 1.24	62.25 ± 0.75	62.25 ± 0.75	43.96 ± 5.26	63.89 ± 1.03	68.07 ± 1.77	-	-	1.065 ± 1.03	1.134 ± 1.77
MacDonald et al (2007)[a]	61.74 ± 0.49	60.06 ± 0.47	-	-	-	-	-	-	-	-
Naranaya et. al. (2005)[b]	62.16 ± 1.5	65.46 ± 2.64	40.38 ± 14.46	39.48 ± 13.92	65.34 ± 1.5	65.46 ± 2.64	-	-	1.089 ± 1.5	1.091 ± 2.64
Sakanaka et al (2012)[c]	2.20 ± 0.198	24.5 ± 0.198	21.5 ± 0.5	21.6 ± 0.4	25.2 ± 0.22	25.37 ± 0.14	-	-	1.5 + 0.22	1.5 + 0.14
Thibouw et. al (2022)[e]	-	-	-	-	-	-	0.14 ± 0.06	0.25 ± 0.118	-	-

[a]SD was calculated manually using basic standard deviation method as per the individual PTV, data were given.
[b]HI = Dmax/Dperscribed [24, 25].
[c]Dmean = Dmean (%) × Prescribed Dose/100.
[d]only studies reported CI = $\frac{V95\%PD}{VPTV}$.
[e]PTV dmean excluded due to mismatch.

99 for IMRT), the comparison between the two modalities show that all symptoms were lower in IMRT compared to 3DCRT, OR 0.56 (95% CI: 0.56–0.95), P = 0.003, Figure 3A. However, while the IMRT show a 17% lowering the risk of GI/II toxicities, this difference was not statistical difference between the two groups, P = 0.18, Figure 3B.

6 Publication bias

Publication bias was assessed using funnel plots for OS, PTV Dmean, CI, PTV Dmax, PTV Dmin, homogeneity index (HI), healthy brain, brainstem Dmean and Dmax, optic chiasm (Dmean, Dmax), right optic nerve (Dmean, Dmax), and left optic nerve

TABLE 2 OAR doses

Study	Modality	Brain Dmean (Gy)	Brainstem Dmean (Gy)	Brainstem Dmax (Gy)	Optic chiasm Dmean (Gy)	Optic chiasm Dmax (Gy)	Right optic nerve Dmean (Gy)	Right optic nerve Dmax (Gy)	Left optic nerve Dmean (Gy)	Left optic nerve Dmax (Gy)
Khaleel et al (2018)	3DCRT	23.88 ± 4.6	25.35 ± 9.87	52.64 ± 9.63	26.83 ± 17.2	37.03 ± 22.0	19.77 ± 18.6	25.17 ± 20.5	18.4 ± 17.63	26.5 ± 20.90
	IMRT	21.79 ± 3.6	20.97 ± 10.5	46.22 ± 9.86	17.72 ± 11.7	26.58 ± 16.0	8.93 ± 7.39	13.41 ± 10.2	10.60 ± 10.6	16.36 ± 14.9
Wang et al (2015)	3DCRT	-	7.09 ± 8.31	14.78 ± 14.77	9.22 ± 11.64	12.53 ± 15.50	-	-	-	-
	IMRT	-	6.52 ± 6.99	14.04 ± 11.62	8.28 ± 8.70	12.76 ± 13.53	-	-	-	-
Hermanto et al (2007)	3DCRT	21.3 ± 4.6	25.0 ± 13.3	51.3 ± 7.3	24.6 ± 16.4	35.6 ± 17.4	11.0 ± 12.4	20.4 ± 18.9	7.4 ± 8.1	15.1 ± 16.0
	IMRT	19.1 ± 4.6	20.0 ± 12.9	45.8 ± 12.8	18.4 ± 16.3	27.6 ± 21.2	6.9 ± 8.6	14.6 ± 17.4	4.4 ± 5.7	9.5 ± 12.6
Zhenget al (2015)	3DCRT	38.6 ± 2.8	23.8 ± 2.2	33.3 ± 2.2	31.4 ± 2.2	42.2 ± 3.2	-	-	-	-
	IMRT	20.1 ± 2.2	23.6 ± 2.8	33.6 ± 2.6	38.8 ± 4.1	47.6 ± 1.2	-	-	-	-
Rather et al. (2022)	3DCRT	-	37.81 ± 10.55	57.98 ± 4.99	38.06 ± 15.92	49.16 ± 13.00	42.29 ± 2.80	49.73 ± 1.82	29.18 ± 4.22	44.13 ± 2.74
	IMRT	-	33.78 ± 5.34	51.84 ± 4.43	36.92 ± 1.99	44.61 ± 3.72	31.93 ± 11.68	44.63 ± 13.54	28.97 ± 6.51	46.08 ± 10.58
Fadda et al. (2019)	3DCRT	24.4 ± 4.2	-	51.3 ± 5.6	-	50.0 ± 5.8	-	-	-	-
	IMRT	28.5 ± 2.9	-	52.5 ± 1.8	-	52.5 ± 2.2	-	-	-	-
Chen et al. (2013)	3DCRT	-	23.19 ± 17.84	43.40 ± 25.45	-	-	-	-	-	-
	IMRT	-	20.73 ± 13.34	39.87 ± 18.30	-	-	-	-	-	-
Sarkar et al. (2011)	3DCRT	31.96 ± 9.77	37.39 ± 22.62	-	35.91 ± 23.99	-	23.15 ± 21.07	-	20.67 ± 19.91	-
	IMRT	28.88 ± 1.0	41.45 ± 23.56	-	29.05 ± 20.02	-	20.30 ± 1.81	-	16.88 ± 17.37	-
Piroth et al (2009)	3DCRT	25.57 ± 3.24	13.37 ± 9.25	-	15.83 ± 13.33	23.56 ± 16.84	7.57 ± 8.66	12.19 ± 12.43	13.50 ± 14.33	18.20 ± 17.69
	IMRT	22.90 ± 4.31	25.57 ± 3.24	-	18.51 ± 12.56	28.16 ± 17.9	8.48 ± 6.49	15.2 ± 12.04	13.02 ± 16.94	18.99 ± 16.39

(Continued on the following page)

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TABLE 2 (*Continued*) OAR doses

Study	Modality	Brain Dmean (Gy)	Brainstem Dmean (Gy)	Brainstem Dmax (Gy)	Optic chiasm Dmean (Gy)	Optic chiasm Dmax (Gy)	Right optic nerve Dmean (Gy)	Right optic nerve Dmax (Gy)	Left optic nerve Dmean (Gy)	Left optic nerve Dmax (Gy)
Naranaya et al. (2005)**	3DCRT	25.14 ± 7.32	36.54 ± 15.12	56.46 ± 10.32	-	48.84 ± 14.88	-	-	-	-
	IMRT	23.34 ± 6.36	33.84 ± 14.28	55.38 ± 11.16	-	47.34 ± 14.4	-	-	-	-
Zayat et. al (2015)	3DCRT	-	-	73.05 ± 34.59	-	-	-	-	-	-
	IMRT	-	-	72.17 ± 29.7	-	-	-	-	-	-
DAĞLI et al (2012)*	3DCRT	25 ± 3.57	15.3 ± 1.07	59 ± 5.21	44.4 ± 17.6	53.2 ± 6.99	9.7 ± 4.85	27.2 ± 5.64	4.5 ± 0.79	25.6 ± 10.63
	IMRT	20 ± 3.57	13.8 ± 1.07	51.7 ± 5.21	20.5 ± 17.6	43.4 ± 6.99	2.9 ± 4.85	19.3 ± 5.64	3.4 ± 0.79	10.7 ± 10.63
Ibis et al (2018)**	3DCRT	34 ± 10.3	-	54 ± 18	53.5 ± 18.7	-	-	-	-	-
	IMRT	21.6 ± 4.3	-	50 ± 10.3	44 ± 11.8	-	-	-	-	-
Thibouw et al (2022)**	3DCRT	27.8 ± 3.14	-	53.2 ± 5.16	-	50 ± 5.8	-	20 ± 5.37	-	14.05 ± 5.06
	IMRT	25.7 ± 3.99	-	45.8 ± 6.4	-	52.9 ± 6.24	-	35 ± 6.19	-	33.3 ± 6.55
Sakanaka et al (2012)***	3DCRT	16.37 ± 0.85	-	-	24.048 ± 0.186	24.12 ± 0.186	-	-	-	-
	IMRT	14.9 ± 0.84	-	-	24.192 ± 0.288	24.408 ± 0.216	-	-	-	-

*Standard deviations were calculated as described [43].**values reported in median, SD, was calculated as described [16].***Dmean = Dmean (%) × Prescribed Dose/100.

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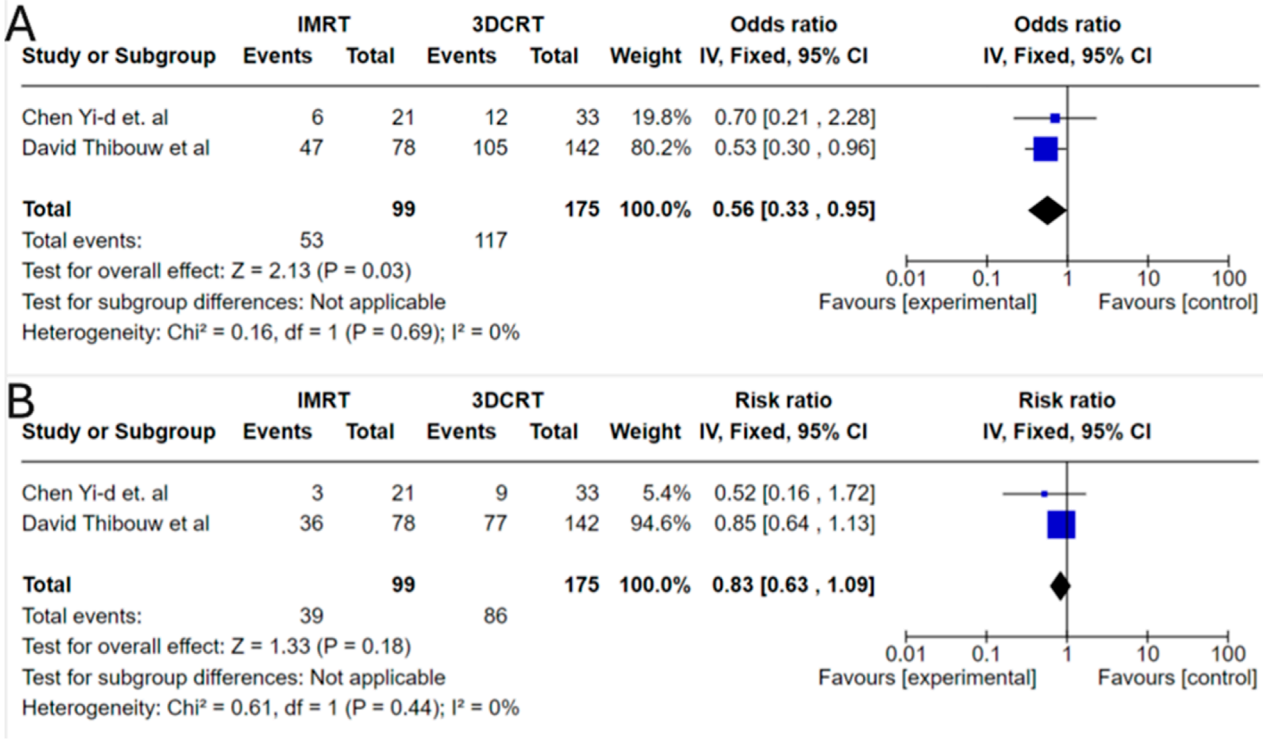

FIGURE 3
(A) overall side effects, and **(B)** acute G1/2 toxicities comparison between IMRT and 3DCRT.

(Dmean, Dmax) funnel plots in Figures 4A–O, respectively. OS (A) shows a symmetrical distribution around the effect size for odds ratios (OR), indicating low likelihood of publication bias. PTV Dmean displays symmetry. Conformity index also exhibits symmetry, while PTV Dmax shows slight asymmetry. PTV Dmin appears symmetrical, indicating minimal bias, whereas HI displays minor asymmetry. Healthy brain reveals symmetry, while brainstem Dmean shows a symmetrical funnel shape, and brainstem exhibits symmetry. Optic chiasm Dmean shows moderate asymmetry indicating potential small-study effects. Optic chiasm Dmax displays symmetry, with low publication bias. Right optic nerve Dmean shows slight asymmetry, while right optic nerve Dmax exhibits a symmetrical distribution. Left optic nerve Dmean displays a symmetrical funnel shape, and Dmax shows symmetry.

7 Discussion

From a dosimetric perspective, the pooled mean difference (MD) for PTV Dmean was 1.26 (95% CI: 0.22 to 2.31; P = 0.02), favouring IMRT. The conformity index showed a mean difference of −0.21 (95% CI: −0.33 to −0.08; P = 0.001) in favour of IMRT, demonstrating better dose conformity. A higher conformity index benefits glioblastoma treatment by improving tumour targeting while sparing healthy brain tissue, reducing neurocognitive side effects, and preserving quality of life. This enhanced coverage may lead to better tumour control and treatment outcomes, supporting IMRT use in glioblastoma management [6, 37].

Studies highlight IMRT's dosimetric advantages, including improved target coverage and organ-at-risk (OAR) sparing, linked to reduced toxicity and better quality of life [7, 13, 40, 44]. These findings align with evidence suggesting IMRT outperforms conventional techniques like 3DCRT in glioblastoma management [9, 12, 37, 38, 44]. IMRT enables dose escalation to tumours while minimizing exposure to critical structures like the optic chiasm and brainstem, contributing to better outcomes [7].

The treatment landscape for glioblastoma multiforme (GBM) is rapidly evolving, with radiotherapy remaining a cornerstone of multimodal approaches that integrate maximal safe surgical resection, chemotherapy (e.g., temozolomide), and emerging therapies such as tumor-treating fields (Optune) and immunotherapies [45, 46]. This meta-analysis demonstrates IMRT's superior dose compliance, evidenced by improved conformity index (CI, MD −0.21, 95% CI: −0.33 to −0.08; P = 0.001) and reduced OAR doses (e.g., optic chiasm Dmean, MD −4.93 Gy, P = 0.02; brainstem Dmean, MD −0.66 Gy, P = 0.01), which enhance tumor control while minimizing toxicities such as neurocognitive decline and visual impairment [6, 12, 45]. These dosimetric advantages are critical in multimodal settings, where precise dose conformation and OAR sparing facilitate combination therapies and re-irradiation for recurrent GBM by preserving neurological function and quality of life for subsequent treatments [46, 47]. Concurrently, Volumetric Modulated Arc Therapy (VMAT) has emerged as a predominant standard in many clinical settings due to its superior treatment efficiency, reduced delivery time, and comparable or improved dosimetric outcomes compared to

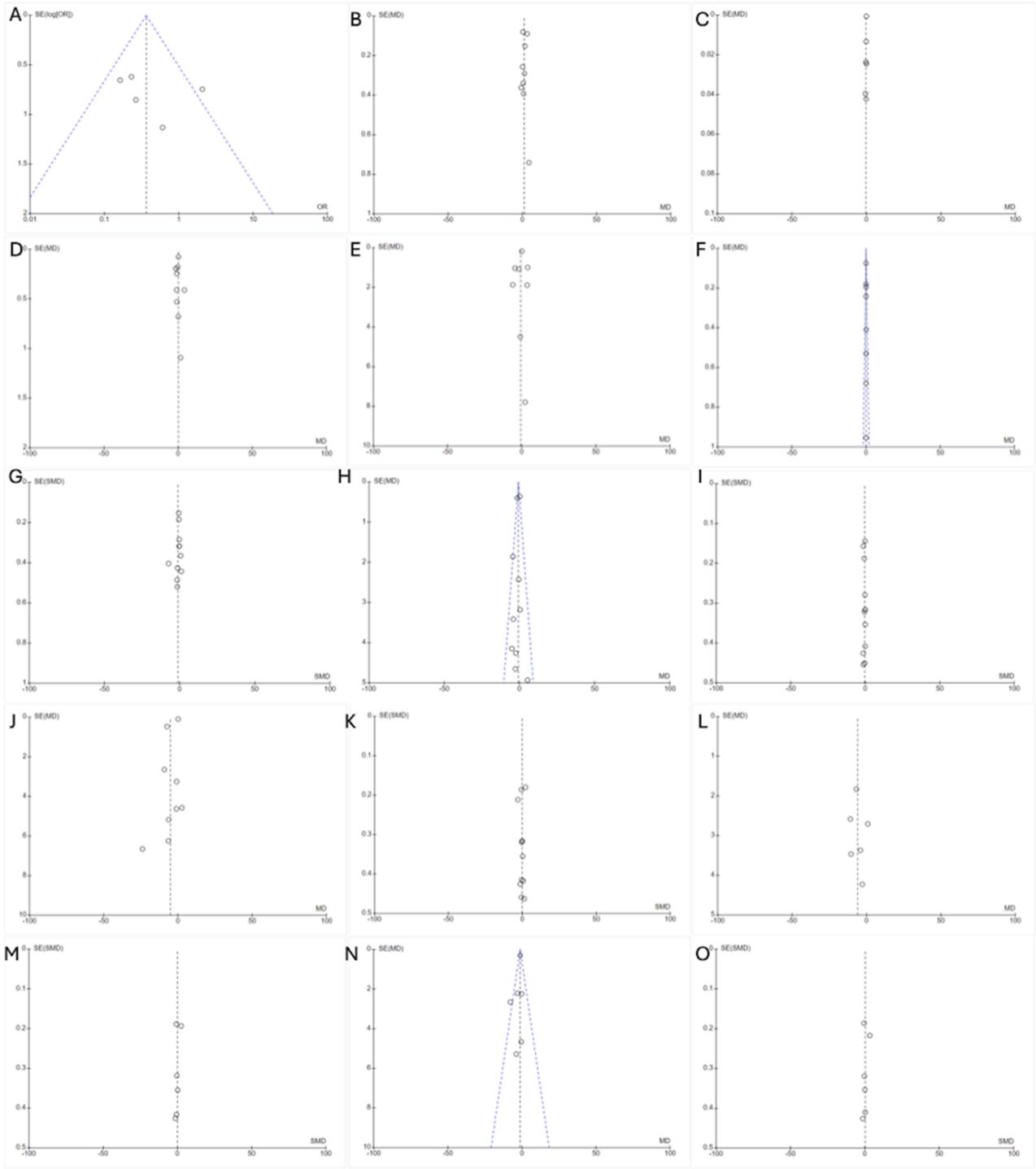

FIGURE 4
(A–O) Publication bias was assessed using funnel plots for OS, PTV Dmean, CI, PTV Dmax, PTV Dmin, homogeneity index (HI), healthy brain, brainstem Dmean and Dmax, optic chiasm (Dmean, Dmax), right optic nerve (Dmean, Dmax), and left optic nerve (Dmean, Dmax), respectively.

IMRT, optimizing dose distributions to complex tumor geometries score [48, 49]. Deite VMAT's advancements, this meta-analysis remains highly relevant in resource-limited settings where VMAT is not yet feasible due to equipment or training constraints, and for elucidating foundational dose–volume principles that underpin modern radiotherapy techniquesteoh [6, 12, 48]. These findings are valuable for multidisciplinary teams managing GBM, as IMRT's precision supports effective tumor control and integration into complex treatment regimens, enhancing patient outcomes in both primary and recurrent settings [46, 49].

Pooled OAR doses showed significant reductions with IMRT compared to 3DCRT. For instance, the optic chiasm and brainstem received lower doses with IMRT, reducing radiation-induced side effects like visual disturbances and neurological complications [7, 44]. This reduction is crucial for preserving neurological function and patient quality of life [50]. Other studies confirm that IMRT significantly reduces doses to OARs compared to 3DCRT, lowering toxicity rates [39, 44]. Chan et al. reported IMRT's superior dose conformity and reduced OAR doses, enhancing quality of life by minimizing radiation-induced complications [35]. Hermanto et al. and Thibouw et al. found IMRT improved homogeneity and conformity indices while sparing critical structures, supporting this meta-analysis [6, 12]. Reduced doses to the optic chiasm and other OARs with IMRT help avoid late side effects and preserve cognitive function [7].

Regarding side effects, two studies comparing toxicity profiles of IMRT and 3DCRT (274 patients: 175 for 3DCRT, 99 for IMRT) showed lower overall symptoms with IMRT (OR 0.56, 95% CI: 0.56 to 0.95; P = 0.003). Though IMRT reduced Grade I/II toxicities by 17%, this was not statistically significant (P = 0.18), suggesting IMRT lowers overall side effects but not mild ones. This reduced toxicity likely results from IMRT's ability to spare healthy tissues, minimizing radiation-induced side effects and enhancing quality of life [7, 13, 36, 50].

Few studies compare IMRT and 3DCRT toxicity in glioblastoma, but IMRT has demonstrated lower side effects in other cancers, including head and neck [51, 52], prostate [53], rectal [54], and cervical cancers [55]. GBM's unique anatomy, with critical structures like the optic nerves and brainstem near the tumour, makes dose conformity crucial. Unlike other cancers, even minimal radiation exposure in GBM can cause neurocognitive side effects. While IMRT's success in reducing toxicities in other cancers supports its potential in GBM, further studies are needed to confirm its benefits in sparing critical structures while maintaining effective tumor control.

Additionally, while our analysis demonstrated dosimetric advantages of IMRT in sparing critical structures, the translation of these benefits to patient-reported outcomes remains unclear. Only two studies reported comparative data on side effects, limiting clinical interpretation. Future prospective studies should incorporate validated patient-centered outcomes, such as neurocognitive function tests, vision-specific assessments, and quality of life instruments like the EORTC QLQ-C30 and QLQ-BN20, to better link dosimetric improvements to meaningful clinical benefits.

In terms of OS, the meta- included five studies comparing overall survival (OS) between IMRT and 3DCRT treatment groups for glioblastoma multiforme (GBM). A total of 556 patients were included, with 306 patients in the IMRT group and 250 in the 3DCRT group. The pooled odds ratio (OR) for OS, using a fixed-effects model, was 0.36 (95% CI: 0.19 to 0.70; P = 0.003), indicating a statistically significant difference favouring the IMRT group. IMRT allows for highly conformal dose distributions, reducing exposure to adjacent healthy tissue and potentially improving treatment outcomes [12, 15, 56, 57]. Although the evidence is yet to be found, a recent Bayesian Network Meta- indicated that the OS probability is 44.9 compared to 26.3 for 3DCRT on SUCRA ranking [50]. Moreover Chen et al. demonstrated in their study that IMRT 1 year OS was better compared to 3DCRT, (89.6% vs. 75.8%), respectively. Additionally, a study by Yahara et al. 2017 demonstrated that IMRT might provide longer OS [58]. This exploratory OS indicates a potential IMRT benefit (OR 0.36), but this must be interpreted cautiously. All included studies were retrospective, and the analysis could not adjust for confounders like treatment era (older 3D-CRT vs. modern IMRT), concurrent temozolomide, or Optune use, which likely influence survival [4]. For example, patients treated with 3D-CRT in earlier studies may not have received temozolomide, which became standard after 2005, or Optune, which has shown survival benefits in newer trials [59]. Patient selection bias may also contribute, as randomized trials have not confirmed technique-related survival differences. Thus, while intriguing, the OS finding is hypothesis-generating and requires prospective validation.

7.1 Practical implications

The findings of this meta-analysis support the clinical use of IMRT over 3DCRT for glioblastoma due to its significant advantages in overall survival and reduced dose to critical structures. IMRT is preferable, particularly for patients at risk of radiation-induced side effects, such as visual impairment or brainstem toxicity. By delivering a precise dose to the tumor while sparing OARs, IMRT enhances survival and minimizes morbidity, preserving neurological function and quality of life [6, 12, 33, 34, 50, 58].

Funnel plots in Figure 4 indicate low publication bias across outcomes. Plot A, representing odds ratios (OR), suggests minimal bias due to its symmetrical distribution. Most studies follow a paired design, reducing bias through within-subject comparisons. Minor asymmetries in plots D, F, J, and L likely result from small-study effects or reporting variations rather than publication bias. The paired design controls for selective reporting, supporting the robustness of these findings [17, 60].

A sensitivity analysis identified sources of heterogeneity. Excluding studies with extreme mean differences or wide confidence intervals reduced heterogeneity to moderate or low levels, indicating that variability arose from reported data differences rather than methodological inconsistencies. Tumour location plays a role in heterogeneity, as tumours near critical OARs require unique dose balancing strategies, influencing dosimetric outcomes [61, 62].

Planning target volume (PTV) size also contributes to heterogeneity. Larger PTVs challenge dose conformity and OAR sparing, introducing variability across studies. Differences in PTV sizes and prescribed dose thresholds reflect clinical practice variations, impacting results despite standardization efforts [47, 63, 64]. While initial heterogeneity reflected diverse radiotherapy strategies, its reduction after exclusions strengthens the reliability of pooled results, reinforcing IMRT's superiority in conformity index and PTV coverage.

Heterogeneity in meta-analyses provides insights into clinical variations rather than limitations. Identifying effect modifiers enhances understanding of radiotherapy practices for glioblastoma. The presence of heterogeneity underscores the need for personalized treatment planning and highlights the role of meta-analyses in informing clinical decisions [65–70].

Future research should aim to further elucidate the specific factors contributing to the survival benefit of IMRT, including

patient selection, tumour characteristics, and advancements in imaging and treatment planning. Emerging applications of deep learning in medical imaging provide valuable insights for advancing precision in radiotherapy planning. Studies applying deep convolutional neural networks for automated classification of complex imaging data, such as skin lesions [71] and gastrointestinal tract abnormalities [72], demonstrate the potential of AI-driven methodologies to enhance decision-making under data-constrained conditions. Incorporating such advanced imaging analytics in radiotherapy could facilitate more personalized and optimized treatment planning for GBM, particularly when anatomical constraints and OAR proximity pose significant challenges. Furthermore, additional randomized controlled trials comparing IMRT and 3DCRT with long-term follow-up are warranted to confirm these findings and provide more definitive evidence for clinical practice.

This meta-analysis has several limitations. The number of studies directly comparing overall survival between IMRT and 3D-CRT was limited, which may affect the robustness of the pooled OS results. Additionally, only two studies compared the side effects of both modalities, limiting the ability to draw definitive conclusions about toxicity profiles. Variability in tumour location, PTV size, and prescribed dose thresholds contributed to heterogeneity, which may impact the generalizability of findings. The retrospective nature of the included studies and the lack of adjustment for confounders such as treatment era and concurrent therapies further limit the interpretation of OS results.

8 Conclusion

This meta-analysis indicates that IMRT offers significant dosimetric advantages and potentially lower toxicity compared to 3D-CRT in the treatment of glioblastoma multiforme. IMRT optimizes radiation delivery and reduces toxicity, with potential survival benefits warranting further study. While an exploratory analysis suggests a possible OS benefit favouring IMRT, this finding requires cautious interpretation due to study limitations, including retrospective designs and unadjusted confounders. IMRT's precision and ability to spare critical structures support its use in GBM treatment, particularly in cases where minimizing toxicity is crucial. Further research, including.

Author contributions

OF: Writing – review and editing, Writing – original draft. DaS: Writing – review and editing. RK: Data curation, Writing – original draft. MA: Writing – original draft, Investigation. DóS: Methodology, Writing – review and editing. KG: Formal Analysis, Writing – review and editing. SM: Investigation, Writing – review and editing. AK: Writing – review and editing, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphy.2025.1632620/full#supplementary-material

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