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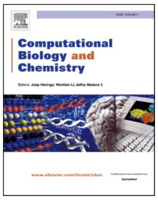

Radiosensitivity enhancement of bismuth-based nanoparticles in radiotherapy: A systematic review and meta-analysis

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ABSTRACT

Introduction: Nano-biomaterials facilitate targeted drug delivery and serve as radio-sensitizers, reducing therapeutic doses and side effects while enhancing efficacy. This meta-analysis aims to investigate the impact of bismuth-based nanoparticles on enhancing radiosensitivity, specifically by evaluating the dose enhancement factor (DEF) in radiotherapy.

Materials and Methods: This systematic review and meta-analysis evaluated the radiosensitizing effect of bismuth-based nanoparticles. PubMed, Web of Science, and Scopus were searched for eligible studies. The cumulative dose enhancement factor (DEF) was assessed, and subgroup and sensitivity analyses were performed to investigate the effect of nanoparticle size and concentration on radiosensitization.

Results: The average dose enhancement factor (DEF) for bismuth concentrations < 50 and ≥ 50 was not statistically different (1.41 vs. 1.47; $p > 0.05$). This indicates that bismuth concentrations above 50 are not more effective against tumor cells. In contrast, the mean DEF for tumor sizes < 10 and > 10 was 1.21 and 1.51, respectively ($P = 0.02$). Nanoparticle size significantly influenced radiosensitization, with particles larger than 10 nm producing higher DEF values compared with smaller particles. In contrast, increasing nanoparticle concentration did not lead to a proportional increase in DEF, suggesting possible biological saturation or toxicity effects.

Conclusions: These findings suggest increasing nanoparticle concentration above 50 μg/mL did not further enhance the radiosensitizing effect against tumor cells. Nanoparticle size significantly influences the dose enhancement factor, with larger (>10 nm) nanoparticles yielding higher DEF values. This highlights the importance of optimizing nanoparticle size to improve radiosensitization in tumor treatment. Our results indicate that bismuth-based nanoparticles enhance radiation effects and may serve as promising radiosensitizers in preclinical models.

1. Introduction

Surgery, chemotherapy, and radiotherapy remain the cornerstones of cancer treatment, significantly improving prognosis in recent decades (Zafar et al., 2025; Mohaghegh et al., 2022). However, their effectiveness may diminish when used in isolation without complementary approaches. Targeting of specific receptors in cancers by antibodies and pharmaceuticals is the common chemotherapy approaches (Khajeh et al., 2018; Asgari et al., 2011). Furthermore, combining radiotherapy and chemotherapy has gained significant attention in

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cancer research, with many studies investigating their combined benefits to enhance treatment outcomes and improve patient prognosis. The synergistic effects of these modalities may provide a more effective strategy against cancer, emphasizing the need for continued exploration of their joint application (Chauhan et al., 2020; Li et al., 2020). Various nano-biomaterials have been developed for use as probes and therapeutic agents, often enhanced by targeting agents on their surfaces (Saberian et al., 2011; Nourizad et al., 2023). Significant advancements in radiation therapy include utilizing gold and bismuth as radiosensitizers. Radiosensitizers are agents that increase the sensitivity of tumor cells to radiation, thereby improving therapeutic efficacy (Khosravi et al., 2024).

Integrating nano-biomaterials into radiotherapy and chemotherapy is essential for creating more effective treatments, enabling targeted drug delivery, reducing dosages, minimizing side effects, and improving overall efficacy (Patra et al., 2018; Tarighatnia et al., 2021). Current research focuses on designing and synthesizing nano-biomaterials, particularly bismuth-based nanoparticles (NPs) (Nezhad et al., 2021; Nosrati et al., 2019). The effective dose remains a critical concern in clinical radiotherapy, and advances in nanotechnology are encouraging the use of high-atomic nanoparticles as physical sensitizers (Abaei et al., 2024). The interaction of these nanoparticles with photons enhances Auger electrons and the photoelectric effect, leading to a local dosimetric enhancement known as dose enhancement factor (DEF). DEF refers to the ratio of the radiation dose required to achieve a given biological effect in the absence of nanoparticles to their presence, and is commonly used to quantify radiosensitivity (Rabus et al., 2019).

As a reminder, the Auger effect refers to the emission of low-energy electrons after inner-shell ionization, which contributes to localized DNA damage in the vicinity of high-Z nanoparticles (Choi et al., 2020). On the other hand, the photoelectric effect, in which incident photons transfer energy to inner-shell electrons, is the dominant physical interaction responsible for dose enhancement by high-Z nanoparticles at diagnostic and therapeutic energies (Jackson et al., 2024). Furthermore, NPs under 100 nm can leverage the enhanced permeability and retention (EPR) effect within tumors, serving as local radio-enhancing agents for improved radiation therapy. It should be noted that the EPR effect describes the tendency of nanoparticles to preferentially accumulate in tumors due to leaky blood vessels and poor lymphatic drainage (Kuncic and Lacombe, 2018).

Numerous studies have explored gold NPs as prototypes, while bismuth-based alternatives show promise in safeguarding soft tissues and organs from radiation. Physical sensitizers have demonstrated interactions between photons, radiosensitizers, and CT image contrast (Chen et al., 2020). High-Z inorganic NPs, such as bismuth, gadolinium, tungsten, and platinum, increase radiation dose element inorganic NPs such as bismuth and platinum have been shown to increase the dose (Ganapathy et al., 2022a). Among these, bismuth stands out with the highest X-ray absorption coefficient and serves as an effective radiosensitizer. Bismuth-based nanoparticles are emerging as prominent radiosensitizers due to their high atomic number, photoelectric cross section, low toxicity, and cost-effectiveness compared to gold or platinum nanoparticles. Investigations into -based NPs have explored their use as dual agents during irradiation, while single-agent NPs are important in cancer therapy (Bartoli et al., 2020). This review and meta-analysis systematically evaluates the radiosensitizing potential of bismuth-based nanoparticles in preclinical studies. Unlike previous reviews on metallic or high-Z nanoparticles, this work focuses exclusively on bismuth, valued for its high atomic number, low toxicity, and cost-effectiveness. By analyzing dose enhancement factor (DEF) data and the impact of nanoparticle size and concentration, this study provides a quantitative assessment of existing evidence. To our knowledge, this is the first meta-analysis dedicated to bismuth-based nanoparticles in radiotherapy. This work addresses a research gap by synthesizing disparate preclinical findings, identifying methodological variations, and outlining future research directions, offering valuable insights for radio-oncology, radiobiologists, and nanomedicine researchers.

2. Methods

This systematic review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, as visually represented in Fig. 1. To enlist the articles investigating the effect of bismuth-based nanoparticles to increase radio-sensitivity in radiotherapy searching the databases was conducted from 2000 to 2025.

2.1. Search strategy

We searched PubMed, Web of Science, and Scopus for relevant studies using keywords and MeSH terms related to radiosensitivity, radiotherapy, nanoparticles, bismuth, and their abbreviations. Boolean operators were used to refine the search. The detailed search strategy and full electronic search strings are available in Supplementary File 1. This search adhered to PRISMA 2020 guidelines (Jackson et al., 2024).

2.2. Inclusion and exclusion criteria

We included studies conducted on bismuth-based nanoparticles for increased radio-sensitivity in radiotherapy. Eligibility criteria were developed following recommendations for systematic reviews of preclinical studies (Hooijmans et al., 2014). Systematic reviews, meta-analyses, case reports, case series, review (narrative) pieces, and editorial studies were not excluded. Also, the studies did not have sufficient information; duplicate studies reported the same results; and studies with 50 % similar data from a single center. A more detailed description is provided in the table below (Table 1).

1. Reviewing process

Two raters (AT and MA) independently reviewed the studies. Any discrepancy was resolved after discussing the issue with the third author (AA) in accordance with best practices outlined by PRISMA and similar preclinical systematic reviews (Hooijmans et al., 2014). The full texts of all eligible articles were saved and evaluated. The full text of all included studies was available in open access, and in cases where only the abstract was available, the article was not included.

2.3. Data extraction

Two independent reviewers (AT and MA) extracted data from the selected studies, including (1) the first name of the author; (2) the type of study; (3) the year of publication; (4) the dose enhancement factor; (5) type of nanoparticle; (6) size; and (7) concentration. Data were extracted using a predefined template, consistent with methodologies reported in comparable nanoparticle meta-analyses (Taha et al., 2024) by two independent researchers, and any disagreement between the reviewers was resolved through discussion. All articles were collected and uploaded to EndNote and duplicated studies were checked and eliminated.

2.4. Statistical analysis

A single-group meta-analysis was conducted in this study. With a 95 % CI, the pooled mean DEF values and 95 % confidence intervals were estimated using a random-effects model (DerSimonian–Laird) (DerSimonian and Laird, 1986). Additional analyses were done using subgroup analyses based on concentration and size category. The statistical significance level was set at $p < 0.05$ and heterogeneity was calculated using the I^2 test. Between-study heterogeneity was assessed using Cochran's Q, I^2, and τ^2 statistics (Higgins and Thompson, 2002). To identify potential sources of heterogeneity, a sensitivity analysis

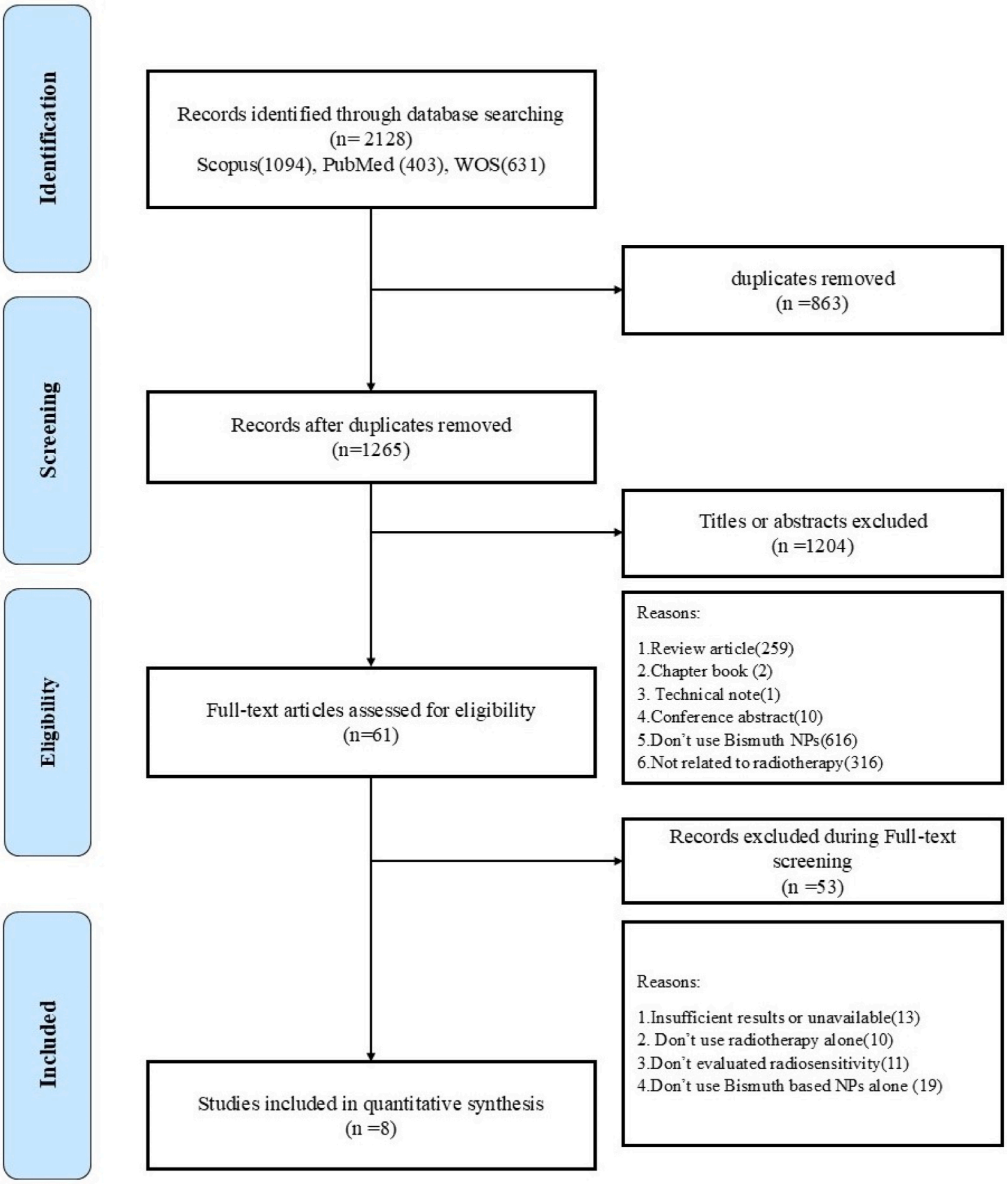

Fig. 1. Flowchart of the selection of studies.

using the leave-one-out meta-analysis was done following standard recommendations. Prediction intervals were calculated to reflect the expected range of effects in new studies (Tendal et al., 2009). Publication bias was investigated using a funnel plot, which shows asymmetry in the distribution of studies and Egger's regression test, which shows the presence of asymmetric funnel plots and publication bias (Higgins et al., 2011; Egger et al., 1997). All statistical analyses were performed in STATA version 17 (StataCorp LP, College Station, TX).

3. Result

3.1. Study selection

In total, 8 primary studies were applied to estimate the pooled effect size of the dose enhancement factor in the size and concentration in this meta-analysis.

3.2. Study characteristics

The majority of existing research in this domain has been structured around the utilization of bismuth compounds, predominantly bismuth oxide (Bi_2O_3). A significant proportion of these studies have employed a pegylated coating on the Bi NPs, which aims to enhance biocompatibility and improve circulation time within biological systems. Despite this, relatively few investigations have incorporated targeted ligands to facilitate specific binding to intended cellular or molecular targets. The concentration of the nanoparticle was 50–200 mg/mL. The size of the nanoparticle was 5–90 nm. Furthermore, the application and evaluation of these bismuth-based formulations have primarily been conducted on breast and uterine cancer cell lines, highlighting a focus on gynecological and breast malignancies. Notably, the dose escalation factors used across these studies have demonstrated considerable variability; in some cases, the escalation has been minimal, whereas other studies have reported nearly threefold increases in DEF, resulting in markedly different levels of efficacy. This variability underscores the need for standardized dose escalation protocols and comprehensive comparative analyses to

Table 1
Inclusion and exclusion criteria based on the PICOS framework.

	Inclusion criteria	Exclusion criteria
Population (P)	Studies involving cancer cells, animal models undergoing radiotherapy	Studies not related to cancer treatment or radiotherapy.
Intervention (I)	Use of bismuth-based nanoparticles as a radiosensitizing agent	Studies using nanoparticles not based on bismuth
Comparator (C)	Presence of a control or comparison group (e.g., radiation alone)	Studies lacking a proper control/comparison group
Outcome (O)	• Studies reporting quantitative outcomes (e.g., DEF,SER, tumor size, survival)	Studies without extractable or relevant outcome data
Study Design (S)	• In vitro, and in vivo studies	Review, editorials, commentaries, letters to the editor, case series, case reports, conference abstract and preprint articles without full text

optimize therapeutic outcomes and maximize the potential of bismuth-based nanocarriers or agents. The photon dose administered across different studies varied, with reported values ranging from 6 eV to 6 MeV. Table 2 summarizes the key methodological features of the included studies. It provides details on the test protocol, including cell lines, nanoparticle size and concentration, radiation energy and dose, and the assay methods used to measure radiosensitivity. It also assesses the diversity of methods used across studies and the potential impact of these differences on the observed dose enhancement factors (DEF).

3.3. *dose enhancement factor*

The pooled mean of DEF is 1.47(126–1.67) in included studies. The forest plot for the mean of DEF with a 95 % CI is presented in Fig. 2. An I^2 of 92.1 % ($p < 0.001$) indicated statistically significant heterogeneity.

3.4. *Sub group analysis on the dose enhancement factor*

The mean of DEF for concentration< 50 and concentration > =50 was 1.41 and 1.47 respectively (Fig. 3). The P-value= 0.74 indicates that there is no statistical difference between these two groups for DEF. The mean of DEF for size< 10 and size > 10 was 1.21 and 1.51 respectively (P-value=0.02). The mean of DEF in these two groups is statistically different (Fig. 4). It seems that the size > 10 group has higher DEF than the size< 10 group.

3.5. *Sensitivity analysis and publication bias*

To find sources of heterogeneity, sensitivity analysis was performed using a one-by-one deletion meta-analysis. The findings show that the deletion of studies individually did not significantly affect the pooled precision (Supplementary file 2, Figure S1). The funnel plot was visually assessed to assess the potential for publication bias in the studies included in this analysis. In addition, the Egger test was performed to provide a statistical assessment of the asymmetry of the funnel plot, and a p-value of 0.07 was obtained. Based on the visual inspection of the funnel plot and the results of the Egger test, there was no strong evidence of significant publication bias in the included studies that examined DEF (as shown in Fig. 5). The p-value obtained from the Egger test did not reach the conventional significance level of 0.05, supporting the conclusion that publication bias is not a significant concern in this setting.

4. Discussion

In the present meta-analysis, 8 studies without publication bias on the effect of the size and concentration of bismuth nanoparticles on radio-sensitivity and increasing the effectiveness of radiation therapy were statistically analyzed. In general, bismuth sensitization in radiotherapy is a field of research that includes the use of bismuth oxide nanoparticles (Bi_2O_3) to increase the effectiveness of radiation therapy in cancer treatment. Bismuth oxide nanoparticles have a significant radio-sensitizing effect due to the optimal physio-biochemical effect.

Table 2
Characteristics of the included studies.

Author (year)	NP Based	Targeted Agents	Coating	Size(nm)	Concentration(μg/mL)	Cell line	DEF	Dose Of Photon (Gy)
Nosrati (2019)	Bi_2S_3	Yes	BSA	8 ± 2	50	4T1	1.27 ± 0.05	6 Gy
							1.15 ± 0.04	2 Gy
Du (2017)	$\mathbf{Bi_2O_3}$	Yes	PEG	45.4 ± 0.6	200	SMMC−7721	1.25 ± 0.05	6 Gy
Stewart (2016)	$\mathbf{Bi_2O_3}$	No	PEG	48.7 ± 5.4	50	L9-SARCOMA	1.48 ± 0.67	0.125 Gy
							1.25 ± 0.44	10 Gy
Alqathami(2016) A1	$\mathbf{Bi_2O_3}$	No	PEG	50 ± 1.2	50	No	1.9 ± 0.13	100kv
Alqathami(2016) A2				5 ± 0.3	25	NO	1.38 ± 0.8	100 kv
Abidin(2019) A1	$\mathbf{Bi_2O_3}$	No	PEG	60 ± 3.4	50	MCF7	1.12 ± 0.21	6ev
Abidin(2019) A2							1.15 ± 0.22	10ev
Abidin(2019) A3				60 ± 3.4	50	MCF7	1.13 ± 0.21	6 MeV
Abidin(2019) A4					5	MCF7	1.06 ± 0.12	12Mev
Abidin(2019) A5				70 ± 2.5	5	MCF7	1.38 ± 0.32	6Mev
Abidin(2019) A6				80 ± 3.4	5	MCF7	2.2 ± 0.45	6Mev
Abidin(2019) A7				90 ± 5.4	5	MCF7	2.83 ± 0.87	6Mev
Abidin2(2019) B1	$\mathbf{Bi_2O_3}$	NA	NA	70 ± 2.2	50	HeLa Cells	1.38 ± 0.2	6 Gy
Abidin2(2019) B2		NA	NA	80 ± 2.3	50	HeLa Cells	2.2 ± 0.21	6 Gy
Abidin2(2019) B3		NA	NA	90 ± 2.6	50	HeLa Cells	2.83 ± 0.22	6 Gy
Sisin(2019)	$\mathbf{Bi_2O_3}$	NO	PEG	60 ± 2.3	50	MCF7	1.06 ± 0.23	0.38 MeV
Jamil(2021) A11	$\mathbf{Bi_2O_3}$	NA	Carbon	60 ± 3.4	5	MCF7	2.6 ± 0.8	6 MeV
Jamil(2021) A22				70 ± 3.6			1.6 ± 0.9	6 MeV
Jamil(2021) A33				80 ± 3.8			1.5 ± 0.1	6 MeV
Jamil(2021) A44				90 ± 4			1.7 ± 0.2	6 MeV
Jamil(2021) A1				60 ± 3.4			1.8 ± 0.8	6 MeV
Jamil(2021) A2				70 ± 3.6			1.7 ± 0.9	6 MeV
Jamil(2021) A3				80 ± 3.8			1 ± 0.1	6 MeV
Jamil(2021) A4				90 ± 4			1 ± 0.2	6 MeV

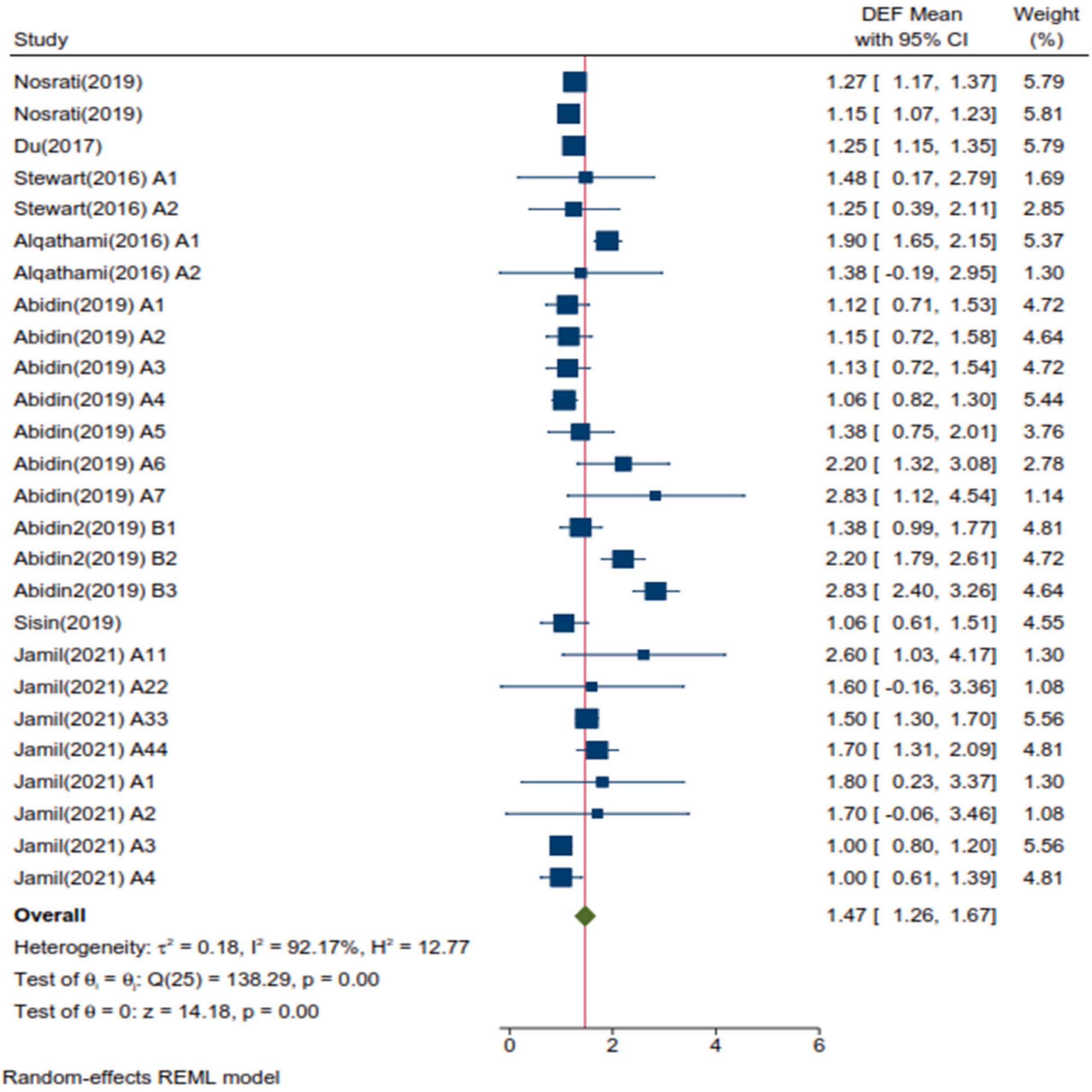

Fig. 2. Forest plot of the pooled mean DEF.

Bismuth is a heavy metal, so it has side effects such as brain toxicity, kidney toxicity, and neurological problems. However, the toxicity effect of bismuth is not clear and needs further investigation to validate these findings *in vivo* and in clinical settings (Jamil et al., 2021a). Bismuth oxide nanoparticles are efficient radio-sensitizers on highly radio-resistant cancer cells (Ganapathy et al., 2022b). Radiation therapy is generally combined with chemotherapy to improve therapeutic efficacy in cancer treatment. Bismuth nanoparticles are considered promising materials for cancer treatments such as radioimmunotherapy, chemotherapy, thermochemotherapy, and thermoradiation, due to their enhanced suppression of cancer cells compared to existing monotherapies. High radiation energy not only damages cancer cells but also neighboring healthy cells and tissues, causing several complications. Therefore, nanoparticles have radio-sensitizing properties and may target the DNA of cancer cells, leaving healthy cells undamaged (Bartoli et al., 2020). Bismuth oxide nanoparticles have been found to have a dose enhancement factor (DEF) through photon and electron beams concerning cancer cell death, and ultra-small Bi_2O_3 nanoparticles regulate efficient radiation therapy. Bismuth nanorods containing ultra-small nanoparticles enhance the DEF, leading to a potential reduction of cancer cells and an explanation for effective radiotherapy (Nezhad et al., 2020). The clinical benefit of radiosensitization with Bi-NPs lies in their ability to enhance local tumor control while potentially reducing the required radiation dose, thereby minimizing collateral toxicity to surrounding normal tissues. Mechanistically, Bi-NPs exert radiosensitizing effects primarily through their high atomic number (Z = 83), which increases photoelectric absorption and augments the production of secondary electrons and reactive oxygen species (ROS) upon irradiation. This enhances DNA double-strand breaks, a critical lesion for cancer cell death. Comparative studies highlight both the advantages and limitations of Bi-NPs versus alternative nanoparticle-based radiosensitizers. For example, $MnZr(PO_4)_2$ materials have been recently reported as promising γ-ray dosimeters and modifiers of radiation response, but their biocompatibility and long-term biodistribution remain underexplored (PrakashBabu et al., 2025). AuNPs share similar high-Z–based radiosensitization but face issues of cost and long systemic retention. In contrast, Bi-NPs are relatively inexpensive, exhibit strong X-ray attenuation, and can be functionalized for targeted

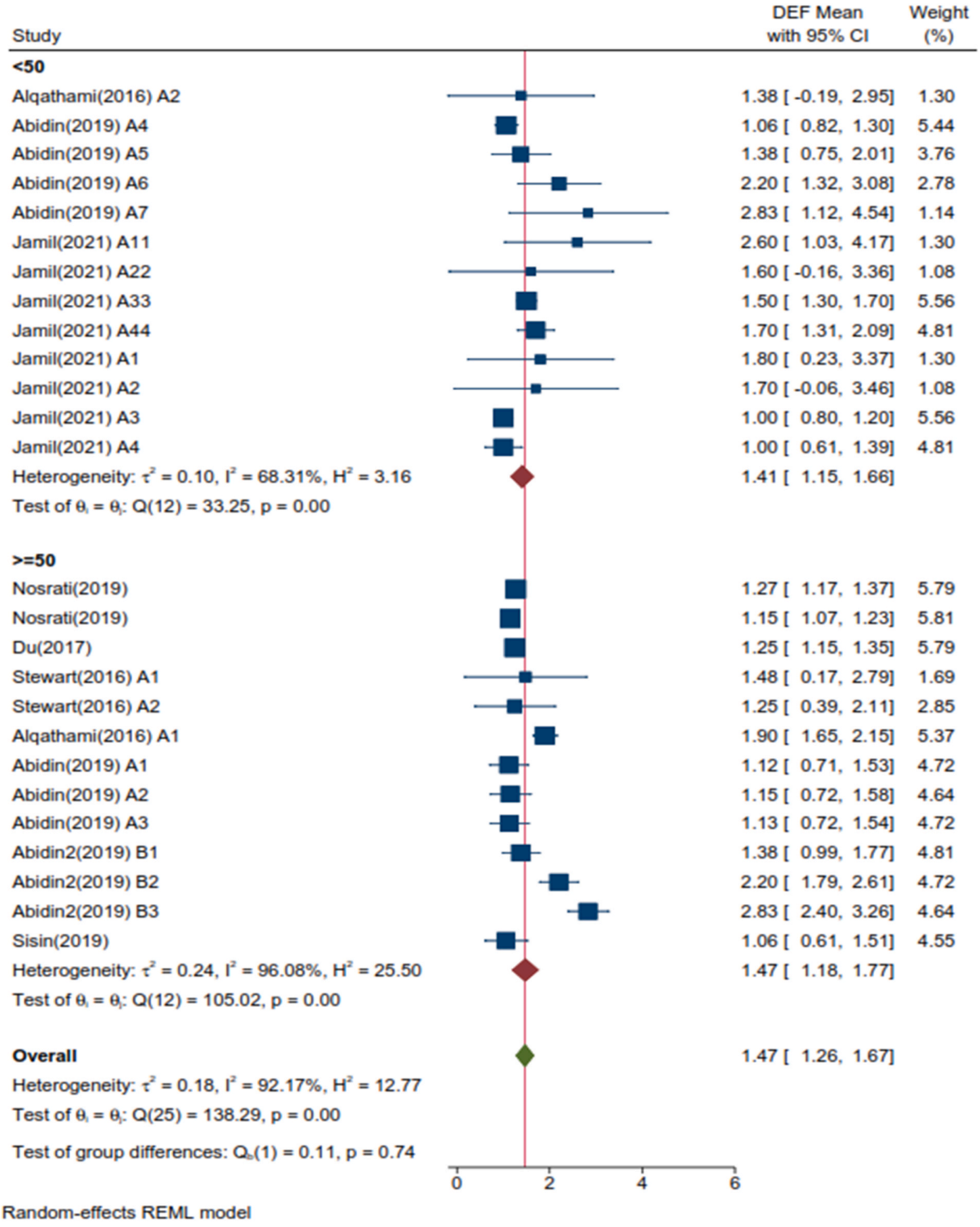

Fig. 3. Forest plot for DEF for in subgroup analysis based on the concentration.

delivery, though they still require extensive toxicological profiling. At the molecular level, radiosensitization by NPs is not limited to physical dose deposition. Recent work on DNA repair pathways demonstrates that ionizing radiation triggers both p53-dependent and p53-independent responses. Notably, the KIN17 gene has emerged as a nuclear DNA-binding protein that is rapidly induced after ionizing and UV radiation, playing a role in replication and repair (Masson et al., 2003).Importantly, KIN17 activation requires intact global genome repair (GGR) machinery, particularly XPA/XPC proteins, independent of p53. This suggests that nanoparticle-mediated radiosensitization may synergize with stress-induced signaling pathways that amplify replication stress, disrupt DNA repair checkpoint fidelity, and push tumor cells toward apoptosis or mitotic catastrophe. Furthermore, the Bi-NPs can amplify genotoxic stress not only through ROS-mediated DNA damage but also by perturbing the balance of DNA damage signaling, possibly enhancing KIN17-related checkpoint responses. This could result in

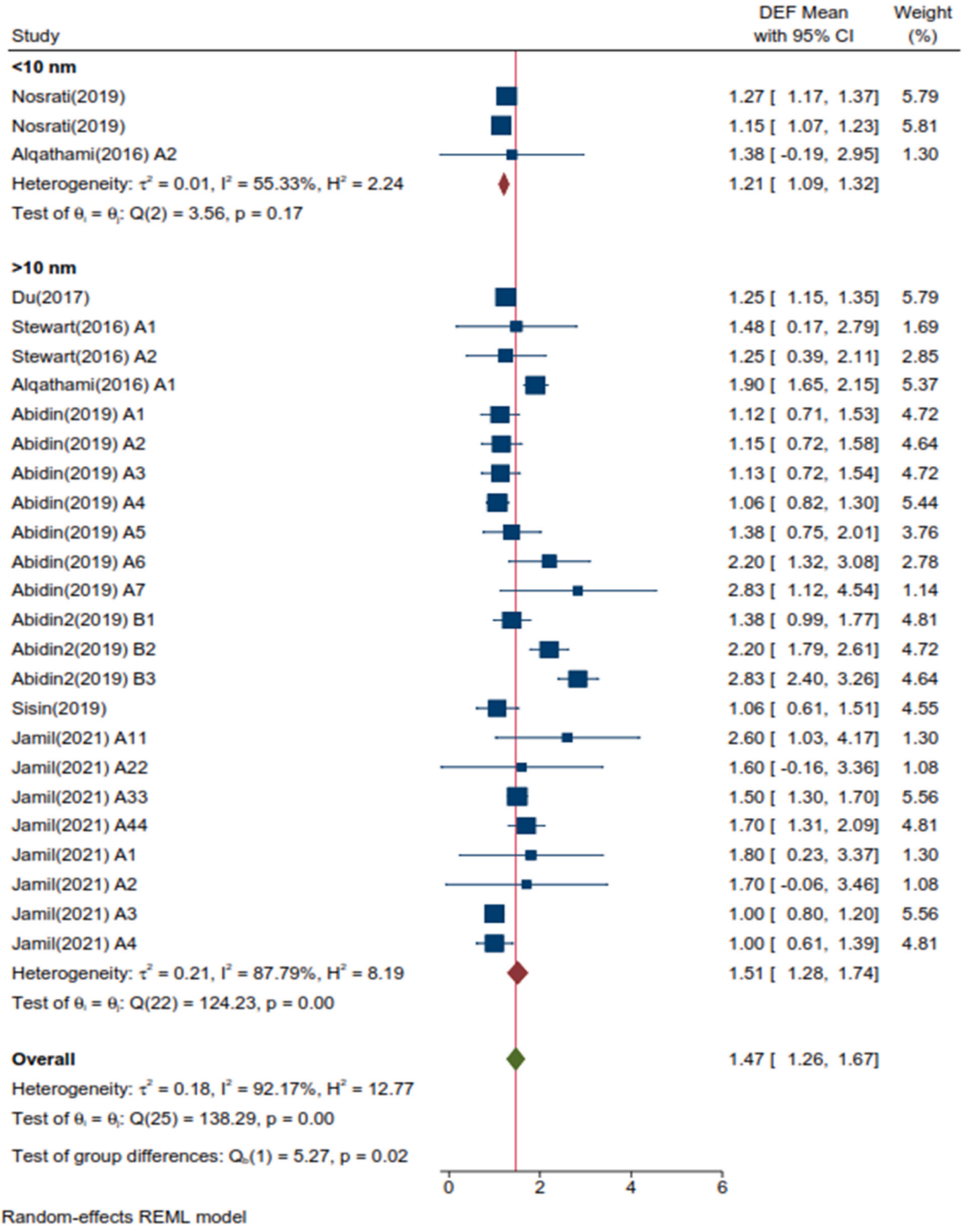

Fig. 4. Forest plot for DEF for in subgroup analysis based on the size.

increased G₂/M arrest, replication fork stalling, and apoptosis in tumor cells with compromised repair machinery, while sparing normal tissues with intact checkpoints. Bi-NPs offer strong radiosensitization, imaging compatibility, and potential for targeted delivery, while their main limitation is the uncertain long-term safety and clearance. Compared with other nanomaterials, they provide a practical balance of efficacy, though further studies on DNA repair pathways, including KIN17 signaling, are needed to fully elucidate their mechanisms (Masson et al., 2001).

However, the toxic and metabolic aspects of Bi compounds are not clear and require further research. Predicting the effect of radiosensitivity with different types of cancer cells such as human squamous cell carcinoma (A431), lung cancer cells (A549), cervical cancer cells (HeLa), and prostate cancer cells (DU145) to analyze the tolerable

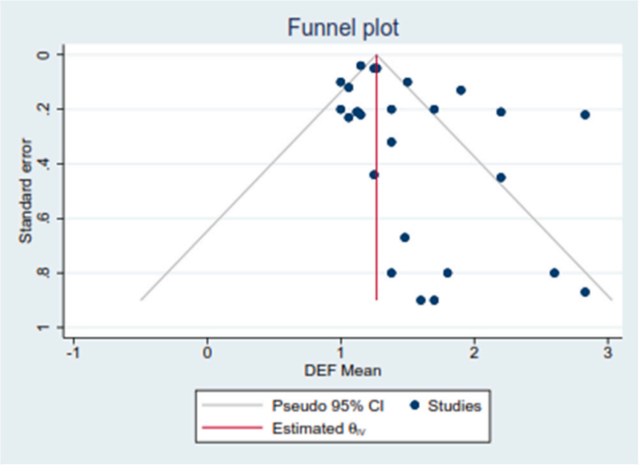

Fig. 5. Funnel plot for DEF for all 11 studies.

characteristics of complications in multiple studies was reviewed (Ganapathy et al., 2022b). A study aimed to investigate the effect of bismuth oxide nanorod sizes (Bi_2O_3-Nr) on radiation sensitization effects on MCF-7 and HeLa cell lines for megavoltage photon and electron beam radiation therapy showed that Bi_2O_3 nanorods in different sizes (60, 70, 80, and 90 nm) had a significant sensitizing effect on cells (Jamil et al., 2021b). This study used a clonogenic method to measure the ratio of increased sensitivity (Jamil et al., 2021b). To increase the effectiveness of synergistic chemoradiation therapy, another study created a suitable radiosensitizer nano-active coordination platform (NP@PVP) using bismuth nitrate and cisplatin prodrug. When a tumor cell internalizes NP@PVP, cisplatin in NP@PVP can prevent DNA damage repair through spatiotemporal coordination, whereas bismuth in NP@PVP can sensitize to radiation therapy (RT) by enhancing DNA damage following X-ray irradiation by boosting the generation of reactive oxygen species. When compared to cisplatin (DEF of 1.78), NP@PVP demonstrated a greater tumor ablation capability and a larger dosage enhancement factor (DEF of 2.29) (Ma et al., 2021). The effect of bismuth nanoparticle size on dose enhancement factor (DEF) in radiotherapy has been the subject of several studies (Nezhad et al., 2020, 2022; Jamil et al., 2021b; Ma et al., 2021; Sisin et al., 2020; Farahani et al., 2020). DEF refers to the extent to which high-Z nanoparticles (NPs) can exacerbate biological damage by inducing a dose-escalation effect in radiotherapy cancer treatment. In a study, it has been shown that the use of bismuth oxide nanoparticles (BiONPs) as a radiation sensitizer increases the effectiveness of brachytherapy (^{192}Ir source) on cervical cancer cells. In this investigation, DEF was measured against different sizes and concentrations of BiONPs. After irradiation with radiation doses from 0 to 4 Gy, cell survival was measured by the clonogenic method and presented in survival curves using the LQ model. The results showed the dependence of DEF on the size and concentration of nanoparticles. The optimal size of BiONPs is 80 nm with a concentration of 0.00025 mM, where the DEF factor was 1.88 (Sisin et al., 2020). Another study demonstrated that BiNPs are desirable options for radiation dose enhancement due to their larger atomic numbers, low cost, excellent biocompatibility, and high biodegradability (Farahani et al., 2020). The objective of this study was to measure the DEFs from BiNPs at clinically relevant energies in comparison to AuNPs. Using nPAG polymer gel impregnated with 0.2 mM (0.04 mg/mL tissue) AuNPs and BiNPs independently, the researchers were able to objectively track the three-dimensional distribution of acquired dose. The samples were exposed to internal sources of iridium-192 (380 kV) and external cobalt-60 (1.25 mV) to investigate the effect of energy. Following irradiation with an iridium-192 source, AuNPs and BiNPs had an average dosage increase of 14.72 ± 0.34 and 16.35 ± 0.38 %, respectively. In contrast, these values dropped to less than 4 % for samples exposed to cobalt-60 γ-ray radiation. Researchers came to the conclusion that iridium-192 brachytherapy augmented by BiNPs might be a promising therapeutic approach to increase the effectiveness of cancer radiation therapy (Farahani et al., 2020). Another study investigated the effect of increasing the dose of synthesized spherical Bi_2O_3 nanoparticles in 6 MV external radiotherapy. Bi_2O_3 was synthesized and a GENIPIN gel dosimeter was produced (Nezhad et al., 2020). Synthesized spherical Bi_2O_3 nanoparticles were also investigated in external radiation therapy and the results showed that the impact of increasing the dose of nanoparticles depends on the radiation energy, type of NPs, size of NPs, concentration of NPs, cell lines, and delivery system of NPs (Nezhad et al., 2020). Monte Carlo simulation results of increasing the dose of 100 nm and 50 nm bismuth-based nanoparticles in ^{125}I and ^{169}Yb brachytherapy sources were reported in another study. DEF was determined for bismuth at the same higher concentration than gold (Au) (Rajaee et al., 2019). Additionally, bismuth ferrite nanoparticles (BFO, $BiFeO_3$) were examined as a novel multifunctional theranostic agent for radiotherapy, computed tomography (CT), and magnetic resonance imaging (MRI) as well as a mediator of magnetic hyperthermia in a different study conducted by Rajaee et al. in 2018. The characteristic of increasing the dose of BFO nanoparticles was examined using gel dosimetry, clonogenic, and cck8 assays after the biocompatibility of the particles, which were created using the traditional sol-gel process, was assessed. The dosage enhancement factor (DEF), as determined by the clonogenic technique, was 1.35 for concentrations of 0.05 mg/mL and 1.76 for doses of 0.1 mg/mL. Overall, the study's findings demonstrated that multifunctional BFO nanoparticles can be employed as a radiothermotherapy and multimodal imaging agent to improve theranostic efficacy (Rajaee et al., 2018). Also, in another study, Wang et al., 2019 created a Schottky-type heterogeneous structure of Au-Bi_2S_3 with a size of 34.5 nm with a promising ability to generate active free radicals under X-ray irradiation to selectively increase the effectiveness of radiotherapy with intracellular H_2O_2 catalysis in tumors. On the one hand, this structure, like many other nanomaterials with high Z-rich elements, Au-Bi_2S_3 can store a higher radiation dose in the form of high-energy electrons inside tumors. Furthermore, even in hypoxic environments, Au-Bi_2S_3 can greatly enhance the usage of a large number of low-energy X-ray-induced electrons during radiation therapy to produce free radicals that are not dependent on oxygen (Wang et al., 2019). As a result of this study, the researchers found that this type of nanoparticle provides an idea for the development of Schottky-type heterostructures with a rational design as an efficient radiation sensitizer for advanced cancer radiation therapy.

In this meta-analysis, the included studies that investigated bismuth nanoparticles and the radiation sensitization effect were examined in terms of the size of bismuth nanoparticles and their concentration. The analysis revealed that the average dose enhancement factor (DEF) did not significantly differ between groups with bismuth concentrations below 50 and those with concentrations of 50 or higher (1.41 vs. 1.47; $p > 0.05$), suggesting that increasing bismuth content beyond the 50 threshold does not confer additional therapeutic benefit against tumor cells. Conversely, tumor size appeared to have a more pronounced impact on DEF; the mean DEF for tumors smaller than 10 mm was 1.21, whereas for tumors larger than 10 mm, it was 1.51, with this difference reaching statistical significance ($P = 0.02$). Although nanoparticle size significantly influenced DEF values, the results indicated that particles exceeding 10 nm produced a notably higher DEF compared to those smaller than 10 nm. More precisely, the biological mechanisms underlying the observed size- and concentration-dependent effects can be described as follows. The dose enhancement factor (DEF) is attributed to the increase in the photoelectric absorption cross section, approximately proportional to Z^3 and inversely proportional to photon energy^3, with bismuth having an atomic number of 83. Larger nanoparticles, containing more bismuth atoms, produce more low-energy secondary electrons (Auger electrons and photoelectrons) upon irradiation. These short-ranged electrons (~nanometers) cause localized ionization and

DNA damage in tumor cells. Moreover, larger nanoparticles may exhibit improved cellular uptake and retention, increasing intracellular concentration and radiosensitization. However, increasing bismuth concentration beyond a threshold does not further improve DEF, potentially due to biological saturation. At high concentrations, aggregation may reduce surface area, bioavailability, and cellular internalization. Suboptimal doses can also induce radiation-independent cytotoxicity or oxidative stress, stimulating cellular defense mechanisms that counteract radiosensitization. These saturation and toxicity thresholds highlight the need to optimize nanoparticle size and concentration for maximal radiosensitization and minimal adverse effects. These findings imply that optimizing nanoparticle size may be crucial for enhancing therapeutic efficacy, whereas simply increasing bismuth concentration beyond a certain point may offer limited additional benefit.

It is important to recognize that the efficacy of increasing DEF is influenced by multiple factors, including nanoparticle size and concentration, the type of radiation employed, and the specific characteristics of the targeted cancer cell line. These variables represent some of the inherent challenges and limitations of the present study. Consequently, further research is warranted to systematically assess and identify the optimal nanoparticle size and concentration that can maximize the dose enhancement factor (DEF) across various cancer models. Such studies are essential to ensure the effective translation of these findings into clinical applications.

This study has several limitations. First, this meta-analysis is limited by the small number of studies ($n = 8$), which reduces statistical power and precision. Significant heterogeneity ($I^2 = 92.1$ %) likely resulted from variations in tumor models, assay methods, nanoparticle characteristics, and radiation protocols. Although we addressed this variability using a random-effects model, subgroup and sensitivity analyses, and a summary of methodological features, the pooled results should be interpreted cautiously. Larger, standardized preclinical studies are necessary to validate the observed radiosensitizing effects of bismuth-based nanoparticles. Second, although this meta-analysis shows that bismuth-based NPs consistently increase dose-escalation in preclinical models, caution is warranted when extrapolating these findings to human patients. Biological barriers such as biodistribution, clearance, systemic toxicity, and tumor microenvironment heterogeneity may alter their radiosensitizing efficacy in clinical settings. Therefore, rigorous *in vivo* validation and, ultimately, clinical trials are necessary to establish safety, optimal dosing, and therapeutic benefits in humans.

5. Conclusion

In summary, the data indicate that increasing bismuth concentration beyond a threshold of 50 does not confer additional gains in radiosensitization efficacy. In contrast, nanoparticle size emerges as a critical determinant of therapeutic performance, with particles exceeding 10 nm associated with significantly enhanced dose enhancement factors. These findings underscore the imperative of carefully calibrating nanoparticle dimensions to optimize their radiosensitizing potential, thereby advancing the development of more effective nanoparticle-mediated radiotherapy strategies. Future investigations should focus on refining nanoparticle parameters to maximize treatment outcomes across diverse oncological contexts. Furthermore, our findings indicate that bismuth-based NPs amplify radiation effects in preclinical models, supporting their potential as effective radiosensitizers. However, translating these results to humans will require additional research through rigorously designed *in vivo* experiments and early-phase clinical trials.

CRediT authorship contribution statement

Azadeh Amraee: Methodology, Investigation, Data curation. **Leili Darvish:** Methodology, Investigation, Formal analysis. **Masoud Amanzadeh:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Ali Tarighatnia:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ayuob Aghanejad:** Writing – review & editing, Supervision, Conceptualization. **Morteza Ghojazadeh:** Methodology, Formal analysis.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.compbiolchem.2025.108767.

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