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Meta-analysis of Radio Sensitivity Enhancement by Gold Nanoparticles in Tumor-Bearing Mice

Running title: Nanoparticles utilization for radio-sensitivity enhancement in tumor model: Meta-analysis.

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Abstract

Gold nanoparticles (Au NPs) have been extensively studied as radio-sensitizers due to their significant photoelectric absorption coefficient, compact size, and excellent biocompatibility. Although several research evaluated the role of Au NPs in radio sensitization, most of them were *in vitro*. At the same time, only a small number of studies analyzed this role at the *in vivo* level. This study aims to address the improvement of radio-sensitization by Au NPs in tumor-bearing mice by meta-analysis. The Cochrane Library, Science Direct, Medline, and PubMed were used in this study. Thirty-six relevant studies investigated the efficacy of Au NPs as radio-sensitizers. Out of these studies, thirty-three studies were excluded; only three studies were eligible for analysis. This study was performed on only three articles that were eligible containing eleven trial comparisons and 189 mice. For the 189 mice that were used in three experiments, statistics on overall survival were available for 89 animals in the treatment group (radiation therapy with Au NPs) and 100 mice in the control group (radiation therapy alone). The pooled odds ratio (ORs) comparing experimental with control in the pooled study was 3.38 (95 percent CI, 1.74-6.56; P=0.0003). This finding demonstrates a correlation between increased survival rates and the use of Au NPs in radiotherapy. This study showed that Au NPs considerably impact on radio-sensitization and radiation therapy effectiveness in tumor-bearing mice.

Keywords: Enhancement, Radio sensitivity, gold nanoparticles, Tumor-bearing mice, Meta-analysis

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Introduction

Nanotechnology has advanced in the biomedical field and nanomaterials have been widely used in the field of oncology (1). One of the crucial methods for treating cancer is radiotherapy. The use of megavolt (6-25MV) X-rays to avoid skin injury, tomotherapy, and intensity-modulated radiation therapy (IMRT) for a more advantageous concentration of the dosage inside the tumor. Despite the important role radiation therapy plays in the treatment of cancer patients, resistance is still a major problem (2).

Among nanoparticles, gold nanoparticles (AuNPs) attract much attention due to their usability, high performance in imaging techniques, easy modification with ligands detected via cancer cell surface receptors, and increased uptake through receptor-mediated endocytosis (3). Numerous studies have demonstrated that the delivery of AuNPs to tumor tissues can selectively increase radiation therapy effectiveness, resulting in differentially increased tumor cell death (4). Despite these advancements, radiation may still fall short of eliminating malignancies that contain radio-resistant malignant cells and lead to radiotoxic effects on normal tissues (5,6). Higher photon absorption of high-Z elements and the subsequent transmission of a greater proportion of primary ionizing photon energy to the tumor tissue are the main causes of radio-sensitization (7,8).

The underlying reason for AuNPs acting as radio-sensitizers in cancer treatment is due to their significant photoelectric absorption coefficient. Double-strand breaks (DSBs) in the DNA play a vital role in how cancer cells react to radiation (9,10). The AuNPs' anti-tumor properties have generally been linked to their ability to induce apoptosis, affect membrane fluidity, and activate oxidative stress (11).

Methodology

Meta-analysis: search strategy

Between 1999 and 2021, Medline, Cochrane Library, Science Direct, and PubMed were used for searching articles about the use of Au NPs as radiosensitizers in cancer treatment. Only searches conducted in English were permitted. The same retrieval approach was used by two reviewers to independently search the literature, evaluate returned titles and abstracts, and download potentially pertinent items for additional evaluation. The following keyword phrase was used by the researchers: radiation therapy, radio-sensitization, and radiation-sensitizing agents. To reduce publication bias, other publications in the retrieved studies were used in reference lists.

In this search strategy, the following requirements were considered eligible:

a. Studies that provided odds ratio/relative risk values for survival rates and a 95% confidence interval; otherwise, data could be transformed into relative risk values and a 95% confidence interval.

b. Research using Au NPs as radio-sensitizers in radiation therapy.

c. Studies carried out on mice (*in vivo* studies).

d. Research that compared two groups: one that received radiation therapy along with Au NPs and the other that received radiation therapy alone. Studies without control groups, those whose abstracts or final reports were unavailable, were also omitted.

Data extraction and outcomes

From the original article's journal name and year of publication, both researchers independently extracted the following data: sample size, information about the animals and tumor cell lines, total number of mice in the treatment group, and total number of mice in the control group, radiation dose, size of the AuNPs, and survival statistics for the treatment and control groups.

Data analysis and statistical method

The effect of the survival rate was examined using the relative risk (RR), which was determined using the Mantel-Haenszel method. Data were obtained and summarized using relative risks with 95% confidence intervals (CIs) by the Review Manager Software version 5.2. The P values less than or equal

to 0.05 were evaluated as statistically significant. The heterogeneity during the meta-analysis of this study with the chi-squared test was reported by calculating the value of I-squared. The P < 0.1 was considered statistically significant. If I2> 56%, it prompts a significant heterogeneity, and trials were pooled using the random effects model; if I2< 31%, it indicates an insignificant heterogeneity, and trials were pooled using the fixed effects model. Potential publication bias was assessed by the Begg test which was conducted by the Stata software version 10.0. Sensitivity analysis was also performed to assess the influence of each study on overall estimates by sequential removal of individual studies. Tau-squared expresses the estimate between-study variance and the smaller the value is the better the goodness of fit of the model becomes. All P values reported are two-sided.

Search Results

Thirty-six relevant studies investigating the effectiveness of AuNPs as radio-sensitizers for radiotherapy were yielded. Out of these studies, thirty-three studies were excluded; only three studies were eligible for analysis. Different reasons were considered for exclusion such as some studies contained only limited data, and other studies did not mention the overall survival either in the treatment or the control group. Therefore, this study was performed on only three articles that were eligible containing eleven trial comparisons and 189 mice.

Results

According to the search on different web engines including the Cochrane Library, Science Direct, Medline, and PubMed. The results showed that there were 36 previous research that investigated the efficacy of AuNPs as radio-sensitizers for radiation therapy. Various criteria were taken into consideration for the elimination of research. For example, some studies had very little data, while others did not discuss the overall survival in the treatment or control groups. As shown in Figure 1, thirty-three of these studies were ineligible for this study after being excluded. Therefore, only three publications were eligible for this study (Figure 1).

The overall survival data were available for the 189 mice included in the eligible three studies. 89 mice in the treatment group (radiation therapy in combination with Au NPs) and 100 mice in the control group (radiation therapy alone) (treatment/control: 89/100). The pooled ORs compared with control were 3.38 (95% confidence intervals (CI), 1.74-6.56; P=0.0003). This result showed that the survival rate in the treatment group with AuNPs was higher than the control groups without AuNPs. The results extracted from the analysis showed an advantage when using AuNPs in addition to radiation therapy (Table 1). For the test of publication bias, we used Egger’s test. The results showed that there was no publication bias (Begg's Test: P=0.998; Egger's Test: P=0.639).

The sensitivity analysis was conducted to assess the influence of each study on the overall measures by sequential removal of individual studies. A sensitivity analysis was carried out in which one study was excluded at a time and the pooled risk ratios (RRs) were recalculated again for the rest of the studies to assess the stability of this meta-analysis. The pooled RR was similar before and after the elimination of each study and this shows the stability of the meta-analysis (Table 2 and Figures 2-4).

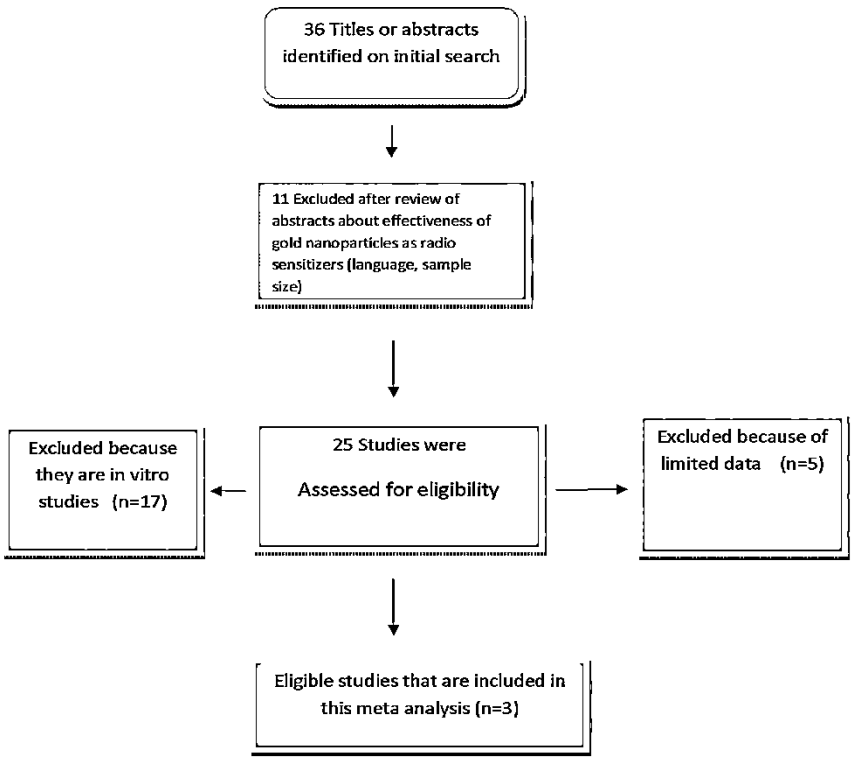

Figure 1. Flow diagram of the study selection process for this meta-analysis.

Taha et al., 2024. Figure 1

Table 1. Data extraction from previous studies on the effect of Au NPs as a radiosensitizer.

Author	Outcome
Hainfeld et al. (2004)	Irradiation only (26 Gy,250 kVp), producing 20% long-term (>1 year) survival (n = 15); gold only (1.35 g Au/kg, no irradiation), all died (n = 4); irradiation after i.v. injection of 1.35 g Au/kg gold nanoparticles, 50% long-term survival (n = 4); diamonds: irradiation after 2.7 g Au/kg injection, producing 86% long-term survival (n = 7)
Hainfeld et al. (2010)	Fraction surviving:30 Gy, 68 keV(−Gold) versus 30 Gy, 68 keV(+Gold):1/7 (14%)vs1/7 (14%);42 Gy, 68 keV(−Gold) versus 42 Gy, 68 keV(+Gold):3/12 (25%)vs8/12 (67%);44 Gy, 157 keV (−Gold) versus 44 Gy, 157 keV(+Gold):0/7 (0%)vs2/7 (29%);50.6 Gy, 157 keV(−gold) versus 50.6 Gy, 157 keV(+gold) :0/8 (0%)vs3/8 (38%);Radiation +heat+1 × 15 Gy(−gold vs+gold):1/10 (10%)vs1/9 (11%),Radiation +heat+1 × 23Gy(−gold vs+gold):3/7 (43%) vs3/6 (50%),Radiation +heat+2× 15Gy(−gold vs+gold):8/20 (40%)vs6/8 (75%),Radiation +heat+1× 30Gy(−gold vs+gold):7/7 (100%)vs11/14 (79%)
Al Zaki et al. (2014)	Only one mouse out of seven in the radiation-only group, with a slow growing palpable tumor, survived 90 days post-treatment. In contrast three of the seven mice that received GPNs prior to radiation survived 90 days post-therapy.GPNs were administered at a dose of 650 mg Au/kg. The radiation dose administered was 6 Gy at 150 kVp.

Table 2. Outcomes after eliminating each comparison at a time.

Comparison omitted	Heterogeneity of RRs			RRs (95% CI)	P#
	Chi^2	I-squared	P*		
1-J. F. Hainfeld-2004	8.54	0%	0.48	3.34(1.68-6.66)	0.0006
2-J. F. Hainfeld-2004	6.05	0%	0.74	2.78(1.38-5.62)	0.004
3-J. F. Hainfeld-2010	7.82	0%	0.55	3.61(1.83-7.16)	0. 0002
4-J. F. Hainfeld-2010	8.15	0%	0.52	3.08(1.51-6.30)	0. 002
5-J. F. Hainfeld-2010	8.39	0%	0.50	3.26(1.65-6.41)	0. 0006
6-J. F. Hainfeld-2010	8.06	0%	0.53	3.14(1.59-6.21)	0. 001
7J. F. Hainfeld-2010	7.92	0%	0.54	3.60(1.82-7.13)	0. 0002
8-J. F. Hainfeld-2010	7.69	0%	0.57	3.73(1.85-7.50)	0. 0002
9-J. F. Hainfeld-2010	8.48	0%	0.49	3.23(1.59-6.58)	0. 001
10-J. F. Hainfeld-2010	5.24	0%	0.81	4.36(2.12-8.98)	0. 0001
11-Ajlan Al Zaki2014	8.52	0%	0.48	3.31(1.67-6.57)	0. 0006

* P values (two-sided) were based on the Q test of heterogeneity. RRs: Risk ratios. CI: Confidence intervals.
# The fixed effects model was used.

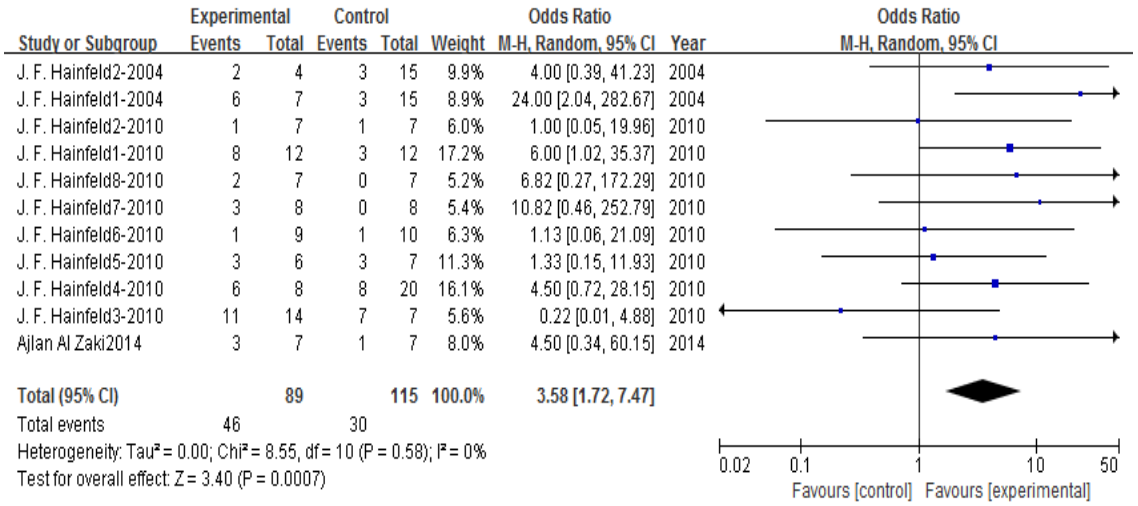

Figure 2. Forest plot showing the odd ratios (ORs) of overall survival comparing experimental to control group.

Taha et al., 2024. Figure 2

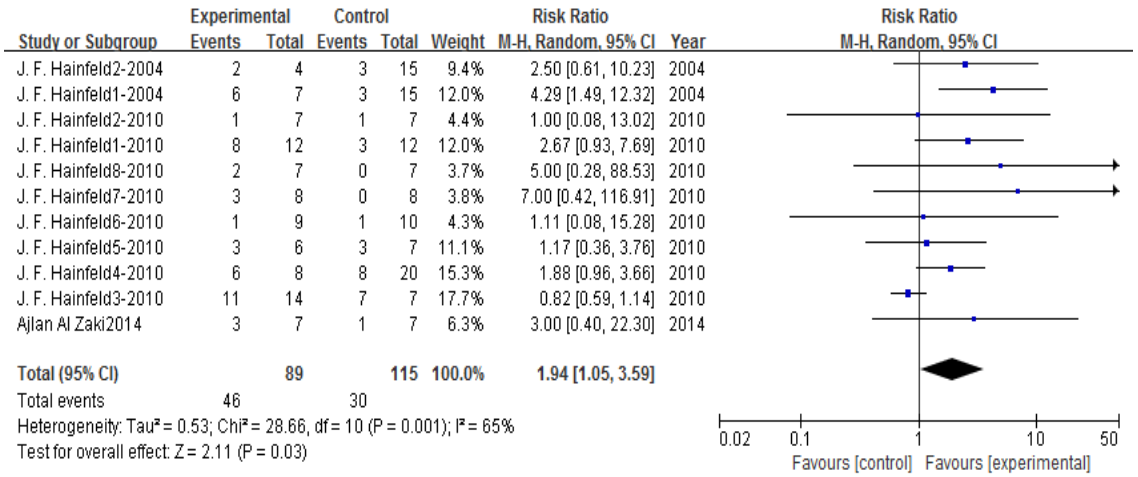

Figure 3. Forest plot of the survival comparing experimental to control groups regarding the relative risks (RRs).

Taha et al., 2024. Figure 3

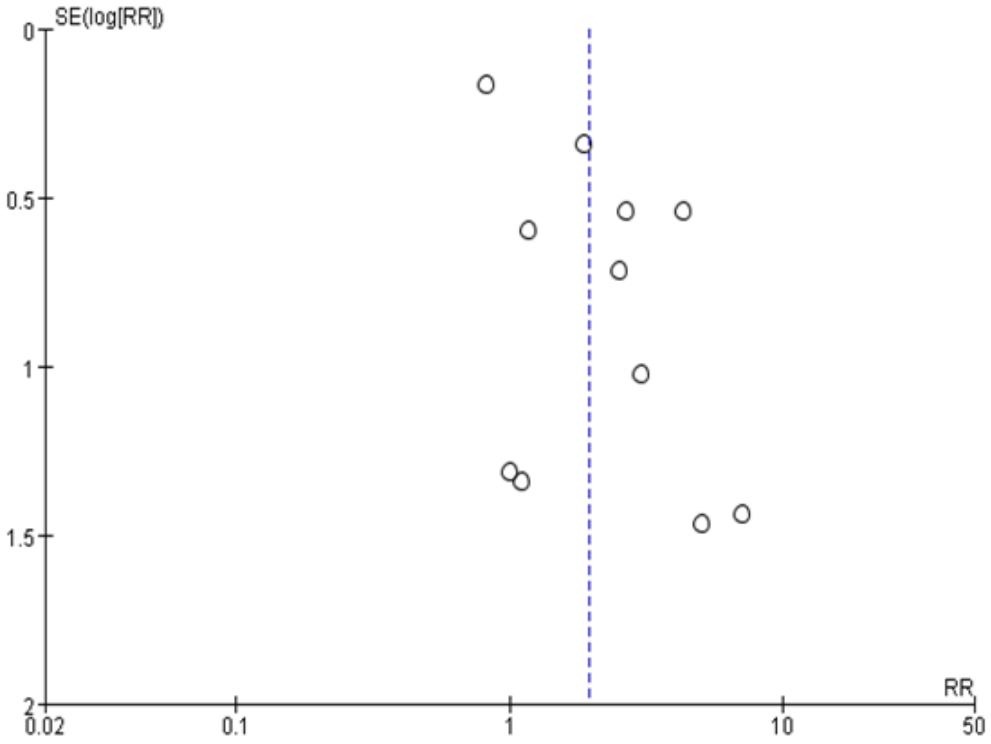

Figure 4 . Funnel plot of the survival regarding the relative risks (RRs).

Taha et al., 2024. Figure 4

Discussion

One of the most prominent areas of scientific study right now is nanotechnology, particularly regarding potential medicinal uses. Gold nanoparticles (AuNPs) have a wide range of drug and protein binding abilities and can biocompatibility target cancer cells aggressively (12,13). Although there is many research evaluating the role of gold nanoparticle radio sensitization, most of these studies assessed the usage of radiation enhancement at the level of in vitro while only a small number of studies analyzed this role at the *in vivo* level. Till now, no clinical studies have been conducted to address these experimental efforts (14-16). Most studies have concluded that radio-sensitization by Au NPs increases the photoelectric photon absorption by high-Z materials at kilovoltage photon energies (17-19).

Au NPs have been shown to increase radio-sensitization in *in-vivo* experiments, according to the study by Hainfeld et al. (2010), they reported that the combinatorial treatment with radiation and Au NPs dramatically increased the overall survival rate in mice (17). Therefore, this setting of treatment had a considerably higher one-year overall survival rate than the control group (only radiation therapy). When AuNPs are included, the one-year overall survival rate rises to 86% from 20% when radiation treatment is used alone. A previous study by Al Zaki et al. (2014) supported the findings of the two earlier studies (20). They reported that the treatment with radiation combined with AuNPs had a 1.7-fold increase in median survival time (20, 21).

In this Meta-analysis, we tried to check the overall survival effects of AuNPs when it was combined with radiation therapy. Previous studies were done to address the effect of AuNPs treatment in combination with radiation therapy, however, only a few preclinical studies were made in this regard on experimental animals (22, 23). Out of these, only three studies containing eleven experiments were included in our meta-analysis because they had enough data to be analyzed for the assessment of the overall survival. In the present study, the meta-analysis data added extra support to the fact that using Au NPs with radiation therapy the overall survival will be improved. In this meta-analysis, the pooled odd ratios (ORs) comparing experimental with control groups were 3.38 (95%CI, 1.74-6.56; P=0.0003).

The majority of the trials' showed that AuNPs could improve radiation therapy; however, more *in vivo* studies are required to find these effects and address the potential mechanisms behind the augmentation of tumor cell cytotoxicity and increasing the survival rates. In summary, according to our findings, combining Au NPs with radiation therapy increases the overall survival rates in tumor-bearing preclinical models, which could open a new avenue to novel trials in clinical settings.

Funding

The authors have no funds.

Conflict of interest

The authors declare that they have no competing interests.

Availability of data and materials

The work contains data that support the conclusions, and any extra data can be obtained from the corresponding author upon request.

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