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Review

Enhancing radiotherapy effect in breast cancer with nanoparticles: A review☆

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ABSTRACT

Amongst all efforts for improving oncological management outcomes, nanoparticles enhanced radiation for breast cancer patient's treatment is a novel approach that has grown interest for research in the last decade. Multiple preclinical data has been published, from all around the globe; however, clinical evidence is still insufficient for implementing the method in routine practice and in disease specific management. Gold nanoparticles (AuNP), which may be among the most studied materials, account for the majority of available data; however, some new materials have also been used in preclinical settings.

Without any safety data available at the moment to support an active use, dosimetric *in vitro* and *in vivo* information seems to be consistent with a very promising and hopeful panorama for clinical applications. This review evaluates existing dosimetric data in breast cancer tissue, and a probable future impact in treatment choices and patient outcomes, as further investigation is required in a clinical setting.

Breast cancer is amongst the most prevalent malignancies around the world, ranked first in terms incidence in women in all regions with an estimated rate for 2012 of 123.2 and mortality rate of 30.9 per 100,000.[1] A multidisciplinary approach must be considered for treatment options, involving surgeons, clinical oncologists and radiation oncologist, as well as other medical and non-medical professionals. As for radiation oncology, the current trend of breast conserving surgery and evidenced based favorable outcomes in disease control and cosmesis have increased this specialty's role, as a cost-effective cornerstone treatment.[2]

One of the main concerns around radiotherapy is how to improve the radiation delivery without compromising healthy tissue. The development of new technology in the last few years have shown better toxicity profiles in the skin, lung and heart[3]; however, enhancing the therapeutic effect of radiation, sparing as much tissue as possible, is still a challenge for radiation oncologists.[4]

Many efforts have been made to achieve better outcomes in breast cancer treatment. The description of new treatment schemes in the last decade has been a great improvement in radiation oncology field,[5] however the question still rises:

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could we improve even more radiation delivery to treatment volumes sparing healthy tissue? A new universe was discovered with protons and heavy ions, which have proven worth in clinical practice, however they are not widely available due to elevated costs.[6]

A novel and different approach has been gaining adepts for the past decade by applying metal nanoparticles, mostly gold, in tumoral tissue to achieve a stronger radiation response. Although clinical data is still scarse and maturing, there's more preclinical information that could be useful for further research. A dosimetric work carried by *Cho et al.* suggested that, due to its increased photoelectric absorption because of its high atomic number, the implementation of gold particles (AuNP) summed to Ir^{192} brachytherapy could enhance by 40% the treatment dose, which could vary depending on the particle concentrations.[7] However, this benefit could be limited in MV (megavoltage) treatments. A Monte Carlo calculation used to determine the added benefit of gold nanoparticles has shown a small role in the MV scenario. The proposed mechanism of photoelectric absorption by the nanoparticle in a kilovoltage scenario would produce secondary low-energy electrons; this would not happen in the MV scenario, due to the predominant Compton Effect.[8] Some different conclusions were achieved by another group who found that silver nanoparticles (AgNP) had better interactions with MV radiation, triggering a pair production phenomenon.[9] Some toxicity has been reported in mice models, due to metal deposit in normal tissue. A bismuth based particle has been developed and used in murine breast cancer to show good clinical results and no reported toxicity secondary to treatment.[10]

Despite all dosimetric and preclinical information, just a few data have been released to date about specific nanoparticle enhanced breast cancer treatment. Some comparison against cisplatin has been presented, though as chemotherapy and AuNP are radiosensitizers, it was hypothesized that the effect of one of them would prevail over the other. Zheng et al. described their findings in a preclinical setting, they found that addition of AuNP and cisplatin to radiation enhanced the ratio of DNA double strand breaks by 7.5, compared to only three-fold increase achieved by adding a single sensitizer to radiation.[11] Based on these results, Cui et al. investigated the effect of this combination in breast triple negative cell culture. Their *in vitro* findings have shown that concentrations of AuNP remain stable after 120 h of infusion, conferring an enhanced effect of radiation sensitizing, equivalent to 3 doses of cisplatin.[12] Another special method, RNA directed Au NP described by Hildebrandt et al. has shown an enhancement of 1.2 ratio on treated cells.[13]

Some other strategies against breast cancer cells have been under research. Wu et al. developed an AuNP conjugated peptid sequence of (R)-glycine (G)-aspartic (D) (RGD) that is located in fibronectin and is the site of association with certain integrins, which play a role in invasive activity of these tumor cells. An increase in invasive activity after 4 Gy dose irradiation was significantly inhibited by RGD-AuNP in evaluated cells. The results of microarray analysis showed that the expression of fibronectin was notably suppressed by treatment of 4 Gy irradiation combined with RGD-AuNP in breast cancer cells. These results could suggest that RGD-conjugated AuNPs may improve the cancer therapy with radiation by suppressing the invasive activity of cancer cells, and the molecular mechanism may be associated with the fibronectin receptors.[14]

An interesting report by Strigari et al. described a mathematical model of AuNP application in the 10 years outcome data set of the START trial **(UK Standardization of Breast Radiotherapy), for** evaluation **of** tumor control probability. They found that an enhancement could be reached with better outcomes by lowering the dose per fraction, thus obtaining a higher RBE **(relative biological effectiveness)**, and probably no inferiority in tumor control **rate, compared to standard treatments.** Despite the *in vitro* nature of this study and that the *in vivo* conditions could change the outcome; these results are promising.[15,16]

More recent evaluations of new materials, like that described by Chen et al., report the use of **selenium** nanoparticles (SeNP). For this experiment, SeNP were used in MCF-7 breast cell cancer and then irradiated. Nano-Se reinforced the toxic effects of irradiation, leading to a higher mortality rate than either treatment used alone, inducing cell cycle arrest at the G2/M phase and the activation of autophagy, and increasing both endogenous and irradiation-induced reactive oxygen species formation. These results suggest that Nano-Se can be used as an adjuvant drug to improve cancer cell sensitivity to the toxic effects of irradiation and thereby reduce damage to normal tissue nearby.[17]

Iron oxide nanoparticles (IONPs) stand out among various other nanoparticles because of their low cost, superparamagnetic behavior, biocompatibility and biodegradability. They have gained immense importance in the field of cancer therapy because of their superparamagnetic property, by virtue of which they can heat up when exposed to an external magnetic field or can be simply guided to a target site using an external magnet. Additionally, it has been described that the movement of these nanoparticles due to magnetic fields could also be a mechanism of tumoral cell destruction, as has been studied in MCF-7 cell cultures. IONPs are also the only metal oxide NPs approved for use in MRI. Superparamagnetic iron oxide nanoparticles (SPIONPs) have various magnetic phases, of which magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are particularly promising in biomedicine.[18]

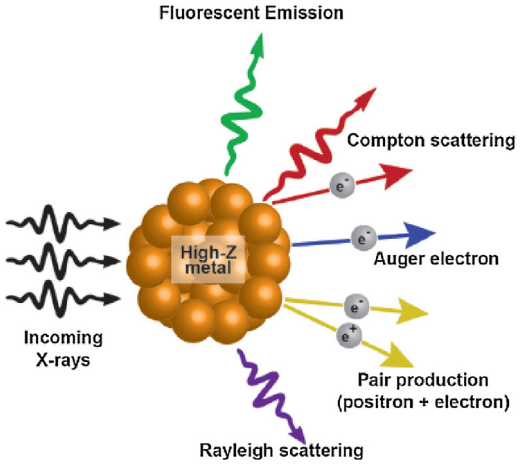

Fig. 1 – Proposed mechanism of metal nanoparticles interaction with radiation. Adapted from Ref.[19]

At the moment, we have encouraging preclinical data supporting nanoparticles use for general cancer treatment enhancement; however, further clinical data is required for opening a wider range of therapeutic tools. As ongoing research projects still need to mature their data, radiosensitizers will still be a promising tool for future development (Fig. 1, [19]). In the following years, will we be descalating our treatment doses because of nanoparticles enhancement? Clinical data will answer this question.

Conflict of interest

No conflict of interest for the authors.

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REFERENCES

1. M. Ervik, F. Lam, J. Ferlay, L. Mery, I. Soerjomataram, F. Bray (2016). Cancer Today. Lyon, France: International Agency for Research on Cancer. Cancer Today. Available from: http://gco.iarc.fr/today, accessed [03/03/2018].
2. Smith B, Jiang J, Shih Y, Giordano S, Huo J, Jagsi R, et al. Cost and complications of local therapies for early-stage breast cancer. *J Natl Cancer Inst* 2016;**109**(1), djw178.
3. Henson K, McGale P, Taylor C, Darby S. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer* 2012;**108**(1):179–82.
4. Kole A, Kole L, Moran M. Acute radiation dermatitis in breast cancer patients: challenges and solutions. *Breast Cancer: Targets Therapy* 2017;**9**:313–23.
5. Haviland J, Owen J, Dewar J, Agrawal R, Barrett J, Barrett-Lee P, et al. The UK Standardization of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol* 2013;**14**(11):1086–94.
6. Verma V, Mishra M, Mehta M. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer* 2016;**122**(10):1483–501.
7. Cho S, Jones B, Krishnan S. The dosimetric feasibility of gold nanoparticle-aided radiation therapy (GNRT) via brachytherapy using low-energy gamma-/x-ray sources. *Phys. Med. Biol* 2009;**54**(16):4889–905.
8. Su X-Y, Liu P-D, Wu H, Gu N. Enhancement of radiosensitization by metal-based nanoparticles in cancer radiation therapy. *Cancer Biol Med* 2014;**11**(2):86–91, http://dx.doi.org/10.7497/j.issn.2095-3941.2014.02.003.
9. Liu P, Jin H, Guo Z, et al. Silver nanoparticles outperform gold nanoparticles in radiosensitizing U251 cells in vitro and in an intracranial mouse model of glioma. *Int J Nanomed* 2016;**11**:5003–14, http://dx.doi.org/10.2147/IJN.S115473.
10. Deng J, Xu S, Hu W, Xun X, Zheng L, Su M. Tumor targeted, stealthy and degradable bismuth nanoparticles for enhanced X-ray radiation therapy of breast cancer. *Biomaterials* 2017, http://dx.doi.org/10.1016/j.biomaterials.2017.10.048.
11. Zheng Y, Sanche L. Gold nanoparticles enhance DNA damage induced by anti-cancer drugs and radiation. *Radiat Res* 2009;**172**(1):114–9.
12. Cui L, Her S, Dunne M, Borst G, De Souza R, Bristow R, et al. Significant radiation enhancement effects by gold nanoparticles in combination with cisplatin in triple negative breast cancer cells and tumor xenografts. *Radiat Res* 2017;**187**(2):147–60.
13. Hildenbrand G, Metzler P, Pilarczyk G, Bobu V, Kriz W, Hosser H, et al. Dose enhancement effects of gold nanoparticles specifically targeting RNA in breast cancer cells. *PLOS ONE* 2018;**13**(1), e0190183.
14. Wu P, Onodera Y, Ichikawa Y, Watanabe Y, Qian W, Hashimoto T, et al. Gold nanoparticles with RGD peptide in radiation therapy suppress the invasion activity of breast cancer cells. *Int J Radiat Oncol Biol Phys* 2016;**96**(2):E574.
15. Ferrero V, Visonà G, Dalmasso F, Gobbato A, Cerello P, Strigari L, et al. Targeted dose enhancement in radiotherapy for breast cancer using gold nanoparticles, part 1: A radiobiological model study. *Med Phys* 2017;**44**(5):1983–92.
16. Strigari L, Ferrero V, Visonà G, Dalmasso F, Gobbato A, Cerello P, et al. Targeted dose enhancement in radiotherapy for breast cancer using gold nanoparticles, part 2: A treatment planning study. *Med Phys* 2017;**44**(5):1993–2001.
17. Chen Feng, Zhang Xiao Hong, Hu Xiao Dan, Liu Pei Dang, Zhang Hai Qian. The effects of combined selenium nanoparticles and radiation therapy on breast cancer cells in vitro. *Artificial Cells Nanomed Biotechnol* 2017, http://dx.doi.org/10.1080/21691401.2017.1347941.
18. Thoidingjam S, Tiku A. New developments in breast cancer therapy: role of iron oxide nanoparticles. *Adv Nat Sci: Nanosci Nanotechnol* 2017;**8**(2), 023002.
19. Kwatra D, Venugopal A, Anant S. Nanoparticles in radiation therapy: a summary of various approaches to enhance radiosensitization in cancer. *Transl Cancer Res* 2013;**2**(4):330–42, http://dx.doi.org/10.3978/j.issn.2218-676X.2013.08.06.