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ORIGINAL PAPER

Tumor dose enhancement by gold nanoparticles in a 6 MV photon beam: a Monte Carlo study on the size effect of nanoparticles

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Abstract. In this study after benchmarking of Monte Carlo (MC) simulation of a 6 MV linac, the simulation model was used for estimation of tumor dose enhancement by gold nanoparticles (GNPs). The 6 MV photon mode of a Siemens Primus linac was simulated and a percent depth dose and dose profiles values obtained from the simulations were compared with the corresponding measured values. Dose enhancement for various sizes and concentrations of GNPs were studied for two cases with and without the presence of a flattening filter in the beam's path. Tumor dose enhancement with and without the presence of the flattening filter was, respectively 1–5 and 3–10%. The maximum dose enhancement was observed when 200 nm GNPs was used and the concentration was 36 mg/g tumor. Furthermore, larger GNPs resulted in higher dose values in the tumor. After careful observation of the dose enhancement factor data, it was found that there is a poor relation between the nanoparticle size and dose enhancement. It seems that for high energy photons, the dose enhancement is more affected by the concentration of nanoparticles than their size.

Key words: Monte Carlo (MC) simulation • medical linac • dose enhancement • gold nanoparticle (GNP) • flattening filter free (FFF)

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Introduction

It is known that by injecting materials with high atomic number into a tumor, the energy deposition can be increased due to various physical interactions between the photons and tumor tissue. Early researchers used iodine, gadolinium and gold microspheres as high atomic number media, but results were not satisfactory [7, 10, 11, 17, 18, 21–23, 26]. Subsequently, in an *in vivo* study, a significant increase in one-year survival in 86% of population in the group treated with radiotherapy and nanoparticles was observed compared to 20% in the group with radiotherapy alone. This study was performed on mice irradiated with 250 kVp X-rays in the presence of 1.9 nm GNPs and the results verify GNPs as a dose enhancer [9]. *In vitro* studies also confirmed this claim [3, 4, 15]. In these studies, a meaningful biological dose enhancement was observed after irradiation of cells and plasmid DNA. Therefore, the use of GNPs for potential clinical purpose has been a field of interest for many researchers.

Dose enhancement within a tumor is influenced by the size, concentration of nanoparticles, photon beam quality, etc. Nanoparticles with sufficient small size can penetrate into the tumor tissue due to the leaky vasculature of tumors [8]. This effect takes advantage of a phenomenon which is known as enhanced permeability and retention (EPR) [16]. Nanoparticles of 1–100 nm size penetrate into a tumor from blood vessels feeding

the tumor. This is because they are smaller than the typical 400 nm size of the pores which exist in the tumor vasculature [25].

There are other studies in which the MC method was used in order to evaluate the various aspects of use of GNPs during teletherapy or brachytherapy [1, 27]. Zhang *et al*. demonstrated that an Ir-192 brachytherapy source provides an increase up to 60% due to 100 nm GNPs. Bahreyni *et al*. quantified the dose enhancement by gadolinium and gold nanoparticles in brachytherapy and gold nanoparticles showed higher dose enhancement than gadolinium nanoparticles.

In a MC study, the interaction of X-rays with individual GNPs with diameters of 2, 50 and 100 nm has been investigated. It was observed that nanoparticles with larger sizes provide higher dose values. In this study GNPs was not loaded into a tumor and the interaction of X-rays with an individual GNP was considered [14]. In another research, the energy deposition due to secondary electrons from GNPs was quantified and the microscopic dose enhancement around GNPs was calculated [12]. Ngwa *et al*. investigated dose enhancement at the subcellular level by modelling a vascular endothelial cell during brachytherapy [20].

Most of the aforementioned studies focused only on a single diameter of nanoparticles without considering size effects. Furthermore, the effect of flattening filter on dose enhancement due to GNPs with different sizes has not been evaluated in these studies. In the present study, the effect of GNPs of various concentrations and sizes on the tumor dose enhancement was evaluated in a 6 MV photon beam of a medical linear accelerator. Dose enhancement was studied for the case in which flattening filter was removed from the beam path as well.

Materials and methods

Monte Carlo modelling of linac

In this study, the head components of Siemens Primus linac as well as a water phantom were simulated for calculation of dosimetric data. For this purpose, MCNPX (version 2.4.0) MC code was used and percentage depth dose and dose profile data were obtained for three different radiation fields: 6×6, 10×10 and 20×20 cm^2.

In linear accelerators electrons are hitting on a target and bremsstrahlung X-rays are created. In the Siemens Primus linac the target includes cylindrical layers of air, gold, graphite and water of different radiuses and thicknesses. Detailed information on the geometry of the Siemens Primus linac can be found in a previous MC study [24].

For calculation of dose values, a water phantom with dimensions of $30 \times 30 \times 30$ cm^3 was considered at a source to surface distance (SSD) of 100 cm. Percentage depth dose data were obtained for three field sizes of 6×6, 10×10 and 20×20 cm^2. Dose profile data were calculated for the same fields at a 5 cm depth. For calculation of percentage depth dose values, a cylindrical cell with a radius equal to one-tenth of field size was defined. The axis of this cylinder was along the central axis of the beam and it was divided into a number of 2 mm thickness cylinders in which the dose values were scored. In calculation of dose profiles, cylindrical cells with a 2 mm radius and a 2 mm thickness were defined at the three aforementioned depths in such a way that the axis of each cylinder was perpendicular to the central axis of the beam [19]. For the cells with depths less than or equal to a build-up depth, the dose value in each cell was scored using an *F8 tally. To speed-up the calculations, beyond the build-up region, dose values were obtained by an F6 tally in MCNPX code. The energy cut-off for photons and electrons was considered as equal to 0.5 and 0.01 MeV, respectively. The obtained values of percent depth dose and dose profiles from MC simulations were compared with the corresponding experimental data. The experimental measurements were performed in a water phantom using a Wellhofer-Scanditronix dosimetry system (RFA-300) and a diode detector.

Introducing nanoparticles into a tumor

In this study, the size of tumor was considered as $2.4 \times 2.4 \times 2.4$ cm^3, and the centre of tumor was positioned at a depth of 5 cm on the central axis of the beam. The field size was 4×4 cm^2 and SSD was considered as equal to 100 cm. GNPs with concentrations of 12, 24 and 36 mg/g tumor were defined in the tumor and in each concentration the dose enhancement was calculated for various diameters of GNPs: 25, 50, 100 and 200 nm. Our rational for choosing these sizes of nanoparticles was that nanoparticles ranging in size from 10 to 200 nm are usually used in the field of nanomedicine [9]. The GNPs were distributed uniformly into the tumor by utilizing a lattice card in MCNPX code. For this purpose, by considering the concentration and diameter of GNPs, the tumor was divided into cubic cells with dimension of nanometers and in each cell a GNP was defined. For example, for nanospheres with a diameter of 100 nm and concentration of 24 mg/g tumor, the number of GNPs was 3.2848×10^{12} and each GNP was placed into a cubic with sides of 749 nm. The tumor dose was calculated with the F6 tally in $0.8 \times 0.8 \times 0.2$ cm^3 cubic cells on the beam's central axis. Dose enhancement factor (DEF) is defined as the ratio of dose in a point on the central axis in tumor with the presence of GNPs to dose at the same point without the presence of GNPs. Then, DEF was averaged over various cubic cells in the tumor on the central axis of the beam and the average value was reported. Furthermore, dose enhancement was repeated for the case in which the flattening filter was removed from the beam path. We named this situation as the case of flattening filter free (FFF).

Results and discussion

Validation of linac simulation

Figure 1a illustrates the simulation and experimental depth dose data for 6×6, 10×10 and 20×20 cm^2 fields for a 6 MV photon beam (SSD = 100 cm). Figure 1b presents the simulation results and experimental measured lateral dose profiles in a 5 cm depth for the same beam

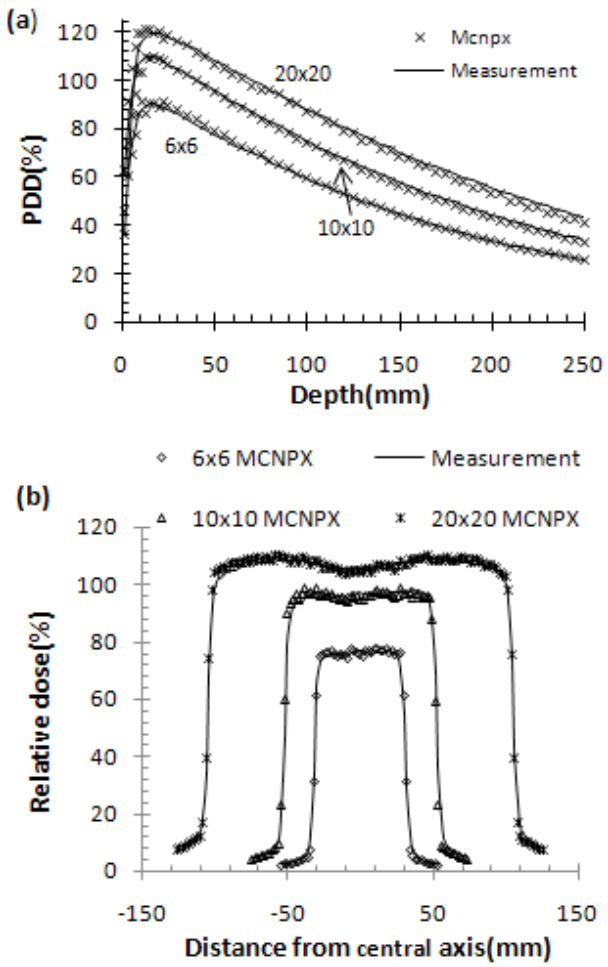

Fig. 1. Obtained results by Monte Carlo simulations and measurements for fields of 6 × 6, 10 × 10 and 20 × 20 cm^2 of 6 MV beam: (a) percent depth dose values which were scaled by 0.9, 1.1 and 1.2, respectively; (b) dose profiles at 5, 10 and 20 cm depths which only for 6 × 6 cm^2 was scaled by 0.8.

and fields. The percentage depth dose and lateral dose profile values were normalized to the maximum dose at the build-up depth. The depth doses and beam profiles of various field sizes were compared with the measurement data in order to verify the simulation results. It has been found that the differences between the results of simulations and measurements in build-up region were less than 5% and beyond this depth the differences were less than 2%. For beam profiles, although there were slight differences between the simulated and measured data, the maximum discrepancy was about 2% in the flat region of beam profile. The agreement between the calculated and the measured results have shown that this model can be used to predict dose distribution in complex situations such as estimation of tumor dose enhancement due to GNPs.

Dose enhancements due to GNPs

Table 1 summarizes the DEF results for the 6 MV photon beam which were obtained in this study. The maximum dose enhancement has been observed when 200 nm GNPs was used and the concentration was 36 mg/g tumor. Dose enhancements ranging from 1–10% was observed, depending on the gold concentration, size of nanoparticles and presence or absence of flattening filter. Figures 2–4 present a comparison between the various sizes of GNPs at the same concentration levels. These figures also illustrate the effect of concentration on DEF for flattened and unflattened photon beams. In each case, the DEF related to the unflattened beam was always larger than that related to the flattened beam. The reason is due to the fact that the unflattened beam contains more low energy photons than the flattened beam and thus the probability of photoelectric interactions increases. As it is shown in Figs. 2a–4a, in each concentration with the presence of flattening filter, the DEF related to each voxel generally decreases with depth within the tumor region. This effect can be due to the attenuation of the photon beam. This decrease can affect the DEF values, depending on the depth of the tumor, SSD and size of the tumor, especially the thickness of tumor along the beam's path. As it is illustrated in Fig. 2b, the DEF is fairly constant with depth in the tumor for an unflattened beam. According to Figs. 3b and 4b for higher concentrations, the photon attenuation increases and thus DEF will decrease with depth. In Figs. 2–4 several enhancements in dose in the build-up region can be considered which are related to the radiation backscatter from GNPs. Since the photons have sufficient energy, the backscattered photons can reach the build-up region. Our results have indicated dose reduction of 2–3% at depths under the tumor. Generally, it seems that for

Table 1. Dose enhancement factor (DEF) average values in a tumor for different diameters and concentrations of gold nanoparticles with presence of flattening filter (FF) and flattening filter free (FFF) cases

Concentration (mg/g tumor)	Diameter of GNPs (nm)							
	25		50		100		200	
	DEF	Uncertainty	DEF	Uncertainty	DEF	Uncertainty	DEF	Uncertainty
	With flattening filter							
12	1.009	1.1%	1.009	1.4%	1.010	1.5%	1.011	1.8%
24	1.026	2.2%	1.027	2.2%	1.033	2.0%	1.033	2.4%
36	1.046	2.4%	1.048	2.7%	1.053	2.9%	1.056	2.9%
	Without flattening filter							
12	10.28	1.5%	1.031	1.8%	1.034	1.4%	1.033	1.6%
24	1.055	2.5%	1.059	2.5%	1.064	2.7%	1.069	2.9%
36	1.083	3.6%	1.083	3.7%	1.092	3.8%	1.100	3.9%

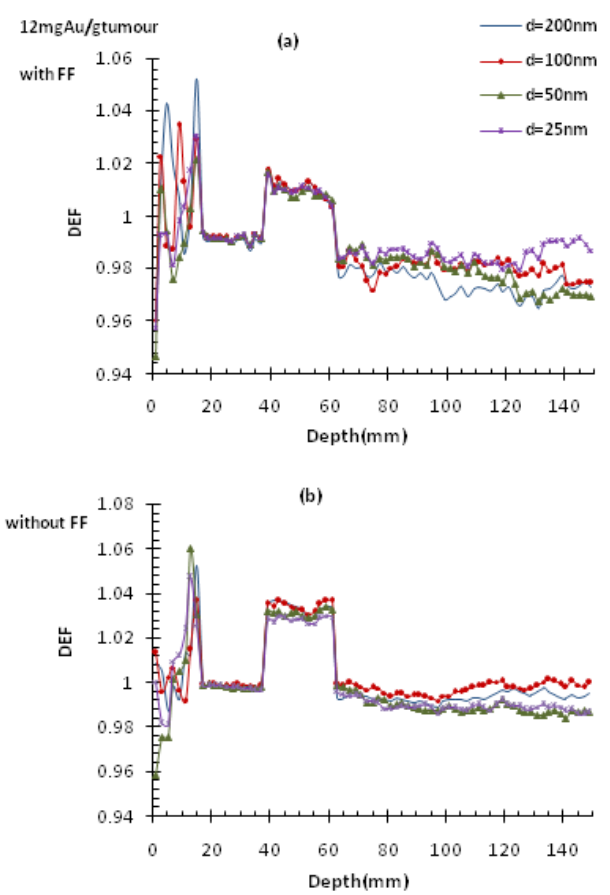

Fig. 2. Dose enhancement factor (DEF) for gold nanoparticle concentration of 12 mg/g of tumor: (a) with presence of flattening filter; (b) without presence of flattening filter.

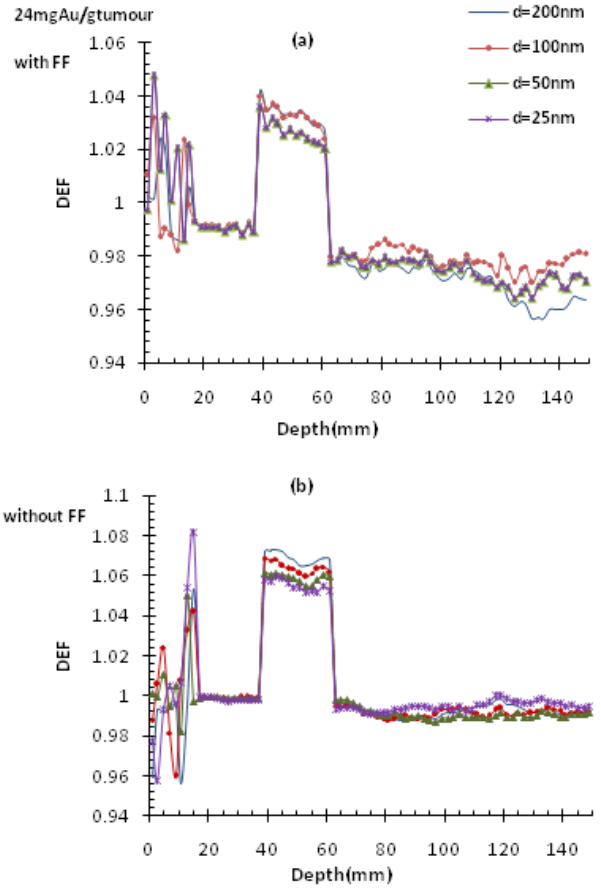

Fig. 3. Dose enhancement factor (DEF) for gold nanoparticle concentration of 24 mg/g of tumor: (a) with presence of flattening filter; (b) without presence of flattening filter.

high energy photons, the dose enhancement is more affected by the concentration of nanoparticles than the size of them. The current results show that the tumor dose enhancement in 12–36 mg/g tumor concentration range is, on average, about 4 and 5.6%, respectively for flattened and unflattened photon beams. However, the increase in tumor dose enhancement due to the increase of nanoparticle size is negligible.

Discussion

In this study, MC calculation was used for the determination of tumor dose enhancement due to GNPs with different diameters and concentrations. According to the results, dose enhancements ranging from 1–10% was observed, depending on the gold concentration, size of nanoparticles and presence or absence of flattening filter. Results of this study indicate that the larger GNPs and higher concentration cause a higher dose enhancement in the tumor. After careful observation of the dose enhancement factor data, it was found that there is a poor relation between the nanoparticle size and dose enhancement. It seems that for high energy photons, the dose enhancement is more affected by the concentration of nanoparticles than the size of them. Similar results were achieved in the previous studies [6, 12–14]. Leung *et al*. showed that the interaction of a low energy photon beam with GNP was stronger than the interaction of a 6 MV photon beam with GNP by two to three orders of magnitude. Lechtman *et al*. observed a 10^3 increase in the rate of photoelectric absorption using ^{125}I compared to 6 MV beams. Cho obtained a significant tumor dose enhancement factor equal to 5.60 at 140 KVp compared to 1.02 at 6 MV when the concentration of GNPs was 30 mg/g tumor. Jones *et al*. showed that the microscopic dose around GNP was increased by factors ranging from 10 to 1000 over 30 μm for a low energy photon compared to the factor of 10 or less for distances greater than 1 μm for 6 MV photons.

According to the previous studies, GNPs irradiated with low energy X-rays or photon-emitting brachytherapy sources showed higher dose enhancement than GNPs irradiated with high energy sources.

In this study without the presence of flattening filter, the maximum dose enhancement of 10% has been observed when 200 nm GNPs was used and the concentration was 36 mg/g tumor. Although this value is not as high as those observed for brachytherapy or low energy photon sources, but is clinically considerable for the 6 MV photon beam as one of the most frequently beams used in radiotherapy. Also it is considerable that in a recent *in vitro* study, GNPs with a 50 nm diameter showed the highest radiosensitization enhancement factor (REF). The REF value was 1.43 at 220 kVp compared to 1.20 and 1.26 for GNPs of 14 and 74 nm, respectively. Using 50 nm GNPs, the REF for 105 kV and 6 MV photons was 1.66 and 1.17, respectively [5]. In another *in vitro* study, in the presence of 50 nm GNPs at a concentration of

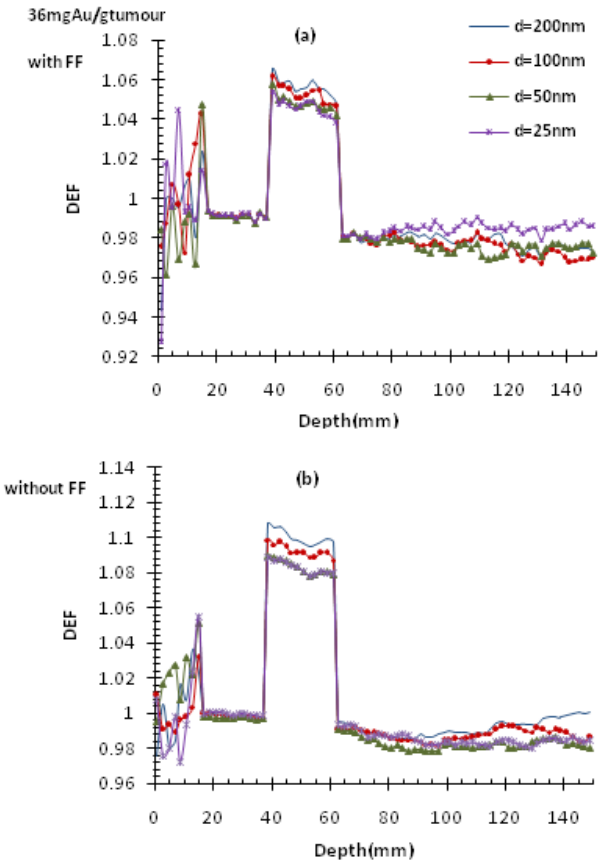

Fig. 4. Dose enhancement factor (DEF) for gold nanoparticle concentration of 36 mg/g of tumor: (a) with presence of flattening filter; (b) without presence of flattening filter.

0.05 mg/ml, the cells were irradiated with 6 MV beams at depths of 1.5, 5, 10, 15 and 20 cm (SAD setup). Results showed that without the flattening filter, a significant dose enhancement between 1.1 and 1.7 was observed for all depths and delivery modes [2]. Obtained values of these studies for 6 MV beams are comparable with brachytherapy and low energy sources. It seems that the concentration and especially the size of GNPs has an important role in dose enhancement due to GNPs. Therefore, it seems that for a 6 MV photon beam, as one of the most frequently beams used in radiotherapy, it is required that the dose enhancement due to GNPs in different size and concentration must be checked.

High energy of the 6 MV photon source results in the decrease of photoelectric absorption and, therefore, the dose enhancement due to GNPs. Removing of the flattening filter from the beam path can affect the dose enhancement. In the current study, the effect of removing the flattening filter from the beam path on the dose enhancement was investigated. According to the results, DEF related to an unflattened beam was always larger than that related to the flattened beam. A meaningful increase of 10% was observed by the utilization of 200 nm GNPs and 36 mg/g tumor concentration. This outcome can be useful for employing GNPs as radiosensitization during teletherapy by 6 MV unflattened photon sources.

In Figs. 2–4 several enhancements in dose in the build-up region can be seen that can be related to the radiation backscatter from GNPs. It is noticeable that this level of energy can damage the normal tissue in this region and this effect should be considered in the clinical use of nanoparticles.

Although the use of GNPs as potential clinical purpose has been a field of interest for many researchers, but the importance of controlling the size and concentration of GNPs to minimize any potential toxic side effect must be taken into consideration.

Recently, the increase of GNPs toxicity due to their tiny physical dimensions has been discussed. In a recent *in vivo* study, it was observed that the toxicity of 10 and 60 nm particles was obviously higher than that of 5 and 30 nm particles [29]. According to this study, it can be concluded that the toxicity of GNPs shows no linear dependence on their size. Furthermore, it was shown that the high concentration of GNPs leads to an increase of toxic effect [28]. On the other hand, the clinical purpose of the use of dose enhancement media is to achieve a higher dose to the tumor and a lower dose to the surrounding healthy cells. In a MC study when the gold concentration in the tumor was 7 mg Au/g, a concentration of 2 mg Au/g was also defined in the surrounding normal tissues. According to the results of the investigation, a dose enhancement up to about 30% was observed in the vicinity of the tumor. However, the DEF in the tumor was still about as much as that for the case without the presence of gold in the normal tissue [6]. Therefore, in the selection of concentration and size of GNPs, the side effects must be taken into consideration. Besides, the function of nanoparticles may be changed partially with markers and antibodies at the time of injection. This can affect the dose enhancement. Nanoparticles that nowadays are being produced have not identical diameter. For evaluation of the effect of these factors, it is needed to perform more biological experiments on cell lines and animal models.

Conclusions

In this study, a 6 MV Siemens Primus linear accelerator was modelled. After successful modelling of the linac, the model was used to study tumor dose enhancement by GNPs with different diameters and concentrations. The obtained results have shown that there is a slight relation between the size of nanoparticles and the level of dose enhancement for 6 MV photon beams. However, to achieve higher tumor dose enhancements nanoparticles with higher concentrations should be used. It seems that for the high energy photons, applying modifications on the nominal energy of the accelerator, it may be feasible to achieve a clinically meaningful dose enhancement level. Although the obtained values in this study, were not as high as those observed for brachytherapy or low energy photon sources, nevertheless are clinically considerable for the 6 MV photon beam as one of the most frequently beams used in radiotherapy.

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