

Technical Note

A study on the imaging characteristics of Gold nanoparticles as a contrast agent in X-ray computed tomography

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Abstract

Aim: In the current study, some imaging characteristics of AuNPs were quantitatively analyzed and compared with two conventional contrast media (CM) including Iodine and Gadolinium by using of a cylindrical phantom.

Methods: AuNPs were synthesized with the mean diameter of 16 nm and were equalized to the concentration of 0.5, 1, 2 and 4 mg/mL in the same volumes. A cylindrical phantom resembling the head and neck was fabricated and drilled to contain small tubes filled with Iodine, Gadolinium, and AuNPs as contrast media. The phantom was scanned in different exposure techniques and CT numbers of three studied contrast media inside test tubes were measured in terms of Hounsfield Unit (HU). The imaging parameters of the noise and contrast to noise ratios (CNR) were calculated for all studied CMs.

Results: AuNPs showed 128% and 166% higher CT number in comparison with Iodine and Gadolinium respectively. Also, Iodine had a greater CT number than Gadolinium for the same exposure techniques and concentration. The maximum CT number for AuNPs and studied contrast materials was obtained at the highest mAs and the lowest tube potential. The maximum CT number were 1033±11 (HU) for AuNP, 565±10 (HU) for Iodine, 458±11 for Gadolinium. Moreover, the maximum CNRs of 433±117, 203±53, 145±37 were found for AuNPs, Iodine and Gadolinium respectively.

Conclusion: The contrast agent based on AuNPs showed higher imaging quality in terms of contrast and noise relative to other iodine and gadolinium based contrast media in X-ray computed tomography. Application of the AuNPs as a contrast medium in x-ray CT is recommended.

Key words: AuNP, contrast media, X-ray computed tomography, nanoparticle.

Introduction

Application of gold and other nanoparticles in radiation therapy and medical imaging have been reported in several studies [1-4]. X-ray computed tomography (CT) is one of the popular medical imaging modalities in terms of availability, efficiency and cost. CT images provide basic anatomical information and pathologic changes regarding lesion location, size and spread [5]. Basically, X-ray CT imaging relies on the different attenuation of X-ray photons in patient body and the ability of CT to distinguish between different tissues is based on the fact that different tissues have different degrees of X-ray attenuation. The attenuation coefficient is determined by the atomic number and electron density of the tissue; the higher atomic number and electron density, the higher attenuation coefficient [6]. In the photon energy range used in X-ray CT,

X-rays are intensely attenuated by the bone, while less attenuation occurs in soft tissues. The different cross sections for photoelectric and Compton interactions exist for both materials. Therefore, to provide clinically useful images of soft tissues, the contrast agents with higher atomic number are utilized in imaging process in order to increase the attenuation properties of different soft tissues [7]. These contrast agents are responsible to provide additional information about vascular anatomy, depict vascular flow and more recently, determine the degree of perfusion [8]. In X-ray CT, contrast agents based on heavy elements such as gold [9,10], bismuth [11] or iodine [12,13] and in some cases gadolinium are used [14].

Conventional contrast agents based on iodine have been routinely used in X-ray CT. Since Iodine (atomic number = 53) has low molecular weight, flows out the blood circulation

immediately after injection and causes a short imaging time. However, it makes low contrast images in heavy patients because of image degradation caused by increased scattered radiation [4]. Moreover, physiological information that can be obtained from iodine contrast medium is limited to vascular system and large organs [8]. There are some disadvantages for the iodine based contrast media including higher osmolality of iodine in heavy concentration [15] causes chemical sensitivity [4], renal toxicity [4,10], vascular permeation, vomiting and even skin irritation [16].

Gadolinium is the mainly used contrast media for magnetic resonance imaging. But because of its high atomic number and density it can be used in x-ray CT in cases where the application of iodine based CM was prohibited such as severe sensitivity to iodine CM. Studies have shown that image contrast obtained by Gd CM in X-ray CT is lower than that was provided conventional iodine CM [14].

To overcome the limitations and disadvantages of iodine-based contrast agents, new agent with better imaging properties and bio-adaptability was needed. Among the studied materials, the use of gold nanoparticles (AuNP) as contrast agent has been regarded by scientists, because of its special chemical and physical features, ease of synthesis and its bio-compatibility. AuNPs (atomic number = 79) with higher probability of photoelectric interaction with energetic photons compared with iodine have shown greater attenuation coefficient and better contrast according to recent studies [5,9,15]. Since AuNPs have a high bio-compatibility, and because of heavier molecular weight than iodine it has longer circulation time after injection to blood stream. Longer circulation time causes more useful imaging time, accurate observation of vessels and survey of vicinity tissues [17]. The viscosity of AuNPs is like water and in addition to stability it provides injection facility [4].

In the previous *in vivo* studies, they focused on cytotoxicity, dose index and contrast enhancement ratio in animals with tumor before and after injection of AuNPs [8,15,18-24]. This study aimed to quantify some imaging properties of AuNPs compared to two conventional contrast agents including iodine and gadolinium. Also, using a head and neck phantom, we tried to find a quantitative way to show how much AuNPs present higher CT number and CNR compared to iodine and gadolinium at the same concentrations and tube potentials ranging from 80 to 140 kVp.

Materials and Methods

AuNP synthesis

Synthesis of citrate-capped AuNPs was carried out using a previously reported method [25,26] with a slight modification. Colloidal AuNPs were prepared according to the standard method for sodium citrate reduction. Briefly, 18 mg of hydrogen tetrachloroauric acid (HAuCl₄) was dissolved in 100 mL of boiling de-ionised water and then 3 mL of sodium citrate solution (1%w/v) was added. Upon the addition of

sodium citrate, the color of the solution started to change from yellow to dark, which subsequently turned into bluish-gray or purple within a few minutes. The solution was boiled for 30 minutes, allowing the reaction to complete and reach ambient temperature. The final color of the solution was deep wine-red. After AuNP synthesis, it was brought to different concentration 0.5, 1, 2 and 4 mg/mL, all in the same volume of 40 mL (**Figure 1a**). Transmission Electron Microscopy (TEM) of samples was prepared by depositing gold colloid drops on a copper grid covered with a holey carbon film. TEM was performed at the potential of 300 kV with a JEOL JEM 3010 microscope equipped with a CCD Camera (**Figure 1b**). All AuNP solutions were characterized by UV-Vis spectroscopy with a Varian Cary 50 spectrometer in 2 mm optical path cells. The size and the concentration of AuNPs were also determined directly from UV-Vis absorption spectra using a method reported previously [27]. The solution contained NPs with an average size range of 16 nm in diameter and a standard deviation of 35% due to a log-normal distribution of sizes characterized by UV-Vis spectrophotometry.

Concentration and volume equalization

We used commercially available Urographin (containing Iodine) and Dotarem (containing Gadolinium) contrast media for comparison purposes. The available concentrations of Urographin and Dotarem were 370 mg/mL and 0.5 mM/mL respectively. To equalize concentrations relative to AuNP solutions, we used the equation of $C_1V_1 = C_2V_2$, in which C stands for concentration and V for volume. First, the required volume for each concentration was calculated and then volume was diluted with distilled water to reach to 40 mL.

Phantom designing

A cylindrical phantom was constructed of polyethylene with the dimension of 160 mm diameters and 100 mm height. In order to evaluate three types of contrast media in a given concentration and variable size of tubes, cylindrical glass tubes with different diameters, 1.75, 3.5, 5, 7 and 7.5 mm, were drilled in the position of central angle of 24 degrees to hold samples. The distance between the center of each tube from the phantom edge was 20 mm.

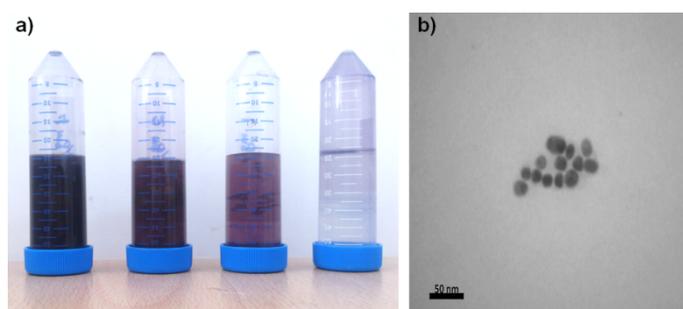


Figure 1. (a) AuNPs' solutions in concentration of 4 mg/ml to 0.5 mg/ml (from left to right). (b) TEM image of our produced gold nanoparticles in the current study, the average diameter of 16 nm was obtained (scale bar = 50 nm).

X-ray CT scanner

A GE Light Speed (General Electric Medical Systems, Waukesha, Wisconsin) 16 slice CT scanner was used for imaging of our samples. The imaging quality assurance was performed by using a GE QA phantom. The QA program included several sections such as contrast scale, high contrast spatial resolution, slice thickness, positioning light accuracy, low contrast detectability, noise and uniformity. Phantom was scanned according to the operator manual and the results of each part were compared with optimal values. The tests were performed in the scan condition of 120 kVp, 100 mAs, 3 s and 10 mm slice thickness. All the results were in the acceptable range recommended by the manufacturer.

Before scanning, the tubes were filled with defined concentrations and shaken well to uniform the contrast media solutions. Scans were performed in the kVp range of 80-140, and tube currents of 80, 100 and 120 mA and 2 mm slice thickness.

Image analysis

All images were analyzed using embedded software in CT scanner and CT number of CMs and their standard deviations (SD) were extracted. Overall 15 slices was obtained for each exposure techniques. Among the slices, one which had better visually contrast was chosen and a region of interest (ROI) of 3 mm² at the center of each sample was used for CT number reading. Average and standard deviation of CT number were provided for each ROI by software. Contrast was defined as the difference between CT numbers of a studied CM and background (phantom material). In each scan, contrast was determined and divided by noise amount to obtain contrast to noise ratio (CNR).

Results

In **Figure 2a**, the CT image of phantom containing the tubes with diameters of 1, 2, 3, 4 and 5 mm has been shown. The results of 5 mm diameter tubes have been used to illustrate the effect of increasing kVp on the contrast of studied CMs (**Figure 2b**). As it can be seen from **Figure 2a**, AuNP provides higher CT number and contrast compared to Iodine and Gadolinium for all tube diameters. Moreover, in tubes with 1 mm diameter, the effect of higher CT number and contrast of AuNP is prominent in terms of tube visibility and detectability compared to other CMs. Besides, it can be observed from both images that the CT number of the Iodine containing tube is higher than Gadolinium tubes for all energies as well as all tube diameters.

In **Figure 3**, variations of CT number for AuNP, Iodine, and Gadolinium with beam energy from 80 to 140 kVp and constant mAs =120 have been shown. For all concentrations and photon energy, AuNP had greater CT number compared to Iodine and Gadolinium. Additionally, the CT number decreased linearly with kVp for all CMs and concentrations. Also, the CT number showed its higher value at the kilovoltage of 80 kVp for all CMs, whereas in 2 and 4 mg/mL

concentrations, the CT number of AuNP was 2 and 3 times higher than Iodine and Gadolinium respectively. Furthermore, in a given concentration and constant kVp, CT number of AuNP was greater than Iodine and the CT number of Iodine was higher than Gadolinium. For instance, at the concentration of 4 mg/ml and 80 kVp, CNR of AuNP was 109% greater than iodine and 165% greater than gadolinium.

The results of CT number measurement for all studied CMs have been tabulated in **Table 1**. According to **Table 1**, the obtained highest CT number for the studied CMs were 1033±12 for AuNP, 552±10 for I and 459±11 for Gadolinium with a concentration of 4 mg/mL and 80 kVp.

Another point is that the CT number reduction with increase in beam energy did not occur at the same rate for all CMs. In concentration of 4 mg/mL and 120 mAs, by changing kVp from 80 to 140, CT number decreased by 8.5% for AuNP, 23% for Iodine and 26% for Gadolinium.

In **Figure 4**, the variation of CNR with kVp have been shown for different concentrations. It is seen that CNR varies considerably with concentration and tube potential. In constant concentration, CNR of CMs increased with kVp. However, this increase was remarkable for AuNP compared to other CMs. The results showed that in a given concentration and constant tube potential, CNR of AuNP was greater than that was seen for Iodine and Gadolinium. Also, the CNR of Iodine was higher than Gadolinium for all energies and concentrations.

In **Table 2** the CNR of CMs for all concentrations and tube potentials has been tabulated. According to **Table 2**, in concentration of 4 mg/mL and 120 mAs, by changing kVp from 80 to 140, CNR increased 390% for AuNP, 342% for Iodine, and 77% for Gadolinium. If one would like to see the effect of concentration on CNR, it can be seen that in a constant kVp of 140, by changing concentration from 0.5 mg/mL to 4 mg/mL, the CNR increased 269%, 113%, and 154% for AuNP, Iodine, and Gadolinium respectively. The maximum CNR was found at highest kVp and concentration. In a concentration of 4 mg/mL and 140 kVp, CNRs of 432±116, 186±48, and 145±36 were observed for AuNP, Iodine, and Gadolinium respectively.

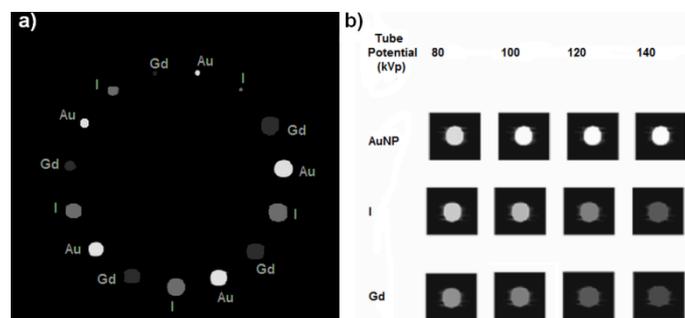


Figure 2. CT images of gold nanoparticles and conventional contrast media, Iodine and Gadolinium. (a) Cross sectional view of the phantom containing CM tubes with different diameters with concentration of 4 mg/mL for all CMs. The exposure technique was 140 kVp and 120 mAs, (b) Cross sectional views of CMs at various tube potentials and 120 mAs with concentration of 4 mg/mL.

Table 1. The measured CT number in terms of HU for AuNP suspension, Iodine (I) and Gadolinium (Gd) CMs at concentrations of 0.5, 1, 2 and 4 mg/ml, and 120 mAs.

Concentration mg/ml	CT Number (HU) 80 kVp			CT Number (HU) 100 kVp			CT Number (HU) 120 kVp			CT Number (HU) 140 kVp		
	AuNP	I	Gd	AuNP	I	Gd	AuNP	I	Gd	AuNP	I	Gd
0.5	463±11	374±11	272±11	400±11	310±11	247±11	352±11	276±11	210±11	306±10	247±12	184±11
1	708±13	445±13	367±12	673±13	414±12	341±13	643±12	380±13	314±13	618±13	350±13	272±12
2	894±11	565±11	406±10	859±13	548±10	380±11	833±11	502±11	359±11	810±10	482±11	318±10
4	1033±12	552±10	459±11	1009±10	506±11	415±10	973±11	482±10	396±11	953±11	449±10	364±10

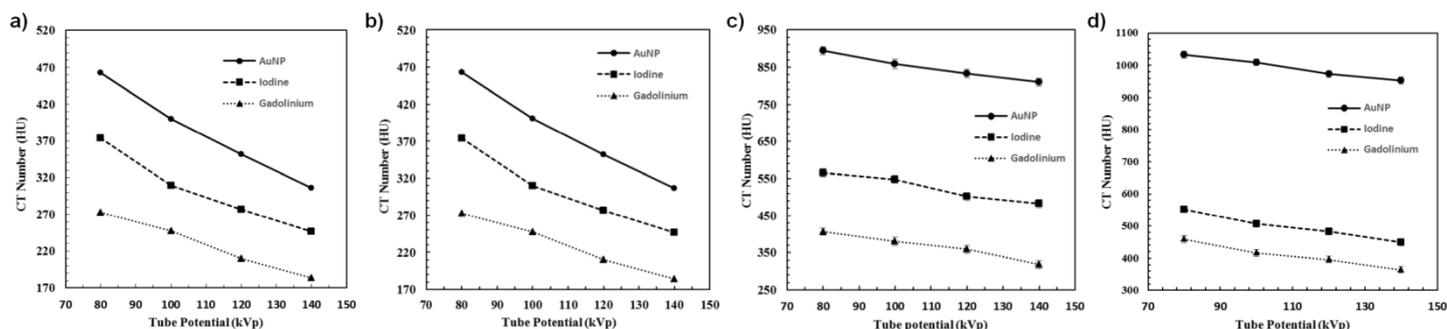


Figure 3. Comparison of CT number variation of studied contrast media with beam energy from 80 kVp to 140 kVp with constant mAs =120 for different concentrations: (a) 0.5 mg/ml, (b) 1 mg/ml, (c) 2 mg/ml and (d) 4 mg/ml.

Table 2. The contrast to noise ratio (CNR) for AuNP suspension, Iodine (I) and Gadolinium (Gd) at concentrations of 0.5, 1, 2 and 4 mg/ml, and 120 mAs.

Concentration mg/ml	CNR at kVp of 80			CNR at kVp of 100			CNR at kVp of 120			CNR at kVp of 140		
	AuNP	I	Gd	AuNP	I	Gd	AuNP	I	Gd	AuNP	I	Gd
0.5	34±11	25±7	16±4	56±10	40±7	25±5	64±15	46±10	31±6	117±28	87±20	57±12
1	57±17	32±9	25±7	104±20	59±11	46±8	132±32	70±16	56±13	268±70	138±33	100±23
2	75±23	44±13	28±9	137±27	82±16	53±10	176±44	99±24	66±15	363±95	203±53	123±30
4	89±27	42±13	33±10	162±33	75±14	58±11	209±53	94±23	74±17	433±117	187±48	145±37

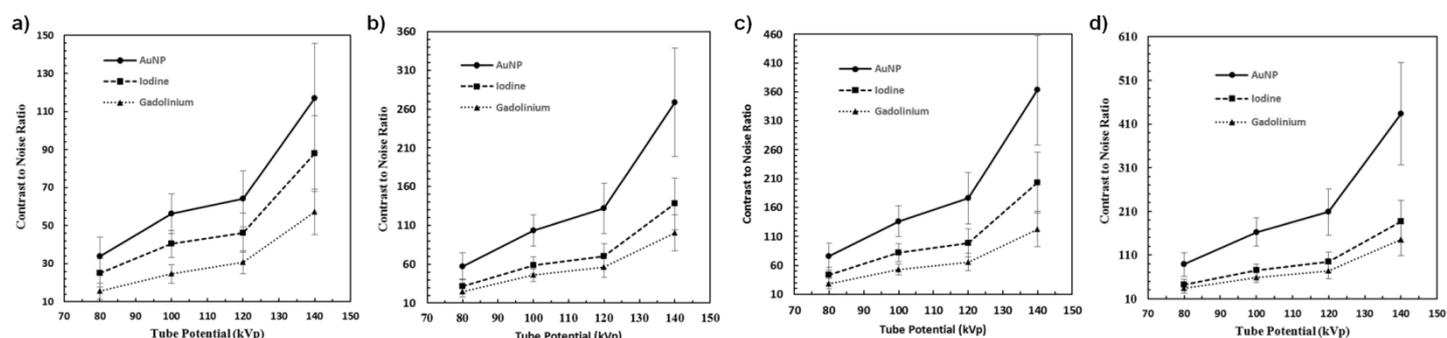


Figure 4. The CNR variation with different kVp and constant mAs of 12: (a) concentration of 0.5 mg/ml, (b) concentration of 1 mg/ml, (c) concentration of 2 mg/ml and (d) concentration of 4 mg/ml. Error bars in CNR represent one standard deviation for each contrast medium.

Discussion

In the current study we compared the imaging characteristics of AuNP with two conventional CMs. Also, we tried to quantify their dependence on tube voltage and CM concentration. Additionally, the CT imaging was performed in different tube currents (mA) and it was found no considerable variation in CT number and CNR with tube current for each of CMs. Our

results indicated that for a given concentration and tube potential, the CT number of AuNP was considerably higher than the CT numbers of Iodine and Gadolinium. Higher CT number and attenuation of AuNP stems from this fact that Au has a higher atomic number and density ($Z = 73$, density = 19.30 g/cm^3) in comparison with iodine ($Z = 53$, density = 4.93 g/cm^3), and gadolinium ($Z = 64$, density = 7.90 g/cm^3). As we know from basic radiation physics, that the main interaction

between photons and atoms of CMs is photoelectric. Therefore, the attenuation coefficient of photons is extremely dependent on atomic number (Z^3). On the other hand, the atomic number and density of Gadolinium ($Z = 64$, density = 7.90 g/cm^3) are higher than Iodine ($Z = 53$, density = 4.93 g/cm^3). However, the results showed higher CT number and CNR for Iodine compared to Gadolinium. To explain this, we have depicted the attenuation coefficient of all three elements in terms of photon energy in **Figure 5**. The maximum intensity (intensity peak) of a photon spectrum happens at the 1/3 of its maximum photon energy. So, for the photon energy spectra used in the current study the peak intensity of photons is located between 26-47 keV approximately. Additionally, it can be seen in **Figure 5** that k-edge absorption of Iodine and Gadolinium atoms occurs at the photon energy of 33.2 KeV and 50.2 KeV respectively. Thus, in the energy range of 26-49 KeV, the attenuation of Iodine atoms is greater than Gadolinium and this leads to higher CT number of Iodine in comparison to Gadolinium.

Considering the variation of CT number with other parameters in CM, the results of the current study were in accordance with findings of Xu *et al* [28] and Kim and Jon [29]. They reported an increment of CT number by increasing the CM concentration. Also, the same results were reported with Boote *et al* [8] about linear increment in CT number with AuNP concentration.

Our results showed that higher concentration of CMs leads to better image quality in terms of CNR. With the increment of concentration, the number of particles in a determined volume increases. So linear attenuation coefficient goes up and causes an increase in the CT number. Moreover, CNRs was enhanced for all CMs by increase in concentration and tube potential.

Additionally, increase in tube potential reduces the number of attenuated photons. Thus, the attenuation coefficient becomes smaller and it causes lower CT number for all studied CM. on the other hand, as the number of detected photons increases, the noise content of the image is decreased and consequently a higher CNR was obtained.

If we compare our results with other similar studies in terms of CNR, our results were in agreement with Jackson *et al* and Papadakis *et al* [16,21]. As they found that CNR is increased by increasing the concentration of CMs (AuNPs, Iodine) and also AuNP showed better CNR in comparison with Iodine at the same concentration. However, there were small discrepancies between our results and their reported value for CNR. This can be attributed to difference in the imaging properties of x-ray CT scanner including the beam spectra and detector performances as well as concentrations and the size of studied AuNPs.

References

- [1] Mesbahi A. A review on gold nanoparticles radiosensitization effect in radiation therapy of cancer. *Rep Pract Oncol Radiother.* 2010;15(6):176-80.
- [2] Mesbahi A, Jamali F, Garehaghaji N. Effect of photon beam energy, gold nanoparticle size and concentration on the dose enhancement in radiation therapy. *Bioimpacts.* 2013;3(1):29-35.

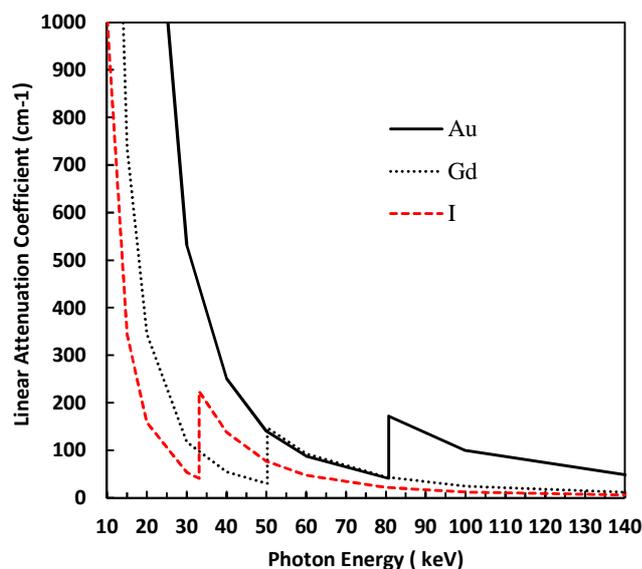


Figure 5. Linear attenuation coefficient versus photon energy for three elements of Au, Gd, and I.

Conclusion

Our results showed better imaging characteristics (contrast and CNR) for AuNP as a contrast medium compared to other conventional CMs. Also, in accordance with previous studies, it was found that for all CMs the CT number and CNR were dependent on the type of CM, concentration and tube voltage. Additionally, the AuNPs showed significantly higher contrast and better CNR relative to Iodine and Gadolinium in all cases. The maximum CT numbers of studied CM were obtained at the highest concentration and the lowest kVp. While, the highest CNR was seen at the maximum tube voltage. As the main finding of this study, it can be concluded that contrast media based on Au, in form of nanoparticles, provided higher contrast (up to 2-2.5 times) relative to conventional iodine-based CM which was dependent on tube voltage and concentration. Thus, its application in X-ray CT can remarkably enhance the image quality and consequently provide better diagnostic results.

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- [3] Saharkhiz H, Gharehaghaji N, Nazarpour M, et al. The Effect of Inversion Time on the Relationship Between Iron Oxide Nanoparticles Concentration and Signal Intensity in T1-Weighted MR Images. *Iran J Radiol.* 2014;11(2):e12667.
- [4] Hainfeld JF, Slatkin DN, Focella TM, et al. Gold nanoparticles: a new X-ray contrast agent. *Br J Radiol.* 2014;79(939):248-253.
- [5] Reuveni T, Motiei M, Romman Z, et al. Targeted gold nanoparticles enable molecular CT imaging of cancer: an in vivo study. *Int J Nanomedicine.* 2011;6:2859-2864.
- [6] Popovtzer R, Agrawal A, Kotov NA, et al. Targeted gold nanoparticles enable molecular CT imaging of cancer. *Nano Lett.* 2008;8(12):4593-4596.
- [7] Cho EC, Glaus C, Chen J, et al. Inorganic nanoparticle-based contrast agents for molecular imaging. *Trends Mol Med.* 2010;16(12):561-573.
- [8] Boote E, Fent G, Kattumuri V, et al. Gold nanoparticle contrast in a phantom and juvenile swine: models for molecular imaging of human organs using x-ray computed tomography. *Acad Radiol.* 2010;17(4):410-417.
- [9] Kim D, Park S, Lee JH, et al. Antibiofouling polymer-coated gold nanoparticles as a contrast agent for in vivo X-ray computed tomography imaging. *J Am Chem Soc.* 2007;129(24):7661-7665.
- [10] Cormode DP, Skajaa T, van Schooneveld MM, et al. Nanocrystal core high-density lipoproteins: a multimodality contrast agent platform. *Nano Lett.* 2008;8(11):3715-3723.
- [11] Rabin O, Perez JM, Grimm J, et al. An X-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. *Nat Mater.* 2006;5(2):118-122.
- [12] Hyafil F, Cornily JC, Feig JE, et al. Noninvasive detection of macrophages using a nanoparticulate contrast agent for computed tomography. *Nat Med.* 2007;13:636-641.
- [13] Mukundan S Jr, Ghaghada KB, Badea CT, et al. A liposomal nanoscale contrast agent for preclinical CT in mice. *AJR Am J Roentgenol.* 2006;186(2):300-307.
- [14] Cormode DP, Jarzyna PA, Mulder WJ, et al. Modified natural nanoparticles as contrast agents for medical imaging. *Adv Drug Deliv Rev.* 2010;62(3):329-338.
- [15] Peng C, Zheng L, Chen Q, et al. PEGylated dendrimer-entrapped gold nanoparticles for in vivo blood pool and tumor imaging by computed tomography. *Biomaterials.* 2012;33(4):1107-1119.
- [16] Jackson PA, Rahman WN, Wong CJ, et al. Potential dependent superiority of gold nanoparticles in comparison to iodinated contrast agents. *Eur J Radiol.* 2010;75(1):104-109.
- [17] Ghaghada KB, Badea CT, Karumbaiah L, et al. Evaluation of tumor microenvironment in an animal model using a nanoparticle contrast agent in computed tomography imaging. *Acad Radiol.* 2011;18(1):20-30.
- [18] Huo D, He J, Li H, et al. Fabrication of Au@Ag core-shell NPs as enhanced CT contrast agents with broad antibacterial properties. *Colloids Surf B Biointerfaces.* 2014;117:29-35.
- [19] Lee N, Choi SH, Hyeon T. Nano-sized CT contrast agents. *Adv Mater* 2013;25(19):2641-2660.
- [20] Nakagawa T, Gonda K, Kamei T, et al. X-ray computed tomography imaging of a tumor with high sensitivity using gold nanoparticles conjugated to a cancer-specific antibody via polyethylene glycol chains on their surface. *Sci Technol Adv Mater.* 2016;17(1):387-397.
- [21] Papadakis AE, Perisinakis K, Raissaki M, et al. Effect of x-ray tube parameters and iodine concentration on image quality and radiation dose in cerebral pediatric and adult CT angiography: a phantom study. *Invest Radiol.* 2013;48(4):192-199.
- [22] Silvestri A, Polito L, Bellani G, et al. Gold nanoparticles obtained by aqueous digestive ripening: Their application as X-ray contrast agents. *J Colloid Interface Sci.* 2015;439:28-33.
- [23] Silvestri A, Zambelli V, Ferretti AM, et al. Design of functionalized gold nanoparticle probes for computed tomography imaging. *Contrast Media Mol Imaging.* 2016;11(5):405-414.
- [24] Zhou B, Zheng L, Peng C, et al. Synthesis and characterization of PEGylated polyethylenimine-entrapped gold nanoparticles for blood pool and tumor CT imaging. *ACS Appl Mater Interfaces* 2014;6(19):17190-17199.
- [25] Ebrahimi M, Johari-Ahar M, Hamzeiy H, et al. Electrochemical impedance spectroscopic sensing of methamphetamine by a specific aptamer. *BioImpacts.* 2012;2(2):91-95.
- [26] Qiu H, Sun Y, Huang X, et al. A sensitive nanoporous gold-based electrochemical aptasensor for thrombin detection. *Colloids Surf B Biointerfaces.* 2010;79(1):304-308.
- [27] Kim CS, Ahn YC, Wilder-Smith P, et al. Efficient and facile delivery of gold nanoparticles in vivo using dissolvable microneedles for contrast-enhanced optical coherence tomography. *Biomed Opt Express.* 2010;1(1):106-113.
- [28] Xu C, Tung GA, Sun S. Size and concentration effect of gold nanoparticles on X-ray attenuation as measured on computed tomography. *Chem Mater.* 2008;20(13):4167-4169.
- [29] Kim D, Jon S. Gold nanoparticles in image-guided cancer therapy. *Inorganica Chimica Acta.* 2012;393:154-164.