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Quantitative dosimetric assessment for effect of gold nanoparticles as contrast media on radiotherapy planning

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HIGHLIGHTS

- We investigate the effect of gold nanoparticle on dosimetry in CT planning.
- A recent volumetric modulated arc radiotherapy is included for study.
- An analytical phantom and clinical scenario are included for study.
- A clinical contrast agent is included for comparisons with gold nanoparticles.

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ABSTRACT

In CT planning for radiation therapy, patients may be asked to have a medical procedure of contrast agent (CA) administration as required by their physicians. CA media improve quality of CT images and assist radiation oncologists in delineation of the target or organs with accuracy. However, dosimetric discrepancy may occur between scenarios in which CA media are present in CT planning and absent in treatment delivery. In recent preclinical experiments of small animals, gold nanoparticles (AuNPs) have been identified as an excellent contrast material of x-ray imaging.

In this work, we quantitatively evaluate the effect of AuNPs to be used as a potential material of contrast enhancement in radiotherapy planning with an analytical phantom and clinical case. Conray 60, an iodine-based product for contrast enhancement in clinical uses, is included as a comparison. Other additional variables such as different concentrations of CA media, radiation delivery techniques and dose calculation algorithms are included. We consider 1-field AP, 4-field box, 7-field intensity modulated radiation therapy (IMRT) and a recent technique of volumetric modulated arc therapy (VMAT). CA media of AuNPs (Conray 60) with concentrations of 10%, 20%, 30%, 40% and 50% containing 28.2, 56.4, 84.6, 112.8 and 141.0 mg of gold (iodine) per mL were prepared prior to CT scanning. A virtual phantom with a target where nanoparticle media are loaded and clinical case of gastric lymphoma in which the Conray 60 media were given to the patient prior to the CT planning are included for the study. Compared to Conray 60 media with concentration of 10%/50%, Hounsfield units for AuNP media of 10%/50% are 322/1608 higher due to the fact that atomic number of Au ($Z=79$) is larger than I ($Z=53$). In consequence, dosimetric discrepancy of AuNPs is magnified between presence and absence of contrast media. It was found in the phantom study that percent dose differences between presence and absence of CA media may be reduced by delivery techniques of 7-field IMRT or VMAT. To manage less than 3% of percent dose difference, it was suggested an upper limit of 15% (or 42.3 mg Au/mL) of AuNP media in the phantom study; 8% (or 22.5 mg Au/mL) in the specific clinical case.

1. Introduction

In clinical CT examinations, patients may be asked to have a medical procedure of contrast agent (CA) administration as required by radiologists. The CA media enhance contrast of CT images in specific targets, organs or blood vessels to their surrounding tissues. Studies show that the contrast media are effective for tumor diagnosis and assessment in patients with

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prostate cancer, lung cancer, nasopharyngeal carcinoma, cervical cancer or head and neck cancer (Choi et al., 2006; Haider et al., 2005; Korporaal et al., 2010; Lazanyi et al., 2010; Lee et al., 2009; Van Camp et al., 2000; Xiao et al., 2010). In radiation therapy treatment, patients may take CA orally, rectally or via a vein injection prior to a CT scanning. The dataset of CA-enhanced images is then used for delineation, optimization and dose calculations. Although the procedure of CA injection to patients improves accuracy of target or organ delineation in planning, dose discrepancies may occur at the scenario in which the same CA media are absent in delivery of irradiation beams to patients.

In a previous report regarding the influence of contrast materials on dose calculations in radiotherapy planning, Shibamoto et al. studied various anatomical regions and concluded that the upper abdominal site could be affected the most by the injection of contrast media (Shibamoto et al., 2007). Other similar studies suggested that irradiation techniques such as the number of incident beams and algorithms of dose calculations may extend a certain impact on dosimetry when CA is administrated to patients in CT planning for accurate contour delineation (Ramm et al., 2001; Rankine et al., 2008; Shibamoto et al., 2007; Wertz and Jakel, 2004; Xiao et al., 2010).

In recent years, technology of material development of gold nanoparticles (AuNPs) and their related studies in small animals have been substantially advanced (Boisselier and Astruc, 2009; Peng et al., 2012; Sharma et al., 2006). Applications include targeted drug delivery in which AuNPs serve as the functional carrier to allow local retention of therapeutic agents at a specific target site. Studies of small animals in x-ray based imaging show that the AuNP is an excellent contrast material (Hainfeld et al., 2008, 2004; Sharma et al., 2006; Wang et al., 2011). Toxicity and clearance tests suggest that the AuNP is biocompatible and low toxicity in cells and animals (Hainfeld et al., 2008, 2006). As a consequence, it is conceivable that the AuNP may be used as a contrast material for clinical imaging applications in the near future if extensive preclinical investigations can be performed and safety can be confirmed.

In this work, we investigate a potential clinical application in radiation therapy that the AuNP is used as the contrast material for contrast enhancement in CT images and assisting target delineation in radiotherapy planning. The effect of AuNPs on dosimetry is quantitatively evaluated in the treatment planning system between scenarios in which AuNP media are present and absent in CT images. AuNP media with various concentrations are prepared prior to CT scanning and their corresponding Hounsfield units are obtained. An analytical phantom and a clinical case of gastric lymphoma are evaluated. As a comparison, Conray 60 (Mallinckrodt, St. Louis, USA), an iodine-based material and currently used in clinical imaging applications, is included in our examination. Two algorithms of dose calculations in the planning software, analytical anisotropic algorithm (AAA) and pencil beam convolution (PBC), are included.

In recent development of radiation therapy, volumetric modulated arc therapy (VMAT) is a new planning and treatment technique for irradiation delivery to patients with dynamic rotational speed of gantry and changing dose rate over one single arc or full rotation. At our clinical facility, we have started to use new VMAT technology with RapidArc radiotherapy (Varian Medical Systems, Palo Alto, CA, USA) for patient treatment since 2009. Contrast to conventional techniques such as intensity-modulated radiation therapy (IMRT) or 3D conformal radiotherapy, RapidArc radiotherapy distributes irradiation beams to patients through a continuous gantry rotation with variable speed. In particular, the volume dose is optimized by simultaneous consideration of leaf position, dose rate and gantry speed in the planning software of RapidArc radiotherapy (Otto, 2008). To our best knowledge, we are not aware of reports for the dosimetric consequence of new VMAT technology on the presence of CA media in CT planning. In addition to RapidArc, irradiation techniques of 1-field AP, 4-field box and 7-field IMRT are included in our work.

In clinical practice, the dosimetric discrepancies due to the CA administration in radiotherapy planning may be overcome by performing two CT scans. However, there are scenarios that it may not be feasible to manage two separate CT scans for patients. For example, the number of patients is much more than that the medical supporting staffs. To maintain a certain throughput of healthcare service of high quality, one set of CT scanning may be the only option. In particular, similar scenarios apply to many developing and under-developed countries when the population is huge or medical resources are very limited. Also our work may serve as an educational study for both patients and medical staffs such as physicians and medical physicists. In particular, our work and upper bound suggestion of CA concentration for the recent RapidArc may provide useful information.

2. Materials and methods

Our samples of AuNPs were purchased from Nanoprobes (AuroVist, Yaphank, New York, USA) and these commercial particles had been tested in several animal studies (Boisselier and Astruc, 2009; Hainfeld et al., 2006). Average hydrodynamic size was measured to be 1.9 nm. Other physical and chemical properties included low acute toxicity, low osmolality and low viscosity (Boisselier and Astruc, 2009; Hainfeld et al., 2006). The lifetime of AuNPs in blood pool system in mice is around 5–10 min.

For the purpose of comparisons, Conray 60 is included in our studies. Conray 60 is an iodine-based contrast agent for clinical X-ray based imaging. Conray 60 contains 600 mg of iothalamate meglumine and organically bound iodine of 282 mg per mL. CA media of AuNPs vs. Conray 60 with concentrations of 10%, 20%, 30%, 40% and 50% containing 28.2, 56.4, 84.6, 112.8 and 141 mg of gold (Au, $Z=79$) vs. iodine (I, $Z=53$) per mL were prepared and then filled in plastic Eppendorf tubes of 2.0 mL prior to the CT scanning for measurements of Hounsfield units.

For acquisitions of Hounsfield units for AuNP and Conray 60 media, CT images were obtained by a scanner (LightSpeed RT 16, GE Healthcare) in our CT simulation facility for radiation therapy. We used the 16-bit option and the extended CT number range is from −1000 to 55535. Eppendorf tubes were placed and aligned at the rotation center of CT scanner. The Eppendorf tube is cylindrical-cone shaped. The geometry of the Eppendorf tube is 1 cm in inner radius and 4.0 in length. We scanned the Eppendorf tube in a sequential manner. Settings of 120 kVp, 240 mAs and slice thickness of 10 mm were used. A circular region of interest of 25 mm^2 at the center of Eppendorf tube was drawn to compute their corresponding Hounsfield units after image reconstruction. A separate tube containing water was prepared for the calibration of Hounsfield units. The supporting frame for the CIRS model 062M electron density phantom (Computerized Imaging Reference Systems Inc., Norfolk, Virginia, USA) was used for CT measurements. Each Eppendorf tube is inserted and placed at the central hole prior to the CT scan. All measurements of Hounsfield units are repeated several times and the uncertainties are estimated to be less than 5%.

To quantitatively evaluate the influence of presence of contrast material on dosimetric calculations, a virtual water phantom of $20\times20\times20$ cm^3 was created in our planning software and a target of 6 cm in diameter and 8 cm in length was placed inside the water phantom. The geometric center of target is located 6 cm below the water surface. The corresponding numerical value of