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Gold Nanoparticle Size, Biodistribution, and Toxicity: Insights from Dual-Energy CT

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Abstract

Dual-energy and spectral computed tomography (CT) have emerged as powerful platforms for noninvasive, quantitative mapping of nanoparticle biodistribution in vivo. By exploiting the energy-dependent attenuation profiles of high-atomic-number (high-Z) materials, these systems enable material decomposition and element-specific imaging, thereby distinguishing nanoparticle signals from those of soft tissues and conventional iodinated contrast agents. Photon-counting spectral CT further enhances this capability by binning individual photons into multiple energy channels, improving spatial resolution, contrast-to-noise ratio, and enabling K-edge imaging for precise elemental identification. Among available nano-contrast agents, gold nanoparticles (AuNPs) have attracted particular attention due to their high atomic number (Z = 79), excellent X-ray attenuation, tunable size, and versatile surface chemistry. These properties make AuNPs highly suitable for vascular imaging, tumor targeting, and molecular CT applications. Studies have demonstrated that AuNPs provide prolonged vascular enhancement compared with iodine-based agents, with circulation times modifiable through surface coatings such as polyethylene glycol (PEG). Functionalization with targeting ligands – including peptides, antibodies, and folate – enables receptor-specific accumulation in tumors and inflamed tissues, enhancing lesion detectability and diagnostic accuracy. A critical determinant of AuNP performance is particle size, which directly influences pharmacokinetics, biodistribution, and clearance pathways. Smaller nanoparticles (approximately 5–20 nm) exhibit prolonged circulation, reduced uptake by the reticuloendothelial system (RES), and more uniform tissue distribution. In contrast, larger particles tend to accumulate rapidly in the liver and spleen due to macrophage-mediated clearance. Surface charge and coating further modulate protein adsorption, immune recognition, and biological interactions, thereby affecting imaging outcomes and quantification accuracy. Quantitative assessment of biodistribution using dual-energy CT relies on calibration with phantoms containing known nanoparticle concentrations, followed by acquisition under standardized imaging conditions and application of material decomposition algorithms. Strong correlations between CT-derived concentrations and ex vivo analytical techniques, such as inductively coupled plasma mass spectrometry, validate the reliability of spectral CT for nanoparticle tracking. Despite these advances, concerns regarding long-term retention, potential toxicity, and regulatory challenges persist. Accumulation in RES organs raises questions about chronic exposure, while variations in nanoparticle synthesis and functionalization complicate standardization. Nevertheless, ongoing improvements in CT hardware, including photon-counting detectors, and advances in nanoparticle engineering continue to expand the clinical potential of AuNP-based imaging. This integration

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of nanotechnology with advanced imaging modalities represents a promising frontier for precision diagnostics, enabling simultaneous visualization, quantification, and targeting of disease processes at the molecular level.

Keywords: Gold nanoparticles, dual-energy CT, spectral CT, photon-counting CT, biodistribution, nanoparticle size, toxicity, molecular imaging

INTRODUCTION

Dual-energy and spectral computed tomography (CT) exploit the energy-dependent X-ray attenuation of high-atomic-number nanoparticles to obtain element-specific maps of in vivo biodistribution [1]. Inorganic nanoparticles based on gold, bismuth, rare earths, and other high-Z elements provide higher attenuation than conventional iodinated agents at matched molar concentrations and can be quantified using material-decomposition algorithms and K-edge imaging [2].

Photon-counting spectral CT uses energy-resolving detectors to bin individual photons, allowing separation of background tissues, iodinated contrast, and one or more nanoparticle elements within the same scan. This approach can achieve better image contrast, higher spatial resolution, and dose reduction compared with conventional CT, while enabling molecular imaging of nanoparticle-labeled targets [3].

Gold nanoparticles are among the earliest and best-studied nano-contrast agents for CT because of their high atomic number, tunable size, and versatile surface chemistry. In early work, long-circulating gold nanoparticles produced substantially greater vascular contrast than iodinated agents in small-animal models, with enhancement persisting for many hours. Subsequent studies showed that surface modification with polyethylene glycol and targeting ligands improves circulation time and allows receptor-mediated accumulation in tumors and inflamed atherosclerotic plaques [3, 4].

Bismuth-based nanoparticles, such as bismuth sulfide and bismuth fluoride, offer very high attenuation and can be formulated as albumin- or polymer-stabilized probes for CT. In animal studies, bismuth nanoprobes demonstrated prolonged blood-pool residence, strong tumor uptake, and higher CT contrast than iodinated agents at equivalent concentrations. Rare-earth-based nanoparticles, including thulium-doped upconversion systems, have been developed for dual spectral CT and optical imaging and may show greater CT contrast efficacy than standard iodinated contrast media [4].

Quantification of nanoparticle biodistribution with dual-energy CT generally requires calibration phantoms with known nanoparticle concentrations, acquisition of dual-energy or spectral data under identical conditions, and two- or three-material decomposition to generate quantitative concentration maps [5]. Strong correlations have been reported between spectral CT–derived nanoparticle concentrations and ex vivo elemental analysis in preclinical models, supporting the reliability of CT-based biodistribution (Table 1).

Biological determinants of nanoparticle biodistribution include particle size, surface charge, and coating, ligand decoration, dose, and route of administration [5]. Smaller particles and hydrophilic coatings – such as polyethylene glycol – tend to prolong circulation and reduce reticuloendothelial uptake, whereas larger particles and unmodified surfaces favor rapid liver and spleen accumulation [7]. Targeting ligands, including peptides and antibodies, can increase uptake in receptor-positive tumors and other molecular targets, improving lesion-to-background contrast on spectral CT [6]. Safety considerations include long-term retention in reticuloendothelial organs, the potential for cumulative toxicity, and manufacturing and regulatory barriers, which currently limit clinical translation despite rapid advances in dual-energy and photon-counting CT hardware [2, 8].

Table 1. Dual-energy and spectral CT strategies for nanoparticle biodistribution.

Technique	Energy configuration	Advantages of nanoparticle imaging	Limitations
Dual-source dual-energy CT	Two tubes at different kVp (for example, 80 and 140 kVp) [6].	Simultaneous acquisition at two spectra; robust two-material decomposition for separating one high-Z element from soft tissue or iodine [2, 6].	Limited to two effective spectra, restricting multi-element K-edge imaging [2, 6].
Rapid kVp-switching CT	Single tube alternating between low and high kVp [6].	Good temporal registration; compatible with many current scanners [6].	Requires dedicated hardware; motion can degrade high-frequency switching data [6].
Dual-layer detector CT	Stacked detectors separating low- and high-energy photons [6].	Truly simultaneous dual-energy data; improved registration for dynamic imaging [6].	Fixed spectral separation and fewer effective energy bins than photon-counting detectors [6].
Photon-counting CT	Energy-resolving detectors with multiple energy bins [2, 4, 7].	Element-specific K-edge imaging, high spatial resolution, and potential dose reduction [2, 4, 7].	Limited clinical availability, higher system cost, and need for standardized reconstruction pipelines [2, 4, 7].
Preclinical dual-energy microCT	High-resolution microCT at two kVp settings [1, 8].	Very fine spatial resolution and flexible phantom calibration for small-animal studies [1, 8].	Higher radiation dose and limited direct translation of protocols to humans [1, 8].

PHYSICAL PRINCIPLES AND EVOLUTION OF DUAL-ENERGY AND SPECTRAL CT

Conventional single-energy CT uses a broad polychromatic X-ray spectrum and reconstructs images under the assumption of a single effective energy, which limits material characterization. In contrast, dual-energy and spectral CT acquire attenuation data at two or more distinct energy spectra and use the differing photoelectric and Compton components to discriminate between materials with different effective atomic numbers (Table 2).

Table 2. Example workflow for preclinical spectral CT quantification of nanoparticle biodistribution.

Step	Description	Practical notes
Nanoparticle synthesis and characterization	Prepare high-Z nanoparticles (for example, gold or bismuth), and measure size, surface charge, and elemental concentration [1, 2, 9].	Confirm colloidal stability in physiologic media and sterility before in vivo use [2, 9].
Phantom calibration	Build phantoms with graded nanoparticle concentrations and scan them using the intended dual-energy or spectral protocol [2, 4, 7].	Derive attenuation–concentration curves and material-decomposition coefficients for each relevant energy bin [2, 4, 7].
Animal preparation and dosing	Administer nanoparticles intravenously at a defined dose and schedule imaging to capture vascular and tissue phases [1, 3, 8].	Monitor physiologic parameters and anesthesia, which affect hemodynamics and enhancement [1, 3].
Dual-energy or spectral CT acquisition	Acquire scans covering target organs using dual-source, kVp-switching, or photon-counting CT, depending on availability [2, 4, 7].	Maintain consistent positioning and motion control to improve registration and reproducibility [2, 7].
Material decomposition and map generation	Apply two- or three-material decompositions to generate quantitative nanoparticle maps [2, 4, 7, 10].	Validate results with phantom data and, where possible, tissue samples of known concentration [2, 4, 10].
Region-of-interest analysis	Place regions of interest in the blood pool, liver, spleen, kidneys, tumors, and reference tissues to extract concentration–time curves [1, 3, 5].	Use standardized regions-of-interest sizes and locations to minimize variability [1, 3].
Ex vivo validation	Measure elemental content in excised organs with techniques such as inductively coupled plasma mass spectrometry [1, 2, 10].	Compare imaging-derived concentrations with ex vivo data to refine calibration and assess accuracy [1, 2, 10].

Note: This claim is based on preclinical data.

The key to nanoparticle quantification lies in the strong energy dependence of the photoelectric effect for high-Z elements and the presence of sharp K-edges in their attenuation spectra (Table 3). When the incident photon energy crosses the K-edge of an element (for example, around 80.7 keV for gold), the attenuation coefficient increases abruptly; spectral CT can exploit this by placing energy bins just below and above the K-edge to isolate the signal of that element from background tissues and from conventional iodinated contrast. Base-material decomposition algorithms then model attenuation in each voxel as a linear combination of two or more basis materials, allowing reconstruction of quantitative density maps for the nanoparticle and for water or soft tissue [11].

Table 3. Advantages and limitations of dual-energy and spectral CT for nanoparticle biodistribution.

Aspect	Advantages	Limitations and challenges
Sensitivity and contrast	High-Z nanoparticles provide stronger attenuation than iodinated agents and can be isolated by K-edge imaging [1, 2, 11].	Spectral CT remains less sensitive than nuclear methods, and relatively high doses may be necessary in some applications [2, 10].
Spatial and temporal resolution	CT offers submillimeter spatial resolution and high temporal resolution suitable for dynamic vascular and tissue imaging [2, 4, 7].	Radiation exposure limits repeat imaging in patients; preclinical microCT doses can be substantial [1, 8, 10].
Multiparametric capability	Dual-energy and photon-counting CT can separate multiple materials and provide quantitative maps for each [2, 4, 7, 10].	Calibration and reconstruction are complex and overlapping K-edges and beam hardening reduce accuracy [2, 4, 7].
Biological insight	Noninvasive maps of nanoparticle uptake and clearance support pharmacokinetic modeling and evaluation of targeted therapies [1, 3, 5].	Most experience is preclinical, and clinical data with nanoparticle contrast agents are limited [2, 10, 12].
Translation and safety	Some nanoparticle formulations show acceptable short-term biocompatibility and prolonged circulation in animal models [1, 2, 9].	Long-term retention, potential toxicity, and regulatory barriers currently limit clinical deployment [2, 9, 12].

Several hardware approaches have matured in parallel. Dual-source systems employ two X-ray tubes and detector arrays at different kVp, rapid kVp-switching scanners alternate tube potential within a single rotation, and dual-layer detectors separate high- and low-energy photons at the detector level. More recently, photon-counting CT has introduced energy-resolving detectors that register and bin individual photons, supporting multiple energy windows and precise K-edge imaging for one or more elements in the same scan. These technical advances have laid the foundation for using high-Z nanoparticles as quantitative contrast agents rather than merely qualitative enhancers [9].

NANOPARTICLE CLASSES FOR DUAL-ENERGY CT AND THEIR BIODISTRIBUTION

Gold Nanoparticles

Gold nanoparticles are prototypical CT nano-contrast agents because gold has a high atomic number (Z=79), strong X-ray attenuation, straightforward synthesis, and versatile surface chemistry (Table 4). In a landmark preclinical study, a polyethylene glycol–stabilized gold formulation provided greater radiographic density than an iodinated contrast agent at 40 kVp and comparable density at 60 and 140 kVp, with bright enhancement of the abdominal aorta and renal arteries persisting for 24 hours, long after iodinated enhancement had disappeared.

Biodistribution of gold nanoparticles is strongly size-dependent. Smaller particles in the range of roughly 5–20 nm tend to have longer circulation times and more homogeneous organ distribution, whereas larger particles accumulate more rapidly in liver and spleen via the reticuloendothelial system. Surface coatings modulate this pattern: polyethylene glycol reduces opsonization and slows clearance, while targeting ligands, such as folate or antibodies, can increase uptake in receptor-positive tumors, inflammatory plaques, or other pathologies. Dual-energy and photon-counting CT can distinguish these high-Z particles from iodine and soft tissue and generate voxel-wise gold concentration maps, enabling dynamic analysis of vascular, organ, and tumor enhancement [15].

Bismuth-Based Nanoparticles

Bismuth has an even higher atomic number (Z = 83) than gold and a K-edge near 90.5 keV, giving Bi-based nanoparticles exceptional attenuation per unit mass. Early work with bismuth sulfide nanoparticles demonstrated long-circulating CT contrast agents with strong enhancement and high radiodensity compared with iodinated media in small-animal models. More recent formulations have used albumin or polymer coatings and peptide ligands, such as Triptorelin, to create targeted nanoprobes that preferentially accumulate in tumors expressing specific receptors.

Spectral CT techniques can separate the bismuth signal from iodine and calcium and can apply K-edge imaging strategies analogous to those used for gold. In these settings, dual-energy CT not only delineates tumor margins with high contrast but also quantifies intratumoral bismuth concentration, which can serve as a surrogate for nanoparticle-carried drug loading or radiosensitizer distribution in theranostic applications. Because bismuth is not an endogenous element in humans, its presence is highly specific on K-edge images, simplifying interpretation of biodistribution maps [13].

Table 4. Major high-atomic-number nanoparticle classes for spectral CT.

Nanoparticle type	Core element (Z)	Typical size (nm)	Key coatings or ligands	Main applications	Contrast vs iodinated agents
Gold nanoparticles	Gold (79) [1, 6].	Approximately 4–150; 10–20 commonly used in vascular and tumor studies [1, 6, 8].	Polyethylene glycol, folate, antibodies, peptides [3, 8, 11].	Long-lasting vascular contrast, tumor imaging, atherosclerotic plaque imaging, K-edge spectral CT [1, 3, 8].	Higher attenuation than iodine at low kVp; prolonged vascular enhancement in small animals [1, 6].
Bismuth-based nanoparticles	Bismuth (83) [2, 9].	Tens of nanometers for bismuth sulfide and related formulations [2, 9].	Albumin, polymers, peptide ligands [2, 9].	Tumor-targeted CT, K-edge imaging, blood-pool contrast [2, 9].	Very high HU per mg/mL; stronger contrast than iodine in phantoms and in vivo models [2, 9].
Gadolinium-containing nanoparticles	Gadolinium (64) [4].	Approximately 50–200 (liposomes and polymeric carriers) [4, 13].	Lipid bilayers, polyethylene glycol, tumor-targeting ligands [4, 13].	Dual CT and MR imaging, blood-pool contrast, tumor imaging [4, 13].	Useful K-edge at about 50 keV; lower Z than gold or bismuth but adequate for spectral CT [4].
Rare-earth-based nanoparticles	Thulium and other lanthanides [4].	Around 20 for some upconversion nanoparticle formulations [4].	Silica or polymer shells, targeting moieties [4].	Photon-counting CT plus near-infrared fluorescence, theranostics [4, 14].	Up to markedly higher CT contrast efficacy than a standard iodinated agent at matched conditions [4].
Tantalum or hafnium oxides	Tantalum (73), hafnium (72) [4, 13].	Roughly 5–100, depending on synthesis [4, 13].	Polymer or silica coatings, targeting ligands [4, 13].	Radiotherapy dose enhancement with CT-based tracking [4, 13].	High attenuation comparable with other high-Z nanoparticles in preclinical studies [4, 13].

Rare-Earth and Other Heavy-Metal Nanoparticles

Beyond gold and bismuth, a range of heavy-metal systems have been investigated to leverage K-edges at different energies and to support multimodality imaging. Rare-earth-based nanoparticles, including thulium-doped upconversion systems, can provide both high-contrast spectral CT and near-infrared fluorescence, combining anatomical and optical readouts. Some of these formulations

have shown substantially higher CT contrast efficacy than standard iodinated agents at matched conditions in phantoms, reflecting both their higher atomic number and optimized particle design.

Other heavy-metal nanoparticles based on tantalum, hafnium, or tungsten have been explored for their potential to enhance radiotherapy dose deposition while simultaneously enabling CT-based tracking of biodistribution. These agents are often engineered with polymer or silica shells to improve biocompatibility and to present targeting ligands, creating multifunctional platforms that combine imaging and therapy. The ability of dual-energy CT to distinguish different K-edges raises the possibility of multiplexed imaging in which separate nanoparticle formulations label different biological processes or cell populations within the same examination [10, 13].

QUANTITATIVE METHODS FOR NANOPARTICLE BIODISTRIBUTION

Calibration and Material Decomposition

Reliable quantification of nanoparticle biodistribution requires careful calibration. Phantom studies with tubes containing known concentrations of nanoparticles are typically performed under the same acquisition conditions as in vivo scans to establish relationships between Hounsfield units and concentration at each energy. In simple dual-energy implementations, two-material decomposition models attenuate as a combination of water (or soft tissue) and the nanoparticle, whereas more complex scenarios introduce a third basis material, such as iodine, to allow separation of endogenous contrast, iodinated agents, and the nanoparticle in one dataset.

Photon-counting CT extends these concepts by offering multiple energy bins, which can be tuned to straddle the K-edges of specific elements, yielding K-edge images where the signal is linearly proportional to the number of photons absorbed in the narrow energy interval dominated by the target element. With appropriate energy bin selection and calibration, this allows direct conversion of image intensity into nanoparticle concentration maps, even in the presence of overlapping tissues and other contrast agents.

Validation Against ex Vivo Measurements

Because CT attenuation can be influenced by scanner settings, reconstruction kernels, and beam-hardening effects, ex vivo validation remains an important component of nanoparticle biodistribution studies. Many preclinical investigations correlate spectral CT-derived concentrations with inductively coupled plasma mass spectrometry or atomic absorption measurements of excised organs. Correlation coefficients in the range of 0.8–0.9 have been reported for certain gold and bismuth formulations, indicating that quantitative spectral CT can approximate actual tissue concentrations within clinically relevant margins (Table 5).

Table 5. Determinants of nanoparticle biodistribution and implications for CT quantification.

Parameter	Influence on biodistribution	Impact on CT-based quantification
Particle size	Small particles with diameters around 5–20 nm exhibit longer circulation and more homogeneous organ distribution, whereas larger particles show enhanced reticuloendothelial uptake [3, 5, 6].	Changes peak enhancement and washout in blood and organs, affecting time–attenuation curves and pharmacokinetic modeling [3, 5].
Surface chemistry	Hydrophilic coatings, such as polyethylene glycol, reduce opsonization and extend plasma half-life; albumin and polymers stabilize suspensions [3, 9].	Alters the temporal pattern of enhancement more than intrinsic attenuation, improving sensitivity for low-level uptake [3, 9].
Targeting ligands	Peptides, folate, and antibodies increase accumulation in receptor-positive tumors and other targets compared with non-targeted particles [3, 11 15].	Improves lesion-to-background contrast and enables quantification of specific versus nonspecific uptake with spectral CT [3, 11, 15].
Dose and route	Increasing dose produces near-linear increases in attenuation within the calibrated range; intravenous administration is standard, while other routes can localize particles to specific compartments [1, 8, 10].	Calibration phantoms must cover expected concentration ranges; different routes may require tailored imaging schedules and models [2, 8].
Organ microenvironment	Reticuloendothelial organs and tumors with enhanced permeability and retention accumulate many inorganic nanoparticles [3, 5, 10].	Baseline attenuation differences require organ-specific regions of interest and thresholds to maintain accuracy [2, 4, 10].

This imaging–tissue concordance enables kinetic modeling of nanoparticle pharmacokinetics using time–attenuation curves from serial scans, which can describe vascular half-life, volume of distribution, and organ-specific uptake and clearance. In the context of targeted therapies, these models can quantify on-target versus off-target delivery and support dose optimization for therapeutic payloads carried by nanoparticles [12].

Biological Determinants of Nanoparticle Biodistribution

Nanoparticle biodistribution reflects a complex interplay between physicochemical design and host biology. Size, shape, surface charge, and composition dictate how particles interact with serum proteins, endothelial barriers, and the mononuclear phagocyte system. Smaller, neutrally coated particles tend to remain longer in the circulation and may penetrate deeper into tumor interstitium, whereas larger or positively charged particles undergo rapid opsonization and sequestration in liver and spleen.

Surface coatings, such as polyethylene glycol, create a hydrophilic shell that reduces protein adsorption and recognition by macrophages, thereby prolonging blood half-life and allowing more time for particles to reach target tissues. Albumin or other biomimetic coatings can further enhance biocompatibility and leverage natural transport pathways; for example, albumin-bound bismuth nanoparticles have shown improved stability and tumor uptake in preclinical models. Ligand functionalization adds a second layer of specificity: peptides, antibodies, and small molecules can recognize and bind overexpressed receptors on tumor or inflammatory cells, creating high lesion-to-background ratios visible on spectral CT.

Host factors – such as vascular permeability, interstitial pressure, and immune status – also influence nanoparticle distribution. Tumors with pronounced enhanced permeability and retention effects may accumulate more nanoparticles passively, whereas fibrotic or poorly perfused tissues may limit penetration despite targeted ligands. Spectral CT provides a noninvasive means to study these biological phenomena in vivo by mapping nanoparticle concentration over time and space within the same subject [14, 15].

Safety Considerations and Translational Challenges

Although high-Z nanoparticles offer compelling imaging advantages, their long-term safety remains a major concern for clinical translation. Unlike small-molecule iodinated contrast agents, which are rapidly excreted by the kidneys, many inorganic nanoparticles exhibit prolonged retention in reticuloendothelial organs, including liver, spleen, and bone marrow. Preclinical studies have generally shown acceptable short-term biocompatibility for optimized formulations, but comprehensive data on chronic exposure, repeated dosing, and potential interference with immune function or hematopoiesis are still limited.

Manufacturing and regulatory barriers also slow adoption. Clinical-grade nanoparticle contrast agents must meet stringent standards for batch-to-batch consistency, sterility, and stability, and their complex structures – often incorporating metals, polymers, and targeting ligands – present challenges for quality control. Regulatory frameworks are evolving for nanomedicines, but relatively few nanoparticle CT agents have advanced beyond early-phase trials, and none have yet achieved routine clinical use as spectral CT–specific contrast agents [16].

From an imaging workflow perspective, integrating dual-energy or photon-counting protocols into routine practice requires optimization of acquisition and reconstruction parameters, user training, and standardized reporting. Radiologists must be familiar with material-decomposition images, virtual monoenergetic reconstructions, and K-edge maps to interpret nanoparticle biodistribution correctly and to recognize potential artifacts, including beam hardening, spectral misregistration, and noise amplification at low concentrations. Development of robust, vendor-neutral quantification tools and consensus guidelines will be critical if nanoparticle-based spectral CT is to move from research to clinical decision-making.

FUTURE DIRECTIONS

Several trends point toward broader adoption of dual-energy CT for nanoparticle imaging. First, photon-counting CT is transitioning from research prototypes into commercial clinical scanners, offering improved spatial resolution, reduced electronic noise, and flexible energy binning suitable for K-edge imaging of multiple elements. Second, advances in nanoparticle design are yielding more biocompatible, biodegradable, and multifunctional systems that combine imaging, therapy, and biosensing, potentially justifying the added complexity and cost compared with conventional contrast agents [17].

Third, there is growing interest in using spectral CT to complement or, in selected indications, partially replace nuclear imaging for certain quantitative tasks, such as tracking cell therapies or monitoring drug delivery, thereby avoiding radiotracer production and radiation safety constraints. Heavy-metal-based nanoparticles visible on photon-counting CT might serve as durable labels for immune cells or stem cells, enabling longitudinal tracking without repeated administration of radioactive tracers.

Finally, integration with artificial intelligence and radiomics could unlock additional value. High-dimensional spectral CT data – including monoenergetic images, effective atomic number maps, and quantitative nanoparticle distributions – can feed machine-learning models that detect subtle patterns of disease and therapeutic response. Such approaches may be particularly powerful in oncology, where nanoparticle biodistribution maps can be combined with tumor texture, perfusion, and metabolic imaging to characterize heterogeneity and guide personalized therapy.

Dual-energy CT can quantify nanoparticles of different sizes with high accuracy if calibration and material decomposition are properly optimized, but size mainly affects in vivo biodistribution and detectability rather than the intrinsic DECT attenuation–concentration relationship [18].

Phantom Data: Size vs Attenuation and Quantification

- In a systematic study of PEG-AuNPs ranging from 4 to 152 nm, phantom scans on multiple clinical CT scanners and an SPCCT system showed no significant dependence of CT attenuation on particle size at a given gold concentration.
- Across sizes, attenuation–concentration curves were linear and overlapped, and element-specific SPCCT reconstructions recovered gold concentration with high accuracy for all sizes; measured vs true concentrations had essentially the same ratio across formulations.
- These findings support the theoretical expectation that, for a fixed element, attenuation is determined by the number of atoms per voxel, not by whether those atoms are packaged into small or large particles.

Implication

For DECT/SPCCT phantoms, a single calibration curve per element is generally valid across clinically relevant NP sizes, so quantification accuracy is not intrinsically degraded by changing core diameter.

In Vivo Biodistribution: How Size Indirectly Affects DECT Accuracy

Size has a major biological effect, which indirectly influences quantification:

- In vivo imaging and ICP-OES in mice showed that AuNP ≤15 nm maintained high blood concentrations at 2 h, whereas ≥50 nm AuNP were rapidly sequestered in liver and spleen.
- DECT/SPCCT attenuation changes in blood and organs at 2 h correlated strongly with ex vivo biodistribution across sizes, with $R^2 \approx 0.90$ between CT-derived and chemical gold measurements.
- Because larger particles cluster more in RES organs, they can create higher local concentrations and stronger DECT signal there, while smaller particles produce lower, more diffuse enhancement that approaches the detection limit in some tissues.

Implication

DECT quantification remains accurate across nanoparticle sizes as long as the local concentration is above the system's detection threshold and appropriate organ-specific ROIs and calibrations are used.

SENSITIVITY, DETECTION LIMITS, AND SIZE

Simulation and phantom work suggest that, under clinical dual-energy conditions, the minimum detectable gold concentration can be on the order of tens of mg/mL, considerably lower than for iodine, highlighting the high sensitivity for gold-based agents.

- SPCCT studies set bin thresholds (e.g., 7–40, 40–50, 50–60, 60–79, 79–118 keV) to maximize separation of gold, calcium, and soft tissue, and demonstrate robust detection and quantification of AuNP even at relatively low concentrations.
- For very small particles that distribute widely and achieve modest organ concentrations, partial-volume effects and noise rather than size per se become the main limits on DECT quantification accuracy.

Material Decomposition Accuracy for Mixed Materials

- In dual-energy CT with iodine and gold present together, a calibrated sensitivity matrix derived from phantoms allows simultaneous solution for gold and iodine concentrations at each voxel.
- Validation experiments using 40/80 kVp DECT showed that this decomposition can accurately recover gold and iodine concentrations in vitro and in vivo, with reported HU-per-mg/mL coefficients stable across conditions.
- Since these calibrations are element-based, they remain valid for different NP sizes of the same element, provided the spectral properties of the element do not change with formulation, which is the case for metallic cores and thin coatings.

Practical Takeaway for "DECT Quantification Accuracy vs NP Size."

- At a given element and concentration, DECT/SPCCT quantification accuracy is essentially independent of nanoparticle size in well-designed phantom experiments.
- Size strongly alters biodistribution (blood half-life, RES uptake, tumor penetration), which changes where and how strongly DECT can detect and quantify nanoparticles in vivo, but R^2 values around 0.9 vs ex vivo gold measurements indicate good quantitative performance across sizes.
- Accuracy deteriorates mainly when local concentrations fall near the system's detection limit or when decomposition is challenged by noise, mixed materials, or motion – not because the nanoparticles are "too small" for the physics of DECT.

Gold nanoparticle (AuNP) size has a strong, non-linear influence on where particles deposit in the body and how long they remain in the circulation, even when coating and dose are controlled.

Circulation Time vs Size

Small PEG-Coated AuNP (around 4–15 nm)

- In a size-controlled in vivo CT study, 4 nm and 15 nm PEG-AuNPs retained >20% of injected dose in blood at 2 hours, indicating relatively long blood circulation half-lives for these small sizes.
- A kinetic study with 4 and 13 nm PEG-AuNPs showed high blood levels for up to 24 hours and a slower initial uptake into liver and spleen than larger particles.

Intermediate AuNP (≈20–50 nm)

- Several studies report that 20–50 nm AuNP often show the highest overall cellular uptake, which translates into strong uptake in liver and spleen and somewhat shorter effective circulation compared with ≈5–15 nm in vivo.
- One systematic in vivo study found that 50 nm AuNP produced the longest blood circulation and highest liver/spleen distribution among 5, 20, and 50 nm formulations, illustrating that the "optimum" can shift with coating and model.

Larger AuNP (≥50–100 nm and Above)

- In mice injected with PEG-AuNPs of different sizes, 50 nm and larger particles were rapidly cleared from blood and taken up into liver, spleen, and lungs, with much lower blood fractions remaining at 2 hours compared with 4 and 15 nm particles.
- A kinetic study of PEG-AuNPs showed that large AuNPs were taken up into liver, spleen, and mesenteric lymph nodes within about 30 minutes, with less apparent elimination phase than smaller particles.

Overall pattern: very small PEG-AuNP (<~15 nm) and some mid-size PEG-AuNP maintain blood levels longer, while larger particles are cleared more quickly from plasma into the reticuloendothelial system [17, 18].

Organ Biodistribution vs Size

Liver and Spleen (RES Organs)

- Across many studies, the liver has the highest gold concentration for almost all AuNP sizes, followed by the spleen.
- For 50–250 nm AuNP, liver and spleen uptake is very high and rapid, whereas for 10 nm AuNP, a larger fraction distributes to kidneys, brain, reproductive organs, thymus, and heart compared with larger particles at the same time point.

Kidneys and Renal Clearance

- Pharmacokinetic modeling and biodistribution compilations indicate that sub-6 nm AuNPs can undergo fast renal clearance with minimal organ accumulation, while >10 nm particles predominantly accumulate in liver and spleen regardless of ligands.
- In some series, 10 nm AuNP show appreciable kidney levels, but still much less renal elimination than truly ultrasmall (<6 nm) particles.

Lung and Other Organs

- For 50 nm AuNP, relatively high lung levels were reported shortly after injection; 100–250 nm particles were hardly detected in lung, likely due to faster trapping elsewhere and size-dependent capillary passage.
- PEGylated 20–50 nm AuNP showed higher brain accumulation (2.7–3.6-fold) than bare AuNP of the same size at 48 hours, indicating that both size and stealth coating affect penetration into less permeable organs.

Mechanistic Reasons for These Size Effects

Protein Corona and Opsonization

- Particle size influences the composition and density of the adsorbed protein corona, which in turn modulates recognition by macrophages and endothelial cells.
- Larger and non-PEGylated AuNP tend to bind opsonins more readily, accelerating uptake by Kupffer cells and splenic macrophages and shortening circulation.

Endothelial Transport and Renal Filtration

- Very small AuNP (<~6 nm) can pass the glomerular filtration barrier and be rapidly excreted, whereas larger AuNP are retained in the vasculature and eventually sequestered in RES organs.
- Intermediate sizes (≈10–30 nm) balance retention and tissue penetration, leading to broader organ distribution but less renal clearance.

Cellular Uptake "Optimum"

- In vitro, 20–50 nm AuNP often show the highest cellular uptake among 5–100 nm sizes, which matches in vivo findings of strong liver/spleen accumulation for these sizes.

- This optimum arises from size-dependent endocytosis kinetics; very small particles are internalized less efficiently per particle, and very large ones are sterically hindered.

Role of PEGylation and Surface Modification

- PEGylation at the same size reduces liver and spleen accumulation and increases blood and brain levels compared with bare AuNP.
- In one mouse study, PEG-coated 20–30 nm and 50 nm AuNP had 3.6-fold and 2.7-fold higher brain gold levels than non-PEGylated particles of the same size at 48 hours.
- PBPK analysis of PEG-AuNPs showed a blood half-life of about 57 hours with primary accumulation in liver and spleen, underscoring that PEG lengthens circulation but does not prevent RES uptake.

The toxicity of gold nanoparticles in vivo is size-dependent but non-linear, and is strongly modified by coating, dose, and exposure time. [REVISED: Toxicity discussion categorized into acute, chronic, and size-dependent effects [19].

Small vs Large PEG-AuNP: Key in Vivo Data

A classic mouse study compared 5, 10, 30, and 60 nm PEG-coated AuNP at 4000 μg/kg over 28 days.

- *5 nm and 30 nm:*
  - No deaths; body weight like controls.
  - White and red blood cells decreased significantly, but liver and kidney function tests (ALT, AST, BUN, bilirubin) showed no significant organ damage.
  - Overall, these sizes were considered to cause minimal hepatic and renal toxicity at the tested dose.
- *10 nm:*
  - Increased white blood cells and elevated ALT/AST, indicating more pronounced liver injury than 5 or 30 nm.
  - Total protein and albumin decreased, suggesting hepatic dysfunction.
  - The authors concluded that 10 nm PEG-AuNPs were among the most hepatotoxic in this size series.
- *60 nm:*
  - Elevated ALT/AST and biochemical evidence of toxicity to both liver and kidney.
  - Total protein and albumin decreased; BUN and bilirubin remained largely unchanged.
  - Overall toxicity was higher than 5 and 30 nm, similar in magnitude to or greater than 10 nm in some parameters.

Conclusion from this work: toxicity is not simply "smaller is more toxic"; instead, 10 and 60 nm PEG-AuNP showed greater systemic and organ toxicity than 5 and 30 nm particles at the same high dose.

Mechanisms and Patterns Behind Size-Dependent Toxicity

- *Wider Distribution for Very Small AuNP:*
  - 5–15 nm AuNP distribute more broadly (liver, spleen, kidney, heart, brain, reproductive organs), which can increase the number of organs exposed, but per-organ concentrations and histologic damage can be modest with PEGylation.
  - Ultrasmall (<6–8 nm) AuNP may undergo partial renal clearance, reduce long-term hepatic retention but potentially exposing kidney glomeruli.

- *High Hepatic and Splenic Load for Mid–Large Sizes:*
  - 20–60+ nm AuNPs are rapidly taken up by Kupffer cells and splenic macrophages.
  - High, persistent liver and spleen concentrations can trigger inflammatory responses, oxidative stress, and mild fibrosis in long-term studies.

  - A long-term mouse study with BSA-coated AuNP found persistent liver and spleen accumulation with early inflammatory and fibrotic changes, and notable kidney effects despite low renal gold levels, underscoring chronic toxicity risk from RES-retained particles [20].

- *Oxidative Stress and ROS:*
  - Reviews indicate that smaller AuNP often generate more reactive oxygen species in vitro, producing size- and dose-dependent cytotoxicity, while larger PEG-AuNP produce ROS mainly when heavily accumulated in liver and spleen.

Role of Surface Chemistry and Dose

- PEGylation generally reduces acute hepatotoxicity versus bare AuNP but does not eliminate size-dependent organ damage.
- At very high doses (e.g., 4000 μg/kg), even PEG-AuNP show measurable hematologic and biochemical changes, with the worst profile at intermediate (10 nm) and larger (60 nm) sizes.
- Lower doses and longer intervals tend to produce subtler changes, but chronic studies still show slow elimination and long-term retention, especially of 10–100 nm particles in the liver and spleen.

CONCLUSION

The integration of gold nanoparticles with dual-energy and spectral CT represents a significant advancement in diagnostic imaging, offering unparalleled opportunities for quantitative, element-specific visualization of biological processes in vivo. Gold nanoparticles stand out among high-Z contrast agents due to their superior attenuation properties, biocompatibility, and adaptability through surface engineering. Their ability to provide prolonged vascular contrast and targeted accumulation in pathological tissues positions them as versatile tools for both anatomical and molecular imaging.

Particle size emerges as a central factor influencing biodistribution, imaging performance, and safety. Smaller AuNPs demonstrate favorable pharmacokinetics, including extended circulation time and reduced sequestration by the reticuloendothelial system, thereby enhancing imaging sensitivity and uniformity. Conversely, larger particles show rapid uptake in the liver and spleen, which, while useful for specific applications, may limit their broader diagnostic utility and raise concerns regarding long-term retention. Surface modifications – such as PEGylation and ligand conjugation – further refine these characteristics, enabling tailored biodistribution profiles and targeted imaging of disease-specific biomarkers. [REVISED: Distinction clarified – nanoparticle size does NOT affect intrinsic DECT attenuation quantification but significantly alters biological biodistribution, which indirectly influences detectability.]

Dual-energy and photon-counting CT technologies have transformed the ability to quantify nanoparticle distribution with high precision. Material decomposition algorithms and K-edge imaging allow differentiation of multiple contrast agents within a single scan, opening avenues for multiplexed imaging and theranostic applications. The strong agreement between CT-based quantification and ex vivo validation methods underscore the robustness of these techniques for preclinical and potential clinical use.

However, translation into routine clinical practice remains constrained by several challenges. Safety concerns related to nanoparticle accumulation, potential cytotoxicity, and unclear long-term effects must be addressed through rigorous toxicological studies. Additionally, variability in nanoparticle synthesis, lack of standardized imaging protocols, and high costs associated with advanced CT systems hinder widespread adoption. Regulatory pathways for nanoparticle-based contrast agents also remain complex, requiring comprehensive evaluation of pharmacokinetics, toxicity, and manufacturing consistency.

Future research should focus on optimizing nanoparticle design for rapid clearance without compromising imaging efficacy, developing biodegradable or excretable formulations, and standardizing imaging and quantification protocols. Advances in photon-counting CT and hybrid imaging systems are expected to further enhance sensitivity, reduce radiation dose, and enable multi-element imaging. Integration with targeted therapeutics could also expand the role of AuNPs into theranostics, combining diagnosis and treatment within a single platform.

In summary, gold nanoparticle-enhanced spectral CT holds immense promise for precision medicine, offering detailed insights into biodistribution and disease targeting. While challenges remain, continued interdisciplinary innovation is likely to overcome these barriers, paving the way for safe, effective, and clinically viable nanoparticle-based imaging solutions.

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