Nanotechnology and Computed Tomography

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Learning objectives

Nanobased contrast agents represent one the most promising applications of nanotechnology. This poster is the first glimpse of nanotechnology through the eyes of a radiologist. This article intends:

a) to provide the general radiologist with "in 2015 must know" terms regarding the applications of nanotechnology in imaging

b) to give young radiologists a theoretical trigger to become actively involved in applied research integrating nanotechnology and imaging.

c) to use computed tomography as an example to demonstrate some of the concerns regarding research in the field of nanosized contrast agents.
Background

In this section we are going to explain and clarify some terms that every radiologist wanting to keep up pace with the applications of nanotechnology in imaging should know in the year 2015.

What do we mean by the term nanotechnology?

Nanotechnology is a relatively elastic term that has been used through time to describe many different things. For the layman nanotechnology describes more or less everything that has to do with the "magical" world of the very small things. In a more scientific context "nanotechnology" refers to the science, engineering and technology conducted at the nanoscale, which is about 1 to 100 nanometers.

It is worth mentioning at this point that x-rays have wave lengths roughly between 0,01 nm and 10nm.

What is different at the nanoscale?

What makes the nanoscale so unique is that the physical phenomena that dominate on this scale are the quantum effects. This means for example that certain physical properties of the materials may take only discrete values like 1,2,3 rather than values from a continous spectrum of numbers like anything between 1 and 3. On the nanoscale these properties are also size dependent and not (necessarily) the same as on the macroscale.

What are the main advantages of nanobased contrast agents over traditional contrast agents?

a) Longer circulation time

b) Targeted delivery

c) Multimodal use

d) Reduction of the rate of renal clearance

e) Leakage through the walls of the capillary vessels due to the small size of the nanoparticles

Some important terms found in the imaging with nanotechnology literature:

a) Biofunctionalization:
The modification of a material in such a way that it attains a desired biological property. One example is the biofunctionalization of surfaces so that they entrap specific substances.

b) Enhance Permeability and Retention effect

What is understood by this term is the increased retention of nanoparticles in the tumor microenvironment. The classical explanation is the leaking pattern of tumor vasculature as opposed to normal vasculature.

c) PEGylation:

PET=polyethylene glycol

Hydrophobic polymer used for the biofunctionalization of the surface of nanoparticles. PEG increases their water solubility and decreases their uptake by the reticuloendothelial system resulting in a longer circulation time. It also decreases the aggregation of the different nanoparticles.

d) Blood pool agents: Contrast media exhibiting long blood circulation times

**How can we directly visualize nanoparticles?**

Atomic Force Microscope:

It is a kind of microscope that can provide a picture of the surface of nanoscaled objects. The reason it is called AFM is that it uses interactions=forces at the atomic level in order to depict the surfaces.

**How can we evaluate the mechanical surface properties of materials and why is this relevant to nanobased imaging?**:

There are two things one always has to remember when thinking of nanoparticles. First of all they possess a high surface to volume ratio and secondly their surface properties have a great influence on their interactions with other substances, as is observed in imaging.

The main tool used in this context is a method called nanoindentation. This method takes advantage of the changes that occur on a material surface when touched by a very sharp tip like a pencil that is writing upon a paper on the macroscale.

**How did nanotechnology evolve throughout the years?**

Nanotechnology dates back to as early as the year 1959 when the physicist Richard Feynman (nobel prize 1965) gave his famous lecture "There is plenty of room at the bottom". In this lecture he talked about the possibility of manipulating and controlling things on a small scale. "The principles of physics, as far as I can see do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate
any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big."

Nowadays, nanotechnology is considered to be one of the key enabling technologies with significant impact on many different medical technologies.
Findings and procedure details

In this section we are going to demonstrate on the example of computed tomography how nanotechnology is currently applied in CT imaging. More specifically, we are going to give a general overview of some important nanobased contrast agents used in CT pointing out some of their interesting features as well as some of the concerns researchers have to face in their manufacture.

It is worth mentioning that nanoparticles of larger sizes (larger than 400nm) tend to be taken up by macrophage cells through opsonization. So, organs with high concentrations of phagocytic cells such as the liver and spleen as well as the lymphatic tissues show a high CT contrast enhancement when imaged with large nanobased contrast agents. This can sometimes cause flu- and allergy like symptoms under the term : CARPA (complement activation related pseudoallergy)

Currently "hot" nanobased computed tomography contrast agents include the following:

I. Iodine-based contrast agents

a) Liposomes:

They are spherical vesicles lined by a double layer of phospholipids. They can be used as carriers of both hydrophilic agents, such as iodinated contrast agents, encapsulated in their inner aqueous core as well as of hydrophobic agents dissolved in their phospholipid bilayers.

Their main advantage is their biocompatibility.

Their main disadvantage is their relatively low stability. Free liposomes, other than PEGylated liposomes, are rapidly taken up by the ReticuloEndothelial System. This has already be used in mice for the detection of liver metastases since in contrast to the normal liver metastases do not contain phagocytic Kupffer cells. Liposomes are also cleared from the blood not via renal filtration but rather via the RES which could lower the risk of nephrotoxicity, especially in patients who undertake multiple CT examinations. On the other hand, the leakage of the encapsulated interior out of the liposomes could cause damage to the kidneys.

In the case of liposomes it has been possible to demonstrate the importance of the use of nanobased contrast agents for the real time observation of the effects of an applied therapy. More specifically liposomes were used to detect pulmonary embolism in a rabbit model an monitor the resolution in real time after the injection of tissue plasminogen activator.
Fig. 1: Representative coronal micro-CT images of LSL-KrasG12D;p53FL/FL and KrasLA1 mice before liposomal contrast-agent injection and at 0 hr, Day 3 and Day 7 post-contrast injection. Note the differential enhancement of tumors at Day 7 post-contrast time point in the LSL-KrasG12D;p53FL/FL lesions only.1

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b)

Nanoemulsions:

A mixture of two fluids that are normally immiscible (that do not mix if put together) is called emulsion. Nanoemulsions form droplets at the nanoscale. The interesting thing about nanoemulsions is that they have a larger surface to volume ratio than ordinary emulsions. Their advantages are that they are thermodynamically stable, simple to decorate and allow the encapsulation of a high amount of an iodinated contrast agent. The classical example of a nanoemulsion is lipiodol.

Nanosuspensions:
Colloidal dispersions of pure (water-insoluble) drug particles stabilized by surfactants. Colloids are mixtures in which particles ranging between 1 and 100 nm in size are evenly distributed in a medium; just like dust is dispersed in air. Surfactants are compounds that lower the interfacial tension between two liquids or between a liquid and a solid.

Nanocapsules:

They are relatively stable nanoparticles consisting of a crosslinked polymeric membrane enveloping a payload-material that is often insoluble/immiscible with the surrounding solvent. The polymeric shell confers the enhanced water solubility

c) Polymeric nanoparticles:

They are fabricated through the incorporation of iodine containing compounds into macromolecular structures. This structures prevents the iodine comounds from leaving the nanoparticle allowing in this way the formation of stable nanoparticles of the desired size.

Two special kinds of polymeric nanoparticles are the dendrimers and the amphiphilic polymers.

The dendrimeric contrast agents (Greek symbol=tree+µ= part of it) are highly branched polymeric macromolecules. The consist of an inner core which is connected to branching patterns. Unlike classical polymers, dendrimers are show low polydispersity values. The number of the branching patterns is related to the properties as well as to the shape of the dendrimer. Low generation dendrimers generally represent open structures while high generation dendrimers are usually globular in shape.

Amphiphilic contrast agents are as the name implies contrast agents which comprise a hydrophilic part, usually PEG, and a hydrophobic part.

Dendrimers?
Fig. 3: Schematic diagram

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II.

Gold nanoparticles (AuNPs)

Gold nanoparticles show a high biocompatibility due to their inert nature.

They are of interest, because their use could lower the radiation dose delivered to the patient.

What makes them excellent CT contrast agents is their app. 2,7 times greater contrast per unit weight in comparison to iodine.

They are manufactured in various different shapes like sphere, rods, shells and cages. Although the different shapes are not related to a different CT contrast effect, the different shapes are related to some differences regarding the behavior of gold nanoparticles, eg. gold nanorods manage to escape from the RES phagocytosis more easily than spherical gold nanoparticles.
What do nanoparticles look like in the Transmission Electron Microscope?

**Fig. 2**: Transmission electron micrograph of GNPs having approximately 12 nm cores

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Important potential applications of CT contrast agents described in the literature include:

a) Blood pool imaging

Nanobased contrast agents could be used as blood pool imaging tools due to their high circulation time which could help in the delination of blood vessels in cardiovascular imaging settings. The size of (spherical) nanoparticles should exceed 15 nm so as to prevent rapid excretion through the kidneys or liver uptake and smaller than app. 200 nm in order to prevent the filtration through the spleen.

b) Imaging of the ReticuloEndothelial System
The uptake of nanoparticles by the ReticuloEndothelial System suggests their potential use in the imaging or macrophage rich organs such as the liver, the spleen and the lymphatics as well as in depicting rupture prone plaques that contain an increased density of macrophages. The latter can be enhanced through the modification of the surface of the nanoparticles through ligands in such a way that it specifically targets the rupture prone plaques.

c) Cancer

The afore mentioned EPR effect as well as the biofunctionalization of nanoparticles for the active targeting of tumor cells represent fields of currently undergone research.

Limitations in the use of nanobased contrast agents in computed tomography

a) Potential toxicity.

b) Price (gold nanoparticles)
"Now, you might say, "Who should this and why should they do it?" Well, I pointed out a few of the economic applications, but I know that the reason that you would do it might be just for fun.

But have some fun! Let's have a competition between laboratories. Let one laboratory make a tiny motor which it sends to another lab which sends it back with a thing that fits inside the shaft of the first motor!"

(Richard Feynman, 1959, "There is plenty of room at the bottom")
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