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Influence of nanoparticles accumulation on optical properties of human normal and cancerous liver tissue *in vitro* estimated by OCT

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Abstract

In this work, the potential use of nanoparticles as contrast agents by using spectral domain optical coherence tomography (SD-OCT) in liver tissue was demonstrated. Gold nanoparticles (average size of 25 and 70 nm), were studied in human normal and cancerous liver tissues *in vitro*, respectively. Each sample was monitored with SD-OCT functional imaging for 240 min. Continuous OCT monitoring showed that, after application of gold nanoparticles, the OCT signal intensities of normal liver and cancerous liver tissue both increase with time, and the larger nanoparticles tend to produce a greater signal enhancement in the same type of tissue. The results show that the values of attenuation coefficients have significant differences between normal...
liver tissue and cancerous liver tissue. In addition, 25 nm gold nanoparticles allow higher penetration depth than 70 nm gold nanoparticles in liver tissues.

Keywords: nanomaterials, optical coherence tomography, optical properties, liver tissue

(Some figures may appear in colour only in the online journal)

1. Introduction

Liver cancer is one of the most common forms of malignancy around the world. Primary liver cancer is the fifth most frequently diagnosed cancer globally and the second leading cause of cancer death (Jemal et al. 2011). The number of new cases is estimated to be 564,000 people every year including 398,000 men and 166,000 women. The incidence of primary liver cancer has increased not only in developed countries but also in many developing countries. This likely to continue for several decades (Bosch et al. 2004, Lozano et al. 2012). Worse still, increased risk of liver diseases in children may be associated with an increased risk of liver cancer caused by hepatoblastoma. Those diseases include Beckwith–Wiedemann syndrome, familial adenomatous polyposis, low birth weight, progressive familial intrahepatic cholestasis, Trisomy 18 etc (Emre and McKenna 2004). Thus, strategies aimed at precise diagnosis of liver diseases are needed urgently.

Imaging plays a critical role in all cancer management including diagnostics, staging, radiation planning and evaluation of therapeutic effects (Popovtzer et al. 2008). Many imaging techniques are used to diagnose liver cancer. These include ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI); positron emission tomography (PET) is commonly used for imaging cancerous tissue. PET uses the high metabolic rates of cancer cells to create contrast. However, all of these techniques mentioned above mainly depend on the high metabolic activity of cancerous liver cells (Ariff et al. 2009). Therefore, without this feature, most techniques will have little effectiveness when they applied in hepatocellular carcinoma. While this is not be limitation of optical coherence tomography (OCT) because OCT images are provide by monitoring the change of optical properties. OCT is a relatively new imaging technique which provides images of tissues up to 1–3 mm deep or less with high resolution of 5–10 µm. It was first used in 1991 to demonstrate tomographic imaging of human eye (Huang et al. 1991). It allows measurement of light attenuation in biological tissues with ballistic and near ballistic-photon (Schmitt et al. 1994). Because of the pathological changes in morphology and structure, cancerous tissue could be distinguished from normal tissue easily by their optical properties. Based on the differences in permeability and optical properties of cancerous liver tissue, OCT technology would be the first choose in this field (de Boer et al. 1998, Fercher et al. 2003).

OCT has been used in previous studies (Zhao et al. 2011, Zhu et al. 2012) and applied to detecting cancerous liver tissues (Tuchin 2007). It can be used for continuous monitoring, visualizing any part of the liver without compromising integrity to guide ablation or to guide resection. It is very useful in reducing iatrogenic injury during liver resection. In all applications, contrast is due to the changing of optical properties which can be modulated by nanoparticles. Thus, OCT can also detail the mechanism by which nanoparticles accumulation in tissue. This mechanism is important for future diagnostic and detection tools (Genina et al. 2010). Real time visualization of nanoparticles inside the organ allows better evaluation of pharmacokinetics. Indeed, as the nanoparticles accumulating, optical properties of the tissues can be manipulated more efficiently (Emerich and Thanos 2003, Zagaynova et al. 2008).
Currently, optical instruments such as near-infrared (NIR) spectroscopy (Gobin et al. 2007), photoacoustics (Fischer et al. 2010), Raman spectroscopy (Movasaghi et al. 2007) and OCT (Huang et al. 1991) have been used for minimally invasive or noninvasive diagnosis in tissues. OCT is an emerging minimally invasive or noninvasive optical imaging technology applied widely to the diagnosis and monitoring of disease (Patterson et al. 1989, Boppart et al. 2001, Koffron et al. 2007, Feuerstein et al. 2008). The low-coherence interferometry was used to produce 2D images of optical scattering from internal tissue microstructures. In a way that is analogous to pulse-echo imaging (Tearney et al. 1995, Schmitt 1999).

There are also many studies on optical properties of normal tissue and cancerous tissue using OCT. Recently, several scientific groups and companies have reported minimally invasive devices that could be used to improve the diagnostic accuracy of early-stage cancer (Tearney et al. 1997, Tuchin 2007, Kim et al. 2009). Also, many groups have demonstrated that photonics-based technologies can combine the highly favorable optical and chemical properties of nanoparticles into biomedical imaging (Huang et al. 2007, Terentyuk et al. 2010, Dykman and Khlebtsov 2012, Terentyuk et al. 2013).

The physical, chemical and biological properties of nanoparticles make them tremendously promising in biomedicine. In the recent years, a variety of nanoparticles including carbon nanotubes, fullerenes, quantum dots, and various metal and metal oxide nanoparticles have been widely used in the diagnosis and treatment of cancers (Parashar et al. 2008). Noble metals, especially Au nanoparticles have immense potential for cancer diagnosis and therapy because of their surface plasmon resonance (SPR) enhanced light scattering and absorption (Jain et al. 2008, Dykman and Khlebtsov 2012, 2014, Khlebtsov et al. 2013, Terentyuk et al. 2014).

Determining the optical properties of liver tissue is essential to integrate nanoparticles into diagnostic and drug delivery scheme. These include the integrating sphere (Jain et al. 2006), frequency domain diffuse reflectance (Pham et al. 2000), time-domain diffuse reflectance (Kienle et al. 1998), spatially resolved steady state diffuse reflectance, etc. To improve the sensitivity, specificity, and cost–effectiveness of these methods, many groups have devised or optimized instruments (Tuchin 2007). Nanotechnology is being used to create new diagnostic pharmaceuticals for applications in medical imaging, including as contrast agents and photothermal cancer therapy (Hu et al. 2005, Tucker-Schwartz et al. 2012, Adleret et al. 2008). Changing parameters and the accumulation of nanoparticles make it possible to shift the extinction maximum to the desired region (Lim et al. 2003). OCT provides such a marvelous possibility as demonstrated by Kim et al. (2009) in a dysplastic region of the hamster cheek. Thus, their work takes full advantage of merits mentioned above.

Considering the wide applications of nanoparticles, combining them with OCT is especially a promising way to improve biomedical imaging. Hence, we here study gold nanoparticles applied to human normal and cancerous liver tissues. Finally, we explore the changing optical properties of human normal liver tissues and cancerous liver tissues after the nanoparticles have been applied to the sample surface.

2. Theory and methods

2.1. Spectral domain-OCT system

This study was performed with a spectral domain OCT (SD-OCT) system. The optical source used in this system is a low-coherence broadband super luminescent diode with a central wavelength of 840 nm, a bandwidth of 80 nm and the output power of which is 5 mW. The axial resolution and the transverse resolution of the SD-OCT system in free space is measured to
be 12 µm and 15 µm, respectively, as determined by the focal spot size of the probe beam. The OCT system is made by Shenzhen MOPTIM Imaging Technique Co. Ltd, China that provides a signal-to-noise ratio of images is 120 dB. Two dimensional (2D) images were obtained by scanning the sample. The imaging capability in the depth direction is provided by the spectral fringes from the line scan camera on the SD-OCT system. The acquisition time is about 180 ms per OCT image, corresponding to the line scan camera frequency of 2000 Hz. A computer is used to control the OCT system with data acquisition software written in Lab View 7.2-D and the OCT images obtained during the experiment were stored in the computer for further processing. No significant increase in temperature (<2 °C) was observed during the experiments.

2.2. Method and materials

Gold nanoparticles were made following the of Frens method (Frens 1973). In a typical synthesis, 100 ml of Milli-Q grade water and 0.01% of chloroauric acid (1% by weight) which was purchased from Alfa Aesar were added to a glass flask. After boiling, sodium citrate (1% by weight) was added under continuous magnetic stirring. The solution changed from transparent to faint blue (nucleation), to brilliant red. Water suspensions of spherically shaped uncharged gold nanoparticles were used in this study. All agents were analytic grade. Milli-Q grade water (Millipore) was used to prepare all solutions.

Gold nanoparticles were characterized by transmission electron microscopy (TEM) and ultraviolet(UV)–visible(vis) spectroscopy. TEM was performed with a JEM-2100HR (JEOL, Japan) microscope. Samples for TEM were prepared by dropping and evaporating the particle suspensions onto a collodion-coated copper grid. The Electron microphotographs of nanoparticles of two sizes are shown as figures 1(a) and (b). The Average particle size was determined by counting more than 200 particles. The UV–vis extinction spectra were measured with a NanoDrop ND-1000 (USA) spectrophotometer. Figure 1(c) shows the UV-vis spectra of gold nanoparticles: 25 nm (marked in red), 70 nm (marked in blue). The 25 nm and 70 nm gold nanoparticles SPR band occurs at 524 nm and 540 nm respectively (Haiss et al 2007).

Patients volunteered for the research program conducted at the Second Affiliated Clinical Hospital of Guangzhou University of Traditional Chinese Medicine, China and signed consent forms, with the procedure being approved by the local Ethics Committee. In previous studies (Bolin et al 1989, Larin and Tuchin 2008, He et al 2012), to guarantee the minimal changes in the physiological status and optical properties of low temperature samples, all tissue samples were prepared and measured within 12h after removal. Liver tissue samples were stored in
0.9% sodium chloride solution after the resection and then placed on in a refrigerator at −70 °C until measurements. Excised surgical specimens were collected from 24 patients. There are two kind of histology tissue according to pathological diagnosis: normal liver tissues (24 samples) and cancerous liver tissue (24 samples). All the samples were randomly divided into three groups, control group (8 samples), 25 nm gold nanoparticles group (8 samples) and 70 nm gold nanoparticles group (8 samples). The control group dropped 0.9% sodium chloride solution to prevent them from dehydration as for contrast. The figure 2 shows the Optical microphotographs of liver tissue stained with hematoxylin/eosin(H&E). The pictures are 40 magnification so we can see the normal liver tissue and cancerous liver tissue clearly. In figure 2(b), only cytoplasm and chromatin are normal, cells and cell nucleus in cancerous liver tissue are twice the size of them in normal liver tissue. Besides heteromorphosis cell nucleus, indicated that this is a typical large cell dysplasia, a kind of liver cell dysplasia focus.

Before experiment, nanoparticle solutions were prepared before using in standard method. The materials with lateral dimension of approximately 1.5 × 1.5 cm² were prepared in freezing state for measurement. The 2D images were continuously obtained by scanning the sample in the lateral and axial direction by the OCT. At the beginning, samples were unfrozen in physiological saline at room temperature for 30 min. The sample was placed on one glass slide immediately and monitored with 2D OCT functional imaging for the next 4 h at room temperature(23 °C) throughout the experiment. The nanoparticle solutions were applied by 75 µl drops on normal human liver and cancerous liver tissues and it monitoring started at once while nanoparticles application. Every 30 min during the monitoring, 0.9% sodium chloride solution was applied again on the tissue to protect them from dehydration. The optical effects caused by the gold nanoparticles were continuously monitored by OCT. The duration of monitoring was 4 h after nanoparticles application. The OCT images were obtained every minute. The OCT images of the liver tissue from control group with 0.9% sodium chloride solution measurement were used as control. Each sample was used only once.

2.3. Calculation methods

In this study, OCT images obtained from normal human liver tissue and cancerous liver tissue. A one-dimensional (1D) curve displaying the distribution of OCT signal intensity in depth plotted in a logarithmic scale was created by averaging the 2D images laterally.

The optical attenuation coefficient of the tissue can be quantified from the OCT intensity of the detected light(dB) versus the depth(microns). For media with absorption as described by
the single-scattering approximation, the light travels in a ballistic way and Beer’s law can be applied to calculate the total OCT attenuation coefficient: \( \mu_t = \mu_a + \mu_s \) or called the total attenuation coefficient (Kholodnykh et al 2003). These are physical properties unique to the biological tissue, which play a vital role in the assessment of the tissue feature (Levitz et al 2004, Kodach et al 2011, Yang et al 2011). In this current OCT system case, the measured signal is defined as: (Thrane et al 2000, Levitz et al 2004, Kodach et al 2011, Yang et al 2011).

\[
\{ \langle \hat{i}^2(z) \rangle \}^{1/2} \approx \left( \langle \hat{i}^2 \rangle_0 \right)^{1/2} \left[ \exp(-2\mu_t z) \right]^{1/2},
\]

where \( \langle \hat{i}^2(z) \rangle \) is the photo detector heterodyne signal current received by an OCT system from the probing depth \( z \) and the mean square heterodyne signal \( \langle \hat{i}^2 \rangle_0 \). The result of the research is the measurement of optical backscattering or reflectance coefficient \( R(z) \propto \left( \langle \hat{i}^2(z) \rangle \right)^{1/2} \) from a tissue versus axial ranging distance, or depth \( z \). The reflectance depends on the optical properties of tissue. (Cheong 1990, Tuchin 2007) The total attenuation coefficient is \( \mu_t \). Thus, combined with equation (1) and \( R(z) \) it follows that the reflected power can be approximately proportional to \( -\mu_t z \) in exponential scale according to the single scattering model:

\[
R(z) = I_0 a(z) \exp(-\mu_t z).
\]

Here \( I_0 \) is the optical power launched into the tissue sample and \( a(z) \) is the reflectivity of the tissue sample at the depth of \( z \).

Therefore, the attenuation coefficient and its temporal behavior can be approximately evaluating by measurement of OCT reflectance for depths \( z_1 \) and \( z_2 \). This evaluation is due to reduction of the tissue-scattering coefficient at nanoparticles’ penetration and accumulation if reflectivity \( a(z) \) is considered as weakly dependent on depth for a homogeneous tissue layer.

The \( \mu_t \) theoretically can be obtained from the reflectance intensity measurements at two different depths \( z_1 \) and \( z_2 \): (Thrane et al 2000, Levitz et al 2004, Kodach et al 2011, Yang et al 2011)

\[
\mu_t = \frac{1}{\Delta z} \ln \left( \frac{R(z_1)}{R(z_2)} \right),
\]

where \( \Delta z = |z_1 - z_2| \). There are more details about the entire formulas derivation process in Tuchin (2012). Noise is inevitable in the measurement; therefore in order to improve the accuracy of determining \( \mu_t \) value a final result should be obtained using a least-square fitting method.

A best-fit exponential curve was applied to the averaged intensity profiles of each group since the noise in the measurement is unavoidable.

2.4. Statistical analysis

The data from all samples were presented as means ±SD. Statistical analyzes were performed by an SPSS 10.0 software paired-test. The \( p < 0.05 \) was considered as statistically significant.

3. Results

Continuous monitoring of the tissues during the 4h permeation experiments was performed by 2D OCT for each tissue sample. The procedure was performed identically with meticulous control for all trials.
Figures 3(a) and (b) illustrate quantitatively the effects of enhancement in light transmittance for normal liver tissue and cancerous liver tissue with and without the gold nanoparticles, respectively. The 1D OCT in-depth reflectance profiles are obtained by averaging the OCT images in the lateral direction of the selected region. Figure 3 shows the average A-scans 240 min after the application of the solutions of 25 and 70 nm gold nanoparticles (GNPs) on normal liver and cancerous liver tissue. In figure 3(a), the average OCT signal intensity of the control group is the lowest. And the signal intensity of normal liver tissue with 25 nm gold nanoparticles is lower than that with 70 nm gold nanoparticles in the depth range of about 300–720 µm. However, the signal intensity after application of 25 nm gold nanoparticles is slightly higher than that after application of 70 nm GNP in the depth over 720 µm. Figure 3(b) is similar to figure 3(a), and this indicates that a similar situation also appears in cancerous liver tissue. Because the same samples in the three cases of control, 25 and 70 nm gold nanoparticles’ applications are scanned under the same OCT operation conditions, the effects of other factors should be common among the three cases. The differences between the three cases must be caused by the penetration and accumulation of different sizes of gold nanoparticles in tissue. By analysis of figure 3, we can conclude that larger gold nanoparticles tend to generate greater OCT signal intensity and smaller gold nanoparticles seem able to penetrate deeper into tissue. The most pronounced change in the experimental groups is the increase in OCT signal intensity. This suggests that the backscattering intensity of normal and cancerous liver tissue becomes stronger after application. This is because GNPs have strong backscattering.

Figure 4 shows the average of average attenuation coefficients in the control group. The value of the average attenuation coefficient in normal liver tissue is $6.2 \pm 0.9 \text{ mm}^{-1}$ and the average attenuation coefficient of cancerous liver tissues is $8.0 \pm 1.1 \text{ mm}^{-1}$. During the 4 h of study, the curve was kept stable shown in figures 4(a) and (b).

Figures 5 and 6 present the values of attenuation coefficients of liver tissues over time after the application of 25 nm and 70 nm gold nanoparticles, respectively. In figure 5, the attenuation coefficients decreased dramatically during the diffusion processes in liver, i.e. from $6.2 \pm 0.9$ to $4.3 \pm 0.6 \text{ mm}^{-1}$ in normal liver tissue group at approximately 113 min and from $8.0 \pm 1.0$ to $5.2 \pm 0.5 \text{ mm}^{-1}$ in cancerous liver tissues group at approximately 86 min. Additionally, the values of the attenuation coefficients decreased prominently during the diffusion process after the 25 nm gold nanoparticle solution applied. In figure 6, the values of...
averaged attenuation coefficients also decreased prominently during the diffusion process from $6.2 \pm 0.9$ to $5.2 \pm 0.7$ mm$^{-1}$ in normal liver tissue group at approximately 129 min and from $8.0 \pm 1.0$ to $5.2 \pm 0.7$ mm$^{-1}$ in cancerous liver tissue group at approximately 98 min. The decrease of the attenuation coefficients during the monitoring shows the scattering of tissues are reduced to allow more photons to penetrate into them.

4. Discussions

We monitored the accumulation of two sizes of gold nanoparticles in normal liver tissues and cancerous liver tissues by OCT in vitro. The OCT images and spectra measurements revealed that nanoparticles penetrate and accumulation both normal liver tissue and cancerous liver tissues, thus changing the optical characteristics of both types of tissue. After application of gold nanoparticles, the OCT signal intensity in both tissues increases with time: larger gold nanoparticles tend to produce a greater signal enhancement. For the same type of tissue,
smaller nanoparticles penetrate and accumulate faster. And for the same size of gold nanoparticles, they penetrate faster in cancerous liver tissue compared with normal liver tissue (Ghosn et al 2007, Genina et al 2012) There are many factors that affect the nanoparticle accumulation in normal liver tissue such as shape, superficial charge, composition, hydrodynamic diameter, physicochemical properties of solvent, etc (Jain et al 2007).

Quantitative intrinsic, optical properties offer an extra objective or classification parameter (Sirotkina et al 2011). Analysis of the decrease in the OCT intensity allows us to quantitatively determine the optical attenuation coefficients via OCT technique. The attenuation coefficients of 25 nm gold nanoparticle group decreased much more than the 70 nm gold nanoparticle (figures 5 and 6). This suggests that 25 nm gold nanoparticles show higher ability of penetration and accumulation in liver tissues. This may be due to the accumulation of gold nanoparticles into tissues. The contrast differences between the two types of tissue are mainly caused by the coefficients of tissue attenuation. This in turn depends on the tissue interstitial space volume fraction, cell diameters and tissue construction (Frosz 2004, Kodach et al 2011).

The fluctuant decrease in the attenuation coefficients is due to a reduction of light scattering inside the tissue. This may be caused by the increasing gold nanoparticle concentration over time. According to equation (2), a decrease in the value of the average attenuation coefficient will lead to an increase in the backscattering intensity. The reflectivity of the tissue sample $a(z)$ will become larger in response to the increasing depth. As shown in figures 5 and 6, there is a similar trend in human normal liver and cancerous liver tissues. From figures 5(a) and 6(a), we see that it takes the normal liver tissues more than 120 min to diffuse and accumulate to reach a relatively stable value. But for the cancerous liver tissues, the whole process only costs about 90 min, which are shown in figures 5(b) and 6(b). It is also apparent that the value of attenuation coefficients decreases faster in cancerous tissue than it does in normal tissues. At that point, stable values of attenuation coefficients are observed. These stable processes could probably due to the accumulation of gold nanoparticles in the tissues. The movement of gold nanoparticles fluid from high concentration areas to lower concentration areas was stopped. And these also show that the visibility, contrast and imaging depth in both tissues were significantly changed after the application of gold nanoparticles. This change resulted from the nanoparticles penetration into the extracellular and intracellular space (Fischer et al 2010, Genina et al 2012). The values of attenuation coefficients normal liver tissues were found to

![Figure 6. Average attenuation coefficients of normal and cancerous liver tissue after the application of 70 nm gold nanoparticle solution (a) normal liver tissue (b) cancerous liver tissue.](image)
have significantly differences from the cancerous liver tissues after the continuous accumulation of gold nanoparticles into the tissues.

Acquiring of fixed position images is very important for applying nanoparticles rightly. Comparative study of different size of gold nanoparticles reveals significant differences between normal liver tissues and cancerous liver tissue. As gold nanoparticles could gave rise to more pronounced alterations in optical properties it can be used in controlling photothermal therapy of tumors with nanoparticles or OCT signal level enhancement.

In addition, 25 nm gold nanoparticles show higher penetration rate than the 70 nm gold nanoparticles. Thus the results of the experiments are the decrease of light attenuation, was much more prominent in the cancerous tissue than that of normal tissue in the same region. Both in 25 nm gold nanoparticles group or 70 nm gold nanoparticles group, normal liver tissues have about 30 min lag time; the gold nanoparticles diffuse and accumulate more quickly in cancerous liver tissues than in normal liver tissues. Successful continuous monitoring of nanoparticles accumulation in normal liver tissues with surface application is promising for using this technique to monitor passive accumulation of nanoparticles in cancerous liver tissues localized immediately under the liver surface. Knowing the changes of optical properties associated with the presence of gold nanoparticles in biotissue can assess the degree of nanoparticles accumulation in tumor with minimally invasive in real time, which makes it possible to determine the time of nanoparticles accumulation in tumor with highly accuracy and it plays an important role for OCT monitoring to become an indispensable tool in future.

However, it should be noted that the experiments were performed in vitro rather than in vivo. The optical properties of excised tissue could change versus live tissue. In addition, we measured the samples at room temperature, which may also have an influence on the results because the optical properties of tissue are temperature-dependent (Germer et al 1998). Therefore our future study is focus on an in vivo study to identify the effect of the differences may have on the measurement.

5. Conclusions

In this work, OCT monitoring normal and cancerous liver tissue after the application of two sizes of gold nanoparticle solutions in vitro was performed. The study demonstrated that gold nanoparticles can penetrate and accumulate in both normal and cancerous liver tissues. Thus, OCT may be a useful tool for monitoring and assessing the time and size of nanoparticles’ accumulation in tumors. And the results suggest that the penetration and accumulation of gold nanoparticles have significant effects on the optical properties of normal and cancerous liver tissues. The study provided information about the process of nanoparticles penetration with high accuracy including when the OCT probe accessed liver tissue. Peritoneocentesis or endoscopic examination can facilitate these studies. Therefore, OCT could easily discriminate cancerous from the normal liver tissues without broke the organ integrity. These promising results could be used as a reference to more properly choose nanoparticles in further studies. These same nanoparticles may also be used for control accumulate into liver tissue or diagnosis some liver diseases. Future work will also further study the mechanism of delivery as well as more effective methods to improving the accuracy and sensitivity of noninvasive liver imaging.

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