学　位　論　文　内　容　の　要　旨

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学　位　論　文　題　名

Gold Nanoparticles as Injectable and Minimally Invasive Markers for Real-Time Image Guided Radiation Therapy

(画像誘導放射線治療用の注射可能な低侵襲金ナノ粒子マーカー)

Radiation therapy (RT) is one of the most common types of cancer treatments, and more than half of cancer patients receive RT as part of their treatment plan. However, the therapeutic effect of RT is governed by factors such as radioresistance and potential damage to surrounding tissues. Metal-based materials have the potential to tackle these limitations by acting in different roles, including radiosensitizers, imaging agents, delivery vehicles, oxygen generators, and radioprotectors. For example, gold-based fiducial markers are essential in real-time image-gated radiation therapy (IGRT). By identifying the fiducial marker, IGRT can accurately track the position of a tumor to avoid geometric uncertainties caused by body motions during RT. IGRT can therefore improve the precision of radiation delivery and reduce the doses to the surrounding tissues. However, currently used fiducial markers with large physical dimensions would lead to complicated and invasive insertion procedures, while injectable fiducial markers based on smaller-sized gold nanoparticles (Au NPs) are obviously promising and preferred in IGRT to relieve patients' pain and improve their clinical experience. Therefore, this study aims to synthesize Au NPs via green, effective, and biocompatible methods for fiducial marker applications to achieve optimal therapeutic efficacy and minimal treatment toxicity.

Chapter 1 is a general introduction of metal nanomaterials engineered for RT, especially the design considerations for metal nanomaterials and their applications for RT enhancements. The motivations and objectives of this study are also introduced.

Chapter 2 presents a one-step preparation of sodium alginate-stabilized Au NPs (alg-Au NPs) using the microwave-induced plasma-in-liquid process (MWPLP). Effects of sodium alginate with various concentrations on the preparation and properties of the synthesized Au NPs, including reaction rate, morphology, size, and optical absorption property, were studied. The introduction of alginate (1) accelerated the reaction rate, (2) prevented aggregation and precipitation due to long-time discharge in MWPLP, and (3) provided long-term colloidal stability. An abnormal size change (from large to small) of Au NPs during particle growth, which was opposite to the typical change in bottom-up chemical reduction, was observed and a possible mechanism was proposed based on the dynamical

and thermodynamical instability of particles during growth. The strategy of drying and redispersion of alg-Au NPs in alginate solution was also studied. The drying and redispersion process had an imperceptible effect on the Au NPs. Consequently, this strategy might be an effective technique for the long-term storage of Au NPs. Alg-Au NPs without the addition of toxic reducing or stabilizing agents can be appropriate for biomedical applications.

Chapter 3 reports the synthesis of Au NPs via a green ethanol reduction method for the development of injectable fiducial markers. The factors that affect their injectability and imaging capability were also determined. Au NPs synthesized in the ethanol-only system had an improved injectability (through 18G and 21G needles) and their imaging performance was almost identical to current fiducial markers used in the clinic. The reducing capacity of the ethanol system was significantly enhanced through the introduction of sodium alginate. Meanwhile, the addition of sodium alginate could also control the size of Au NPs, ranging from 21. 8 to 14.1 nm. The product alg-Au NPs with smaller sizes enabled an injectability up to 100% even through 25G needles with an extrusion force less than 17 N, which is superior for the injection of high-concentration Au NPs, exhibiting a minimally invasive property. The X-ray visualization test also verified a better imaging performance of alg-Au NPs than clinically used markers.

Chapter 4 describes a ready-to-use injectable fiducial marker based on Au NPs and a body temperature-activated *in situ* gel-forming system. Gram-scale alg-Au NPs were synthesized through MWPLP, and the body temperature-activated in situ gel-forming system was developed using sodium alginate and a temperature-sensitive calcium source (glucono delta lactone (GDL) and $CaCO_3$). The injectable fiducial marker GDL/$CaCO_3$/alg-Au NPs could remain liquid state at a low temperature to maintain its injectability. At body temperature, however, Ca^{2+} would be released as a result of high temperature-activated hydrolysis of GDL and its subsequent reaction with $CaCO_3$, initiating the gelation process of sodium alginate. The injectable fiducial marker can be delivered via injection and then gelate at the target site to inhibit marker movement or the leakage of Au NPs *in vivo*. Rheological characterization demonstrated the stability and gelation behavior of GDL/$CaCO_3$/alg-Au NPs at different temperatures. Furthermore, the injectability and imaging ability of GDL/$CaCO_3$/alg-Au NPs were also investigated.

Chapter 5 reviews the research findings and conclusions. The contributions and perspectives are also summarized in this chapter.