Photothermal therapy of tumors in lymph nodes using gold nanorods and near-infrared laser light with controlled surface cooling

Tessai Sugiura1, Daisuke Matsuki2, Junnosuke Okajima3, Atsuki Komiya3, Shiro Mori4, Shigenao Maruyama3, and Tetsuya Kodama2 (*)

1 Department of Mechanical Systems and Design, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan
2 Laboratory of Biomedical Engineering for Cancer, Department of Biomedical Engineering, Graduate School of Biomedical Engineering, Tohoku University, Sendai 980-8575, Japan
3 Institute of Fluid Science, Tohoku University, 2-1-1 Katahira, Aoba Ward, Sendai 980-8577, Japan
4 Department of Oral and Maxillofacial Surgery, Tohoku University Hospital, Sendai 980-8575, Japan

Received: 13 July 2015
Revised: 17 August 2015
Accepted: 19 August 2015

© Tsinghua University Press and Springer-Verlag Berlin Heidelberg 2015

KEYWORDS
lymph node metastasis, photothermal therapy, gold nanorods, temperature control

ABSTRACT
Photothermal therapy (PTT) using near-infrared (NIR) laser light and gold nanorods (GNRs) shows promise as a novel cancer treatment modality. However, the laser intensity required to destroy tumor cells located beneath the skin is greater than the threshold intensity that causes skin damage; thus, irradiation with laser light damages the skin as well as the tumor. Here, we show that a temperature control system allows metastatic lymph nodes (LNs) to be treated by PTT using NIR laser light and GNRs, without skin damage. A mouse model of LN metastasis was developed by injection of tumor cells, and the tumor-bearing proper axillary LN was treated with NIR laser light after injection of GNRs. The skin temperature was maintained at 45 °C during irradiation by using a temperature control system. Bioluminescence imaging revealed that tumor progression was less in LNs exposed to NIR laser light and GNRs than in LNs exposed to NIR laser light alone or controls (no irradiation or GNRs). Furthermore, the skin and LN capsule were macroscopically intact on day 9 after irradiation with NIR laser light, whereas tumor cells within the LN showed apoptosis. A numerical analysis demonstrated that the high-temperature zone and the LN region showing damage were localized to an area up to 3 mm in depth. The proposed novel PTT technique, using NIR laser light and GNRs with controlled surface cooling, could be applied clinically to treat metastatic LNs located within or outside the area accessible for surgical dissection.

Address correspondence to kodama@bme.tohoku.ac.jp
1 Introduction

Metastasis to regional lymph nodes (LN) is related to tumor aggressiveness. LN status is an important predictor of patient survival, and is used as an indicator in disease evaluation and the selection of therapy. The use of LN dissection is limited to those patients who are in sufficiently good physical condition to tolerate surgery and who present minimal risk of metastatic foci invading other major organs [1]. LN dissection is invasive and does not destroy micrometastases located outside the dissection area; thus, adjuvant treatments such as radiotherapy and chemotherapy are required. However, since adjuvant treatments cause side effects, there is a genuine need for a new non-invasive therapy for LN metastasis that could be a viable alternative to the currently used cancer management strategies.

Optical transparency is high in the near-infrared (NIR) region (700–1,000 nm). Thus, NIR laser light has the ability to penetrate deep into the body, while causing minimal adverse effects to the irradiated region [2]. Gold nanorods (GNRs) show a strong longitudinal surface plasmon resonance mode along the elongated direction when irradiated with NIR laser light. In addition, the absorption wavelength of GNRs can be tuned by changing the GNR aspect ratio [3], thereby ensuring effective heat production. Thus, photothermal therapy (PTT) using GNRs and NIR laser light represents a potentially attractive new treatment modality for localized cancer [4–6]. However, it is difficult to determine the distribution of laser light inside a biological tissue because the tissue has strong light scattering properties. The scattering and absorption of light in a biological tissue strongly affect the penetration depth of the laser light, and these effects have to be considered when evaluating the temperature distribution at different depths of a biological tissue.

Most previous studies of PTT using GNRs and NIR laser light utilized experimental systems in which tumor cells were injected subcutaneously, GNRs were administered systemically or locally, and laser light was typically applied to the skin at an intensity of ~3 W/cm² [6, 7]. However, this laser intensity is greater than the threshold of ~420 mW/cm² for induction of skin damage [8]. Indeed, skin damage was reported in all of these published papers. Thus, a new PTT methodology that utilizes NIR laser light and GNRs without inducing skin damage is required.

A damage function has been defined to evaluate thermal injury [9]. According to this function, damage is defined by time and temperature. Thus, skin damage would not be induced if the PTT using NIR laser light and GNRs ensured that skin exposure was below the threshold defined by the damage function.

In the present study, we developed a new PTT protocol for the treatment of LN metastasis using NIR laser light, GNRs, and a skin temperature control system. An experimental model of a tumor-bearing (metastatic) LN was developed in MXH10/Mo-lpr/lpr (MXH10/Mo/lpr) inbred mice [10] by injection of a solution containing a mixture of tumor cells and GNRs into the proper axillary LN (PALN). Skin temperature was maintained at 45 °C during irradiation with NIR laser light by using a temperature control system. The temperature distribution and region of the LN showing damage were determined by numerical analysis after considering the degree of light scattering. We found that this new PTT approach exerted an anti-tumor effect in the metastatic LN but did not induce macroscopic damage to the skin or PALN capsule (Cap). This technique could be developed into a new clinical treatment method for LN metastasis that would eliminate the adverse effects of LN dissection and adjuvant therapies.

2 Numerical analysis

2.1 Temperature distribution after irradiation of an LN with NIR laser light

The LN was assumed to be an isotropic bio-simulated material that did not include GNRs, and it was assumed that there was “glass” on the isotropic bio-simulated material. The temperature distribution in the bio-simulated material after irradiation with NIR laser light was calculated using the Pennes bioheat transfer equation [11] and a radiative transfer equation. The temperature distribution in the bio-simulated material was analyzed in a two dimensional (2D) axisymmetric model.

The Pennes bioheat transfer equation is given by