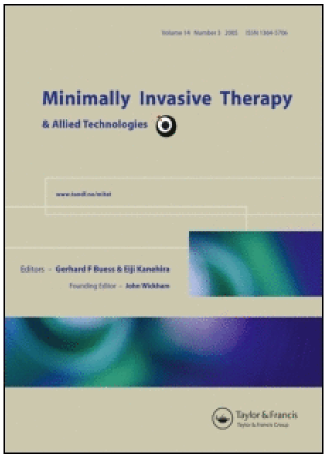

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ORIGINAL ARTICLE

Minimally invasive thermotherapy method for tumor treatment based on an exothermic chemical reaction

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Abstract

In tumor thermotherapy treatment, it is very difficult to achieve the objective of exactly killing the tumor while minimizing the injury of healthy tissues or organs surrounding the tumor. In this study, we describe a new minimally invasive thermotherapy protocol for tumor treatment using heat released from an exothermic chemical reaction, which can safely deliver a totally localized and uniform heating to exactly kill the tumor. Both *in vitro* and *in vivo* experiments were performed to test the feasibility of this thermotherapy method based on an exothermic chemical reaction. After injection of only a small amount of matched reactants into the target tissue by medical syringes, an exothermic reaction takes place, and then releases tremendous heat to elevate the temperature to its thermally lethal value. Compared with most of the currently existing thermotherapy strategies, this heating is highly localized, completely safe and uniform, which will remarkably reduce the thermal damage and mechanical trauma to the surrounding healthy tissues. This study opens the clinical possibilities for tumors to be treated in a minimally invasive way by a thermotherapy treatment based on an exothermic chemical reaction.

Key words: *Tumor hyperthermia, thermotherapy, minimally invasive treatment, exothermic chemical reaction, reaction heat*

Introduction

Thermotherapy has long been an important cancer treatment modality in which tumor tissue is exposed to an elevated temperature to destroy cancerous cells. Unlike the routinely adopted radiotherapy and chemotherapy, this therapy induces only minor side effects so that it could be called a "green" therapy (1). To date, a wide variety of thermotherapy methods have been established, such as heating by microwave (2), ultrasound (3), radiofrequency (4), electromagnetic source (5–8), laser (9), and hot medium (10). However, a common characteristic of these techniques is that they will inevitably cause thermal damage to the healthy tissues along the path heat energy is transmitted to the tumor. To encourage widespread clinical applications of thermotherapy, two important but extremely hard issues are waiting to be solved: First, generation of a high enough temperature increase should be confined to the inside of the target region (tumors), leaving all other sites unaffected; second, temperature detection and control within as well as outside the target region should be easily available (11,12). Due to the irregularly shaped tumors encountered in clinical practice, there is still a long way for the current thermotherapy techniques to achieve the objective of safely delivering a conformal lesion to exactly kill the tumor as desired, while minimizing the injury of normal tissues or organs surrounding the tumor. Therefore, we attempted to find a new tumor thermotherapy method to overcome the above mentioned shortcomings of the currently existing thermotherapy strategies.

Material and methods

The *in vivo* study was approved by the Institutional Review Committee and performed in accordance with National Institutes of Health guidelines.

Here, we present a thermotherapy method for localized killing of tumors based on an exothermic chemical reaction, in which the reactants at room

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temperature are directly introduced into the target tissues through a medical syringe (Figure 1a). A tremendous reaction heat can then be released only in the target tissue to elevate its temperature to above tissue thermally lethal threshold value, which is usually 45°C for tumor tissue (11). However, the remaining product is completely nontoxic for the human body. Several evident merits of this treatment can be summarized as follows: It is easy to operate, extremely low in cost, highly targeted, minimally invasive, works with a simplified device design, and can possibly be implemented on an outpatient basis. Such properties have in fact been pursued for many years by oncological clinicians. In this way, a "green" thermotherapy causing almost no side effects can be established.

In order to perform an ideal thermotherapy treatment using exothermic chemical reaction, there are three constraint conditions limiting the selection of reactants:

I. The reaction heat should be strong enough to guarantee a complete thermal damage on target tissues.
II. The reactants and resultants should be acceptable by the human body after the treatment has been finished.
III. The reactants can be easily introduced into the target tissues via a minimally invasive approach without causing any thermal, mechanical or chemically poisonous damage to the surrounding healthy tissue along the insertion path.

Figure 1b depicts the transient temperature of solutions during the process of a neutralization reaction, in which at 100s (time) 5g 40% w/w sodium hydroxide (NaOH) solution was added into 5g 37.5% w/w hydrochloric acid (HCl). It indicates that the highest solution temperature during the neutralization reaction has even reached 100°C, far higher than that requested to kill a tumor tissue. In our experiment, a boiling phenomenon with vapor generation in the solutions was observed. Clearly, the neutralization reaction of HCl and NaOH has accommodated constraint condition I. In addition, constraint condition II is also not a problem, since the reaction of HCl and NaOH leads to completely friendly matters such as NaCl and H_2O. For condition III, it has been flexibly solved since the injected solutions are at medium temperature which inflicts no hurt to the tissues and the medical syringe used to inject the solution is extremely small with a diameter of 0.8 mm. All the above properties have long been rather difficult objectives to achieve by many traditional heating strategies. In this study, HCl and NaOH were specifically chosen as the reactants for demonstrating the concept, although other reactants could also have been chosen.

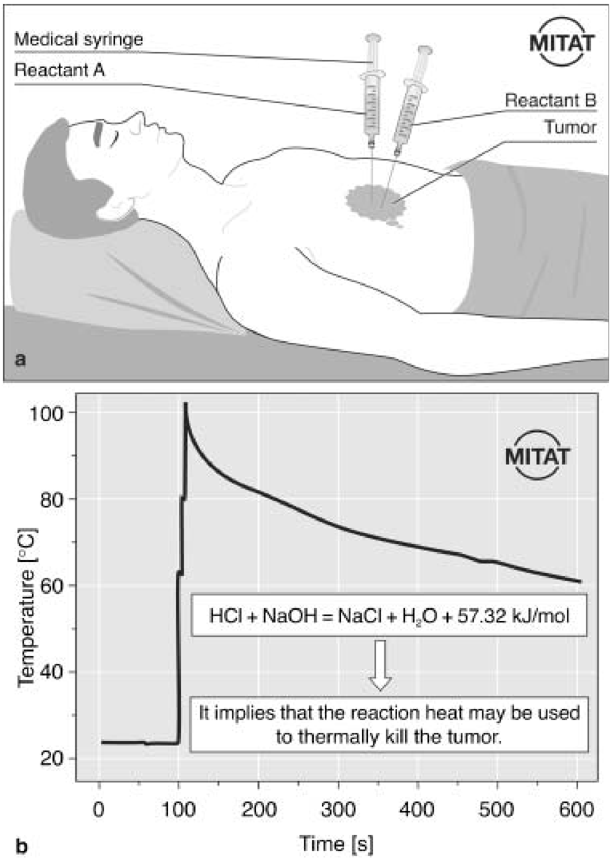

Figure 1. Principle of the exothermic chemical reaction enabled tumor thermotherapy therapy. (a) Schematic for administering the treatment. (b) The temperature response of solutions during the process of neutralization reaction in which the reactants are 5g 40% w/w sodium hydroxide (NaOH) solution and 5g 37% w/w hydrochloric acid (HCl).

Both *in vitro* and *in vivo* experiments were performed to test the feasibility of a thermotherapy method based on an exothermic chemical reaction, in which *in vitro* pork tissues and a 2kg New Zealand rabbit were selected as experimental materials, respectively. The temperature sensors used in all experiments were T-type copper-constantan thermocouples calibrated in advance. To prevent the chemical corrosion of hydrochloric acid, the copper-constantan thermocouple was packaged by a capillary glass tube with an outer diameter of 1.4 mm and an inner diameter of 0.8 mm, in which one end of the capillary tube and the thermocouple head were sintered together.

Results

The typical results for the *in vitro* experiments are depicted in Figures 2 and 3. Considering that the

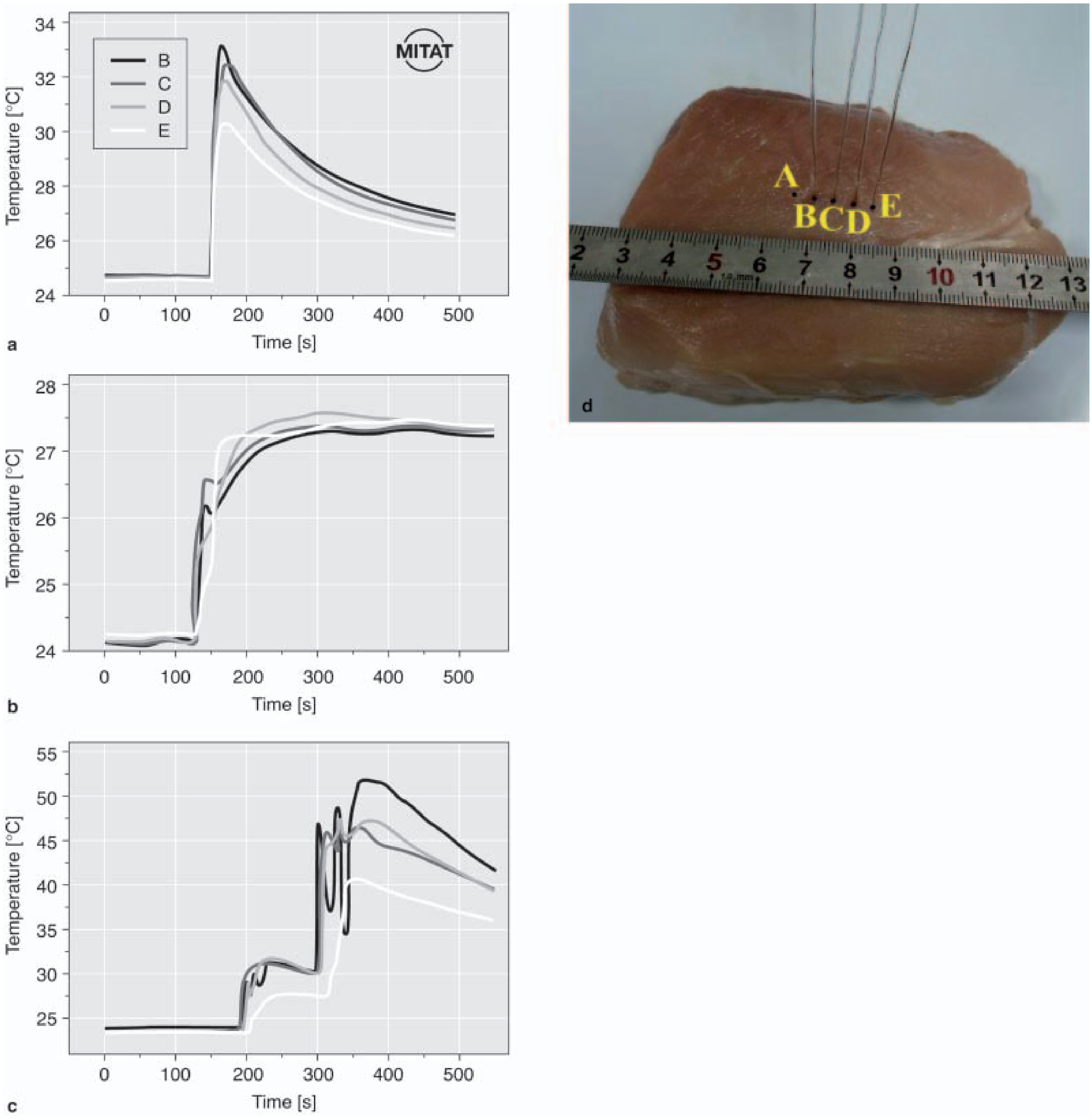

Figure 2. The temperature responses at four locations of *in vitro* pork tissue, in which (a) is for the case of injection of only 5g 37% w/w HCl into the tissue, (b) is for the case of injection of only 5g 40% w/w NaOH into the tissue, and (c) is for the case of injection of 5g 37% w/w HCl and 5g 40% w/w NaOH into the tissue. (d) One of *in vitro* tissue experiments in which A is the injection spot of reactants, B, C, D, and E are the measuring spots for tissue temperature responses which are depicted as curves B–E in (a), (b) and (c), respectively. The distance between any two adjacent spots of A, B, C, D, and E is 5mm. The depths of the injection spot and the measuring spots are all taken as 2cm.

concentrated HCl and NaOH will generate heat when diluted separately in the tissues and may contribute to the expected thermotherapy, experiments were also performed in which only HCl or NaOH were injected. In Figure 2a, HCl was injected into the *in vitro* tissue at 150s; in Figure 2b, NaOH was injected at the time of 120s; in Figure 2c, HCl and NaOH were injected into the tissue from the same spot at 180s and 300s, respectively; Figure 2d illustrates one of the *in vitro* tissue experiments, in which point A is the injection spot of reactants, points B, C, D, and E are the measuring spots of tissue temperature responses. The results as shown in Figure 2 indicate that the maximum temperature increase is about 8°C and 3°C for injection of 5g 37% w/w HCl and 5g 40% w/w NaOH, respectively.

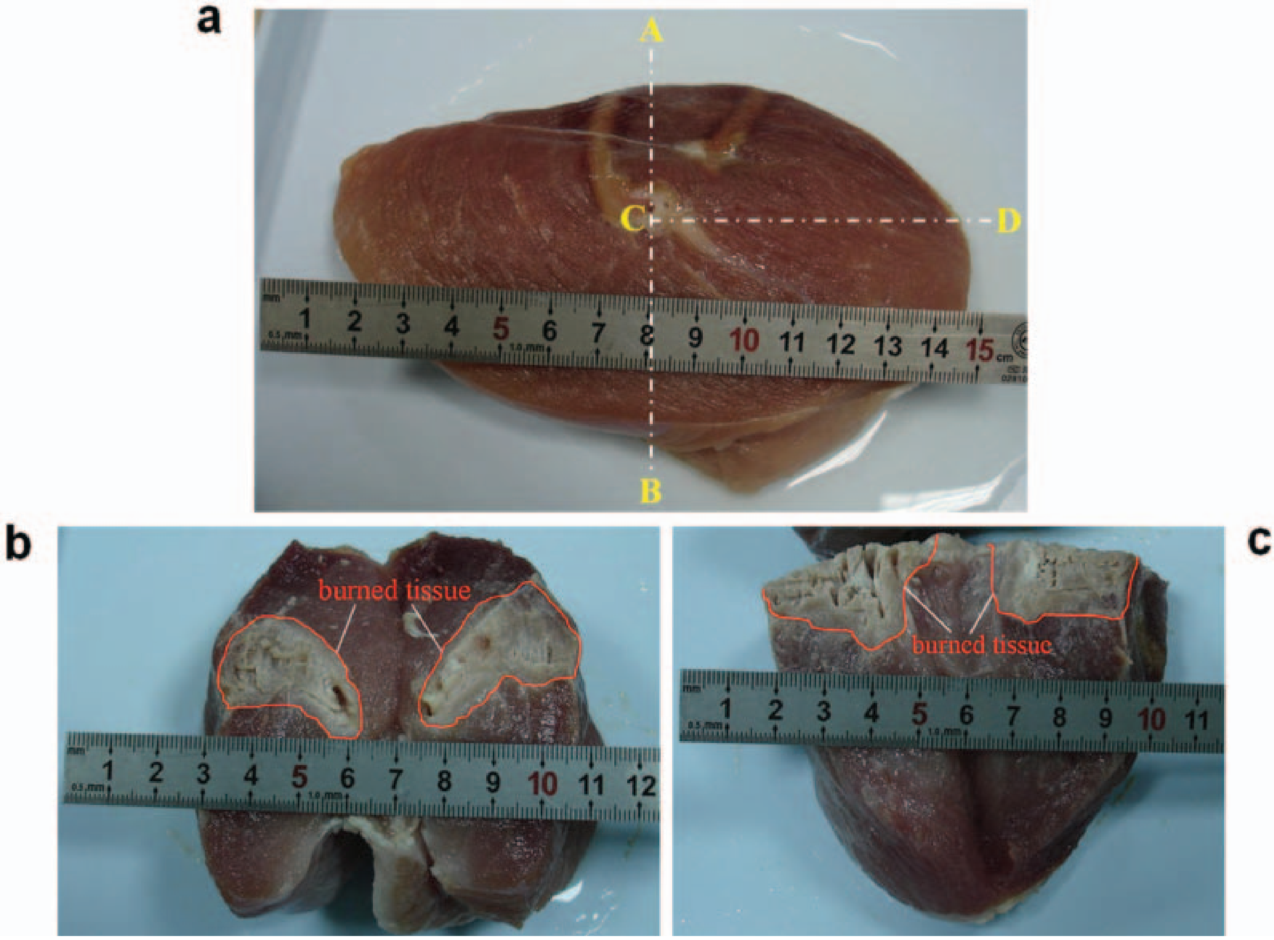

Figure 3. Output of experiment on *in vitro* pork tissue, in which the reactants are 5g 37% w/w hydrochloric acid and 5g 40% w/w sodium hydroxide solution, respectively. (a) Illustration of the positions from where the pork tissue was sliced after the experiment. (b and c) Profiles of the thermally burned area, in which the pork tissue was sliced off via the white line AB and CD as shown in (a), respectively.

Although injection of concentrated HCl and NaOH does generate heat which resulted in a visible temperature increase in the tissue, such heat dosage is much lower than that released from the exothermic chemical reaction taking place at 300s in Figure 2c, which resulted in the maximum temperature increase of about 22°C (from 30°C to 52°C) in the target tissue. Figure 2c also shows that the tissue temperature even at position D, i.e. 1.5 cm away from the injection spot, is still obviously higher after the chemical reaction occurred than the thermally lethal threshold value for tumor tissue. This indicates that the present approach is highly feasible to perform an extremely efficient and localized thermotherapy treatment. The most attractive feature of this thermotherapy method is that the reaction heat can be released only in the target region if the dosage and the injection area of solutions are appropriately controlled. It causes no thermal damage or mechanical trauma to the normal tissues along the insertion path, which is however inevitable by many popularly used thermotherapy devices. Figure 3 shows the burned tissue area following this experiment, in which Figure 3a illustrates the positions from where the pork tissue was sliced after the experiment, Figures 3 b and c show the profiles of the thermally burned area. It indicates that the area of thermally burned tissue is about 3 cm in diameter.

To further illustrate the feasibility of the present thermotherapy method, *in vivo* experiments were also performed on an anesthetized rabbit. Some representative results are presented in Figures 4–6. During the experiment, HCl was injected into the rabbit thigh tissue at 360s, and NaOH was injected from the same spot immediately after injection of HCl. Figure 4 shows that the highest temperature in the target tissue can reach about 52.5°C after the exothermic chemical reaction occurred, and that even at the position (spot E), 2 cm away from the injection spot, the temperature increase is still large enough to thermally damage the tumor tissue. The primary objective of thermotherapy is to raise the

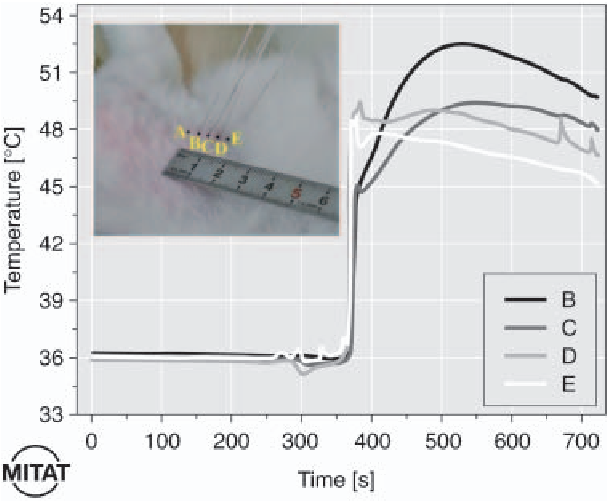

Figure 4. The temperature responses at four locations of *in vivo* rabbit thigh tissue subjected to the heating of an exothermic chemical reaction. A is the injection spot of reactants, B, C, D, and E are the temperature measuring spots. The reactants are 4g 37% w/w HCl and 4g 40% w/w NaOH. The distance between any two adjacent spots of A, B, C, D, and E is 5mm. The depths of the injection spot and the measuring spots are all taken as 1cm.

temperature of the diseased tissue to the therapeutic value, typically >45°C. To fully destroy the tumor, such therapeutic temperature in the target tissue should be sustained for several minutes. Figure 4 also illustrates that the temperature of the target tissue can be quickly elevated and maintained high for a long period (exceeding 5 minutes even at spot E). It can thus be concluded that using the heat released from the exothermic chemical reaction to perform a safe or "green" thermotherapy treatment is highly feasible. In addition, the maximum temperature difference between the measuring spots B and E is only about 5°C. It indicates that the temperature increase at the target tissue produced by chemical reaction heat is very uniform compared with many existing thermotherapy protocols. This is another attractive feature of the present method. The burned area (about 3cm × 5cm) on the thigh tissue of the rabbit sacrificed after the *in vivo* experiments can be found in Figure 5, which clearly shows that a rather large area has been burned and completely destroyed. Besides the experiments on rabbit thigh, the *in vivo* experiments were also performed on rabbit liver. Similar results were again obtained. For brevity, such experiments have not been presented here in detail. The typical output for the burned area on the rabbit liver tissue can be found in Figure 6, in which the burned area is about 2 cm × 3 cm.

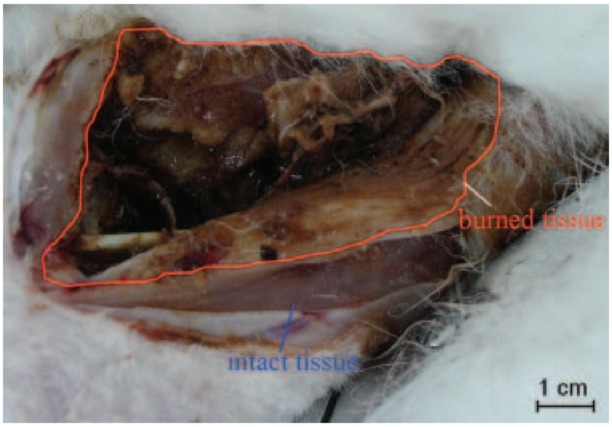

Figure 5. Profiles of the burned area for the experiment on *in vivo* rabbit thigh tissue, in which the reactants are 4g 37% w/w hydrochloric acid and 4g 40% w/w sodium hydroxide solution, respectively.

Figure 6. Profiles of the burned area for experiment on *in vivo* rabbit liver tissue, in which the reactants are 2g 37% w/w hydrochloric acid and 2g 40% w/w sodium hydroxide solution, respectively.

Discussion

In summary, we have shown that an exothermic chemical reaction can serve as an efficient heating protocol for tumor thermotherapy. The safety of this therapy is easy to guarantee, since reaction of HCl and NaOH leads to completely friendly matters such as NaCl and H_2O, although the strong acid and the strong base are individually very destructive to tissues. In fact, either acid or base solution can be used for tumor treatment (13,14). Therefore, this thermotherapy based on a chemical reaction would be safe for possible use in the human body. In addition, the mechanical trauma caused by insertion of a medical syringe is much smaller than most current percutaneous minimally invasive surgeries in which the typical diameters of the inserted probes range from 2 mm to 5 mm, or even larger. For irregularly shaped tumors, a conformal treatment can be administered by injecting reactants into multiple regions under guidance of a medical imaging system such as ultrasound, MRI or X-CT. Due to its highly localized feature, this method is rather beneficial in maximizing the tumor-killing while minimizing thermal injury to healthy tissues. Moreover, it is expected that in the near future such tumor treatment can possibly be performed on an outpatient basis.

Acknowledgments

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