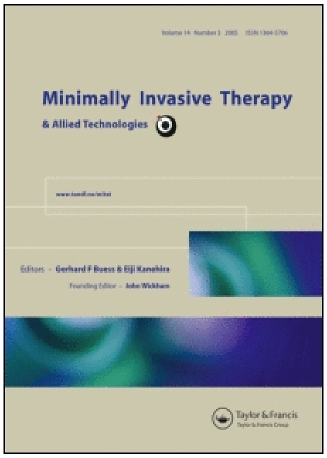

Minimally Invasive Therapy and Allied Technologies

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713683124

Tumor thermal ablation therapy using alkali metals as powerful self-heating seeds

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First Published on: 05 December 2007
To cite this Article: Rao, Wei and Liu, Jing (2007) 'Tumor thermal ablation therapy using alkali metals as powerful self-heating seeds', Minimally Invasive Therapy and Allied Technologies, 17:1, 43 - 49
To link to this article: DOI: 10.1080/13645700701803826
URL: http://dx.doi.org/10.1080/13645700701803826

Minimally Invasive Therapy. 2008; 17:1; 43–49

ORIGINAL ARTICLE

Tumor thermal ablation therapy using alkali metals as powerful self-heating seeds

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Abstract

The aim of this study is to demonstrate a new tumor thermal ablation therapy, which might lead to a highly economic, safe and efficient heating of target tissues. The alkali metals, usually seen as hazard mediums in daily life, were proposed for the first time as perfect self-heating seeds which can significantly raise the temperature of the tumor tissues. Owing to the tremendous heat released at only the target site during reaction between the metal and the intrinsically existing wet environment of the biological body, the tumor tissues can be efficiently ablated without causing thermal damage to the surrounding healthy tissues. Several conceptual experiments were performed to demonstrate the new thermal ablation principle. Mammary adenocarcinoma cells in culture were found to be quickly destroyed due to the thermal and chemical effects induced by the alkali metal. Further, a significant temperature increase by a magnitude of > 40°C or even combustion has been found easily available at the target site; this temperature increase produces a sufficiently large coagulation and necrosis area within selected areas either for *in vitro* or *in vivo* tests. The unique merit of the present thermal ablation therapy is that its remaining reactant can be absorbed by the tissue itself without causing any damage. This study opens possibilities of using the alkali metals to thermally ablate the target tumor in future clinical applications.

Key words: *Targeted tumor thermal ablation therapy, minimally invasive treatment, self-heating seeds, alkali metal, exothermic chemical reaction, physical therapy*

Introduction

The most widely adopted methods for tumor treatment are radiotherapy or chemotherapy, which however may cause serious side effects to human health during or after treatment. A long-standing issue is therefore to reduce this adverse effect to occur as well as possible. As an alternative, the physical way of thermal ablation using high temperature to kill tumor is playing an increasingly important role in tumor clinics (1). Based on different heat generation principles such as high intensity focused ultrasound (2,3), magnetic nano fluids (4,5), radiofrequency (6,7), microwave (8,9) and laser heating (10,11) etc., many thermal ablation apparatuses have now been successfully developed. However, a major drawback implied in these approaches is that they are generally expensive and always cause inevitable thermal damage to the surrounding healthy tissues along the path where heat is transferred from the outside to the target tumor embedded inside the human body. Therefore, establishing a highly targeted, economic, safe, efficient and powerful heating strategy for tumor thermal ablation has always been a desirable objective for the quick recovery of patients.

We present a promising method to fulfil the above requirement introducing for the first time alkali metals as perfect heat generation seeds. After injection or transplantation of only an extremely small amount of such metals into the target tissues, a significant temperature increase or even combustion at the target site can be obtained, which immediately results in a powerful thermal ablation effect on the tumor. This is owing to the strong exothermic reaction between the alkali metal and the intrinsically existing water contained in the target tissues.

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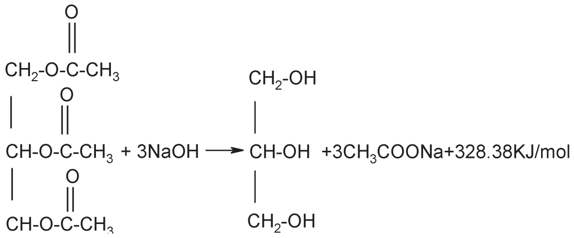
ISSN 1364-5706 print/ISSN 1365-2931 online
DOI: 10.1080/13645700701803826

The heat generation rate thus achieved is tremendously high. For example, pouring alkali metal of sodium particle with a matched amount of water would release a significant amount of heat, which can be quantified by equation 1. The same is true when sodium materials are used to saponify tissue fat (the heat release can be quantified by equation 2). Besides, the subsequently produced immediate product NaOH continuously contributes to this heating if dissolved with enough water, which again causes further temperature increase in the targeted tissue areas.

$$2Na + 2H_2O = 2NaOH + H_2\uparrow + 281.778KJ/mol \quad (1)$$



$$\begin{array}{l} CH_2\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \\ | \\ CH\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \\ | \\ CH\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \end{array} + 3NaOH \longrightarrow \begin{array}{l} CH_2\text{-}OH \\ | \\ CH\text{-}OH \\ | \\ CH_2\text{-}OH \end{array} + 3CH_3COONa + 328.38KJ/mol \quad (2)$$

As illustrated in Figure 1, the above event has multi-mode therapeutic effects. For example, the extraction of a considerable amount of water from cells may cause damage to the tissues due to the hygroscopic nature of alkalis (12). Alkalis also dissolve proteins of the tissues to form alkaline proteinate, which are soluble and contain hydroxyl ions. These ions cause further chemical reaction and magnify a deeper injury of the tissue (13). One unique merit of the present method to thermally ablate a tumor still is that the remaining reactant such as Na^+ is absorbable by the living tissues without causing any damage, since it consists of the most basic element of the physiological fluid. Therefore, after finishing its thermal ablation role, the reactant of the alkalis leaves no toxicity to the tissue. This is a highly desirable objective long expected in tumor clinics. Since such treatment is safe, easy for both operation and post-care management, and rather economic, it allows a potentially wide adoption in the near future for the clinical treatment of tumors. This paper presents the first demonstration of the alkali metal-based tumor thermal ablation therapy.

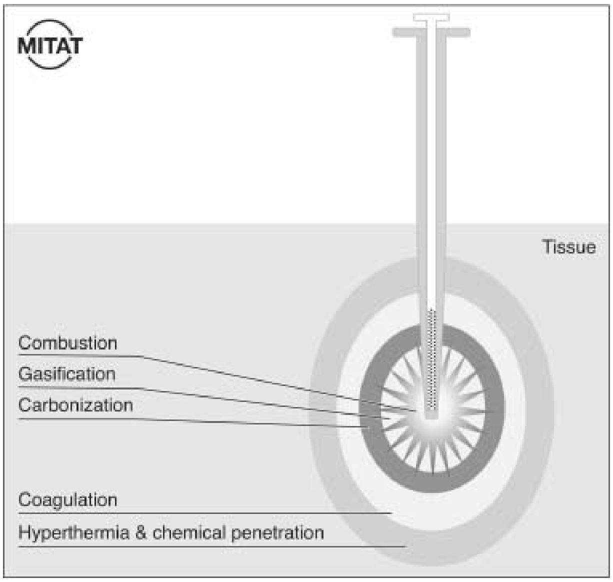


Figure 1. Illustration of the thermal and chemical effects in target tissues due to the exothermic chemical reaction between the alkali metal and the wet environment of biological bodies.

Material and methods

Experimental tumor models

The test subjects include mammary tumor cells, *in vitro* tissues of pork and beef and an *in vivo* animal SD rat, respectively. The MA891 mammary adenocarcinoma cell line, growing *in vitro*, was obtained from the Cancer Institute & Hospital, the Chinese Academy of Medical Sciences, Beijing, China. A 12–16 weeks old, 400 g SD/SPF male rat was used in the experiment. It was bought from the Department of Laboratory Animal Science, Peking University Health Science Center, Beijing, China and kept in standard laboratory conditions with free water and food. The rat was anesthetized by an intra-peritoneal injection of 20% urethane (6 ml/kg). All procedures performed complied with the International Laboratory Animals Care Convention.

The present study is aimed for a proof-of-concept of the new method. Therefore, a tweezer was adopted to manipulate and insert the alkali metal into target tissues, although a medical device thus fabricated can be superior to this. At the present stage, we choose to wear thin rubber gloves to avoid contact with the alkali metal and deliver the metal using tweezers. Figure 2 illustrates the specific operational steps when using alkali metal for thermal ablation experiments. Here, sodium is formed as a slim cylinder and placed in a transparent package to avoid reaction with water vapour in air before tests (Figure 2 a). Then, a puncture needle is percutaneously inserted into the tissues to cut a slot there (Figure 2 b). Finally, the sodium is delivered into the tissue via the slot by tweezers (Figure 2 c). A strong exothermic reaction between the alkali metal and the intrinsically existing water in the target tissues will occur after that.

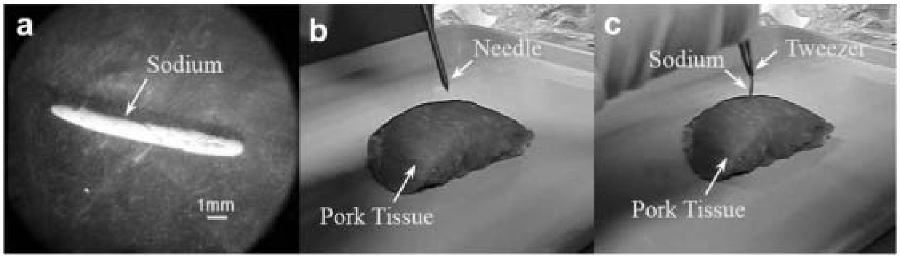


Figure 2. Procedures for delivering sodium: (a) A slim cylinder of sodium; (b) using needle to cut a slot in pork tissues; (c) Using tweezer to insert sodium into tissue via a slot.

Thermal ablation dosage of alkali metal

To quantify the thermal dosage for the alkali metal-enabled thermal ablation therapy, the temperature increase at the targeted tissues was adopted, which can be described using the following equation based on an energy conservation relation:

$$\Delta T = \frac{\sum Q}{V_t(1-\phi)\rho_t C_t \eta} \tag{3}$$

where Q is the released heat of the chemical reaction (W), Σ represents the total heat release due to subsequent series of reaction, V_t the volume of target tissue (m^3), ϕ the volumetric ratio of metal in the total tissues, ρ_t the density of tissue (kg/ m^3), η the heat release efficiency of exothermic reaction, which is related to the shape, quantity of alkali metal and interface area between the alkali metal and the tissue. The temperature magnitude depends heavily on the metal dosages as administered during operation.

The relation as given by equation 3 may have a generalized purpose in quantifying the magnitude of the temperature increase at the target tissues. It should be pointed out that the heat release efficiency of an exothermic reaction η may not be a constant. It is related to the shape, quantity of alkali metal and the interface area between the alkali metal and the tissues. Therefore, an empirical formula for the parameters contained in the above equation requests a lot of experimental calibrations in the near future. As a preliminary test, a series of *in vitro* experiments were conducted to quantitatively evaluate the extent of damage caused to the tissues by alkali metal. Since heat generation effects during reaction between alkali metal and water in tissue are rather obvious, some commonly used temperature sensors such as thermal couples or an infrared thermometer can be adopted for evaluation and administration of the therapy.

Implementary methods

Conceptual experiments were performed to demonstrate the working principle of the new thermal ablation strategy. To obtain a larger contact area and deeper insertion depth, the metal used in the *in vitro* and *in vivo* experiments is made as a slim cylinder with a height of 1 cm and a diameter ranging from 1.5 to 5 mm, respectively. And it is delivered by tweezers.

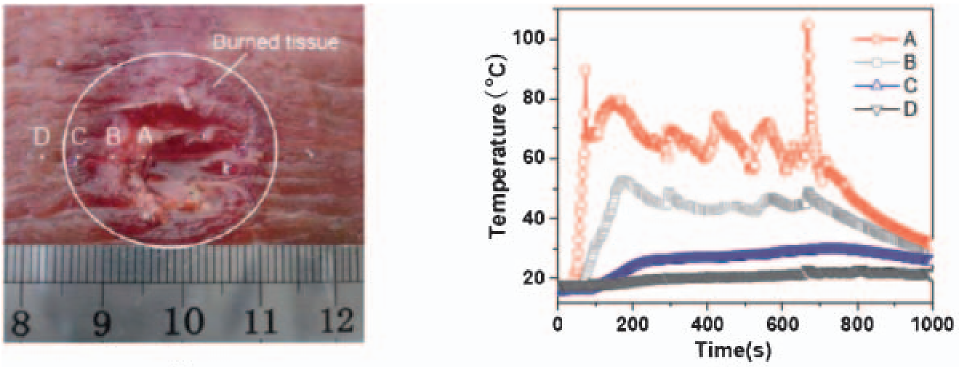
Temperature measurement

The temperature sensors used in the *in vitro* and *in vivo* experiments were T-type copper-constantan thermocouples which were connected to an Agilent 34970 multimeter (Agilent Technologies, Santa Clara, CA, USA). To prevent the chemical corrosion of the reactant, 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. The thermocouples were calibrated in advance and an accuracy of ±0.1°C was obtained.

To reduce bleeding due to insertion in the *in vivo* experiment, only one thermocouple was fixed at the reaction site to record the temperature there. But for the *in vitro* experiment, four thermocouples indicated by points A, B, C, D respectively (Figure 3) with a 3 mm interval between each other were inserted into the surrounding tissue and aligned in the same horizontal line for simultaneously monitoring the temperature responses at those multiple sites. The thermocouples were set by a fixture at the interface between sodium and tissue.

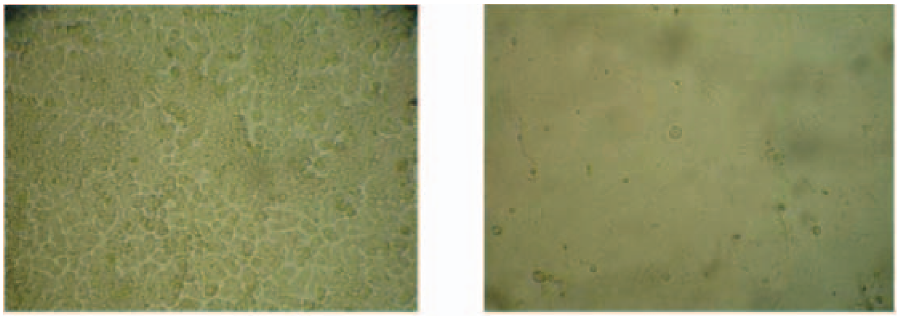
Results

A typical result from sodium reacting in mammary adenocarcinoma cancer cells is depicted in Figure 4, in which an extremely small amount of sodium with a weight of 0.00069 g was added to the 3 ml culture medium. When subjected to the alkaline environment, tumor cells were found to disappear quickly. Figure 4 a depicts normal mammary cancer cells, while Figure 4 b shows mammary cancer cells after



(a) (b)

Figure 3. Typical experiments on *in vitro* tissue, in which 0.3 g sodium was added at 50 s into beef. (a) Profile of the burned area after the reaction; (b) tissue temperature transients during the reaction process.



(a) (b)

Figure 4. Output comparison of mammary cancer cells before (a) and after (b) sodium was added to petri dish in culture.

sodium had been added to the petri dish for 40 s. This phenomenon accords with the previous discovery that a tumor cannot easily survive in an alkaline environment.

To estimate the damage extent due to reaction between sodium and tissue, three sodium cylinders with a height of 1 cm and a diameter of 1 mm, 1.5 mm, and 2 mm, respectively, were inserted into fresh pork tissues. A typical alkali-burned interface generally appears to have three concentric zones, which can be divided into liquefaction necrosis, coagulation necrosis and congestive district from interior to the outside, respectively. The liquefaction necrosis zone appears in solution-state due to dehydration, protein dissolved and fat melted. The coagulation necrosis zone takes on a gray colour due to assembly of free erythrocytes. The congestive zone takes on a red colour which is due to the expansion of micro artery, capillary and micro-vein. Liquefaction and coagulation necrosis indicate irreversible damage. The output of the experiments is listed in Table I. As indicated by these carefully made measurements, the damage scope depends on the diameter of the sodium cylinder. The coagulation diameter (including congestive diameter) and the loaded amount of sodium follows an approximately linear relation. In other words, the former increases with the latter. Besides, the destruction scope is generally localized for each group, which guarantees the safety of the operation.

Table I. The reaction results of sodium with pork

Experiment #	Sodium mass (g)	Sodium diameter (mm)	Coagulation diameter (mm)	Congestive diameter (mm)	Reaction time (min)
Group I	0.0071	1	2	10	6
Group II	0.0178	1.5	3	13	17
Group III	0.0310	2	7	16	28

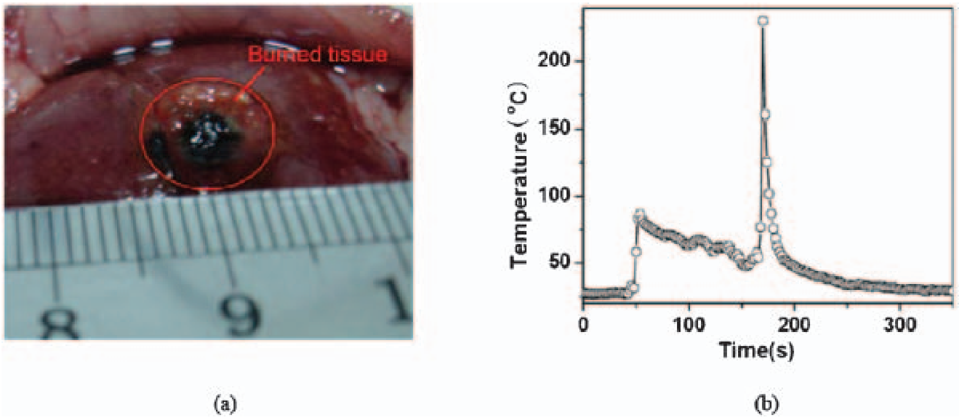
The right column in Table I represents different reaction times between sodium cylinders with different diameters and tissue types. For the same tissue environment, the reaction time is dependent on the quantity of alkali metal and the interface area between the metal and the tissue. Since these two factors vary from each other in the three groups, the reaction time in each case is different. For a tumor with specific shape and size, the injected sodium should be carefully chosen in advance. Although a large number of quantitative experiments were performed in the similar tissues, the density, thermal conductivity and other physical parameters may change case by case. In addition, the mass of sodium will affect the reaction time and heat transfer loss during the exothermic process, thus the heat release efficiency of the exothermic reaction may not always be the same in the three group experiments. Our overall result is an approximate relation between coagulation area and the sodium mass, which offers readers a preliminary grasp on the new thermal ablation method.

The thermal ablation appearance and temperature outputs for *in vitro* tests on fresh beef are depicted in Figure 3, in which 0.3 g sodium was added into the beef at 50 s. Figure 3 a shows the profile of the burned area, in which a necrosis area was specifically indicated using white circle. Figure 3 b presents the temperature transients of tissue during the reaction process. Clearly, a sufficiently strong temperature increase by a magnitude of >40°C has been realized at site A which is at the centre of the reaction region. It indicates that the highest temperature level during the reaction can be quickly elevated to 90°C and then kept at above 60°C, far higher than that requested to thermally kill a tumor tissue. At point B, the temperature is still kept > 40°C during the reaction process. At points C and D, temperature elevation is however not obviously high. A later inspection on the target tissues clearly shows that (Figure 3 a) an almost round area with radius of 2.5 cm has been burned, indicating that the target tissue was completely destroyed. All these results were achieved via a rather simple way by injecting only an extremely small amount of sodium into the target site.

To further demonstrate the feasibility of the new thermal ablation method, *in vivo* experiments were also performed on an anesthetized rat. Some representative results are illustrated in Figure 5. Here, 0.02 g sodium was added to the liver of the rat after opening its chest out. Figure 5 a indicates the partial carbonization in the targeted tissue. Figure 5 b presents the temperature transients of tissue during the reaction process of sodium, which again reflects an extremely strong heating effect. At the beginning of the reaction, the temperature at the injection spot was elevated to 90°C, and then deceased. When the temperature reached 50°C, the addition of a drop of water to the sodium surface even resulted in a strong combustion at the target tissue and thus an instantaneous temperature increase, whose peak value reached 225°C. This shows the powerful heating performance of the new minimally invasive ablation therapy.

Discussion

The exothermic chemical reaction between alkali metal and water suggests a perfect self-heating protocol for the combined tumor thermal ablation and chemical therapy. Using tremendous heat released from the exothermic chemical reaction, a safe (or "green") thermal ablation treatment can be obtained and confined to within the target. In addition, the temperature increase at the reaction



(a) (b)

Figure 5. Output of an experiment on *in vivo* rat liver, in which 0.02 g sodium was added to the rat liver. (a) Indication of partial carbonization in the targeted tissue; (b) The transient temperature of tissue during the reaction process of sodium.

spot was significant enough and the alkaline environment still induces a swelling of tissue with liquefied and coagulation necrosis, and hence cell death. Such a powerful self heating performance, almost impossible to achieve by many current state-of-the-art advanced thermal ablation applicators, guarantees a highly efficient and minimally invasive tumor thermal ablation treatment through injection of only a small amount of alkali metal. It is worth mentioning that the sodium used as the ablation seed is at room temperature, which is completely safe from the point view of thermal damage. Therefore unnecessary burning injury to the healthy tissues can be avoided. This is a very attractive merit of the present method.

In this therapy, water is one of the most important factors to determine the heat release rate of the chemical reaction. The temperature rise is very much dependent on the water content. Meanwhile, the heating magnitude also relies heavily on the amount of the delivered sodium. Therefore, through appropriately administering the dosage of both metal and intentionally supplied water, the thermal ablation area can be well controlled within a safe range. In the present study, what is presented in Figures 3 and 5 only partially illustrates the controllability of the sodium heating. Here, water was adopted as a flexible tool to control the heat generation. From the experimental curves, one can observe that a temperature fluctuation occurs when a certain amount of water is supplied to the target. Compared with quite a few existing hyperthermia apparatuses, the present method appeared rather useful in realizing a highly targeted heating. For specific tissues in the biological body, water content is generally at a constant level. For instance, water content in breast cancer in BALB/c mice is about 65%. In future practical situations, the water content in the target tissue can possibly be detected in advance before performing the surgery. With such information in mind, clinicians can control the dosage via a relatively quantitative way. Clearly, a complete understanding of the relation between temperature response and water content of tissue still needs much work in the near future.

It should be mentioned that a safe administration of the alkali metal can be done via various injection ways. For example, the metal can be designed as "sodium blade" or spurted to deeply seated target tumor by a micro jet. During a practical treatment process, a hollow pipe can be placed at the reaction site to guide the possible release of gases to the external environment. It is worth pointing out that the metals can also be fabricated as nano particles in the near future, or contained in solutions with certain "green" chemical agents. Thus a highly convenient treatment protocol can be pushed even to an outpatient basis. In the near future, what a clinician needs to do is just to operate the syringe by following the guidance of the user menu. A carefully designed syringe with alkali metal loaded inside allows a highly safe operation. If appropriately packed, the sodium metal itself will not contact with the tissue along the insertion path and thus could not release heat until it was injected into target tissues and reacted there. For the purpose of safe injection, the solid metal can be loaded in advance at room temperature in a specially designed syringe. A piston can then be used to push the metal into the tissue. After that, it can be pulled back to guide the release of possible gases to the external environment during the chemical reaction process of the metal. Thus the sodium has no chance to get into contact with the healthy tissues along the path before being injected. This makes the present thermal ablation method rather safe and convenient. But a clinically practical device still needs careful design both on the structure and the material of the syringe in the near future.

Generally speaking, a larger quantity of sodium supplied with matched water will guarantee a higher temperature level, a longer heating period and a larger necrotic area. In addition, for irregularly shaped tumors, a conformal treatment can be conveniently administered by injecting reactants into multiple regions under guidance of a medical imaging system such as ultrasound, MRI or X-CT. Due to its powerful and highly localized features, the present method is rather beneficial in maximizing the tumor-killing effect while minimizing thermal injury to the healthy tissues. Moreover, as a simple, safe and economic method, the combination of thermal ablation and chemical effects could possibly find wide applications in future tumor treatment.

From the point of view of surgical monitoring and guidance, the present method also allows excellent flexibility for such demand. Since the injected amount of the metal is rather small and it takes no anti-electromagnetic effect, the present thermal ablation method is compatible with most routinely used clinical image devices such as MRI, ultrasound or X-CT. Besides, injection of alkali metals can also possibly be adopted as a way to enhance the imaging accuracy of such devices. Except for guiding the injection of the alkali metal, the imaging system can also help show lesions of the internal structures of target tissues, such as hemorrhage, necrosis and fat degeneration. For example, dynamic MRI with multiphase scanning can fully demonstrate the lesion characteristics of the blood supply. In the near future, one can adopt MRI as a tool to monitor blood flow and tumor vascular necrosis during the course of thermal ablation surgery using alkali metal. After reaction between sodium and water in tissue, changes in tumor surrounding can then be flexibly displayed on the computer screen, which will serve as a valuable guidance for planning the subsequent treatment.

In future applications, to detect *in situ* the heat generation effects during reaction between alkali metal and water in tissue, some commonly used temperature sensors such as thermal couples or infrared thermometer can also be adopted for monitoring and administrating the ablation process. This will help control the treatment on a relatively accurate level.

Recently, in a comparable study, we had also proposed a new method of using heat released from an exothermic chemical reaction between solutions of acid and alkali such as HCL and NaOH (unpublished data), which can safely deliver a localized and uniform heating to exactly kill the tumor. According to the states of the reactants used to thermally ablate the tissues, this previously described way can be termed as a ''wet'' ablation strategy, in which solution was used as heating seeds. A special feature for performing the HCl+NaOH ablation lies in that delivering such reactants may put a high demand on the device materials with strong capability of anti-corrosion. Another point lies in that the temperature elevation has its specific range there. Such a method is more suitable for ablating a small tumor. For the reasons explained above, using alkali metal–sodium as a hyperthermia seed can be classified as a ''dry'' ablation method (sodium is solid, and only reacts when meeting with water). Due to its solid state and highly localized feature, such a method may be more controllable. But a complete evaluation of the differences between the ''wet'' and ''dry'' ablation methods is not yet available at the present stage. Clearly, both methods have their distinctive merits which warrant many interesting applications in future tumor clinics.

Finally, we should emphasize that the new therapy is still at its incubation and proof-of-concept stage. Quite a few efforts are needed on animal and clinical tests to justify the new therapy before it can be used in a real tumor treatment on humans in the near future. The present research is expected to serve as a valuable guidance for such an endeavour.

Acknowledgments

The experimental supports from Prof. Yixin Zhou, Ms. Yang Yang and Mr. Jingfu Yan are greatly appreciated. This research is supported by the NSFC under Grant 50325622, 50436030.

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