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Investigating the cryoablative efficacy of a hybrid cryoprobe operating under freeze–thaw cycles ☆

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ABSTRACT

Cryoprobes are minimally invasive tools that apply extremely low temperatures to eradicate undesirable cancerous tissue during cryosurgery. At times, they may generate thermal injury to neighboring good tissue leading to the case of over-ablation. The magnitude of this problem becomes significant when tumors are complex, large size and irregular in shape. In this work, we propose a simple yet pragmatic hybrid cryoprobe which can potentially promote better surgical efficacy by improving tumor ablation while reducing undesired thermal injury to the neighboring tissue. To evaluate the performance of the proposed probe operating under cyclic freeze–thaw conditions, a detailed bioheat transfer model incorporating tissue death functions was developed. In-vitro experiments conducted to validate the model yielded a good agreement of 6.7%. We numerically studied the thermal impact of employing the hybrid cryoprobe on tissue temperature distributions. Evaluating the hybrid cryoprobe's control ability, we showed that the proposed device was able to regulate the growth of the ice front while sustaining an excellent coverage of the ablation zone. We also noted the existence of a diminishing temperature effect when alternate freeze–thaw cycles were applied. The performance of the hybrid cryoprobe could potentially lead to a portable and cost-effective device that may prove hugely beneficial for the purposes of surgical planning, rehearsal and control.

Introduction

Some liver cancer patients cannot undergo surgical excisions because of unfavorable anatomical location, the presence of multiple tumors or poor hepatic reserve [3,18,30]. Complex tumor therapy motivates the development of simple, affordable, and better precise techniques with lower morbidity rate. Cryosurgery is a promising minimally invasive therapy which utilizes cryoprobes at extremely low temperatures to eradicate undesirable cancerous tissue. It has been widely applied to treat the cancer cells of liver, lung, encephalon and bone [1,17,31,41,58]. At times, cryotherapy, can produce insufficient freezing due to difficulties in regulating freeze–thaw cycles, leading to a high probability of recurrence [19].

It is of paramount importance to understand the connection between tissue cryo-freezing and the corresponding cell death mechanism so as to determine key controllable parameters that enable surgeons to achieve greater surgical success. It is generally believed that the intracellular ice plays an important role in cryoinjury by either electrical transient at the ice interface [45] or critical gradient in osmotic pressure across the membrane [26,55]. To control and regulate the lethal temperature region, often demarcated at below 233 K [24], repeating several freeze–thaw cycles has been known to be an effective therapy [2,13,14]. However, the physical mechanism involving cell destruction during freeze–thaw process, particularly when freezing and peripheral thawing are executed to control and enhance the cryoablation, has not been covered in depth. Some studies have defined specific temperatures to demarcate the lethal temperature boundary [14] while some have applied freezing/cooling rate as the main cell ablating method [7]. Though there are existing works that study the ablating mechanism involving a single freeze–thaw cycle, few have considered the biophysical implication of several overlapping freezing/thawing cycles on quantitative cell damage. Fig. 1 relates different freezing regimes that mark the cell damage rates to the cell freezing rates [15].

Studies +apparatus to regulate ice ball formation to better control of the lethal temperature region [32,33,35,48,54]. Cryoheaters have been proposed and developed based on a temperature-controlled cartridge heater as a thawing probe to regulate the ice ball formation [32,35]. Employing thermal analysis tools, feasibility studies on cryoheater's performance have been published [32,33,35,48]. In these cases, the temperature of the thawing probe has been maintained below 313 K to avoid tissue charring [33,35].

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Nomenclature

D_S	damage rate
E	deviation modulus
E_a	activation energy (J/mol)
ΔG	the Gibbs free energy of inactivation (J)
i	number of iteration step
m	total number of iteration
n	number of the freeze–thaw cycles
P_k	Planck's constant
R_{al}	length between the 233 K and 323 K isotherm at line A in the first freeze–thaw cycle (m)
R_{bl}	length between the 233 K and 323 K isotherm at line A in the last freeze–thaw cycle (m)
r	radial distance from the center of cryoprobe (m)
t	time (s)
T	temperature (K)
T^*	critical temperature for boundary conditions (K)
T_1^*	minimum temperature for all tissue to survive (K)
T_2^*	maximum temperature for all tissue to survive (K)
T_{fc}^*	confirmed lethal temperature of freezing (K)
T_{tc}^*	confirmed lethal temperature of heating (K)

Greek symbols

α	constant
β	constant
ε	pre-exponential factor
γ	Boltzmann's constant
τ_1,τ_2	parameters of overlapping effects of the damage induced by freeze–thaw cycle
φ_l	general variable
Φ	function of the probe temperature at the initial stage

Subscripts

a	tissue frozen region
amb	ambiance
b	tissue mushy region
c	tissue unfrozen region
fc	freezing cycle
ini	initial condition
tc	thawing cycle
p	probe
sta	steady condition
t	tissue

Using a single heating probe is usually ineffective as far as the treatment of solid large tumors is concerned. A complex tissue structure further reduces the reliability of such stand-alone heating apparatus. The effectiveness of cryoablative procedures has triggered considerable interest in dealing with large and irregularly shaped tumors. To address this problem, a common cryoablating approach is to adopt more probes to enlarge the lethal temperature region. However, the allocation of the probes must be carefully planned and judiciously carried out. The improper positioning could induce greater thermal damage to healthy tissue or cause insufficient damage to the targeted tumor cells.

In this work, we propose a hybrid cryoprobe that combines both cryo-freezing and peripheral thawing in one single-device. The proposed concept of a hybrid cryoprobe offers tangible benefits such as non-uniform controlled thawing in different tumor sections, versatility in shaping ice-front along the tumor boundary and greater cell ablation region characterized by reduced spatial gap of incomplete cell destruction region. Here we report the detailed investigation of such a hybrid cryoprobe and evaluate some of its key benefits.

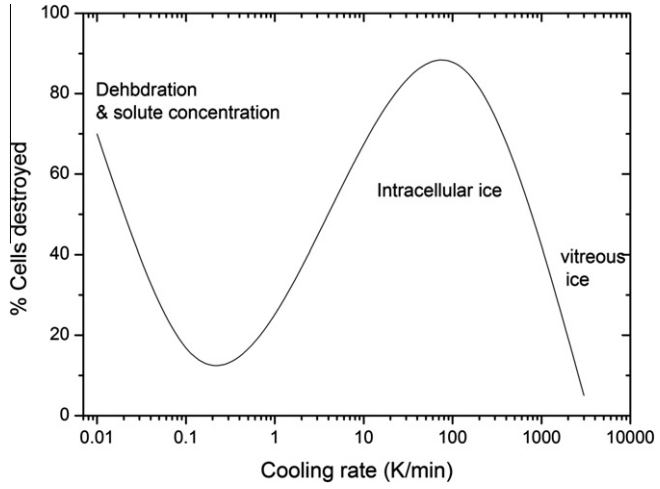

Fig. 1. Percentage of cell destruction based on the rate of cooling [15].

System configuration and design

Experiments

The schematic diagram of the experimental set-up is shown in Fig. 2. Pressurized liquid nitrogen was stored in a cylinder and control released using a needle valve. A lab-designed cryoprobe of 6 mm in diameter vaporized the freezing medium in a small chamber after it passed through a nozzle located near to the tip of the cryoprobe. A vacuum layer was applied to insulate a portion of the cryoprobe. A temperature-controlled cartridge heater (OMEGA, CIR series) was adopted as a heat source to generate boundary heating and contain the ice ball formation. The heater was controlled by a linear AC power source (GWINSTEK, APS-1902). Six type-T copper-constantan thermocouples were used to measure the tissue temperature with the essential labels marked. TC1–TC3 and TC4–TC5 were linearly aligned at equidistance of 5 mm. The distance between TC1 and the cryoprobe center was 7 mm while the distance between TC4 and cryoheater center was 5 mm. The data was digitally logged with data acquisition (Agilent, 34970A) at intervals of 10 s. The flow rate of the freezing medium was measured using a gas flow meter (Malema, MTF-4130-D) located at the downstream of the temperature controlled bath.

The cryoprobe, flushed with hypertonic saline, was inserted into the porcine liver at a depth of 1.5 cm. Temperature control bath was maintain at 308 K before the commencement of the liquid nitrogen flow. An adjustable power supplier for cryoheaters (GW Instek, APS-9102) was used to produce either 9 W or 12 W for the cryoheaters to sustain a desired thawing temperature for 10 min [44].

Numerical analysis of heat transfer

Tissue thermal intensity affects the degree of cell damage and defines the efficacy of a selected cryotherapy. A minor temperature change causes an inflammation but a drastic temperature difference leads to tissue destruction due to protein denaturation [56]

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