Cryobiology 67 (2013) 201–213

Contents lists available at SciVerse ScienceDirect

Cryobiology

journal homepage: www.elsevier.com/locate/ycryo

A novel approach to improve the efficacy of tumour ablation during cryosurgery ☆

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ARTICLE INFO

Article history:
Received 15 March 2013
Accepted 27 June 2013
Available online 15 July 2013

Keywords:
Cryosurgery
Efficacy
Active length
Optimal offset
Multi-block grid
Numerical simulation

ABSTRACT

Freezing tumours and ablating it using cryosurgery is becoming a popular surgical procedure for treatment of carcinomas. In order to improve the efficiency of the cryosurgical procedure different approaches have been implemented till now, e.g., injecting high thermal conductivity fluid inside the tumour, low latent heat fluids inside the tumour prior to cryosurgery etc. These techniques improve the cryosurgical process to some extent but lack in minimising the damage to the surrounding healthy tissues. In this study, a novel concept is proposed which advocates the use of solutions with specific thermophysical properties around the interface of tumour. Numerical modelling has been done to determine the location of the ice fronts in the presence of this solution around the boundary of the tumour. It is noticed that in the presence of solution layer, owing to its distinct thermophysical properties like low thermal conductivity, not only the cellular destruction is enhanced but also the damage to the surrounding healthy tissue is minimised. Further, results indicate that this strategy leads to a faster ablation rate reducing the surgical time immensely. Also, an optimal offset, the minimum distance between the tip of cryoprobe and the boundary of the tumour, is identified for a given tumour radius with a given active length which gives maximum tumour necrosis in less time. This optimal offset which has been identified for each case will help the surgeons in proper planning of cryosurgery and improving the effectiveness of this technique greatly, making it a better treatment modality than its counterparts in many ways. It is also observed that for a 2 mm increase in activelength of the cryoprobe, the decrease in optimal offset is approximately 1 mm, i.e. optimal offset decreases linearly with an increase in the activelength for a given radius of the tumour. Also, for tumour with different radii, ranging between 10 mm to 15 mm, with same active length, the time taken for complete ablation by the larger tumour is nearly 2.7 times the time taken by the smaller one for every 2.5 mm increase in the tumour radius.

1. Introduction

Owing to rise in the number of cancer cases sharply over the last five decades, improvements in methods for treatment of cancers has become a necessity [1]. Although, a lot of treatment modalities like chemotherapy, radiation therapy, surgical ablation are available currently, these have catastrophic side effects. With the advent of modern cryosurgery, a safe and effective method of tumour ablation has come into existence [2]. Being a minimally invasive technique, it has advantages like lesser vascular complications, a short surgical time, cost effectiveness. It finds application in ablation of tumours of prostate, breast, liver, kidney, bone, skin and uterus [3].

For a cryosurgical procedure to be effective, the rate of freezing should be optimal so that the tumour ablation is uniform with minimal damage to the surrounding healthy tissue. It is very well known that lower temperature in the tissue leads to higher destruction and for a complete destruction a lethal or critical temperature should be achieved. It is suggested that the critical temperature for cell destruction must be in the range of −40 °C to −50 °C [4,5]. This critical temperature is achieved due to the ice formation during the cooling of tissue. When the rate of cooling is very high, water cannot be transported quickly across the cell membrane to maintain an osmotic equilibrium. Therefore, ice formation takes place inside the cells to maintain this equilibrium, making the intracellular environment thermodynamically supercooled and unstable [6,3]. The rapid formation of intracellular ice crystals damages the cell membrane and leads to destruction of tumours. But in presence of slow cooling, extracellular ice crystals are formed. Due to osmosis the concentration of extracellular solution increases and water in the cells pass across the cell membrane, leading to extracellular ice formation or solution effect [6,7]. Apart from these existing cellular mechanisms of cryoinjury to tissue [8], studies suggest that a cell can sustain injury through multiple

☆ Statement of funding: This work is not supported by any funding agency.
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0011-2240/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cryobiol.2013.06.013

Nomenclature

c	specific heat (J/kgK)
H	specific total enthalpy (J/kg)
h	specific sensible enthalpy (J/kg)
k	thermal conductivity (W/mK)
L	specific latent heat of fusion (J/kg)
$\dot{Q}_m$	metabolic heat generation (W)
T	temperature (K)
t	time (s)
$\dot{m}_b$	blood perfusion rate (kg blood per m^3 of tissue per second)

Subscripts

b	blood
f	frozen tissue
l	point at which freezing starts
s	point at which freezing ends
u	unfrozen tissue

mechanisms which might be vascular or immunological in nature. Due to freezing there is a shutdown of vasculature in the tissue which causes thrombosis and ischemia leading to cell death [9]. Another cause of injury is the release of antigens present within the cells into blood stream when the cells lyse due to cryodestruction. This results in the induction of immune reaction in which the antigens stimulate the immune cells to produce antibodies against the rest of the tumour [10–13]. Also, during cryosurgery it has been seen that cell death by apoptosis occurs in the periphery of iceball [14,15]. The in vivo evidence is not well documented and hence further investigations should be carried out for the same. There is also a need to study the extent of cell death due to necrosis and apoptosis during the cryosurgical process. These molecular pathways play a critical role in freezing induced cell death and understanding these pathways will improve the efficacy of cryosurgery immensely [16].

Advances in imaging techniques such as magnetic resonance imaging (MRI), ultrasound, X-ray, electrical impedance tomography (EIT) have facilitated in performing cryosurgeries with ease and made this technique popular but each one of them has its own limitations [17–21]. Each imaging procedure available currently helps us in visualising the iceball interface but it is unable to predict the exact location of the lethal front or critical temperature isotherm which is extremely crucial for detremining the extent of damage to cancerous cells. To tackle these problems and provide online monitoring of temperature at finite number of points within the tissue, thermocouples are being used. But the exact placement and positioning of these thermocouples again requires details like precise location of critical temperature isotherm. To solve this issue, models have been developed not only to determine the temperature around the cryoprobe but also within the iceball that is formed during this process. The earliest model that was developed was for a single cryoprobe in a one dimensional plane which assumed immediate cooling around the probe [22]. This model proposed conduction as the significant driving force of heat transfer inside biological tissues. Newer and complex models were developed later to conduct a parametric study of freezing of tissue in a two dimensional and axisymmetric cylindrical cryoprobe using finite difference scheme. Also, an exact time dependent location of the iceball was visualised but the temperature within it was not calculated [23]. Rapid advancements led to the development of three dimensional heat transfer models for multiprobe cryosurgery [24,25]. In the same context, Rewcastle et al. proposed a three dimensional finite difference method that simulated freezing and temperature evolution in a medium with a multiprobe arrangement [26]. For betterment in effectiveness of this surgical process, computerised planning is done by variable insertion depth of cryoprobes [27]. All these real time modelling studies are incomplete without experimental studies and therefore, require in vivo and in vitro studies to validate their results.

A plethora of in vivo and in vitro studies have been carried out to improvise cryosurgery and increase its efficacy. Cryosurgery has been used to perform hepatic surgery for colorectal masses [28] and porcine kidney tumours [29]. Another in vivo study showed that phosphate buffered saline solution of antifreeze proteins type-I at a concentration of 10 mg/ml can cause cell death and acts as an adjuvant. This is due to the spicular nature of ice crystals formed which rupture the cell and cause its membrane to lose its integrity [30]. Several chemical adjuvants, used in chemotherapy, like peplomycin and adriamycin have been used along with this procedure and have shown good results [31]. Recently, it has been shown that eutectic freezing can also elevate tissue damage during cryotherapy [32]. Further, if a solution of high thermal conductivity or low latent heat is injected into the tumour, with the same probe configuration, a larger iceball has been produced [33]. In another study, experimental results demonstrated that injection of appropriate solution like water, aluminium oxide nanoparticles in water, ethanol and 10% solution of dimethyl sulfoxide enhanced the tumour killing during cryosurgery without affecting the freezing process [34]. Studies have been carried out to investigate the role of vasculature in enhancing cryosurgical cell death. Pre-conditioning of the tumour before cryosurgery using TNF-α, which is a vascular cytokine, has shown promising results. The cryolesion diameter increased significantly when the cryosurgery was performed after injection of this cytokine [35]. Thus, showing that even vascular adjuvants increase the efficacy of cryosurgery greatly. Chua and Chou [36] suggested that employing more number of freeze–thaw cycles facilitates greater cell destruction within the tissue. These techniques improve the cryosurgical process to some extent but lack in minimising the damage to the surrounding healthy tissues. To further improve cryosurgery by minimising the healthy tissue damage, the use of a cryoheater is recommended, a device which aids the cryoprobe by heating the tissue to shape the freezing of iceball [37].

Although, a lot of research has been done on improving cryosurgery process but still a lot of drawbacks exist and to overcome the same, we propose a novel concept that can improve the efficacy of modern cryosurgical process immensely. The objective of the current study is to propose a new concept that advocates the use of a solution layer of low thermal conductivity like perfluorocarbons around the tumour such that it is completely covered or surrounded by that layer following which cryosurgery is used for its ablation. It should be noted that the solution layer can be made by using perfluorohexane, a perfluorocarbon, which is widely used in the field of medicine for liquid breathing. This liquid has a very low thermal conductivity of 0.057 W/m °C and very low solubility in water.Tumour cells have unique cell surface receptors which are quite different from their normal counterparts. Different type of tumour cells express different antigens; these tumour antigens can be targeted by monoclonal antibodies, which is already in practice in biological research [38]. It is proposed that this