MINISTRY OF EDUCATION AND TRAINING
THE UNIVERSITY OF DANANG

LE MINH TRI

RESEARCH ON APPLYING THE CRYOGENIC TECHNIQUE INTO MEDICAL FIELD IN VIETNAM

Major Field: Thermal engineering
Code: 62.52.01.15

DOCTORAL THESIS ABSTRACT

Danang- 2017

This thesis will be completed at the University of Danang

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This thesis can be viewed at:
- The Learning and Information Resource Center, the University of Danang
- The National Information Resource Center, Hanoi.

INTRODUCTION

1. Reasons for the research

In the recent years, Cryotech has strong and fast development because of its feature and potiental applications into medical field. Two main applications of this technique are: Producing cold environment for preserving cold medical products and applying in Cryosurgery.

In the technology of preserving cold medical products, medical products such as bio-chemicals, blood products, embryos, stem cells, sperm ... are stored in specialized equipment in Cryo temperature. Freezing preservation is the technique to store live cells and tissues at low temperature conditions in a very long time.

In cryosurgery technology, this method has been used to treat a number of skin diseases in benign disorders and malignancies, to treat warts, moles, skin tags, solar keratoses, Morton nerve tumour and small skin cancers. Cryosurgery is also used for liver cancer, prostate cancer, lung cancer, mouth cancer, cervical disorders, hemorrhoids, plantar fasciitis, and soft tissues such as fibroids (benign tumors of connective tissue). The treatment is suitable and effective for solid tumors bigger than 1 cm.

With the research purpose is to examine ice ball making needle to destroy demolition organizations and cancer cells located deep inside the body. We use a needle to create ice ball making needle which is capable of shocking hot- cold temperatures for the cells exposed. Hot and cold shocking process consists of 2 processes: the

process of granting the cold and the heating process. In the process of granting cold, ice ball making needle is cooled by liquid nitrogen temperatures -196^{0}C. During the heating process, the needle will be rapidly increased in temperature with hot water at 42^{0}C. The hot and cold shocking process made the cells lack of blood and oxygen and causing necrosis to inactivate cancer cells.

The study of heat shock time, created ice layer size is to precisely control the scope of the affected cells. We carried out theoretical calculations heat transfer process when frozen, thawed and locally applied cells in experimental animal models.

Cryoprobe has been widely applied in a number of countries around the world such as China, the US ..., but in Vietnam, it is still relatively undeveloped, there is no established research so far.

These above reasons motivate me to choose the topic **"Research on applying the Cryogenic technique into medical field in Vietnamese conditions"** as my Phd thesis.

2. Research objectives:

- Theoretical study: calculate process of heat transfer when freezing locally cells by Cryo cold technique. Build mathematical models that set the formula to measure parameters during cell vitrification.

- Empirical Research: exploring the possibility of killing liver cells on healthy animals tissue as well as the capacity of destroying cancer cells in the human liver tissue separated from the body.

3. The research content

- Developing theoretical basis calculations for cell's quick vitrification process.

- Developing mathematical models for different devices for cold surgery (cryotherapy equipment, icicle and ice ball ceating needle).

- Setting the formula to calculate the heat tranfer when freezing heat transfer locally engineered cells Cryo cold.

- Developing software to calculate parameterdus ring vitrification.

- Producing experimental model of ice ball needle

- Exploring the possibilities to destroy liver cells by ice ball needle on healthy liver tissues of mouse and rabbit.

- Exploring the potential to kill cancer cells by ice ball needle devices in liver tissue separated from the body of patients with liver cancer.

4. Object and scope of the study

4.1. Research subjects

- The parameters of the process of heat transfer when freezing locally the cells by Cryo technology.

- The livers of mouse from 6 to 8 weeks old.

- The liver of rabbits from 3 to 5 months old.

- Samples of liver cancer tumors of patients, collected after the surgery at Hue Central Hospital which are larger than 15 x 15 x 7(mm).

4.2. Research scope

In the application of cryosurgery to destroy cancer cells, this is a very new field, the authors just did the research with the investigating level on dead threshold of healthy liver tissue in mouse and rabbits, from which study effectively how to destroy cancer cells in the human liver tissue separated from the body.

5. Thesis structure

Chapter 1. Literature review

Chapter 2. Method of the research

Chapter 3. Calculate the heat transfer when freezing locally cells by Cryo cold technology.

Chapter 4. Research the ability to kill liver cancer cells with ice ball needle.

Chapter 5. Conclusions and recommendations.

CHAPTER 1. LITERATURE REVIEW

1.1. Technical overview of Cryo technlogy

1.2. Research, technical applications of Cycro cold technology in cold surgery technology.

1.3. Liver and the situation in liver disease research

1.4. Treatment of liver disease

A technical treatment of liver cancer applied in some countries such as China, USA, ... is cooling to very low temperatures to destroy liver cancer cells (cryosurgery) by using the device of Cryoprobe (Cryoprobe), this is a new technique which has not been applied in Vietnam.

Cryoprobe has a needle shape, is used to kill cancer cells deep within the liver tissue. By vitrification technique at Cryo temperature, then cancer tumors will be heated rapidly to a certain extent. The reversing hot and cold treatment completely destroyed the illness organizations, directly causing the cancer cells drainage and disrupt, or destroy small blood vessels of the tumor, which makes it lacks of oxygen, and kill cancer cells.

At the same time after the destruction, the tumor organization which died on that spot can regulate antigen, trigger an immune response to fight cancer, cancer cells after freezing will become more sensitive to chemotherapy and radiation effedcts, enhance the effect of radiation chemistry. Although this is a form of surgery but it is not open surgery and does not create side effects as chemotherapy or radiotherapy.

CHAPTER 2: METHOD OF THE RESEARCH

2.1. Theoretical study of heat transfer when freezing locally cells by Cryo cold technology

- Analytical methods: This method is widely used and popular when establishing formulas and equations. The advantage of this method is that the relationship between the quantities is clearly expressed. The calculation is simple, much easier than the numerical method. The calculation process does not depend on the software set up by the programmer.

- Method of differential and integral: This is the basic method of mathematics. This method is based on the principle of subdivision of the surveyed area, then integrated into the process results. This method is used to construct heat transfer equations in thermal engineering.

- Application of energy conservation laws and Fourier's law on heat conduction to investigate mobile boundary problems, especially the problem of solid-bound computation and finding of this problem is the function of temperature distribution in surveyed objects, The speed and acceleration of the shift phase, the set of equilibrium equations for heat transfer in Cryo techniques, are used to determine the duration of freezing of moisture in three common shapes: flat, cylindrical and globular.

2.2. Subdivision of empirical exploration cold needle treatment efficiency

2.3. Experimental methods histopathology and cells in vitro

2.4. In vitro fed liver cells

CHAPTER 3. THE HEAT TRANSFER PROPERTIES WHEN FREEZNG LOCALLY CELL WITH COLD CRYO TECHNOLOGY.

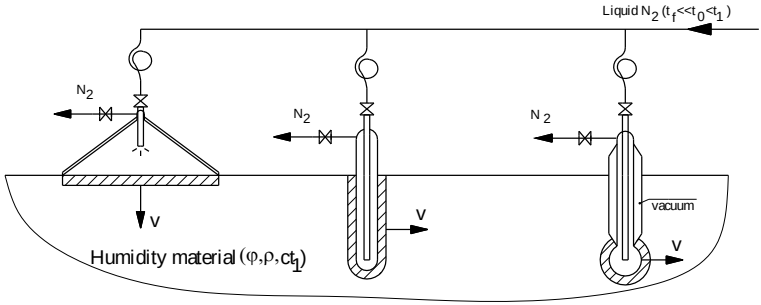
In this chapter, the author proposes to solve the problem of heat transfer in a new solutions, using analytical methods. This is a necessary job, suitable to the process of cells freezing locally by Cryo technology

3.1. Building the theoretical basis calculation of parameters during freezing locally engineered cells by Cryo cold technology

3.1.1. Theoretical overview of the process of transition

3.1.2. Physical thermal properties of food

3.1.3. Addressing the problem of heat transfer when fast freezing cells



Picture 3.3. Equipment arrangment when fast freezing cells

For moist material with ω humidity, the density ρ, specific heat c, t_1 initial temperature, expose to cold walls by thin flat or cylindrical or sphere of radius r_0 metal. Wall surface is cooled by the cold boil liquid, evaporating temperature $t_0 = t_f << 0^0C$, ice surrounding the wall has the freezing temperatures t_0 and r_c as its solidification. It is neccessary to look for the freeze paramter.

3.1.4. Refer to solve equations done by F.sun

3.1.5. Constructing hypotheses in cell partial fast-freezing

1. Consider the inner ice surface is the marginal category 1, with a constant temperature = t_f of boiling cold liquid.

2. Consider the temperature down from t_1 to t_0 and heat transfer process when freezing r_c is happening very quickly and simultaneously.

3. Consider the heat flow q instantaneously at τ (q (τ)) by heat conduction from the ice refrigerant transition to the refrigerant in a very short time dτ is stable.

4. Consider the cell as a humidity material with the physical parameters (moisture ω, density ρ, specific heat C, thermal conductivity λ, temperature and heat transfer freeze phase t_0 and r_c) is evenly distributed and not changed in space and time the survey.

3.1.6. Analyzing the impact of hypotheis on calculation result

3.1.7. Ice forming process on flat surface of semi-infinite humidity material

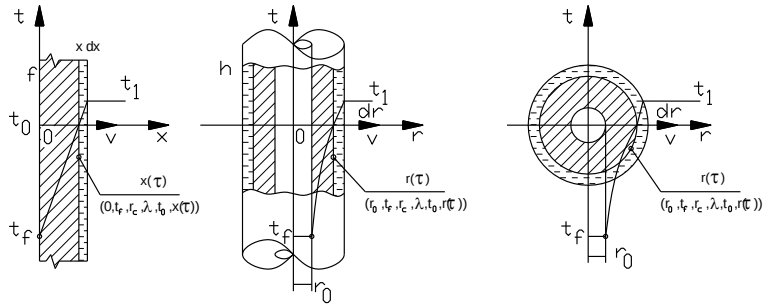


Figure 3.9. Geometric representation of three math problems of solidification in humidity material

Set x as the thickness of created ice layer before τ, dx as the thickness of created ice layer after the infinitesimal time dτ. According to the Law of conservation of energy, the instant heat equation of equilibrium at the time ofτ for the ice layer dV= f.dx to be created after the time of dτ can be presented as follow: heatemission when dV lowers the temperature down to t_0 and freezes = heat transfer through thick ice partition out to freezing environment. The equation is as follow:

$$f.dx.\{(\rho_i.C_i+\xi.\beta.C_b.\rho_b).(t_1-t_0)+\rho_i.\eta.\omega.r_c\}=\frac{\lambda_i}{x}(t_0-t_f).f.d\tau,[J] \quad (3.44)$$

In which

i - examined cells;

C_i, ρ_i, λ_i- physical parameters of the cell;

C_b, ρ_b, λ_b - physical parameters of blood;

ξ, η - coefficient dependent cell types which are being surveyed;

β= 7% - the percentage of blood volume in the human body.

$$\int_0^{\tau} d\tau=\int_0^{x}\frac{(\rho_i.C_i+\xi.\beta.C_b.\rho_b).(t_1-t_0)+\rho_i.\eta.\omega.r_c}{\lambda_i.(t_0-t_f)}.x.dx \rightarrow \tau(x)=\frac{A}{2}x^2; \quad (3.45)$$

$$\text{with A} \triangleq \frac{(\rho_i.C_i+\xi.\beta.C_b.\rho_b).(t_1-t_0)+\rho_i.\eta.\omega.r_c}{\lambda_i.(t_0-t_f)},[s/m^2] \quad (3.46)$$

Inverse functionof τ(x) is$x(\tau)=\sqrt{\frac{2\tau}{A}}$, [m]. (3.47)

+ Velocity:$v \triangleq \frac{dx}{d\tau}=\frac{1}{A.x(\tau)}=\frac{1}{\sqrt{2.A.\tau}}$,[m/s] (3.48)

+ Acceleration:$a \triangleq \frac{dv}{d\tau}=\frac{-1}{2\sqrt{2A\tau^3}}<0$,[m/s^2] (3.49)

+ Unstable temperature field in ice layer:

$t(x,\tau)=t_f-(t_f-t_0)\frac{x}{x(\tau)}$, [^{0}C] (3.50)

3.1.8. The process of forming ice cylinder inside humidity material

Set r as the radius of created ice layer before τ, dr as the thickness of created ice layer after the infinitesimal time dτ. According to the Law of conservation of energy, the instant heat equation of equilibrium at the time of τ for the cylindrical ice layer dV= 2.π.r.h.dr to be created after the time of dτ can be presented as follow: heatemission when dV lowers the temperature down to t_0 and freezes = heat transfer through thick ice partition out to freezing environment. The instant heat equation of equilibrium is as follow:

$$2\pi.r.h.dr\left\{\left(\rho_i.C_i+\xi.\beta.C_b.\rho_b\right)\left(t_1-t_0\right)+\rho_i.\eta.\omega.r_c\right\}=2.\pi.\lambda_i.(t_0-t_f).h.d\tau/\ln(r/r_0),[\text{J}]. \quad (3.51)$$

$$\tau(r)=\frac{A}{4}(2r^2\ln\frac{r}{r_0}-r^2+r_0^2),[\text{s}]; \quad (3.52)$$

Inverse function of τ(r) is $r(\tau)=\tau^{-1}(r)$ it can be shown under the form of a cardinal number

+ Velocity $v=\frac{dr}{d\tau}=\left(A.r.\ln\frac{r}{r_0}\right)^{-1}$, [m/s] (3.53)

+ Acceleration $a=\frac{dv}{d\tau}=\frac{-\ln(e.r/r_0)}{A^2(r.\ln(r/r_0))^3}<0$, [m/s^2] (3.54)

+ Unstable temperature field in mobile ice layer at $r\in(r_0,r(\tau))$ has the form of:

$$t(r,\tau)=t_f-\frac{(t_f-t_0)}{\ln(r(\tau)/r_0)}\ln\frac{r}{r_0}; \quad (3.55)$$

3.1.9. The process of forming ice ball inside humidity material

Set r as the radius of created ice layer before τ, dr as the thickness of created ice layer after the infinitesimal time dτ. According to the Law of conservation of energy, the instant heat equation of equilibrium at the time of τ for the cylindrical ice layer dV= 4.π.r^2.dr to be created after the time of dτ can be presented as

follow: heatemission when dV lowers the temperature down to t_0 and freezes = heat transfer through ice partition to core. The instant heat equation of equilibrium is as follow:

$$4\pi.r^2.dr\left\{\left(\rho_{.i}C_i+\xi.\beta.C_b.\rho_b\right)\left(t_1-t_0\right)+\rho_i.\eta.\omega.r_c\right\}=4.\pi.\lambda_i.(t_0-t_f)d\tau/(1/r_0-1/r),(J) \quad (3.57)$$

$$\tau(r)=\frac{A}{6.r_0}(2r^3-3r_0.r^2+r_0^3),[s]; \quad (3.58)$$

Inverse function of $\tau(r)$ is a cubic function with the form:

$r^3-\frac{3r_0}{2}r^2+\left(\frac{r_0^3}{2}-\frac{3r_0\tau}{A}\right)=0$, set $r\overset{\Delta}{=}x+\frac{r_0}{2}$, the equation has the form

$x^3 + px + q = x^3-3\left(\frac{r_0}{2}\right)^2x+\left(r_0^3-\frac{3r_0\tau}{A}\right)=0$, in which

$p = -3r_0^2/4$,[m^2] and $q = r_0^3-3r_0\tau/A\overset{\Delta}{=}q(\tau)$, [$m^3$]. (3.59)

Using Cardano formula, we can describe the root $r(\tau)$ as follow:

$$r(\tau)=\sqrt[3]{\frac{-q(\tau)}{2}+\sqrt{\left(\frac{q(\tau)}{2}\right)^2+\left(\frac{p}{3}\right)^3}}+\sqrt[3]{\frac{-q(\tau)}{2}-\sqrt{\left(\frac{q(\tau)}{2}\right)^2+\left(\frac{p}{3}\right)^3}}+\frac{r_0}{2},[m]; \quad (3.60)$$

+ Velocity $v=\frac{dr}{d\tau}=\frac{r_0}{A.r.(r-r_0)}$,[m/s] (3.61)

+ Acceleration $a=\frac{dv}{d\tau}==-\frac{r_0^2.(2.r-r_0)}{A^2.r^3.(r-r_0)^3}$,[m/s^2] (3.62)

+ Unstable temperature field with $r\in(r_0,r(\tau))$

$$t(r,\tau)=t_f-\frac{\left(t_f-t_0\right)}{(1/r_0-1/r(\tau))}\left(\frac{1}{r_0}-\frac{1}{r}\right), \quad (3.63)$$

3.1.10. The process of creating ice when spraying liquid onto the skin surface

Considering the skin layer thickness δ_d, λ_d thermal conductivity; subcutaneous cells have thermal conductivity λ_i (Figure 3.11). The outer surface of the skin is frozen by refrigerant

temperature t_f, with a coefficient of heat α. We can specify the thickness of the transition x (τ); thickness of ice at temperature -10^0C (x (-10^0C)) and -5^0C (x (-5^0C)).

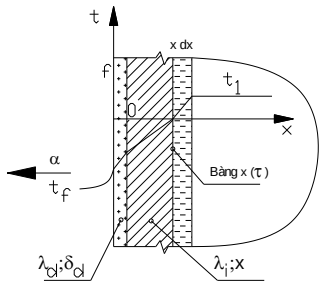


Figure 3.11. Geometry result of the problem when spraying the liquid onto the skin surface.

Because there is no latent hardening heat skin, so we only see as an insulating layer of thickness δ_d, the coefficient of thermal conductivity λ_d.

We can speak: Heat of phase transition of ice dV = Thermal transmitted via thick ice layer x, heat transfer through the skin layer thickness δ_d, radiate to cold environments with heat coefficient ratio. The mathematical equations can be written as:

$$f.dx.\{(\rho_i.C_i+\xi.\beta.C_b.\rho_b).(t_1-t_0)+\rho_i.\eta.\omega.r_c\}=\frac{(t_0-t_f)}{\left(\frac{1}{\alpha}+\frac{\delta_d}{\lambda_d}+\frac{x}{\lambda_i}\right)}.f.d\tau \text{ ,[J]} \quad (3.64)$$

Root of equation is:

$$x(\tau)=\frac{\sqrt{\left(\frac{1}{\alpha}+\frac{\delta_d}{\lambda_d}\right)^2.A^2.\lambda_i{}^2+2.A.\tau}-\left(\frac{1}{\alpha}+\frac{\delta_d}{\lambda_d}\right).A.\lambda_i}{A}; \quad (3.65)$$

Therefore:

$$x(-5^0 C) = x(\tau).\left(1 - \left|\frac{5}{t_f}\right|\right) \quad (3.66)$$

$$x(-10^0 C) = x(\tau).\left(1 - \left|\frac{10}{t_f}\right|\right) \quad (3.67)$$

3.1.11. Survey and comparison of the ice creation process in material

3.1.12. Define liquid providing time for cryosurgery devices

Supposed that there is a mass of cancer cells, the size was determined. We may specify the time required for the liquid providing cryosurgery equipment, so that the boundary layer of the tumor reaches t_c temperature (t_c- die temperature of bacteria; $t_c <= 0^0$C).

3.1.13. Defining the time of thawing and warming

After the ice has reached the required size r_c, the liquid providing of refrigerant to cryosurgery device is suspended, followed by the process of thawing and warming. When the liquid providing stops, blocks of ice will absorb heat from the environment around and temperature rise. However to ensure the tumor has the equal temperature to the body heat, they the cryosurgery device with warm water with temperatures $t_{f1} \leq 42^0$C (body temperature can tolerate).

To destroy the tumor radically, the surgeon will process cold providing and thawing process repeatedly for many times.

We will solve the problem of determining the time to defrost and warm the cells.

3.1.14. Comparing results between calculation methods and methods of analysis done by F.sun

3.1.14.1. Results of solving the problem by methods of analysis done by F.sun

3.1.14.2. Results of solving the problem by analytical method

3.1.14.3. Comparing the results between the two methods of solving problem

The deviation between the calculation methods by using analytical and numerical methods implemented by F.sun was 12,9%

3.1.15. Using finite difference method finite difference method to solve the problem when fast freezing cells in the case of cryotherapy equipment

3.3.15.1. Solving the math problem

3.3.15.2. Comparing results calculated between finite difference methods and analytical methods

The devistion of calculation results between analytical methods proposed by the authors and the finite element method was 13.4%.

3.2. Forming software to calculate parameters in fast-freezing cell process

3.2.1. Flowcharts

3.2.2. Data input

3.2.3. The program for parameters calculating

3.2.4. Export Results

3.3. Widen the scope to apply heat-transfer calculating formulas

3.3.1. Calculating the heat transfer when fast freezing the cells from cover to core

3.3.2. Practical situations to apply

CHAPTER 4. STUDY OF THE POSSIBILITY OF DESTROYING LIVER CANCER CELLS BY CRYOPROBE

In this chapter, we fabricate the device cryoprobe to verify the accuracy of the formulas which was established in the math problem of heat transfer when the locally freezing cells. Then using this device, we conduct empirical expriment on the potentia of killing healthy liver cells in vivo in animals. On that basis, we experimented the ability to destroy liver cancer cells in the liver tissue separated from the body of patients with liver cut indicated at Hue Central Hospital.

To evaluate the possibility of cell killing, we rely on empirical methods of histopathology and cell in vitro feeding.

4.1. Cryoprobe making

4.1.1. Cryoprobe composition

Cryoprobe made by us has an ability to cool the head by method of dẫn lỏng qua ống mao thẳng kết hợp thân kim được cách nhiệt bằng chân không. It is made up of three stainless steel tubes nested together (Figure 4.3).

Head of tube 1 is wedged, one end is connected to the liquid level control valve on the 8, one end of the tube is placed freely in tube 2, adjacent to the cold needle 5. Liquid nitrogen is supplied to the device through the tube into the cavity 1 to cooling chamber 6. Nitrogen created with the remain liquid will freely exited solvent flowing slit 2. Top 6 is a conical mass made of silver, with radius r = 2.25 mm welded closely with tube 2 and 3.

Because needle 5 is made of silver is capable of very good thermal conductivity, we can see the temperature of needle 5 by liquid nitrogen temperature in the tube 1 and can be measured at position 9.

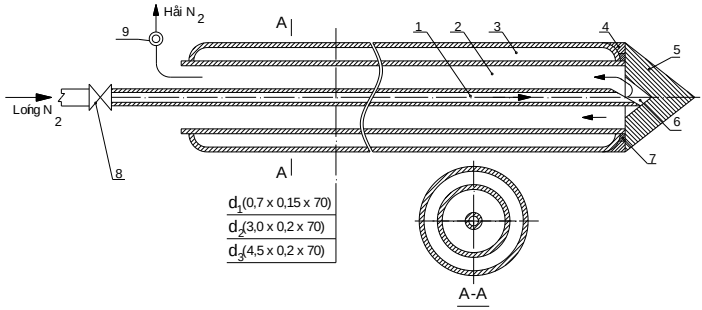


Figure 4.3. Structural diagram of Cryoprobe

4.1.2. The operation principle of Cryoprobe

We offer operation principles of Cryoprobe by leading a low temperature of liquid nitrogen directly contact with a needle. By the heat conduction through the metal to metal at the top of the cell locally cooling in the contact area, vapor born and liquid nitrogen excess will be led out through the vents. Insulation between the metallic body and a drain in a vacuum, this is the best type of insulation so the needle body should not affect body cells when the cold needle get through.

4.1.2.1. Cooling process

Liquid nitrogen from the tank is fed into the needle 1, creating pressure in the tank by compressed air to maintain a stable flow of liquid nitrogen spray. At this time, the head of pipe 1 has the same temperature with liquid nitrogen. Next, the pipe 1 will be taken

to the location in the pipe 2, liquid nitrogen with cool the needle head and liver samples exposed. After the experimental period, pull tube 1 out of the tube 2. End of the cooling process.

4.1.2.2. Heating process

Heating process is carried out immediately after the end of the cooling process. 42 ^{0}C temperature hot water is poured in the pipe 2 to replace nitrogen. Now the hot water transfer heat quickly to defrost and warm the liver samples. After the experimental period, withdraw the hot metal from the tube 2. End the heating process.

4.2. Measure the temperature of Cryoprobe's cold head

4.3. Check the insulation capacity of cold needle's head

4.4. Calculate the correlation between the size of the freezing solidified with size calculated from the formula established

4.5. Calculate the correlation between the size of the lesion cell and size calculated from the formula established

4.6. Investigate the effectiveness of cold needle handling on healthy mouse liver

4.7. Investigate the effectiveness of cold needle handling on healthy rabbit liver

4.8. Investigate the effectiveness of cold needle handling on liver tumors in humans

4.9. Cells fed in vitro

CHAPTER 5. CONCLUSIONS AND RECOMMENDATIONS

Conclusion

*** Theoretical research**

1. Establishing, building hypotheses, setting heat transfer equations, calculating the parameters of the locally freezing cells process by analytic method.

2. Comparing of results between analytical methods and numerical methods implemented by F.Sun: the average deviation between two methods was 12.9%.

3. Using the finite difference method to solve the problem of fast freezing of cells in cryotherapy device cases: the average deviation between two methods was 13.4%.

4. Develop software to calculate parameters during fast freezing process of cells: the software is programmed in MATLAB 7.0, the parameters can be calculated and plotted the temperatures range when rapidly locally freezing cells.

5. Expand the scope of application of the heat transfer formula established: these formulas can be used in case of quick frozen material from the outer shell into the moist center.

*** Empirical research**

6. Production of Cryoprobe:

- Pressure is suitable for the operation of the ice ball creating cold needle is 3.5kg/cm^2.

- After 15.4 seconds cooling for the Cryoprobe, the temperature reached at the head of the needle is -195,9^{o}C.

7. Check the insulation capacity of cold needle body on the agar material:

- Agar is frozen only at the head of the cold needle.

- The needle body has absolutely no phenomenon of glaciation or steam covered.

8. The correlation between the size of the freezing solidified area and the size calculated from the formula established:

- Measure the size of ice ball on agar jelly: the average deviation between theory and experiment was 24.21%.

- Measure the size of the ice ball on the out of body rabbit liver: the average deviation between theory and experiment was 30.65%.

9. Measuring the correlation between the size of the lesion cell area and the size calculated by the formula established:

- Measure the size of the rabbit liver lesions on the liver separated from the living organism: the average deviation between theory and experiment was 33.58%.

- Measure the size of the liver lesions in healthy rabbit liver in vivo: the average deviation between theory and experiment was 34.88%.

10. The assessment results of cell live and death by means of histology and cells fed *in vitro*:

- In mice: the equipment cryoprobe killed completely mouse liver cells handled by cold needle in 3 heat shock processes' experiments of 90s, 60s and 45s.

- In rabbits: the equipment cryoprobe just completely killed rabbits liver cells in 90s process; 60s process only killed partially; in 45s process, rabbit liver cells did not die but were only hurt.

- in human tumor samples: the equipment cryoprobe killed liver cells in 90s-540s process.

Recommendations

1. Cryoprobe is effective in kiling liver cells in mouse and rabbits, but is not able to kill l healthy liver cancer cells in humans. We should continue to examine the heating shock process by increasing the time of cooling or repeat the process of cooling and heating.

2. Cryoprobe has simple structure, can be manufactured with materials available in the market, in accordance with the conditions of technology and machinery of Vietnam. Research should complete this needle form. With the need of disposable needle, the need of ice ball creating is extremly considerable.

3. Basic physical parameter table of the materials commonly used was not searchable in a low temperature range. If additional developments are possible, it will create a data source not only for Cryo technlogy but also for other research sectors.

THE AUTHOR'S PAPERS HAVE BEEN PUBLISHED:

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4. Hoang Ngoc Dong, Nguyen Thanh Van, Le Minh Tri (2015), "*study of experimentally transfering heat while partially quick freezing cells by cryoprobe*", Journal of Science and Technology of Danang University, 9(94).2015.
5. Le Minh Tri, Nguyen Thi Tuoi Xanh, Le Viet Truong, Che Thi Cam Ha (2017), "*Research on applying heat transfer by cryoprobe on rabbits' livers*", Proceedings of the seminar on biotechnology and applied biology in the South East Region, Binh Duong Province, June 2017.