Introduction

Cryotherapy is often preferred to more traditional kinds of surgical therapy because of its minimal pain, scarring, and cost. The therapy has been gaining significant acceptance as a minimally invasive therapy for treatments of various malignant cancers. In a cryosurgical treatment, a single or multiprobe metal system is placed in contact with the target tissue through the skin. We have placed the emphasis of this paper on the treatment of a malignant lung tumor, since its application to lung cancer has been practiced on a trial basis for some years in Japanese medical schools [1].

The cryoprobe in consideration houses a small coaxial nozzle internally. A high-pressure gas supply line is connected to the probe so as to supply argon gas, which expands through the nozzle to the probe tip and then flows backwards through the internal channel leading to the cryoprobe outlet. Due to the Joule–Thompson effect, the outer surface temperature of the probe decreases below −135°C. As the tissue temperature is lowered, an ellipsoidal ice ball forms around each probe that is increasing in size, eventually encompassing and invading the entire tumor. This freezing process continues for 5–15 min. Then, the thawing process takes place as helium gas is supplied. Because of the difference in the inversion temperature, the probe temperature during this process increases to about 20°C to thaw the frozen tissue. This freezing-thawing sequence is repeated several times to kill abnormal cells or tissues, such as those found in malignant tumors. Cryoinjury is believed to be due to two primary mechanisms: one is the direct injury to the cells from the freeze-thaw cycle and the other is the indirect injury that results from the biological response to the damage caused by freezing, primarily the vasculature of the tumor.

As with any medical treatment, there are risks involved, primarily that of damage to nearby healthy tissue [2]. We must know the exact time required to freeze the entire cancer without damaging its surrounding healthy tissue. However, some standards for setting clinical parameters such as freezing rate and time are quite empirical today. Therefore, improvements in cryosurgery depend on developing reliable mathematical models and pre-operative simulation tools based on them.

The Limiting Radius for Freezing a Tumor During Percutaneous Cryoablation

The freezing front in a tumor during percutaneous cryoablation therapy was traced both analytically and numerically exploiting a bioheat equation. It has been shown that there exists a limiting size of the tumor, which one single cryoprobe can freeze at the maximum. The freezing front moves radially outward from the cryoprobe and reaches the end, where the heat from the surrounding tissue to the frozen tissue balances with the heat being absorbed by the cryoprobe. An excellent agreement between the analytical and numerical results has been achieved for the time required to freeze the tumor using the cryoprobe of a single needle. An analytical expression for estimating the limiting radius has been derived to give useful information for cryotherapy treatment plans.

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Bioheat Equation

Pennes [12] proposed a simple bioheat equation for living tissue in which the perfusion heat source was introduced as follows:

\[
\rho c_v \frac{dT}{dt} = \frac{\partial}{\partial x} \left( k \frac{\partial T}{\partial x} \right) + \rho c_p \rho_p \rho_{\text{Penes}}(T_{\text{ao}} - T) + S_n
\]

where \( T \) is the tissue temperature, while \( T_{\text{ao}} \) is the mean brachial artery temperature. \( k, \rho, \) and \( c \) are the thermal conductivity, den-
ity, and specific heat capacity, whose subscripts s and f refer to tissue and blood, respectively. Moreover, \( \omega_{\text{Pennes}} \) is Pennes’ blood perfusion rate (i.e., the rate of perfusion to the tissue per unit volume of tissue), while \( S_m \) is the metabolic heat generation rate. Pennes’ model is often adequate for roughly describing the effect of blood flow on the tissue temperature. Nevertheless, a considerable number of modifications have been proposed by various researchers. Wulff [13] and Klinger [14] considered the local blood mass flux to account for the blood flow direction, while Chen and Holmes [15] examined the effect of thermal equilibration length on the blood temperature and added the dispersion and microcirculatory perfusion terms to the Klinger equation. Furthermore, Xuan and Roetzel [16] replaced the perfusion rate with the interfacial convection term. On the other hand, Nakayama and Kuwahara [11] have exploited the volume averaging theory in porous media, and showed that all these existing bioheat equations are included in their general bioheat equation. The general bioheat equation, for the case of isolated blood vessels, runs as

\[
\frac{\partial T}{\partial t} = \frac{1}{\rho c} \left( \frac{\partial}{\partial x} \left( k \frac{\partial T}{\partial x} \right) \right) + \rho c \omega(T_f - T) + a_j h(T_j - T) + S_m
\]

where the second time and the third term on the right-hand side correspond to the blood perfusion on the tissue and the interfacial heat transfer from the blood to the tissue through the vessel wall, respectively. Similarity between our equation and Pennes’ equation is obvious as we rewrite the foregoing equation as

\[
\frac{\partial T}{\partial t} = \frac{1}{\rho c} \left( \frac{\partial}{\partial x} \left( k \frac{\partial T}{\partial x} \right) \right) + \rho c \omega_{\text{eff}}(T_f - T) + S_m
\]

where

\[
\omega_{\text{eff}} = \omega + \frac{a_j h}{\rho c f}
\]

is the effective perfusion rate. However, \( \omega_{\text{eff}} \) conceptually differs from Pennes’ perfusion rate \( \omega_{\text{Pennes}} \), which is purely empirical. It should also be noted that \( T_j \) in \( (T_f - T_j) \) is the local blood temperature, whereas \( T_{a0} \) in Eq. (1) is the mean brachial artery temperature. Perhaps Pennes considered that the blood perfusion is the predominant heat source for the tissue and did not bother to describe the interfacial convective heat transfer between the blood and tissue via the vascular wall. Instead, he introduced \( T_{a0} \) to adjust the total heat transfer, which takes place as the blood enters and leaves the tissue. However, the interfacial convective heat transfer between the blood and tissue can never be insignificant for the countercurrent bioheat transfer. Even when there is no perfusion, i.e., \( \omega_{\text{Pennes}} = 0 \), the effective perfusion rate never vanishes since \( \omega_{\text{eff}} = a_j h / \rho c_f \). Thus, Eq. (4) must always be used for countercurrent bioheat transfer for the case of closely aligned pairs of vessels.

**Numerical Analysis Based on Enthalpy Method**

The enthalpy method is often used for locating an interface in phase change problems, since it allows us to use a fixed mesh. An easy approach to implement this method is to include the latent heat by artificially increasing the specific heat capacity around the freezing point, thus making it a function of temperature as illustrated in Fig. 1.

This simple temperature function satisfies the obvious relationship among the latent heat of solidification \( h_g \), artificial maximum heat capacity \( c_{\text{max}} \), and artificial temperature band \( DT \), namely, \( h_g = c_{\text{max}} (2 DT) \). The temperature band \( DT \) should be set according to the mesh resolution. Naturally, a finer grid system allows us to use a smaller \( DT \), which provides us with a sharper freezing front where \( T = T_g \). In this study, \( DT \) was set from 1°C to 5°C. The temporal development of the freezing front is found fairly insensitive to \( DT \) in this range.

**Fig. 1 Effective specific heat capacity**

Any standard scheme may be used to discretize the governing equation (3). We shall use a finite volume method as proposed by Patankar [17] to obtain a two-dimensional finite volume expression. We consider a control volume of size \( \Delta x \Delta y \) centering the node \( P \) (pole), as shown in Fig. 2, and let the uppercase letters \( E \) (east), \( W \) (west), \( N \) (north), and \( S \) (south) denote its neighboring nodes. Furthermore, we let the lowercase versions of the same letters \( e, w, n, s \) denote the four faces of the control volume, and \( (\delta x)_e, (\delta y)_n, (\delta y)_s \), denote the distances between the nodes. Then, the discretized version of the bioheat equation may be written as follows (see Ref. [18] for details):

\[
a_P T_P = a_Q T_E + a_Q T_W + a_Q T_N + a_Q T_S + b
\]

where

\[
a_E = \frac{\Delta y}{\delta x_e} \left( \frac{1}{T_E - T_P} \int_{T_P}^{T_E} k(T)dT \right)
\]

\[
a_W = \frac{\Delta y}{\delta x_w} \left( \frac{1}{T_P - T_W} \int_{T_W}^{T_P} k(T)dT \right)
\]

\[
a_N = \frac{\Delta x}{\delta y_n} \left( \frac{1}{T_N - T_P} \int_{T_P}^{T_N} k(T)dT \right)
\]

\[
a_S = \frac{\Delta x}{\delta y_s} \left( \frac{1}{T_P - T_S} \int_{T_S}^{T_P} k(T)dT \right)
\]

\[
a_P = \frac{(\Delta x \Delta y)}{\Delta t} \left( \frac{\rho c}{\rho c_f} + a_E + a_W + a_N + a_S + \rho c f \omega_{\text{eff}} \Delta x \Delta y \right)
\]

\[
b = \frac{(\Delta x \Delta y)}{\Delta t} \left( \rho c f T_P + (\rho c f \omega_{\text{eff}} T_j + S_m) \Delta x \Delta y \right)
\]

\[
\overline{a_p} = \frac{1}{\rho c f T_P - T_P^o} \int_{T_P^o}^{T_P} \rho c(T)dT
\]

The superscript o indicates the value at the old time \( t \), whereas no superscript is assigned for the value at the new time \( t+\Delta t \).

**Fig. 2 Grid nomenclature**
The present computer code is capable of dealing with arbitrary two-dimensional shapes of the cryoProbe and tumor, as illustrated in Fig. 3. The initial and boundary conditions for the freezing process using the cryoProbe of outer radius \( R_p \) are given as follows:

\[ t=0: \]
\[ T = T_f \quad \text{(everywhere)} \] (7)

\[ t > 0: \]
\[ T|_{z=0} = T_f \quad \text{(cryoProbe outer surface)} \] (8a)

\[ T|_{z=R_m} = T_f \quad \text{(deep tissue region)} \] (8b)

Computations were carried out using highly nonuniform grid systems, namely, \((250 \times 500)\) to cover the right half domain \(30 \times 60 \text{mm}^2\) for the case of the longitudinal tumor of \(20 \times 27 \text{mm}^2\), and \((350 \times 700)\) to cover the right half domain \(160 \times 160 \text{mm}^2\) for the case of determining the limiting radius. The results associated with the limiting radius are found to be independent of any additional expansion of the calculation domain. Grid nodes are laid out densely around the probe. Grid refinement tests were carried out to ensure that the results are independent of grid systems. Convergence was measured in terms of the maximum change in temperature during an iteration, which was set to \(10^{-5}\).

Analytical Treatment Based on Integral Method

In what follows, we shall exploit an integral method to derive an analytical expression for the limiting radius of the tumor, which one single cryoProbe can freeze at the maximum. For the sake of simplicity in this analytical treatment, we shall assume that the probe is a circular cylinder and that the tumor is so large that heat transfer to the healthy lung tissue is negligible.

The temperature around the cryoProbe is schematically shown in Fig. 4, where \( T_p \) and \( T_i \) are the temperatures of the probe and the freezing front, respectively, while \( T_0 \) is the body temperature.

Upon referring to the figure, we may introduce the energy balance at the freezing front at \( z=0 \):

\[ \rho_l h_l R_i \frac{dT}{dt} = R_k c_p \frac{dT}{dr} \bigg|_{r=R_i} - R_k c_p \frac{dT}{dr} \bigg|_{r=R_f} - \rho_l c_v (T_0 - T_f) \frac{dR}{dt} \quad \text{at} \quad r = R_i \] (9)

where the subscripts \( i \) and \( c \) refer to the frozen and unfrozen regions, respectively. The first, second, and third terms on the right-hand side correspond to the conduction heat flux evaluated at the ice side, the conduction heat flux evaluated at the unfrozen side, and the sensible heat entering the interface as the interface (freezing front) at \( r=R_i(t) \) moves radially outward from the cryoProbe, respectively.

The freezing front moves so slowly that a quasisteady approximation may be valid. Thus, assuming that the temperature profile within the frozen region follows that obtained at the steady state, namely,

\[ \frac{T-T_p}{T_i-T_p} = \frac{\ln(r/R_m)}{\ln(R_m/R_p)} \quad \text{for} \quad R_p \leq r \leq R_i \] (10)

where we may estimate the first term on the right-hand side as

\[ R_k c_p \frac{dT}{dr} \bigg|_{r=R_i} = k_{c} \frac{T_i - T_p}{\ln(R_m/R_p)} \] (11)

In order to estimate the second term on the right-hand side (representing the heat flux from the unfrozen tumor to the interface), we write the bioheat equation (2) for the unfrozen tumor region using the cylindrical coordinate system, which, under the quasisteady approximation, may be integrated to give

\[ -k_{c} R_i \frac{dT}{dr} \bigg|_{r=R_i} - \rho_l c_v \omega_{eff} \int_{R_i}^{R_m} r(T-T_0) dr + S_m \int_{R_i}^{R_m} rdr = 0 \] (12)

Let us assume that the temperature in this unfrozen region follows

\[ \frac{T-T_0}{T_i-T_0} = \left( 1 - \frac{r-R_i}{R_m-R_i} \right)^2 \quad \text{for} \quad R_i \leq r \leq R_m \] (13)

The equation satisfies \( T=T_0 \) at \( r=R_i \) and \( T=T_i \) and \( dT/dr=0 \) at \( r=R_m \) such that the boundary condition given by Eq. (8b) is satisfied in an approximate sense. Then substituting this temperature profile into Eq. (12), we have

\[ 2k_{c} R_i \frac{T_i-T_0}{R_m-R_i} - \rho_l c_v \omega_{eff} (T_i-T_0) \left( \frac{1}{3} (R_m-R_i) R_i + \frac{1}{12} (R_m-R_i)^2 \right) + S_m \frac{R_m^2 - R_i^2}{2} = 0 \] (14)

which forms a cubic equation for \( R_i/(R_m-R_i) \). The root of the cubic equation is quite complex. However, it is found that the following explicit expression based on Newton’s shooting method gives a quite accurate value for the root:

\[ \frac{R_i}{R_m-R_i} = \left( \frac{1}{6} \frac{\omega_{eff}}{\omega_c} + \frac{S_m}{k_c (T_0-T_i)} \right)^{-1} + \frac{1}{8} \left( \frac{\omega_{eff}}{\omega_c} + \frac{S_m}{k_c (T_0-T_i)} \right) \] (15)

where \( \omega_c = k_c/\rho_c c_v \) is the thermal diffusivity of the unfrozen tumor. Thus, the second term on the right-hand side of Eq. (9) may be estimated as
\[ R_k \frac{dT}{dr} \bigg|_{r=R_i} = 2k_i(T_0 - T_i) \left( R_1 \frac{1}{6} \frac{\omega_{\text{eff}}}{\alpha_c} + \frac{3}{k_i(T_0 - T_i)} \right) + \frac{1}{8} \left( \frac{\omega_{\text{eff}}}{\alpha_c} + \frac{3}{k_i(T_0 - T_i)} \right) \]

Upon substituting Eqs. (11) and (16) into Eq. (9), we have

\[ \frac{\rho h_{\text{id}} + \rho_c (T_0 - T_i)}{R_i} \frac{dR_i}{dt} = \frac{T_i - T_p}{\ln \left( \frac{R_i}{R_p} \right)} - 2k_i(T_0 - T_i) \left( R_1 \frac{1}{6} \frac{\omega_{\text{eff}}}{\alpha_c} + \frac{3}{k_i(T_0 - T_i)} \right) + \frac{1}{8} \left( \frac{\omega_{\text{eff}}}{\alpha_c} + \frac{3}{k_i(T_0 - T_i)} \right) \]

which reduces to

\[ \frac{dr}{dt} = \frac{1 + Sr}{\text{Stefan number}} \times \frac{R_i \ln R_i^*}{1 - \ln \frac{R_i^*}{Cr}} \frac{dR_i^*}{dt} \]

\[ R_i^* = \frac{R_i}{R_p} \]

\[ t^* = \frac{\alpha_c}{R_p} \]

is the Fourier number and where \( \alpha_c = k_i / \rho_c c_i \) is the thermal diffusivity of the ice. Moreover, the following dimensionless parameters are introduced:

\[ \text{Ste} = \frac{c_i(T_i - T_p)}{h_{\text{id}}} \quad \text{Stefan number} \]

\[ \text{Sr} = \frac{\rho_c c_i(T_0 - T_i)}{\rho h_{\text{id}}} \]

\[ \omega^* = \frac{\omega_{\text{eff}} R_p^2}{\alpha_c} \]

\[ \text{Cr} = \frac{k_i(T_0 - T_p)}{k_i(T_0 - T_i)} \]

\[ \text{Met} = \frac{S_m R_p^2}{k_i(T_0 - T_i)} \]

The foregoing ordinary differential equation (18) may readily be integrated using any standard integration scheme such as Runge–Kutta–Gill, to find the dimensionless time \( t^* = \alpha_c t / R_p^2 \) required for freezing the tumor of a given dimensionless radius \( R_i^* = R_i / R_p \). Obviously, the quasisteady assumption is valid when \( t^* \text{Ste} / (1 + \text{Sr}) > 1 \), which roughly gives \( t > 1 \) s. Thus, the assumption holds for most parts of the freezing process except at its initial short period.

It is interesting to note that there exists the limiting radius \( R_{\text{lim}}^* \) of the tumor that one single cryoprobe can freeze at the maximum. Its dimensionless value \( R_{\text{lim}}^* = R_{\text{lim}} / R_p \) may be obtained by setting \( dR_{\text{lim}}^*/dt = 0 \), for which Eq. (18) yields

\[ \ln \frac{R_{\text{lim}}^*}{Cr} \left( \frac{2}{3} \omega^* + 3 \text{Met} \right) R_{\text{lim}}^* + \frac{\omega^* + 6 \text{Met}}{4(\omega^* + 3 \text{Met})} = 1 \]

This implicit equation gives the dimensionless limiting radius \( R_{\text{lim}}^* \) for a given set of the dimensionless values, Met, Cr, and \( \omega^* \). Usually, \( \omega^* \) is much larger than Met. For such cases, the following explicit expression based on Newton’s shooting method may be used to give a reasonably accurate value for \( R_{\text{lim}}^* \):

\[ R_{\text{lim}}^* = \left( \frac{3}{2 \omega^* - Cr + R_0^*} \right) R_0^* + \sqrt{\frac{3}{32 \omega^*}} \left( 1 - \ln R_0^* \right) \]

where

\[ R_0^* = \left( \frac{3 \text{Cr}^2}{2 \omega^* - Cr} + \frac{3 \text{Cr}}{8 \omega^*} \right) \left[ 1 - \ln \left( \frac{\sqrt{3 \text{Cr}^2}}{2 \omega^*} \right) \right] + \frac{3}{32 \omega^*} \]

For the present case of \( \text{Cr} = 15.4 \), Eq. (22) along with Eq. (23) gives \( R_{\text{lim}}^* = 29.9 \) and 12.9 for \( \omega^* = 0.031 \) (\( \omega = 0.004 \) s) and 0.310 (\( \omega^* = 0.04 \) s), respectively.

### Results and Discussion

Some tissues freeze over a fairly large range of temperatures. However, for the case of lung cancer, the blood comes out from the vessels during the freezing-thawing sequence. The subsequent freezing takes place around the probe surrounded by the blood as a conducting medium. To a first approximation, we may use a single temperature for the phase change. Numerical calculations based on the enthalpy method were carried out for the case in which the cryosurgical and biological parameters are given by

\[ R_p = 1 \text{ mm}, \quad T_p = -135 ^\circ \text{C}, \quad T_i = 0 ^\circ \text{C} \]

\[ T_f = T_0 \text{ (body temperature) = } 37 ^\circ \text{C} \]

\[ S_m = 1200 \text{ W/m}^3 \]

The effective perfusion rate \( \omega_{\text{eff}} \) within the tumor can be quite high since some blood vessels are connected to the tumor. Here, we assume the effective perfusion rate in the range of \( \omega_{\text{eff}} = 0.004 – 0.04 / s \). Moreover, the thermophysical properties for frozen and unfrozen tissues in the lung are listed in Table 1, according to Ref. [19].
For the case in which $T_p = -135^\circ C$, $T_i = 0^\circ C$, $T_0 = 37^\circ C$, $S_m = 1200$ W/m$^3$, $\omega_{eff} = 0.004$ /s, and $R_p = 1$ mm, we have Ste = 0.808, Sr = 0.443, Met = $6.24 \times 10^{-5}$, Cr = 15.4, and $\omega^* = 0.031$. A typical evolution of the isotherms obtained for a longitudinal tumor of $20 \times 27$ mm$^2$ is presented in Figs. 5(a)–5(c). The outermost isotherm in each figure corresponds to the freezing front (i.e., $T = T_i = 0^\circ C$). Figure 5(c) clearly indicates that ill-placement of the probe may result in a substantial damage to the surrounding healthy tissue.

Let us consider the freezing process when the probe is placed in a large tumor. The temporal evolutions of the freezing front for the cases of $\omega_{eff} = 0.004$ /s (low perfusion) and 0.040/s (high perfusion) are illustrated in Figs. 6(a) and 6(b), respectively, along with the curve analytically obtained by integrating the ordinary differential equation (18). The figures may also be used to know the time required to kill the circular tumor of radius $R_i$. The numerical results obtained for these two cases in the figures clearly show that the limiting radii $R_{lim}$ for $\omega_{eff} = 0.004$ /s and 0.040/s are around 29.9 mm and 12.8 mm, respectively, which are estimated on the basis of the analytical expression (22).

Finally, the curve representing the limiting radius is generated from Eq. (22) and plotted against the effective perfusion rate in Fig. 7. We learn from the figure that a single probe, even when placed in the center of the target, is capable of freezing only the size of a tumor whose equivalent radius is less than the limiting radius $R_{lim}$. The figure indicates that, for the case of comparatively high perfusion rate, a single probe of radius 1 mm can freeze a tumor only within a radius of 20 mm or less. This is consistent with the fact reported by Nakatsuka et al. [1]. In practice, we may introduce a factor $\lambda$ and estimate the range of the killed tissue by $r \leq \lambda R_{lim}$. The factor $\lambda$ has to be chosen carefully, depending on
the specific clinical and surgical constraints such as the number of cryoprobes available, the time set for a single freezing process, and the level of malignancy.

Conclusions

The bioheat equation recently proposed by Nakayama and Kuwahara to account for the blood perfusion has been exploited to find the freezing front in a tumor during percutaneous cryoablation therapy. Two-dimensional numerical calculations based on the enthalpy method were conducted to simulate the ice formation around the cryoprobe. Using a cylindrical coordinate system, an analytical treatment was also made to estimate the time required to kill the entire tumor. Both sets of the results are found to be in good accord with each other. The analysis reveals that there exists a limiting size of the tumor, which one single cryoprobe can freeze at the maximum, as the heat flowing from the surrounding tissue to frozen region compensates for the heat absorbed by the cryoprobe. An explicit expression is obtained for estimating the limiting radius, which is believed to provide useful information for the preliminary planning of cryotherapy treatment. In reality, a multiprobe system may be used. Thus, future work needs to be done before real clinic applications.

Nomenclature

- \( a_f \) = specific surface area
- \( c \) = specific heat
- \( Cr \) = dimensionless parameter associated with the thermal conductivity ratio
- \( h_f \) = interfacial heat transfer coefficient
- \( h_s \) = latent heat of solidification
- \( k \) = thermal conductivity
- \( Met \) = dimensionless number associated with metabolic reaction rate
- \( r \) = radial coordinate
- \( R_f \) = radius of the freezing front
- \( R_{lim} \) = limiting radius
- \( S_m \) = metabolic reaction rate
- \( Ste \) = Stephan number
- \( t^* \) = Fourier number
- \( T \) = temperature
- \( T_{ph} \) = phase change temperature
- \( T_p \) = probe temperature

- \( T_0 \) = body temperature
- \( x_c \) = Cartesian coordinates
- \( a \) = thermal diffusivity
- \( \rho \) = density
- \( \omega \) = perfusion rate
- \( \omega_{eff} \) = effective perfusion rate
- \( \omega^* \) = dimensionless perfusion rate

Subscripts and Superscripts

- \( c \) = unfrozen tumor
- \( i \) = ice, interface
- \( p \) = cryoprobe
- \( * \) = dimensionless

References


