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Computational Modeling of Intraperitoneal Drug Delivery for the Treatment of Peritoneal Carcinomatosis

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ABSTRACT: Intraperitoneal injection of chemotherapy has been proposed as a promising method for the treatment of peritoneal metastasis, and its use in conjunction with cytoreductive surgery has shown interesting results in the treatment of patients. However, drug penetration into the tumor is limited in this method, and a better understanding of the factors influencing this low penetration depth is necessary. For this purpose, in the present study, a numerical model has been developed to investigate drug transport during intraperitoneal chemotherapy. Using this model, first, the Spatio-temporal distribution of free, bound and internalized drug concentrations are calculated. Then, by calculating the drug penetration depth and the fraction of killed cells, the effectiveness of the treatment is evaluated. Results of a 10mm tumor after 60 minutes of treatment showed that the drug is available only in a limited area of the outer region of the tumor. The values of fraction of killed cells and drug penetration depth were 1.2% and 11.4%, respectively, which indicates a poor treatment efficiency. The findings of this paper can be used in future numerical and experimental studies to gain a deeper insight into the mechanisms of drug delivery to the tumor by intraperitoneal injection.

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1- Introduction

While chemotherapy with systematic injection has not been successful in treating patients with Peritoneal Metastasis (PM), the recent use of Intraperitoneal Chemotherapy (IPC) along with cytoreductive surgery has shown promising outcomes for the patients with PM [2]. However, poor drug penetration into the tumor has prevented the widespread clinical use of this method.

Mathematical modeling can provide more insights into the causes of this low drug delivery efficacy. Au et al. [1] developed a model for Intraperitoneal (IP) delivery of paclitaxel. This model was validated by the data of a murine model with IP tumors. Rezaeian et al. [2] developed a model for investigating the effectiveness of IP drug delivery using temperature-sensitive liposomes.

In the present study, IP injection of doxorubicin has been studied by considering the mechanism of drug binding and internalization into cancer cells. Fluid flow and mass transfer equations are used in this model. The pathophysiology of the tumor has been reconstructed by considering the tumor's leaky vasculature, a denser extracellular matrix, and lack of an effective lymphatic system.

2- Materials and Methods

A schematic of drug delivery by IP injection is shown in Fig. 1. Drug particles are injected into the peritoneal cavity and gradually absorbed into the tumor tissue.

2- 1- Governing equations

Darcy's law in porous media is used to explain the interstitial fluid flow [2]:

$$v_i = -\kappa \nabla P_i \tag{1}$$

Here κ is the interstitium's hydraulic conductivity. Also, P_i and v_i are Interstitial Fluid Pressure (IFP) and Interstitial Fluid Velocity (IFV), respectively. The steady-state mass conservation equation for the incompressible interstitial fluid is as follows:

$$\nabla \cdot v_i = \phi_B - \phi_L \tag{2}$$

In this equation, ϕ_B is the net flow rate from blood vessels into the interstitium per unit volume. ϕ_L is the net lymphatic drainage per unit volume.

Drug transfer is expressed by the convection-diffusion-reaction equations. The concentration of free, bound, and internalized drugs, as well as the fraction of killed cells, are calculated as follows:

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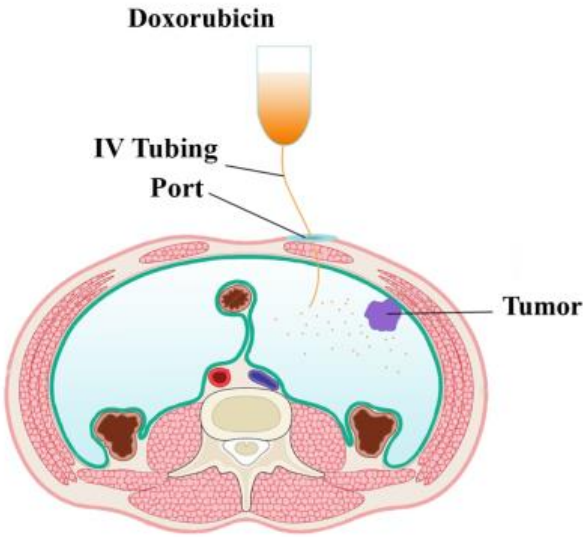

Fig. 1. Schematic of IP drug delivery system.

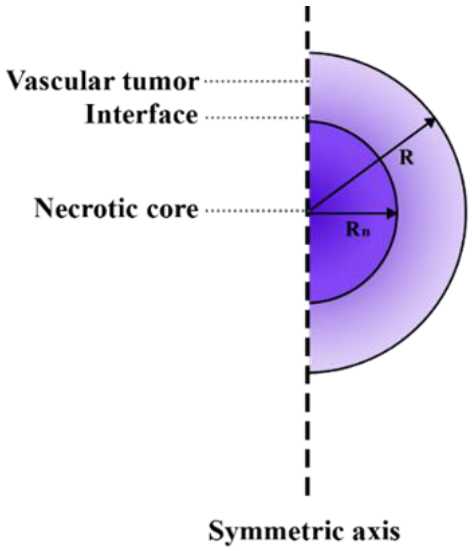

Fig. 2. The geometry corresponding to the model.

$$\frac{\partial C_F}{\partial t} = -v_i \nabla C_F + D_F \nabla^2 C_F - \frac{1}{\varphi} K_{ON}\ C_{rec} C_F + K_{OFF} C_B + \Phi \tag{3}$$

$$\frac{\partial C_B}{\partial t} = \frac{1}{\varphi} K_{ON}\ C_{rec} C_F - K_{OFF} C_B - K_{INT} C_B \tag{4}$$

$$\frac{\partial C_I}{\partial t} = K_{INT}\ C_B \tag{55}$$

$$FK = 1 - \exp(-\omega \cdot C_I) \tag{6}$$

In which C_F, C_B, and C_I are respectively the concentration of free, bound, and internalized drugs. C_{rec} represents the drug concentration at the cell-surface receptors and D_F indicates effective diffusion coefficient. Φ represents the net rate of total free drug gained through blood vessels and lost through lymphatic vessels. K_{ON}, K_{OFF}, and K_{INT} are the constants for binding, unbinding, and internalization, respectively.

2- 2- Model geometry and boundary conditions

A biologically related structure, including an area with a necrotic core and a surrounding with leaky vasculature, is defined as a tumor (Fig. 2). The symmetry boundary condition, as well as the continuity condition for internal boundaries, are considered. For the outer boundary, a boundary condition of constant pressure and concentration is considered.

2- 3- Validation

Fig. 3 shows a comparison of simulated concentration profiles in terms of penetration depth into the tumor at ٦ hours after injection compared with experimental work by Au et al. [1]. As can be seen, there is a relatively good agreement between the two concentration profiles. The difference between the concentration values is due to the different properties of the tissue and the drug in the two studies.

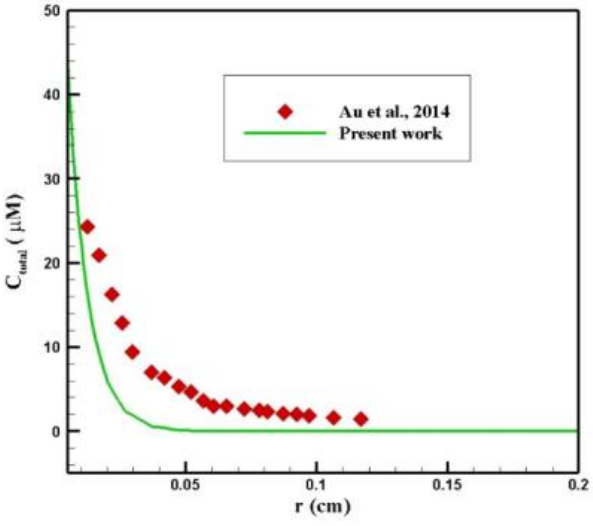

Fig. 3. Comparison of concentration values in terms of penetration depth after six hours of injection with the results of Au et al. [1].

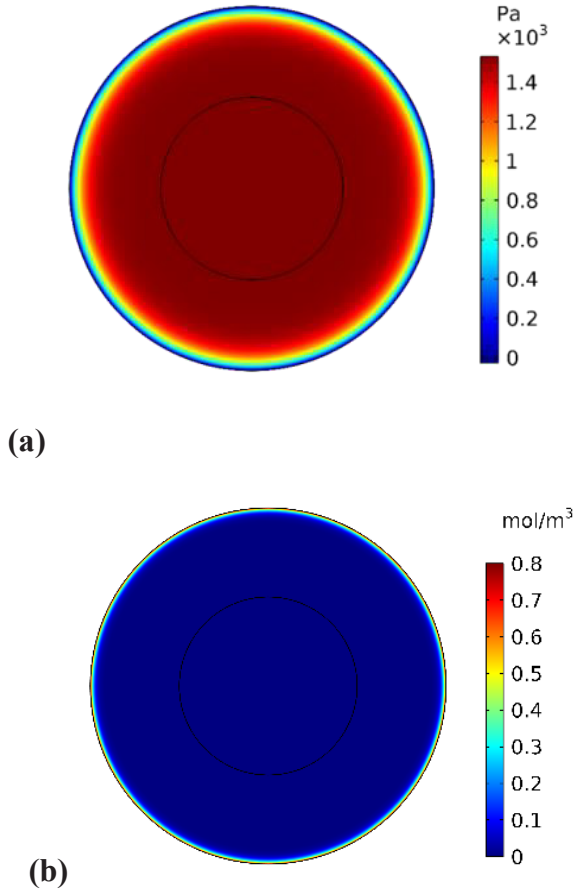

Fig. 4. Counters of a) IFP and, b) CF distribution after 60 minutes of treatment.

3- Results and Discussion

Fig. 4(a) shows the distribution of IFP in the tumor. In the center of the tumor, IFP has its highest value (1533 Pa) and near the outer border of the tumor, the pressure decreases with a large slope. Fig. ٤(b) shows the free drug concentration contour one hour after injection. As it turns out, drug penetration into the tumor is limited to a very small area of the outer border of the tumor and a large portion of the tumor is not available for drug delivery. To evaluate the performance of drug delivery during IPC, the drug penetration into the tumor ($\%w_{1/2}$) as a distance from the tumor where the drug concentration is equal to 50% of drug concentration at the tumor boundary, is calculated. After 60 minutes of treatment, the values of *FK* and $\%w_{1/2}$ are 1.2% and 11.4%, respectively, which indicates a poor treatment efficiency. This low efficiency is related to the adverse pressure gradient at the tumor boundary (Fig. ٣(a)), leading to an outward convention flow at the tumor boundary which prevents the drug from effectively entering the tumor.

4- Conclusions

In this paper, a mathematical model based on fluid flow and mass transport equations was developed to study the performance of drug delivery during IPC. The results of this model show the low efficiency of this treatment method with a fraction of killed cells (*FK*) and the drug penetration depth ($٪w_{2/1}$) of ٪١,٢ and ٪١١,٤, respectively. The results also show that there is a reverse pressure gradient at the outer border of the tumor that opposes drug entry into the tumor. Despite the rationale behind IP injection, the results of this study show that finding a solution to improve the efficacy of this method is an essential need.

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