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A mathematical prognosis model for pancreatic cancer patients receiving immunotherapy

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HIGHLIGHTS

- Pancreatic cancer is one of the most deadly types of cancer with extremely poor prognosis.
- Develop a mathematical prognosis model to predict the overall survival of patients receiving immunotherapy.
- Model simulations are quantitatively consistent with the clinical data.
- Immunotherapy that will benefit the cancer patients would increase the killing rates of CD8+ T cell and NK cells.

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ABSTRACT

Pancreatic cancer is one of the most deadly types of cancer since it typically spreads rapidly and can seldom be detected in its early stage. Pancreatic cancer therapy is thus a challenging task, and appropriate prognosis or assessment for pancreatic cancer therapy is of critical importance. In this work, based on available clinical data in Niu et al. (2013) we develop a mathematical prognosis model that can predict the overall survival of pancreatic cancer patients who receive immunotherapy. The mathematical model incorporates pancreatic cancer cells, pancreatic stellate cells, three major classes of immune effector cells CD8+ T cells, natural killer cells, helper T cells, and two major classes of cytokines interleukin-2 (IL-2) and interferon-γ (IFN-γ). The proposed model describes the dynamic interaction between tumor and immune cells. In order for the model to be able to generate appropriate prognostic results for disease progression, the distribution and stability properties of equilibria in the mathematical model are computed and analysed in absence of treatments. In addition, numerical simulations for disease progression with or without treatments are performed. It turns out that the median overall survival associated with CIK immunotherapy is prolonged from 7 to 13 months compared with the survival without treatment, this is consistent with the clinical data observed in Niu et al. (2013). The validity of the proposed mathematical prognosis model is thus verified. Our study confirms that immunotherapy offers a better prognosis for pancreatic cancer patients. As a direct extension of this work, various new therapy methods that are under exploration and clinical trials could be assessed or evaluated using the newly developed mathematical prognosis model.

1. Introduction and motivation

The pancreas is a glandular organ in the digestive system and endocrine system of vertebrates. The anatomy of the pancreas is shown in Fig. 1. In humans, it is located in the abdominal cavity behind the stomach. It is an endocrine gland producing several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide which circulate in the blood. The pancreas is also a digestive organ, secreting pancreatic juice containing digestive enzymes that assist digestion and absorption of nutrients in the small intestine.

Pancreatic cancer is the fourth leading cause of cancer death in the United States since it typically spreads rapidly and can seldom be detected in its early stage. It has extremely poor prognosis with a one-year survival rate of about 25% and a five-year survival rate less than 5% (Louzoun et al., 2014). Most of the malignant tumors are located at the exocrine part of the pancreas, and they do not have any or at least specific symptoms in the early stages and hence pancreatic cancer is characterised by its late detection. Habisch et al. (2010) concludes that pancreatic cancer is characterised by its late detection because of no symptoms in early stages, aggressive growth, intense infiltration into adjacent tissue, early metastasis, resistance to chemotherapy and radiotherapy, and a strong desmoplastic reaction. Pancreatic cancer is rarely diagnosed in those persons younger than 40, and the median age

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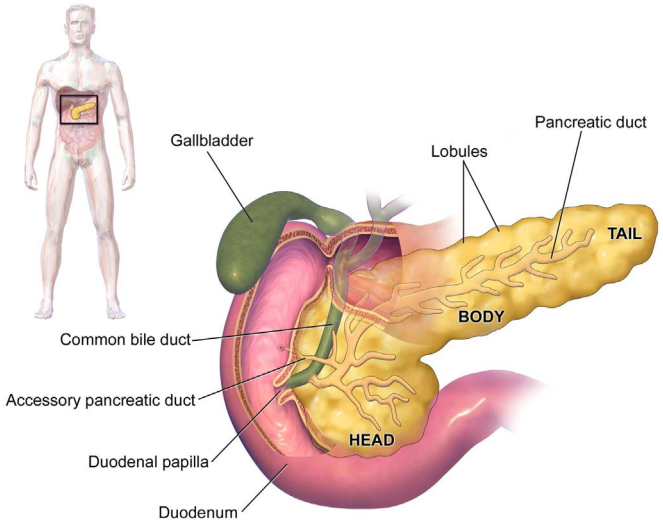

Fig. 1. Anatomy of the pancreas Blausen.com-staff (2014).

of diagnosis is 71. As summarized in Ryan et al. (2014), risk factors associated with pancreatic cancer include smoking, obesity, diabetes, and certain rare genetic conditions including: multiple endocrine neoplasia type 1 and hereditary nonpolyposis colon cancer among others.

In addition to the poor survival rate, pancreatic cancer patients have a great deal of suffering, with a particularly high incidence of pain, mostly caused by the invasion of tumor to the perineural space of nerves in the celiac plexus (Sun et al., 2014). Current treatment options for pancreatic cancer including surgery, radiation and chemotherapy can prolong survival and/or relieve symptoms in many patients, but rarely lead to cure (Haeno et al., 2012; Stathis and Moore, 2010; Hidalgo, 2010). Development of pancreatic cancer therapy methods is thus a challenging task, and appropriate prognosis or assessment for pancreatic cancer therapy is of critical importance.

Due to the high cost in exploration and assessment of cancer therapy methods, mathematical modelling of the immune system is viewed as a potentially powerful tool in development of improved treatment regimens and prediction of disease progression (Chrobak and Herrero, 2011; de Pillis and Radunskaya, 2003; de Pillis et al., 2008). In recent years, many mathematical models have been developed to describe the interaction between cancer cells and the immune system, such as Galante et al. (2012), Radunskaya and Hook (2012), Robertson-Tessi et al. (2012), Louzoun et al. (2014), Li and Xu (2015), Wilson and Levy (2012). In particular, Louzoun et al. (2014) develop a mathematical model for pancreatic cancer growth and treatments, which is used to qualitatively explain a variety of biomedical clinical data. However, to the best of our knowledge, no mathematical model has been developed to predict the overall survival of pancreatic cancer patients who receive either chemotherapy or immunotherapy or other treatments based on clinical data. Overall survival (OS) is a statistical term referring to the percentage of people in a group who are alive after a defined length of time. It is often used to estimate the patient's prognosis. If there is a slight increase in survival, it can be considered as evidence of meaningful clinical benefit. Similarly, median overall survival is also commonly used to express survival rates, which is the amount of time after which 50% of the patients have died and 50% have survived.

In this work, we develop a mathematical prognosis model for pancreatic cancer based on available clinical data in Niu et al. (2013), which can be used to predict the overall survival of patients with or without immunotherapy after cyrosurgery. The mathematical model incorporates pancreatic cancer cells (PCCs), pancreatic stellate cells (PSCs), three major classes of immune effector cells CD8+ T cells, natural killer (NK) cells, helper T cells, and three major classes of cytokines interleukin-2 (IL-2), interferon-γ (IFN-γ) and transforming growth factor beta (TGF-β). The proposed model describes the dynamic interaction between tumor and immune cells. Moreover, the location and stability properties of equilibria in the mathematical model are computed and analysed in order for the model to be able to generate appropriate prognostic results for disease progression. In addition, numerical simulations for disease progression with or without treatments are performed. It turns out that the median overall survival associated with CIK immunotherapy is prolonged to 13 months, while if no immunotherapy is administrated, the median overall survival is only 7 months. This result is consistent with the clinical data observed in Niu et al. (2013), which thus verifies the validity of the proposed mathematical prognosis model. Our study confirms that immunotherapy offers a meaningful clinical benefit to pancreatic cancer patients. In addition, sensitive analysis of the immune system will be carried out in terms of the killing rate of $CD8^+$ T cells, from which possible effective therapy methods will be discussed for pancreatic cancer.

The paper is organized as follows. Section 2 develops a mathematical prognosis model for pancreatic cancer. In Section 3, both the location of equilibria and their stability analysis are presented. Further, numerical simulations with or without treatments are performed in Section 4. Section 5 gives a brief conclusion.

2. The mathematical prognosis model for pancreatic cancer

We first develop a more detailed model, namely, the full model, which includes the PCCs, PSCs, three major classes of immune effector cells CD8+ T cells, NK cells, helper T cells, and three major classes of cytokines IL-2, IFN-γ and TGF-β. Then we use steady-state approximation to simplify the full model to a reduced order model consisting of five ODEs describing the dynamics of the PCCs, PSCs, CD8+ T cells, NK cells, and helper T cells.

In this work, we focus on tissue near the tumor site and assume a homogeneous tumor cell population. Similarly to Li and Xu (2015), de Pillis et al. (2008), the specific biological assumptions are first presented as follows:

(1) The cancer cells grow logistically in the absence of an immune response.
(2) Both NK-cells and $CD8^+$T cells are capable of killing cancer cells.
(3) Both NK-cells and $CD8^+$T cells are activated by cancer cells.
(4) Both NK-cells and $CD8^+$T cells eventually become inactivated after some number of interactions with tumor cells.

2.1. Variables and notations

The model describes the dynamic interaction between tumor and immune cells. Denote cell populations and concentrations of cytokines as follows:

- $C(t)$, pancreatic cancer cell (PCC) population.
- $P(t)$, pancreatic stellate cell (PSC) population.
- $T(t)$, $CD8^+$T cell population.
- $N(t)$, NK cell population.
- $H(t)$, helper T cell population.
- $I(t)$, IL-2 concentration.
- $F(t)$, IFN-γ concentration.
- $T_\beta(t)$, TGF-β concentration.