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Clinical study and numerical simulation of brain cancer dynamics under radiotherapy

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ABSTRACT

We perform a clinical and numerical study of the progression of brain cancer tumor growth dynamics coupled with the effects of radiotherapy. We obtained clinical data from a sample of brain cancer patients undergoing radiotherapy and compare it to our numerical simulations to a mathematical model of brain tumor cell population growth influenced by radiation treatment. We model how the body biologically receives a physically delivered dose of radiation to the affected tumorous area in the form of a generalized LQ model, modified to account for the conversion process of sublethal lesions into lethal lesions at high radiation doses. We obtain good agreement between our clinical data and our numerical simulations of brain cancer progression given by the mathematical model, which couples tumor growth dynamics and the effect of irradiation. The correlation, spanning a wide dataset, demonstrates the potential of the mathematical model to describe the dynamics of brain tumor growth influenced by radiotherapy.

1. Introduction

Cancer ranks second among the most common causes of death in the US, surpassed only by heart disease. It is a cause of nearly 1 in 4 deaths and more than an estimated 1.5 million new cases of cancer and over half a million deaths due to cancer are expected yearly in the US. The incidence of cancer increases with age and about 77% of all cancer cases occur in the age group of 55 years and older. The risk of developing or dying from cancer in a human lifetime for males is about 1 in 2 and for women the risk is about 1 in 3. The main reason for death after the onset of the disease is the metastasis or spread of the cancer to other locations in the body, and the chances of patient survival vary greatly and depend on the cancer type, location, and stage at diagnosis describing the extent of the primary tumor and whether it has began spreading to other areas of the body. Early detection for the timely delivery of treatment options is crucial for patient survival and may result in better outcomes with less extensive treatment [1].

An organism's ability to sustain healthy development relies on the interaction of millions of cells undergoing various phases in the cell cycle. These cellular interactions are maintained by signals which control cell division, differentiation and cell death. The onset of cancer is triggered by a collapse of this normal cellular interaction process, leading to an uncontrolled growth of cells within the organism. Without the intervention of outside treatment options, this uncontrolled cell growth leads to eventual patient death.

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The treatment of brain cancer depends on the type, size and location of the tumor. The tumors respond differently to radiotherapy, depending on their molecular subtype, [2,3]. In cases where the tumor is located in an area of the brain that is physically unaccessible for surgery, or where surgery carries likely risks, such as for tumors near nerves that control vital bodily functions, alternative effective treatment options are needed such as radiotherapy and chemotherapy. Side effects of radiotherapy depend on the type and dose of radiation, and whether the delivered dose is focused on the tumor location or applied in small doses to a wider area of the brain [4,5].

Of fundamental importance in the success of treatment planning is the ability to predict the impact of the application of radiotherapy and a formalism for describing time-dose relationships. The most commonly used method in radiation biology for the evaluation of radiotherapy schedules is the LQ formalism, which has over the years proved remarkably reliable and has been developed with considerable progress, see e.g. [6–13]. It has been widely used in the assessment of dose-dependence of repair and in treatment planning [14–16] and has demonstrated validation with experiments and other established models [17–21]. In an effort to improve the effectiveness of current cancer treatment strategies, the LQ model has also been extended [22,23] to a general form that applies to radiation treatments with both low and high dose rates to encapsulate the effect of therapies given in fewer, larger doses.

For this paper, we perform a clinical study with a sample of brain cancer patients undergoing treatment in the form of stereotactic radiotherapy, with a high dose radiation delivery. We analyze the clinical data obtained for this paper and compare it to our numerical simulations for a model of brain tumor progression. The model incorporates the effects of large dose irradiation. We are particularly interested in the outcomes of radiotherapy and its interaction with the host tumorous regions of the brain. We will consider the coupling of radiation therapy with tumor growth dynamics emanating from the affected region of the brain and the result of radiation therapy influenced by tumor growth.

The organization of the paper is as follows. In Section 2, we describe our clinical study of brain cancer patients undergoing radiotherapy treatment. In Section 3 we present a mathematical model for untreated brain cancer growth and incorporate treatment in the form of radiotherapy using LQ formalism in Section 4. We present numerical simulations and the correlation to our clinically obtained data in Section 5 and conclude with remarks and future directions in Section 6.

2. Clinical study of brain cancer treatment

A group of patients with brain metastases were treated with stereotactic radiotherapy in Olsztyn, Poland from Aug. 2011 to Nov. 2012. Patients have had 1–3 metastases of max. diameter of 3 cm, were in a good general condition (KPS$>$70) and their disease of the brain was under control. Radiotherapy doses delivered depended on the number of metastases and their diameters. The doses ranged from 15 Gy to 24 Gy. Planning was done in iPlan, BrainLab based on fused CT (computed tomography) and MR (magnetic resonance) images. The PTV (planing target volume) was defined as the visible tumor plus a 2–3 mm margin of brain tissue. Tumors were irradiated with 6 MV photon energy using a Siemens linear accelerator with microcollimator (Siemens Moduleaf) with 2.5 mm leaves. The prescribed dose covered 98% of PTV volume. After 6–8 weeks at follow-up visits patients had MR exams which were used for volumetric analysis of response to radiotherapy.

Fig. 2.1 shows a screenshot from the planning system (Iplan RT 4,5, BrainLab, Germany) used for stereotactic radiotherapy. These are CT scans of a patient immobilized in an individual thermoplastic mask. Colored tumors (metastases to the brain) – purple one in the right frontal lobe and green one in the right parietal lobe – were defined using MR diagnostic imaging. The corresponding MR and CT scans are shown in Fig. 2.2. MR is used for the best possible definition of target definition since on CT scans, the tumor does not differentiate well from surrounding brain tissue. On the other hand, CT is used for the dose calculation by the planning system.

The collected clinical data for the sample of brain cancer patients treated with stereotactic radiotherapy is shown in Table 2.1, showing the volume of the tumor before and after therapy, the physically delivered dose, and the length of time between the two measurements. Initial tumor volumes ranged from 0.084 to 8.444 cm^3 and comparison to the tumor volume after therapy indicates better outcomes for tumors detected at an early stage of development. Success rates for patients treated at advanced stages of the disease are lower even with higher delivery doses.

Stereotactic radiotherapy of the brain is mostly used in metastatic tumors as the borders of the metastases are well defined in magnetic resonance imaging. In the case of malignant primary tumors (e.g. malignant gliomas), stereotactic therapy is not advised because their growth is diffusive and infiltrating; large (2 cm) margins to the magnetic resonance-defined borders are required in conventional radiation therapy [24]. In our series, all treated tumors were metastases from common primary cancers. The most common primary cancers are lung cancer and breast cancer. They are responsible for the majority of brain metastases. Details related to the primary location of the tumor, its histopathology and grade of differentiation are shown in the Table 2.2.

3. Mathematical model for the progression of brain cancer tumor cell population growth

We consider a nonlinear reaction–diffusion type model used to describe the evolution of a brain tumor cell population. We first consider tumor growth without exposure to radiation, for which the tumor is allowed to develop on its own without imposed outside intervention. We then consider the effects of radiotherapy treatment.