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Simulation of metastatic progression using a computer model including chemotherapy and radiation therapy

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ABSTRACT

Introduction: Despite considerable research efforts, the process of metastasis formation is still a subject of intense discussion, and even established models differ considerably in basic details and in the conclusions drawn from them. Mathematical and computational models add a new perspective to the research as they can quantitatively investigate the processes of metastasis and the effects of treatment. However, existing models look at only one treatment option at a time.

Methods: We enhanced a previously developed computer model (called CaTSiT) that enables quantitative comparison of different metastasis formation models with clinical and experimental data, to include the effects of chemotherapy, external beam radiation, radioimmunotherapy and radioembolization. CaTSiT is based on a discrete event simulation procedure. The growth of the primary tumor and its metastases is modeled by a piecewise-defined growth function that describes the growth behavior of the primary tumor and metastases during various time intervals. The piecewise-defined growth function is composed of analytical functions describing the growth behavior of the tumor based on characteristics of the tumor, such as dormancy, or the effects of various therapies. The spreading of malignant cells into the blood is modeled by intravasation events, which are generated according to a rate function. Further events in the model describe the behavior of the released malignant cells until the formation of a new metastasis. The model is published under the GNU General Public License version 3.

Results: To demonstrate the application of the computer model, a case of a patient with a hepatocellular carcinoma and multiple metastases in the liver was simulated. Besides the untreated case, different treatments were simulated at two time points: one directly after diagnosis of the primary tumor and the other several months later. Except for early applied radioimmunotherapy, no treatment strategy was able to eliminate all metastases. These results emphasize the importance of early diagnosis and of proceeding with treatment even if no clinically detectable metastases are present at the time of diagnosis of the primary tumor.

Conclusion: CaTSiT could be a valuable tool for quantitative investigation of the process of tumor growth and metastasis formation, including the effects of various treatment options.

1. Introduction

The formation of cancer metastases has been defined as one of the hallmarks of cancer [1,2]. The clinical importance of metastasis is highlighted by the fact that more than 90% of cancer patients die because of distant metastases and not because of the primary tumor, which can often be treated locally [3]. Despite its clinical importance, metastasis formation remains an enigmatic aspect of cancer biology that is not well enough understood to develop strategies to prevent their formation [4].

As a complement to experimental research and clinical studies, mathematical models are valuable tools for investigating the progress of tumor growth and metastasis and for devising optimal treatment strategies, such as for chemo- and/or radiation therapy. Thus, in recent years a variety of mathematical models have been developed. In 2000 Iwata et al. [5] published a model for the growth and size distribution of multiple metastatic tumors, which

Abbreviations: CaTSiT, cancer and treatment simulation tool; EBRT, external beam radiation therapy; MIRD, Medical Internal Radiation Dose; XML, Extensible Markup Language; XSD, XML Schema Definition.

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has since been further investigated, validated and developed by a number of researchers, including Struckmeier [6], Barbolosi et al. [7], Devys [8], Haustein and Schumacher [9], Hartung et al. [10] and Benzekry, who enhanced this model by including the effects of angiogenesis [11] and dormancy [12]. Another mathematical approach was developed by Newton et al. [13,14], who calculated a transition matrix using a stochastic Markov chain model to describe the growth of primary lung cancer and the spread of metastases to distant sites.

Further models have been developed that also modeled chemo- and radiation therapy. The effects of cytotoxic drugs on tumor growth were modeled by Wheldon [15], Birkhead [16,17], Usher [18], Panetta [19–21] and Dua [22], for example. Chemotherapy in combination with antiangiogenic drugs was modeled by d'Onofrio [23] and Benzekry [24], while de Pillis examined the combination of chemotherapy with immunotherapy [25]. Models describing the effects of radiation therapy were developed by Wang [26], Bernhardt [27,28], Wheldon [29] and Leder [30], among others. However, in radiation therapy the use of mathematical models has been limited mainly to calculating optimal doses [27,28] or obtaining optimal treatment schedules [30,31].

For the analysis of data from mouse models or clinical studies, it is important to include the effects of different treatment modalities on the same case, because several treatment modalities are often combined in practice. In this article a computer model, named CaTSiT (cancer and treatments simulation tool), is presented that enables commonly applied treatment options to be simulated. The original model was published in [32], where it was used to compare two models of metastatic progression, the linear and parallel progression model [33], in a case of a hepatocellular carcinoma. The comparison of the simulated data with the clinical data revealed that in this particular case metastasis formation is an early event and only the first metastases seeded from the primary tumor contribute significantly to the tumor burden and thus cause the patient's death, if he is left untreated. In [34] the computer model was used to analyze the experimental data of an HT29 human colon cancer xenograft mouse model. In this context the computer model was enhanced to model dormancy. The simulation results showed that natural killer cells decelerate the growth of the primary tumor, kill 80% of the circulating tumor cells that could have otherwise established a new metastasis and hamper the establishment and proliferation of the malignant cells in distant tissue, possibly because of an induction of dormancy in disseminated tumor cells.

In the work presented here the computer model was further enhanced to model different treatment modalities. Besides the already implemented complete resection of the primary tumor, the computer model was now enhanced to model partial resection and two other commonly applied treatments: chemotherapy and external beam radiation. Furthermore, two specialized treatments were added to the computer model: radioimmunotherapy and radioembolization. In this process the original computer model was slightly modified by introducing a piecewise-defined growth function to facilitate the model and its implementation.

As a demonstration the application of the enhanced computer model is represented in the results section on data of one patient with hepatocellular carcinoma und multiple metastases in the liver.

Owing to the structure of the computer model and the software, it is easy to extend CaTSiT to include further new findings about metastatic progression and novel treatments in the future. CaTSiT is available as open source software under the GNU General Public License version 3. To our knowledge no existing software package can provide a similar wide range of functionality.

2. Methods

2.1. Compartments and events

The basic structure of the computer model was first described in [32] and [35]: It is developed as a building kit [32] that provides different kinds of building blocks, from which various simulation setups can be assembled [30,33]. The two main types of building blocks are compartments and events. A compartment describes a physical entity that can contain malignant cells; it can be, for example, the primary tumor, the bloodstream or a metastasis [32]. An event describes what occurs in a compartment at a specific time. In contrast to [32] and [35], events now can have either local or global effects: local events influence only one compartment, whereas global events can affect more than one compartment. Global events are mostly used to describe therapies such as radiation therapy. Local events are further subdivided into events that influence the whole compartment, such as dormancy or resection of the primary tumor, and events that affect tumor progression, such as cell division, apoptosis and cell transfer (e.g. intravasation and extravasation).

Compartments can be modeled either discrete or continuous [32]. In a continuous compartment, all internal processes are modeled by continuous mathematical functions. The growth of the compartment size is described by a growth function and the spread of malignant cells by a colonization rate, which depends on the size of the compartment and therefore on its growth function. The growth function and colonization rate can be parameterized individually for different compartments, for instance the primary tumor and different kind of metastases. Larger compartments, such as the primary tumor and metastases, are usually modeled as continuous compartments [32].

In a discrete compartment, all internal processes are modeled with discrete tumor progression events. The increase or decrease in the number of malignant cells in a discrete compartment is modeled by simulating each cell division, apoptosis or translocation event into a different compartment. One can think of a discrete compartment as a bucket, which cells can be placed into or removed from. For each discrete compartment a set of possible event types can be defined, and associated with each event is a probability of occurrence (see Fig. 1). Discrete compartments are mostly used to model the bloodstream [32,35].

With these building blocks, various simulation setups can be constructed to investigate different scenarios of metastatic progression and treatment strategies. A sample setup involving an untreated hepatocellular carcinoma with metastases in the liver and the lung is shown in Fig. 1.

2.2. Modeling tumor growth using a continuous compartment

In a continuous compartment that models the primary tumor or a metastasis, the growth function $x(t)$ represents the number of cells in the tumor at time t and is the solution of

$$\frac{dx}{dt} = g(x), \quad x(0) = N_0, \tag{1}$$

where the parameter N_0 is the number of cells at time $t = 0$. When modeling tumor growth in a human patient, N_0 is taken to be 1, because it is assumed that the primary tumor or a metastasis starts as a single malignant cell [5,36–38]. When modeling experimental data, such as data from a mouse model, N_0 could be the number of cells injected into the mouse, for instance.

Different functions can be chosen for the growth rate $g(x)$, such as linear, exponential or power laws. Most tumors exhibit a Gompertzian growth rate, which is given by

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