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ISTER (Immune System - Tumor Efficiency Rate): an important key for planning in radiotherapic facilities

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Abstract—The use of the oncologic index ISTER allows for a more effective planning of the radiotherapic facilities in the hospitals. Any change in the radiotherapy treatment, due to unexpected stops, may be adapted by recalculating the doses to the new treatment duration while keeping the optimal prognosis. The results obtained in a simulation model on millions of patients allow the definition of optimal success probability algorithms.

Keywords—mathematical model; radiation oncology; dynamical systems applications

I. Introduction

Dynamical system techniques use a population dynamics model [1–4] to mathematically describe the tumour behavior and its interaction with the immune system. Some of these works model tumour behavior under clinical treatments like cytokines [5] or radiovirotherapy [6] and properly explain the qualitative behaviors of several tumours. Even though great efforts had been made to describe cancer radiotherapy treatments , they "are vaguely tied to [clinical] observations" [2] and their large number of variables and coefficients make their results hardly transposable to a clinical context.

The relevance of immune system tumor interaction in a radiotherapy treatment (RT) and the importance of its study have been highlighted in a previous work [7]. The role of immune system in tumor control has been described in [1] and widely discussed in further works [2, 8–12]. However, in our opinion, its study and characterization has not been sufficiently addressed in the context of the clinical practice to plan alternative or contingency treatment.

In reference [7] the interplay between the immune system and the tumour was analysed. From that work one conclusion is drawn: the system behavior is determined by the efficiency of the immune system over tumor growth, and the "deficiency" of the immune system due to tumor growth. Of these two properties, the most decissive was shown to be the first one, the dimensionless parameter called $ISTER$. That parameter allowed to find the success probability of a fractionated radiotherapy treatment, using the survival fraction of tumour cells, even if other parameters involved were unknown. The calculation provided a way to classify patients, based on their $ISTER$ value, and to approach to the optimum treatment.

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There is an increasing concern about finding the suitable planning that maximizes the outcome of a radiotherapy (RT) treatment [13]. Many of the previous works assume normal radiotherapy treatment development [14]. However, delays and treatment interruptions occur in real life, and must be taken into account. The problem of how to apply radiation treatments in an optimal way under the influence of external factors is, in our opinion, far from being fully solved. So some algorithm is needed capable to determine the optimal dose to end the treatment without significant loss of performance.

On the other hand the number of devices in radiotherapy services is limited hence the appearance of waiting lists. Waiting times have been shown to be a major problem in the achievement of high treatment efficiency [15, 16].

The objective of this work is to aid in decision making of the treatment priorization and planning recovery on device failure, so that changes in treatment duration must not necessarily imply a worser prognosis.

II. The model

We are going to use the model introduced in [7] to simulate the evolution of one million patients under radiotherapy treatment. A short description of the model follows.

A Lotka-Volterra like model describes the tumor evolution [5]. Tumor cells growth $\dot{X}$ (as usual, a dot over a quantity represents its time derivative) depends on the current tumor population as aX and its interaction with lymphocytes, $-bXY$. Lymphocyte population grows due to tumor-immune system interaction, dXY, and die with a rate $-fY$. The tumor is assumed to secrete interleukins which produce an immunity depression effect [17, 18], $-kX$. A constant flow, u, of lymphocytes is assumed to arrive from the immune system.

As a result of RT treatment a fraction of cells of both populations, lymphocytes and tumor cells is affected. The lymphocytes population gets quickly reduced in a fraction B_l in what is called the interphase death. However, affected tumor cells will not die immediately; a fraction B_t will loss its reproductive capacity and die in the mitosis process. The fraction of affected cells in both populations and is the complement of the survival factors $S_t = 1 - B_t$ (tumor) and $S_l = 1 - B_l$ (lymphocytes). The inclusion of both population affections brings a new equation for the tumor non clonogenic

cells [6], Z, originated from radiation damage. Those cells will also stimulate the lymphocyte population, as pZY, will decay exponentially as $-rZ$ due to the death of damaged cells, and as $-qZY$ due to the interaction with immune system. Finally we arrive to

$$\begin{aligned}\dot{X} &= aX - bXY - \dot{B}_t(T)X \\ \dot{Y} &= dXY + pZY - fY - k(X+Z) + u - \dot{B}_l(T)Y \\ \dot{Z} &= \dot{B}_t(T)X - rZ - qZY\end{aligned} \tag{1}$$

where $\dot{B}_t(T) = B_t \sum \delta(T - T_n)$ and $\dot{B}_l(T) = B_l \sum \delta(T - T_n)$ represent the amount of tumor cells and lymphocytes affected by radiation per unit time. T_n are the time instants when radiation doses are applied and $\delta(T - T_n)$ denotes Dirac's delta function centered at T_n. All parameters were estimated and interpreted as in [19] or [12].

The linear stability analysis [7] of the dimensionless version of system (1) shows that its qualitative behavior is determined by just a set of dimensionless parameters: $\sigma = ub/a^2$, $\lambda = f/a$, $\kappa = kb/ad$. We can see that σ/λ is the efficiency of immune system over tumor growth, and κ is the "deficiency" of the immune system due to tumor growth. σ/λ was defined as the $ISTER$ parameter, and together with κ will be the only relevant parameters of the problem.

For $\sigma/\lambda < \kappa < 1$, tumor will grow and tumor eradication will be achieved only by bringing the system close enough to the "tumor free" state, so that the immune system can get rid of the tumor. We will focus our study to this region, beacuse for $\kappa > 1$ and $\sigma/\lambda < 1$, the main effects of the tumour will be the depression of immune system. Patient will perform badly according to Karnofsky performance scale (KPS) [20] and will not fulfill physical requirements to be subject to therapeutic treatment (although a palliative treatment is always possible).

Eqs. (1) allow for unrealistic X values (even less than one cell). However when the number of tumor cells becomes small enough (thousands, for instance), immune system may kill them [21]. We will assume that if the immune system has a high efficiency it will have higher probabilities of killing the tumor remaining cells and if the immune system has a low efficiency the probability of killing those tumor cells will be low. The simplest linear approximation to the probability of tumor regression is then:

$$P(\sigma/\lambda) = \begin{cases} \sigma/\lambda & \text{if } \sigma/\lambda < 1 \\ 1 & \text{if } \sigma/\lambda \geq 1 \end{cases} \tag{2}$$

If no regression occurs, tumor will eventually regrow.

The goal of a radiotherapy treatment is to get $X = 0$, that is, the tumor has disappeared. However, ther is a chance that lymphocyte population becomes. Then, we will assume the tumor escapes lymphocyte control and grows limited only by space and nutrient considerations. At this point, we consider treatment has failed.

In [7] the dynamics given by equations (1) and (2) was simulated for one million "virtual patients" using physiological random values for the parameters. The authors define the "success probability", P_s, as the fraction of "virtual patients" with no tumor by the end of treatment. Moreover, they conclude that P_s is a function of the tumor cell survival factor, S_t, and the patient $ISTER$. Also, the long term survival of patients does not improve with higher doses of radiation, on the contrary, it is possible to get the maximum success probability at intermediate doses. That maximum P_s for the standard treatment simulated in [7] will be denoted as $P_{max}(ISTER)$, for it only depends on the $ISTER$. This standard protocol in ideal conditions will be taken in what follows as the reference protocol or "gold standard", against which modified treatments will be compared.

III. Simulation and results

The simulation will mimic different radiation treatments using Eqs. (1) and condition (2). For the sake of realism, a radiation session will be applied every workday (5 consecutive days) and none in weekends (2 days). All treatments begin the tenth day, and apply a variable number of sessions, N, from 20 to 40 for each patient [13, 22].

We have taken a random value for the survival fractions of each patient tumor, to proceed in a more general way than taking up a sort of tumors (e.g. breast, colon, etc.); so no experimental expression were needed to calculate the survival fraction of cells for the treatment dosage. The rest of the model parameters were drawn from random log-normal distributions (to avoid negative values) as described in [7, 19]. Those values not giving a $ISTER < 1$ were rejected. Survival factors [21] were also taken as random values. Initial conditions were taken as Gaussian distributed.

We define the effect potential for tumor cells as

$$\chi = -\ln(S_t) \tag{3}$$

in terms of the survival fraction of tumoral cells S_t. This quantity grows monotonously with the radiation dose. In exponential radiation effect models (linear or LQ, for instance) χ becomes the tissue effect. For other models (see [21]) χ is still a valuable magnitude, although its relation to the dose is not so direct as in the case for the tissue effect.

The treatment success probability, P_s, was represented as a function of $ISTER$, N and χ,

$$P_s = \mathcal{G}(ISTER, N, \chi) \tag{4}$$

As expected, for each value of N we got similar results as obtained in [7]. The surface represented in figure 1 corresponds to a fixed value of the $ISTER$. This shows that whenever the value of N increases, the optimized value of P_s can be achived with a lower value of χ per session. Those values of χ that optimize P_s, for each value of N, are represented in figure 2 in the form of a family of hyperbolas determined by the $ISTER$ value.

From these results (depicted in figures 1 and 2), the following expression was found to relate χ and N in the boundary of the maximum success probability $P_s \simeq P_{max}$:

$$\frac{\chi N}{P_{max}} = R \tag{5}$$

Here R is a function of the $ISTER$ that can be fitted as the power law

$$R = A \times ISTER^m \tag{6}$$

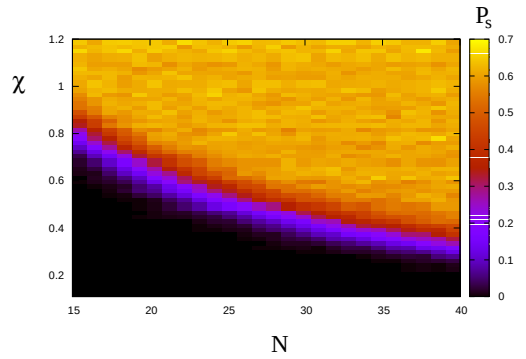

Fig. 1. P_s representation for $ISTER = 0.7$ as a function of the effect potential and the number of radiation sessions. Closer to black means lower, yellow means closer to 0.7.

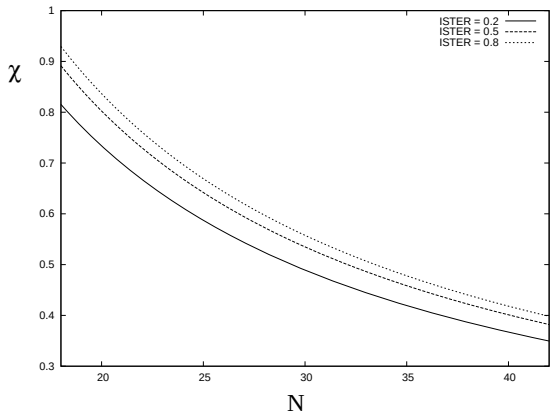

Fig. 2. Effect potential per session that maximize the success probability P_s for each value of N plotted for some values of $ISTER$ parameter.

Our simulations provided $m = -1.1 \pm 0.1$ and $A = 17 \pm 1$. We want to point out that P_{max} is almost constant in the yellow region in figure 1 or, what is the same, above each line in figure 2. Thus P_{max} is a function only of $ISTER$.

IV. Discussion

Expressions (5) and (6) show how to take into account the patient immunological state in order to classify him/her.

Once determined the $ISTER$ for a patient we know the prognosis of the patient, that is, the maximum success probability achievable with any treatment. This P_{max} determines the hyperbolas in figure 2 that relate the number of programmed sessions with the minimal dose per session providing that maximum success probability. This condition also satisfies the ALARA principle [23].

In many cases the presence of the surrounding tissues does not allow the administration of the former minimal dose for the given N. In that case, equation (5) provides the number of sessions needed to achieve the maximum probability with the maximum dose rate allowed by the surrounding tissue.

Given the previous arguments, the value of the $ISTER$ of a patient determines the total radiation dose he needs to receive in order to guarantee the best prognosis at the "minimum cost", that is, given the $ISTER$ and the location of the tumor (appropriate χ) equation (5) gives N.

Any change on N or the $ISTER$ of the patient along the treatment can be addressed using equation (5) to adapt the treatment to the new conditions, while keeping the same prognosis.

This methodology can be also applied to multifractionation [24].

V. Conclusions

The present work introduces a generalization of [7] to a scenario with a possibly variable number of sessions. Starting from a system of equations and introducing a probabilistic cut-off system, the simulations allows us to find the corresponding effect potential per radiation session providing the maximum value of the success probability. Consider, the following two scenarios: the first one, for some time interval the RT machines become unavailable when a patient needs an urgent treatment; our work could guide the radiotherapists to design a parallel treatment as efficient as that initially recommended for that patient and adapted to the available time interval. The second one, consider a patient with a dramatic change in his/her KPS affecting his/her $ISTER$; our study allows to redesign a new treatment adapted to the new situation, again with the best prognosis and the lowest cost for the patient's health, avoiding the interruption of the treatment.

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