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Mathematical Biosciences 199 (2006) 38–54
Mathematical Biosciences
www.elsevier.com/locate/mbs

An alternative approach to modelling relapse in cancer with an application to adenocarcinoma of the prostate

Dirk Veestraeten *

University of Amsterdam, Department of Economics, Roetersstraat 11, 1018 WB Amsterdam, The Netherlands

Received 5 March 2005; received in revised form 29 July 2005; accepted 24 October 2005
Available online 20 December 2005

Communicated by Eberhard Voit

Abstract

This paper proposes an alternative approach to modelling relapse in cancer. In particular, the dynamic model for the tumor or biomarker will be subjected to a lower elastic boundary at which the process either will be absorbed or reflected. The likelihood of reflection then can be interpreted as the probability of relapse. This framework will be exemplified for prostatic cancer by extending the recently proposed stochastic model of Dayananda et al. [P.W.A. Dayananda, J.T. Kemper, M.M. Shvartsman, A stochastic model for prostate-specific antigen levels, Math. Biosci. 190 (2004) 113] that focussed on the dynamics of the prostate-specific antigen (PSA) biomarker. Analytical results for the conditional density function, given a non-negative lower boundary, are obtained for the extreme cases of certain cure and of certain relapse. Simulations illustrate the relevance of the relapse probability and of the normal value of the biomarker for the design of treatment strategies. The paper thus points to two additional (patient-specific) characteristics that might enter treatment design and monitoring of progress in therapy.

MSC: 60J35; 60J70; 60K30; 92B15

Keywords: Absorbing boundary; Cancer; Conditional probability density function; Elastic boundary; Prostate cancer; Prostate-specific antigen (PSA); Reflecting boundary; Relapse; Stochastic differential equations

* Tel.: +31 20 5254194; fax: +31 20 5254254.
E-mail address: Dirk.Veestraeten@uva.nl

0025-5564/$ - see front matter
doi:10.1016/j.mbs.2005.10.002

1. Introduction

Treatment of cancer is often hampered by relapse of tumor growth and/or by resistance of cancer cells to the treating agent or therapy. The mechanism of relapse is still not well understood and extant approaches examined several driving forces and their combinations, such as the presence of tumor cells that (inheritably) are or grow resistant [2–5], of insufficient initial levels of cancer-killing lymphocytes [4,5] or of basically treatment-independent relapse [6,7]. The purpose of this paper is to propose an alternative, flexible manner through which relapse can enter (stochastic) modelling. The proposed modelling strategy will focus on the behaviour of the stochastic variable, be it the tumor itself or the biomarker, upon reaching a specified lower boundary or barrier. More in particular, at attaining the lower boundary due to therapy, the process is halted (absorption) or can reverse again, i.e. the patient experiences a relapse (reflection). The likelihood of relapse will then be explicitly incorporated into the stochastic model as the (patient-specific) parameter γ with $0 \leqslant \gamma \leqslant 1$. Following the elastic-barrier framework in [8–11], the process is reflected with probability γ and with probability $(1-\gamma)$ it is absorbed. Thus, the design of treatment strategies and the process of monitoring, for instance, the evolution of the biomarker then can explicitly incorporate priors on the likelihood of relapse. Such predictions on the reversal of the cancer-reduction process can be based on patient-specific characteristics/experiences but also reflect the general level of the clinical effectiveness of the therapy in question.

The elastic-boundary set-up can be connected in a straightforward manner to various types of dynamic models, also across various types of cancer. We choose to illustrate our approach for the case of adenocarcinoma of the prostate. Prostatic cancer figures amongst the most frequently encountered types of cancer in adult men and is usually treated via surgery or radiation therapy [1,6,7]. Since the 1980s, research has intensively discussed the merits of the prostate-specific antigen (PSA), a serine protease in prostatic tissue, as a serum marker useful in predicting prostatic cancer and monitoring therapy. Recently, the authors in [1] proposed an elegant mathematical model for the dynamics of this biomarker under radiotherapy in which uncertainty entered in the form of Wiener shocks to the PSA level. As such, potentially erratic behaviour in the PSA level was governed by a volatility parameter of which the numerical level could relate to the characteristics of the patient in question. By extending the model of [1] towards elastic boundaries, we directly incorporate a second source of uncertainty, namely the unpredictability of success in treatment, i.e. the potential of relapse. Next to the imposition of elastic barriers, we will also digress on the effect of the normal level of PSA, i.e. the lower boundary of the PSA process, on the treatment intensity. In fact, men that are not affected by prostatic cancer already possess differing amounts of the biomarker, see [1,12–15], such that treatment could benefit from taking account of the variation in the normal presence of the serum marker. It will be shown through some numerical examples that these two extensions primarily affect the lower tail of the resulting conditional density function whilst keeping the shape for the rest of the domain of the PSA level virtually unaffected. However, it is precisely the lower tail of the distribution, i.e. the probability mass of low PSA levels, that is of prime interest when designing, implementing and monitoring treatment.

The remainder of the paper is organised as follows. Section 2 briefly summarises the main features of the stochastic model that was advanced in [1]. In Section 3, we discuss an alternative modelling strategy for relapse and derive the conditional probability density functions for the two