

A PARAMETRIC ANALYSIS OF TUMOR RECURRENCE DATA

T. HOANG*, A. TSODIKOV†, B. ASSELAIN‡ and A. YAKOLEV§

* *Université René Descartes, 45 rue des Sts Pères, 75006 Paris*

† *IMISE, Universität Leipzig, Liebigstr. 27, 04103 Leipzig, Germany*

‡ *Institut Curie, 26 rue d'Ulm, Paris*

§ *Department of Statistics, The Ohio State University,
141 Cockins Hall, Columbus, OH 43210-1247, USA*

Received 24 June 1994

Revised 27 September 1994

ABSTRACT

The evaluation of cancer treatment efficiency is often based on the risk of local recurrence. When applied to the statistical analysis of tumor recurrence data, a pertinent parametric method has the following distinct advantages: (1) it allows a natural interpretation in terms of parameters bearing clear biological meaning, (2) it provides a prediction of the recurrence risk forward in time beyond the follow-up period, (3) it offers a means of estimating survival fraction (probability of tumor cure) from the time-to-recurrence observations. This paper discusses a stochastic model of tumor recurrence based on the consideration of biological processes of tumor latency within the random minima framework. A parametric family of distributions is obtained that allows for a survival fraction, thereby providing an estimate of the probability of tumor cure. When applying the model to data on breast cancer, we estimate the expected number of clonogens which give rise to early and late recurrences and their progression rate parameters. The prime object of our concern is discrimination between true recurrence and spontaneous carcinogenesis on the basis of the temporal characteristics of the tumor latency. As evidenced by the data analysis, such a discrimination is feasible and allows to conclude that the contralateral breast cancer may be interpreted as a preexisting subclinical tumor at the time of treatment.

Keywords: Stochastic models, tumor recurrence, parametric estimation, breast cancer.

1. Introduction

The term "tumor recurrence" commonly means the reappearance of a tumor of the same histological type and localization as the treated one. Being subject to considerable interindividual variations, the time from treatment to tumor recurrence must be thought of as a random variable (r.v.). Let U represent this time in a patient sampled from a given homogeneous population, and let $G(u)$ be its cumulative distribution function (c.d.f.). If $t = 0$ corresponds to the time of treatment, then

$$P(\text{tumor recurrence before } t) = P(U < t) = G(t). \quad (1)$$

To estimate the probability $G(t)$ from time-to-recurrence observations in a follow-up study one might apply the well-known nonparametric methods of survival data analysis [2,3,7,12], the Kaplan–Meier estimator being a natural choice. However, nonparametric estimators are incapable of providing a projection of the recurrence risk forward in time beyond the follow-up period. Only a pertinent parametric method may be useful in long-term predictions.

Another problem arises when the probability of tumor cure (no recurrence), or survival fraction, is to be estimated. Due to the censoring effects inherent in data on survival of patients treated for cancer, its estimation is not trivial. The Kaplan–Meier estimator appears to be unstable for high values of t in the presence of heavy censoring [21]. Most parametric survival models implicitly assume a zero limiting survival probability. The importance of allowing for a survival fraction in failure-time models has been recognized by several authors [16,18,19,33,38]. Within the parametric framework this difficulty can be overcome, at least in theory, by using some substochastic (also known as improper) distributions. A biologically-based model of tumor recurrence might suggest such a distribution in a natural way. In the paper by Yakovlev *et al.* [34] an attempt was made to develop a simple stochastic model that allows to interpret the time-to-recurrence data in terms of parameters bearing clear biological meaning. The model yields a substochastic distribution $G(t)$ in formula (1), thereby providing a means for estimating the probability of tumor cure.

When considering the causes of local failures, one meets with three meaningful possibilities:

- (i) The tumor detected after treatment represents the true recurrence, i.e., it originates from the surviving primary tumor cells, including those from subclinical tumor foci preexisting at the time of treatment.
- (ii) The observed tumor is induced by irradiation or/and chemotherapy (direct carcinogenic effect of a treatment).
- (iii) The observed tumor is a new one, its appearance being due to an enhanced transformation rate and depression of the immune system in the organism treated by high doses of irradiation or/and chemotherapy (indirect carcinogenic effect of a treatment).

Case (i) seems most likely to be an explanation of cancer recurrence in the majority of clinical situations, but the other two cases cannot *a priori* be excluded from theoretical consideration. At present there are no pathological or clinical criteria for discrimination between these possible causes of local failures. An appropriate solution to the problem may hopefully be found by studying the temporal characteristics of tumor latency, this issue being the prime concern of this paper. Some preliminary ideas of that kind will be sketched below. We consider the model of true recurrence that corresponds to case (i) in Sec. 2, while cases (ii) and (iii), referred to as radiation-induced and spontaneous carcinogenesis, respectively, are discussed in

Sec. 3. In Sec. 4 we propose an estimation procedure. Applications to data analysis of breast cancer are given in Sec. 5. We present results for the contralateral breast cancer showing that discrimination between true recurrence and spontaneous carcinogenesis is feasible. For the sake of completeness, the results are supplemented with those obtained in [10] with regard to tumor recurrence in the ipsilateral breast.

2. A Latent Time Distribution of Tumor Recurrence

At the end of treatment, the cells that will propagate into a newly detectable tumor — we call them clonogens — are surviving neoplastic cells capable of giving rise to tumor regeneration. Consider the case where tumors are exposed to large single doses of radiation or chemotherapy. In this case it is natural to assume that the number N of clonogens prior to irradiation is very large but the probability, p , of their survival after treatment is very low. If N is nonrandom, one may confidently consider the number, ν , of surviving clonogens as a Poisson random variable. The probability η of tumor cure (no surviving clonogens) is given by

$$\eta = P(\nu = 0) = e^{-\theta} \quad (2)$$

where $\theta = Np$ is the mean number of clonogens surviving the treatment.

If N is random the situation is not simple except when N is also a Poisson variable — in which case formula (2) remains valid. Considering that cell proliferation may occur during the time intervals between successive fractions of radiation, in principle one can no longer expect the number of surviving clonogens to be Poisson. In a computer experiment, Tucker *et al.* [31] showed that deviations from Poisson statistics might result in a bias of about 10% for the estimate of the probability of cure in most standard treatment regimens. However in our view this (small) bias has been overestimated due to the chosen probability of cell division between consecutive fractions. This probability — set by the authors to be 0.4 — is too high in view of

- the typical mitotic cycle duration in tumors,
- the asynchronous entry of cells into the prereplicative period after irradiation,
- the radiation-induced block of DNA synthesis and mitosis which frequently exceeds the one-day interval chosen by Turker *et al.* (see the discussion in [36]).

Therefore, we rejoin most authors in maintaining the assumption that the number of remaining clonogens is a Poisson variable [20,22,23,26,27]. We proceed from this assumption to develop our model of tumor recurrence.

Each surviving clonogenic cell possesses in the long run the capacity of giving rise to an overt tumor. Let X_i be the random time for the i th clonogen to produce a detectable tumor. By analogy with the terminology accepted in carcinogenesis studies we call X_i the progression time. Nonnegative r.v.'s X_i , $i = 1, 2, \dots$, are assumed to be independent and identically distributed with the common c.d.f. $F(x)$. The time to tumor recurrence (latent period) can be defined as the random

minimum

$$U = \min_{0 \leq i \leq \nu} X_i ,$$

where $X_0 = +\infty$ with probability one.

Remark. The notion of the progression time should not be taken too literally. It rather refers to *potential progression time*, serving to model the temporal organization of tumor latency in a relatively facile way.

If ν is a Poisson r.v. independent of the sequence X_1, X_2, \dots , the survival function, $\bar{G}(t) = 1 - G(t)$, for the r.v. U can be obtained easily as follows

$$\bar{G}(t) = P(U > t) = \sum_{k=0}^{\infty} \frac{\theta^k}{k!} e^{-\theta} (1 - F(t))^k = e^{-\theta F(t)} . \quad (3)$$

The key advantage of this model is to show explicitly the contribution of the two characteristics of tumor growth: the mean number of clonogens θ and the rate of their progression described by the function $F(t)$. Their estimation, if feasible, furnishes additional information on the biology of tumor recurrence, thereby offering a more refined interpretation of observational data. The survival function \bar{G} corresponds to a substochastic distribution and its limiting value $\bar{G}(+\infty) = e^{-\theta}$ represents the probability of tumor cure (compare with formula (2)).

The hazard function, $\lambda(t)$, defined with respect to $\bar{G}(t)$ is

$$\lambda(t) = \theta f(t) , \quad (4)$$

where f is the density of the distribution F . If the progression time distribution F is unimodal, then the hazard function $\lambda(t)$ has a maximum. Note that the assumption on the exponentiality of F , $F(t) = 1 - e^{-at}$, $t > 0$, should be rejected since that would correspond to the unrealistic case of a monotone decreasing hazard.

To describe a possible heterogeneity of clonogens with respect to the progression time distribution, introduce k different types of tumor cells with distributions $F_j(t)$. Then the progression time distribution F is represented by a finite mixture

$$F(t) = \sum_{j=1}^k q_j F_j(t), \quad 0 < q_j < 1, \quad \sum_{j=1}^k q_j = 1 . \quad (5)$$

This mixture of distributions yields the independent competing risks model for the function \bar{G} , i.e.,

$$\bar{G}(t) = \prod_{j=1}^k \exp(-\theta_0 q_j F_j(t)), \quad (6)$$

where θ_0 is the expected total number of viable clonogens of various types existing in the treated tumor. Within the framework of this model the hazard functions λ_j are additive and

$$\lambda(t) = \theta_0 \sum_{j=1}^k q_j f_j(t) .$$

In view of the last formula, it is not surprising that the bimodal shape of the hazard function arises when tumor recurrences originate from two distinct subpopulations of progenitor cells as in the example presented in Sec. 5.

Note that the function \bar{G} , given by (3), is monotone with respect to the parameter θ . Therefore, θ induces a stochastic ordering of latent times and, introducing a prior distribution of θ , one may construct a randomized version of the model in order to describe inhomogeneity of a population of patients under study. Most convenient for this purpose are the gamma distributions and the class of $\frac{\alpha}{2}$ — stable distributions [13,25].

3. Radiation-Induced and Spontaneous Carcinogenesis

Proceeding from a similar consideration of biological processes for tumor latency within the random minima framework, Klebanov *et al.* [13] proposed a stochastic model which includes the description of radiation-induced and spontaneous carcinogenesis as special cases. A non-stationary generalization of this model is given in [35].

In the case of an acute irradiation, the model yields the following expression for the latent time distribution

$$\bar{G}(t) = e^{-\gamma D F(t)}, \quad (7)$$

where γ is the expected number of neoplastically transformed cells per unit dose, D the dose of irradiation, and $F(t)$ the progression time distribution. Recalling the model of tumor recurrence given by (3), it is easy to see that its structure is similar to that of model (7), the only distinction is the biological meaning of the parameters involved in the description of these entirely different processes. Therefore, one may conclude that cases (i) and (ii), mentioned in the introduction, are formally similar in the parametric analysis for a fixed dose value. Radiation-induced cancers are believed to have longer latencies than the true tumor recurrence, but considering the randomness of the latent period this observation cannot be easily put into use in practice.

At first glance it would seem that the difficulty could be overcome with the help of dose-effect considerations. Actually, the survival of irradiated tumor cells is a decreasing function of dose, while the radiation-induced cancer incidence exhibits an extremum in the dose-response curve [24]. Since at high doses the radiation-induced cell killing causes a reduction of cancer incidence, expression (7) should be modified in such a way as to take into account the survival of normal cells. Let $S(D)$ be the probability of cell survival at dose D , then (7) becomes

$$\bar{G}(t; D) = \exp(-\gamma D S(D) F(t)). \quad (8)$$

Assuming that $S(D)$ has a hazard rate $\lambda(D)$, it is easy to obtain the necessary condition for the minimum of $\bar{G}(t; D)$ with respect to D :

$$\lambda(D) = \frac{1}{D^*}$$

at some point $D^* \in (0, +\infty)$. In particular, the "multihit-one target" model [32] of radiation cell survival satisfies this condition. In clinical applications, the function $S(D)$ should be represented in such a form as to describe multifractional regimens of irradiation [6,29,30] although the corresponding generalization of formula (8) appears to be quite cumbersome. To reveal the dissimilar behavior of the dose-effect relationship, regression analysis — with the irradiation dose as covariate — is faced with encompassing a sufficiently wide range of dose values. It seems doubtful, however, whether relevant data are available to provide such an analysis. Besides, the radiation-induced cancer risk is expected to be fairly small as compared to the risk of tumor recurrences.

On the contrary, a model of spontaneous carcinogenesis [13,35] possesses distinctive properties that can be used to discriminate between cases (i) and (iii), when analyzing the temporal aspect of tumor recurrence.

In its general form [35] the model is specified by the following expression for the survival function

$$\bar{G}(t) = \exp \left(- \int_0^t h(x)F(t-x)dx \right), \quad (9)$$

where $h(t)$ is the transformation rate, i.e., the expected intensity of the process (assumed to be Poisson) of formation of precancerous lesions which are capable of producing an overt tumor.

Assume that $F(0) = 0$. Corresponding to (9) is the hazard function

$$\lambda(t) = \int_0^t h(t-x)dF(x),$$

which is bounded from above if the rate h is bounded, the latter assumption being natural from the biological viewpoint. Note that for the existence of $\lambda(t)$ in this case the progression time distribution needs not be absolutely continuous.

When $h(t)$ is constant in time, we have the following special case of (9)

$$\bar{G}(t) = \exp \left(- h \int_0^t F(x)dx \right), \quad (10)$$

which is best matched to model (3) as far as estimation purposes are concerned. Consider the hazard function, $\lambda(t)$, defined for the survival function given by (10). It is easy to see that

$$\lambda(t) = hF(t) \leq h, \quad (11)$$

i.e., $\lambda(t)$ is a nondecreasing function bounded from above. Thus, this function exhibits a drastically different temporal pattern as compared with the hazard function in (4) which is usually of the extremal type. The dissimilar behavior of hazard rates in the two models can be a useful indicator for discriminating cases (i) and (iii) on the basis of time-to-tumor data. A preliminary distinction could be made with the aid of nonparametric estimators for the hazard function [2] when the sample is

sufficiently large and does not contain too many censored observations. But it is the parametric model that can provide a large part of explanation of an observed pattern.

4. Estimation Procedure

Within the scheme of right independent censoring [12] the likelihood for a random sample of size n is of the form

$$L = \prod_j g(t_j) \prod_k \bar{G}_k(s_k), \quad (12)$$

where $g(t) = -\bar{G}'(t)$ is the corresponding probability density function, t_j , $j = 1, \dots, m$ (m is random), represent the observed failure times, and s_k , $k = 1, \dots, n-m$, are the censored observations. When analyzing data on the ipsilateral and contralateral breast cancer recurrence in Sec. 5, we proceed from this type of censoring because there are grounds to believe that the latent times for the two breasts are mutually independent [1].

If one selects a two-parameter family of distributions to approximate the function F in (3), then there will be only three parameters to be estimated from the time-to-recurrence observations, the estimation of which is feasible from real data, using numerical methods to maximize the likelihood function L . Because of its flexibility, we choose F to be a gamma distribution with the density

$$f(t) = \frac{\beta^\alpha}{\Gamma(\alpha)} t^{\alpha-1} e^{-\beta t}, \quad \alpha > 1, \quad t \geq 0,$$

where α and β are shape and scale parameters, respectively. The mean, $\tau = \frac{\alpha}{\beta}$, and the standard deviation, $\sigma = \frac{\sqrt{\alpha}}{\beta}$, of the progression time can be computed. This failure time model, very simple as it is, reflects the multistage structure of the tumor development process. There are two other reasons for such a choice.

First, finite mixtures of gamma distributions are identifiable [26,37], and so are the competing risks models of type (6) when applied to description of tumors arising from a heterogeneous population of clonogens. Second, in computer simulations of tumor promotion and progression where proliferation, differentiation and death of cells, and the growth control are taken into account, the gamma distribution shows to be a good fit to the sample of progression times [11].

To maximize the log-likelihood $l = \log L(\theta, \alpha, \beta)$ with respect to the unknown parameters θ, α, β we use the following 3-step procedure.

- Step 1: apply the random search algorithm [39] that requires the specification of a domain A containing the overall maximum but not a starting point for the optimization.
- Step 2: apply the Davidon–Fletcher–Powell algorithm [8] with the initial points provided by step 1. If the boundary of the set A is attained then go to step 3, otherwise step 2 gives the final solution.

- Step 3: apply the Zoutendijk algorithm [8] allowing for constraints which specify A .

In order to simplify the computations, we confine the search for the value of α that maximizes the loglikelihood l to the set of positive integers. The above-outlined numerical algorithm has been used to analyze data on breast cancer (see Sec. 5). Further insight into the properties of the estimates for finite samples is provided by statistical decision theory: It can be shown that the maximum likelihood estimator is close to a minimax estimator [14].

5. Data Analysis

In recent years, conservative treatment of breast cancer by local surgery and/or radiotherapy has become a widely accepted alternative to mutilating mastectomy. The evaluation of such treatment techniques is often based on the risk of local recurrence [5,17]. Local recurrence refers to any tumor relapse within the treated breast. Within 5 years of the primary treatment local failure occurs in 2% to 30% of patients. From 5 years up to 20 years and perhaps beyond, the local recurrence rate is 5% to 25% [17]. Early recurrence seems to be related to metastasis [4,5,15]. Since it carries poorer prognosis than late recurrence it is considered as a marker of aggressive tumor biology.

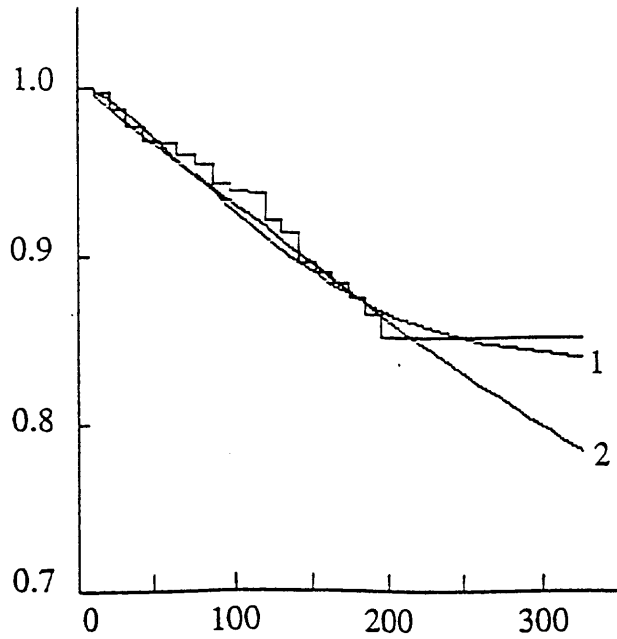
We apply the above methods to analyze data on breast cancer recurrence for 877 patients treated and followed at the Curie Institute from 1960 to 1988. Description of the cohort is given by Fourquet *et al.* [5]. The data include the localization of the recurrences in terms of their occurrence in the ipsilateral (treated) breast and in the contralateral (opposite) one. The data include local failure times and the censoring index values.

Table 1. Maximum likelihood estimates of the parameters for model of true recurrence.

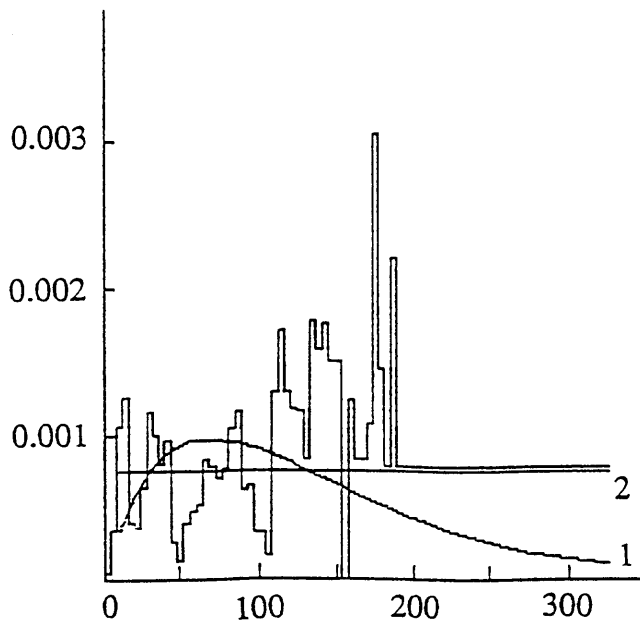
Localization	# clonogens		Time		Std deviation	
	θ_1	θ_2	τ_1	τ_2	σ_1	σ_2
Contralateral breast	0.18	–	140	–	99	–
Ipsilateral breast	0.11	1.07	53	431	26	193

clonogens: expected # clonogens, time: mean progression time (months), std deviation: standard deviation.

First consider the contralateral breast. Plots of the parametric estimate, based on model (3), and the Kaplan–Meier estimate of the survival function (disease free curve) are shown in Fig. 1a. The maximum likelihood estimates of the parameters are given in Table 1. Within the framework of this model the recurrence in the contralateral breast appears to originate from a small population of clonogens (mean number equalling 0.18). In other words, there seem to be preexisting subclinical tumor foci in the contralateral breast. The goodness of fit test developed by Hjort [9]



(a)

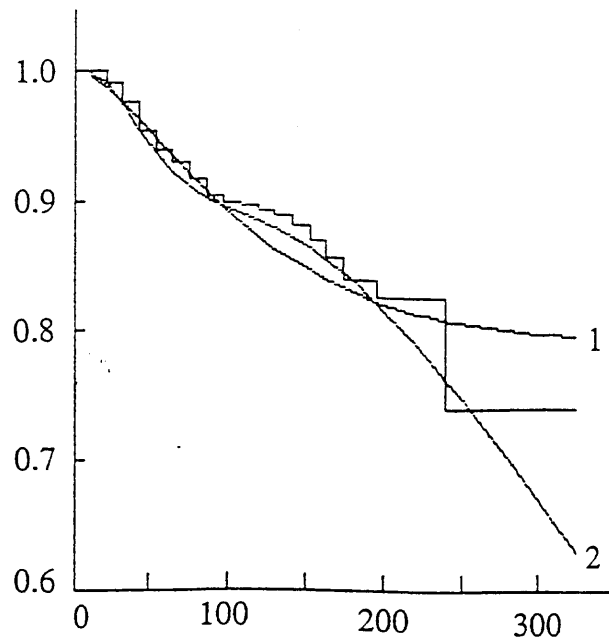


(b)

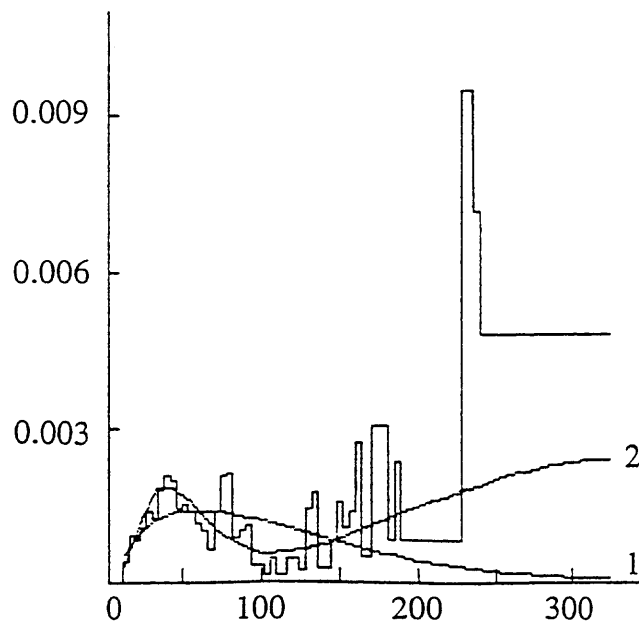
Fig. 1. Disease-free and hazard curves for the contralateral breast cancer (a) Estimated disease-free curves: (1) model of true recurrence, (2) model of spontaneous carcinogenesis, stepwise curve is the Kaplan-Meier estimate. (b) Estimated hazard rates: (1) model of true recurrence, (2) model of spontaneous carcinogenesis, stepwise curve is the kernel estimate.

does not reject the null hypothesis even at a significance level of 0.2. This evidence against the hypothesis is very weak and we can confidently consider the model as consistent with observations.

Another meaningful possibility, described as case (iii) in the Introduction, is that the observed recurrence represents a new tumor caused by indirect carcinogenic



(a)



(b)

Fig. 2. Disease-free and hazard curves for the ipsilateral breast cancer (a) Estimated disease-free curves: (1) model with one population of clonogens, (2) model with two fractions of clonogens, stepwise curve is the Kaplan-Meier estimate. (b) Estimated hazard curves: (1) model with one population of clonogens, (2) model with two fractions of clonogens, stepwise curve is the kernel estimate.

effect of the treatment. To explore this possibility we turn to model (10). The estimated survival function is depicted in Fig. 1a (curve 2). Graphical analysis does not allow to discriminate between the two models. The same is true for the corresponding estimates of the hazard function as compared to the kernel estimate

[2] because it is not clear whether the true hazard rate is monotone or of extremal type (Fig. 1b).

On the other hand, there is no need whatever for testing the goodness-of-fit in order to decide whether or not the tumor in the contralateral breast is a new one. Model (10) gives the estimated value of $\tau = 4.8$ months which seems unrealistic in view of the fact that even animal carcinogenesis studies [13] reveal longer progression times. The results of the parametric analysis favor the model of true recurrence to a greater extent.

Shown in Fig. 2 are the results of a similar analysis of cancer recurrence in the ipsilateral breast. The model given by formula (6) provides a good description of the data for $k = 2$ (curve 2 in Fig. 2a, and curve 2 in Fig. 2b). This model implies two competing subpopulations of clonogens that give rise to the tumor recurrence, their characteristics being presented in Table 1. When the model with a single risk, i.e., formula (3), is applied to these data, the results are much less satisfactory (curve 1 in Fig. 2a, and curve 1 in Fig. 2b). Note that both the life-table and the kernel estimates indicate the bimodal shape of the hazard function in this case. For $k = 1$, the goodness of fit test by Hjort [9] rejects the null hypothesis at a significance level of less than 0.001. When we assume $k = 2$, the significance level is approximately 0.1, thereby indicating that the two competing risks model is consistent with the data.

In further applications the estimated parameters could be regressed on covariates such as age, hormonal status or lymph node status to identify significant prognostic factors.

Acknowledgement

The research of Drs. A. D. Tsodikov and A. Yu. Yakovlev was supported by a Fellowship of the Ligue Nationale Française Contre le Cancer and by the Yvette Mayent Fellowship.

References

- [1] Asselain B., Fourquet A., Hoang T., Myasnikova C. and Yakovlev A. Yu., Testing the independence of competing risks: an application to the analysis of breast cancer recurrence, *Biometrical J.* **36** (1994) pp. 465–473.
- [2] Belayev, Yu. K., *Statistical Methods of Incomplete Data Analysis in Reliability* (Znanie, Moscow, in Russian, 1987).
- [3] Cox D. R. and Oakes D., *Analysis of Survival Data* (Chapman and Hall, London, 1983).
- [4] Fisher B., Anderson S. and Fisher E. *et al.*, Significance of ipsilateral breast tumour recurrence after lumpectomy, *The Lancet* **338** (1991) pp. 327–331.
- [5] Fourquet A., Campana F. and Zafrani B. *et al.*, Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up, *Int. J. Radiat. Oncol. Biol. Phys.* **17** (1989) pp. 719–725.
- [6] Hanin L. G., Rachev S. T., Goot R. E. and Yakovlev A. Yu., Precise upper bounds for the functionals describing the tumor treatment efficiency. In *Lecture Notes in Mathematics* **1432** (Springer-Verlag, Berlin, 1989) pp. 50–67.

- [7] Harris E. K. and Albert A., *Survivorship Analysis for Clinical Studies* (Marcel Dekker Inc., New York, 1991).
- [8] Hjort N., Goodness of fit tests in models for life history based on cumulative hazard rates, *Ann. Statist.* **18** (1990) pp. 1221-1258.
- [9] Himmelblau D. M., *Applied Nonlinear Programming* (McGraw-Hill, Austin, Texas, 1972).
- [10] Hoang T., Tsodikov A., Yakovlev A. and Asselain B., Modeling breast cancer recurrence. In *Mathematical Population Dynamics: Analysis of Heterogeneity, Vol. 2: Carcinogenesis and Cell and Tumor Growth*, ed. by Arino O., Axelrod D. and Kimmel M. (Wuerz Publications, Winnipeg, Manitoba, Canada) pp. 283-296.
- [11] Ivankov A. A., Tsodikov A. D. and Yakovlev A. Yu., A simulation model of tumor recurrence, *Biological Systems*, to appear.
- [12] Kalbfleisch J. D. and Prentice R. L., *The Statistical Analysis of Failure Time Data* (John Wiley & Sons, New York, 1980).
- [13] Klebanov L. B., Rachev S. T. and Yakovlev A. Yu., A stochastic model of radiation carcinogenesis: latent time distributions and their properties, *Math. Biosci.* **113** (1993) pp. 51-75.
- [14] Klebanov L. B., Rachev S. T. and Yakovlev A. Yu., On the parametric estimation of survival functions, *Statistics and Decisions* No. 3 (1993) pp. 83-102.
- [15] Kurtz J. M., Amalric R., Brandone H. et al., The prognostic significance of late local recurrence after breast conserving therapy, *Int. J. Radiat. Oncol. Biol. Phys.* **18** (1990) pp. 87-93.
- [16] Laurence A. F. and Morgan B. J. T., Observations on a stochastic model for quantal assay data, *Biometrics* **45** (1989) pp. 733-744.
- [17] Lonning P. E., Treatment of early breast cancer with conservation of the breast — a review, *Acta Oncologica* **30** (1991) pp. 779-792.
- [18] Miller R. G., *Survival Analysis* (John Wiley, New York, 1981).
- [19] Morgan B. J. T., North P. M. and Pack S. E., *Collaboration between university and industry. The Statistical Consultant in Action*, ed. by Hand D. J. and Everitt B. S. (Cambridge Univ. Press, Cambridge, 1986) pp. 134-151.
- [20] Munro T. R. and Gilbert C. W., The relation between lethal doses and radiosensitivity of tumor cells, *Br. J. Radiol.* **34** (1961) pp. 246-251.
- [21] Pepe M. S. and Fleming T. R., Weighted Kaplan-Meier statistics: a class of distance tests for censored survival data, *Biometrics* **45** (1989) pp. 497-507.
- [22] Porter E. H., The statistics of dose/cure relationships for irradiated tumours Part I, *Br. J. Radiol.* **53** (1980) pp. 210-227.
- [23] Porter E. H., The statistics of dose/cure relationships for irradiated tumours Part II, *Br. J. Radiol.* **53** (1980) pp. 336-345.
- [24] Puri P. S., A hypothetical stochastic mechanism of radiation effects in single cells: some further thoughts and results, *Probability Models and Cancer*, ed. by Le Cam L. and Neyman J. (North-Holland Publishing Company, Amsterdam, 1982) pp. 171-187.
- [25] Rachev S. T. and Yakovlev A. Yu., Random minima scheme and carcinogenic risk estimation *The Mathematical Scientist* **18** (1993) pp. 20-36.
- [26] Suit H. D., Sedlacek R., Fagundes L., Goitein M. and Rothman K. J., Time distributions of recurrences of immunogenic and nonimmunogenic tumors following local irradiation, *Radiat. Res.* **73** (1978) pp. 251-266.
- [27] Suit H. D., Shalek R. J. and Wette R., Radiation response of C3H mammary carcinoma, *Cellular Radiation Biology* (Williams & Wilkins, Baltimore, 1965) pp. 514-530.
- [28] Teicher H., Identifiability of finite mixtures, *Ann. Math. Statist.* **32** (1961) pp. 244-248.

- [29] Thames H.D., An incomplete-repair model for survival after fractionated and continuous irradiations, *Int. J. Radiat. Biol.* **47** (1985) pp. 319–339.
- [30] Thames H. D., Repair of radiation injury and the time factor in radiotherapy, *Cancer Modeling* (Marcel Dekker Inc., New York, 1987) pp. 269–314.
- [31] Tucker S. L., Thames H. D. and Taylor J. M. G., How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics? *Radiat. Res.* **124** (1990) pp. 273–282.
- [32] Turner M. M., Some classes of hit-target models, *Math. Biosci.* **23** (1975) pp. 219–235.
- [33] Yakovlev A. Yu., Letter to the Editor, *Statistics in Medicine* **13** (1994) pp. 983–986.
- [34] Yakovlev A. Yu., Asselain B., Bardou V.-J., Fourquet A., Hoang T., Rochefodiere A. and Tsodikov A. D., A simple stochastic model of tumor recurrence and its application to data on premenopausal breast cancer, in *Biometrie et Analyse de Donneés Spatio-Temporelles* No. 12, ed. by Asselain B., Boniface M., Duby C., Lopez C., Masson J. P. and Tranchefort J. (Société Française de Biométrie, ENSA Rennes, France, 1993) pp. 66–82.
- [35] Yakovlev A. Yu., Tsodikov A. D. and Bass L., A stochastic model of hormesis, *Math. Biosci.* **116** (1993) pp. 197–219.
- [36] Yakovlev A. Yu. and Zorin A. V., *Computer Simulation in Cell Radiobiology, Lecture Notes in Biomathematics* **74** (Springer Verlag, Berlin, 1988).
- [37] Yakowitz S. J. and Spragins J. D., On the identifiability of finite mixtures, *Ann. Math. Statist.* **39** (1968) pp. 209–214.
- [38] Yamaguchi K., Accelerated failure-time regression models with a regression model of surviving fraction: an application to the analysis of permanent employment in Japan, *J. Am. Stat. Assoc.* **87** (1992) pp. 284–292.
- [39] Zhigljavsky A., *Theory of Global Random Search* (Kluwer, Dordrecht, 1992).