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A parametric regression model of tumor recurrence: An application to the analysis of clinical data on breast cancer

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Abstract

A new parametric model is proposed for the regression analysis of relapse-free time data. It offers a natural classification of covariates in terms of their predominant effect either on the expected number of clonogens in a treated tumor or on the time of tumor progression. Within the framework of the model, the probability of local control is uniquely determined by the mean number of surviving clonogenic cells. Two versions of the model are considered; in one of them every mode of treatment is represented by indicator variables while in the other version the linear-quadratic model of radiation cell survival is used to describe the effect of radiotherapy. Maximum likelihood estimation of the model parameters is provided by a nonlinear programming procedure which has been shown to be computationally tractable. The results are reported of the analysis of relevant data on breast cancer recurrence after conservative treatment of the primary tumor. The most striking finding is that age of a patient exerts a very strong effect on the mean number of surviving clonogens in the ipsilateral breast, or equivalently, the probability of tumor cure, while its effect on the progression time appears to be negligible. On the other hand, the primary tumor size contributes significantly to both characteristics of tumor latency. No significant covariate effects emerged from the analysis of the contralateral breast cancer recurrence.

Keywords: Accelerated failure time model; Breast cancer; Cancer recurrence; Failure time; Parametric models; Covariates; Proportional hazards model

1. Introduction

The seminal paper by Cox (1972) gave a vigorous impetus to the widespread use of regression survival analysis in clinical studies. The proportional hazards model, and its modifications, have since been supplanting parametric regression survival models from their place in biomedical applications. This is not so surprising, since a semiparametric model is, at least partially, free from strong distributional assumptions which might result in incorrect statistical inference. On the other hand, the parametric approach has distinct strengths that outweigh its weaknesses when a model provides an adequate description of reality. One could expect this

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most for a theoretically derived model based on biologically plausible assumptions. Such a model allows interpretation in terms of parameters endowed with clear biological meaning and it may be instrumental in giving further insight into pathogenesis of human cancers.

Parametric regression has much potential for assessing the role of various prognostic factors when cure of a disease is considered possible. In this case the limiting value of the survivor function, as time tends to infinity, is greater than zero and represents the cure probability which is often called a surviving fraction, the notion being meaningful for any failure time observations. Within the parametric framework, this concept leads us to employing substochastic (improper) distributions in the analysis of time-to-failure observations. Such distributions should not necessarily be of the mixture type as discussed recently by Yakovlev (1994).

When incorporating covariates into a survival model, one may expect that some of them exert a predominant influence on the surviving fraction whereas other covariates contribute to a larger extent to the timing of the failure's occurrence (Yamaguchi, 1992). Such a distinction is essential to the understanding of the biomedical significance of various prognostic factors and parametric approach makes this feasible. The alternative is to use spline approximations of the hazard rate (Etezadi-Amoli and Ciampi, 1987). In this paper, an attempt is made to assess the effects of explanatory variables on the time to tumor recurrence, taking advantage of a simple biologically-based model (Yakovlev et al., 1993) whose structure appears to be very convenient for designing a pertinent regression model. We describe a regression version of the model and estimation of its parameters in the next section. In Section 3, an application is given to the analysis of breast cancer recurrence. Section 4 presents a brief discussion of the results of data analysis.

2. The models and estimation procedure

2.1. The basic model

According to the stochastic model of tumor recurrence (Yakovlev et al., 1993; Tsodikov et al., 1995), the relapse-free time is thought of as a random variable with the following survivor function:

$$\overline{G}(t) = \exp\{-\theta F(t)\}, \tag{1}$$

where θ is the expected number of surviving clonogenic tumor cells, also known as clonogens, after treatment, and $F(t)$ is the cumulative distribution function for the potential time of tumor progression, i.e., the time it takes for a single clonogen to propagate into a newly detectable tumor. The idea underlying this model is very simple. At the end of treatment, the number of surviving clonogens is assumed to be a Poisson random variable ν with expectation θ. Let X_i be the ith clonogen progression time. The nonnegative random variables X_i, $i = 1,2,\ldots$, are assumed to be independent and identically distributed with a common distribution function $F(t)$. This assumption is plausible if the surviving tumor clonogens are in small proportion and wide apart from each other after treatment. It counts in favor of this assumption that the values of θ estimated from time-to-recurrence observations are typically small (Ivankov et al., 1993). The tumor latency time is defined as $U = \min\{X_i, 0 \leqslant i \leqslant \nu\}$, where $\Pr\{X_0 = +\infty\} = 1$ and ν is independent of the sequence $X_1, X_2, \ldots$ It follows from the law of total probability that the survivor function for the random minimum U is given by formula (1).

Corresponding to (1) is the following hazard function:

$$\lambda(t) = \theta f(t), \tag{2}$$

where f is the density of the progression time distribution. Given the time of tumor latency to be distributed in accordance with (1), the probability of tumor cure is equal to $\overline{G}(+\infty) = \exp\{-\theta\}$, its value dependent

solely upon the expected number of clonogens. To put formula (1) to practical use in the parametric analysis of tumor recurrence, it remains to specify the progression time distribution $F(t)$. In our previous works, preference was given to the two-parameter gamma distribution by virtue of its flexibility and the fact that this parsimonuous model, very simple as it is, reflects a multistage structure of the process of tumor development. Computer simulations conducted with a comprehensive model of tumor recurrence (Ivankov et al., 1992, 1993) support this choice. In constructing a regression model, we shall proceed from this choice as well, assuming the progression time to be gamma distributed with shape parameter ρ and scale parameter μ, given a vector of covariates for an individual. Based on model (1), many analyses of real data have been performed without regard of covariates (Yakovlev et al., 1993; Ivankov et al., 1993; Asselain et al., 1994; Hanin et al., 1994; Tsodikov et al., 1995; Hoang et al., 1995). In all cases, the model provided a good description of clinical data as corroborated by the application of Hjort's goodness-of-fit test for censored observations (Hjort, 1990).

2.2. Model 1

The principal problem dealt with in the regression analysis of survival data is that of determining the relationship between the observed failure time U and a vector, $z = (z_1, \ldots, z_m)$, of m covariates which are accessible to measurement for every individual under observation. Such a relationship is commonly specified by allowing the hazard rate, $\lambda(t)$, to be a function of the covariates z. Thus, a regression survival model is formulated in terms of the conditional hazard function $\lambda(t; z)$ representing the hazard rate at time t for an individual with covariates z.

To construct a regression counterpart of model (1), introduce a p-dimensional vector z of covariates. As it was mentioned in the Introduction, some of the vector z components, in particular some of those associated with treatment (extent of surgery, irradiation regimen, etc.), may be expected to exert their effect only on the surviving fraction, i.e. the probability of tumor cure. Let x be a subvector of such covariates and r its dimensionality. The covariates constituting x are assumed to act multiplicatively on the parameter θ in formula (2) so that the conditional hazard is

$$\lambda(t; x) = \theta e^{\alpha x} f(t), \tag{3}$$

where α is a transposed vector of regression coefficients related to $x = (x_1, \ldots, x_r)$. We denote by y the rest of the vector z components and assume that they may contribute to both the cure rate and the timing of tumor recurrence. To retain the model tractability, we incorporate the time scaling factor into the progression time distribution in much the same way as in the accelerated failure time model (Yamaguchi, 1992). This gives the following extension of formula (3):

$$\lambda(t; z) = \theta e^{\alpha x + \beta y} f(t e^{-\gamma y}) e^{-\gamma y}, \tag{4}$$

where $\beta' = (\beta_1, \ldots, \beta_s)$ and $\gamma' = (\gamma_1, \ldots, \gamma_s)$, $s = p - r$, are vectors of regression parameters describing the effect of y on the surviving fraction and the progression time distribution, respectively. The regression counterpart of survivor function (1) corresponding to (4) is

$$\bar{G}(t; z) = \exp\{-\theta e^{\alpha x + \beta y} F(t e^{-\gamma y})\}. \tag{5}$$

If $\gamma = 0$ the model given by (5) is the proportional hazards model; it reduces to the accelerated failure time model when $\alpha = 0$ and $\beta = 0$ simultaneously. But in general, the model does not belong to either of these two types. By estimating α, β and γ we gain a possibility to interpret the role of various covariates in terms of their effect on the mean number of surviving clonogens and the time of tumor recurrence progression. In what follows, the model given by (5) will be referred to as Model 1.

2.3. Model 2

Let $\boldsymbol{D} = (D_1,\ldots,D_n)$ be a sequence of fractional doses and $S(D_i)$ the survival probability of a cell exposed to the dose $D_i \geqslant 0$, $i = 1,\ldots,n$. Assume that time intervals elapsing between the doses $D_1,\ldots,D_n$ are long enough for accomplishment of the transient processes of inactivation and recovery of damaged cells. Besides we assume that the repair of radiation damage is complete in the surviving cells. This implies the representation (Hanin et al., 1994):

$$S(\boldsymbol{D}) = \prod_{i=1}^{n} S(D_i).$$

In this model, the overall survival probability, $S(\boldsymbol{D})$, does not depend on the order of doses constituting a given irradiation regimen.

Some of the components of $\boldsymbol{x}$ may correspond to the effect of fractionated irradiation which is unlikely to be described by a linear function of $\boldsymbol{D}$. Confining ourselves to uniform regimens of irradiation, i.e. $D_1 = D_2 = \cdots = D_n$, we accomplish this within the framework of the linear-quadratic model (see Dale, 1990) of radiation cell survival in its simplest form:

$$S(D) = \exp\{-aD - bD^2/n\}, \tag{6}$$

where $S(D)$ is the probability of cell survival for the total dose D, n is the number of dose fractions, a and b are nonnegative constants to be estimated from a given sample. In doing so, we can frequently reduce the number of unknown parameters. The resultant regression model is of the form:

$$\overline{G}(t;z) = \exp\{-\theta e^{\alpha u+\beta y-aD-bD^2/n} F(te^{-\gamma y})\}, \tag{7}$$

where the subvector $\boldsymbol{u}$ corresponds to characteristics of treatment other than the parameters D and n. We call it Model 2 to make a distinction between the two versions of the regression model under consideration.

2.4. Estimation

For estimating the model parameters, the maximum likelihood method is a natural choice. On the assumption of an independent right censoring mechanism, the likelihood function is constructed in the ordinary way (Kalbfleisch and Prentice, 1980). To maximize the log-likelihood with respect to all the parameters incorporated in the model, we use a 3-step nonlinear programming procedure based on the random search (Zhigljavsky, 1992), the algorithm by Davidon, Fletcher and Powell (Himmelblau, 1972), and the Zoutendijk algorithm (Himmelblau, 1972). The procedure has been described at length in (Hoang et al., 1995).

3. Breast cancer recurrence

3.1. Data and statistical methods

We apply the above model to analyze data on breast cancer recurrence for 877 female patients treated and followed at the Curie Institute from 1960 to 1988. The general treatment policy for the patients was aimed at breast preservation by combining radiotherapy and limited surgery, i.e., the conservative treatment. A detailed description of the subcohort of these patients is given by Fourquet et al. (1989). The data include the localization of recurrences in terms of their occurrence in the ipsilateral (treated) breast and in the contralateral (opposite) one, the time to recurrence and the censoring index value. In our analysis, we use an extended data set with the following covariates representing the vector $\boldsymbol{y}$: y_1 – primary tumor size, y_2 – clinical axillary

Table 1
Inference based on Model 1 (full and reduced models). Pooled data for both breasts

Mode of action	Tumor size			Node status			Age			Therapy		
	χ_1^2	χ_2^2	d.f.	χ_1^2	χ_2^2	d.f.	χ_1^2	χ_2^2	d.f.	χ_1^2	χ_2^2	d.f.
Surviving fraction, full model	5.7	4.7	1	1.6	1.3	1	14	16	1	16	23	10
Progression time, full model	12	13	1	0.4	0.3	1	0.2	0.2	1	–	–	–
Surviving fraction, final model	5.3	4.8	1	–	–	–	34	32	1	16	23	10
Progression time, final model	12	13	1	–	–	–	–	–	–	–	–	–

lymph node status (nodal involvement) and y_3 – age of a patient. While the variables y_1 and y_3 are of quantitative type, y_2 is a binary variable: $y_2 = 1$ if a patient has pathologically involved axillary nodes and $y_2 = 0$ otherwise.

The vector $\boldsymbol{x}$ in Model 1 (formula (5)) is formed as to represent various treatment characteristics such as extent of surgery (2 grades), irradiation dose (3 ranges: $\leqslant 50$ Gy, 51–60 Gy, > 60 Gy) and a binary variable that describes a "*boost*" to the tumor bed, the boost-delivered irradiation dose being included in the total dose value. The above listed covariates are supposed to exert their effect on the mean number of surviving tumor clonogens, thereby affecting the probability of local control but not the progression time parameters. All of them can be expressed by the use of indicator variables. As a result we have twelve groups of patients corresponding to all possible combinations of therapy characteristics. This way of representation of the treatment variables was chosen to more adequately account for possible interactions between them; alternatively these variables could be treated separately. Some of the treatment groups thus created were found to contain too few patients. Such patients were omitted from the analysis. Their pooling with the adjacent groups does not affect the results of regression analysis. The vector $\boldsymbol{u}$ in Model 2 (formula (7)) is represented by two indicator variables for the extent of surgery and boost, respectively, which gives four therapy groups. The irradiation dose in this model is treated separately and its total value does not include the boost dose.

Asymptotic confidence limits for the regression coefficients and baseline parameters of the model are constructed using the observed information matrix whose entries have been derived analytically. Large sample theory is applied to testing statistical hypotheses as well. For this purpose we use the likelihood ratio test along with the test based on the Wald statistic (Kalbfleisch and Prentice, 1980). In the former case the corresponding statistic will be denoted by χ_1^2, in the latter case the notation χ_2^2 will be used. With the aim of selecting the most important covariates use is made of a backward stepwise regression based on the likelihood ratio statistic. We also employ the likelihood ratio in the overall significance test.

3.2. Results of data analysis

First we consider breast cancer recurrences, irrespective of their localizations. We start with Model 1 involving all of the regressor variables. Table 1 shows statistics for testing the hypothesis of no effect for each covariate. The column "d.f." indicates the degrees of freedom in the chi-square approximation of a test statistic distribution that holds for both χ_1^2 and χ_2^2 under the hypothesis being tested.

The values of χ_1^2 and χ_2^2 are in good agreement and they clearly demonstrate dissimilar effects of the covariates under study. No apparent dependence of relapse-free time on lymph node status manifests itself neither through the mean number of clonogens nor through time of recurrence progression. On the contrary, tumor size contributes significantly to both characteristics of the recurrence latency, with the null hypothesis being rejected at a significance level of less than 0.05. From Table 1 it seems clear that a distinct prognostic

Table 2
Final Model 2. Pooled data for both breasts

Mode of action	Tumor size			Age			Therapy		
	χ_1^2	χ_2^2	d.f.	χ_1^2	χ_2^2	d.f.	χ_1^2	χ_2^2	d.f.
Surviving fraction	5.4	4.8	1	36	34	1	9.3	11	3
Progression time	11	12	1	–	–	–	–	–	–

Table 3
Estimated regression coefficients for Model 1 and Model 2 after the backward elimination of covariates. Pooled data for both breasts

Model	Mode of action	Tumor size		Age	
		Estimate	Confidence limits	Estimate	Confidence limits
1	Surviving fraction	– 0.292	±0.262	– 0.050	±0.017
	Progression time	– 0.386	±0.211	–	–
2	Surviving fraction	– 0.290	±0.260	– 0.051	±0.017
	Progression time	– 0.371	±0.212	–	–

effect of treatment has been identified. An intriguing fact is that age exerts a very strong effect on the mean number of clonogens, or equivalently, the probability of tumor cure, while its influence on the time of recurrence progression appears to be negligible. The overall test gives the chi-square statistics value to be equal to 68 which is highly significant on 19 degrees of freedom. After a backward elimination of regressor variables the four of them, shown in Table 1, remain to be significant: mode of treatment, tumor size with respect to the progression time, age and tumor size with respect to the mean number of clonogens. Amongst these factors, the dependence on age of the mean number of clonogens appears to be the dominant one.

The application of Model 2 results in the same selection of prognostic factors, their contributions being very close to those obtained under Model 1. Table 2 suggests that there is no significant effect of irradiation dose. The backward elimination procedure has resulted in the same ordering of covariates as in Model 1. The estimated regression coefficients for the final versions of both models are given in Table 3.

The findings for the ipsilateral breast only (not shown) closely parallel those described above but, in a quantitative sense, the observed effects of covariates are more pronounced. This is also evidenced by the overall significance test that yields a much higher value of the test statistic, i.e., $\chi_1^2 = 108$ on 19 degrees of freedom. The backward elimination of covariates leads to the same final collection of the most important factors with the same ordering of them as in the case of pooled data. All the above conclusions remain valid for Model 2. The model does not show any noticeable effect of irradiation dose on recurrence in the ipsilateral breast. This pertains equally to its linear and quadratic dose-dependent components (formula (6)).

The results obtained for the contralateral breast only indicate a significant effect of age and of primary tumor size on the recurrence progression time in presence of the other covariates. But the backward elimination of covariates does not confirm the presumption – no significant factors remain after the completion of this procedure. The overall test does not identify strong regression effects for the contralateral breast cancer as well. Thus, we may conclude that the effects documented for the ipsilateral breast provide a large part of the explanation of the regularities uncovered by a similar analysis of the pooled data for both breasts. The analysis based on Model 2 also provides support for this view.

4. Discussion

The above findings are in complete agreement with those obtained by means of the proportional hazards model (Fourquet et al., 1989) as to the basic relationships between the factors under study. However, the application of the proposed model furnishes additional information on dissimilar effects of the selected covariates. It should be stressed that our study was concerned with the conservative management of breast cancer. For another method of treatment, results of the regression analysis may be totally different from those described above as in the case of radical mastectomy (Ewers et al., 1992).

It is not particularly surprising that the pre-treatment size of primary tumor affects the mean number of clonogens that survive the treatment. The effect of this covariate on the progression time also seems quite plausible because a more advanced tumor is likely to contain clonogenic cells more autonomous in their growth and possessing a higher resistence to immune attacks. The most striking observation as regards the selective effect of age on the mean number of surviving clonogens still awaits its biological interpretation. No effects of covariates have been found to manifest themselves in the course of the contralateral breast cancer development. Boice et al. (1992) found that radiotherapy contributes little to the already high risk of cancer in the contralateral breast. This conclusion seems plausible as applied to both the therapeutic and carcinogenic action of irradiation. Besides there are grounds (Holmberg et al., 1988; Asselain et al., 1994) to believe that cancers in both breasts develop independently of one another after the treatment, the point being consistent with the above analysis of covariates. When applied to the same data set, Cox's proportional hazards model also failed to detect any significant regressor variables. On the other hand, our result is at variance with that of Zedeler et al. (1992). They indicate a significant effect of primary tumor size on recurrence in the contralateral breast, this factor being the only one to remain after the backward elimination of covariates. This discrepancy is difficult to attribute to any special features of the two data sets, though a smaller range of tumor sizes in our study might be a part of the explanation. The difference in therapy represents another possibility. It is worth noting that the effect of age and of tumor size on the progression time in the contralateral breast was prevailing at every stage of our elimination procedure.

No sensible effect of irradiation dose was observed when Model 2 was applied to these data on breast cancer recurrence. It should be especially noted that the above two versions of the regression model (Model 1 and Model 2) lead us to conclusions which basically are very much alike. This means that the form of parametrization with respect to irradiation dose is of little consequence for the net results of the regression analysis based on this model.

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