Discrete Strategies of Cancer Post-treatment Surveillance. Estimation and Optimization Problems

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SUMMARY

We consider the cancer post-treatment surveillance to be represented by a discrete observation process with a non-zero false-negative rate. Using a simple stochastic model of cancer recurrence derived within the random minima framework, we obtain parametric estimates of both the time-to-recurrence distribution and the probability of false-negative diagnosis. Then assuming the false-negative rate known, we give a nonparametric maximum likelihood estimator for the tumor latency time distribution. When designing an optimal strategy of post-treatment surveillance, we proceed from the minimum of the expected delay in detecting tumor recurrence as a pertinent criterion of optimality. To solve this problem we give a dynamic programming algorithm. We illustrate the methods by analyzing data on breast cancer recurrence.

1. Introduction

The post-treatment cancer surveillance represents a discrete observation process yielding incomplete information on the time of tumor recurrence, i.e., instead of the accurate time of recurrence only the time of its diagnosis is available. The diagnostic time is usually discretized according to a specific schedule of examinations. Moreover, false-positives and -negatives of the diagnostic test may be present. Such samples can no longer be treated as conventional follow-up data with independent censoring. Similar estimation problems arise when screening programs are applied to a target population of seemingly asymptomatic persons for the early detection of a chronic disease and the estimation of its natural history. In recent years, mathematical modeling of screening schedules, that embody the discrete follow up, has become an accepted alternative to the epidemiological inference based on proportions. There exists a broad range of literature on parametric and nonparametric estimation of the disease natural history from discrete observations of the screening type (Zelen and Feinleib, 1969; Albert, Gertman, and Louis, 1978; Albert et al., 1978; Louis, Albert, and Heghiman, 1978; Prorock, 1984; Schwartz, 1984; Brookmeyer and Day, 1978; Flehinger and Kimmel, 1987, 1991). The nonparametric approach is of limited utility, because the available information is usually too sparse as compared to the number of parameters to be estimated. On the other hand parametric models that have been proposed are essentially phenomenological, the majority of them being predominantly concerned with case-control studies with a focus on epidemiological biases. Nevertheless, the parametric approach to the statistical problems associated with screening or discrete follow-up studies seems to be most promising and deserving of further elaboration.

It is obvious that a more reliable and substantive inference from real data on tumor recurrence might be provided by using biologically based models, rather than by selecting a suitable latent time distribution among standard parametric families. Surprisingly, such models are a rarity in the literature on cancer surveillance. In an effort to obtain further insight into the regularities in tumor recurrence, we proposed a simple stochastic model incorporating parameters that have clear biological meaning (Yakovlev et al., 1993). In this work, the tumor latency was described within the random minima framework along the lines of the model of carcinogenesis proposed by Klebanov,

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Rachev, and Yakovlev (1993). The model enabled us to obtain some unobservable characteristics of breast cancer recurrences, in particular, we estimated the expected number of clonogens, giving rise to early and late recurrences, and their progression rate parameters. Besides, the model makes it feasible to discriminate between true recurrence and spontaneous carcinogenesis (a new cancer of the same histological type) on the basis of the temporal characteristics of the tumor latency. As evidenced by this analysis, the contralateral breast cancer may be interpreted as a pre-existing subclinical tumor at the time of treatment (Ivankov et al., 1993).

When analyzing the data on breast cancer recurrence, we proceeded from the continuous follow-up assumption and applied the corresponding methods of survival analysis (Kalbfleisch and Prentice, 1980), thereby neglecting the pattern of the diagnostic time discretization. In the present paper we extend this approach to allow for the discrete follow-up process. The parametric model of tumor recurrence is briefly described in Section 2. The maximum likelihood estimation of the model parameters is given in Section 3. This method allows the estimation of not only the numerical parameters of tumor latency but the value of detection probability as well. The cofidence limits for the model parameters are obtained on the basis of the asymptotic likelihood theory. It is always desirable to compare the parametric estimate with the nonparametric one. The ordinary life-table estimator is no longer suitable for this purpose under conditions of the discrete surveillance strategy. But, assuming that the detection probability for the diagnostic test is known, we develop a nonparametric estimator for the time-to-tumor distribution which has its origin in the life-table methodology.

Having identified a parametric model of tumor latency, one may formulate the problem of optimal cancer surveillance as proposed by some authors (Parmigiani, 1991; Tsodikov and Yakovlev, 1991; Tsodikov, Yakovlev, and Petukhov, 1991; Tsodikov, 1992). We use the minimum expected delay time approach (Tsodikov and Yakovlev, 1991) and a dynamic programming algorithm for this purpose in Section 4. In Section 5 an application is presented to the breast cancer recurrence in patients treated and followed up at the Curie Institute.

2. The Model of Cancer Recurrence

In this section we outline briefly the main idea of the parametric model that was proposed earlier (Yakovlev et al., 1993). 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 clonal growth, and thus to tumor regeneration. The initial number of clonogens, ν, is thought of as a Poisson random variable (r.v.) with expectation θ (Munro and Gilbert, 1961; Porter, 1980a; 1980b; Suit et al., 1978; Suit, Shalek, and Wette, 1965; Yakovlev, 1993).

Let X_i be a random time for the ith clonogen to produce an overt tumor. By analogy with the terminology accepted in carcinogenesis studies we call X_i a potential progression time. The non-negative r.v.'s X_i, $i = 1, 2, \ldots$, are assumed to be independently and identically distributed with a common cumulative distribution function (c.d.f.) $F(t)$. This assumption is quite natural if the surviving tumor clonogens are in small proportion and wide apart from each other which is likely to occur in a treated tumor. 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. Let Φ stand for its c.d.f. If ν is a Poisson r.v. independent of the sequence $X_1, X_2, \ldots$, the survival function, $\bar{\Phi}(t) = 1 - \Phi(t)$, for the r.v. U can be obtained easily:

$$\bar{\Phi}(t) = \sum_{k=0}^{\infty} \frac{\theta^k}{k!} e^{-\theta}[1 - F(t)]^k = e^{-\theta F(t)}. \tag{1}$$

The key advantage of expression (1) is to show explicitly the contribution of the two distinct characteristics of tumor growth: the expected number of surviving clonogens θ and the rate of their progression described by the c.d.f. $F(t)$. Estimation of both characteristics is feasible and furnishes additional information on the biology of tumor recurrence, thereby offering a more refined interpretation of observational data. Another advantage is due to the fact that survival function (1) corresponds to an improper (substochastic) distribution and its limiting value $\bar{\Phi}(+\infty) = \exp(-\theta)$ represents the probability of tumor cure (no recurrence) or the surviving fraction. The difficulties associated with the estimation of surviving fraction from censored observations within the non-

parametric framework are well known (Pepe and Fleming, 1989; Cantor and Shuster, 1992). Most parametric survival models implicitly assume a zero limiting survival probability (Kalbfleisch and Prentice, 1980; Cox and Oakes, 1983; Cohen and Whitten, 1988). The importance of allowing for a surviving fraction in failure-time models has been recognized by many authors (Miller (1981), Laurence and Morgan (1989), Laska and Meisner (1992), Yamaguchi (1992), to name a few). Within the parametric framework, this concept leads us to employing improper distributions in the analysis of failure time data. Such distributions should not necessarily be of the mixture type as discussed recently by Yakovlev (1994). The model given by (1) allows for the surviving fraction in a natural way.

The hazard function $\lambda(t)$ defined with respect to $\Phi(t)$ is

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

where f is the density of the c.d.f. F. If the progression time distribution F is unimodal, then $\lambda(t)$ has a maximum. Note that the assumption on the exponential c.d.f. $F(t)$ should be rejected since that would correspond to the unrealistic case of a monotone decreasing hazard.

To describe heterogeneity of clonogens with respect to the progression time distribution, we introduce k distinct types of clonogens with c.d.f.'s $F_j(t)$, their proportions being equal to c_j, $j = 1, \ldots, k$. The progression time distribution is represented by a finite mixture

$$F(t) = \sum_{j=1}^{k} c_j F_j(t),\ 0 < c_j < 1,\ \sum_{j=1}^{k} c_j = 1. \tag{2}$$

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

$$\bar{\Phi}(t) = \prod_{j=1}^{k} \exp[-\theta_0 c_j F_j(t)], \tag{3}$$

where θ_0 is the expected total number of clonogens of various types existing in the treated tumor. The corresponding hazard functions λ_j are additive and hence

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

In view of the last formula, it is not suprising that the bimodal shape of the hazard function arises when recurrences originate from two distinct subpopulations of progenitor cells as shown for the ipsilateral breast cancer (Ivankov et al., 1993).

Parametric representation of the progression time distribution in formulas (1) and (3) is still an unsettled problem. In this work, preference is given to the two-parameter gamma distribution by virtue of its flexibility and the fact that this parsimonious model, very simple as it is, reflects a multi-stage structure of the process of tumor development. There are two other reasons for such a choice. First, finite mixtures (2) of gamma distributions are identifiable (Teicher, 1961; Yakowitz and Spragins, 1968), and so are the competing risks models of type (3) when applied to describing tumors arising from a heterogeneous population of clonogens. Second, computer simulations were conducted (Ivankov et al., 1992; 1993) to provide a realistic description of biological processes underlying tumor promotion and progression at the cellular level: proliferation, differentiation, and death of tumor cells, along with growth control in neoplastic tissues. A good fit was demonstrated of a gamma distribution to the samples of progression times generated in this simulation study. For the reasons given above, we use a gamma distributed progression time in all the computations presented in Section 5.

3. Estimation of Parameters

Let τ_i, $i = 1, \ldots, n$, be the time points at which the patients are examined repeatedly following treatment. They satisfy the inequalities $\tau_0 = 0 \leq \tau_1 \leq \cdots \leq \tau_n \leq T$, where $\tau_0 = 0$ is the treatment time and T the planning period of observation. The set $S_n = \{\tau_i\}_{i=1}^{n}$ will be referred to as the surveillance strategy. Each individual is assumed to follow one and the same strategy of surveillance; otherwise the target population should be stratified with respect to the strategy. A diagnostic test is characterized by the false-negative rate $q = 1 - p$, where p is the detection probability. We assume that q is constant for a given surveillance strategy. Since all patients with the false-positive diagnosis are usually returned to the surveillance process by the time of the next examination, the

false-positive rate is set to be zero. The tumor recurrence remains latent until either it is detected or a censoring event occurs. Let G be the c.d.f. for the time to censoring event that is considered as an independent competing risk with respect to the recurrence under study. We aggregate all censored data in each interval $[\tau_{i-1}, \tau_i)$, relating them to the point τ_{i-1}, for the following reason. Suppose $P(U = \tau_i) = 0$, $i = 1, \ldots, n$. If the censoring event occurs within $[\tau_{i-1}, \tau_i)$ then the patient has no chance to be detected at τ_i irrespective of whether this event is prior to cancer recurrence or not (or whether it is placed at τ_{i-1}).

At the end of the study, the typical sample is represented by the numbers m_i, n_i, N, where m_i is the number of patients with cancer recurrence detected at time τ_i, $i = 1, \ldots, n$ (recurrence prevalence at the ith examination); n_i the number of patients censored in the interval $[\tau_{i-1}, \tau_i)$, $i = 1, \ldots, n$; N the total size of the population under surveillance.

For any function R, introduce the following notation: $\bar{R} = 1 - R$; $R_k = R(\tau_k)$; $\Delta R_k = R(\tau_k) - R(\tau_{k-1})$. The log-likelihood for the sample under consideration is

$$1 = \sum_{j=1}^{n} \left\{ m_i \log \left[\sum_{k=1}^{i} \Delta F_k \bar{G}_i q^{i-k} p \right] + n_i \log \left[\Delta G_i \left(\bar{\Phi}_{i-1} + \sum_{k=1}^{i-1} \Delta \Phi_k q^{i-k} \right) \right] \right\}$$
$$+ \left[N - \sum_{i=1}^{n} (m_i + n_i) \right] \log \left[\bar{G}_n \left(\bar{\Phi}_n + \sum_{k=1}^{n} \Delta \Phi_k q^{n-k+1} \right) \right]. \tag{4}$$

Let Q_i be the probability of tumor detection by the time τ_i in the absence of censoring. Then $\bar{Q}_0 = 1$ and

$$\Delta Q_i = \sum_{k=1}^{i} \Delta \Phi_k q^{i-k} p, \qquad i = 1, \ldots, n. \tag{5}$$

Now it is possible to represent (4) as the sum of two log-likelihoods of the life-table type

$$1 = 1_1(G) + 1_2(Q),$$

where

$$1_1(G) = \sum_{i=1}^{n} (m_i \log \bar{G}_i + n_i \log \Delta G_i) + N_n \log \bar{G}_n,$$

$$1_2(Q) = \sum_{i=1}^{n} (m_i \log \Delta Q_i + n_i \log \bar{Q}_{i-1}) + N_n \bar{Q}_n,$$

$$N_n = N - \sum_{i=1}^{n} (m_i + n_i),$$

and ΔQ_i is given by (5).

To obtain the parametric estimate of the c.d.f. Φ, one has to maximize $1_2(Q)$ with respect to the detection probability p and the numerical parameters incorporated in the latent time distribution given by (3). This problem may be solved by a three-step optimization procedure based on random search, the algorithm of Davidon, Fletcher, and Powell, and the Zoutendijk algorithm (for details see Himmelblau (1972)).

To construct a nonparametric estimate for the survival function, we use the invariance property of the maximum likelihood estimator (MLE). Assume that p is known. For the MLE values $\Delta\hat{\Phi}_i$ of $\Delta\Phi_i$, $i = 1, \ldots, n$, the following recurrence relations hold

$$\Delta\hat{\Phi}_1 = \hat{\Phi}_1 = \frac{m_i}{p(N - n_1)}$$

$$\Delta\hat{Q}_1 = \frac{m_1}{N - n_1}$$

$$\Delta\hat{\Phi}_i = \frac{1}{p}(\Delta\hat{Q}_i - q\Delta\hat{Q}_{i-1})$$

$$\Delta\hat{Q}_i = m_i\left(\frac{m_{i-1}}{\Delta\hat{Q}_{i-1}} - \frac{n_i}{1 - \sum_{k=1}^{i-1}\Delta\hat{Q}_k}\right)^{-1}, \tag{6}$$

for $i = 2, \ldots, n$.

Note that should p be estimated using (6) with the same sample, it would be unidentifiable. To see this, consider another way to derive (6). Take the distribution of individual histories as a multinomal distribution whose MLE probabilities are equal to the observed frequencies. Then

$$\bar{G}_i \sum_{k=1}^{i} \Delta\Phi_k q^{i-k} p = \frac{m_i}{N}$$

$$\Delta G_i\left[1 - \sum_{j=1}^{i} \Delta\Phi_j(1 - q^{i-j})\right] = \frac{n_i}{N}, \tag{7}$$

for $i = 1, \ldots, n$. Since (7) contains $2n$ equations for $2n + 1$ unknowns, p cannot be obtained. To overcome this difficulty, one might substitute the parametric MLE for p in (6).

The expression for $\Delta\hat{Q}_i$ in (6) is just another form of the life-table estimator for $\bar{Q}$ when censored observations within each interval $[\tau_{j-1}, \tau_i)$ are related to its origin. We may write

$$\hat{\bar{Q}}_i = \prod_{j=1}^{i} r_j$$

with

$$r_j = \frac{N - \sum_{k=1}^{i}(m_k + n_k)}{N - \sum_{k=1}^{j-1}(m_k + n_k) - n_j}. \tag{8}$$

The denominator of the estimator r_j for the corresponding conditional survival probability in (8) represents the population size at τ_{j-1} reduced by the number of those cases that are censored in the interval $[\tau_{j-1}, \tau_j)$ and bring no information on the probability $\bar{Q}_i$.

The estimator $\Delta\hat{\Phi}_i$ being a linear combination of $\Delta\hat{Q}_i$ and $\Delta\hat{Q}_{i-1}$, its consistency and asymptotic unbiasedness follow from the properties of the life-table estimator.

4. Optimal Surveillance Strategy

Let A be a r.v. representing the time of recurrence detection conditional on $\{U < T\}$. We assume that $A = T$, if the tumor recurrence remains latent up to $\tau_n + 0$. If the censoring effects are independent of both the tumor latency and the surveillance process they do not need to be taken into account when designing the optimal strategy S_n^* (Tsodikov and Yakovlev, 1991). We now introduce the r.v.

$$D = \begin{cases} A - U, & U < T \\ 0, & U \geq T, \end{cases}$$

that describes the delay between the actual recurrence and its detection. We call D the delay time. Then we are in a position to formulate the optimal surveillance problem as the search for a strategy S_n^* that provides

$$\min_{S_n} \mathbf{E}(D) \tag{9}$$

for a fixed value of n. The well-known results of reliability theory (Barlow and Proschan, 1964; Beichelt and Franken, 1983) cannot immediately be applied to this problem as they are confined to the case $p = 1$. It can be shown (Tsodikov and Yakovlev, 1991) that

$$\mathbf{E}(D) = \int_0^T V(t)\, dt,$$

where $V(t) = \mathbf{P}$ {an individual is ill at time t but undetected}. Furthermore, when self-detection can be neglected, problem (9) is equivalent to

$$\min_{S_n} I(S_n), \tag{10}$$

where

$$I(S_n) = \sum_{k=1}^{n+1} [V(\tau_{k-1} + 0) + \bar{\Phi}(\tau_{k-1})]\Delta\tau_k$$

and n is fixed. In our particular case

$$I(S_n) = \sum_{k=1}^{n+1} \Delta\tau_k \bar{Q}_{k-1}, \quad \tau_{n+1} = T.$$

It is natural to consider the values of τ_i belonging to the grid $\{\sigma k\}_{k=1}^{k_{\max}}$ on the interval $[0, T]$, $\sigma = T/k_{\max}$, i.e. σ is a time unit in terms of which the time to tumor is registered. By looking over all possible combinations of $\{\tau_i\}$ on the grid the solution of (10) can be found. Owing to the structure of the functional I given by

$$I = \sum_{k=1}^{n+1} \varphi_{k-1}(\tau_1, \ldots, \tau_k), \qquad \varphi_{k-1} = \Delta\tau_k \bar{Q}_{k-1}$$

an exhaustive search algorithm can be constructed in a way that only a part of the functional I be computed at each step. If φ_{k-1} were dependent only on τ_{k-1} and τ_k (which is the case with $p = 1$), it would be possible to reduce the exhaustive search procedure to a dynamic programming one. This might also be an approximate solution when p is close to 1 and τ_{k-1} constitute the most part of the dependence of φ_{k-1} on the past as in the example that follows below (Section 5).

Let S_m^*, $m \leq n$ be the optimal solution to the problem

$$\min_{0 \leq \tau_1 \leq \cdots \leq \tau_m \leq \tau_{m+1}} I(S_m).$$

Consider the value $I(S_m^*)$ as a function of τ_{m+1}, i.e.,

$$I(S_m^*) = \psi_m(\tau_{m+1}).$$

Then for S_{m+1}^* we have

$$I(S_{m+1}^*) = \psi_{m+1}(\tau_{m+2}) = \min_{\tau_{m+1}} \{\psi_m(\tau_{m+1}) + \varphi_{m+1}(\tau_1, \ldots, \tau_{m+2})\}, \tag{11}$$

where $0 \leq \tau_1 \leq \cdots \leq \tau_{m+1} \leq \tau_{m+2}$. Solving (11) with respect to τ_{m+1}, we obtain $\psi_{m+1}(\tau_{m+2})$ as a function of τ_{m+2}. Starting from $k = 1$, we proceed with $\psi_k(\tau_{k+1})$ until $k = n$. Setting $\tau_{n+1} = T$ in $\psi_n(\tau_{n+1})$, we obtain the optimal value I^* and the optimal strategy S_n^*.

At step $m + 1$, to obtain φ_{m+1} maximum use is made of the computations at step m. In (11) a minimum is searched for with respect to τ_{m+1}, the values $\psi_m(\tau_{m+1})$ and $\bar{Q}_m$ being known. It suffices to evaluate the only term dependent on τ_{m+1}, $\Delta\Phi_{m+1}$, in the expression for φ_{m+1} according to the recursive relations

$$\bar{Q}_{m+1} = \bar{Q}_m - \Delta Q_{m+1}$$

$$\Delta Q_{m+1} = q\Delta Q_m + p\Delta\Phi_{m+1}.$$

In some circumstances, ethics or other medical reasons such as monitoring side effects might dictate constraints on the distribution of examinations within the planning period. The previous procedure can be modified easily as follows. Consider a partition $[t_{i-1}, t_i)$, $i = 1, \ldots, k$, of the interval $[0, T]$. Let the number of examinations in each subinterval be bounded by n_i, $\Sigma_{i=1}^k n_i = n$. Then the domain $0 \leq \tau_{m+1} \leq \tau_{m+2}$ in expression (11) is replaced by

$$t_{i-1} \leq \tau_{m+1} \leq \tau_{m+2}, \qquad \text{if } \sum_{j=1}^{i-2} n_j \leq m \leq \sum_{j=1}^{i-1} n_j - 2$$

and

$$t_{i-1} \leq \tau_{m+1} \leq t_i, \qquad \text{if } m = \sum_{j=1}^{i-1} n_j - 1, \qquad n_{i-1} \geq 1$$

for some $i \leq k$.

5. Example: Breast Cancer Data

We apply the method to analyze data on breast cancer recurrence for 877 patients treated and followed up at the Curie Institute from 1960 to 1988. Description of the subcohort is given by Fourquet et al. (1989). The data include local failure times and the censoring index values. Since in the majority of cases the recurrence in the treated breast is not accompanied by or occurs prior to that in the contralateral breast we confine ourselves to studying surveillance of the ipsilateral breast cancer recurrence. As mentioned in Section 2, we use gamma distributions with shape parameters α_j and scale parameters β_j, $j = 1, \ldots, k$, to specify the progression time distributions $F_j(t)$ in the survival function (3). To simplify the computations, the search for the values of α_j that maximize the log-likelihood l_2 is limited to the set of positive integers. For the mean number of clonogens of the jth type we use the notation $\theta_j = c_j\theta_0$, $j = 1, \ldots, k$.

Proceeding from the assumption that the data represent the regular follow-up study, we identified model (3) for $k = 2$ (Ivankov et al., 1993), i.e., for two competing subpopulations of clonogens giving rise to the tumor recurrence (Table 1). The goodness of fit test developed by Hjort (1990) for censored observations does not reject the null hypothesis at a significance level of .1. After the treatment, the current practice of recurrence surveillance at the Curie Institute is to examine the patients:

—once per semester for the first 4 years;
—once per year for the next 6 years; and
—once every 2 years for the remaining period.

For this strategy, the estimate of the false-negative rate appears to be $\hat{q} = .2$ which is consistent with the estimate obtained by other means (Day and Walter, 1984).

Table 1

Estimates of the model parameters for discrete surveillance and regular follow up. Data on the ipsilateral breast cancer recurrence.

	Surveillance strategy		Follow up	
Parameter	Estimate	Asymptotic confidence interval	Estimate	Asymptotic confidence interval
θ_1	.13	.09, .17	.11	.08, .14
α_1	3.00	1.73, 4.27	4.00	3.52, 4.48
β_1	.051	.018, .084	.076	.064, .088
θ_2	.87	.00, 2.86	1.07	.00, 3.19
α_2	11.00	8.31, 13.69	5.00	1.33, 8.67
β_2	.038	.013, .063	.012	.000, .027
p	.80	.77, .83		

The results in Table 1 show that, when the discrete surveillance is taken into account, the parameter estimates describing the rapidly evolving subpopulation of clonogens differ but slightly from those obtained under the regular follow-up conditions. The discrepancy between the two sets of estimates is somewhat more pronounced for the slowly evolving subpopulation, but these estimates are expected to be less reliable because of the censoring effects. Shown in Figure 1 are parametric and non-parametric estimates of the time-to-recurrence distribution $\Phi(t)$. Both estimates are constructed for the currently practiced surveillance strategy consisting of 19 examinations.

Using the estimated c.d.f. $\Phi(t)$, the optimal strategy can be computed for the same number of tests. Table 2 shows a 33% reduction in the expected delay time or alternatively a similar delay as in the current surveillance practice with 13 instead of 19 examinations. The parametric estimate of the hazard function based on model (3) for $k = 2$ is depicted in Figure 2. One can see in this figure that the tests comprising the optimal surveillance tend to be more frequent when the hazard is high. It is generally believed that the early recurrence of breast cancer carries poorer individual prognosis

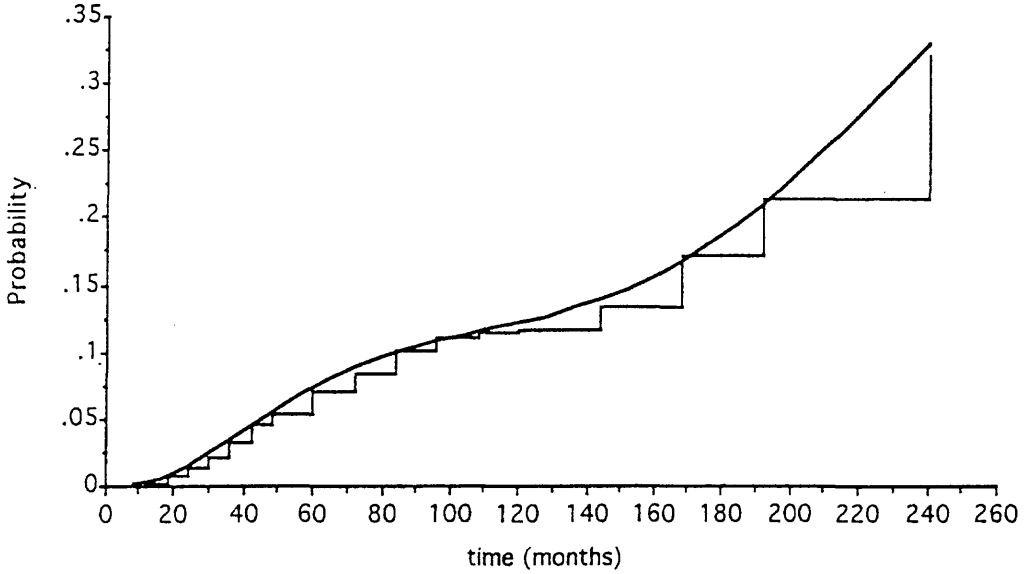

Figure 1. Parametric and nonparametric estimates of the time-to-recurrence distribution function.

Table 2
Optimal strategies for the breast cancer surveillance

Test	Time points $\{\tau_i\}_{i=1}^{i=n}$ for examination of patients (months)		
	Currently used strategy n = 19	Optimal strategy n = 19	Optimal strategy n = 13
1	6	24	30
2	12	35	45
3	18	45	61
4	24	56	79
5	30	67	101
6	36	80	127
7	42	94	152
8	48	111	171
9	60	129	187
10	72	145	201
11	84	159	213
12	96	171	225
13	108	181	240
14	120	190	
15	144	199	
16	168	209	
17	192	219	
18	216	229	
19	240	240	
Expected delay time (months)	4.10	2.75	3.93

than the late one. The proposed approach, in its present form, does not allow for a dissimilar relative importance of detecting early and late recurrences. This might be an issue for future research.

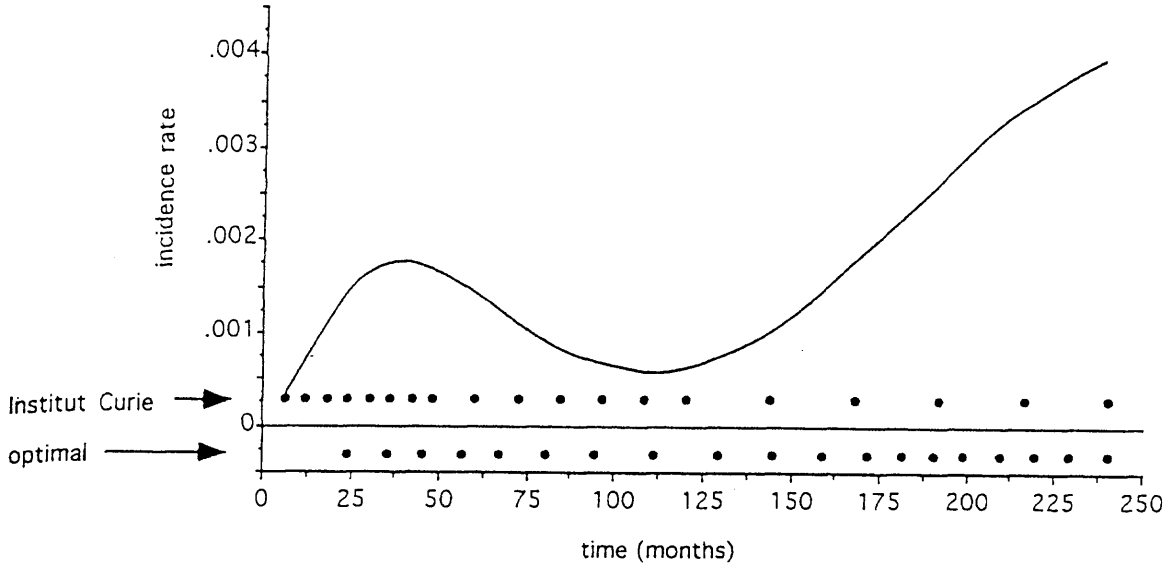

Figure 2. Surveillance strategies and parametric estimate of incidence rate. Dots on the upper line represent the surveillance times as currently practiced at Institut Curie; dots on the lower line represent the optimal surveillance times based on the parametric model of breast cancer recurrence. The curve is the parametric estimate of the incidence rate.

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RÉSUMÉ

Nous considérons la surveillance apres traitement d'un cancer comme un processus d'observation discret associé a un taux de faux negatifs non nul. A l'aide d'une modélisation stochastique simple du risque de recidive du cancer, dérivée d'un schema de randomisation aléatoire, nous obtenons simultanément la distribution des délais de recidive et la probabilité d'un diagnostic faussement négatif. Partant alors d'un taux de faux negatifs connu, nous proposons un estimateur non paramétrique du temps de latence tumorale base sur la méthode du maximum de vraisemblance. Pour établir une stratégie optimale de suivi apres traitement, nous proposons comme critère d'optimisation pertinent la minimisation du retard a la detection d'une recidive tumorale. Pour résoudre ce problème, nous utilisons un algorithme de programmation dynamique. Les méthodes sont illustrées par un exemple portant sur les récidives de cancer du sein.

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