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COMPUTER SIMULATION OF TUMOR RECURRENCE

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ABSTRACT

Computer simulations have been conducted to provide a realistic model of tumor recurrence in a cancer patient, following treatment. The simulation model incorporates description of the temporal organization of various biological processes underlying tumor development at the cellular level: proliferation, differentiation, death of tumor cells, growth control in neoplastic tissues along with the tumor treatment effect. The prime object of our concern is whether the simple parametric model of tumor recurrence proposed by Hoang *et al.* [6] allows estimation of actual value of the tumor growth potential. A good fit has been demonstrated of the parametric model when applied to the samples of simulated tumor recurrence times as well as to real data samples of tumor recurrence in breast cancer patients with various regimen of radiotherapy.

Keywords: Stochastic models, computer simulation, tumor recurrence, breast cancer.

1. Introduction

According to the stochastic model of tumor recurrence proposed by Hoang *et al.* [6], the relapse-free time is thought of as a random variable with the following survivor function

$$\bar{G}(t) = \exp\{-\theta F(t)\}, \tag{1.1}$$

where θ is the expected number of surviving clonogenic tumor cells, also known as clonogens, after the treatment, and $F(t)$ is the cumulative distribution function for the potential time of tumor progression, i.e., the time it takes 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

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distributed with a common distribution function $F(t)$. The tumor latency time can be defined as

$$U = \min\{X_i, 0 \le i \le \nu\},$$

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 (1.1). Given the time of tumor latency distributed in accordance with (1.1), the probability of tumor cure is equal to $\bar{G}(+\infty) = \exp\{-\theta\}$, its value being dependent solely upon the expected number of clonogens.

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

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

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

$$\bar{G}(t) = \prod_{j=1}^{k} \exp\big(-\theta_j F_j(t)\big), \tag{1.2}$$

where $\theta_j = \theta_0 q_j$ and θ_0 is the expected total number of viable clonogens of various types existing in the treated tumor.

To put formulas (1.1) and (1.2) to practical use, it remains to specify the progression time distribution. In the work of Hoang *et al.* [6], preference was given to the two-parameter gamma distribution by virtue of its flexibility and the fact that this parsimonuous model, simple as it is, reflects a multistage structure of the process of tumor development. Computer simulations conducted with a comprehensive model of tumor progression [7] add substantially to our confidence in using gamma distribution for the function $F(t)$ in formula (1.1). In a like manner, one may validate the basic structure of model (1.1) that describes the time to tumor recurrence dependent on the number of surviving clonogens. This would call for an extension of the simulation model, given in our previous paper [7], by incorporating a description of the tumor treatment effect. The main problem in question is whether or not the simple parametric model of tumor recurrence allows estimation of actual value of the tumor growth potential, i.e., the mean number of surviving clonogenic cells. A computer simulation study described in Secs. 2 and 3 has been undertaken to answer this question. Applications to the analysis of clinical data on breast cancer are given in Sec. 4.

2. A Simulation Model of Tumor Recurrence

When constructing the model of clonal expansion we proceed from the following premises:

1. A proliferating cell, in its passage through the mitotic cycle, is delayed for this cycle duration which is assumed to be a gamma-distributed random variable with shape parameter δ and scale parameter ρ . Thus the mean and the standard deviation of the mitotic cycle duration are equal to $\tau = \frac{\delta}{\rho}$ and $\sigma = \frac{\sqrt{\delta}}{\rho}$, respectively. No possibility is allowed for a cell to enter the resting phase before mitosis.

2. As a result of mitosis two daughter cells arise which either retain the capacity for further reproduction or become sterile and die the reproductive type of death. Three possible outcomes of the mitotic cycle, for irradiated tumor cells, are taken into account:

(i) both daughter cells retain the reproductive capacity;
(ii) both daughter cells are sterile;
(iii) one of the daughter cells is capable of proliferation, the other one is sterile.

Each of the above events occurs with the probabilities p_1, p_2 and p_3, $\sum_{i=1}^{3} p_i = 1$, respectively. The sterile cell is delayed for a random time obeying the exponential distribution with parameter λ. After a lapse of this time the sterile cell is eliminated from the clone.

3. Immediately after completion of the mitotic cycle every nonsterile cell goes to the resting phase and stays there until it is stimulated to either proliferation or terminal differentiation, the latter process resulting in the competence of a cell for specialized tissue functions and eventually in its death. Initial steps of cell differentiation (or maturation) are known to be reversible; they correspond to "deepening" of the resting phase documented for cell cultures [1, 2]. We introduce three stages of reversible differentiation, their durations being exponentially distributed with parameter μ. A cell loses the capacity for proliferation after its passage through the third stage. The reverse process is modeled by the backward passage of a cell through the stages already passed (including the one it is staying at the moment) in the course of differentiation, and by its subsequent transition to the phase G_1 of the mitotic cycle. The temporal parameters of forward and backward passages are assumed identical. By dedifferentiation we mean transformation of a reversibly differentiated cell into a proliferating one. This fits the concept of transformation period detected in systems with induced cell proliferation [12]. The fraction, d , of the resting cells set off to differentiation is assumed to be constant in time and independent of the total number of tumor cells.

4. To simulate the growth control mechanism operating in a neoplastic tissue we specify the fraction of cells entering the mitotic cycle by

$$r = \frac{1}{1 + aN^b}, \tag{2.1}$$

where a and b are constants, N is obtained by summing up the cells in all stages of their life cycle, i.e., proliferating, differentiating , resting and dying cells. If the value rN exceeds the current number of resting cells then some reversibly differentiated

cells start the dedifferentiation process, the top priority being assigned to the cell whose differentiation process is the least advanced.
To simulate the effect of fractionated irradiation the above assumptions are supplemented with the following ones:

5. Let a sequence of fractional doses $D_1, D_2, \ldots, D_n$ represent the irradiation regimen. We begin with modeling the events occurring in a population of tumor cells after the first irradiation. In doing so, we use a *multihit-one target* model of radiation cell survival [10] specified by the following survivor function

$$S(D) = \sum_{k=0}^{m} \frac{(xD)^k}{k!} e^{-xD}, \tag{2.2}$$

where D is the irradiation dose, x is the mean number of hits per unit dose, m is the critical number of hits a cell can bear without being killed. In applying expression (2.2) of the dose-effect relationship to simulation of irradiated cell kinetics, we proceed from a somewhat different interpretation of its parameters which will become evident subsequently.

With probability $1-S(D_1)$ every irradiated cell is classified as *damaged*, and with probability $S(D_1)$ it is considered as remaining *undamaged* after the first fractional dose. The parameter m value is taken to be the same for all phases of the cell cycle but the other parameter of radiosensitivity, x, is allowed to vary with the position of a cell in its life cycle. To specify such variations a baseline value, x_0, of the parameter x is chosen. This value is multiplied by a scale factor with values depending on the cell cycle phase. More specifically, we set this factor equal to 1.0, 1.5 and 1.0 for the phases G_1, S, and $G_2 + M$, respectively. For the differentiation stages, as well as for the G_0-phase, the factor is assigned a value of 0.5.

The second irradiation is simulated similarly, except that the parameter m is set equal to 1 for all damaged cells and those found to be *dead* are eliminated from the model (interphase type of death). The simulation model is designed in such a way as to allow for a gradual increase of the parameter x_0 for undamaged cells with increasing the current total dose of irradiation. Both the undamaged and damaged cells enter the value of N in formula (2.1).

6. After every fraction of irradiation, each cell, no matter whether it is damaged or not, is delayed in its passage through the mitotic cycle. The radiation induced blocks $G_1 \to S, S \to G_2, G_2 \to M$ are introduced in the simulation model under discussion in much the same way as that was employed in the book by Yakovlev and Zorin [11]. The delay time, T, for every block is dependent on the fractional dose D_i, the dependence being specified by the following simple formula

$$T = T_0(1 - e^{-vD_i}),\ i = 1, \ldots, n,$$

where T_0 and v vary depending on the mitotic cycle phase wherein a given cell is exposed to the dose D_i.

7. The processes of repair or reproductive death occur just prior to the mitotic division of a damaged cell. The enzymatic repair of radiation damage manifests as the transition of a damaged cell to the pool of undamaged cells. The probability, P, of this event is given by

$$P = P_{\max} \frac{ht^2}{1 + ht^2},$$

where h is a positive constant, and t is the time measured from the last irradiation. With probability η, every unrepaired cell is transferred to the pool of perishing cells from which it is subsequently eliminated after an exponentially distributed delay with mean $1/\lambda$. With probability $1 - \eta$, the unrepaired cell splits into two daughter cells entering the G_0 phase immediately afterwards. Undamaged cells die the reproductive type of death following the rules identical to those for unirradiated cells (Assumptions 1–4).

8. Each of a large number of tumors is initialized independently to contain a single progenitor cell. Irradiation is initiated at a prescribed tumor size. With the simulation of an irradiation regimen completed, the clonal growth of irradiated tumor cells is simulated until the size, N_c, of a detectable tumor is attained. Replicates of the simulation experiment yield an output sample consisting of times to tumor recurrence measured from the last irradiation.

3. A Computer Simulation Study

In this study, a uniform regimen of fractionated irradiation was simulated, i.e. $D_1 = D_2 = \cdots = D_n = D$. The value of D was taken equal to 7 Gy (Grays). This number should be considered as arbitrary though it provides, in combination with other parameter values, a reasonably good description of reality. We are not striving to produce quantitative results as close to a particular dose-effect relationship as possible.

The following plausible values of the model parameters were prescribed: $\tau = 24, \sigma = 7.4$ (for the mitotic cycle phases: $\tau(G_1) = 12, \sigma(G_1) = 6; \tau(S) = 7, \sigma(S) = 3.5; \tau(G_2 + M) = 5, \sigma(G_2 + M) = 2.5), x_0 = 1.5, T_0(G_1 \to S) = 100, T_0(S \to G_2) = 140, T_0(G_2 \to M) = 160, v(G_1 \to S) = v(S \to G_2) = v(G_2 \to M) = 0.01, P_{\max} = 0.2, h = 0.25, a = 1.3 \times 10^{-10}, b = 2, \lambda = 0.01, \mu = 0.02, d = 0.2, p_1 = 0.95, p_2 = 0.04, p_3 = 0.01, \eta = 0.5$.

The value of N_c was set equal to 10^6. The irradiation was initiated when the number of tumor cells attained a value of 0.8×10^6.

There is not a grain of evidence that the simple parametric model of tumor recurrence, expressed by (1.1), will be consistent with data generated by the comprehensive simulation model. But this does happen as shown by results of the computer simulations given below.

When the number of fractions was varied from 10 to 15, six samples were generated, each containing 950 values of the time to tumor recurrence. Each of the samples was individually centered with respect to the initial recurrence-free period.

With these samples the parametric model of tumor recurrence was validated, for which purpose the c.d.f. $F(t)$ in formula (1.1) was specified by the generalized gamma distribution [9] given by the following expression for its density

$$f(t) = \frac{\beta\varepsilon(\beta t)^{\varepsilon\alpha-1}\exp\{-(\beta t)^{\varepsilon}\}}{\Gamma(\alpha)} . \tag{3.1}$$

Table 1. Testing the hypothesis: $\varepsilon = 1$.

Number of fractional doses	χ^2 – statistic	Degrees of freedom	Significance level
10	1.0	1	$\rho > 0.3$
11	4.4	1	$\rho < 0.05$
12	4.4	1	$\rho < 0.05$
13	1.2	1	$\rho > 0.2$
14	2.6	1	$\rho > 0.1$
15	1.0	1	$\rho > 0.3$

Being a hierarchical family of distributions, expression (3.1) includes the two-parameter gamma distribution as a special case ($\varepsilon = 1$). The hypothesis: $\varepsilon = 1$, can be tested by the likelihood ratio test. Table 1 shows the results of testing the hypothesis for every sample resulting from computer simulations. As is seen from this table, in four cases out of six, model (1.1) appears to be statistically consistent with simulations. This gives more grounds to use the gamma distribution for the function $F(t)$ in formula (1.1). By way of illustration two (for $n = 12$ and $n = 15$) estimates, based on model (1.1), and the corresponding nonparametric estimates of the survivor function are presented in Fig. 1.

The dose-effect curve, depicted as a function of the number of dose fractions, is given in Fig. 2. The most important result is shown in Fig. 3. Referring to this figure, the application of model (1.1) provides a reasonable estimate of the *actual* mean number of surviving clonogens. The estimated parameter θ in (1.1) only slightly overestimates the number of undamaged cells in this simulation study. Considering the total number of irradiated tumor cells (damaged + undamaged), only some of them may be clonogenic. As of now, there is no way in which such an observation can be made except by conducting computer simulations.

4. Breast Cancer Data

In this section we apply the model of tumor recurrence given by (1.1) to real clinical data. Shown in Table 2 are the estimates of the model parameters for three groups of patients treated for cancer of the breast in the Kharkov Institute of Medical Radiology (Prof. T. P. Yakimova). All these patients underwent radical mastectomy with axillary lymph node dissection. For Group 1, radiation therapy was initiated following surgery, the order being reversed for Groups 2 and 3. Patients of Group 3 were given radiotherapy in large fractions (each fractional dose of 5 Gy) with the

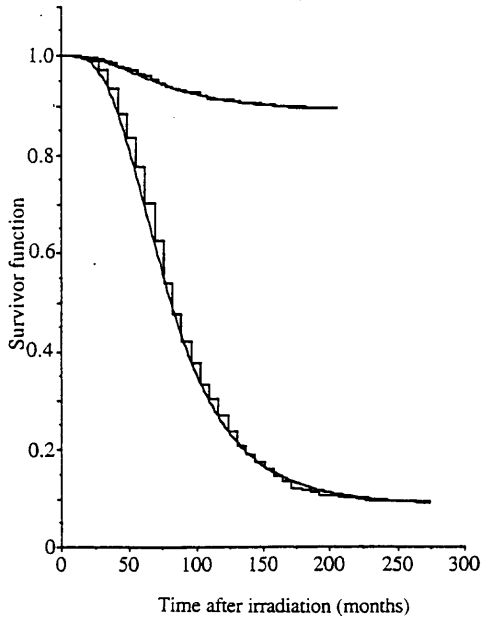

Fig. 1. Parametric versus nonparametric estimation of the survivor function. Solid lines – parametric estimates, stepwise curves – the Kaplan–Meier estimates accomodated for grouped data. Upper curves correspond to the number of fractions $n = 12$, lower curves are given for $n = 15$.

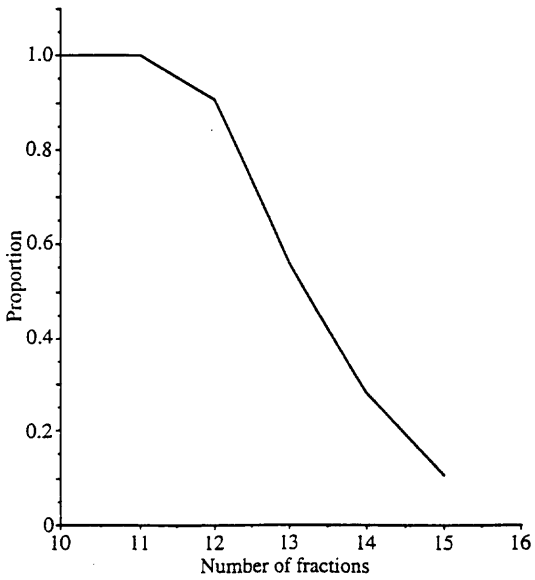

Fig. 2. The proportion of surviving tumors as a function of the number of fractional doses. Computer simulations.

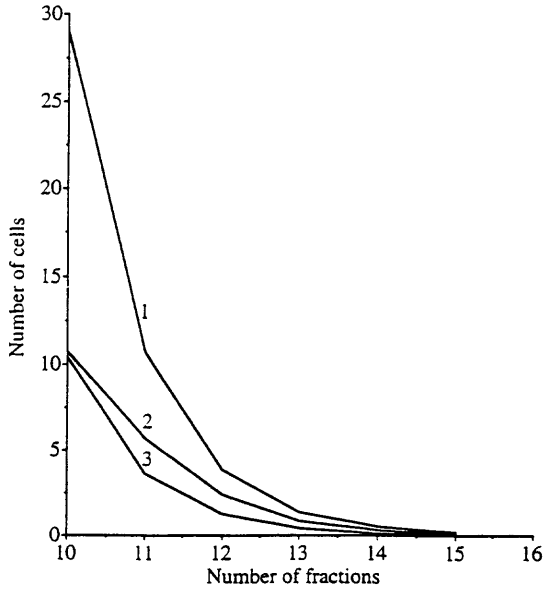

Fig. 3. Estimation of mean number of clonogens.
1. — the total number (damaged + undamaged) of surviving cells after a fractionated irradiation.
2. — the predicted number of surviving clonogens given by the estimated value of θ,
3. — the number of undamaged cells.

Table 2. Estimates of the model parameters obtained from breast cancer data.

Group of patients	Estimates and 0.95-confidence intervals						Hjort test	
	$\hat{\theta}_1$	$\hat{\alpha}_1$	$\hat{\beta}_1$	$\hat{\theta}_2$	$\hat{\alpha}_2$	$\hat{\beta}_2$	χ^2	d.f.
Group 1	0.97	2	0.07	–	–	–	1.8	11
(325 patients)	±0.15	±0.4	±0.02					
Group 2	0.49	2	0.1	3.5	3	0.02	10.9	10
(292 patients)	±0.20	±0.20	±0.02	±28.4	±6.6	±0.15		
Group 3	1.09	2	0.017	–	–	–	13.6	10
(151 patients)	±2.21	±1.2	±0.04					

d.f. — degrees of freedom

total dose to the tumor being equal to 25 Gy. For Groups 1 and 2, conventional irradiation regimen was used with the total dose of 50–55 Gy given in 2-Gy fractions. The dose of irradiation delivered to regional lymph nodes was nearly the same for the three groups of patients. The data include local failure times and the censoring index value. We will take the gamma distribution, given by

$$\varphi(t;\alpha,\beta) = \frac{\beta^\alpha}{\Gamma(\alpha)} t^{\alpha-1} e^{-\beta t}, \qquad t,\alpha,\beta > 0,$$

for the progression time distribution in all the computations that follow. The following notation will be used:

θ — the mean number of surviving clonogens,
$\tau = \alpha/\beta$ — the mean progression time,
$\sigma = \sqrt{\alpha/\beta}$ — the standard deviation of the progression time.

In some cases model (1.2) for $k = 2$ will be used to represent a mixture of two subpopulations (fractions) of surviving clonogens. The parameters θ, α, β, τ and σ will then be indexed by the number of the fraction to which they correspond. For testing the goodness of fit, we use the statistical test developed by Hjort for censored observations [5].

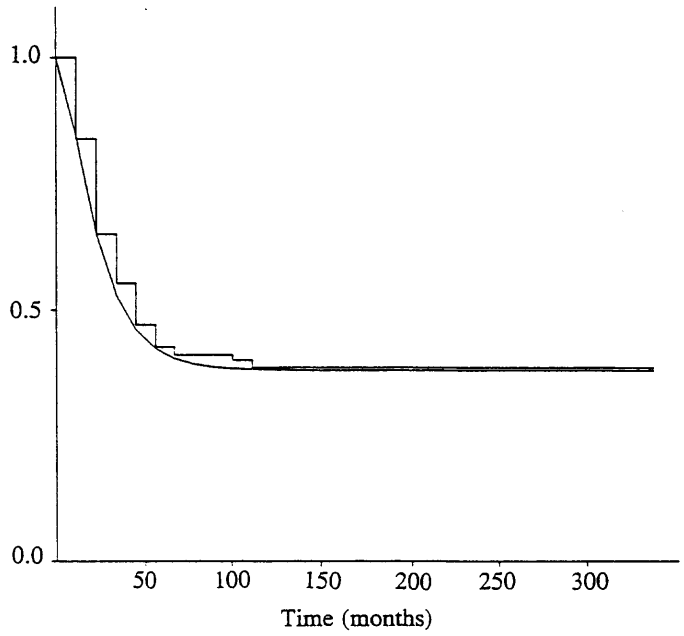

Fig. 4. Disease-free curves for breast cancer (Group 1). Solid line: parametric estimation. Stepwise curve: the Kaplan–Meier estimate.

It follows from Table 2 that the goodness of fit test indicates a very good agreement between the one-component model of tumor recurrence and the corresponding data for Groups 1 and 3. The estimated survivor functions for these groups of patients are given in Figs. 4 and 6. The results for Group 1 shown in Fig. 4 are not without strong appeal. Even leaving aside biological considerations, it is not easy to invent a sufficiently simple model that would provide so excellent quantitative description of this sort of data. However, when applied to Group 2, the Hjort test rejects the model at a significance level of much less than 0.001. Once the second subpopulation of clonogens has been introduced, the model becomes consistent

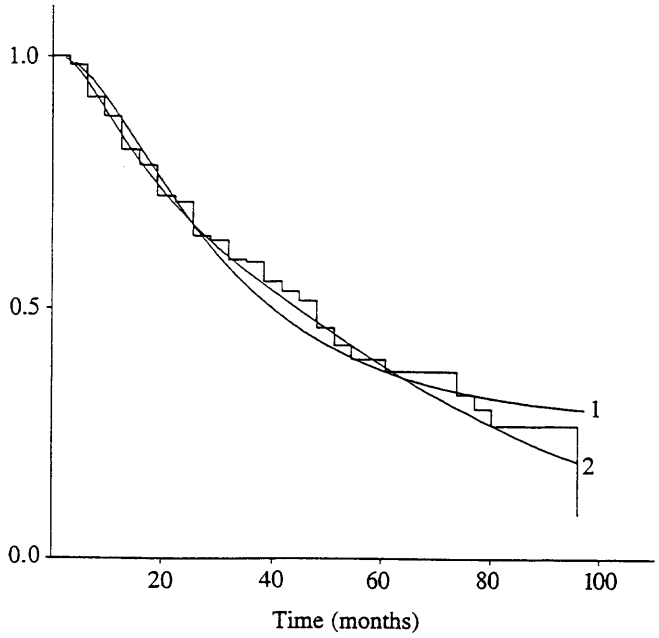

Fig. 5. Disease-free curves for breast cancer (Group 2). Solid line: parametric estimation. Stepwise curve: the Kaplan–Meier estimate.

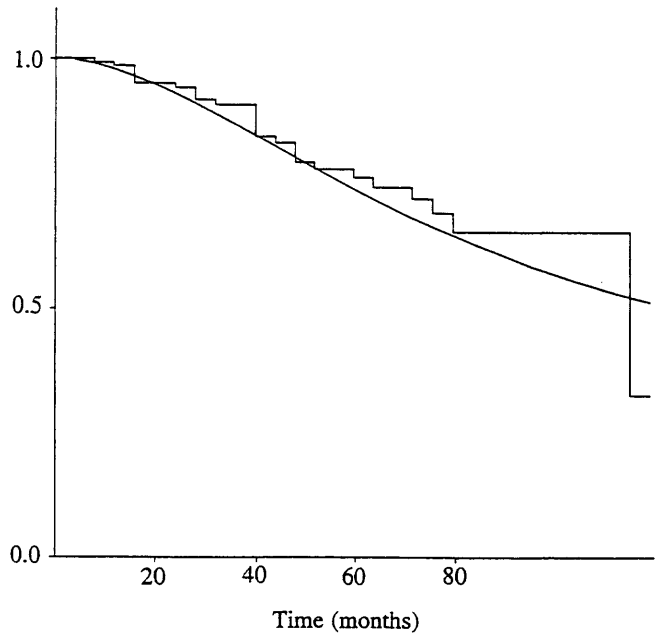

Fig. 6. Disease-free curves for breast cancer (Group 3). Solid line: parametric estimation. Stepwise curve: the Kaplan–Meier estimate.

with observations ($p > 0.3$). Both parametric estimates of the survivor function for Group 2 are depicted in Fig. 5.

To compare different treatment groups, use was made of three nonparametric statistical tests of homogeneity [3, 4, 8]. Group 3 differs significantly from the other two, the hypothesis of homogeneity being rejected at a significance level of 0.001 by all the above mentioned tests. For Groups 1 and 2, the only test that allowed us to reject the null hypothesis was a modified Kolmogorov–Smirnov test proposed by Fleming *et al.* [3].

The treatment used for patients of Group 3 appears to be superior to those received by patients of Groups 1 and 2. This can be explained by slower progression of surviving clonogens (Table 2) when the course of irradiation consisted of large fractional doses. For Group 2, a rapidly developing ($\tau_1 = \frac{\alpha_1}{\beta_1} = 20$ months) subpopulation of clonogens may be responsible for poor therapeutic efficiency. It seems likely that radiation therapy given in small fractions before surgery is incapable to block the development of an agressive cell clone that may manifest itself after the treatment. Another part of the explanation is that a higher total dose of irradiation given in small fractions might more heavily depress the immune and defensive responses of the organism.

For Groups 1 and 3, the possibility of using the gamma distribution to describe the progression time may be tested within the hierarchical family of distributions given by (3.1). The likelihood ratio test gives $\chi^2 = 0.4$ for Group 1 and $\chi^2 = 1.8$ for Group 2 on one degree of freedom. This is a significant indication that the selected approximation is satisfactory.

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