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Estimation of Survival Based on Proportional Hazards When Cure is a Possibility

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Abstract—Inference based on the proportional hazards model is discussed in the presence of long-term survivors. The model is formulated as a cure model yielding an improper survivor function. An algorithm is proposed to fit the proportional hazards model restricted by the fixed survival rates at the end of observation period. A parametric cure model is used to estimate the proportion of long-term survivors. To combine the stability of the parametric method with the flexibility of the nonparametric one, the survival function is estimated nonparametrically conditional on the cure rates provided by the parametric analysis. The methods are applied to the data collected in clinical trials on Hodgkin's disease.

Keywords—Cure models, Proportional hazards, Semiparametric methods.

1. INTRODUCTION

Time to relapse or freedom from treatment failure is an endpoint used in many cancer clinical trials when evaluation of the efficiency of primary therapy of cancer is of interest. Usually the semiparametric proportional hazards (PH) model [1] is used to estimate the treatment effects. A usual approach is to characterize the difference between the treatment groups by the hazard ratio which is captured by the Cox's partial likelihood, the other model parameters being treated as nuisance. However, when cure is a possibility, estimation of the cure rates in different treatment groups in addition to their ratios might provide a better summary of the therapy effects.

Given the cumulative hazard $H(t)$, the population survivor function G is represented in the form

$$G(t) = \exp\{-H(t)\},$$

where $H(t) = \int_0^t h(x)\,dx$ and $h(t)$ is the hazard function. Whatever the cure model, the population survivor function $G(t)$ is improper. That means that the cumulative hazard is bounded

$$H(t) \leq \theta, \qquad \lim_{t\to\infty} H(t) = \theta. \tag{1}$$

A convenient way to adjust for the above property is to consider $H(t) = \theta F(t)$, where $F(t)$ is the distribution function of a nonnegative random variable. If θ is related to the covariates or

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treatment groups while F is treated nonparametrically, we get an alternative parameterization of Cox's model with an improper survivor function

$$G(t) = \exp\{-\theta F(t)\}. \tag{2}$$

This formulation calls for a likelihood which would allow one to estimate the cure rates without having to estimate the other nuisance parameters (F) jointly. If censoring is of Type I, the probability of cure can simply be estimated by the proportion of censored observations from a homogeneous sample. Within the framework of the PH model under Type I censoring, a marginal likelihood has been suggested which allows to estimate the cure rates [2], if covariate information is available. It is noteworthy that the ranks marginal likelihood is no longer the same as Cox's partial likelihood if cure is a possibility.

If the hazard ratio is of primary interest, Cox's semiparametric PH model is preferred to a parametric model because of its high flexibility and relative efficiency [3–5]. Although a parametric model is fully efficient (if correctly specified), overall it is not appreciably better than the robust Cox's model [6].

However, the semiparametric PH model is less efficient than a parametric one as far as estimation of cure rates in absolute terms is concerned [7]. A distinct advantage of the parametric approach is its stability when estimating the cure rates. For example, if the last observation is uncensored, the Kaplan-Meier estimate of the cure rate from a homogeneous sample becomes zero. Much like the Kaplan-Meier estimate (see also [8]), a nonparametric estimate of survivor function under proportional hazards is unstable close to the end of the study. It is not uncommon that a difference in the estimates of survival in a number of treatment groups at the end of the study is misinterpreted even if the difference is not significant. A misclassification of the cause of failure in unclear cases and composed endpoints might also be a part of the reason for the instability.

Another point is that the nonparametric estimate is unable to extrapolate the survivor function beyond a limited observation period. While the nonparametric model estimates the cure rates by the proportion surviving at the end of the study, the parametric model extrapolates beyond the observation period, thus reducing the bias associated with the limited observation period.

The above observation calls for methods that would resolve the bias versus variance (and/or stability) tradeoff combining the advantages of both the parametric and the nonparametric approaches.

In an attempt to marry the stability of the parametric estimation of the cure rate with the flexibility of the nonparametric estimation of the survival function, we use the parametric approach to estimate the cure rate, and then estimate the function F nonparametrically as if the cure rate were known. We restrict ourselves to a k-sample problem. Extentions to other designs are trivial.

2. ESTIMATION OF CURE RATES UNDER A CONTINUOUS MODEL

Along with model (2) with a parametrically specified F [9], there exists a variety of other parametric cure models. Most them are of the mixture type. The simplest model of this type would assume that the population is divided into two subpopulations due to some unobserved prognostic factor, so that an individual is either a long-term survivor with some probability or has a proper survivor function otherwise [10]. More complex approaches proceed by assuming that the unobserved heterogeneity is described by a random variable (r.v.) as following some mixture distribution which assigns a positive probability to some value corresponding to infinitely large time to failure. The population survivor function is then given by an expectation taken with respect to the frailty [11–13]. It is remarkable that model (2) can be simultaneously interpreted both as a mixture model, as well as a simple model of carcinogenesis [9,14–16]. According to the

carcinogenic interpretation, the observed tumor originates from clonogens that have a random progression time X with the distribution function (d.f.) F. It is assumed that the number ν of such clonogens in a patient is Poisson distributed with parameter θ. The observed tumor onset is associated with completing of the progression by one of the competing clonogens, so that the tumor onset time U is given by

$$U = \min_{i=0,\ldots,\nu} X_i, \tag{3}$$

where X_i, $i = 1, 2, \ldots$, is the time for the i^{th} clonogen to produce a detectable tumor (progression time). The variable X_0 is set to ∞ by definition, since $\nu = 0$ corresponds to the absence of the disease. Let X_i, $i = 1, 2, \ldots$ be independent and identically distributed with the d.f. F. Given ν, we have $S(t; \nu) = [1 - F(t)]^{\nu}$. If the number of clonogens in a patient could be measured, we would have a PH model with the baseline cumulative hazard $H_0(t) = -\log(1 - F(t))$, $H_0(\infty) = \infty$. Since ν is unobservable, we take an expectation over the frailty and obtain expression (2) for the population survivor function. When interpreted in the mixture context, model (2) is a particular case of the model by Aalen [13], which assumes a compound Poisson distribution for ν.

Suppose that the ordered times to failure assume the values t_i on the time axis, $i = 1, \ldots, n$, $t_0 = 0$, $t_{n+1} = \infty$. Let m_{ij} be the number of failures at t_i in the treatment group $j = 1, \ldots, k$, and n_{ij} be the number of censored observations. Denote by θ_j, $j = 1, \ldots, k$, the value of θ in the treatment group j. The probabilities of cure are then given by $\exp(-\theta_j)$. The likelihood of the data under a continuous model can be written as

$$\ell_c = \sum_{i=1}^{n} \sum_{j=1}^{k} \left\{ m_{ij} \log \left[\theta_j f(t_i) \right] - (m_{ij} + n_{ij}) \theta_j F(t_i) \right\}, \tag{4}$$

where f is the probability density corresponding to F. From the score equations

$$\frac{\partial \ell_c}{\partial \theta_j} = 0, \qquad j = 1, \ldots, k,$$

we get the MLE for θ_j in the form

$$\hat{\theta}_j = \frac{M_j}{\sum_{i=1}^{n} (m_{ij} + n_{ij}) F(t_i)} = \frac{M_j}{\sum_{i=1}^{n} R_{ij} \Delta F_i}, \tag{5}$$

where M_j is the number of failures in the treatment group j, R_{ij} is the number of patients at risk at $t_i - 0$ in group j. Here and in what follows, we assume $\Delta V_i = |V(t_i) - V(t_{i-1})|$, $V_i = V(t_i)$, for any function V. Let S_j be the survivor function corresponding to the time to censoring event in group j. Let us rewrite estimate (5) in the form

$$\hat{\theta}_j = \frac{M_j \theta_j}{(M_j + N_j) \sum_{i=1}^{n} \left(R_{ij} \theta_j / (M_j + N_j) \right) \Delta F_i}, \tag{6}$$

where θ_j is the true value. We shall have in probability as $n \to \infty$

$$\sum_{i=1}^{n} \frac{R_{ij} \theta_j}{(M_j + N_j)} \Delta F_i \to \int_0^{\infty} \theta_j S_j(t) G_j(t) \, dF(t) = \Pr\{\text{failure in group } j\},$$

where N_j is the number of censored observations and G_j is the survivor function of the time to failure in group j. Also, $M_j/(M_j + N_j) \to \Pr\{\text{failure in group } j\}$. Thus, $\hat{\theta}$ is consistent. If the true survivor function is a proper one, the estimate $\hat{\theta}$ will be infinite as $n \to \infty$, since the true value of θ is infinite.

A closely related estimate for θ has been suggested by Klebanov and coauthors [17] within the framework of the statistical decision theory. The idea was to find a survivor function $\tilde{G}$ which minimizes the risk of the estimator given by the expectation of the loss function

$$L(\tilde{G}) = \theta \int_0^\infty \left[\tilde{G}(t) - G(t)\right]^2 dt.$$

In minimizing L, the function F was treated as known. The solution in the class of estimators invariant with respect to the choice of a measurement unit for t has the form

$$\tilde{G}_j(t) = \left[1 + \frac{F(t)}{\sum_{i=1}^{n} (m_{ij} + n_{ij}) F(t_i)}\right]^{-(M_j+1)} \tag{7}$$

in the treatment group j. It is clear that according to (6) the second term in square brackets in (7) becomes infinitely small in probability as $n \to \infty$ if $\theta_j < \infty$, and we get the MLE $\hat{G}_j$ as the first term of the Taylor expansion of (7). A parametric method can be used to estimate F by maximum likelihood as if the sought-for survival function were in form (7). However, the two estimates (7) and the "pure" MLE $\hat{G}_j$ are almost identical in practice [9]. This observation gives one more reason to use the MLE (5) to estimate the cure rate.

3. RESTRICTED ESTIMATE OF SURVIVOR FUNCTION GIVEN THE CURE RATES

In order to estimate F nonparametrically, we treat it as a step-function and use θ as estimated from a continuous model, following the usual line of reasoning with the PH model. The generalized likelihood of the data on the class of step-functions acquires the form

$$\ell_d = \sum_{i=1}^{n} \sum_{j=1}^{k} \{m_{ij} \log [\Delta G_{ij}] - n_{ij} \theta_j F_i\}, \tag{8}$$

where $\Delta G_{ij} = G_j(t_{i-1}) - G_j(t_i)$ and $F_n = 1$. Let us consider ℓ_d as a function of ΔF_i, $i = 1, \ldots, n-1$, where $\Delta F_n = 1 - \sum_{i=1}^{n-1} \Delta F_i$. To obtain the maximum likelihood estimate of F, the likelihood ℓ_d is maximized with respect to ΔF_i, $i = 1, \ldots, n-1$. This is accomplished by the following numerical algorithm.

- Define the functions $y_i = \varphi_i(x)$ as solutions to the following equations (solved numerically):

$$\sum_{j=1}^{k} \frac{\theta_j m_{ij}}{1 - \exp\{-\theta_j y_i\}} = \sum_{j=1}^{k} \{R_{ij} - m_{nj} - n_{nj}\} + \sum_{j=1}^{k} \frac{m_{nj} \theta_j}{1 - \exp\{-\theta_j x\}}, \tag{9}$$

  $i = 1, \ldots, n-1$.
- Solve the equation

$$x + \sum_{i=1}^{n-1} \varphi_i(x) = 1. \tag{10}$$

Let x^* be the solution of (10). As a result of the above estimation procedure, we have

$$\Delta \hat{F}_i = \varphi(x^*), \qquad i = 1, \ldots, n-1, \qquad \Delta \hat{F}_n = x^*.$$

It can be shown that the above algorithm indeed finds the maximum likelihood estimator for F.

PROOF. Using the method of Lagrange multipliers, consider unrestricted optimization of the likelihood

$$\tilde{\ell}_d = \ell_d + \lambda \left(1 - \sum_{i=1}^{n} \Delta F_i\right)$$

with respect to the independent variables ΔF_i, $i = 1, \ldots, n$, and λ. Taking the derivatives, we obtain the equations

$$\frac{\partial \ell_d}{\partial \Delta F_i} - \lambda = 0, \quad i = 1, \ldots, n, \qquad \text{and} \qquad \sum_{k=1}^{n} \Delta F_k = 1.$$

Expressing λ as $\lambda = \frac{\partial \ell_d}{\partial \Delta F_n}$, we obtain the score equations

$$\frac{\partial \ell_d}{\partial \Delta F_i} - \frac{\partial \ell_d}{\partial \Delta F_n} = 0, \qquad i = 1, \ldots, n-1, \tag{11}$$

to be solved simultaneously with the equation

$$\sum_{i=1}^{n} \Delta F_i = 1. \tag{12}$$

It is easy to see that equations (11),(12) take the form of (9),(10), respectively, y_i and x replaced by ΔF_i and ΔF_n, respectively. Solution of the score equations (11) defines the increments ΔF_i, $i = 1, \ldots, n-1$, as functions φ_i of ΔF_n. Consider the function $\psi(\Delta F_n) = \Delta F_n + \sum_{i=1}^{n-1} \varphi_i(\Delta F_n)$. It is easy to show by induction that ψ is an increasing function. Besides, $\psi(0) = 0$ and $\psi(1) > 1$. Therefore, the equation $\psi(x) = 1$ has the unique solution x^*. We thus obtain the sought-for estimates as $\Delta \hat{F}_i = \varphi_i(x^*)$.

4. JOINT ESTIMATION OF θ AND F

The full PH model (2) can be fitted by iteratively applying the algorithm of the previous section and solving (5). This approach has much in common with the one usually used to fit the PH model: estimation of regression parameters is carried out under a continuous model by the partial likelihood, with the subsequent plug-in estimation of the survivor function [3].

An approximation $1 - \exp(-\theta \Delta F) \approx \theta \Delta F$ can be used if the size of the sample and/or the probability of cure $\exp(-\theta)$ is large. In this case, we get

$$\Delta F_i = \frac{\sum_j m_{ij}}{\sum_j \theta_j \left[R_{ij} - m_{nj} - n_{nj}\right] + \sum_j m_{nj} / \Delta F_n} \tag{13}$$

instead of (11). From (5) and (13), we derive

$$M = \sum_i \frac{\sum_j m_{ij}}{1 + \left[\sum_j m_{nj} \Big/ \Delta F_n - \sum_j \theta_j \left(m_{nj} + n_{nj}\right)\right] \Big/ \sum_j \theta_j R_{ij}}. \tag{14}$$

Note that the right part of (14) is monotonic in ΔF_n, and therefore, the unique solution is given by $\Delta F_n = \sum_j m_{nj} / \sum_j \theta_j R_{nj}$. On substitution in (13), we get

$$\Delta F_i = \frac{\sum_{j=1}^{k} m_{ij}}{\sum_{j=1}^{k} \theta_j R_{ij}}, \qquad i = 1, \ldots, n. \tag{15}$$

Excluding ΔF_i from (5) and (15) results in

$$\frac{M_j}{\theta_j} - \sum_i R_{ij} \frac{\sum_r m_{ir}}{\sum_r \theta_r R_{ir}} = 0,$$

which is a score equation for the Cox's partial likelihood adjusted for ties. It remains to choose the free parameter θ_1 in (15) to satisfy the constraint $\sum_i \Delta F_i = 1$.

Finally, we note that estimate (15) multiplied by θ_1 is just the Breslow's estimate for the baseline hazard [18], where "baseline" refers to the treatment group 1. In the absence of covariates, this estimate turns into the Nelson-Aalen one.

5. EXAMPLE

We shall compare two estimation methods for the two-sample problem.

METHOD A. Estimate the PH model parametrically. Fix θ_j as based on the parametric model and reestimate the survivor function under the restriction given by the parametric cure rates.

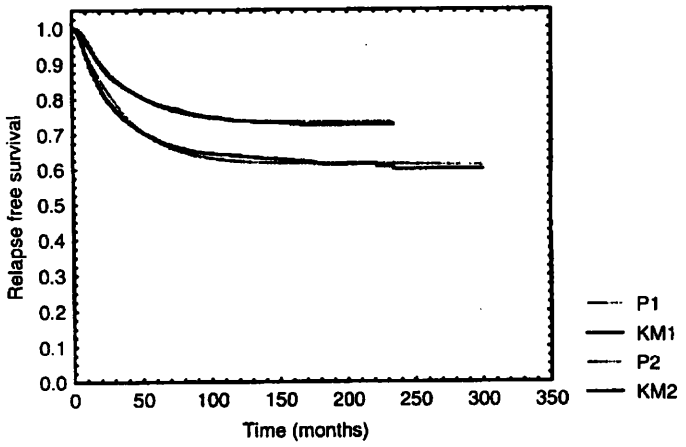
METHOD B. Alternatively, we use a conventional approach. Estimate the ratio θ_2/θ_1 by the partial likelihood. Fix the ratio θ_2/θ_1 as estimated from the partial likelihood and then estimate the survivor function nonparametrically.

In the subsequent analysis, use was made of the International Database on Hodgkin's Disease (IDHD) collected at 15 cancer centers and five cooperating groups (see the Appendix). The data set includes records of 14315 newly diagnosed patients with HD treated between 1960 and 1987. Patients of all disease stages were included if older than 15 years. The majority of patients were less than 60 years of age. A wide variety of treatment strategies ranges from involved field irradiation in Stage I to intensive combined modality treatment in Stage IV. Over 85% of the chemotherapy regimens used were MOPP-like not containing adriamycin. The records also contained follow-up data for each patient including date of relapse, death, cause of death. We refer the reader to [19] for other details.

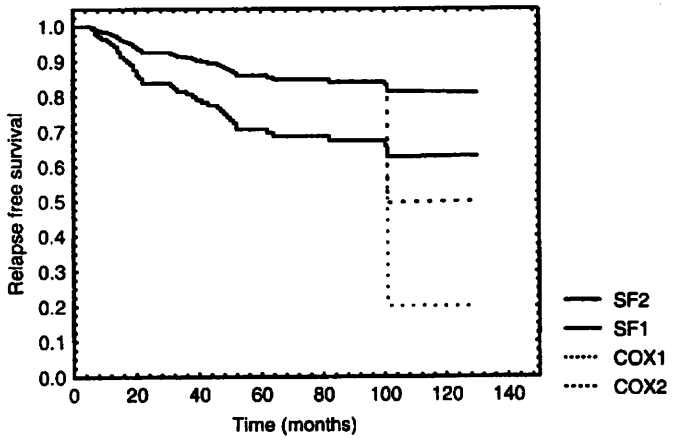
Consider two groups of patients with respect to the type of primary treatment. Patients assigned to the Group 1 received radiotherapy alone (RT), while those assigned to the Group 2 received MOPP-like chemotherapy. To specify the parametric form of F, we use the Weibull distribution. The results with F specified as Gamma distribution were very similar, and therefore, they are not presented here. Since the IDHD dataset is very large, the IDHD-based Kaplan-Meier estimates will be thought of as being the true curves. The parametric PH model was fitted to the freedom from relapse IDHD data (Figure 1a). Although there is some discrepancy between the estimates, the cure rates provided by the parametric method (0.73 and 0.61 in the two groups, respectively) are only about 0.01 biased as compared to the Kaplan-Meier estimates (0.73 and 0.60, respectively). To test the robustness of the method, we create a late failure perturbed sample. The curves shown in Figure 1a are bootstrapped with 200 patients in each group under the additional Type I censoring at time 100 (months). Then a single censored observation at $t = 100$ in Group 1 is turned into a failure and moved a small amount to the right. Method A estimates practically do not change. We see in Figure 1b that estimate B is deranged by the late failure perturbation.

Bootstrapping the curves given in Figure 1 with 1000 replicates, and varying group sizes, we estimated the variance of the θ_j-estimates as given by Methods A and B. As is seen in Figure 2, Method A is preferable within a wide range of sample size encountered in the practice of clinical trials.

Apart from the experiment shown in Figure 1b, we have encountered a similar situation when comparing the relapse free survival in patients treated by a conventional chemotherapy and in



(a) Kaplan-Meier (KM1, KM2) relapse free curves versus parametric (P1, P2) curves under proportional hazards in the two treatment groups.



(b) A perturbed bootstrap realization of the trial as given in Figure 1a. SF1, SF2—the curves provided by Method A in the two groups. COX1, COX2—the curves based on partial likelihood (Method B). See text for explanations.

Figure 1. Analysis of the IDHD data on relapse free survival.

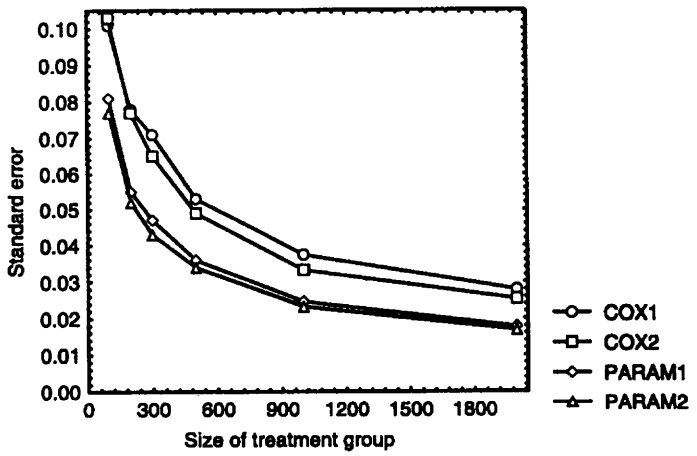
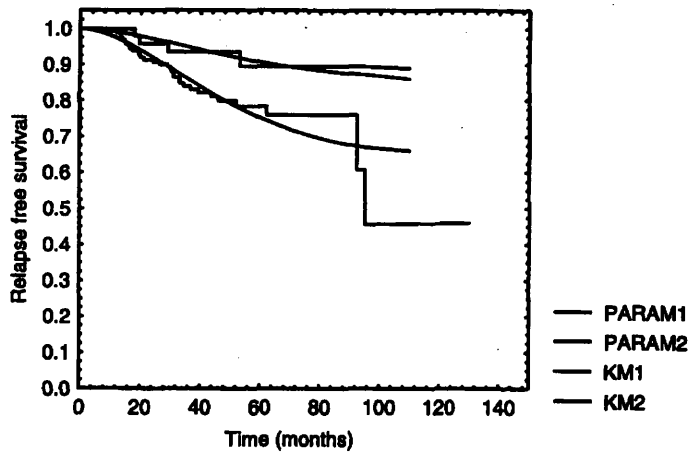
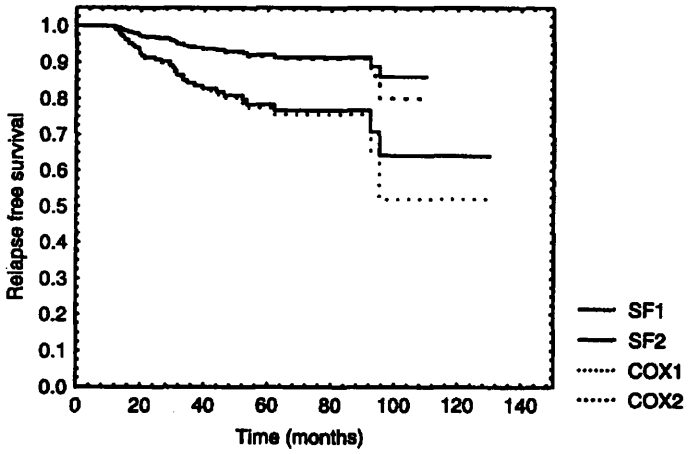


Figure 2. The variance of the estimates of θ_j as provided by Methods A (PARAM1, PARAM2) and B (COX1, COX2) by sample size. See text for explanations.



(a) Kaplan-Meier (KM1, KM2) relapse free curves versus parametric (PARAM1, PARAM2) curves under proportional hazards in the two treatment groups.



(b) SF1, SF2—the curves provided by Method A in the two groups (GHSG vs. EBMT). COX1, COX2—the curves based on partial likelihood (Method B). See text for explanations.

Figure 3. Analysis of the GHSG and EBMT data on relapse free survival.

patients who have undergone a high dose chemotherapy with subsequent autologous bone marrow transplantation to restore the hemopoiesis [20]. The transplanted treatment group (2) was taken from the European Bone Marrow Transplantation (EBMT) register. The similar patients treated conventionally (assigned to Group 1) were taken from the clinical trials of the German Hodgkin's Lymphoma Study Group (GHSG). Shown in Figure 3a are the Kaplan-Meier curves in the two groups together with the parametric curves as based on the PH model. We notice an unexpected behavior of the Kaplan-Meier curve in the first group. From Figure 3b, we see that Method B is much more susceptible to this instability, while the method A still provides a reasonable curve.

APPENDIX

LIST OF STUDY CENTERS AND PRINCIPAL INVESTIGATORS INVOLVED IN THE IDHD

- British National Lymphoma Investigation (BNLI), London, U.K.: M.H. Bennett, B.W. Hancock, K.A. MacLennan, B. Vaughan Hudson, G. Vaughan Hudson
- EORTC Lymphoma Cooperative Group: P. Carde, J.M. Cosset, M. Hayat, M. Henry-Amar, J.H. Meerwaldt, R. Somers, J. Thomas

- Stanford University Medical Center, U.S.A.: R.S. Cox, R.T. Hoppe
- Princess Margaret Hospital, Toronto, Canada: D.E. Begrsagel, G. DeBoer, M. Gospodarowicz, S. Sutcliffe
- Southwest Oncology Group (SWOG), U.S.A.: C.A. Coltman, S.J. Dahlberg
- University of Texas M.D. Anderson Cancer Center, Houston, U.S.A.: D.O. Dixon, L.M. Fuller, F.B. Hagemeister
- Royal Marsden Hospital, London, U.K.: S. Ashley, A. Horwich
- St. Bartholomew's Hospital, London, U.K.: W. Gregory, T.A. Lister
- Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA), Argentina: S. Pavlovsky, M.T. Santarelli
- Universita di Pavia, Italy: P.G. Gobbi
- Joint Center for Radiation Therapy, Boston, U.S.A.: N.C. Coleman, P. Mauch
- Finsen Institute, Copenhagen, Denmark: N.I. Nissen, L. Specht
- Fondation Bergonié, Bordeaux, France: F. Bonichon, H. Eghbali, B. Hoerni
- German Hodgkin Study Group, Germany: V. Diehl, D. Hasenclever, M. Loeffler, M. Pfreudschuh
- Groupe Pierre et Marie Curie, France: H. Eghbali, A. Najman, R. Zittoun
- Christie Hospital & Holt Radium Institute, Manchester, U.K.: D. Crowther, R. Swindell
- The Institute of Oncology, Ljubljana, Yugoslavia: V. Pompe Kirn, M. Vovk
- University of Minnesota Health Science Center, Minneapolis, U.S.A.: D.M. Aeppli, C.K.K. Lee, S.H. Levitt
- University of Nebraska, Omaha, U.S.A.: J. Anderson, J.O. Armitage
- Yale University, New Haven, U.S.A.: S. Dowling, C.S. Portlock

REFERENCES

1. D.R. Cox, Regression models and life tables, *J.R. Stat. Soc. B* **34**, 187–220, (1972).
2. A. Tsodikov, A proportional hazards model taking account of long-term survivors, *Biometrics* **54**, 1508–1516, (1996).
3. J. Kalbfleisch and R. Prentice, *The Statistical Analysis of Failure Time Data*, Wiley, New York, (1980).
4. T.R. Fleming and D.P. Harrington, *Counting Processes and Survival Analysis*, Wiley, New York, (1991).
5. A. Tsiatis, A large sample study of Cox's regression model, *Annals of Statistics* **9**, 93–108, (1981).
6. Y.H. Li, J.P. Klein and M.L. Moeschberger, Effects of model misspecification in estimating covariate effects in survival analysis for small sample sizes, *Computational Statistics and Data Analysis* **22**, 177–192, (1996).
7. A.D. Tsodikov, Asymptotic efficiency of a proportional hazards model with cure, *Statistics and Probability Letters* **39**, 237–244, (1998).
8. M. Pepe and T. Fleming, Weighted Kaplan-Meier statistics: A class of distance tests for censored survival data, *Biometrics* **45**, 497–507, (1989).
9. A. Yakovlev and A. Tsodikov, *Stochastic Models of Tumor Latency and Their Biostatistical Applications*, World Scientific, Singapore, (1996).
10. V.T. Farewell, The use of mixture models for the analysis of survival data with long-term survivors, *Biometrics* **38**, 1041–1046, (1982).
11. P. Hougaard, Survival models for heterogeneous populations derived from stable distributions, *Biometrika* **71**, 75–83, (1986).
12. P. Hougaard, Frailty models for survival data, *Lifetime Data Analysis* **1**, 255–274, (1996).
13. O.O. Aalen, Modelling heterogeneity in survival analysis by the compound Poisson distribution, *The Annals of Applied Probability* **2**, 951–972, (1992).
14. A. Yakovlev, Parametric versus non-parametric methods for estimating cure rates based on censored survival data, *Statistics in Medicine* **13**, 983–986, (1994).
15. A.D. Tsodikov, B. Asselain, A. Fourquet, T. Hoang and A.Yu. Yakovlev, Discrete strategies of cancer post-treatment surveillance. Estimation and optimization problems, *Biometrics* **51**, 437–447, (1995).
16. A. Asselain, A. Fourquet, T. Hoang, A. Tsodikov and A. Yakovlev, A parametric regression model of tumor recurrence: An application to the analysis of clinical data on breast cancer, *Statistics and Probability Letters* **29**, 271–278, (1996).
17. L. Klebanov, S. Rachev and A. Yakovlev, On the parametric estimation of survivor functions. *Statistics and Decisions* (Suppl. 3), 83–102, (1993).
18. N.E. Breslow, Analysis of survival data under the proportional hazards model, *Int. Stat. Rev.* **43**, 45–58, (1975).

19. M. Henry-Amar, D.M. Aeppli, J. Anderson, S. Ashley, F. Bonichon, R.S. Cox, S.J. Dahlberg, G. DeBoer, D.O. Dixon, P.G. Gobbi, W. Gregory, D. Hasenclever, M. Loeffler, V.P. Kirn, M.T. Santarelli, L. Specht, R. Swindell and B.F. Hudson, Workshop statistical report, In *Treatment Strategy in Hodgkin's Disease, Colloque INSERM, Volume 196*, pp. 169–425, (1990).
20. D. Hasenclever, O. Brosteanu, A. Carella, P. Colombat, S. Proctor, M. Legros, S. Bradley, R. Pearce, V. Diehl and A.H. Goldstone, Early high-dose therapy to consolidate patients with high-risk Hodgkin's disease in first complete remission?—Results of an EBMT/GHSG matched-pair analysis, *37th Annual Meeting of ASH. Blood, Volume 86* (Suppl. 1, Abstract #1742), (1995).