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Using a Counting Process Method to Impute Censored Follow-up Time Data

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Abstract: Censoring occurs when complete follow-up time information is unavailable for patients enrolled in a clinical study. The process is considered to be informative (nonignorable) if the likelihood function for the censoring model cannot be partitioned into a set of response parameters that are independent of the censoring parameters. In such cases, estimated survival time probabilities may be biased, prompting the need for special statistical methods to remedy the situation. The problem is especially salient when censoring is skewed toward the early phase of a study. In this paper, we describe a method to impute censored follow-up times using a counting process method.

Keywords: counting process; censoring; Cox proportional-hazard regression; Kaplan-Meier; imputation; survival analysis

1. Introduction

Ideally, censoring in a survival analysis should be non-informative and not related to any aspect of the study that could bias results [1-7]. For example, toxic side effects of an investigational drug may prompt the most ill patients to withdraw early from the study. Other patients may opt to leave before the intended end of a trial if the treatment is effective and they feel well. Even when censoring is non-informative (e.g., relocation to another city because of plant closure), by chance alone, it may still have a serious effect on estimated survival probabilities, especially if the dropouts occur early in the study.

In this paper, we present an example of early censoring to illustrate how the resulting survival probabilities may be biased. We then describe a method to impute censored follow-up times by rearranging the data as a counting process and generating jump-point plots.

2. Materials and Methods

2.1 Imputing Censored Follow-up Times

Let $\xi_{(j)}$ denote the follow-up time for the j^{th} ordered observation, given a total of (n) observations and (k) integer valued time (t) points

$$(t_2 = t_1 + 1, t_3 = t_2 + 1, \dots, t_k = t_{k-1} + 1; t_k \geq n). \quad (1)$$

Accordingly,

$$\xi_{(1)} \leq \xi_{(2)} \dots \leq \xi_{(n)} \quad (2)$$

and

$$t_1 \leq \xi_{(1)} \leq \xi_{(2)} \dots \leq \xi_{(n)} \leq t_k. \quad (3)$$

38 Then,

$$\forall \xi_{(j)} \wedge t_i \ni j = 1 \text{ to } n, i = 1 \text{ to } k, \quad (4)$$

39 the counting process “indicator” variable (ζ) assumes the value 0 if $t_i \leq \xi_{(j)}$ and $\xi_{(j)}$ corresponds
 40 to a censored follow-up time (i.e., the outcome event, such as death, has yet to occurred by time $\xi_{(j)}$).
 41 Otherwise, when the observation denotes an event, (ζ) assumes the value 0 if $t_i < \xi_{(j)}$ and the
 42 value 1 if $t_i \geq \xi_{(j)}$ [8].

43 Next, we fit a multiple logistic regression model with $(p + 1)$ covariates to the above counting
 44 process data, i.e.,

$$P(\zeta = 1 | \beta_0, \beta_1, \beta_2, \dots, \beta_{p+1}) = \frac{1}{1 + e^{-\{\beta_0 + \beta_1(t_i) + \beta_2(x_1) + \beta_3(x_2) + \dots + \beta_{p+1}(x_p)\}}} \quad (5)$$

45 where the first covariate denotes time (t_i) and the remaining (p) covariates (x_1, x_2, \dots, x_p)
 46 represent outcome related risk factors. Note that the selection of this model is arbitrary and any other
 47 binary predictor equation could be substituted at this step. For example, the addition of a higher
 48 order term to the model or taking the logarithm of a covariate might be desirable. Other possible
 49 options include using a log-binomial or negative-binomial equation to model the data [9-10]. Model
 50 fit may be assessed by examining diagnostic leverage and residual plots, in lieu of standard goodness
 51 of fit tests, which would assume that the underlying counting process data are independently
 52 distributed [11-13].

53 A jump-point plot for a particular covariate pattern corresponding to a censored follow-up time
 54 ($\xi_{(j)}^c$) may be obtained by plotting the model predicted values (\hat{p}) against the time variable (t_i). Let
 55 $\xi_{(j)}^c$ denote the value of (t_i) that maps to $\hat{p} = .50$ (i.e., maximum likelihood estimate of the mean
 56 jump-point observation). The imputed censored follow-up time is given as

$$\widehat{\text{imp}}\xi_{(j)}^c = \inf\{\sup(\xi_{(j)}^c, \xi_{(j)}^c), \xi_{\max}\}, \quad (6)$$

57 where (ξ_{\max}) is the natural upper limit for a patient's follow-up time. For example, in the case of
 58 cancer therapy, the maximum life expectancy of a patient rarely exceeds 101 years of age. For a patient
 59 aged 89 at diagnosis, we see that ξ_{\max} is computed as $(101 - 89)$. The original censored follow-up
 60 times are then replaced with $\widehat{\text{imp}}\xi_{(j)}^c$. However, it is important to note that these follow-up times are
 61 still treated as censored values rather than events when computing survival probability estimates.

62 Assuming Martingale independence and considering the event times to be binomially
 63 distributed [i.e., the probability (π_v) of an event (ζ_v) occurring in a particular risk set (v) is equal
 64 to its expectation $E(\zeta_v)$ divided by the risk set size n_v (accounting for censored and event times),
 65 with corresponding variance equal to $n_v\pi_v(1 - \pi_v)$], it follows that the resulting data be may
 66 analyzed using standard methods for handling censored time-to-event observations (e.g., Kaplan-
 67 Meier and Cox proportional-hazards models) [14-15]. Here, the sampling variability for estimating
 68 the imputed censored follow-up times is absorbed into the sampling variability for each binomially
 69 distributed event time, given that the estimates are asymptotically consistent and adhere to certain
 70 regularity conditions.

71 3. Results

72 3.1 Kaplan-Meier (Product-Limit) Example

Consider the data in Appendix A, which provides the event and censored follow-up times for 250 cancer patients undergoing treatment and their simulated complete values (for illustrative purposes). Approximately 10% of the follow-up times were censored, with the majority of these values occurring early in the study. Figure 1 shows a Kaplan-Meier (KM) plot comparing the original censored data with the dataset of complete follow-up times. The probability of surviving 5 years (60 months) was ~26% for the original censored data compared with ~18% for the complete dataset. In Figure 2, we compare the complete dataset with the imputed censored dataset. At 5 years, rounding to the nearest whole number, we see that the survival times are identical (i.e., 26%). Indeed, the survival curves are similar until ~90 months, at which point the survival times for the imputed censored time curve are divergently lower than those for the complete dataset. This lack of fit at the extreme end of the KM curves is evident when examining the panel of diagnostic plots in Figure 3.

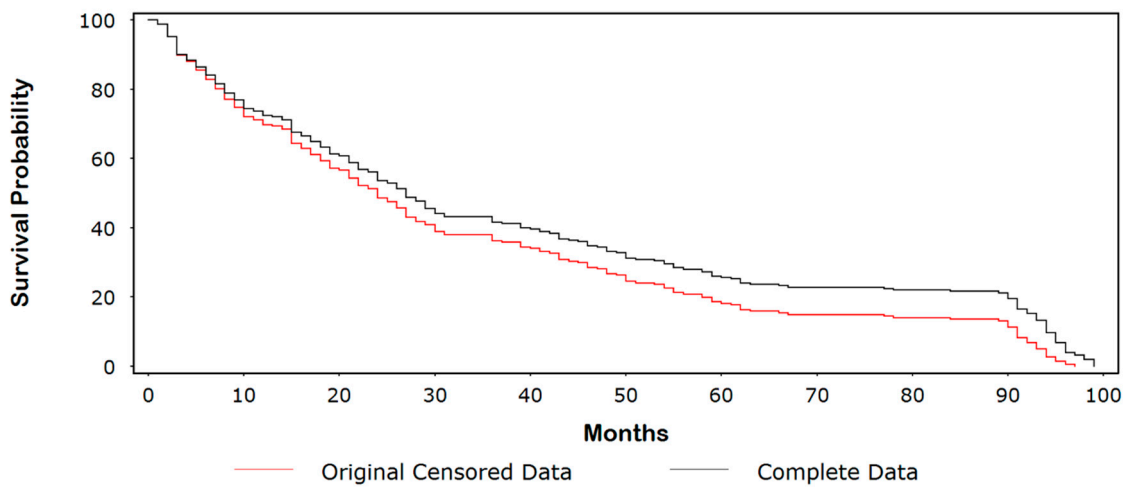


Figure 1. Kaplan-Meier (KM) plot comparing the original censored data with the dataset of complete follow-up times.

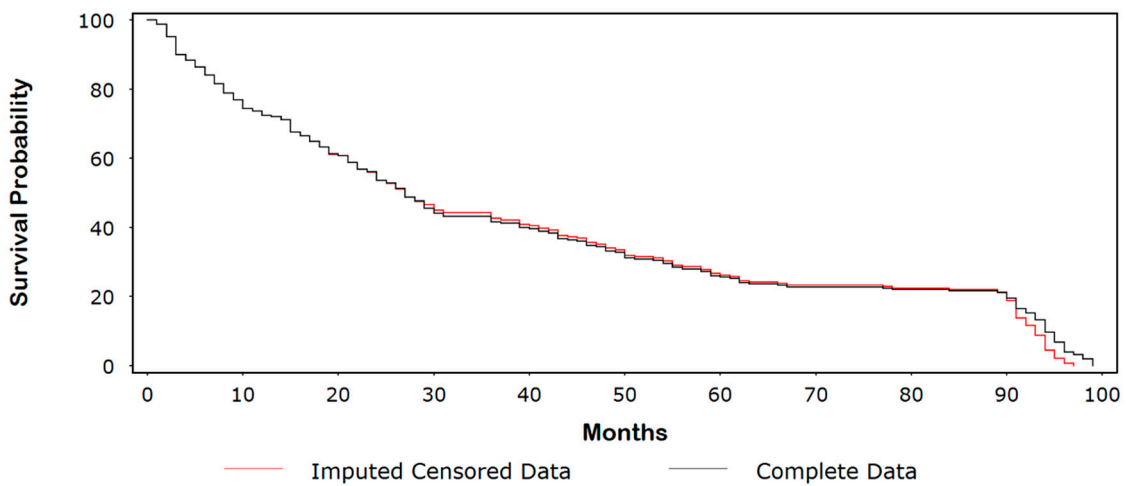


Figure 2. Kaplan-Meier (KM) plot comparing the imputed censored data with the dataset of complete follow-up times.

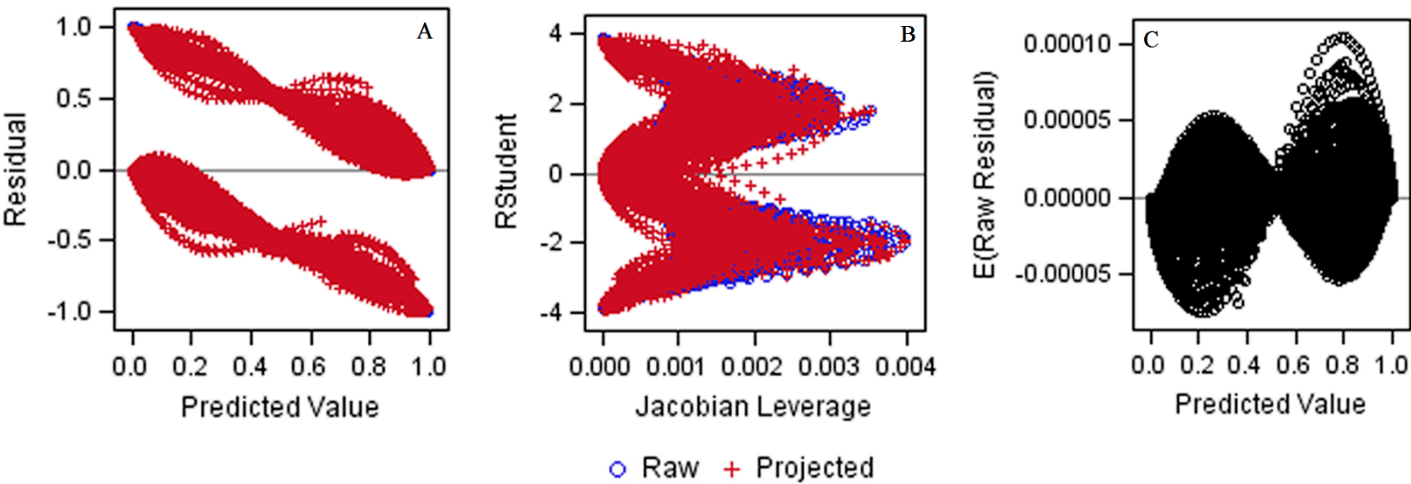


Figure 3. Diagnostic plots. A: Residual by predicted values; B: RStudent by Jacobian leverage; C: Expected raw residuals by predicted values.

3.2 Generating The Jump-Point Plot

The jump-point plot corresponding to covariate pattern

$$(x_1 = 76, x_2 = 3, x_3 = 0, x_4 = 0, x_5 = 1, x_6 = 0) \tag{7}$$

is shown in Figure 4. Here, the variables (x_1, x_2, \dots, x_6) correspond to age (years), grade (I-IV), lymph node invasion (1=yes, 0=no), positive margins (1=yes, 0=no), no hormone therapy (1=yes, 0=no), and no radiation therapy (1=yes, 0=no), respectively. We see that the imputed censored follow-up time of 29.33 months closely matches the actual event time of 29 months. This observation was originally censored at 1 month.

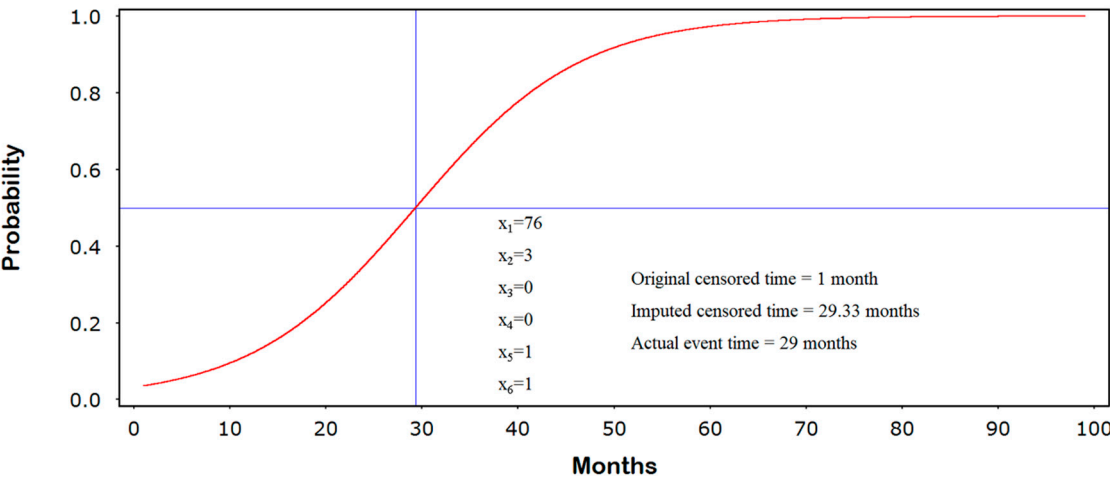


Figure 4. Jump-point plot.

3.3 SAS Code

The SAS code use to generate the jump-point plot is shown in Figure 5. In this code, it is assumed that the data contained in Appendix A has been previously read into the dataset “a”. The counting process variables are created in dataset “b” and then modeled using the “PROC LOGISTIC”

procedure. The predicted probabilities generated by this procedure are plotted against time (ranging from 1 to 99 months) to obtain the jump-point plot. Analyses were performed using SAS Version 9.4. (Cary, NC).

```

data b;
  set a;
  do j=1 to 99;
    if os_censor=1 then do;
      if j<os_tm then dead=0;
      else if j>=os_tm then dead=1;
      tm=j;
      output;
    end;
    else if os_censor=0 then do;
      if j<=os_tm then do;
        tm=j;
        dead=0;
        output;
      end;
    end;
  end;
ods output "Parameter Estimates"=parest;
proc logistic data=b descending;
  model dead=tm agex gradex nstage posmarg hormno rtno/risklimits clodds=pl;
run;
quit;
ods output close;
proc transpose data=parest out=out1;
  var estimate;
data flipparest (keep=col1-col8 rename=(col1=beta0 col2=beta1 col3=beta2 col4=beta3
  col5=beta4 col6=beta5 col7=beta6 col8=beta7));
  set out1;
data c;
  set flipparest;
  agex=76;
  gradex=3;
  nstage=0;
  posmarg=0;
  hormno=1;
  rtno=1;
  do tm=1 to 99 by 0.0001;
    pdead=1/(1+exp(-(beta0+beta1*tm+beta2*agex+beta3*gradex+beta4*nstage+beta5*posmarg
      +beta6*hormno+beta7*rtno)));
    output;
  end;
proc plot data=c;
  plot pdead*tm;
run;

```

Figure 5. SAS code used to generate jump-point plot.

4. Discussion

In this manuscript we have introduced a simple method to partially correct for nonignorable early censoring. By rearranging the data as a counting process we are able to account for the follow-up times of all patients, regardless of their censoring status. For example, if a patient is censored at 50 months, the counting process creates 50 observations corresponding to each month and accordingly assigns the value of 0 to an indicator variable. On the other hand, if the patient had an event at 50 months, the counting process would create 49 observations with the indicator variable set

to 0 and similarly create new observations for each month thereafter until the last month of the study, but instead assigning the value of 1 to the indicator variable.

These counting responses are then analyzed with logistic regression, or another appropriate model for fitting binary data. In addition to including outcome related covariates, a variable denoting the time (e.g., month) associated with the indicator variable is added to the model. The predicted value generated by the model for a particular covariate pattern (associated with a censored observation) is then plotted against the time variable (spanning each month of the study) to obtain a jump-point plot. Dropping a line from the midpoint of this plot to the x-axis gives an imputed censored follow-up time. We then replace the original censored time with this value if it larger of the two values. Also, the imputed value is constrained by a natural upper bound to prevent impossible censored follow-up times (e.g., the value must be consistent with a patient’s maximum biologic lifespan).

An important aspect of this technique is identifying a well-fitting model for the counting process data so that it is able to accurately predict if the outcome is 0 or 1. Understanding the dynamics of the disease or process under study will aid in the selection of appropriate outcome-related covariates. However, formally testing for model goodness of fit is not practical given the highly correlated nature of the counting process data. In theory, while it may be possible to assess model goodness of fit for dependent data using a robust “Huber-White” approach, the regularity conditions for such estimates are quite stringent [16-18]. Instead, we recommend using leverage and residual diagnostic plots to rule out ill-fitting models [11-13]. In some cases, including power and trigonometric terms into the model may potentially improve the efficiency of the fitting algorithm.

The advantage of using a counting process approach is that the imputed censored follow-up times, when appropriately constructed, will better reflect the survival prospects of those who continued in the study. However, because the method is modeled based, it may not be suitable for small datasets or those lacking a set of reasonably predictive covariates. Additionally, it may not always be possible to identify a well-fitting model if there are abrupt changes in the hazard function of the underlying data. The method at hand should not be used if patients who enroll later in study survive longer (e.g., treatment improves over time) or if enrollment criteria change over the course of the study (e.g., worst patients are excluded midway through recruitment) [5].

5. Conclusions

Overall, the best means for handling informative censoring is to avoid the problem in the first place. Careful planning at the study design stage, routine patient monitoring, and implementing proactive strategies to minimize patient dropout are some important steps to ensure the fidelity of a survival time study.

While it was beyond the scope of the current manuscript, it will be informative in future analyses to compare our method with other approaches for dealing with censored values, especially highlighting best and worst-case scenarios [3, 19-24].

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152 **Author Contributions:** Jimmy T. Efird and Charulata Jindal conceive and design the project, analyze the data,
153 and wrote the manuscript. Both authors approved the final version of the manuscript.

154 **Conflicts of Interest:** The authors declared no conflict of interest.

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157 **Appendix A. Example cancer dataset (N=250)**

	A	B	C	D	E	F	G	H	I	J	K	A	B	C	D	E	F	G	H	I	J	K	A	B	C	D	E	F	G	H	I	J	K
1	93	4	1	1	1	1	1	1	1	--	1	71	99	3	0	0	1	1	14	14	--	1	141	78	2	0	0	0	0	31	31	--	1
2	90	3	1	1	1	1	1	1	1	--	1	72	83	2	1	1	1	1	14	14	--	1	142	64	4	1	0	0	0	31	31	--	1
3	89	4	1	1	1	1	1	1	1	--	1	73	85	4	1	1	0	1	15	15	--	1	143	69	3	1	0	1	1	36	36	--	1
4	89	4	1	0	1	1	1	2	2	--	1	74	83	3	1	1	0	1	15	15	--	1	144	68	2	1	0	0	0	36	36	--	1
5	86	3	1	1	1	1	0	2	2	--	1	75	81	3	1	0	1	1	15	15	--	1	145	62	2	1	0	0	0	36	36	--	1
6	86	3	1	0	1	1	1	2	2	--	1	76	98	1	1	0	0	1	15	15	--	1	146	58	3	1	0	1	1	36	36	--	1
7	95	4	1	1	1	1	1	2	2	--	1	77	94	3	1	0	0	1	15	15	--	1	147	69	4	1	0	0	1	37	37	--	1
8	90	3	1	1	1	1	1	2	2	--	1	78	93	4	1	0	0	0	15	15	--	1	148	68	3	0	0	0	1	39	39	--	1
9	86	3	0	1	1	1	1	2	2	--	1	79	90	2	1	0	1	1	15	15	--	1	149	65	3	1	0	0	1	39	39	--	1
10	84	4	1	0	0	1	1	2	2	--	1	80	88	3	1	0	1	1	15	15	--	1	150	65	3	1	1	0	0	39	39	--	1
11	82	4	1	0	1	1	1	2	2	--	1	81	82	3	1	0	1	1	15	15	--	1	151	68	3	1	1	1	0	40	40	--	1
12	91	2	1	1	1	1	1	2	2	--	1	82	85	4	1	1	0	0	16	16	--	1	152	68	4	1	0	1	1	41	41	--	1
13	96	4	1	0	0	1	1	3	3	--	1	83	88	2	1	0	0	0	16	16	--	1	153	63	3	1	1	0	1	41	41	--	1
14	95	3	1	0	1	1	1	3	3	--	1	84	82	3	1	0	1	0	16	16	--	1	154	62	3	0	0	1	0	42	42	--	1
15	89	2	1	1	1	1	1	3	3	--	1	85	84	4	1	1	0	0	17	17	--	1	155	68	1	1	0	1	1	43	43	--	1
16	88	4	1	0	1	0	3	3	3	--	1	86	90	2	1	1	0	1	17	17	--	1	156	68	2	0	0	0	0	43	43	--	1
17	91	3	1	1	0	1	1	3	3	--	1	87	93	3	1	0	1	0	17	17	--	1	157	69	2	0	0	1	1	43	43	--	1
18	91	3	1	1	1	1	1	3	3	--	1	88	90	4	1	1	1	1	17	17	--	1	158	62	3	1	0	1	1	43	43	--	1
19	90	4	1	1	1	1	1	3	3	--	1	89	88	3	0	0	1	0	18	18	--	1	159	67	3	0	1	1	1	44	44	--	1
20	98	4	1	0	1	1	1	3	3	--	1	90	97	3	1	1	1	1	18	18	--	1	160	68	2	1	0	1	1	45	45	--	1
21	94	3	1	1	1	1	1	3	3	--	1	91	94	4	1	1	0	0	18	18	--	1	161	64	3	1	0	0	1	46	46	--	1
22	96	3	1	0	1	1	1	3	3	--	1	92	85	2	1	0	1	1	18	18	--	1	162	62	2	1	1	0	0	46	46	--	1
23	88	3	1	0	1	1	1	3	3	--	1	93	84	4	1	0	1	1	19	19	--	1	163	64	3	0	0	0	0	46	46	--	1
24	95	3	0	1	1	1	1	3	3	--	1	94	83	2	1	1	1	1	19	19	--	1	164	61	3	0	0	1	1	47	47	--	1
25	83	3	1	0	1	1	1	3	3	--	1	95	99	4	1	0	0	1	19	19	--	1	165	58	4	1	1	0	0	48	48	--	1
26	88	3	1	0	1	1	1	4	4	--	1	96	93	3	1	1	0	1	19	19	--	1	166	52	3	0	0	0	1	48	48	--	1
27	95	4	1	1	1	1	1	4	4	--	1	97	83	2	1	0	0	0	19	19	--	1	167	51	2	1	0	0	1	48	48	--	1
28	95	2	1	1	0	1	1	4	4	--	1	98	81	3	0	0	1	1	20	20	--	1	168	51	2	1	0	1	1	49	49	--	1
29	92	3	1	1	0	0	4	4	4	--	1	99	87	3	1	1	0	1	21	21	--	1	169	53	3	1	0	0	1	50	50	--	1
30	96	4	1	0	1	1	1	5	5	--	1	100	85	4	1	1	1	1	21	21	--	1	170	81	3	0	0	0	1	50	50	--	1
31	96	3	1	0	1	0	5	5	5	--	1	101	85	3	1	1	0	1	21	21	--	1	171	77	3	1	1	0	0	50	50	--	1
32	90	3	1	1	0	1	5	5	5	--	1	102	82	3	1	0	0	1	21	21	--	1	172	44	3	1	0	1	1	50	50	--	1
33	89	4	1	1	1	1	5	5	5	--	1	103	80	3	1	1	1	1	21	21	--	1	173	68	3	1	0	0	1	51	51	--	1
34	87	3	1	0	1	1	5	5	5	--	1	104	81	2	1	1	1	1	22	22	--	1	174	72	3	0	1	0	0	53	53	--	1
35	97	2	1	1	1	1	6	6	6	--	1	105	80	4	1	0	0	1	22	22	--	1	175	87	3	0	1	1	1	54	54	--	1
36	96	4	1	0	1	1	6	6	6	--	1	106	91	3	0	1	0	1	22	22	--	1	176	74	4	1	0	0	1	54	54	--	1
37	93	3	1	0	1	1	6	6	6	--	1	107	75	3	1	0	1	0	22	22	--	1	177	52	1	0	0	0	1	55	55	--	1
38	94	3	1	0	0	1	6	6	6	--	1	108	72	4	0	0	1	1	22	22	--	1	178	69	3	1	0	0	0	55	55	--	1
39	93	3	1	1	1	1	6	6	6	--	1	109	83	3	1	1	0	0	23	23	--	1	179	41	3	0	0	1	1	55	55	--	1
40	97	3	1	1	1	1	6	6	6	--	1	110	79	3	1	1	1	1	23	23	--	1	180	64	3	1	0	0	1	56	56	--	1
41	97	3	1	0	1	1	7	7	7	--	1	111	79	4	1	0	0	1	24	24	--	1	181	64	2	1	0	1	1	58	58	--	1
42	97	2	1	0	1	1	7	7	7	--	1	112	78	3	1	1	0	1	24	24	--	1	182	58	3	1	0	1	1	58	58	--	1
43	86	3	1	1	1	1	7	7	7	--	1	113	75	4	1	0	0	1	24	24	--	1	183	53	2	0	1	1	1	59	59	--	1
44	85	3	1	0	1	1	7	7	7	--	1	114	84	3	1	0	0	1	24	24	--	1	184	53	3	1	0	0	1	59	59	--	1
45	91	3	1	0	1	1	7	7	7	--	1	115	78	2	1	1	1	1	24	24	--	1	185	58	1	0	0	0	0	59	59	--	1
46	94	3	1	1	1	1	7	7	7	--	1	116	78	2	1	0	1	1	24	24	--	1	186	54	3	1	0	0	1	60	60		

Appendix A (Continued)

A	B	C	D	E	F	G	H	I	J	K	A	B	C	D	E	F	G	H	I	J	K
211	49	3	1	0	1	1	92	92	--	1	246	47	1	0	0	1	1	99	3	85.42	0
212	52	2	1	0	1	1	92	92	--	1	247	43	2	0	0	1	1	99	10	86.12	0
213	47	2	0	0	1	1	93	4	79.9	0	248	42	1	1	0	1	1	99	5	88.18	0
214	48	2	1	0	0	0	93	93	--	1	249	42	1	1	0	0	0	99	2	90.24	0
215	44	2	1	1	0	1	93	93	--	1	250	46	1	0	0	0	1	99	4	91.71	0
216	50	3	1	0	0	1	93	93	--	1											
217	40	1	0	0	0	1	93	93	--	1											
218	40	3	1	0	1	1	94	2	80.3	0											
219	56	2	1	1	0	1	94	94	--	1											
220	51	2	1	0	1	1	94	94	--	1											
221	48	2	0	0	0	1	94	94	--	1											
222	51	1	0	0	1	1	94	94	--	1											
223	51	2	1	1	1	1	94	94	--	1											
224	52	1	1	1	1	1	94	94	--	1											
225	48	2	0	1	0	1	94	6	85.4	0											
226	42	2	1	0	0	1	94	1	87.4	0											
227	49	1	0	0	1	1	95	95	--	1											
228	49	2	1	1	1	1	95	95	--	1											
229	51	2	1	0	1	1	95	2	68.7	0											
230	51	3	0	0	1	1	95	95	--	1											
231	45	1	1	0	0	0	95	8	85.6	0											
232	45	1	1	1	0	1	95	4	90.5	0											
233	43	2	0	0	0	0	95	2	88.2	0											
234	47	1	1	1	0	1	96	3	87.4	0											
235	42	1	1	0	1	1	96	96	--	1											
236	46	3	0	0	1	1	96	1	76	0											
237	47	2	1	1	1	1	96	96	--	1											
238	45	2	0	0	1	1	96	4	83	0											
239	46	1	1	1	1	1	96	7	84.2	0											
240	46	2	0	1	0	1	96	1	88.5	0											
241	46	1	1	0	0	1	97	7	86.7	0											
242	46	2	1	1	1	1	97	97	0	1											
243	46	3	0	1	1	1	98	4	78.2	0											
244	46	2	0	0	1	1	98	5	81.5	0											
245	46	3	1	0	0	1	98	2	75.7	0											

A=Observation number, B=Age, C=Grade, D= Lymph node invasion, E=Positive margin, F=No hormonal therapy, G=No radiation therapy, H=Actual follow-up time, I=Original censored time, J=Imputed censored time, K=Censoring variable.

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