Statistical Computing and Graphics

Extensions and Applications of Event Charts

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Event charts, which are used to track and plot timed events at the individual level, are highly effective for presenting multiple time-to-event data, can serve as valuable data-monitoring tools, and can be used to supplement conventional survival plots. Depending on the information chosen and the format to be plotted, commonly used event charts are classified as calendar, interval, or Goldman event charts. A very flexible S-Plus routine was developed for drawing standard event charts and for providing many extensions, such as sorting, subsetting, alignment, and multiple point and line formats, to facilitate the graphical data presentation. If used appropriately, these extensions are useful for revealing the correlation between covariates and multiple events. For example, they can be set up so that a continuous time-invariant covariate such as age of diagnosis is plotted on the y axis, and multiple timed events are plotted on the x axis. They can also be set up so that discrete time-invariant covariates such as the treatment arm are sorted and characterized using different line formats (line type, width, and color). In addition, discrete time-varying covariates can be shown by changing the line formats between line segments. The strengths and weaknesses of various event charts and their applications are shown using examples ranging from historical cohort studies to randomized clinical trials.

KEY WORDS: Exploratory data analysis; Graphical presentation; Monitoring clinical trials; Multiple time-to-event data.

1. INTRODUCTION

The idea of the graphical presentation of timed-events data is not new. For example, a chart of the British Royal genealogy from 1660 to 1850, originally published in 1885 by Marey, can be found in Tufte's landmark book (Tufte 1983). The idea of plotting events such as time and age on a coordinate system was introduced by Lexis (1875) to allow the simultaneous tracking of the time cohort and the age cohort. As survival analysis methods advance and increasingly more clinical trials in medical research are being conducted, the need for plotting multiple time-to-event data (e.g., disease diagnosis date, registration date, recurrence date, and date of last follow-up or death) arises. To address this need, we have developed an easy-to-use and versatile graphical tool for displaying these timed-event data at the individual level. We use the term *event chart* as a general name for this entire class of timed-events plots. Event charts, if applied properly, can serve as a highly effective way of presenting and monitoring complex time-to-event data and can be used to supplement conventional survival plots such as the Kaplan–Meier curve, the cumulative hazard plot, and the hazard function plot.

Unlike the commonly used survival plots which show aggregated information, event charts display the "raw data" at the individual level by illustrating the transition of events on the scale of either the calendar time (dates) or the interval time (interval between dates). The simplest form of event chart, which shows the event history for each patient along the x axis, can be used to introduce censoring and to describe different censoring patterns. Scattered descriptions of event charts can also be found in the literature (Enas 1987; Dublin, Rosenberg, and Goedert 1992). Recently, Goldman (1992) introduced the EVENTCHART, which is a modified Lexis diagram, and showed its usefulness in presenting multiple timed-event data. Modifications of similar plots can be found in Therber and Delucchi (1992), Lesser, Kohn, Napolitano, and Pahwa (1995), and Francis and Fuller (1996). Despite the potential usefulness of event charts, the lack of a systematic treatment and the limited availability of software for generating them have considerably discouraged their use. The main objectives of this article are:

1. to review the basic formats of event charts and to compare their strengths and weaknesses;
2. to provide a user-friendly, yet powerful, graphical routine written in S-Plus (Becker, Chambers, and Wilks 1988) for drawing event charts; and
3. to discuss several useful extensions of event charts and their applications.

Three basic formats of event charts and their characteristics are outlined in Section 2. Extensions of event charts are

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Table 1. Data on A Selected Subset of 20 Patients with Head and Neck Cancer*

Patient ID	Age (yr)	p53 status†	Registration at NED[1]	Recurrence	SPT[2]	Death	Last follow-up
1	54	0	01/11/80	09/15/80			07/02/90
2	58	1	02/06/80	10/17/80		11/21/80	
3	60	0	02/22/80				10/11/90
4	58	1	03/10/80		11/23/82	11/30/85	
5	67	1	04/03/80	11/04/80		01/19/81	
6	62	1	06/10/80		07/01/87	09/01/88	
7	74	1	10/24/80	01/08/81		05/05/81	
8	68	0	12/08/80				09/07/93
9	54	1	12/19/80	10/27/81		09/17/82	
10	43	1	02/10/81	02/03/82	09/01/82	09/17/82	
11	57	1	02/19/81				02/14/91
12	57	0	03/25/81	03/09/82			10/25/90
13	57	0	05/29/81				1/27/86
14	57	0	08/21/81				02/08/91
15	56	1	08/31/81		11/01/87	11/16/88	
16	45	1	01/26/82	11/19/84		12/03/85	
17	61	1	02/19/82	01/20/83	10/24/88	12/17/88	
18	47	0	03/01/82				05/01/92
19	65	0	03/30/82		01/13/87	06/27/87	
20	56	1	04/21/82		01/19/88	04/26/88	

NOTE: * Data were extracted from Shin et al. 1996
† 0 = negative; 1 = positive
[1] NED = no evidence of disease
[2] SPT = second primary tumor

covered in Section 3 followed by the conclusion in Section 4.

2. THREE BASIC EVENT CHARTS

Depending on the choice of information to be plotted on the x axis and y axis, event charts can be classified into the calendar event chart, the interval event chart, and the Goldman event chart. The common feature of event charts is that each individual—for example, a patient, a subject, or a study unit—is represented by a single horizontal line and corresponding events are denoted by various symbols placed along the line. The distinguishing characteristics of the three basic formats of the event charts are as follows:

(a) The calendar event chart displays the calendar date of each event along the x axis and subject identification (ID) along the y axis. Multiple events pertaining to the same subject are connected by a horizontal line.

(b) The interval event chart focuses on the time that has elapsed since a starting event, such as the time since a patient was registered in a study. Intervals for all other events are calculated as the elapsed time from that starting event. The interval event chart plots the interval date along the x axis and subject ID along the y axis.

(c) The Goldman event chart plots the interval date along the x axis and calendar date along the y axis to show both data simultaneously in one plot. One unique feature of the

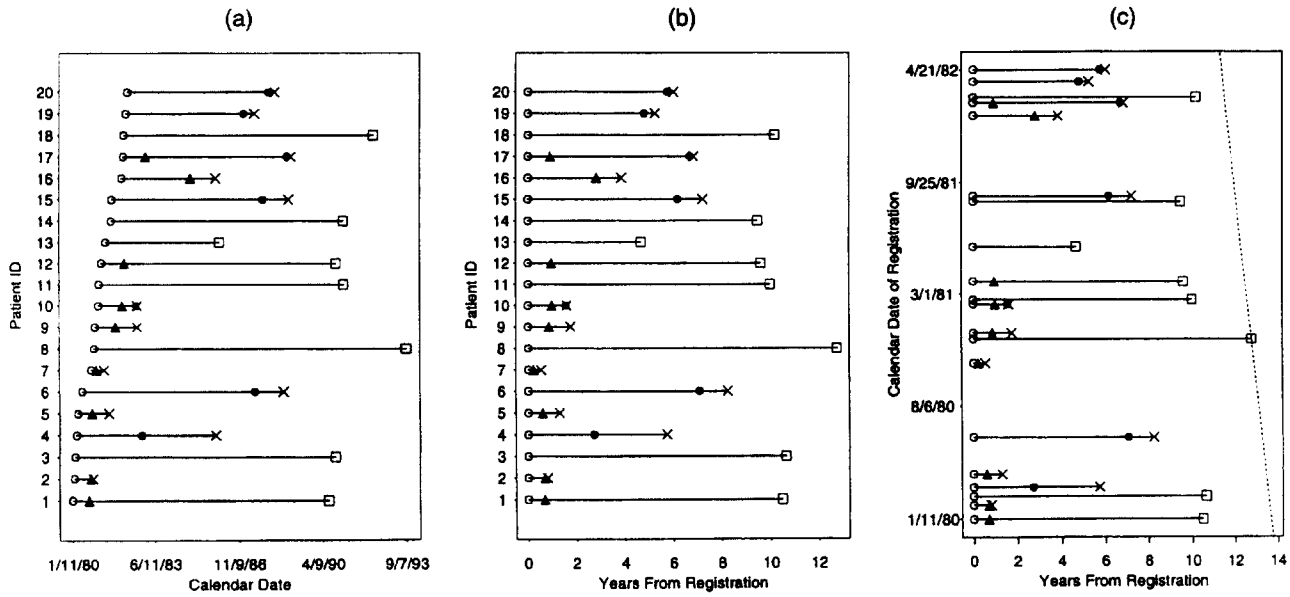

Figure 1. Three Basic Event Charts for Head and Neck Cancer Data. (a) Calendar event chart; (b) interval event chart; (c) Goldman event chart. ○ = date of registration; ▲ = date of recurrence; ● = date of SPT; × = date of death; □ = date of last follow-up.

Table 2. Characteristics of Three Basic Event Charts

Feature	Calendar event chart	Interval event chart	Goldman event chart
Subject ID	y axis	y axis	Can be added
Calendar date	x axis	Not shown	y axis
Interval date	Not shown explicitly	x axis	x axis
Now line	Vertical	Not shown	Diagonal
Equally spaced lines along y axis	Yes	Yes	No

Goldman event chart is that the current time, called the *now line*, can be shown along a diagonal line in the plot.

We give a dataset in Table 1 to illustrate the basic formats of these three types of event charts. The dataset consists of a representative sample of 20 patients entered in a retrospective study (Shin et al. 1996). The study consists of 69 patients who showed no evidence of disease (NED) and were registered in the study between 1980 and 1983. It was found that the p53 protein, a molecular marker, is a prognostic factor for early recurrence, the development of a second primary tumor (SPT), and poor survival in patients with head and neck cancer. Only a small subset of the data has been chosen so that a detailed event history of selected patients can be examined more closely. The findings in this small subset, therefore, only describe the characteristics of these selected subjects. Readers are referred to the original article for a complete description and scientific assessment of the study.

Figure 1 shows the three types of event charts for the data given in Table 1. The key of the plotting symbols for five events (i.e., registration, recurrence, SPT, death, and last follow-up) is given in the figure legend. According to Table 1, Patient 1 was registered on 1/11/80, had a recurrence on 9/15/80, and was last followed up on 7/2/90. These three events can be easily identified in the calendar event chart shown in Figure 1(a). This calendar event chart also shows that the registration dates range from 1980 to 1982, which characterize one of the patient eligibility criteria (i.e., patients need to be registered between 1980 and 1983 to be eligible for this retrospective study). This calendar event chart indicates that the last event in the dataset was the last follow-up date of Patient 8 which occurred on 9/7/93. It also shows that six patients did not have a recurrence or SPT and were alive at the last follow-up. On the other hand, two patients (ID = 10 and 17) both had a recurrence first and SPT developed at a later date. The calendar event chart can also be used to identify the patient cohort by calendar date (i.e., on-study patients at a particular date) by drawing a vertical line on that date.

Figure 1(b) shows the interval event chart of the same dataset using the date of registration as the starting date. Plotting the interval time since registration on the x axis enables one to quickly see a wide range of the on-study time, such as the fact that Patients 2 and 7 died within 1 year after registration because of early recurrence whereas Patient 8 was still alive after more than 12 years since registration. The interval event chart is also useful for identifying risk sets by the on-study time by drawing a vertical line at a given time. The interval event chart can be made more useful by combining sorting and alignment features discussed in the next section.

The Goldman event chart for the head and neck cancer data is shown in Figure 1(c). The default now line is a dotted line drawn at the last event date (9/7/93), which corresponds to almost 14 years after the first patient had NED (1/11/80). The interval cohort and the calendar cohort can be tracked simultaneously by running a vertical line and a diagonal line parallel to the now line. The steep now line is due to the early accrual cutoff date (1983), and therefore, the range of the y axis accounts for two-plus years while the x axis spans for 14 years. The Goldman event chart also reveals a nonuniform accrual in the subset by the clustered lines.

Table 3. Strengths and Weaknesses of Three Types of Event Charts

Feature	Calendar event chart	Interval event chart	Goldman event chart
Identify individual subject	Easy	Easy	OK for well-spaced or jittered lines
Identify risk sets on calendar time	Yes	No	Yes
Identify risk sets on interval time	No	Yes	Yes
Handle ties on the reference date	Yes	Yes	No
Show subject accrual rate	In slope	No	In line density
Allow sorting by an event, time between events, and covariate on the y axis	Yes	Yes	No
Allow aligning by an event on the x axis	No	Yes	Yes

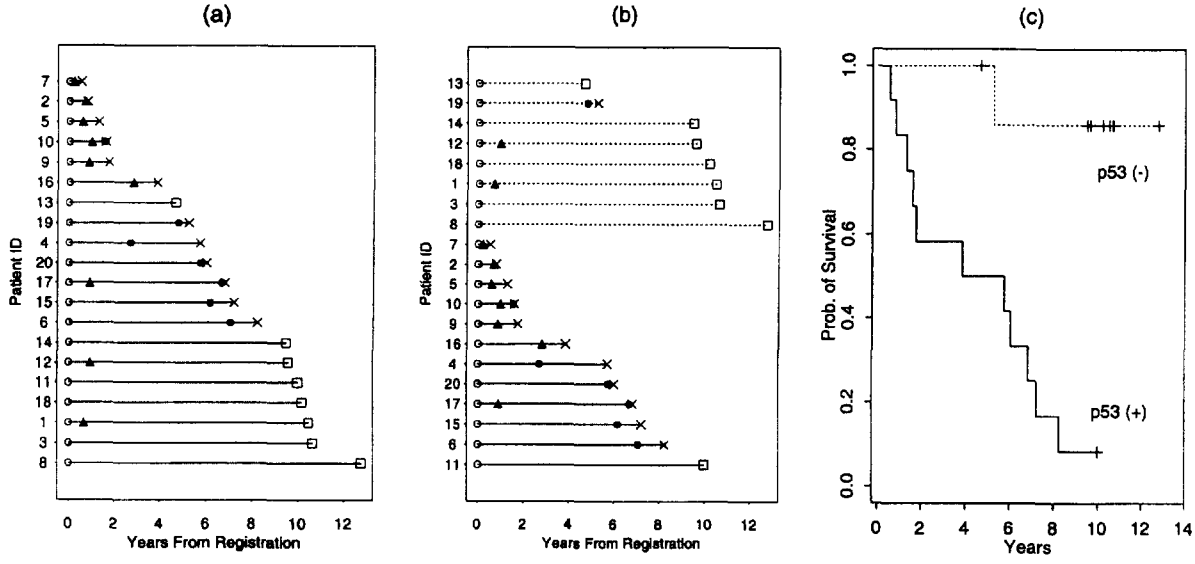

Figure 2. Sorting Extensions of Event Charts and Survival Plots for Head and Neck Cancer Data. (a) Interval event chart by on-study time; (b) interval event chart by p53 status and on-study time; (c) overall survival by p53 status. ○ = date of registration; ▲ = date of recurrence; ● = date of SPT; × = date of death; □ = date of last follow-up. Lines: - - - - p53(−), —— p53(+).

Main characteristics of these three basic event charts are summarized in Table 2 according to the way in which the subject ID, calendar date, and interval date are shown in the figure. Because we limit our attention to two-dimensional graphs, only two of these three key features can be shown explicitly in each event chart. A calendar event chart focuses on ID and calendar date, whereas an interval event chart emphasizes ID and interval date. In contrast, the Goldman event chart plots calendar date and interval date together. As a result, it is easier to identify subjects and track events in calendar or interval event charts because equally spaced lines are ordered by subject ID. The Goldman event chart is more useful for tracking events by both calendar and interval dates, but it can be difficult to identify individuals when there are ties in calendar dates. The relative strengths and weaknesses of the three types of event charts are listed in Table 3. Extension and more illustrations of these points are given in Section 3.

We developed an S-Plus function: `'event.chart()'` to provide a user-friendly environment for drawing event charts. We chose the S-Plus language because of its excellent graphical capability and high portability across different operating systems (Becker, Chambers, and Wilks 1988). The `event.chart` function can be used to draw the standard event charts discussed earlier as well as more sophisticated event charts, which are discussed in the next section. The `event.chart` function, help file, and sample datasets can be obtained by downloading /pub/S/event.chart.shar.Z through anonymous ftp from the Internet node odin.mdacc.tmc.edu (143.111.62.32) or from the S Archive in the StatLib (http://lib.stat.cmu.edu). More examples and technical details of event charts can be found in Dubin, Lee, and Hess (1997).

3. EXTENSIONS OF EVENT CHARTS

Examples of the three basic event charts discussed in Section 2 can be found throughout the literature. In this section, we describe several useful extensions that can be added to event charts. Sections 3.1, 3.2, and 3.3 introduce the extensions of sorting and plotting subjects by event time, groups, and a continuous covariate, respectively. Section 3.4 illustrates the extension of aligning events. Section 3.5 shows how a categorical time-varying covariate can be visualized by changing the line type. The use of event charts for monitoring clinical trials is discussed in Section 3.6.

3.1 Extensions on Sorting Subject by Event Time

The interpretability and usefulness of event charts can be greatly enhanced by plotting subjects according to a carefully chosen order on the y axis. For example, Figure 2(a) shows an interval event chart sorted by the on-study time (from the registration date to the last on-study date). We can see that six patients died before four years and another six patients died between five and nine years. One patient was censored around five years and the remaining eight patients were still alive at their last follow-up. The plot also shows that recurrences tend to occur early, while SPTs develop in a later date.

3.2 Extensions on Sorting Subjects by Groups

Event charts can also be useful in showing multiple timed-events by groups or other categorical time-invariant covariates. Figure 2(b) is an interval event chart similar to Figure 2(a), but patients are sorted first by their p53 status and then by their on-study time. There are 8 p53(−) patients—shown in dashed lines in the upper half of the plot—and 12 p53(+) patients shown in solid lines in the lower half of the plot. It can be seen that 7 of the 8 p53(−) patients survived, but 11 of the 12 p53(+) patients died. The corresponding Kaplan-Meier survival curves in Figure 2(c)

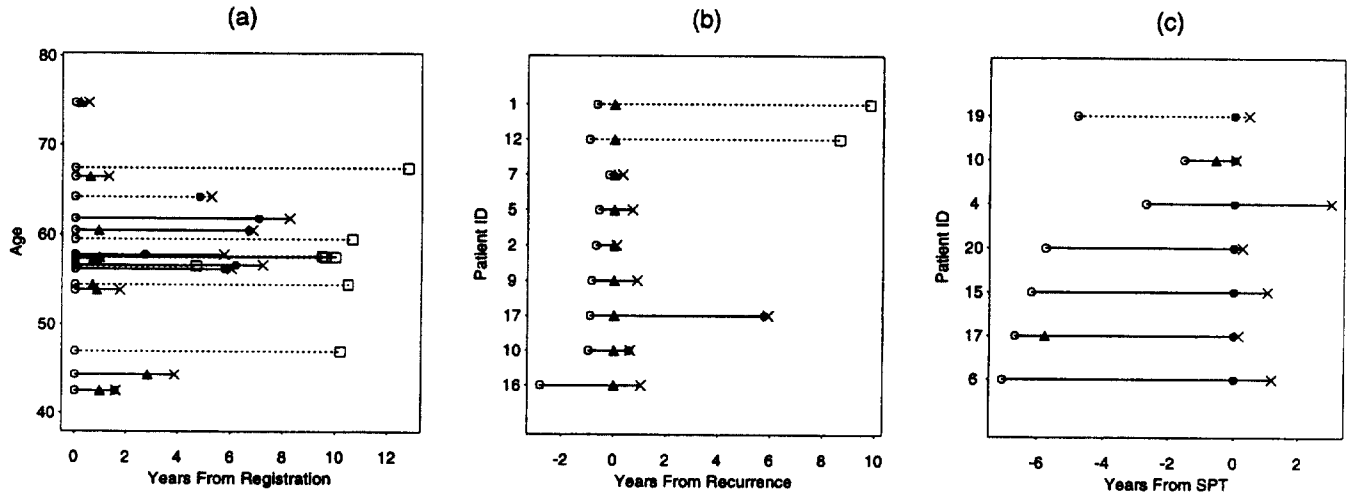

Figure 3. Plotting and Alignment Extensions of Event Charts. (a) Interval event chart by age; (b) interval event chart by p53 status and time to recurrence; (c) interval event chart by p53 status and time to SPT. ○ = date of registration; ▲ = date of recurrence; ● = date of SPT; × = date of death; □ = date of last follow-up. Lines: - - - - p53(−), —— p53(+).

also show a clear survival advantage for p53(−) group. One interesting observation is that the event charts are similar in shape to the Kaplan–Meier curves except that the step size is fixed and does not correspond to the change in the survival probability. Plotting events by groups is also very effective in identifying different failure patterns. Specifically, p53(−) patients had less recurrences and SPTs than p53(+) patients. Furthermore, even though two p53(−) patients had recurrence, they were likely to be successfully treated and survived for a long period of time (ID = 1 and 12). Conversely, most of the p53(+) patients who developed recurrence died early. By looking at Figures 2(b) and 2(c) together, one can obtain the grouped survival information as well as the detailed event history of these 20 patients. Event charts and survival curves complement each other by offering "microscopic" and "macroscopic" views, respectively.

3.3 Extensions on Plotting Subjects by a Continuous Covariate

The effect of a continuous covariate can be shown in event charts by plotting events according to the value of the covariate along the y axis. For example, Figure 3(a) shows the interval event chart by age for the head and neck cancer data. The p53 status is shown by the same line types as before. From Table 1, Patient 10 is the youngest patient at registration. This patient was 43 years old, had both recurrence and SPT, and died within two years of NED. At the other extreme, Patient 7 was 74 years old, had an early recurrence, and died within seven months of NED. Both patients can be easily identified in Figure 3(a). The figure reveals that there is no clear indication of the prognostic value of age. There is also no evidence of correlation between age and p53 status.

When a continuous covariate is plotted along the y axis, subject ID is suppressed in the figure. Nevertheless, subject ID can be easily added to the plot using the S-Plus functions `text(x, y, labels=ID)` or `identify()`. Another consideration when plotting events by a continuous covariate is the need for handling ties. For example, Table 1 shows that four patients were 57 years old, two patients were 54 years old, and another two patients were 58 years old. When events are plotted along the y axis of age, tied observations will be shown at exactly the same y location and overlap with one another. To avoid this problem, we have added a "jitter" option to break the ties by adding a small random noise as shown in Figure 3(a). The amount of jittering and the seed of the random number generator can be specified in the function. The jitter option is also available in our program to separate the tied or nearly tied observations when plotting the Goldman event chart for subjects with the same calendar date.

3.4 Extensions on Aligning Events

In addition to sorting events on the y axis by events or by groups, extensions can be made to the interval event chart by choosing a reference event as the starting event and then aligning subjects on the x axis accordingly. For example, Figures 3(b) and 3(c) take recurrence and SPT, respectively, as the reference event. These two figures are very helpful in characterizing two distinct failure patterns in head and neck cancer patients. Figure 3(b) shows the nine patients who had recurrence. All recurrences occurred within two years of NED, except in Patient 16 who had a slightly longer time to recurrence. Five patients who had recurrence but no SPT died shortly after the recurrence. Two patients (ID = 10 and 17) developed SPT after recurrence

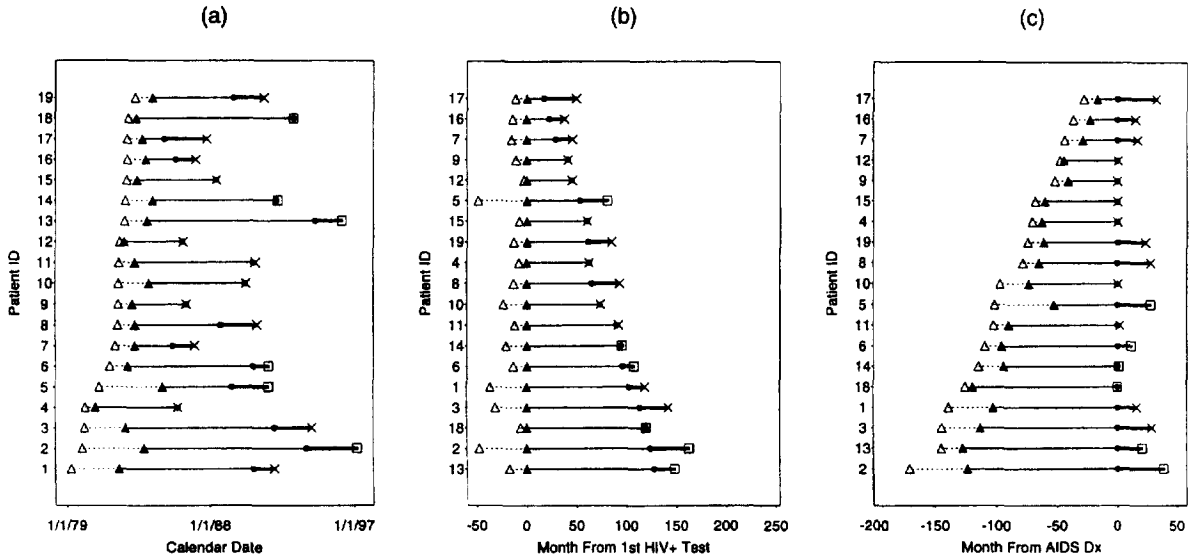

Figure 4. Event Charts for Multicenter Hemophilia Cohort Study. (a) Calendar event chart; (b) interval event chart aligned by first HIV(+) test; (c) interval event chart aligned by AIDS diagnosis. △= date of last HIV(−); ▲ = date of first HIV(+); ● = date of AIDS; × date of death; □ = date of last alive. Lines: - - - - HIV(−) to (+); —— HIV(+) to AIDS; —— AIDS to last follow-up.

and died shortly afterward. All of these patients had positive p53. The remaining two patients (ID = 1 and 12) were p53(−) and were successfully treated for their recurrences and lived for more than eight years after the recurrence.

Compared to recurrence, a different failure pattern of SPT can be found in Figure 3(c). SPT developed in a total of seven patients. SPT can occur from one to seven years after NED, but most of the SPT developed four years after NED in this patient population. Except for one patient, all patients died shortly after the SPT diagnosis regardless of their p53 status. The findings in this subset are consistent with the head and neck cancer literature.

3.5 Extensions on Changing the Line Types

The change of a time-varying, categorical covariate in event charts can be shown by plotting the line segments using different type, width, or color according to the value of the covariate. To illustrate this, we have taken a subset of data from the Multicenter Hemophilia Cohort Study (O'Brien et al. 1996) as an example. The dates of last HIV(−) test, first HIV(+) test, AIDS diagnosis, and death or last known alive are shown in Figure 4 for 19 patients between 18 to 34 years old who had complete information on the above dates. We consider the disease status of a patient as a time-varying covariate. The time between the last HIV(−) and first HIV(+) tests is plotted in a dashed line segment. The time from the first HIV(+) test to AIDS diagnosis is plotted in a thin, solid line segment. The time from AIDS diagnosis to death or last known alive is shown in a thick, solid line segment. Figure 4(a) is a the calendar event chart sorted by the date of last HIV(−) test. The figure shows that the study period extends from 1979 to 1997.

An interval event chart aligned by the first HIV(+) date and sorted by the time from the HIV(+) test to AIDS diagnosis is shown in Figure 4(b). It can be seen that the time from HIV(−) to the HIV(+) test is generally less than two years but two patients (ID = 2 and 5) had intervals close to 50 months. The time from the first HIV(+) test to AIDS diagnosis ranges from 17 months (ID = 17) to 128 months (ID = 13). No correlation is seen between the time from HIV(−) to HIV(+) and the time from HIV(+) to AIDS. Figure 4(c) shows the interval event chart aligned by AIDS diagnosis and sorted by the time from the last HIV(−) test to AIDS diagnosis. There are six censored patients and the remaining 13 patients all died shortly after the AIDS diagnosis. The figure suggests that there is also no correlation between the time from the last HIV(−) test to AIDS or the time from the first HIV(+) test to AIDS and the survival time after AIDS. Survival analysis with time-dependent covariates can be applied to verify this speculation.

3.6 Useful Features for Monitoring Clinical Trials

Event charts can provide many useful features to facilitate the monitoring of clinical trials especially in checking study progress and assessing data quality. We use data from an ongoing multicenter lung cancer chemoprevention study (National Cancer Institute) for illustration. In this study, eligible and consenting patients were registered to begin an eight-week placebo run-in period for evaluating their compliance. Compliant patients were randomized, then, followed at three months, six months, and every six months thereafter. The study opened in December 1992 and as of March 1996, there were 1,133 patients registered in the study. Because of the large number of patients in the study, we have selected only one out of every 10 patients (i.e., Patient ID = $1, 11, 21, 31, \ldots, 1{,}131$) to plot in Figure 5. The calendar event chart shown in Figure 5(a) gives a chronological overview of the event history. As can be seen at the bottom of the plot, Patient 1 was registered on 12/8/92 and randomized on 2/5/93, and had follow-up visits on

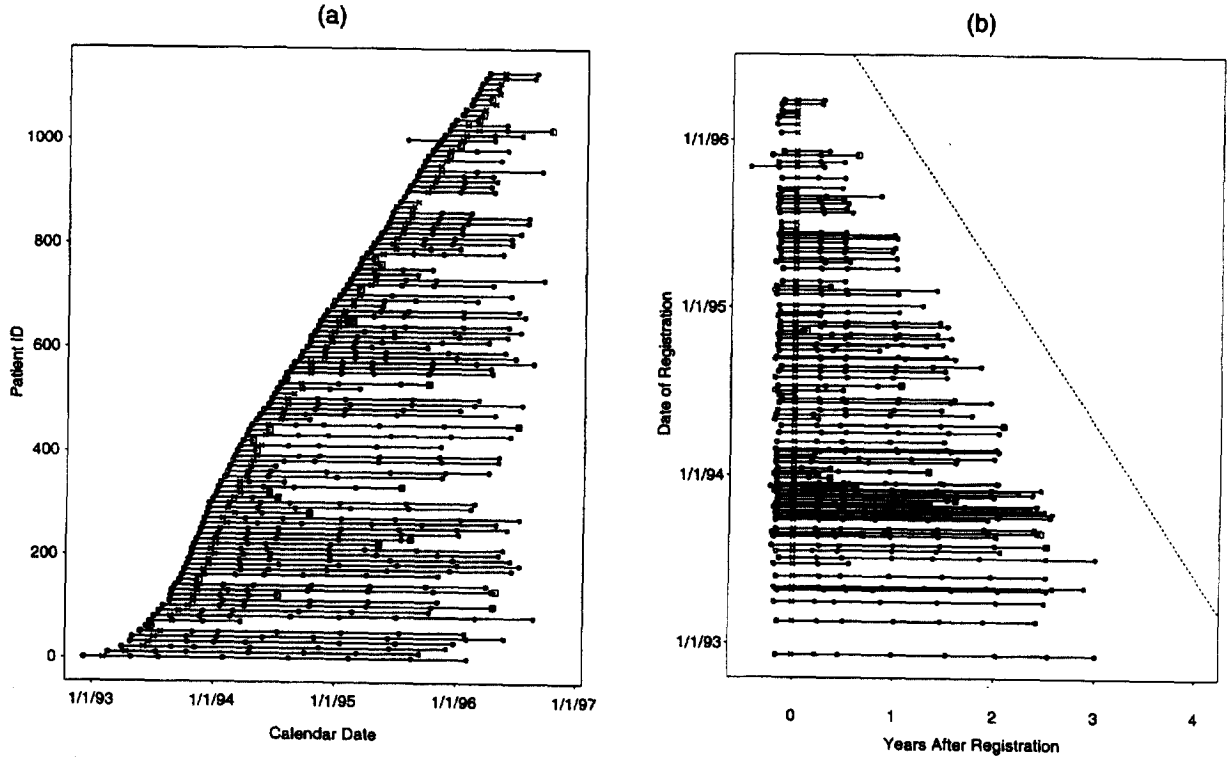

Figure 5. Event Charts for the Lung Chemoprevention Trial. (a) Calendar event chart; (b) Goldman event chart. ○ = date of registration; × date of randomization; ● = date of follow-up visits; ■ = date of death; □ = date of off-study.

4/30/93, 7/23/93, 2/1/94, 8/17/94, 2/14/95, 8/21/95, and 2/7/96. The last patient shown in the figure is Patient 1131, who was registered on 3/28/96, randomized on 5/16/96, and had the first follow-up visit on 8/22/96. Such calendar event charts are very useful for data screening by observing one eye-catching event in this chart: Patient 1001 had one follow-up visit before registration. The event history for this patient was: registration on 11/3/95, randomization on 1/9/96, first follow-up visit on 4/15/96, and second follow-up visit on 7/26/95. After reviewing the record, we found that the second follow-up visit actually occurred on 7/26/96. Such a data entry error, which may not be obvious by looking at the printout of all data, can be easily identified in an event chart. Another less obvious error caught in this chart is in Patient 651, who died on 1/31/95 but is shown to have an off-study date of 2/17/95. The error was resulted from the miscoding of the off-study date. Both errors identified by the event chart have been corrected in the database. Figure 5(a) also shows that there are a few patients whose last follow-up visit dates have not been updated for a while. For example, Patient 71 had a last visit on 3/24/94 but there were no indications that the patient was off study or dead. Although reporting delays are not uncommon in a large-scale, multicenter trial such as this one, event charts can be helpful in identifying cases that require special attention. Queries can be sent to the institutions regarding patients with overdue follow-ups.

Our version of the Goldman event chart for the same dataset is shown in Figure 5(b). Compared with the original Goldman event chart, Figure 5(b) has been modified slightly so that events are aligned according to the randomization date. Therefore only the randomized patients are included. As discussed earlier, the Goldman event chart is very useful for tracking the calendar cohort and the interval cohort simultaneously. Both data errors noted in Figure 5(a) can also be identified in Figure 5(b). One additional useful feature of the Goldman event chart as well as the interval event chart (not shown here) is that they can be used to check whether follow-up visits are on schedule or not. We can see from the chart that the visit times are clustered around 3, 6, 12, 18, 24, 30, and 36 months after randomization, as specified in the protocol.

As indicated in Table 3, the accrual rate of a study can be detected in the slope of calendar event chart and in the line density of Goldman event chart. By carefully examining Figure 5, one can see that the study had a slow start in the beginning, had a high accrual rate from October 1993 to March 1994, and had a steady accrual rate thereafter. The average accrual in this study has been about 30 patients per month. Event charts are highly effective in tracking study accrual. With these features, event charts can be very useful for presenting a graphical data summary of important toxicity and efficacy events to the Data Monitoring Committee or the Institutional Review Board meetings during the interim monitoring of a trial.

4. CONCLUSION

The first step in a successful data analysis is to make sure that the data are relevant to the research objective and are of good quality. We have shown that event charts can be instrumental in screening data and in error checking. If the

timed events are plotted on a calendar or an interval time scale, these charts can also help reveal the sampling scheme and allow investigators to check for possible selection bias. Compared with data printouts or tables, event charts provide a more efficient and more effective way of presenting data. Event charts display the "raw data" contained in timed events without making any model assumptions. The use of event charts is in accord with the fundamental principle of exploratory data analysis—"let the data speak for themselves."

We have also shown that event charts complement standard survival plots and, together, we can see the "forest" and the "trees". A complete picture of the multiple time-to-event data can be best revealed by showing the standard survival plots which present the collective information at the global level as well as the event charts which show the detailed events at the individual level. We recommend that event charts be drawn before survival curves are plotted because event charts can help investigators gain insight into the data and because event charts are very useful in error checking. In addition, by plotting the relationship between timed events and covariates, event charts can be helpful in model building and in choosing the proper analysis.

We have demonstrated that various extensions on sorting, aligning, and plotting can make event charts more useful. These extensions, when using alone or in combination, can greatly enhance data presentation. With this readily available software, we hope to see the increased use of event charts to monitor clinical trials and analyze multiple timed-events data.

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