1

Introduction

1.1 HISTORICAL NOTES

In the middle of the seventeenth century John Graunt, a haberdasher by trade, started to collect and tabulate the information included in the Bills of Mortality published weekly at that time in London. This work, probably done in collaboration with Sir William Petty, appeared in 1662 and contained a demographic summary of causes of death in England and Wales. As a result, John Graunt was elected a member of the Royal Society at the recommendation of King Charles II, not a small feat considering the hierarchical structure of the society existent at the time. In 1693, the famous astronomer, Edmund Halley, developed the concept of life tables in a format not unlike that used today in survival analysis. His data were based on the register of births and deaths for the city of Breslau (now Wrocław, in southwestern Poland). In 1760 Daniel Bernoulli applied Halley's method to demonstrate the advantages of smallpox inoculation. He calculated the increase in Halley's survivor function if smallpox were eliminated as a cause of death. In this way, Bernoulli founded the theory of competing risks. A summary of his work on competing risks can be found in David and Moeschberger (1978). From the eighteenth century, mathematics developed, notations changed and statistics branched out as a science in its own right. The great discoveries of the nineteenth century in physics and biology led to a deterministic

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view of the universe. However, as the tools for measurement grew more and more precise it became apparent that some unexplained, random factors were at work. In the twentieth century, due in part to the need to explain the random variation and in part to the extraordinary development of computing capabilities, the theory of statistics saw significant progress. Based on Bernoulli's work, the theory of competing risks, referred to in actuarial sciences as *multiple decrements,* has also developed.

1.2 DEFINING COMPETING RISKS

This chapter presents an introduction to the topic of competing risks. It is intended for statisticians who have not had any exposure to competing risks and for non-statisticians whose research involves time-to-event data. The analysis of such data is usually referred to as *survival analysis,* because the theory was developed using death as the event. It is also called the *analysis of incomplete data.* The term *incomplete* refers to records where an event has not been observed, but is bound to take place if followed long enough. This type of observation is called *censored* and its definition can be found in Chapter 2. The event need not be death. It can be any event that occurs over time, such as relapse of disease, recidivism or discharge from hospital. Survival techniques are well developed and implemented in major statistical software. Yet, there are some situations where it may not be appropriate to apply the usual survival methods to the time-to-event analysis. One such situation is where competing risks are present. The competing risks situation can be defined in several different ways, as shown in Chapter 3. In general, a competing risks situation arises when an individual can experience more than one type of event and the occurrence of one type of event hinders the occurrence of other types of events. To illustrate this definition, suppose that a group of patients diagnosed with heart disease is followed in order to observe a myocardial infarction (MI). If by the end of the study each patient was either observed to have MI or was alive and well, then the usual survival techniques can be applied. In real life, however, some patients may die from other causes before experiencing an MI. This is a competing risks situation because death from other causes prohibits

the occurrence of MI. MI is considered the event of interest, while death from other causes is considered a competing risk. The group of patients dead of other causes cannot be considered censored, since their observations are not incomplete.

1.3 USE OF THE KAPLAN–MEIER METHOD IN THE PRESENCE OF COMPETING RISKS

In the presence of competing risks, the usual survival methods should be applied with caution and one has to be aware of the consequences of their use. The Kaplan–Meier method is the most common as well as the most controversial technique in the competing risks framework. It is a method for estimating survival probabilities (Kaplan and Meier, 1958) at different time points. It is relatively easy to apply and interpret and can be depicted visually. Its wide availability in the statistical software makes its use appealing. When competing risks are present, Kaplan–Meier estimates (denoted by KM) cannot be interpreted as probabilities. Their complement $(1 - KM)$ can be interpreted as the probability of an event of interest in an ideal world where the other types of events do not exist. However, this concept is not useful in practice. Kalbfleisch and Prentice (1980) suggested an approach that accounted for the competing risks. This method is labelled the *cumulative incidence function* (CIF, introduced in Chapter 4). Using this technique, the probability of any event happening is partitioned into the probabilities for each type of event. For example, in the hypoxia trial described in Section 1.6.2, the possible events are local relapse (L), concomitant local and distant relapse (L&D) and distant relapse only (D). Usually death is a competing risk event. However, in this dataset, at the time of the analysis, there were no deaths without a local or distant relapse. The probability of *any* type of event occurring can be estimated using the Kaplan–Meier method $(1 - KM)$. The probability of *one* type of event is estimated using the CIF. At any point in time, $1 - KM$, calculated for all events, is equal to the sum of the cumulative incidence for each type of event. In Figure 1.1 the dashed line represents the cumulative incidence for events of type L only, and the thin solid line represents the CIF for L in addition to L&D. Therefore, the portion in between the first

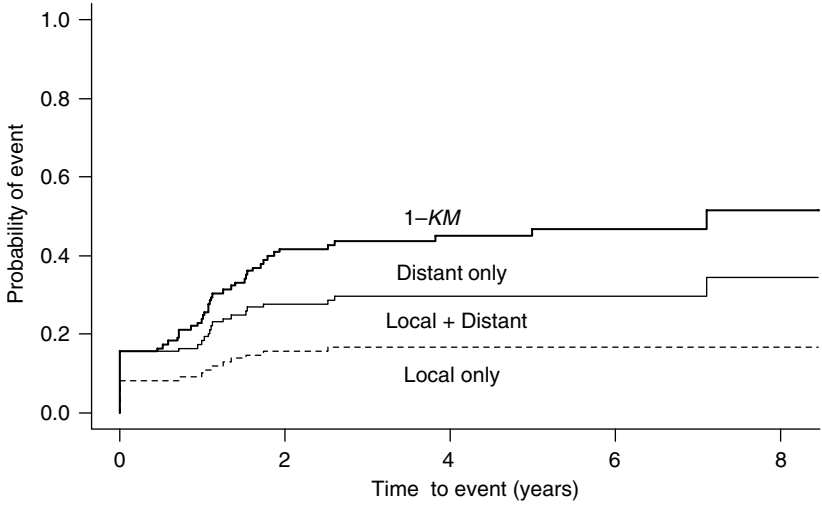

Figure 1.1 Partition of the complement of the Kaplan–Meier estimate ($1-KM$) into the three cumulative incidence functions – local, local and distant, and distant only – in the hypoxia trial.

and second lines is the probability of L&D. If the probability of D is added then the probability of any event is obtained, depicted as the solid thicker line.

In the presence of competing risks, $1-KM$ does not estimate the probability of the occurrence of a type of event. To illustrate this idea, consider that the group of heart disease patients described earlier contains 20 individuals and they all either experienced an MI or died of other causes. The time and type of failure are given in Table 1.1. The time is given in months and the type of failure is coded as MI or D, the latter being used if the patient died of other causes. It is obvious that by 16 months 50% of the patients experienced MI. The cumulative incidence for MI at 16 months (calculated as shown in Chapter 4) is also 50%. However, the $1-KM$ estimate at 16 months is 84%. Furthermore, $1-KM$ for the competing risks (for D) at 16 months is 100%. If we interpret $1-KM$ as the probability of the event occurring by a certain time t, then the sum of the value of $1-KM$ for MI and the value for $1-KM$ for D gives the probability that any of these events happened by time t. In this case, the $1-KM$ estimates at 16 months are 0.84 and 1,

Table 1.1 Failure time for the heart disease example.

Failure time (months)	1	1.5	2	3.2	4	4.3	5	6.1	7	7.3	8	8.1	8.5	9	10	10.5	11	12	15	16
Type of failure	MI	MI	D	MI	D	D	D	MI	D	MI	MI	D	D	D	MI	MI	MI	D	MI	D

resulting in a sum of 1.84 which, as a probability, is nonsensical since it is larger than 1. Hence, in the competing risks framework, in contrast to the cumulative incidence approach, $1 - KM$ cannot be interpreted as the probability of an event happening by time t.

1.4 TESTING IN THE COMPETING RISK FRAMEWORK

In the previous section it was shown that the classical (Kaplan–Meier) technique for summarizing time-to-event data is not recommended in the presence of competing risks. In contrast, when testing a covariate, the standard methods as well as the newly developed methods can be applied. The log-rank test and Cox regression are well established methods of analysis in the survival literature. These methods ignore the competing risks and test the 'pure' effect, which may be useful. In contrast, the more recent techniques developed by Pepe and Mori (1993), Gray (1988) and Fine and Gray (1999) take into account the competing risks. Therefore, the analysis of time-to-event data in the presence of competing risks has two main approaches: testing the 'pure' effect by ignoring the competing risks and incorporating the competing risks. Each of these methods gives a different clue regarding the effect of the covariate.

Choosing which test to use should be a collaborative effort between researcher and statistician. The statistician needs to understand the experiment and the researcher needs to understand the implications of using any of these methods. To illustrate the principles involved, a real-life example follows.

Hodgkin's disease (HD) is a type of cancer which is common among young people (the median age is 30 years). Let us consider

a group of 616 patients diagnosed with early stage Hodgkin's disease, treated with radiation therapy. This is a subset of the dataset presented in Section 1.6.5. Since the early stage disease (stages I and II) is well controlled by treatment and the patients are young (80% of them younger than 45 years), they tend to live a long time after the treatment. Analysing this group of patients can give information about the late effects of radiation. Suppose that the event of interest is the incidence of second malignancy. Inevitably, some patients die before the appearance of another malignancy. Death without malignancy constitutes the competing risk. There are 84 patients for which a second malignancy was documented and 195 who died without a second malignancy. The remaining individuals did not experience any event and are considered censored. The main question is whether the younger group (aged 30 or younger) differs with respect to the occurrence of second malignancy compared to the older group (aged over 30). Since a malignancy is more likely to occur as one grows older, it is expected that the older group has more second malignancies than the younger one. Figure 1.2 shows the cumulative incidence curves for the second malignancy in the two groups and the *p*-values for

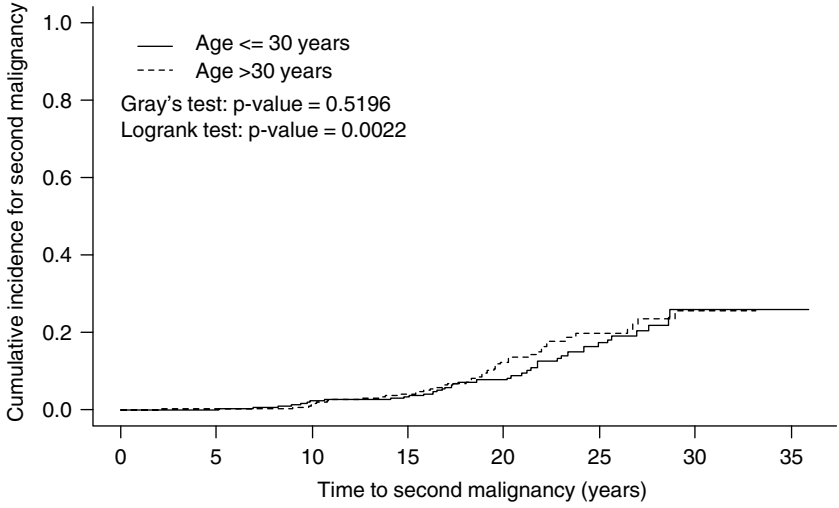

Figure 1.2 Cumulative incidence for malignancy by age group.

Gray's test and for the log-rank test. Counter-intuitively, Gray's test and the curves suggest that the two groups are similar. The log-rank test, which ignores the competing risks, seems to be more consistent with our prior expectations. The results of these tests are strikingly different because they convey different information. The cumulative incidence curves for the competing risk (death without second malignancy) in the two groups differ greatly (Figure 1.3). The older group has a far larger incidence of death without malignancy than the younger group.

It is to be expected that the older a person gets, the more likely he/she is to have other fatal conditions. Because an older person may die of other causes a second malignancy may not have a chance to be observed and therefore the two groups end up having a similar number of second malignancies, hence the non-significance of Gray's test. The log-rank test expresses the fact that if the deaths of other cases did not occur the probabilities for the second malignancy would be different in the two groups. A specific preventive measure for the second malignancy in the older population need not be taken since the

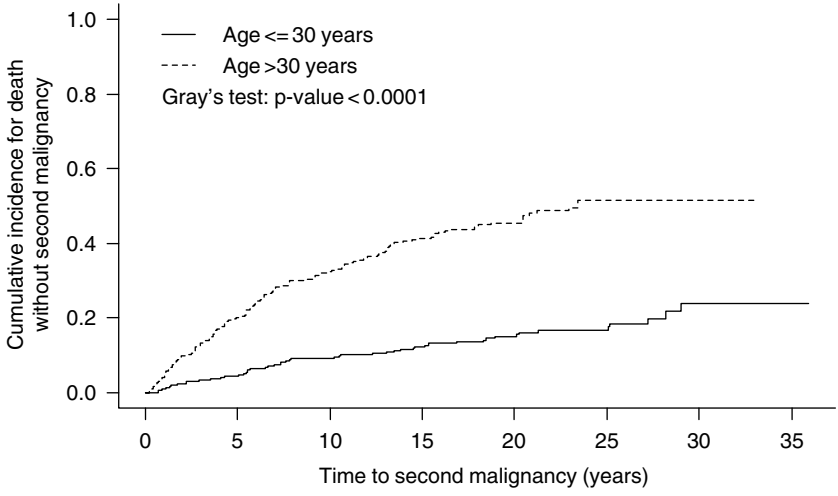

Figure 1.3 Cumulative incidence for death without second malignancy (competing risk).

number of malignancies is about the same as in the younger population. However, the significance of the log-rank test suggests that the biology of getting a second malignancy in the older population is different than in the younger group. Therefore, it may be worthwhile to analyse genetically the tumour tissue from the second malignancy and contrast the findings between the young and old population. In conclusion, the older patients do indeed have a higher risk of getting the second malignancy, but they also have a higher risk of getting other life-threatening diseases which makes the number of second malignancies observed about the same as in the younger group.

Suppose that this group of HD patients is compared with a group of patients registered at a hospital for a disease other than cancer who were not treated with radiation. In this case the log-rank test tells us whether the HD patients treated with radiation have a larger risk of second malignancy. One hypothesis which can be generated is that radiation causes second malignancies. Gray's test answers the question whether more second malignancies are observed in one group, a result which is sensitive to the group to which we compare the HD patients. Thus, Gray's test will give different results when the HD population is compared with a group of young, healthy individuals who came into the hospital due to a sports injury and with a group of young heart disease patients. However, the test takes into account the competing risks, giving information on the observed difference between groups. For more information on the interpretations included in this book the reader can consult Sections 3.3.3 and 4.1.

In conclusion, while both techniques can be applied each gives different information. More details on these tests and modelling are given in Chapters 5 and 6.

1.5 SAMPLE SIZE CALCULATION

One step in the process of planning a study is the calculation of the total number of subjects necessary to detect a specific difference in the outcome with the two types of error (α and β) set to pre-specified values. This section is intended for those researchers who do not wish to make these calculations themselves but employ a

statistician for this purpose. Therefore, the focus is on conveying the general ideas involved and the necessary data that the researcher needs to supply to the statistician.

The sample size calculation in time-to-event analysis is more complex than for other types of endpoint. If the endpoint of a study is the average of some variable one only needs to know the difference to be detected, the standard deviation and, of course, the two types of error. To be able to calculate a sample size when the endpoint is a proportion, one only needs the two hypothesized proportions and the two types of error.

In survival analysis the necessary number of events is calculated first, followed by the total number of patients that produces the number of events needed. This is why more information is needed for the calculation of the sample size for time-to-event outcomes than for any other types of outcome. If the outcome is survival then besides the hypothesized percentage survival at a certain point in time one also needs to know the rate of accrual and the length of follow-up after the accrual ends. While the former helps to estimate the number of events necessary, the latter is used to calculate the number of individuals necessary to produce the required number of events. In addition, when competing risks are present, an estimate of the incidence of competing risks is needed. Extra care has to be given to the method used to estimate the hypothesized percentages for the event of interest as well as for the competing risks. Therefore, it is important to know whether the hypothesized percentages are based on the cumulative incidence approach or are obtained from an older study where $1 - KM$ was used. The computation of sample size is dealt with in Chapter 7.

1.6 EXAMPLES

This section presents the examples that will be used throughout this book. They are based on real-life examples for which relevant references are given where possible. However, the data are not identical to those used in the original publications. To eliminate missing data, some records have been excluded or changed. The missing values were substituted either by the median value, when there were very few (two or three), or by a randomly generated

number from the same distribution as the original variable. Only a subset of the variables available in the original datasets are used in this book. The follow-up may not be the most recent or the same as that used in the published sources. Although we have modified the data, we have tried not to change them in a fundamental way. The types of events, their pattern of occurrence, and the way in which they were collected are the same as in the original studies. Time is calculated in years. These examples have been included to illustrate statistical issues that arise in practical research, and not for purposes of drawing medical conclusions. For each of the five real-life examples a portion of the data (20 records) is shown in tables together with a description of the variables. All these datasets can be downloaded from the website address given in the Preface and read in R or SAS (see Sections B.1.5 and B.2 in Appendix B).

1.6.1 Tamoxifen trial

In December 1992 a multicentre randomized clinical trial for patients with node negative breast cancer began accruing subjects. Between 1992 and 2000, a total of 769 women were randomized: 383 in the tamoxifen-alone arm (Tam) and 386 in the combined radiation and tamoxifen arm (RT+Tam). The last follow-up was conducted in the summer of 2002. Only those patients accrued at a single contributor institution are included here: 321 patients in the Tam arm and 320 in the RT+Tam arm. The original design was for an equivalence study with disease-free survival as the main endpoint. However, for the purpose of this book this fact will be ignored the data analysed as an effectiveness trial, investigating whether RT+Tam is better than Tam alone. The events recorded were local relapse, axillary relapse, distant relapse, second malignancy of any type, and death. The time of the first occurrence of each type, of event was documented. For example, if a patient experienced local relapse at 1 year, another local relapse at 2 years and an axillary relapse at 3 years, the only events recorded are the local relapse at 1 year and the axillary relapse at 3 years. The local relapse at 2 years is the second relapse of the same type and is not recorded. For each type of event there is a censoring variable, which indicates whether the event occurred.

The time was calculated in years from the date of randomization to occurrence of the event or last follow-up date. Table 1.2a contains a portion of the data and Table 1.2b contains the list of variables and their description. The clinical aspects of the study and details of the original analysis can be found elsewhere (Fyles *et al.*, 2004).

1.6.2 Hypoxia study

Between 1994 and 2000, 109 patients diagnosed with primary cervical cancer were treated at a cancer centre, and data on these patients were collected prospectively. Two tumour markers were investigated in this study: a hypoxia marker (HP5) and the interstitial fluid pressure (IFP). The oxygenation level, recorded in millimetres of mercury (mmHg), was measured in each tumour 25–30 times along a track, with 3–4 tracks per tumour. The hypoxia marker was defined as the percentage of measurements in a tumour that had oxygen level less than 5 mmHg. The IFP was measured at a number of locations in the tumour and a mean value per patient was calculated. More details on how HP5 and IFP were measured can be found in the original reports (Wong *et al.*, 1997; Milosevic *et al.*, 1998). The main goal of this study was to determine whether HP5 and IFP influence outcome, and if so, to point researchers toward new treatment strategies designed to target cells with low levels of oxygen or high levels of IFP. Full reports of the effect of HP5 and IFP on outcome and a comprehensive description of the study can be found elsewhere (Fyles *et al.*, 2002; Milosevic *et al.*, 2001).

The outcome variables recorded for this study are response to treatment, relapse and death. Tables 1.3 contain a portion of the data and the description of the variables. The response to treatment is presented here in a simplified version: complete response (CR) when the tumour has completely disappeared after treatment and the patient was disease-free at the end of the treatment; and no response (NR) when either the tumour has not disappeared or the disease has progressed to other sites (see Figure 1.4). When the response is NR the location of disease is recorded in the appropriate fields: if disease progressed distantly then `disrec=Y`; if the tumour

Table 1.2a Tamoxifen trial: extract from the `tamrt` dataset.

stnum	tx	pathsize	hist	hrlevel	hgb	nodediss	age	survtime	stat	loctime	lcens	axltime	acens	distime	dcens	maltime	mcens
1	B	1	DUC	POS	140	Y	51	8.268	0	8.268	0	8.268	0	8.268	0	8.268	0
2	B	0.5	DUC	POS	138	Y	74	6.174	0	6.174	0	6.174	0	1.352	1	6.174	0
3	B	1.1	DUC	POS	157	Y	71	7.176	0	7.176	0	7.176	0	7.176	0	7.176	0
4	B	0.8	DUC	POS	136	Y	52	9.506	0	9.506	0	9.506	0	9.506	0	9.506	0
5	B	1.5	DUC	POS	123	Y	62	9.095	0	9.095	0	9.095	0	9.095	0	9.095	0
6	B	0.7	DUC	POS	122	Y	75	8.096	1	5.812	0	5.812	0	5.812	0	8.096	0
7	B	2.4	DUC	POS	139	Y	77	0.726	1	0.726	0	0.726	0	0.602	1	0.726	0
8	B	2	DUC	POS	142	Y	78	4.964	0	4.964	0	4.964	0	4.964	0	4.964	0
9	B	2	DUC	POS	121	Y	65	8.849	0	8.849	0	8.849	0	8.849	0	8.849	0
10	B	1.2	DUC	POS	132	Y	67	5.164	0	5.164	0	5.164	0	5.164	0	5.164	0
321	T	2.5	LOB	POS	134	Y	72	8.027	0	8.027	0	8.027	0	8.027	0	2.393	1
322	T	3	DUC	NEG	133	Y	70	3.242	1	0.925	1	3.242	0	3.242	0	2.281	1
323	T	0.8	DUC	POS	135	Y	66	9.284	0	9.284	0	9.284	0	9.284	0	9.284	0
324	T	1.2	DUC	POS	128	Y	56	9.700	0	9.700	0	9.700	0	9.700	0	9.700	0
325	T	0.4	DUC	POS	148	Y	57	9.676	0	9.676	0	9.676	0	9.676	0	9.676	0
326	T	2	DUC	POS	140	Y	56	9.624	0	4.747	1	9.624	0	9.624	0	9.624	0
327	T	1.1	DUC	NEG	152	Y	65	9.229	0	5.331	1	9.229	0	9.229	0	9.073	1
328	T	3	DUC	POS	154	Y	53	9.142	0	9.142	0	9.142	0	9.142	0	9.142	0
329	T	1	DUC	POS	141	Y	66	8.704	0	8.704	0	8.704	0	6.138	1	8.704	0
330	T	1	DUC	POS	136	Y	74	4.871	1	4.871	0	4.871	0	4.871	0	4.871	0

Table 1.2b Tamoxifen trial: description of variables in the dataset.

Variable name	Description
stnum	Patient ID
tx	Randomized treatment: T=tamoxifen, B=radiation + tamoxifen
Variables assessed at the time of randomization	
pathsize	Size of the tumour (cm)
hist	Histology: DUC=Ductal, LOB=Lobular, MED=Medullary, MIX=Mixed, OTH=Other
hrlevel	Hormone receptor level: NEG=Negative, POS=Positive
hgb	Haemoglobin (g/l)
nodediss	Whether axillary node dissection was done: Y=Yes, N=No
age	Age (years)
Outcome variables	
survtime	Time from randomization to death or last follow-up
stat	Status at last follow-up: 1=Dead, 0=Alive
loctime	Time from randomization to local relapse or last follow-up
lcens	Local relapse: 1=Yes, 0=No
axltime	Time from randomization to axillary relapse or last follow-up
acens	Axillary relapse: 1=Yes, 0=No
distime	Time from randomization to distant relapse or last follow-up
dcens	Distant relapse: 1=Yes, 0=No
maltime	Time from randomization to any second malignancy or last follow-up
mcens	Malignancy: 1=Yes, 0=No

did not disappear then `pelrec=Y`. If the patient had a complete response (CR) after treatment the disease may have relapsed either in the pelvis (`pelrec=Y`) or distantly (`disrec=Y`). Therefore, when `pelrec=Y` it may mean either that the patient did not respond to treatment or that the disease relapsed in the pelvis. The response to treatment indicates which of these cases applies. Note that for this dataset no death occurred before a relapse, thus death does not appear as an event. The time to event is calculated in years

Table 1.3a Hypoxia study: extract from the `hypox` dataset.

stnum	age	hgb	tumsize	IFP	HP5	resp	pelvicln	pelrec	disrec	survtime	stat	dftime	dfcens
1	78	119	7	8.0	32.14	CR	N	N	N	6.152	0	6.152	0
2	69	131	2	8.2	2.17	CR	N	N	N	8.008	0	8.008	0
3	55	126	10	8.6	52.33	NR	N	Y	N	0.621	1	0.003	1
4	55	141	8	3.3	3.26	CR	N	Y	Y	1.120	1	1.073	1
5	50	95	8	8.0	85.43	NR	Y	Y	N	1.292	1	0.003	1
6	57	132	8	20.0	19.35	CR	N	N	N	7.929	0	7.929	0
7	53	127	4	21.8	44.58	CR	E	N	N	8.454	0	8.454	0
8	62	142	5	31.6	59.68	CR	N	Y	Y	7.116	0	7.107	1
9	23	145	5	16.5	29.17	CR	N	N	N	8.378	0	8.378	0
10	57	142	3	31.5	85.71	CR	N	N	N	8.178	0	8.178	0
11	74	124	4	8.0	8.065	CR	N	N	N	3.395	1	3.395	1
12	67	133	5	12.8	77.63	NR	Y	Y	Y	1.016	1	0.003	1
13	72	133	4	18.4	33.33	CR	N	Y	N	3.699	1	1.350	1
14	66	116	8	8.0	99.22	NR	E	Y	Y	0.630	1	0.003	1
15	47	82	10	21.0	66.29	CR	Y	N	Y	8.194	0	0.512	1
16	61	118	5	23.6	55.00	CR	N	N	Y	4.764	1	1.714	1
17	78	95	7	21.0	81.60	NR	N	Y	N	2.590	1	0.003	1
18	52	150	6	11.1	56.76	CR	N	N	N	7.707	0	7.707	0
19	33	119	7	14.6	52.04	CR	N	Y	Y	1.478	1	0.939	1
20	45	125	5	30.9	46.77	CR	N	N	N	7.316	0	7.316	0

Table 1.3b Hypoxia study: description of variables in the dataset.

Variable Name	Description
stnum	Patient ID
Variables assessed at the time of diagnosis	
age	Age (years)
hgb	Haemoglobin (g/l)
tumsize	Tumour size (cm)
IFP	Interstitial fluid pressure (marker, mmHg)
HP5	Hypoxia marker (percentage of measurements less than 5 mmHg)
pelvicln	Pelvic node involvement: N=Negative, E=Equivocal, Y=Positive
Outcome variables	
resp	Response after treatment: CR=Complete response, NR=No response
pelrec	Pelvic disease observed: Y=Yes, N=No
disrec	Distant disease observed: Y=Yes, N=No
survtime	Time from diagnosis to death or last follow-up time
stat	Status at last follow-up: 0=Alive, 1=Dead
dftime	Time from diagnosis to first failure (no response to treatment, relapse or death) or last follow-up
dfcens	Censoring variable: 1=Failure, 0=Censored

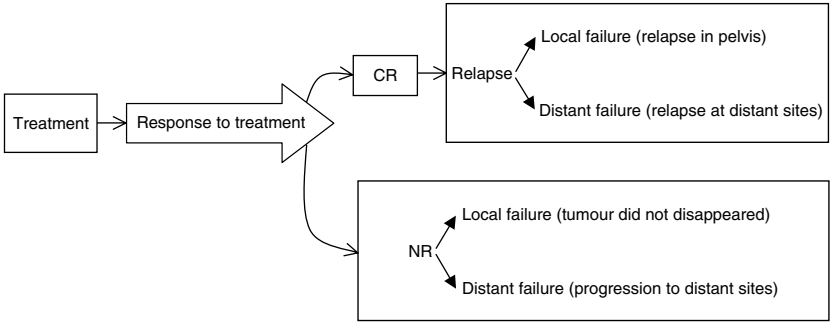

Figure 1.4 Types of failure in the hypoxia study.

from the date of diagnosis to first failure. Note that if the patient did not respond to treatment she was never disease-free. Therefore, the time to first failure is taken to be 1 day. For patients without any event the time is calculated up to the last follow-up date.

1.6.3 Follicular cell lymphoma study

A hospital database of lymphoma patient data was created at the Princess Margaret Hospital, Toronto, with records dating from 1967. Currently, the database is prospective, patients being entered as they register for treatment at the hospital. The subset of 541 patients that will be used throughout this book includes all patients identified as having follicular type lymphoma, registered for treatment at the hospital between 1967 and 1996, with early stage disease (I or II) and treated with radiation alone (RT) or with radiation and chemotherapy (CMT). The goal of this study was to report the long-term outcome in this group of patients. The outcome recorded included response to treatment, first relapse (local, distant or both) and death. The response to treatment is given here in a simplified version: CR is complete response and NR is no response. Those with a CR may have relapsed later locally, distantly, or both locally and distantly. Those with NR were never disease-free and are considered local failures. The time to first failure is calculated in years from the date of diagnosis. For the patients with no response the time to first failure is taken to be 1 day. For those with CR but without relapse, the time to first failure is calculated up to the last follow-up date. Part of the dataset and the list of variables are shown in Tables 1.4. A report on a part of this dataset can be found in Petersen *et al.* (2004b).

1.6.4 Bone marrow transplant study

In January 1996, a multicentre randomized clinical trial was initiated for patients with a myeloid malignancy who were to undergo an allogeneic bone marrow transplant. The donors in all cases were matched siblings. Traditionally, donated cells have been

Table 1.4a Follicular cell lymphoma study: extract from the `follic` dataset.

stnum	age	hgb	clinstg	ch	rt	resp	relsite	survtime	stat	dftime	dfcens
1	56	140	2		Y	CR	B	0.698	1	0.238	1
2	36	130	2		Y	CR	D	14.502	1	12.419	1
3	39	140	2	Y	Y	NR		4.914	1	0.003	1
4	37	140	1		Y	CR		15.685	1	15.685	1
5	61	110	2		Y	NR		0.235	1	0.003	1
6	69	120	1		Y	CR		8.419	1	8.419	1
7	57	110	2		Y	CR		25.150	1	25.150	1
8	32	120	2		Y	CR		31.102	0	31.102	0
9	24	110	2		Y	CR		14.574	0	14.574	0
10	49	110	2		Y	CR	B	22.664	1	0.808	1
11	44	130	2		Y	CR	D	15.261	1	5.615	1
12	82	120	1		Y	NR		1.725	1	0.003	1
13	58	130	1		Y	CR	D	15.559	1	13.049	1
14	32	140	2		Y	CR	D	2.563	1	0.151	1
15	51	140	2		Y	CR		29.667	1	29.667	1
16	73	130	2		Y	CR	D	3.305	1	2.193	1
17	64	130	1		Y	CR	D	1.999	1	0.405	1
18	56	129	1		Y	CR	D	11.614	1	11.184	1
19	38	160	2		Y	CR		11.274	0	11.274	0
20	68	160	2		Y	CR	D	4.736	1	4.005	1

Table 1.4b Follicular cell lymphoma study: description of variables in the dataset.

Variable name	Description
stnum	Patient ID
Variables assessed at the time of diagnosis	
age	Age (years)
hgb	Haemoglobin (g/l)
clinstg	Clinical stage: 1=stage I, 2=stage II
ch	Chemotherapy: Y=Yes, blank=No
rt	Radiotherapy: Y=Yes, blank=No
Outcome variables	
resp	Response after treatment: CR=Complete response, NR=No response
relsite	Site of relapse: L=Local, D=Distant, B=Local and Distant, blank=No relapse
survtime	Time from diagnosis to death or last follow-up
stat	Status: 1=Dead, 0=Alive
dftime	Time from diagnosis to first failure (no response, relapse or death) or last follow-up
dfcens	Censoring variable:1=Failure, 0=Censored

harvested from the pelvic bone of the donor (BM). This study was aimed at comparing the traditional method with a newer technique in which cells are collected from the peripheral blood of the donor (PB). These two cell collection methods formed the two arms of this study. The endpoint for which the study was designed was time to neutrophil recovery. In this book other types of endpoint will be examined: time to relapse, time to chronic graft versus host disease (CGVHD) and time to death. Only the first event of each type was recorded. The time is calculated in years from the date of transplant to the date of each specific event. In the situation where the patient did not experience any event, the time is calculated to the last follow-up date. For each type of event there is a censoring variable indicating whether the event occurred. Between 1996 and 2000, when the study closed, there were 228 patients accrued. In this book only the subgroup of 100 patients treated at the Princess Margaret Hospital are included. Tables 1.5 give a part of the dataset and the list of variables. A full report on this study can be found in Couban *et al.* (2002).

1.6.5 Hodgkin's disease study

Patients treated for Hodgkin's disease at the Princess Margaret Hospital between 1968 and 1986 were entered into a database and their records were updated regularly. There are 865 records in this dataset. All patients have early stage disease (I or II) and were treated either with radiation (RT) or with radiation and chemotherapy (CMT). The goal of this study was to report the long-term outcome in this group of patients. The outcome recorded included the first relapse, the second malignancy (malignancy diagnosed after the Hodgkin's disease) and death. The time to failure is given in years and is calculated from the date of diagnosis. Part of the dataset and the list of variables are shown in Tables 1.6. A report on a part of this dataset can be found in Petersen *et al.* (2004a).

Table 1.5a Bone marrow transplant study: extract from the `bmt` dataset.

stnum	dx	tx	extent	age	survtime	reltime	agvhtime	cgvhtime	stat	rcens	agvhdgd	agvh	cgvh
1	CML	PB	L	36	4.895	4.895	0.099	0.520	0	0	1	1	1
2	AML	PB	L	57	3.474	0.753	0.101	0.408	1	1	3	1	1
3	CML	PB	L	48	4.950	4.950	4.950	0.348	0	0	0	0	1
4	AML	PB	L	52	4.643	4.643	0.057	0.482	0	0	2	1	1
5	AML	PB	L	45	4.066	4.066	0.137	0.378	0	0	3	1	1
6	AML	PB	L	47	1.558	0.416	0.055	1.558	1	1	3	1	0
7	CML	PB	L	40	4.512	4.512	0.09	0.381	0	0	1	1	1
8	AML	PB	L	38	4.041	4.041	0.082	0.914	0	0	3	1	1
9	AML	PB	L	41	4.164	4.164	0.055	0.923	0	0	2	1	1
10	CML	PB	L	50	4.011	4.011	4.011	0.397	0	0	0	0	1
50	CML	BM	L	45	4.572	4.572	0.066	0.619	0	0	3	1	1
51	AML	BM	L	45	4.616	4.616	0.101	0.452	0	0	3	1	1
52	AML	BM	L	42	4.000	4.000	0.027	0.290	0	0	2	1	1
53	CML	BM	L	22	4.238	4.238	4.238	0.479	0	0	0	0	1
54	AML	BM	L	47	0.110	0.110	0.074	0.110	1	0	4	1	0
55	AML	BM	L	48	4.030	4.030	0.101	0.857	0	0	2	1	1
56	AML	BM	L	49	3.124	2.527	0.115	1.993	1	1	2	1	1
57	CML	BM	L	38	0.515	0.515	0.079	0.463	1	0	2	1	1
58	CML	BM	L	39	4.222	3.149	0.085	0.496	0	1	1	1	1
59	CML	BM	L	40	4.027	4.027	0.104	0.422	0	0	3	1	1

Table 1.5b Bone marrow transplant study: description of variables in the dataset.

Variable name	Description
stnum	Patient ID
Variables assessed at the time of randomization	
tx	Randomized treatment: BM=cells harvested from the bone marrow, PB=cell harvested from the peripheral blood
dx	Diagnosis: AML=acute myeloid leukaemia, CML=chronic myeloid leukaemia MDS=myelodysplastic syndrome
extent	Extent of disease: L=limited, E=extensive
age	Age (years)
Outcome variables	
survtime	Time from date of transplant to death or last follow-up
reltime	Time from date of transplant to relapse or last follow-up
agvhtime	Time from date of transplant to acute GVHD or last follow-up
cgvhtime	Time from date of transplant to chronic GVHD or last follow-up
stat	Status: 1=Dead, 0=Alive
rcens	Relapse: 1=Yes, 0=No
agvhdgd	Grade of acute GVHD
agvh	Acute GVHD: 1=Yes, 0=No
cgvh	Chronic GVHD: 1=Yes, 0=No

Table 1.6a Hodgkin's disease study: extract from the `hd` dataset.

stnum	age	sex	trtgiven	medwidsi	extranod	clinstg	survtime	stat	dftime	dfcens	rcens	cscens	maltime	mcens
1	64	F	RT	N	N	1	3.102	1	3.102	1	0	0	3.102	0
2	63	M	RT	N	N	1	15.885	1	15.885	1	0	0	15.885	0
3	17	M	RT	N	N	2	1.103	1	0.882	1	1	1	1.103	0
4	63	M	RT	N	N	2	13.120	1	13.120	1	0	0	13.120	0
5	21	M	RT	L	N	2	35.923	0	35.923	0	0	0	35.923	0
6	37	M	RT	N	N	1	1.834	1	1.106	1	1	1	1.834	0
7	41	M	RT	N	N	2	2.494	1	2.494	1	1	1	2.494	0
8	35	M	RT	N	N	2	7.767	1	0.003	1	1	1	7.767	0
9	27	F	CMT	N	N	2	28.841	1	4.052	1	1	0	25.06	1
10	32	M	RT	N	N	2	28.093	0	28.093	0	0	0	28.093	0
11	68	F	RT	N	N	1	1.706	1	1.689	1	1	1	1.706	0
12	27	F	RT	N	N	2	18.33	1	1.210	1	1	0	18.33	0
13	61	M	RT	N	N	1	1.051	1	1.051	1	1	1	1.051	0
14	27	M	RT	S	N	2	1.303	1	0.537	1	1	1	1.303	0
15	34	M	RT	N	N	2	2.689	1	0.715	1	1	1	2.689	0
16	26	M	RT	N	N	1	2.185	1	1.101	1	1	1	2.185	0
17	19	M	RT	L	N	2	5.520	1	1.634	1	1	1	5.520	0
18	19	M	RT	N	N	2	0.671	1	0.660	1	1	1	0.671	0
19	31	M	RT	N	N	2	32.271	0	32.271	0	0	0	32.271	0
20	17	M	RT	N	N	1	30.467	0	30.467	0	0	0	30.467	0

Table 1.6b Hodgkin's disease study: description of variables in the dataset.

Variable name	Description
stnum	Patient ID
Variables assessed at the time of diagnosis	
age	Age (years)
sex	Haemoglobin (g/l)
trtgiven	Radiotherapy: RT= Radiation, CMT=Chemotherapy and radiation
medwidsi	Size of mediastinum involvement: N= No, S= Small, L= Large
extranod	Extranodal disease: Y=Extranodal disease, N= Nodal disease
clinstg	Clinical stage: 1=Stage I, 2=Stage II
Outcome variables	
survtime	Time from diagnosis to death or last follow-up
stat	Status: 0=Alive, 1=Dead
dftime	Time from diagnosis to first failure (relapse or death) or last follow-up
dfcens	Censoring variable:0=Censored, 1=Failure
rcens	Response and relapse: 0= Disease-free, 1= Relapse or no response to treatment
cscens	Cause specific death: 0= Death due to other causes or alive, 1= Death due to Hodgkin's disease
maltime	Time from diagnosis of Hodgkin's disease to second malignancy or last follow-up
mcens	Second malignancy: 0= No, 1= Yes