Competing Risk regression – a practical approach

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Outline of the talk

- Short introduction to competing risk
- Comparissons between Kaplan-Meier methods and cumulative incidences calculated with CR
- Examples
- Discussion – what do we really model with CR?

Motivating Example

- Comparison of fertility rate of young cancer patients and their controls.
- A primary outcome was the first time reproduction rate. Eg we wanted to compare times to the birth of first child after end of treatment
- Study Design: Each patient was age- and gender matched with 5 controls from the general population.
- Problem: patients are much more likely to die compared to their controls

Introduction to survival analysis

- Survival data
  - Survival data are quantitative in the sense that they consist of 'times' elapsed from an initiating event, e.g. randomization in a clinical trial, to a terminating event, e.g. death.
  - Since survival data are collected 'in real time', the study may be terminated before the event has occurred to all patients (or the investigator may die before the patient).
  - Therefore, survival data also have a categorical component: some patients are observed to die, some may be not.
  - The observation times for those patients who are not observed to die are incomplete: right censoring.

The target population; censoring

- We wish to estimates parameters like S(t) and h(t) based on the censored data. These parameters refer to the potentially completely observed target population.
- For this to be feasible:

1. The complete population (i.e without censoring) should be well defined
2. Censoring should not leave us with a biased sample

Requirement 1: the event under study should happen for every one in the population (easy for overall mortality – everyone has to die at some point). But what if the event is death from a specific disease or a relapse?

Requirement 2: independent censoring (also called non-informative)

Independent censoring

- Individuals censored at any time t should not be a biased sample of those who are at risk at time t.
- In other words: the hazard h(t) gives the event rate at time t, the failure rate given that the subject is still alive (T>t)
- Independent censoring thus means that the extra information that the subject is not only alive, but also uncensored at time t does not change the failure rate.

Independent censoring (cont)

- Typically, independent censoring cannot be tested from the available data – it is a matter of a discussion
- Censoring caused by being alive at the end of the study can usually safely be taken to be 'independent' . However, one should be more suspicious to other kinds of loss to follow-up before end of study.
- It is strongly advised always to keep track of subjects who are lost to follow-up and to note the reason for loss to FU (for ex drop outs)

Competing Risks

- In some cases, we can identify events that are related to the outcome, but compete with the outcome of interest
- Events "compete" with each other
- Once one event is observed, the other one either cannot be observed, or the consequences of observing one changes the likelihood of the other occurring
  - Transplant trials: death due to disease and treatment-related mortality
  - Radiation trials: time to locoregional recurrence and distant recurrence
- Instead of events being either observed or censored, we add additional categories

Why can't we just censor the other patient times at their competing event times?

- It biases the results
- Example:
  - Event of interest is locoregional recurrence
  - Imagine two patients: one is lost to follow-up at time t. The other has distant recurrence at time t.
  - Is it reasonable to assume that the risk of locoregional recurrence would have been the same in these two patients?

Example: Locoregional Recurrence

- By the end of study, patients can have
  - Locoregional recurrence
  - lymph node recurrence or distant recurrence or death
  - No event
- The competing events are locoregional recurrence and lymph node/distant recurrence and death prior to recurrence
- Kaplan-Meier approaches no longer apply

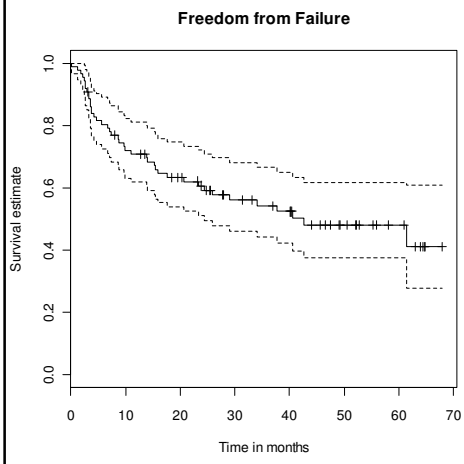
No more Kaplan-Meier curves

- Too bad: they are pretty easy to interpret
- But, why?
- Survival curves show attrition: beginning from 100% without event at time 0, KM curves show fraction of patients still "surviving" without event
- But, when you have attrition due to more than one type of event, the fraction surviving cannot distinguish between different event types

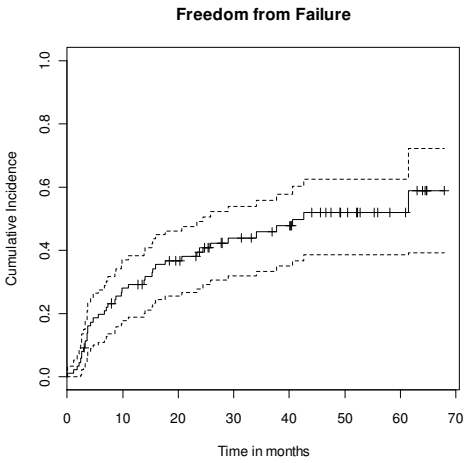
Cumulative Incidence Curves

- Instead of counting down from 100% event-free, show increasing fraction with event
- More than one event can be shown and cumulative incidence need not increase to 1.
- In the event of only one event type, the cumulative incidence curve is the "mirror" of a KM curve.
- In other words, 1 – S(t) = cumulative survival

Kaplan-Meier Curve

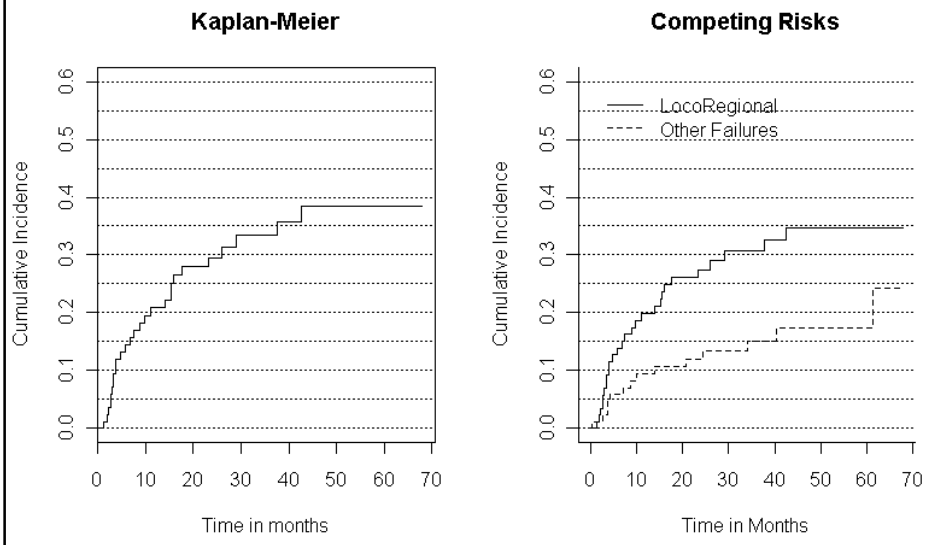


Cumulative Incidence Curve



Locoregional Survival

- Two event types:
  - Locoregional recurrence
  - Other failures: death and distant recurrence
- Each patient time is coded as
  - 1 = locoregional recurrence
  - 2 = other failure
  - 0 = censored at last time known to not have either type of event



Comparison of Cumulative Incidence of Locoregional Recurrence

	KM	Competing Risks
12 month	0.21	0.19
24 month	0.30	0.27
36 month	0.33	0.31
48 month	0.38	0.35

KM vs. Competing Risks

- If competing risks are ignored, the cumulative incidence is assumed to be HIGHER (i.e., survival is assumed to be lower)
- Accounting for competing risks more accurately reflects the lower locoregional recurrence rate
- No technical details, but the big difference is how the “risk set” is calculated at each time point
- For more details, see Haesook Kim, Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clinical Cancer Research. 13(2), 2007.

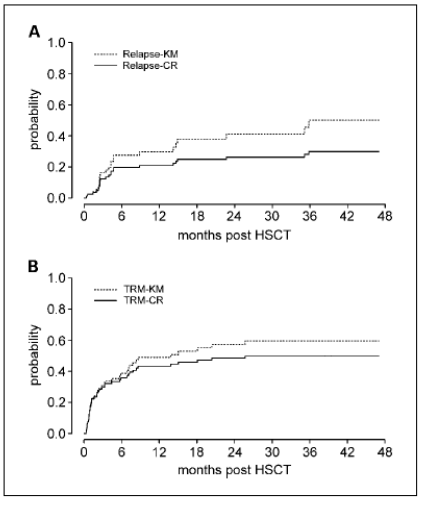


Fig. 2. Myeloablative versus nonmyeloablative allogeneic HSCT for patients >50 years of age. *A*, comparison of cumulative incidence of relapse between the KM and CR methods. *B*, comparison of cumulative incidence of TRM between the KM and CR methods.

Haesook Kim, Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clinical Cancer Research. 13(2), 2007

Competing Risks: Comparing Groups

- Cox regression can still be used
- Recall the hazard ratio (HR)
- HR = ratio of the risk of an event in one group compared to another group at any given point in time
- Assumes constant proportional risk over time
- Example: *Once-Daily Radiotherapy to ≥59.4 Gy versus Twice-Daily Radiotherapy to ≥45 Gy, with Concurrent Chemotherapy for Limited-Stage Small-Cell Lung Cancer: A Comparative Analysis of Toxicities and Outcomes.* Watkins, Fortney, Wahlquist, Shirai, Garrett-Mayer, Aguero, Sherman, Sharma. Accepted, Japan Journal of Radiology.

Back to example….

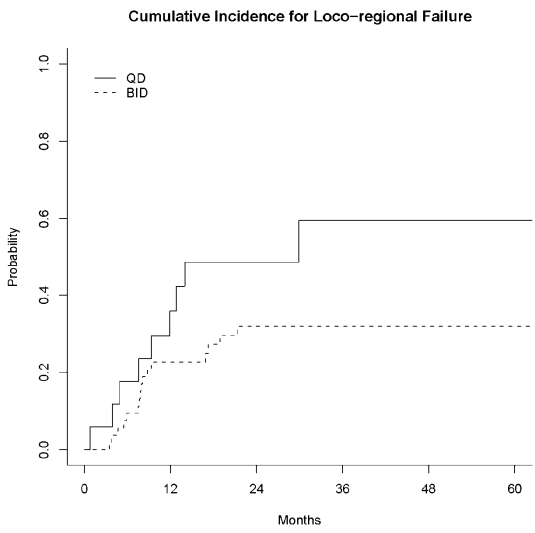
Endpoint categorizations

- Overall survival was measured from date of radiotherapy initiation to last follow-up or death
- Freedom from failure was measured from date of radiotherapy initiation to date of recurrence (earliest sign of clinical, radiographic, or pathologic disease) or last follow-up if there was no evidence of disease recurrence
- Local failures were defined as occurring within irradiated volumes or at the field margin.

Comparing across groups

- "Competing risks analysis was used to assess the cumulative incidence of loco-regional recurrence.
- Loco-regional recurrence was treated as a risk that competes with distant recurrence and death from any cause.
- Differences in cumulative incidence were compared between the two groups (QD vs. BID) using competing risks regression."

Focus on Locoregional Failure

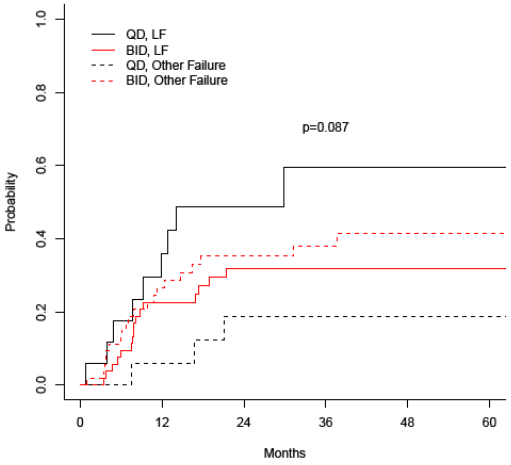


Looks like better outcomes with BID versus QD.

HR = 0.5

Borderline significant (p=0.089)

Other failures?



Relationship is reversed for other failures:
QD has lower incidence of other failures.

HR = 1.81

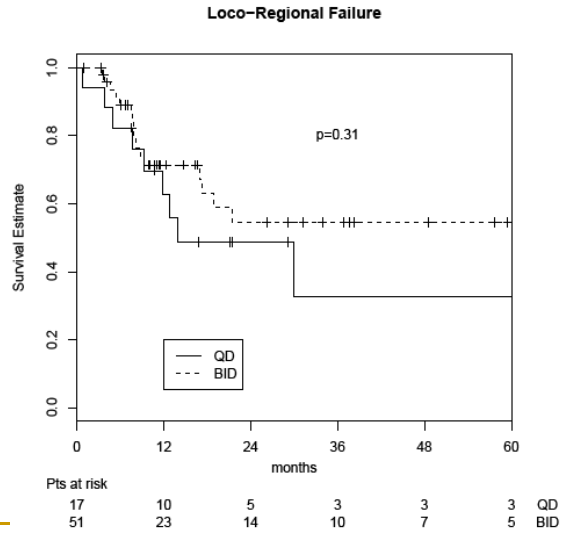
Borderline significant (p=0.10)

Meaningful?

Comparison

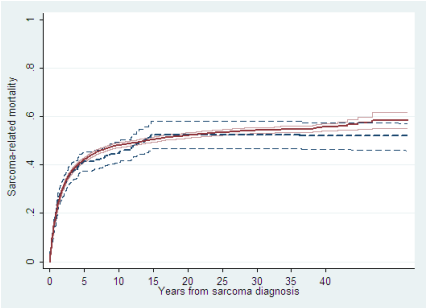
- Just as in the case when there is one event type, you can estimate the hazard ratio comparing risk of events in the two groups
- Interpretation is essentially the same

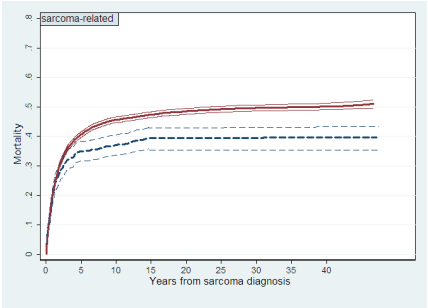
What if KM had been used instead?



More examples: sarcoma related mortality (red: sporadic, blue: second)

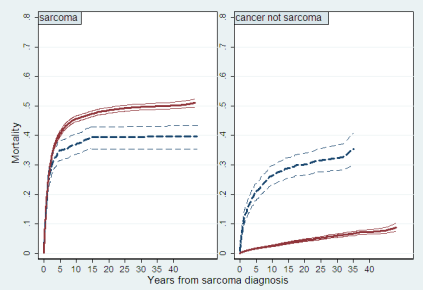
Kaplan-Meier **CR**



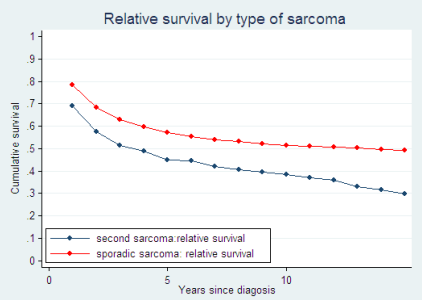


sarcoma related mortality (red: sporadic, blue: second), cont

CR

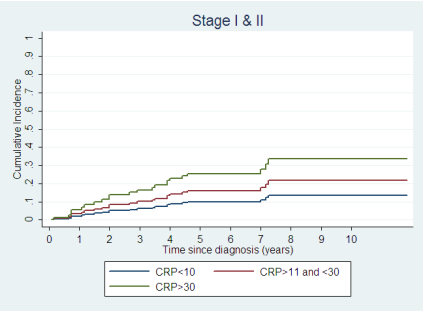


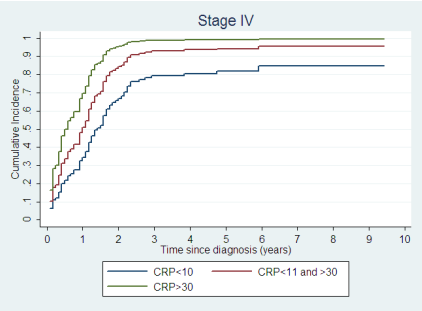
Relative survival



Example: colorectal cancer, death due to colon cancer

Fine & Grey regression





Example 2, cont

- Competing risk regression (F&G)

Stage I & II	Stage IV
SHR=4.11, p=0.02	SHR=2.36, p<0.01

- Does it make sense?
- How can one explain it (to a clinician)?