# Age-Cohort Models for Recurrent Events in Longitudinal Studies

H.M. Hudson[1,2], M.B. Barton[3], G. Delaney[3], Z. Hao[1,3], S. Allen[3]

[1] Dept. Statistics, Macquarie University, Australia
[2] Faculty of Medicine, University of Sydney
[3] Faculty of Medicine, University of New South Wales

Malcolm.Hudson@mq.edu.au

1 June, 2011

## Aims

1. **Compare different marginal methods for counting recurrent events**
   - recurrent events ('retreatments') ended by a terminal event ('death')
   - variety of marginal estimates of mean function
2. **Case study of cancer *retreatments* in LMCTC**
   - Liverpool and Macarthur Cancer Therapy Centres (LMCTC) database
   - our goal, estimation of **mean retreatments** and risk factor effects **following initial RT** for Breast and Lung cancer



## Background

- **Survival with intermediate events**
  - recurrent events ('retreatments') ended by a terminal event ('death')
  - focus on the **retreatment process** rather than **survival**
- **Patterns of Retreatment by Radiotherapy in LMCTC**
  - 8300 cancer patients accrued following **initial RT** in the period 1997-2006
  - **follow-up to end of 2010** for further *retreatments* and deaths
  - supplemented by NSW State Cancer Registry mortality data
  - descriptive analysis[a] available

[a] Barton et al, Clinical Oncology 23 (2011) 10–18

## LMCTC analysis

- **First-event analysis options**
  - Complication-free survival time (i.e. time to first event)
    deaths may dominate K-M plots
  - Competing risk analysis: CIF of time to first retreatment
    directed at outcome of interest
- **Multiple recurrence analysis**:
  - **first-event unsuitable** for comprehensive summaries and cost implications
  - summaries of **number of events** do not address variations in survival $\Rightarrow$ **uninterpretable**
  - summaries of **events-per-p.y.** don't distinguish terminators (end-of-study vs. death)

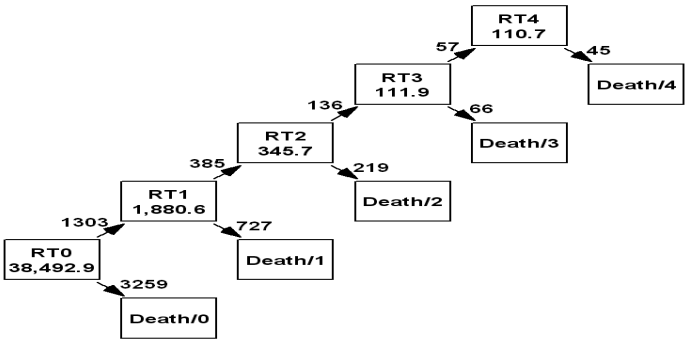


## Frameworks for Analysis

- **Intensity based conditional methods**
  - Probability of new event may depend on previous event history
  - Models valid under *adaptive censoring* (censoring conditionally independent of events)
  - Problems in interpreting effects of treatments or baseline covariates in trials
- **Marginal methods**:
  - Marginal features: event rates or cumulative mean; time to a specified event; gap times.
  - Many well developed methods valid under *independent censoring*
  - Cumulative mean can be estimated by methods of Cook and Lawless[a].

[a] Cook, Lawless, et al JASA 2009

## MSM diagram: LMCTC




State transition diagram and statistics.
Number of events from each node's person years (p.y.'s)

⇒ *ratio obsd retreatments to deaths* increase from 1:3 to 1:1 after more RTs
⇒ *event rates per p.y.* increase from **1 in 10** to **1** after two or more RTs



## Multi-state recurrence model

- Conditional model but interpretable (marginal features)
- MSM of recurrences easily adapted for terminal events [Figure]
- cumulative mean function (**CMF**)
- robust estimates of **state occupancy** probabilities[a]

⇒ robust estimation of the *marginal* distribution of the cumulative number of events over time:

  - probabilities of 0, 1, 2, . . . retreatments before time t (allowing for death terminating)

[a] Aalen et al 2001, Datta & Satten, 2001, Gunnes et al 2007

## Homogeneous cohort

- **Target**
  - P$(N(t) \geq 1)$ (**prevalence**)
  - Mean number of events by time t (**CMF**)
- **End of at risk interval**
  - ends on administrative censoring (EOF date)
  - Methods differ: **end f/u** on **death** preceeding EOF?
    - Cook and Lawless marginal methods – YES
    - Multi-state models (Aalen-Johansen) – YES
    - MCUT (life table) models – NO ⇒simply **ignore deaths!**



## Methods

Events and follow-up

| Method | Events data | Intervals | censor time | Reference |
|---|---|---|---|---|
| MCUT | retreatments | RT0-RTk, RT0-eof | censor at eof | KP, ZM |
| C-L | retreatments and death | RT0-RTk, RT0-death | death (or eof) | CL 4.1 |
| Pepe2 | retreatments and death | RT0-RTk, RT0-death | death (or eof) | CL 4.2 |
| N-A | death/RT (composite) | RT0 -'event' | eof | * |
| A-J | retreatments and death | inter-events-death | death (or eof) | CL 4.3 |

eof = End date of follow-up

RT0 = Date of initial radiotherapy
RTk = Date of k-th retreatment
CL = Cook, Lawless et al, JASA, 2009
KP = Kalbfleisch & Prentice (text)
ZM = Zhang-Salomons and Mackillop, Comp.Meth.Prog.Biomed., 2008

## Results – All pts

Cumulative mean numbers: retreatments per 1000 RT patients

| Method | Year | | | |
|---|---|---|---|---|
| | 2 | 4 | 8 | 12 |
| MCUT | 159 | 197 | 233 | 253 |
| C-L | 159 | 197 | 234 | 255 |
| Pepe | 159 | 197 | 233 | 254 |
| Composite | 159 | 197 | 233 | 255 |
| A-J | 159 | 197 | 234 | 253 |

All methods show a high level of agreement



## Results – Subgroups

Cumulative mean numbers: retreatments per 1000 RT patients

| LUNG CANCER | | | | |
|---|---|---|---|---|
| Method | Year | | | |
| | 2 | 4 | 8 | 12 |
| MCUT | 298 | 318 | 324 | 329 |
| C-L | 297 | 318 | 325 | 329 |
| Pepe | 298 | 318 | 324 | 328 |
| Composite | 298 | 319 | 325 | 329 |
| A-J | 298 | 319 | 326 | 330 |
| BREAST CANCER | | | | |
| Method | Year | | | |
| | 2 | 4 | 8 | 12 |
| MCUT | 83 | 146 | 218 | 248 |
| C-L | 83 | 148 | **228** | **261** |
| Pepe | 83 | 146 | 219 | 250 |
| Composite | 83 | 148 | **228** | **259** |
| A-J | 83 | 148 | **225** | **257** |

## Findings for LMCTC

Concerning methods

- Since all patients experience at least 4 years follow up, all methods provide the same mean number of events up to time $t = 4$.
- Thereafter, some estimates differ.
- But differences are small, for mean retreatments to $t = 8$ and $t = 12$ years
- Even for Breast Cancer, with continuing incidence of new retreatments to 12+ years.
- **Is follow-up of *deaths* necessary in this context?**



## Multiple Cohorts

**Theorem 1 (Deaths in cohort analysis)** *Assume longitudinal data is available on **first recurrence***

- *homogeneous patient cohorts* $1, 2, \ldots, I$ *:*
- *a common entry date in each cohort;*
- *a common exit date (other than death);*
- *cohort* $i$ *has a pre-specified length of follow up* $\tau_i$*;*
- *this **administrative censoring** is the only source of censoring.*

*Then the **empirical CIF** of time from entry to **first recurrence**, allowing for death as competing cause, is the **proportion** of first recurrences **observed before time** $t$ on study, and is **independent of times of death** up to the maximum time of follow-up.*

## Factors affecting the CMF of retreatments

Data

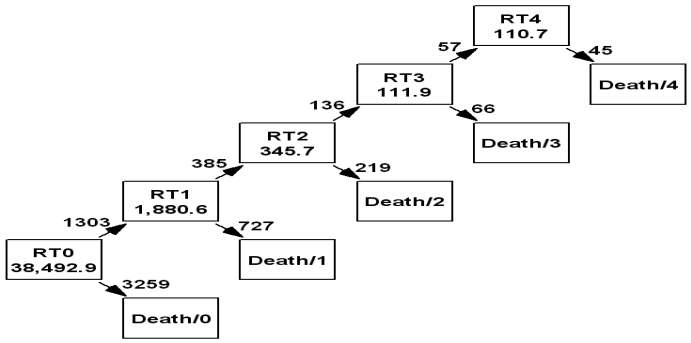
- all methods are informed by dates of **initial RT** and **retreatment** events.
- standard method utilise date of **death** (terminal event).
- CMF may depend on risk factors for competing events: retreatment(s) and death

LMCTC

- Breast and Lung cancer patients differ in retreatment timings (CMF)
- Now explore effects of fixed covariates **age** and date of initial RT (**dst** or 'cohort')
- **Is follow-up of *deaths* necessary in this context?**



## MSM diagram: Liverpool Hospital




The first competing events after initial RT are first retreatment (RT1) and death.

## Results – Risk factors

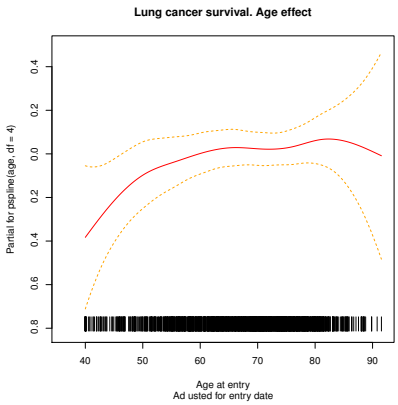
Coefficients[a] of Age* and Year of Entry (start date of RT)

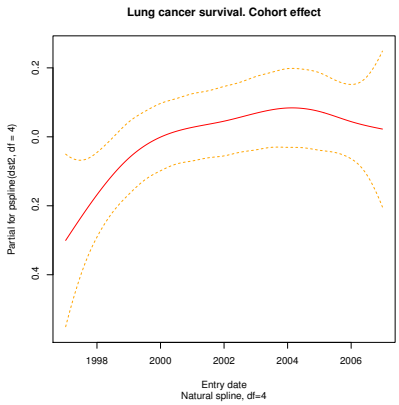
| LUNG CANCER Outcome | age | P | start | P |
|---|---|---|---|---|
| Survival | .0058 | 0.02 | .0244 | 0.04 |
| Survival as 1st event | **.0137** | <0.001 | .0265 | 0.06 |
| Time to 1st retreatment (MCUT) | **-.0376** | <0.001 | .0203 | NS |
| Time to 1st retreatment (CR) | **-.0316** | <0.001 | .0387 | 0.06 |
| Time to 1st retreatment (FG) | **-.0316** | <0.001 | .0387 | 0.06 |
| Gap to 2nd/later retreat (CR) | .0085 | NS | -0.038 | NS |
| **BREAST CANCER Outcome** | **age** | **P** | **start** | **P** |
| Survival | **.0289** | <0.001 | **-.0525** | 0.001 |
| Survival as 1st event | **.0459** | <0.001 | **-.0919** | <0.001 |
| Time to 1st retreatment (MCUT) | -.0049 | **NS** | -.0054 | NS |
| Time to 1st retreatment (CR) | -.0017 | **NS** | -.0107 | NS |
| Time to 1st retreatment (FG) | -.0048 | **NS** | -.0103 | NS |
| Gap to 2nd/later retreat (CR) | -.0155 | 0.05 | .0072 | NS |

[a] Anderson-Gill via coxph



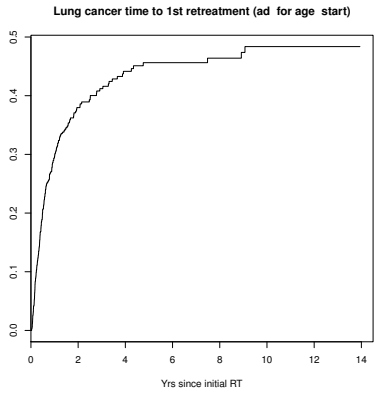
## Factors affecting survival in Lung Cancer

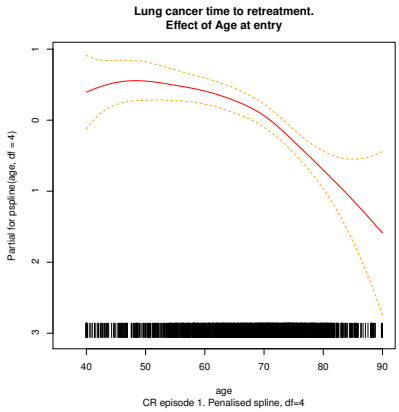



Linear age effect: shorter *survival* at older ages in lung cancer patients

## Factors affecting retreatment incidence in Lung Cancer

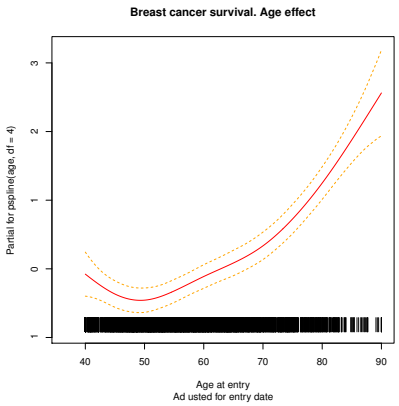


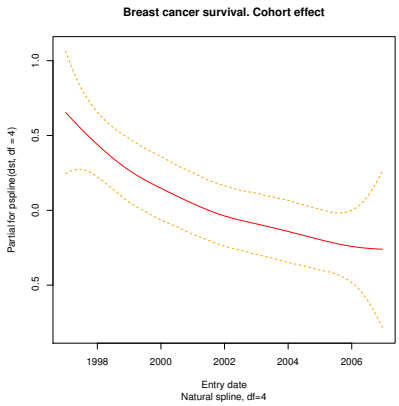




Anderson-Gill model of time to retreatment, censoring death.
Older Lung Cancer patients **not utilising retreatment as early** as others in Lung Cancer, when death has not intervened



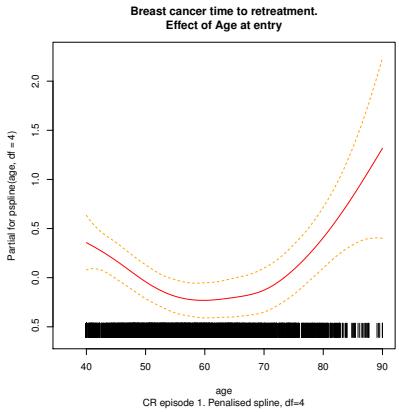
## Factors affecting survival in Breast Cancer




In Breast Cancer *survival*, age effect is non-monotonic, hazard bottoms at age 50 and accelerates beyond 70.
Large monotonic hazard reduction with increasing calendar date of first RT.
Both age and cohort effects are strongly significant.

## Factors affecting retreatment incidence in Breast Cancer


**Younger and older** Breast Cancer patients utilise **retreatment earlier**



## Findings – covariates

Methods and data required

- **Each** marginal method has a corresponding **model** for hazards of events (conditional, CR, etc).
- Competing risks model separates **interpretation of effects** on recurrent events and terminal event.
- Some factors affect death and event incidence (sometimes in opposite directions).
- Useful to **integrate effects** on risk of death with effects on retreatment incidence (given alive). **Can we understand the net effect of a covariate on the CMF?** Answer depends on method.

LMCTC findings concerning methods

- **Coefficients**, their **SE**s and **P-values** differ little between **MCUT (ignoring deaths)** and **competing risk analysis** (retreatment 1 versus death).
- Follow-up of *deaths* **does not add much** to findings in LMCTC data.
- We found **no evidence of efficiency gain** in estimating CMFs and risk factor effects using death data.

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