

Multi-state models and trial data

Terry Therneau

Mayo Clinic

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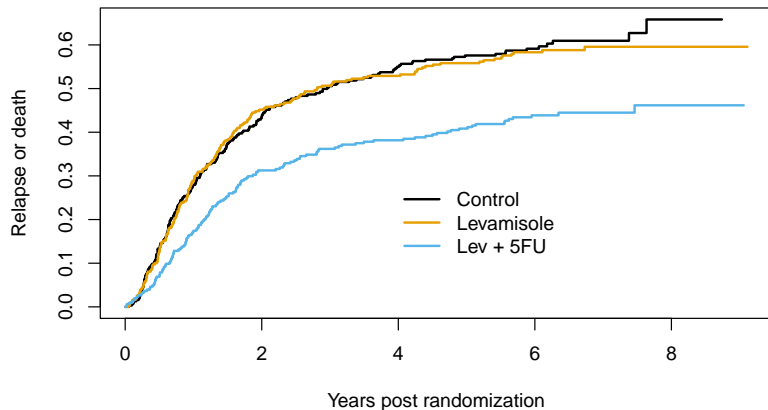
- ▶ "A single yes/no is the least amount of information that can be gleaned from a patient". Charlie Odoroff
- ▶ "A single yes/no p-value is the least amount that can be learned from a research study".
- ▶ Learn as much as you can.

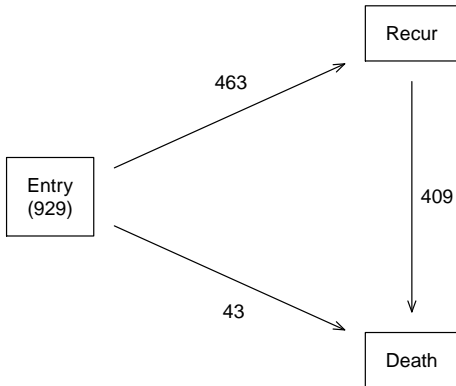
Multi-state models

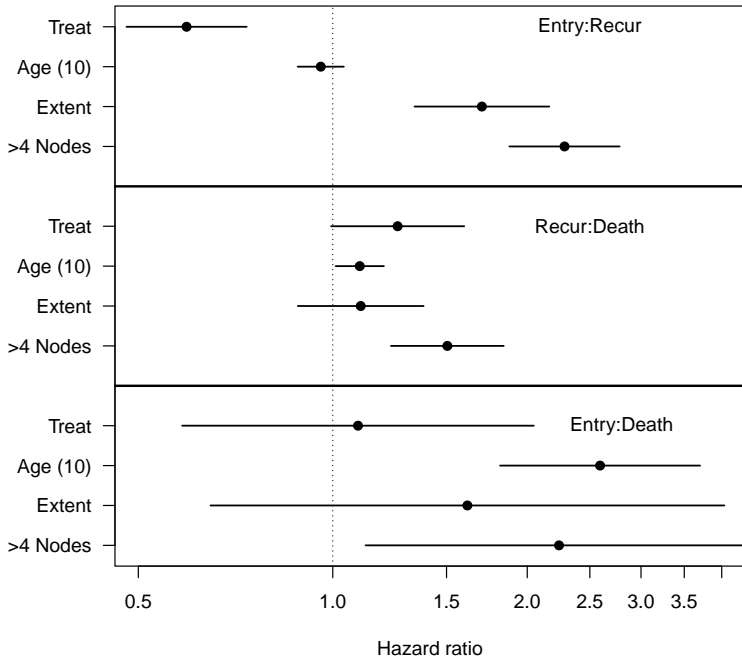
- ▶ Disease processes are multi-factorial, the path is much more interesting than any single way station.
- ▶ Natural extension of the PH model
- ▶ They help me to glean more understanding about the disease process under study
- ▶ Easy to use

Colon cancer data

- ▶ 929 patients: control, levamiol, levamisole + 5FU
- ▶ time to recurrence and death
- ▶ HR for progression free survival (PFS): 1, .97, .62 (.50-.78)

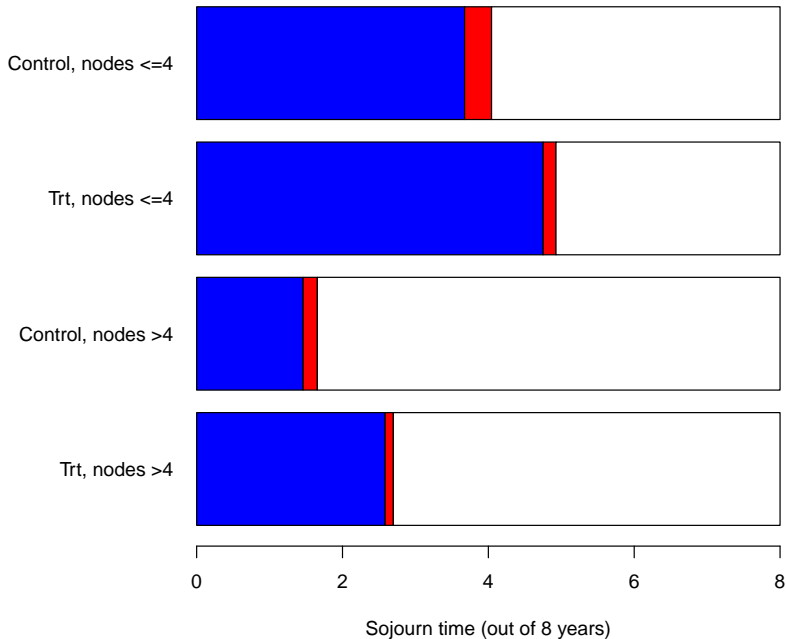


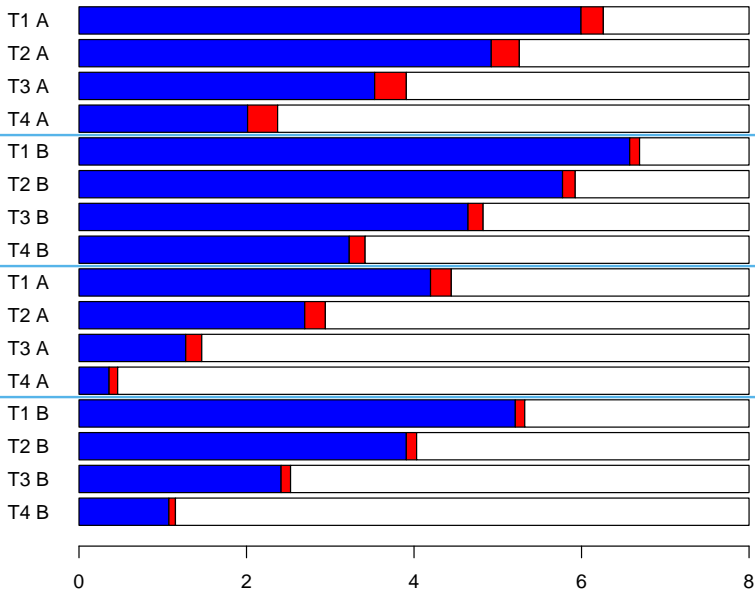




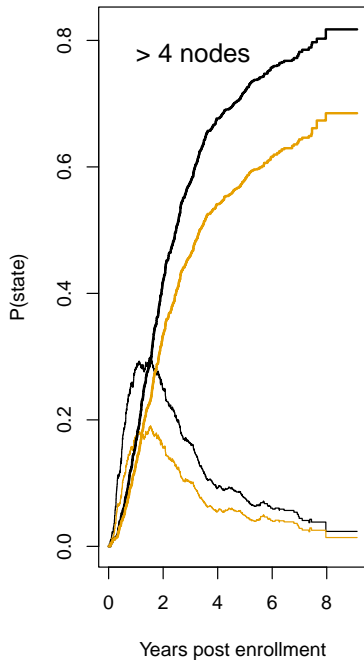
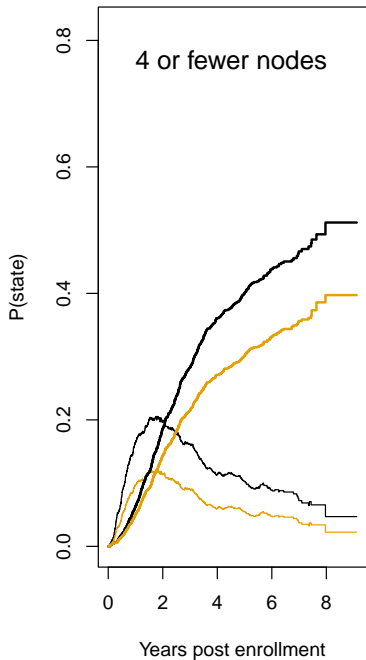
Absolute risk

- ▶ Hazard ratios are not enough
- ▶ $p_k(t; x)$ = probability in state k at time t
- ▶ $E(N_k(t); x)$ = number of visits to state k
 - ▶ P(ever visit state k)
- ▶ E(sojourn time in each state) up to time t
- ▶ E(sojourn, per vist)



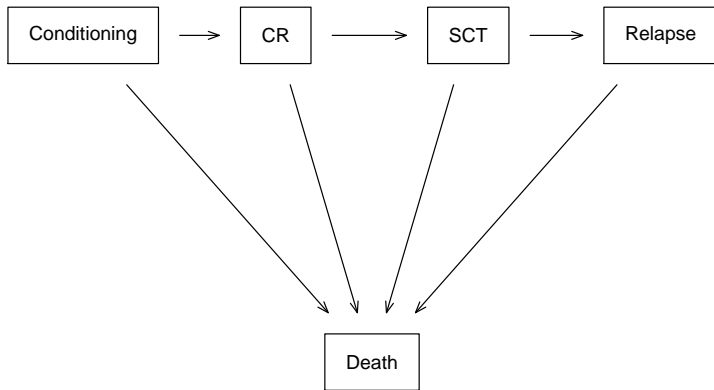


	Sojourn		P(recur)	Duration of recur
	initial	recur		
Control, nodes ≤ 4	3.67	0.37	0.49	0.76
Trt, nodes ≤ 4	4.75	0.18	0.33	0.54
Control, nodes > 4	1.46	0.19	0.76	0.25
Trt, nodes > 4	2.58	0.11	0.58	0.19

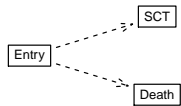
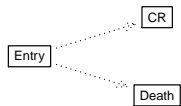
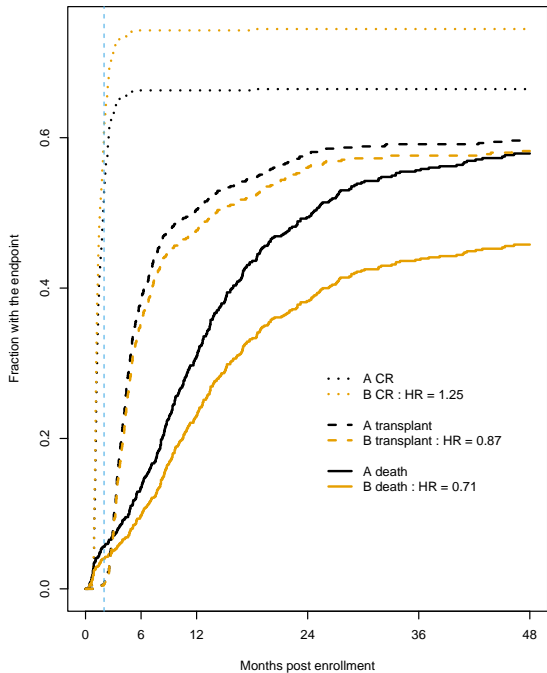


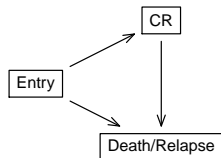
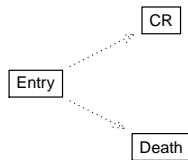
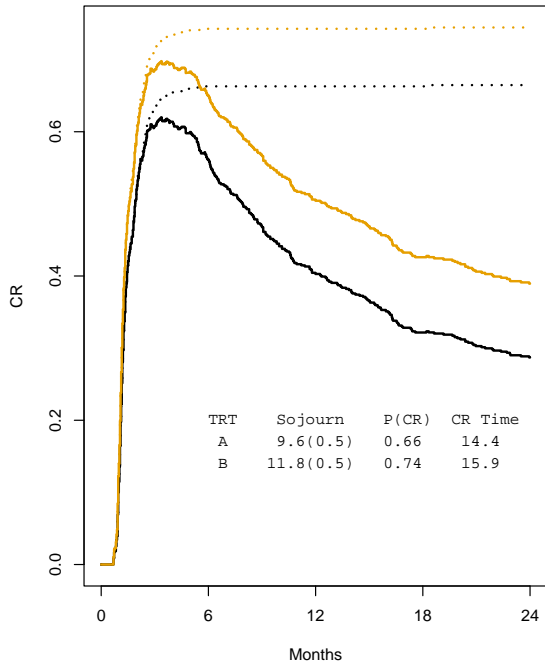
Myeloid Data

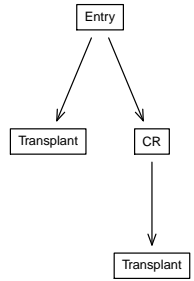
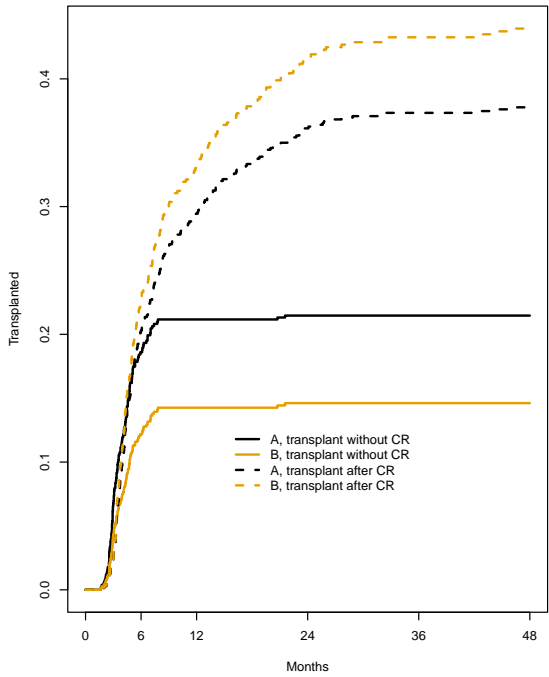
- ▶ Analysis based on CALGB trial of patients with acute myeloid leukemia with FLT3 mutation
- ▶ Chemo \pm midostaurin arms
- ▶ Primary analysis: stratified log-rank test
- ▶ Modified/blinded dataset



from	to				
	CR	SCT	relapse	death	(censored)
Entry	443	106	13	55	29
CR	0	159	164	15	105
SCT	0	0	49	151	163
relapse	0	99	0	99	28
death	0	0	0	0	0







Standard errors

- ▶ $p_{\text{state}} = p_k(t; x) = P(\text{in state } k \text{ at time } t, \text{ covariates } x)$
- ▶ $J(t; x) = \text{infinitesimal jackknife} = \text{effect of obs } i \text{ on } p(t)$
- ▶ (number of observations) \times (number of time points) \times
(number of states)
- ▶ std for everything else follows

Summary

- ▶ This is a useful addition to your toolkit
- ▶ Take the time to look deeper into your data
 - ▶ Resist the “tyranny of the urgent”
- ▶ Hazards are important, hazards are not enough
- ▶ Software
 - ▶ all done with the survival package in R
 - ▶ ongoing work to make it even easier