The effect of surgical margins on disease progression in high-grade soft tissue sarcoma patients: through the eyes of a multi-state model

A.J. Rüten-Budde and M. Fiocco

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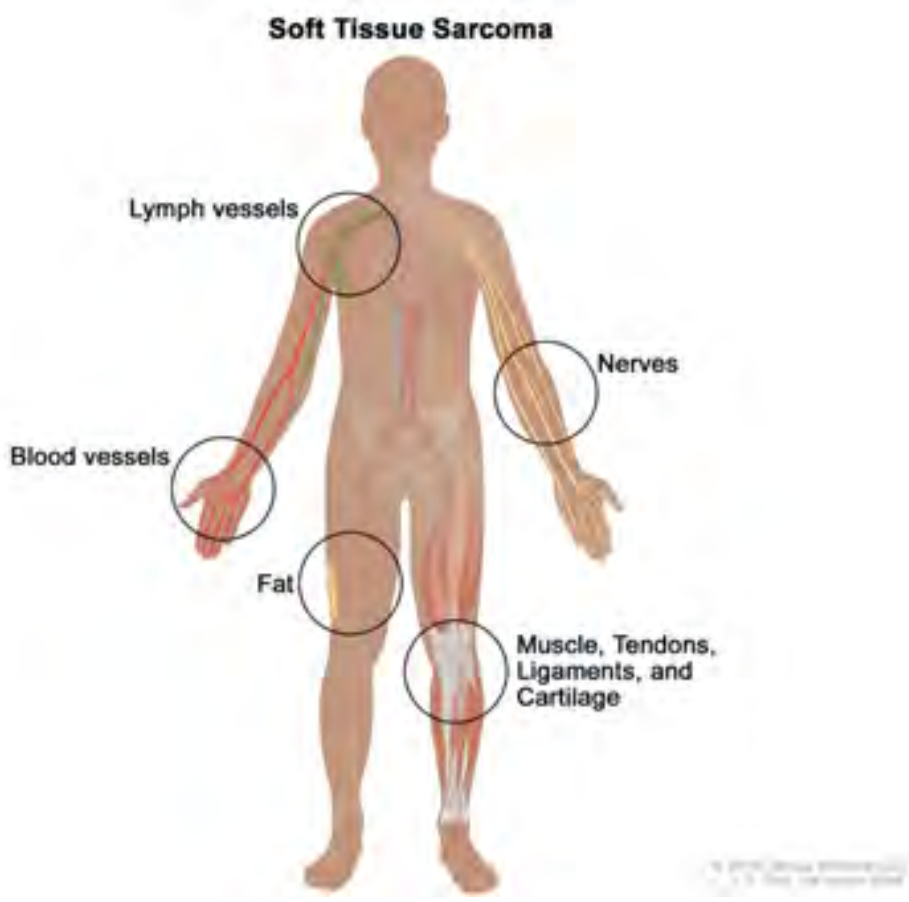
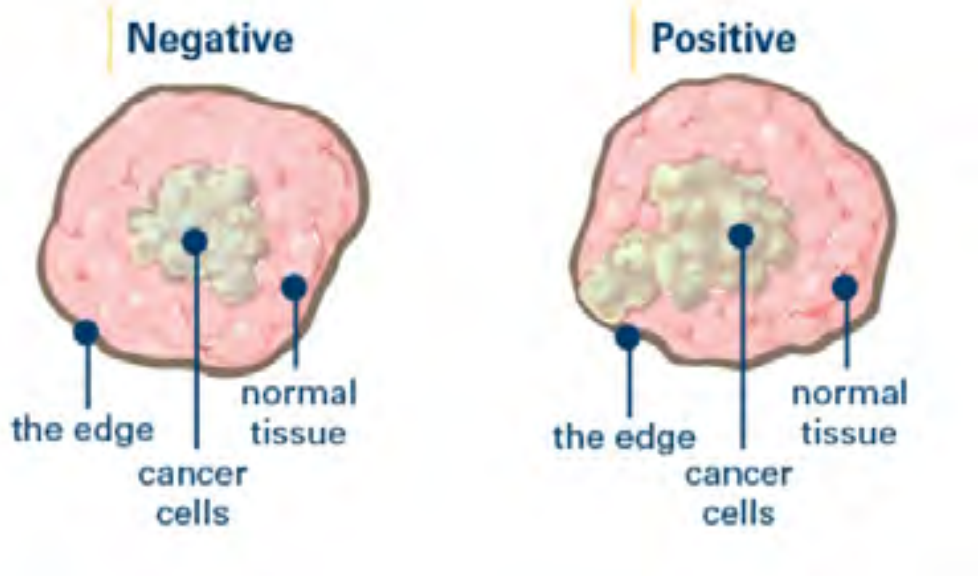
Soft tissue sarcoma

- Cancer developed in the soft tissue
- Surgery as standard treatment
- Disease related events after surgery: local recurrence, distant metastasis, death
- Effect of margin on disease progression

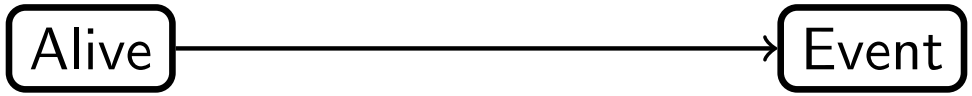


Surgical margin

- Intralesional margin (positive margin)
- Marginal margin ($\leq$ 2mm)
- Wide margin ($>$2mm)

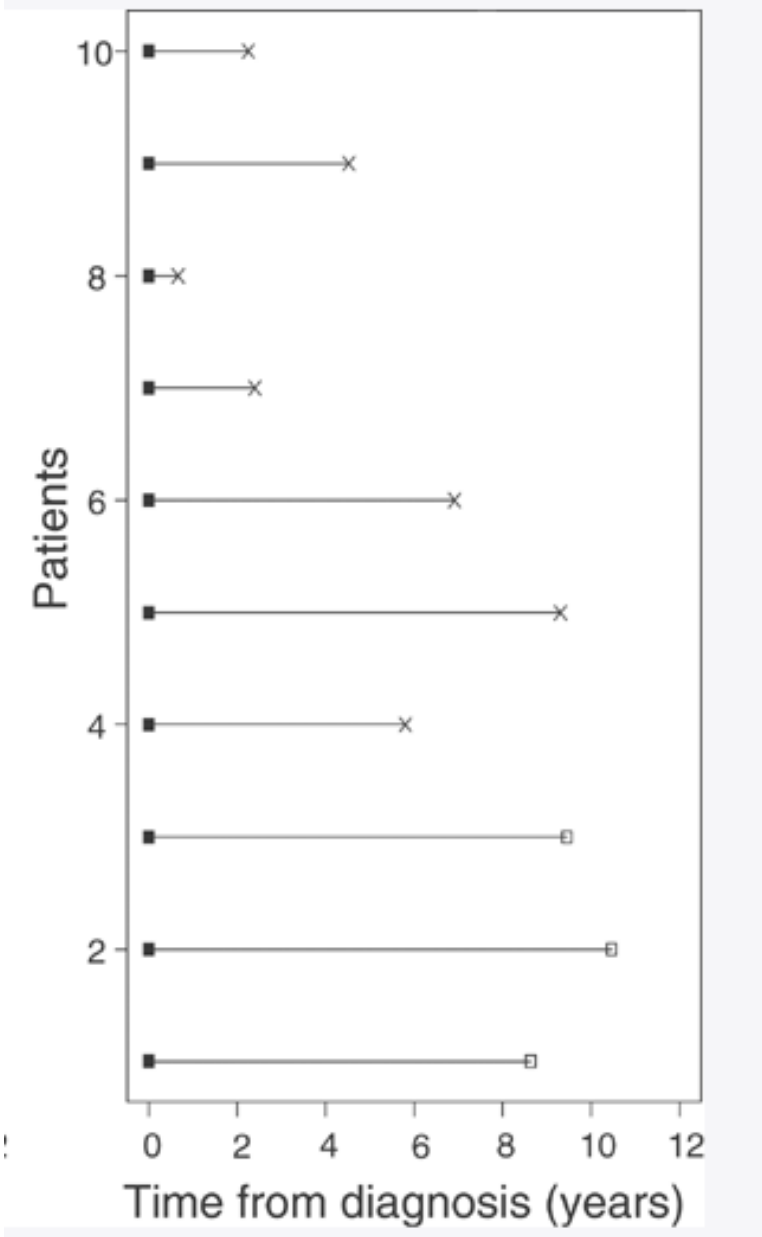


Survival analysis



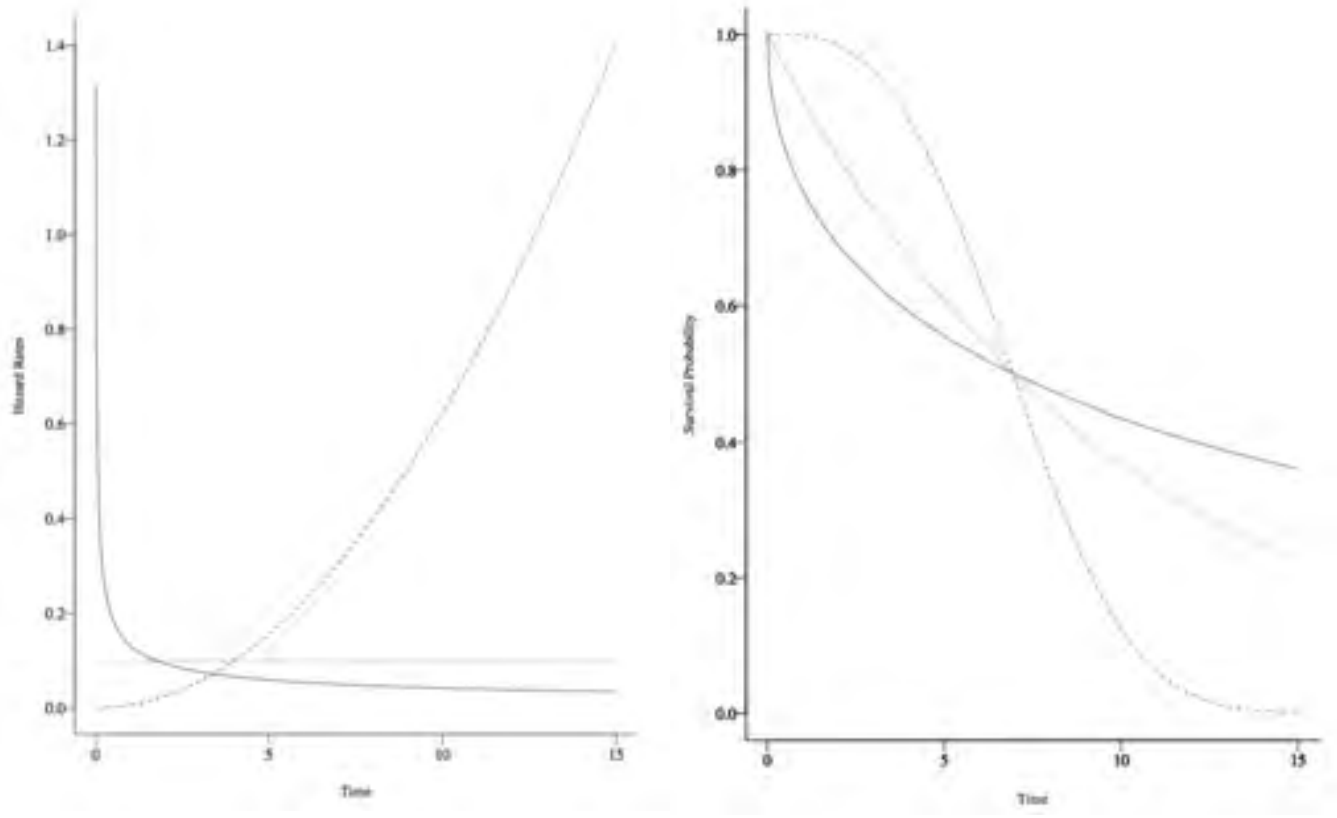
Single failure model.

Censoring



- Survival function $S(t)$: Probability of surviving until time t.
- Hazard function $\lambda(t)$: Conditional probability of failing in the next instant given event-free at time t.
- Cumulative incidence function $I(t)$: Probability of failing before time t.

Survival and hazard function



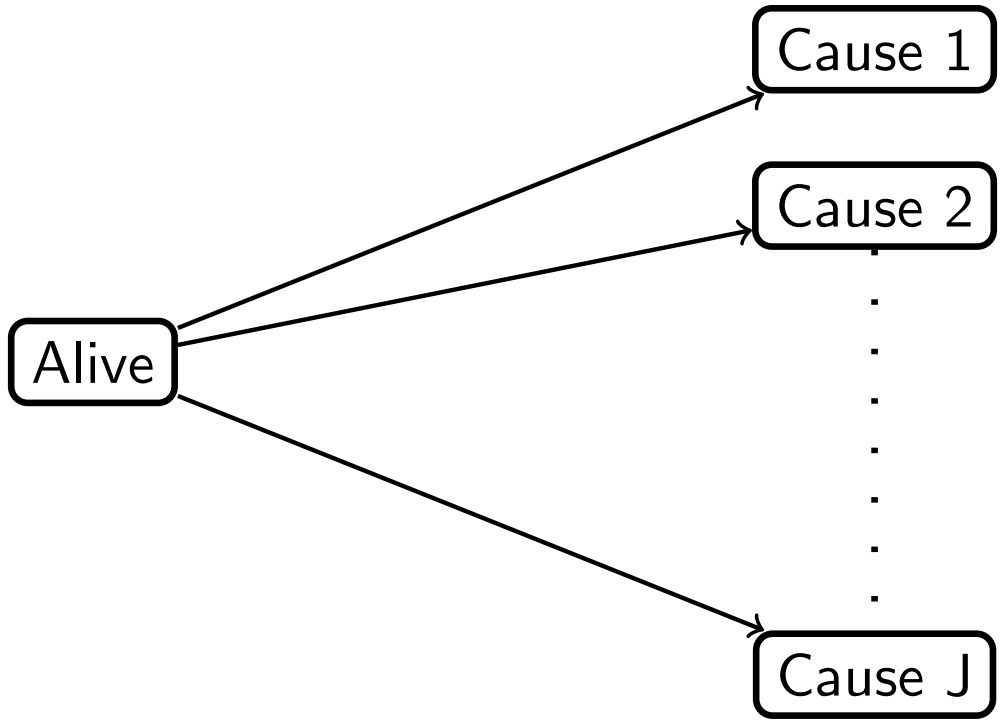
Cox proportional hazards model

- Estimates covariate effects (age, sex, etc.) on the risk of experiencing the event.
- The hazard at time t for an individual i with covariate vector $\boldsymbol{X}_i$ is

$$\lambda(t|\boldsymbol{X}_i) = \lambda_0(t)e^{\boldsymbol{\beta}^T\boldsymbol{X}_i},$$

where $\lambda_0(t)$ is the baseline hazard function.

Competing risks



Competing risks model with J causes of failure.

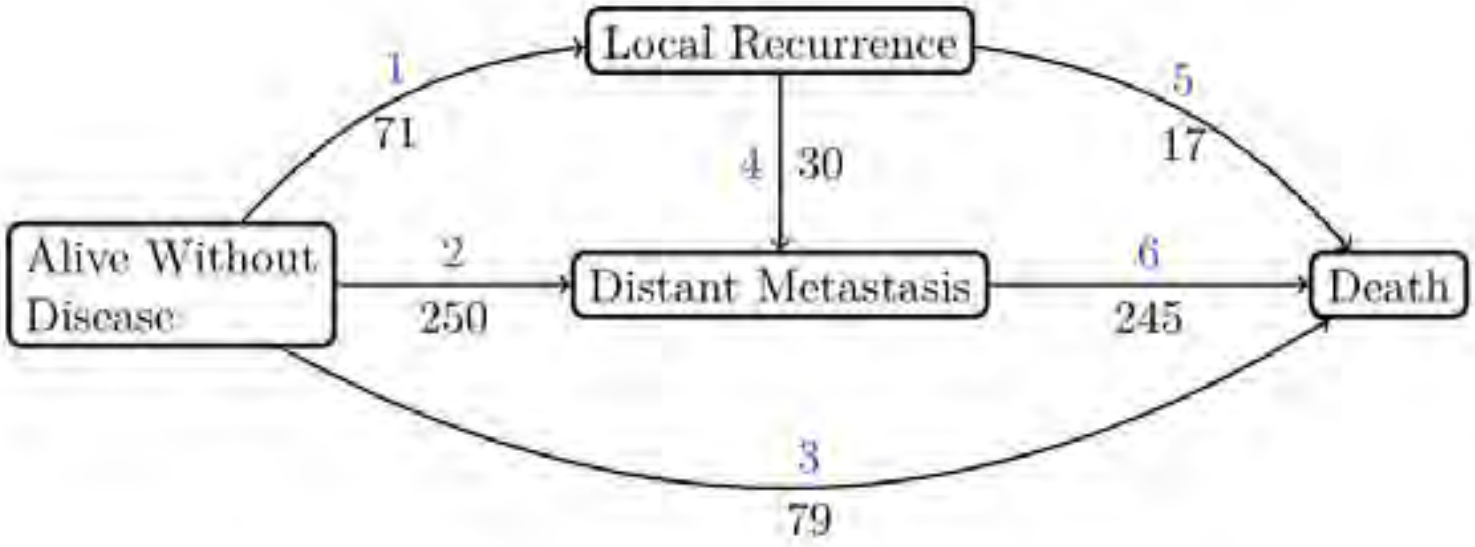
Competing risks

Let $T_1, T_2, ..., T_J$ be the event times for J competing events. Only $T = \min(T_1, T_2, ..., T_J)$ and an event indicator $\delta = 1, ..., J$ are observed. The cause-specific hazards function for cause j for an individual i with covariate vector $\boldsymbol{X}_i$ is given as

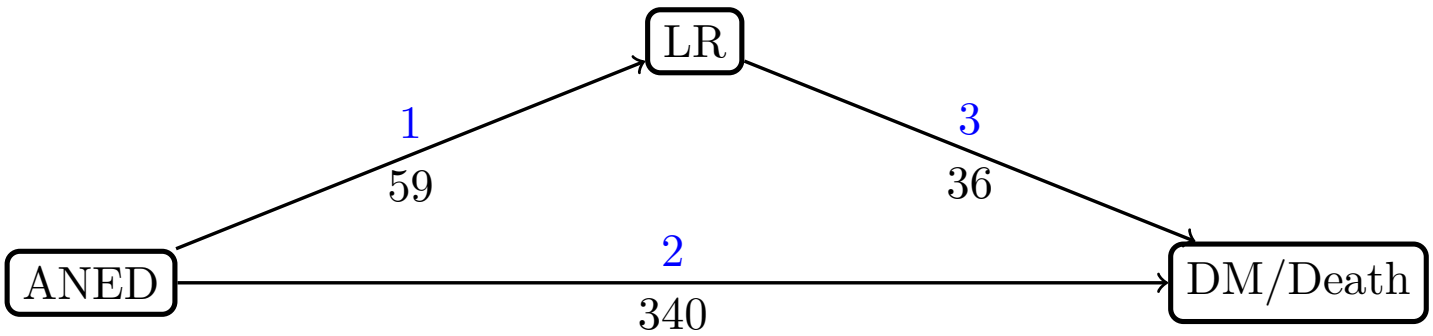
$$\lambda_j(t|\boldsymbol{X}_i) = \lambda_{j0}(t)e^{\boldsymbol{\beta}_j^T \boldsymbol{X}_i},$$

where λ_{j0} is the cause-specific baseline hazard and $\boldsymbol{\beta}_j$ assesses the effect of covariate vector $\boldsymbol{X}_i$ on cause j.

Multistate model



Multistate model



Multistate model for progression of soft tissue sarcoma.

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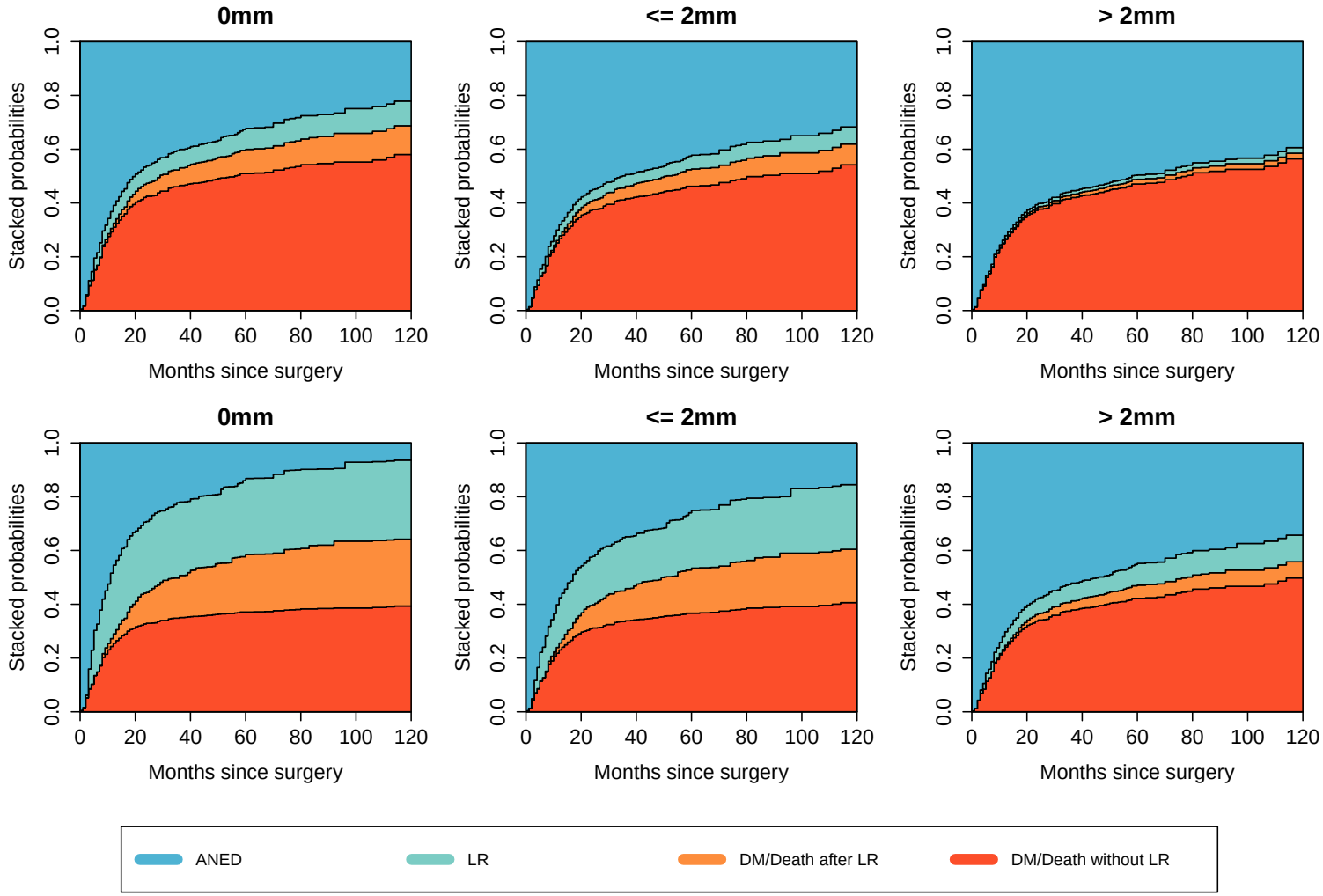
[1] Willeumier et al. 2017 BMJ Open 7:2

Multistate model

Variable	ANED → LR			ANED → DM / Death			LR → DM / Death		
	P value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI
Age									
<25		1			1			1	
25-50	0.649	0.76	0.23–2.50	0.077	1.64	0.95–2.85	0.413	0.50	0.10–2.60
>50	0.955	1.03	0.32–3.31	0.023	1.90	1.09–3.29	0.302	0.47	0.11–1.97
Tumor presentation ("whoops"[1] vs. primary)	0.344	1.43	0.68–3.03	0.586	0.91	0.66–1.26	0.539	1.39	0.48–4.03
Tumor location (lower vs. upper)	0.116	0.61	0.33–1.13	0.919	1.01	0.78–1.32	0.474	1.43	0.54–3.83
Tumor size, cm	0.018	1.06	1.01–1.11	0.000	1.06	1.04–1.08	0.114	1.05	0.99–1.12
Depth									
Deep		1			1				
Superficial	0.093	0.51	0.23–1.12	0.653	0.92	0.66–1.30			
Deep and superficial	0.226	0.26	0.03–2.33	0.253	1.31	0.82–2.09			
Histopathology									
Angiosarcoma		1			1				
MPNST[2]	0.034	0.23	0.06–0.90	0.845	1.08	0.51–2.26			
Myxofibrosarcoma	0.085	0.34	0.10–1.16	0.777	0.90	0.44–1.84			
Synovial sarcoma	0.023	0.21	0.05–0.80	0.972	0.99	0.47–2.07			
Spindle cell sarcoma	0.078	0.32	0.09–1.14	0.910	0.96	0.46–2.01			
Sarcoma NOS[3]	0.918	0.90	0.13–6.14	0.702	0.82	0.31–2.22			
MFH/UPS[4]	0.032	0.19	0.04–0.87	0.560	1.26	0.58–2.76			
Surgical margin									
0mm		1			1			1	
≤2mm	0.113	0.61	0.33–1.12	0.211	0.82	0.61–1.12	0.746	1.15	0.50–2.62
>2mm	0.000	0.16	0.07–0.41	0.193	0.80	0.56–1.12	0.949	1.04	0.32–3.36
Type of surgery (limb-sparing vs. amputation)	0.486	1.55	0.45–5.32	0.717	0.93	0.61–1.40			
Radiotherapy									
Neoadjuvant		1			1				
Adjuvant	0.015	4.36	1.34-14.24	0.840	0.96	0.63-1.46			
No radiotherapy	0.000	14.20	4.14-48.75	0.340	1.24	0.80-1.91			

[1]Incomplete excision elsewhere prior to referral; [2]Malignant peripheral nerve sheath tumor; [3]Not otherwise specified; [4]Malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma

Multistate model



Two patients with different baseline characteristics in different margin scenarios.

Goal of project

- Use multistate models to predict disease progression on individual basis
- Provide updated predictions for patients taking into account events a patient experienced (LR, DM)
- For this need to develop methodology to validate a multistate model for prediction
- External data will be used for validation

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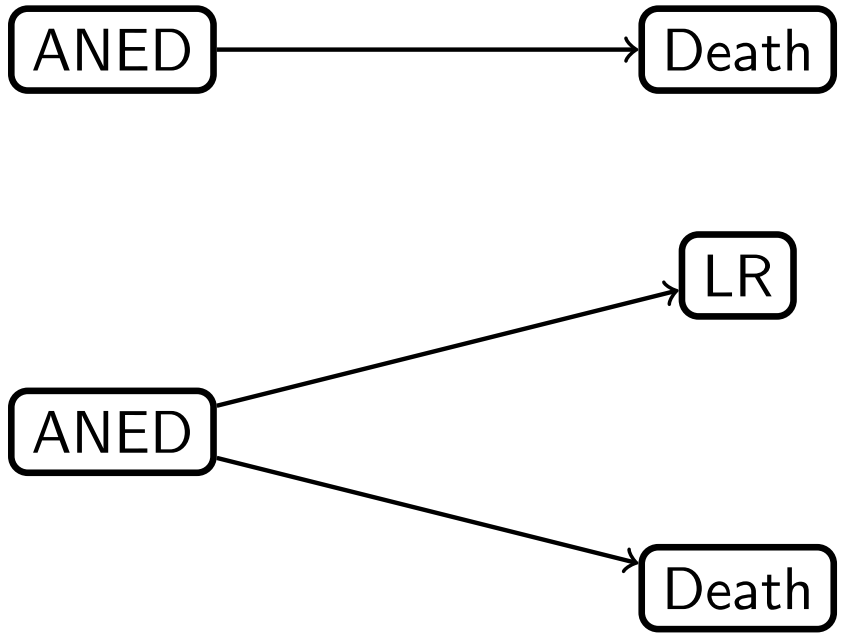
What we can do now

- Update data
- Use simpler models for prediction
- Use available methods and cross validation



Internal validation

Use available methods to validate the models without external data using cross validation

- Harrell's C index
- Visualizing discrimination
- Calibration plots

Cox regression model for OS

	HR	95%CI	P value
Age	1.018	1.011-1.024	<0.001
Size	1.068	1.052-1.085	<0.001
Depth*			0.377
Deep	1.000		
Superficial	0.813	0.591-1.117	
Deep and superficial	1.110	0.736-1.674	
Histology			0.492
Myxofibrosarcoma	1.000		
MPNST	1.422	0.989-2.044	
Synovial sarcoma	1.261	0.869-1.831	
Spindle cell sarcoma	1.211	0.884-1.661	
MFH/UPS	1.293	0.890-1.876	
Margin			0.080
0 mm	1.000		
0.1-2 mm	0.786	0.599-1.033	
>2 mm	0.711	0.524-0.964	
RT			<0.001
No RT	1.000		
Neoadjuvant	0.548	0.399-0.753	
Adjuvant	0.638	0.486-0.837	

Fine and Gray model for LR

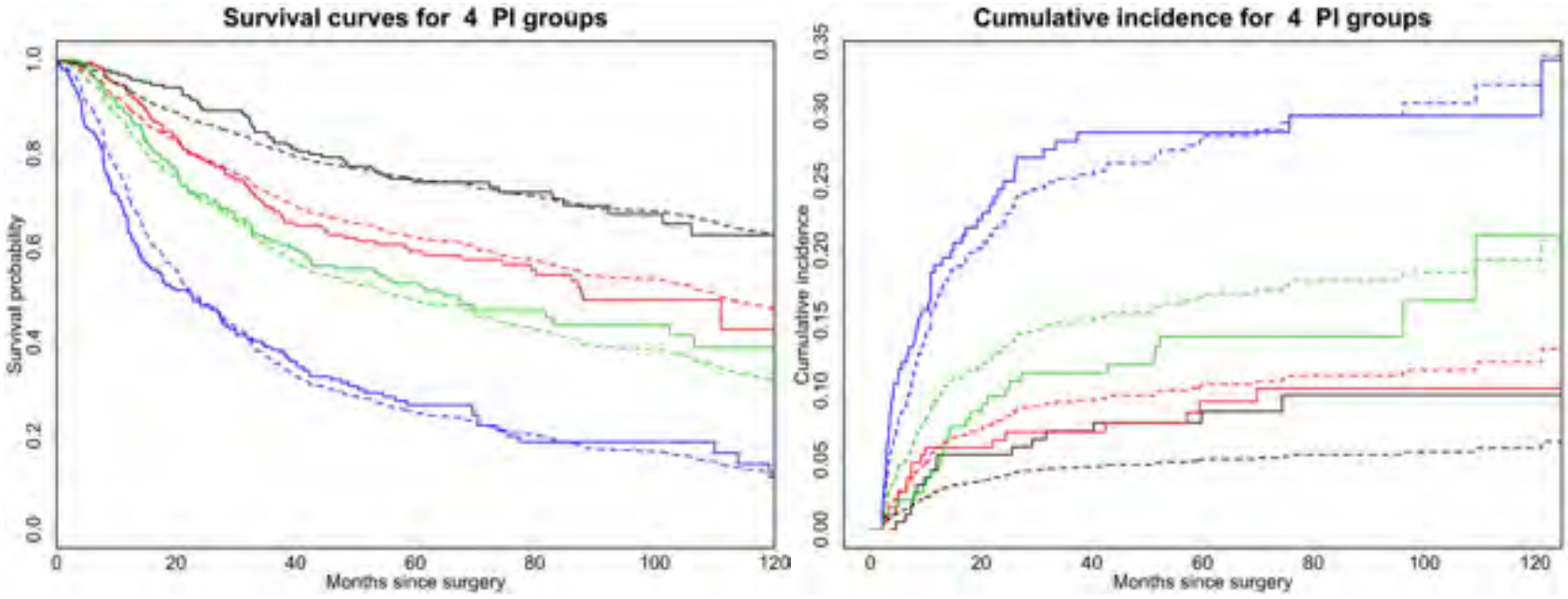
	sHR	*95%CI*	*P value*
Age	1.005	0.994-1.017	0.337
Size	1.031	1.001-1.063	0.042
Depth*			0.559
Deep	1.000		
Superficial	0.907	0.536-1.535	
Deep and superficial	0.563	0.198-1.604	
Histology			0.864
Myxofibrosarcoma	1.000		
MPNST	1.079	0.580-2.009	
Synovial sarcoma	0.779	0.379-1.602	
Spindle cell sarcoma	0.979	0.570-1.681	
MFH/UPS	1.096	0.557-2.156	
Margin			<0.001
0 mm	1.000		
0.1-2 mm	0.635	0.406-0.992	
>2 mm	0.282	0.159-0.500	
RT			0.010
No RT	1.000		
Neoadjuvant	0.312	0.146-0.668	
Adjuvant	0.700	0.417-1.175	

C index

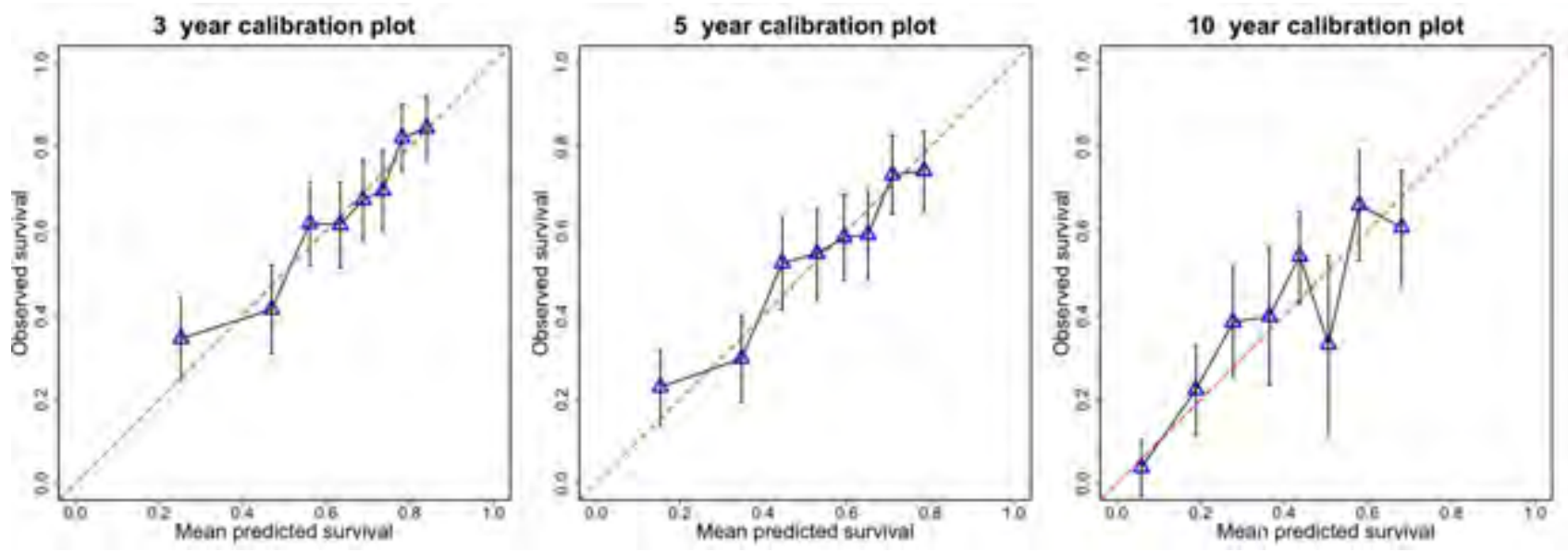
- Harrell's concordance index is defined as the proportional of observations for which the order of survival times and model predictions are concordant.
- Can be defined for competing risks using risk set definition as in Fine and Gray model [2]
- For OS 0.677 (95% CI 0.643 to 0.700)
- For LR 0.696 (95% CI 0.629 to 0.743)

[2] Wolbers 2009, Epidemiology 20:4

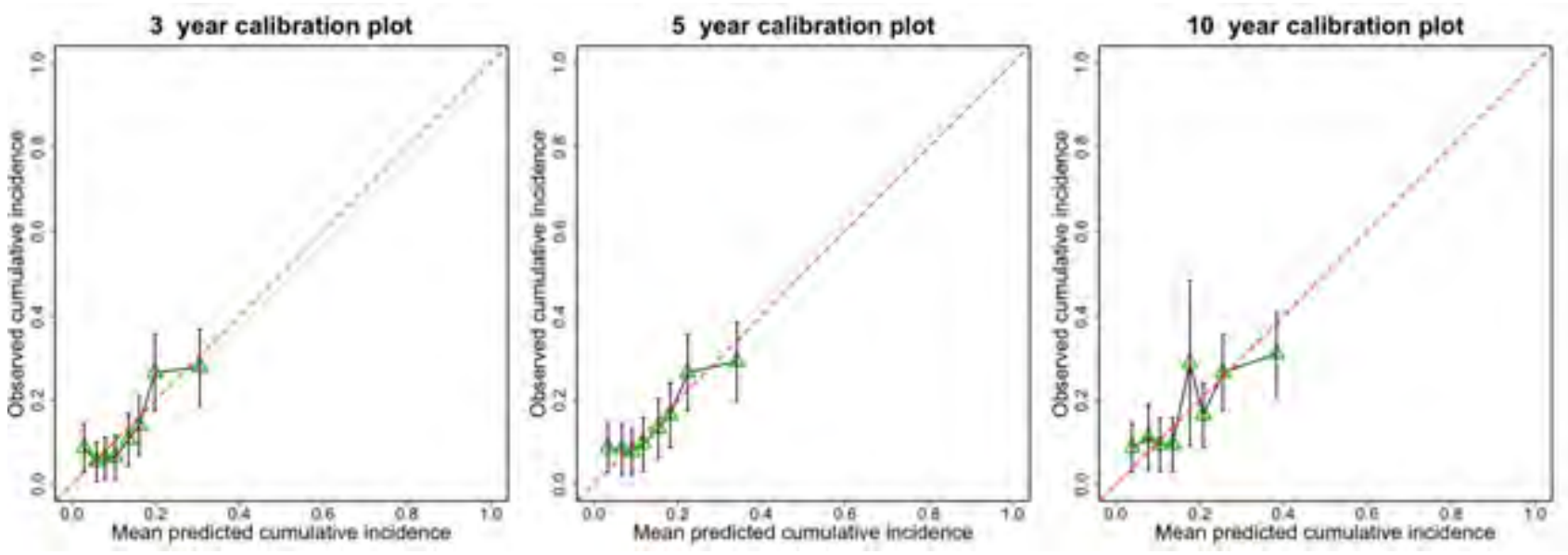
Visualizing discrimination



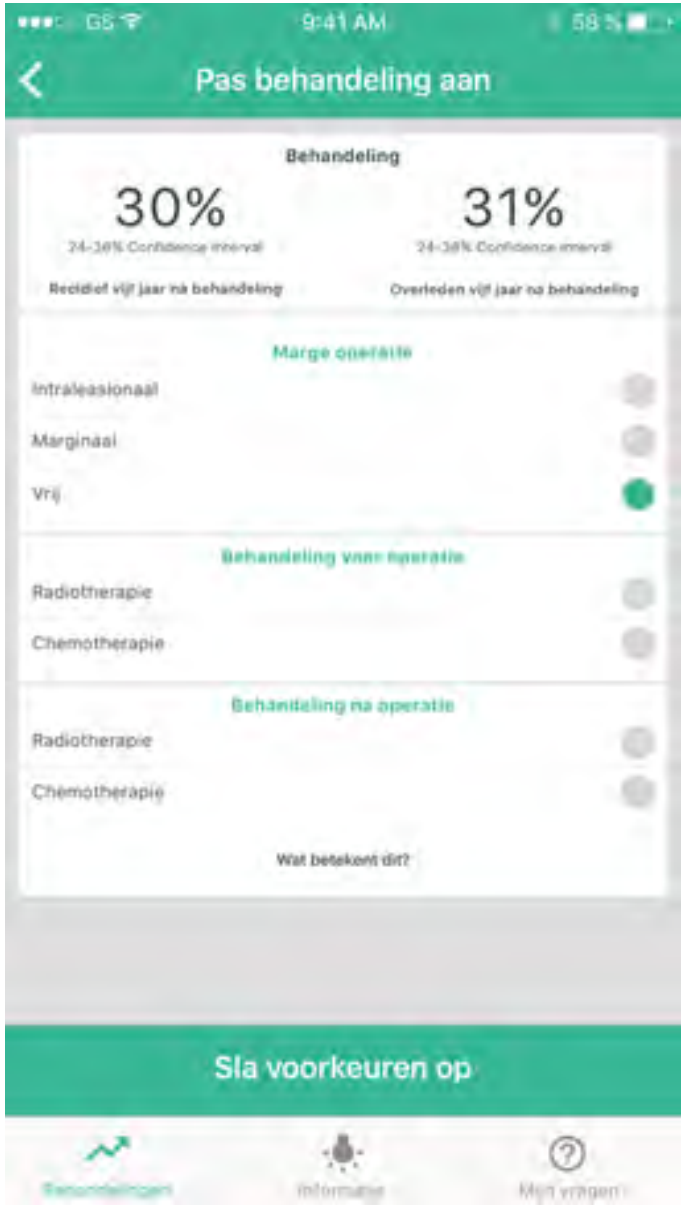
Calibration plots for OS



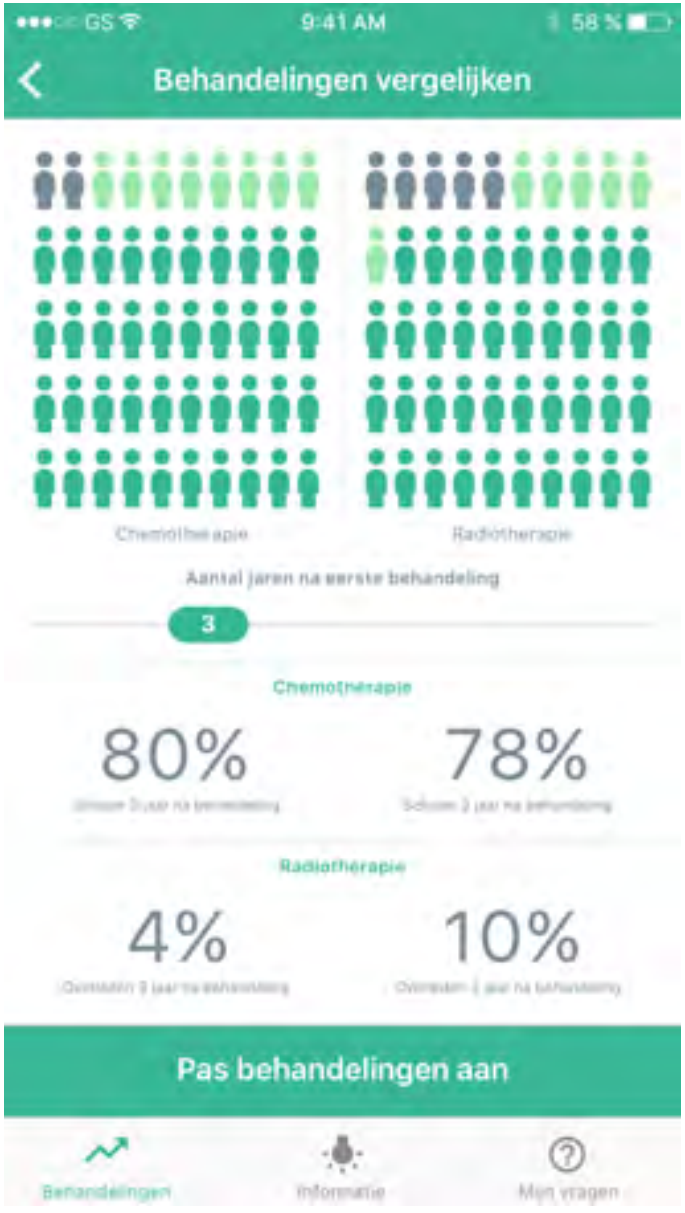
Calibration plots for LR



App: idea for visualization



App: idea for visualization



Thank you!

- Willeumier JJ et al. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. BMJ open. 2017;7(2):e012930.
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