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The effect of surgical margins on local recurrence and survival after resection of high-grade soft tissue sarcomas of the extremities: through the eyes of a multi-state model.

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Introduction
In literature the prognostic relevance of surgical margins and local recurrence (LR) on survival, in the context of specific subgroups of patients, with high-grade soft tissue sarcomas (STS) of the extremities differs largely. Depending on baseline characteristics such as age and tumor size, the surgical planning is different. Therefore it is important to predict the effect of our surgical planning and intended margins on the course of the disease for each patient and tumor specifically.

Purposes
- To study the effects of prognostic factors associated with LR and overall survival in a large multicenter cohort of patients with only high-grade STS.
- To investigate the course of the disease and assess prognostic factors associated with transitions between disease states using a multi-state model.

Patients and Methods
A retrospective multicenter analysis of 687 patients surgically treated between 2000 and 2010 for primary, non-disseminated, high-grade angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma, and (pleomorphic) STS not-otherwise-specified (NOS) with a minimal follow-up of 5 years was performed.

Data was analyzed using a multi-state model (fig 1a). In addition, the effects of presumed prognostic factors on survival and LR were studied with the more common multivariate Cox regression analysis with LR as time-dependent covariate, and competing risk analysis accounting for the competing risk of death, respectively. The advantage of a multi-state model is its ability to describe the disease/recovery process of patients in more detail and offer insight into the effect of prognostic factors on disease progression. After surgery a patient may be without evidence of disease (ANED), may experience a local recurrence (LR), or develop distant metastases (DM) or might die of disease. Death and DM were pooled into one state, as DM, with very few exceptions, predominantly leads to death in this patient population. The effect of prognostic factors on the three transitions in the multi-state model was quantified by adjusted hazard ratios (HR) with 95% confidence intervals (CI) obtained by employing a multivariate Cox model. The following risk factors were incorporated in the analysis: age at diagnosis, tumor location, size (cm), depth, histopathology, surgical margin (intralesional; marginal (up to 2mm); wide), and primary amputation. All results were corrected for center effect and use of radiation therapy.

Results
The multivariate Cox regression analysis with LR as time-dependent covariate showed a significance of age (HR 2.24; 95%CI 1.27-3.97 for >50 years), size (HR 1.06; 95%CI 1.04-1.08 for every cm), and the presence of LR (HR 3.59; 95%CI 2.68-4.80) on survival.
In the multi-states model the majority of patients moved from ANED to DM/death directly (48%). Forty-two percent of the patients have no further disease and remained in their post-operative status ANED. A small group (10%) developed local recurrence, of which the majority (66%) moved to the state DM/Death.
Prognostic factors for these transitions are shown in Table 1. The main prognostic risk factor for transition 1 (ANED to LR) is tumor size (HR 1.05; 95%CI: 1.01-1.10 for every cm increase). Wider resection margins protect for the risk of LR with HR of 0.50 (95%CI: 0.29-0.86) and 0.11 (95%CI: 0.05-0.26) for marginal and wide margins, respectively. For transition 2(ANED to DM/death) no significant effect of margins was detected. Age (HR: 1.84; 95%CI: 1.06-3.20) and tumor size (HR: 1.06; 95%CI: 1.04-1.08) were significant prognostic risk factors.
The multi-state model facilitates patient-specific transition probabilities, as shown in figure 1. These figures visualize the outcomes over time for each margin for one specific patient. As figures 1a-1c show, the intended margin does not result in significant changes in the outcome over time for patient A (age 70, 7cm tumor, radiotherapy, STS-NOS, lower-extremity). For patient B (age 70, 7cm tumor, radiotherapy, angiosarcoma, upper-extremity; figures 1d-1f), the intended margin does result in different outcomes.

Conclusions
The multi-state model provides new in depth awareness of the course of disease after surgery for high-grade STS and factors predictive of disease progression. While baseline characteristics (i.e. age, size, histology) bring

their own intrinsic risk at presentation, the surgical margin remains an important prognostic factor in individual cases. The impact of surgical margins on LR and survival is associated with baseline patients' characteristics and should be incorporated in personalized care. This study furthermore confirms the negative effect of LR on survival.
This model will be incorporated in an online application for high-grade STS of the extremities to predict the effect of planned surgical margins on the risk of local recurrence and survival in individual cases.

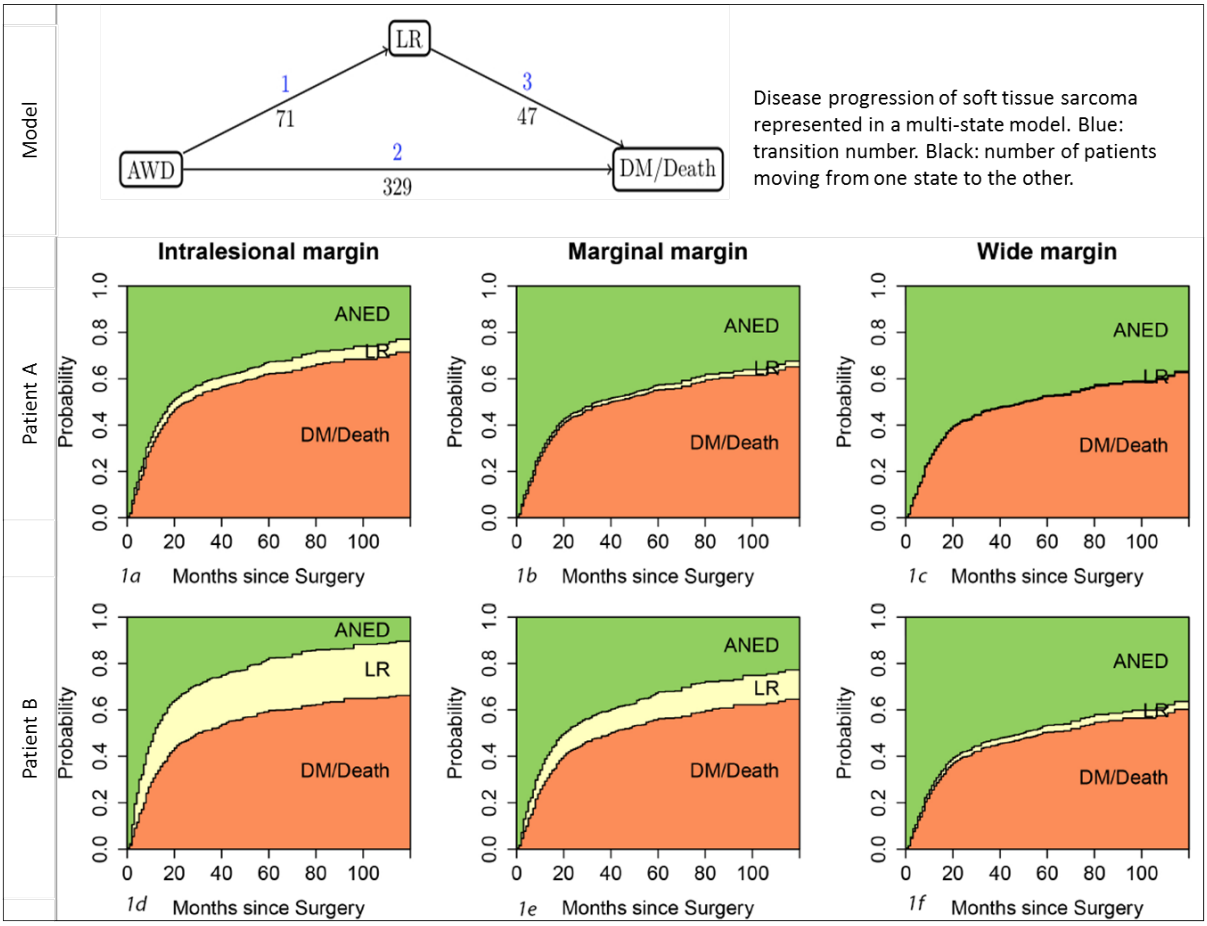
Model
LR
1
71
3
47
AWD
2
329
DM/Death
Disease progression of soft tissue sarcoma represented in a multi-state model. Blue: transition number. Black: number of patients moving from one state to the other.
Intralesional margin
Marginal margin
Wide margin
Patient A
Patient B
Probability
ANED
LR
DM/Death
0.0 0.2 0.4 0.6 0.8 1.0
0 20 40 60 80 100
1a Months since Surgery
1b Months since Surgery
1c Months since Surgery
1d Months since Surgery
1e Months since Surgery
1f Months since Surgery

Figure 1.

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	0.729620	0.81	0.25-2.61	0.078985	1.64	0.94-2.84	0.400161	0.50	0.10-2.49
>50	0.720753	1.23	0.40-3.80	0.030633	1.84	1.06-3.20	0.286982	0.46	0.11-1.91
Presentation (whoops vs. primary)	0.378737	1.36	0.69-2.68	0.782356	0.96	0.69-1.32	0.363968	0.64	0.25-1.67
Location (lower vs. upper)	0.816813	0.93	0.53-1.65	0.850101	0.97	0.75-1.27	0.124930	2.11	0.81-5.47
Size in cm	0.017329	1.05	1.01-1.10	0.000000	1.06	1.04-1.08	0.258366	1.03	0.98-1.09
Depth									
Deep		1			1				
Superficial	0.244899	0.66	0.33-1.33	0.571187	0.90	0.64-1.28			
Deep and superficial	0.119456	0.19	0.02-1.51	0.156830	1.40	0.88-2.23			
Histopathology									
Angiosarcoma		1			1				
MPNST	0.066602	0.29	0.08-1.09	0.933455	1.03	0.49-2.17			
Myxofibrosarcoma	0.062668	0.33	0.10-1.06	0.818580	0.92	0.45-1.88			
Synoviosarcoma	0.039074	0.26	0.07-0.93	0.866024	0.94	0.45-1.97			
Sarcoma nos	0.670578	0.70	0.14-3.55	0.603758	0.76	0.27-2.12			
Spindle cell sarcoma	0.115391	0.38	0.11-1.27	0.777740	0.90	0.43-1.89			
MFH/UPS	0.074503	0.30	0.08-1.13	0.772589	1.12	0.51-2.47			
Surgical margin									
Intralesional		1			1			1	
Marginal (≤2mm)	0.012117	0.50	0.29-0.86	0.292154	0.84	0.62-1.16	0.201631	1.57	0.78-3.16
Wide (>2mm)	0.000001	0.11	0.05-0.26	0.352166	0.85	0.59-1.20	0.340668	1.75	0.55-5.50
Limb sparing (yes vs. no)	0.461225	1.56	0.48-5.06	0.650156	0.91	0.60-1.38			

Table 1.