CHAPTER 5

A prediction model for treatment decisions in high-grade extremity soft-tissue sarcomas: Personalised sarcoma care (PERSARC)

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Abstract

Background: To support shared decision-making, we developed the first prediction model for patients with primary soft-tissue sarcomas of the extremities (ESTS) which takes into account treatment modalities, including applied radiotherapy (RT) and achieved surgical margins. The PERsonalised SARcoma Care (PERSARC) model, predicts overall survival (OS) and the probability of local recurrence (LR) at 3, 5 and 10 years.

Aim: Development and validation, by internal validation, of the PERSARC prediction model.

Methods: The cohort used to develop the model consists of 766 ESTS patients who underwent surgery, between 2000 and 2014, at five specialised international sarcoma centres. To assess the effect of prognostic factors on OS and on the cumulative incidence of LR (CILR), a multivariate Cox proportional hazard regression and the Fine and Gray model were estimated. Predictive performance was investigated by using internal cross validation (CV) and calibration. The discriminative ability of the model was determined with the C-index.

Results: Multivariate Cox regression revealed that age and tumour size had a significant effect on OS. More importantly, patients who received RT showed better outcomes, in terms of OS and CILR, than those treated with surgery alone. Internal validation of the model showed good calibration and discrimination, with a C-index of 0.677 and 0.696 for OS and CILR, respectively.

Conclusions: The PERSARC model is the first to incorporate known clinical risk factors with the use of different treatments and surgical outcome measures. The developed model is internally validated to provide a reliable prediction of post-operative OS and CILR for patients with primary high-grade ESTS.

§5.1 Introduction

Multimodality treatment of high-grade soft-tissue sarcomas of the extremities (ESTS) has improved over the years; however, local recurrence (LR), distant metastasis (DM) and poor survival remain of great concern [164]. Although the effect of several patient-related prognostic factors on overall survival (OS) and LR is well described, the lack of a validated prediction model that includes treatment modalities complicates decision-making aimed at balancing oncologic cure and minimising the risk of disability after treatment.

Factors such as vascular invasion[54], peripheral tumour growth[54], tumour size [54, 107, 74, 29], infiltrative growth[54], necrosis[54], site[107], adjuvant chemo- and/or radiotherapy (RT) [45], histological grade [107, 74, 29] (for fibro- and liposarcomas [145]) and histological subtype [107, 74] have been shown to have a significant impact on survival. While some studies indicate that the prognostic value of tumour depth[54], state at presentation [45], tumour site [102] and age [102] remains unclear, others found some of these factors to be good predictors of outcome[107, 74, 29]. The effect of limb sparing surgery and neoadjuvant chemotherapy and/or RT remains debatable [45]. Surgical margins have an impact on LR [164, 74], but no clear association with OS has been established [164, 74].

In 2003, a prognostic model based on 175 patients with ESTS became available [77] and expanded twice [38, 128]. The first update included patients who were diagnosed at a time (1967) when magnetic resonance imaging (MRI) was not part of the standard care. Prognostic factors included in those studies were tumour size, vascular invasion, necrosis, grade, peripheral growth, depth and location, whereas age, gender, recurrence and metastasis, margins and histology were not included in the model. Callegaro et al. (2016) developed two nomograms for soft-tissue sarcomas of the ESTS and trunk using age, tumour size, histological grade and subtype, using exclusively patients with macroscopically complete surgical resections [37]. In addition, several models only provide prognosis for OS and DM, whereas others underline the relevance of LR. Willeumier et al. (2017) underlined the importance of individual prognostication of LR and OS based on different combinations of surgical margins and possible (neo) and/or adjuvant therapy, while also taking different patient and tumour characteristics into account [21].

To support shared decision-making between patients and physicians, this study aims to develop a prognostic Personalised Sarcoma Care (PERSARC) model to predict the cumulative incidence of LR (CILR) and OS for a patient with high-grade ESTS with specific clinical characteristics and possible treatment modalities at baseline. The prediction model is internally validated by calibration and discrimination.

§5.2 Methods

This multicentre study was approved by each of our hospitals' human subjects review boards.

§5.2.1 Study population

The study population included a consecutive series of 838 patients with primary high-grade ESTS who underwent surgical treatment at one of the five international collaborating hospitals between January 2001 and December 2014. Due to missing values for 72 patients, 766 individuals were included in development of the PERSARC model. Eligible diagnoses included high-grade (Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade III) angiosarcoma, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma and (pleomorphic) soft-tissue sarcomas not-otherwise-specified. Excluded patients include those that were treated without curative intent, had LR or DM within 2 months after primary treatment (ruled out by pre-treatment and follow-up (FU) staging with lung computed tomography (CT) scan), had a tumour in their abdomen, thorax, head or neck or received (neo) adjuvant treatment other than RT or chemotherapy.

All collaborating sarcoma centres implemented the guidelines of the European Society for Medical Oncology for soft-tissue sarcoma FU [56]. Patients visited the outpatient clinic for their scheduled clinical and radiographic FU: every 3-4 months in the first 2-3 years, then every 6 months and after 5 years yearly. It was common that FU was ended after 10 years evidence of no disease.

§5.2.2 Study design

This was a retrospective observational study, in which clinical information was gathered retrospectively (medical records) and by using existing prospective sarcoma databases (including documentation of clinic visits, operation reports, histology and radiographic reports). This information included demographics (centre, patient gender and age at presentation, event and FU), tumour characteristics (presentation, localisation, depth, diameter, histology and grade), treatment characteristics (goal, time of operation [weeks], resection margin and categorical, type and dose of [neo] adjuvant therapy), development of LR and/or DM and last known status. All patients had a minimal FU of 2 years or experienced an event (LR, DM or death) before. The primary outcome measure was survival, if the patient was alive at their last documented visit information on the tumour status was gathered. Secondary outcome measure was LR. Long-term FU was obtained through reviewing documentation of all clinical and radiographic FU.

A sarcoma was considered primary if it was previously untreated, a biopsy or whoops excision had been performed before presentation at one of the five contributing specialised sarcoma centres, with no evidence of metastatic disease. LR was defined as the presence of viable tumour at the site of the original tumour bed confirmed by clinical findings, pathological tissue diagnosis or radiological reports more than 2 months after primary surgery. Distant recurrence was defined by clinical or radiological evidence of systemic spread of tumour outside the primary tumour bed.

Tumour size was defined as maximum diameter at pathologic analysis. In patients that received neo-adjuvant RT and/or chemotherapy, tumour size was defined as maximum diameter measured by CT or MRI before treatment. Surgical margin

was defined as follows: intralesional for tumour cells present at the margin of the resection specimen (<0.1 mm), marginal for tumour cells found within 0.1-2 mm of the margin and free for tumour cells found at least 2 mm away from the margin citewilleumier, rueten2017, kainhofer2016. Tumour grade was classified as high-grade based on established criteria of the FNCLCC.

§5.2.3 Statistical analysis

Multivariate Cox regression model

To assess the effect of prognostic factors on OS a multivariate Cox proportional hazards regression model was used. Predictor variables incorporated in the model were age, tumour size, depth, histology subtype, surgical margin and RT. Initially, tumour site and tumour presentation were considered; however, previous studies [37] and an initial multivariate analysis (Wald test p-value: tumour site p = 0.818, tumour presentation p = 0.696) showed no strong predictive value.

Fine and Gray model

To estimate the effect of risk factors on the CILR, a competing risks model, which accounts for the competing event death was used (Appendix 5.A, Figure 5.A.1) [119]. After surgery, a patient may be alive with no evidence of disease. He may then develop LR or die. The cumulative incidence function is defined as the probability of the event occurring before a certain time point. Fine and Gray's method models the effect of covariates on the cumulative incidence in the presence of competing events. Subdistribution hazard ratios (sHRs) estimate the effect of risk factors on the probability of event occurrence directly. The same covariates used in the Cox model were considered.

Prediction and validation

Predictions for OS and LR at 3, 5 and 10 years after surgery together with 95% confidence intervals (95% CIs), which indicate the uncertainty surrounding the estimates are provided. To justify their use in clinical practice, predictive performance of the prediction models was assessed internally by using leave-one-out cross validation (CV). CV is a technique to simulate model performance on new data.

Following van Houwelingen (2000), a prognostic model is defined as a rule to compute probabilities, given the relevant covariates and their validity can be argued on the basis of model calibration.

Calibration refers to how well predicted probabilities agree with observed probabilities. A common practice is to group patients from 'good' to 'bad' prognosis. A model is well calibrated if true and predicted group probabilities do not differ.

The prediction model can be used to categorise patients based on their prognosis. A patient's risk factor information can be summarised into a prognostic index (PI), which is a weighted mean of prognostic variables, where weights are derived from the prognostic model. Patients with a higher value of PI have a higher predicted risk.

Hence, the PI can be used to divide data into four equal sized groups as follows: 'good prognosis', 'fairly good prognosis', 'fairly poor prognosis' and 'poor prognosis'.

Calibration plots visualise model calibration on a given set of data [150, 165]. Data are divided into prognostic groups. At specific time points the groups' observed outcome (OS or CILR) is plotted against their predicted outcome. If the points are scattered around the diagonal (x = y), the model is valid without adjustment. To investigate calibration for data subgroups, one-sampled T-tests are used, where predicted outcomes were considered the 'fixed' value and observed outcomes as the evaluated variable [47].

Discrimination refers to the ability of the model to assign higher predicted risk to patients who experience the event earlier compared with those experiencing the event later or not at all. To visualise this aspect, non-parametric curves are plotted showing the observed outcome (OS or CILR) for different prognostic groups [124]. The spread of the curves indicates how well a model can discriminate. The C-index quantifies discrimination as the proportion of patient pairs that experience events in the order of risk predicted [149]. It can be adjusted for competing risks [165] and can be interpreted as follows: a C-index of 1 means that the model has perfect discrimination and a C-index of 0.5 means that the model predicts just as well as flipping a coin [9].

All statistical analysis was conducted using R software [122]. A p-value of 0.05 was defined as statistically significant.

§5.3 Results

Table 5.1 summarises patients' characteristics at baseline for the included 766 patients from the five international sarcoma centres. The median FU was 71.8 months (95% CI: 67.6-75.9), assessed with the reverse Kaplan-Meier method. In total, 369 patients died and 116 developed an LR. The majority of patients with an LR died (n = 83; 72%). OS was estimated to be equal to 63%, 53% and 39% at 3, 5 and 10 years, respectively. CILR was estimated to be equal to 13.3% (95% CI: 10.9-15.8), 15.1% (95% CI: 12.4-17.7) and 17.2% (95% CI: 13.9-20.5) at 3, 5 and 10 years, respectively. The centre effect on disease progression was investigated but no significant effect was found.

Age, tumour size and additional RT show an independent significant effect on OS (Table 5.2). Patients with larger tumours have a significantly increased risk of dying with HR equal to 1.068 (95% CI: 1.052-1.085) for a unit increase of 1 cm. Older age is associated with a higher risk of death with HR equal to 1.195 (95% CI: 1.116-1.268) for a 10-year increase in age. Note that age and size are included as linear terms in the model, implying that a 'k*10' year change in age and a 'k' cm change in size multiply the hazard by HRk. Surgical margin has a marginally significant effect on OS, with HR equal to 0.786 (95% CI: 0.599-1.033) and 0.711 (95% CI: 0.524-0.964) for margin equal to 0.1-2 mm and >2 mm, respectively (reference category 0 mm). RT treatment is associated with a decreased risk of dying compared with surgery alone with HRs equal to 0.548 (95% CI: 0.399-0.753) and 0.638 (95% CI: 0.486-0.837) for neoadjuvant and adjuvant RT, respectively.

Table 5.1: Patient characteristics

Characteristics	N(%)
Total	766
Age, mean (SD), years	58.28 (19.39)
Age (%)	
30-60 years	281 (36)
$<$ 30 years	82 (11)
$>$ 60 years	403 (53)
Sex (%)	
Male	435 (57)
Female	331 (43)
Depth (%)	
Deep	579 (76)
Superficial	134 (17)
Deep and superficial	53 (7)
Tumour size, mean (SD), cm	10.06 (6.21)
Tumour location, no. (%)	
Upper extremity	182 (24)
Lower extremity	584 (76)
Tumour presentation (%)	
Primary	622 (81)
'Whoops'*	144 (18)
Histopathology (%)	
Myxofibrosarcoma	238 (31)
MPNST	91 (12)
Synovial sarcoma	142 (18)
Spindle cell sarcoma	167 (22)
MFH/UPS	77 (10)
Other	51 (7)
Surgical margin (%)	
0 mm	140 (18)
$\leq$2 mm	343 (45)
$>$2 mm	283 (37)
Limb-sparing (%)	
No	81 (11)
Yes	685 (89)
Radiotherapy, no. (%)	
Neoadjuvant	184 (24)
Adjuvant	400 (52)
No radiotherapy	182 (24)

Notation: N, number of patients; *Incomplete excision elsewhere prior to referral; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; Depth: relative to the investing fascia.

Table 5.2: Multivariate Cox model for overall survival: hazard ratio (HR) along with 95% confidence interval (n = 766).

	HR	95% CI	p-Value
Age	1.195	1.116–1.268	<0.001
Tumour size	1.068	1.052–1.085	<0.001
Depth			0.377
Deep	1		
Superficial	0.813	0.591–1.117	
Deep and superficial	1.110	0.736–1.674	
Histopathology			0.492
Myxofibrosarcoma	1		
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	
Surgical margin			0.080
0 mm	1		
≤2 mm	0.786	0.599–1.033	
>2 mm	0.711	0.524–0.964	
Radiotherapy			
No RT	1		
Neoadjuvant	0.548	0.399–0.753	
Adjuvant	0.638	0.486–0.837	

The HR of age corresponds to a unit increase of 10 years, and the HR of size corresponds to a unit increase of 1 cm. **Notation:** CI, confidence interval; HR, hazard ratio; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; RT, radiotherapy. Depth: relative to the investing fascia. Depth: relative to the investing fascia

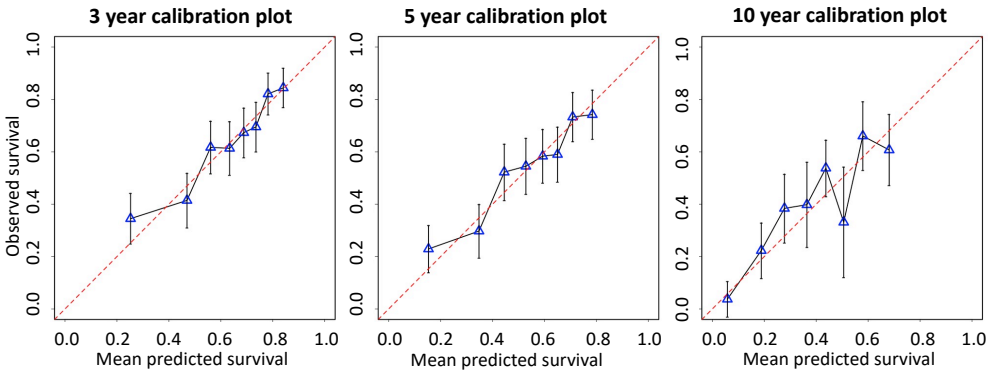

Figure 5.1: Calibration plots for overall survival. Observed survival obtained using Kaplan-Meier estimator is plotted against predicted survival for patients in eight equal sized risk groups identified by their predicted survival at (A) 3 years, (B) 5 years and (C) 10 years, as assessed by cross validation.

Figure 5.1 shows calibration plots for OS at 3, 5 and 10 years. The 3-, 5- and 10-year calibration plots show points (representing risk groups) scattered close to the diagonal, which is contained in the 95% CIs of the observed group survival.

A detailed comparison of observed and predicted survival at 3, 5 and 10 years for data subgroups is given in Table 5.3. Observed and predicted outcome do not differ significantly; however, for smaller and medium sized tumours (<5 cm, 5-10 cm) survival is underestimated at 3, 5 and 10 years, respectively.

Figure 5.2 shows good discrimination of the model visualised by the spread of the Kaplan-Meier estimates (solid lines). Model-based estimates (dotted lines) show the mean predicted survival per group close to the observed survival, indicating good calibration.

The C-index for OS was estimated to be 0.677 (95% CI 0.643-0.701).

In the Fine and Gray model, tumour size, surgical margin and RT show a significant effect on CILR (Table 5.4). Bigger tumours are associated with a higher probability of LR with sHR equal to 1.031 (95% CI: 1.001-1.063) for a unit increase of 1 cm. Patients with larger margins have a significantly lower CILR with sHR equal to 0.635 (95% CI: 0.406-0.992) and 0.282 (95% CI: 0.159-0.500) for 0.1-2 mm and >2 mm, respectively. RT treatment is associated with a lower CILR compared with surgery alone with sHRs equal to 0.312 (95% CI: 0.146-0.668) and 0.700 (95% CI: 0.417-1.175) for neoadjuvant and adjuvant RT, respectively.

Calibration plots for LR are shown in Figure 5.3. Points are scattered around the lower diagonal that lies within the 95% CIs of the observed cumulative incidence, indicating a good calibration. However, the small distance between lower risk groups and the fact that groups observed outcome not always monotonically increases indicate the relative difficulty to discriminate among patients with lower risk profiles.

Figure 5.4 shows crude cumulative incidence curves (solid lines) and model-based estimates (dotted lines) computed as the mean predicted cumulative incidence for LR. The high-risk groups can clearly be distinguished from the rest. However, the

Table 5.3: Comparing observed and predicted overall survival, assessed by cross validation, for subgroups of data at 3, 5 and 10 years.

	n (%)	3 years			5 years			10 years		
		Pred	Obs (se)	Diff (% 95 CI)	Pred	Obs (se)	Diff (% 95 CI)	Pred	Obs (se)	Diff (% 95 CI)
Age										
30-60	281 (36.7)	68.9	70.7 (2.8)	-1.8 (-7.3 to 3.7)	60.2	60.5 (3.1)	-0.3 (-6.4 to 5.8)	46.4	45.4 (4.7)	1.0 (-8.2 to 10.2)
<30	82 (10.7)	77.8	74.6 (4.9)	3.2 (-6.4 to 12.8)	70.7	68.9 (5.3)	1.8 (-8.6 to 12.2)	58.7	58.3 (6.9)	0.4 (-13.1 to 13.9)
>60	403 (52.6)	54.0	54.9 (2.6)	-0.9 (-6.0 to 4.2)	43.6	44.4 (2.7)	-0.8 (-6.1 to 4.5)	29.1	28.9 (4.1)	0.2 (-7.8 to 8.2)
Size										
<5cm	123 (16.1)	77.2	87.0 (3.1)	-9.8 (-15.9 to -3.7)	69.8	78.2 (4.1)	-8.4 (-16.4 to -0.4)	57.2	57.8 (8.1)	-0.6 (-16.5 to 15.3)
5cm-10cm	295 (38.5)	69.4	68.7 (2.8)	0.7 (-4.8 to 6.2)	60.3	59.7 (3.0)	0.6 (-5.3 to 6.5)	45.8	53.1 (3.6)	-7.3 (-14.4 to -0.2)
>=10cm	348 (45.4)	50.4	49.3 (2.8)	1.1 (-4.4 to 6.6)	40.0	38.6 (2.8)	1.4 (-4.1 to 6.9)	26.0	20.7 (3.8)	5.3 (-2.1 to 12.7)
Depth*										
Deep	579 (75.6)	60.9	62.8 (2.1)	-1.9 (-6.0 to 2.2)	51.4	52.7 (2.2)	-1.3 (-5.6 to 3.0)	37.3	37.5 (3.1)	-0.2 (-6.3 to 5.9)
Superficial	134 (17.5)	69.3	67.6 (4.2)	1.7 (-6.5 to 9.9)	60.7	60.9 (4.5)	-0.2 (-9.0 to 8.6)	46.9	56.1 (4.9)	-9.2 (-18.8 to 0.4)
Deep and superficial	53 (6.9)	55.0	51.2 (7.0)	3.8 (-9.9 to 17.5)	45.7	37.9 (7.4)	7.8 (-6.7 to 22.3)	32.7	19.0 (10.2)	13.7 (-6.3 to 33.7)
Histology										
Myxofibrosarcoma	238 (31.1)	62.7	62.4 (3.2)	0.3 (-6.0 to 6.6)	53.3	53.4 (3.4)	-0.1 (-6.8 to 6.6)	39.1	36.3 (5.0)	2.8 (-7.0 to 12.6)
MPNST	91 (11.9)	60.0	57.7 (5.2)	2.3 (-7.9 to 12.5)	50.2	50.1 (5.4)	0.1 (-10.5 to 10.7)	35.9	33.4 (7.7)	2.5 (-12.6 to 17.6)
Synovial sarcoma	142 (18.5)	73.8	75.1 (3.8)	-1.3 (-8.7 to 6.1)	65.8	66.6 (4.2)	-0.8 (-9.0 to 7.4)	52.7	50.9 (5.9)	1.8 (-9.8 to 13.4)
Spindle cell sarcoma	167 (21.8)	55.6	59.9 (3.9)	-4.3 (-11.9 to 3.3)	45.4	47.4 (4.3)	-2.0 (-10.4 to 6.4)	30.9	41.5 (5.0)	-10.6 (-20.4 to -0.8)
MFH/UPS	77 (10.1)	53.7	54.8 (5.9)	-1.1 (-12.7 to 10.5)	43.60	44.8 (6.1)	-1.2 (-13.2 to 10.8)	29.6	29.2 (9.0)	0.4 (-17.2 to 18.0)
Margin										
0 mm	140 (18.3)	52.3	51.5 (4.3)	0.8 (-7.6 to 9.2)	42.40	46.8 (4.4)	-4.4 (-13.0 to 4.2)	28.8	37.1 (4.8)	-8.3 (-17.7 to 1.1)
0.1-2 mm	343 (44.8)	63.1	64.6 (2.6)	-1.5 (-6.6 to 3.6)	53.50	52.4 (2.8)	1.1 (-4.4 to 6.6)	39.1	37.9 (3.7)	1.2 (-6.1 to 8.5)
> 2 mm	283 (36.9)	65.5	66.4 (2.9)	-0.9 (-6.6 to 4.8)	56.50	57.5 (3.2)	-1.0 (-7.3 to 5.3)	42.9	39.5 (6.3)	3.4 (-8.9 to 15.7)
RT										
No RT	182 (23.8)	50.9	53.6 (3.8)	-2.7 (-10.1 to 4.7)	40.80	44.5 (3.9)	-3.7 (-11.3 to 3.9)	27.2	29.5 (6.1)	-2.3 (-14.3 to 9.7)
Neoadjuvant	184 (24)	69.3	69.2 (3.5)	0.1 (-6.8 to 7.0)	60.70	60.3 (3.8)	0.4 (-7.0 to 7.8)	47.0	40.3 (6.0)	6.7 (-5.1 to 18.5)
Adjuvant	400 (52.2)	63.7	64.1 (2.5)	-0.4 (-5.3 to 4.5)	54.30	53.7 (2.7)	0.6 (-4.7 to 5.9)	40.0	43.3 (3.1)	-3.3 (-9.4 to 2.8)

Notation: Pred, predicted; Obs, observed; se, standard error; Diff, difference; CI, confidence interval; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; RT, radiotherapy. * Depth: relative to the investing fascia.

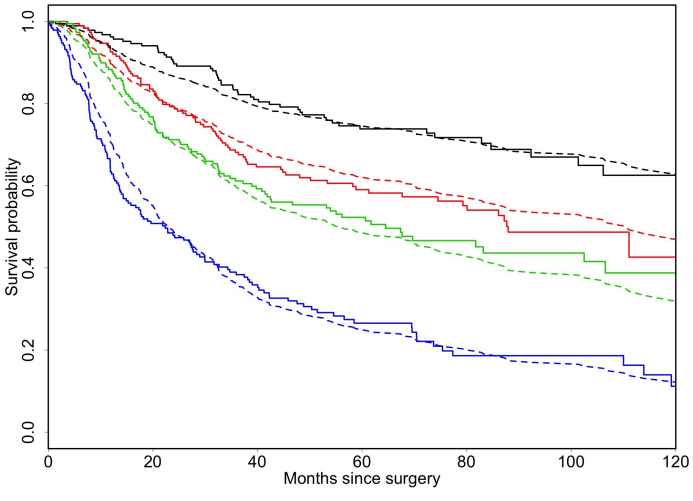

Figure 5.2: Survival curves for four prognostic index groups. Kaplan-Meier survival curves (solid lines) plotted with the model-based survival curves (dotted lines) for four different prognostic index groups. The numbers of patients at risk was 423, 265 and 33 at 3, 5 and 10 years, respectively. Black: patients with good; red: fairly good; green: fairly poor and blue: poor prognosis.

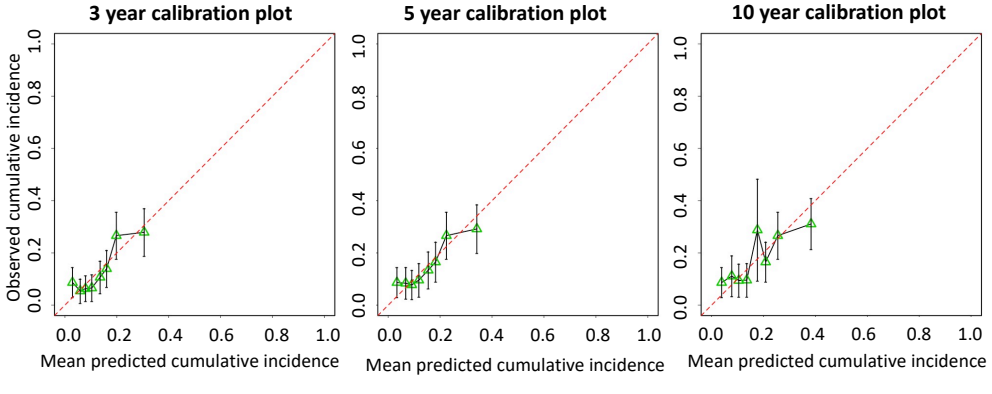

Figure 5.3: Calibration plots for local recurrence. Observed local recurrence (LR) is plotted against predicted LR for patients in eight equal sized risk groups identified by their predicted probability for LR, as assessed by cross validation.

Table 5.4: Fine and Gray model for local recurrence. Subdistribution hazard ratio (sHR) along with 95% confidence interval (n = 766).

	sHR	95% CI	p-Value
Age	1.051	0.942-1.184	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 & superfiscial	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	

The sHR of age corresponds to a unit increase of 10 years and the sHR of size corresponds to a unit increase of 1 cm. **Notation:** MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; RT, radiotherapy.* Depth: relative to the investing fascia.

curves of the lower risk groups are located very close to each other, which indicates some difficulty to discriminate between patients with low risk resulting from the small number of LRs observed in those groups.

Figure 5.5 shows the effect of RT on OS and CILR for two patients with the same risk factors (70 years old, 9 cm tumour size, deep depth, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma, resection margin of 0.1-2 mm) with and without neo- adjuvant RT. The patient without RT (red lines) has worse OS and higher CILR.

Detailed comparisons of observed and predicted probabilities for LR for data subgroups are shown in Table 5.5. No significant differences between observed and predicted outcomes were evident. The C-index for LR was 0.696 (95% CI 0.629-0.743).

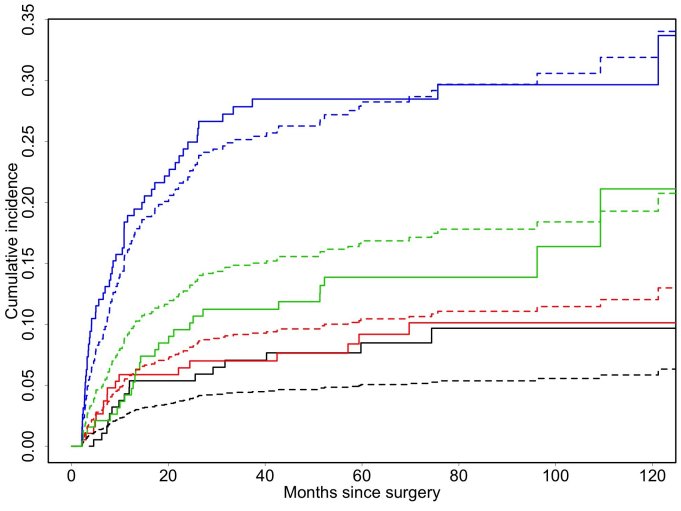

Figure 5.4: Cumulative incidence of local recurrence for four prognostic index groups. Crude cumulative incidence curves (solid lines) plotted with the model-based cumulative incidence curves (dotted lines) for four different prognostic index groups. The numbers of patients at risk were 388, 237 and 29 at 3, 5 and 10 years, respectively. Black: patients with good; red: fairly good; green: fairly poor and blue: poor prognosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

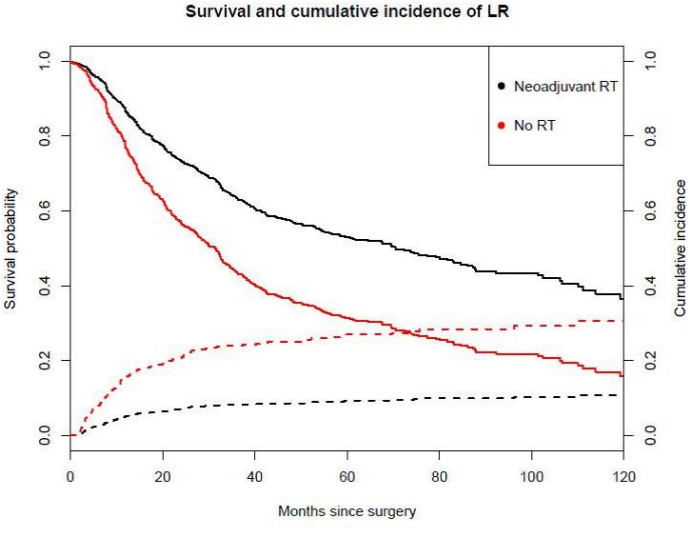

Figure 5.5: Survival and CILR for patient of 70 years, tumour size 9 cm, deep depth, MFH/UPS and resection margin 0.1-2 mm. In red: curves for patient treated with neoadjuvant RT. In black: patient without RT. Solid lines: survival curves. Dotted lines: cumulative incidence for LR. LR, local recurrence; RT, radiotherapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 5.5: Comparing observed cumulative incidence and predicted probabilities of local recurrence, assessed by cross validation, for subgroups of data at 3, 5 and 10 years.

	n (%)	3 years			5 years			10 years		
		Pred	Obs (se)	Diff (95% CI)	Pred	Obs (se)	Diff (95% CI)	Pred	Obs (se)	Diff (95% CI)
Age										
30-60	281 (36.7)	11.4	10.2 (1.8)	1.2 (-2.3 to 4.7)	13.0	11.5 (2.0)	1.5 (-2.4 to 5.4)	14.8	12.9 (2.1)	1.9 (-2.2 to 6.0)
<30	82 (10.7)	9.6	12.6 (3.7)	-3.0 (-10.3 to 4.3)	10.8	15.7 (4.2)	-4.9 (-13.1 to 3.3)	12.4	15.7 (4.2)	-3.3 (-11.5 to 4.9)
>60	403 (52.6)	15.5	15.6 (1.8)	-0.1 (-3.6 to 3.4)	17.5	17.4 (2.0)	0.1 (-3.8 to 4.0)	19.9	20.8 (2.8)	-0.9 (-6.4 to 4.6)
Size										
<5cm	123 (16.1)	9.9	8.4 (2.6)	1.5 (-3.6 to 6.6)	11.3	11.9 (3.2)	-0.6 (-6.9 to 5.7)	12.9	18.2 (5.6)	-5.3 (-16.3 to 5.7)
5cm-10cm	295 (38.5)	11.5	10.1 (1.8)	1.4 (-2.1 to 4.9)	13.1	11.9 (2.0)	1.2 (-2.7 to 5.1)	15.0	14.1 (2.5)	0.9 (-4.0 to 5.8)
>=10cm	348 (45.4)	16.2	17.8 (2.1)	-1.6 (-5.7 to 2.5)	18.3	18.8 (2.1)	-0.5 (-4.6 to 3.6)	20.7	19.4 (2.2)	1.3 (-3.0 to 5.6)
Depth*										
Deep	579 (75.6)	13.9	13.9 (1.5)	0.0 (-2.9 to 2.9)	15.7	15.6 (1.6)	0.1 (-3.0 to 3.2)	17.8	17.9 (1.9)	-0.1 (-3.8 to 3.6)
Superficial	134 (17.5)	13.4	12.3 (2.9)	1.1 (-4.6 to 6.8)	15.2	14.8 (3.3)	0.4 (-6.1 to 6.9)	17.3	16.7 (3.7)	0.6 (-6.7 to 7.9)
Deep and superficial	53 (6.9)	8.1	9.6 (4.1)	-1.5 (-9.5 to 6.5)	9.2	9.6 (4.1)	-0.4 (-8.4 to 7.6)	10.5	9.6 (4.1)	0.9 (-7.1 to 8.9)
Histology										
Myxofibrosarcoma	238 (31.1)	12.1	11.9 (2.1)	0.2 (-3.9 to 4.3)	13.7	12.9 (2.2)	0.8 (-3.5 to 5.1)	15.7	15.7 (3.0)	0.0 (-5.9 to 5.9)
MPNST	91 (11.9)	15.6	17.7 (4.0)	-2.1 (-9.9 to 5.7)	17.6	17.7 (4.0)	-0.1 (-7.9 to 7.7)	20.0	19.6 (4.3)	0.4 (-8.0 to 8.8)
Synovial sarcoma	142 (18.5)	7.2	4.5 (1.8)	2.7 (-0.8 to 6.2)	8.2	9.1 (2.6)	-0.9 (-6.0 to 4.2)	9.4	10.4 (2.9)	-1.0 (-6.7 to 4.7)
Spindle cell sarcoma	167 (21.8)	16.8	16.7 (2.9)	0.1 (-5.6 to 5.8)	19.0	19.0 (3.3)	0.0 (-6.5 to 6.5)	21.6	26.3 (7.3)	-4.7 (-19.0 to 9.6)
MFH/UPS	77 (10.1)	18.1	19.3 (4.6)	-1.2 (-10.2 to 7.8)	20.3	20.9 (4.8)	-0.6 (-10.0 to 8.8)	23.0	20.9 (4.8)	2.1 (-7.3 to 11.5)
Margin										
0 mm	140 (18.3)	23.9	26.2 (3.8)	-2.3 (-9.7 to 5.1)	26.9	26.2 (3.8)	0.7 (-6.7 to 8.1)	30.3	26.2 (3.8)	4.1 (-3.3 to 11.5)
0.1-2 mm	343 (44.8)	14.5	13.4 (1.9)	1.1 (-2.6 to 4.8)	16.4	15.9 (2.0)	0.5 (-3.4 to 4.4)	18.7	19.3 (2.6)	-0.6 (-5.7 to 4.5)
> 2 mm	283 (36.9)	6.8	6.7 (1.5)	0.1 (-2.8 to 3.0)	7.8	8.3 (1.8)	-0.5 (-4.0 to 3.0)	9.0	9.1 (1.9)	-0.1 (-3.8 to 3.6)
RT										
No RT	182 (23.8)	16.4	15.3 (2.7)	1.1 (-4.2 to 6.4)	18.5	18.6 (3.1)	-0.1 (-6.2 to 6.0)	20.9	19.9 (3.3)	1.0 (-5.5 to 7.5)
Neoadjuvant	184 (24)	6.0	7.3 (2.0)	-1.3 (-5.2 to 2.6)	6.9	7.3 (2.0)	-0.4 (-4.3 to 3.5)	7.9	7.3 (2.0)	0.6 (-3.3 to 4.5)
Adjuvant	400 (52.2)	15.4	15.1 (1.8)	0.3 (-3.2 to 3.8)	17.4	17.0 (1.9)	0.4 (-3.3 to 4.1)	19.9	21.0 (2.8)	-1.1 (-6.6 to 4.4)

Notation: CI, confidence interval; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; RT, radiotherapy; *Depth: relative to the investing fascia.

§5.4 Discussion

In cancer care, patient characteristics are generally set at presentation, whereas the combination and timing of treatment(s) is a clinical decision based on each patient's specific circumstances. Previously, we developed a multistate model to investigate how these variables affect patient outcomes [21]. In this study, we developed the PERSARC model which uniquely presents clinicians with the possibility to accurately predict outcome of OS and CILR and compare different treatment modalities, for patients with high-grade ESTS that undergo surgical resection with curative intent. It clearly shows the possible added value of (neo) adjuvant RT at an individual patient level (Figure 5.5). Surgical margins, adjuvant therapies and individual baseline characteristics are all incorporated in this model. To assess the predictive value of this model, internal validation was performed.

This prognostic model illustrates that as the tumour size increases, the prognosis worsens for LR and OS with sHR equal to 1.031 (95% CI: 1.001-1.063) and HR equal to 1.068 (95% CI: 1.052-1.085), respectively. These findings are similar to results reported by other groups. As expected, age was an adverse prognostic risk factor for OS[107], which can only be partially explained by comorbidities. Margins are clearly associated with LR and seem to have a marginally significant effect on OS (Tables 5.2 and 5.4). The effect of recurrence on OS might be attributed to biological aggressiveness of the tumour rather than margins itself (Tables 5.2 and 5.4) [164, 75].

Patients who received RT seem to have better outcomes than those who did not (Tables 5.2 and 5.4) [112]. These patients may have been selected out of the total group of ESTS patients based on clinical characteristics, presenting scenarios or capability to undergo neoadjuvant RT [111]. All patients included in this study were treated at one of the five high-volume sarcoma centres following discussion of their case at a multidisciplinary tumour board. Although selection bias may be present, it only reflects every day care decisions. There are two prospective randomised trials on this topic; in both studies, adjuvant RT has shown a decrease in LR but had no significant impact on survival. However, both studies also included patients with low-grade tumours. Furthermore, due to low number of events (death) per arm, they could only detect a minimal benefit of 20% (as mentioned in the trial that had the most patients per arm) [33, 28]. Previous studies along with the results from this investigation suggest that neoadjuvant RT should be considered at multidisciplinary tumour board discussions for all patients undergoing surgery for primary high-grade ESTS [112, 10, 108, 127, 170]. Patients treated with neoadjuvant radiation are at significantly increased risk of wound healing complications, whether they receive conventional treatment or intensity-modulated RT [112]. Therefore, certain patients such as the elderly, those with significant medical comorbidities or those with prosthetic implants adjacent to the location of the sarcoma, may be considered inappropriate candidates for neoadjuvant radiation.

The outcomes presented above must be interpreted with caution because this model is based on clinical routine data and is therefore, susceptible to selection bias. In addition, margin categories are based on millimetres, and histology was not re-evaluated centrally. Therefore, margin assessment and evaluation of specific margins

'close' to anatomic structures; e. g. periosteum, perineurium or fascia may be subjective to variability [111]. For patients treated in centres where other margin criteria (e. g. Enneking) are in place, this model may be less applicable. Further research should focus on evaluating the different classification methods and agreeing on one standardised margin description for patients with ESTS [55, 90, 81].

While some patients may accept the increased risk of an LR and potential need for subsequent treatment by opting for less aggressive therapy including minimal margins, others may want to minimise the risk of another surgery, for example because of age and comorbidities or because of the potential effect on survival. These trade-offs are delicate and have to be based on clinical experience and substantial evidence. The prediction model developed in this study provides some indication about the possible evolution of the disease and helps in shared decision-making. The Personalised Sarcoma Care model is freely available in the Appstore and Google apps.

Appendix

§5.A Competing risks model

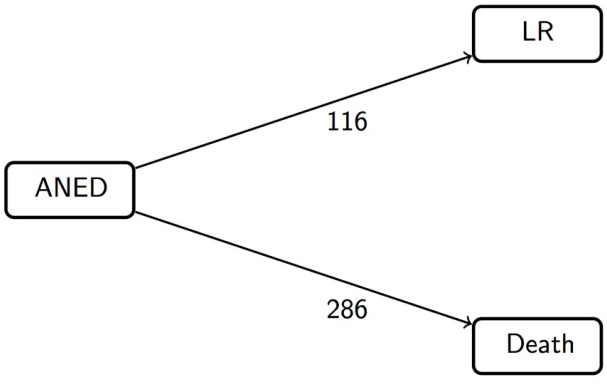

Figure 5.A.1: Competing risk model. A patient enters the state of being alive with no evidence of disease (ANED) after surgery and may move to the state of local recurrence (LR) or death.