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Dynamic prediction of overall survival for patients with high-grade extremity soft tissue sarcoma

A.J. Rueten-Budde[a,*,1], V.M. van Praag[b,1], , PERSARC studygroup (Lee M. Jeys, Minna K. Laitinen, Rob Pollock, Will Aston, Jos A. van der Hage, PD Sander Dijkstra, Peter C. Ferguson, Anthony M. Griffin, Julie J. Willeumier, Jay S. Wunder, Emelie Styring, Florian Posch, Olga Zaikova, Katja Maretty-Kongstad, Johnny Keller, Andreas Leithner, Maria A. Smolle, Rick L. Haas), M.A.J. van de Sande[b,2], M. Fiocco[a,c,2]

[a] Mathematical Institute, Leiden University, Niels Bohrweg 1, 2333 CA, Leiden, the Netherlands
[b] Department of Orthopaedic Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands
[c] Department of Biomedical Data Sciences, Leiden University Medical Center, Einthovenweg 20, 2333 ZC, Leiden, the Netherlands

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ABSTRACT

Purpose: There is increasing interest in personalized prediction of disease progression for soft tissue sarcoma patients. Currently, available prediction models are limited to predictions from time of surgery or diagnosis. This study updates predictions of overall survival at different times during follow-up by using the concept of dynamic prediction.

Patients and methods: Information from 2232 patients with high-grade extremity soft tissue sarcoma, who underwent surgery at 14 specialized sarcoma centers, was used to develop a dynamic prediction model. The model provides updated 5-year survival probabilities from different prediction time points during follow-up. Baseline covariates as well as time-dependent covariates, such as status of local recurrence and distant metastases, were included in the model. In addition, the effect of covariates over time was investigated and modelled accordingly in the prediction model.

Results: Surgical margin and tumor histology show a significant time-varying effect on overall survival. The effect of margin is strongest shortly after surgery and diminishes slightly over time. Development of local recurrence and distant metastases during follow-up have a strong effect on overall survival and updated predictions must account for their occurrence.

Conclusion: The presence of time-varying effects, as well as the effect of local recurrence and distant metastases on survival, suggest the importance of updating predictions during follow-up. This newly developed dynamic prediction model which updates survival probabilities over time can be used to make better individualized treatment decisions based on a dynamic assessment of a patient's prognosis.

1. Introduction

High-grade soft tissue sarcomas (STS) are highly aggressive tumors with poor prognosis [1,2]. Soft tissue sarcomas of the extremities account for approximately 60% of all STS diagnoses [3]. The effect of prognostic factors measured at the time of surgery (e.g. age, surgical margin, radiotherapy, tumor size, depth, and histology subtype) on overall survival has been previously investigated [1–6] and is used in the form of prediction tools such as nomograms and online applications to make patient-specific predictions of disease progression [4,5]. The continuous prediction of OS during treatment and follow-up has proven its clinical benefit in shared decision making and choosing the optimal individualized treatment strategy in several carcinoma cohorts [7–9].

A weakness of current sarcoma models is that they are designed for use at baseline, such as at the time of diagnosis or surgery, and cannot be used to make adequate predictions at later time points during follow-up. After surgery approximately 10% of high grade STS patients develop local recurrence (LR) with or without synchronous distant

* Corresponding author. Mathematical Institute, Leiden University, Niels Bohrweg 1, 2333 CA, Leiden, the Netherlands.
E-mail address: a.j.ruten-budde@math.leidenuniv.nl (A.J. Rueten-Budde).
[1] Shared first authorship.
[2] Shared last authorship.

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Table 1
Patient demographics.

Characteristics		Overall
Total		2232
Age mean (sd)		60.86 (18.74)
Gender (%)	Male	1203 (53.9)
	Female	1029 (46.1)
Tumor size in cm mean (sd)		8.95 (5.85)
Tumor depth (%)	Deep	1269 (56.9)
	Superficial	551 (24.7)
	Unknown	412 (18.5)
Histology (%)	Myxofibrosarcoma	432 (19.4)
	MPNST	167 (7.5)
	Synovial sarcoma	277 (12.4)
	Sarcoma – NOS	108 (4.8)
	Spindle cell sarcoma	492 (22.0)
	MFH/UPS	604 (27.1)
	Other	152 (6.8)
Margin (%)	R1-2	274 (12.3)
	R0	1890 (84.7)
	Unknown	68 (3.0)
Radiotherapy (%)	No radiotherapy	916 (41.0)
	Neoadjuvant	265 (11.9)
	Adjuvant	1004 (45.0)
	Unknown	47 (2.1)
Chemotherapy (%)	No chemotherapy	1876 (84.1)
	Neoadjuvant	98 (4.4)
	Adjuvant	228 (10.2)
	Unknown	30 (1.3)

N, number of patients; sd, standard deviation; cm, centimeters; MPNST, malignant peripheral nerve sheath tumor; sarcoma – NOS, (pleomorphic) soft tissue sarcomas not-otherwise-specified; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; Histology "Other", angiosarcoma, leiomyosarcoma, liposarcoma, malignant rhabdoid tumor, alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, rhabdomyosarcoma (adult form) and conventional fibrosarcoma. [a]Depth: relative to the investing fascia.

metastases (DM). Both will have a significant impact on future disease progression and the difference in prognosis should be incorporated in future treatment protocols. Even the fact that a patient survived a length of time after surgery might give an indication about his future prognosis. In addition, the effect of prognostic factors may change over time (time-varying effect), which has not yet been studied. For example, surgical margin and radiotherapy might have a strong impact on survival in the immediate time after surgery; however, their effect may change during follow-up. The use of time-dependent covariates, such as LR and DM status, and time-varying effects to update survival probabilities during follow-up is known as dynamic prediction [10]. To the best of our knowledge, no previous prediction model has been published taking the time-varying effect of risk factors into account for patients with STS. This study fills a gap in current research by investigation the effect of risk factors for death in high-grade extremity STS patients over time.

The aim of this study was to develop a dynamic prediction model for high-grade (FNCLCC grade II and III [11]) extremity STS patients that updates overall survival probabilities during follow-up. The effect of prognostic factors over time was studied and modelled accordingly in the dynamic model. The model predicts a patient's probability of surviving an additional five years from different prediction time points (t_p) after resection of their sarcoma. Specific patient examples are used to illustrate how predicted probabilities change at different prediction time points during follow-up. To implement these findings in clinical practice, this model will be made available in the updated PERSARC app and online [4].

2. Methods

2.1. Study design

In this study a dynamic prediction model, using a retrospectively collected cohort of patients with STS of the extremities, was developed and internally validated. Clinical data were collected between January 1st, 2000 and December 31st, 2014, at 14 different international specialized sarcoma centers, thereby creating the largest multinational dataset of high-grade surgically treated extremity STS patients in the world. Included centers are Leiden University Medical Center (Leiden, the Netherlands), Royal Orthopaedic Hospital (Birmingham and Stanmore, UK), Netherlands Cancer Institute (Amsterdam, the Netherlands), Mount Sinai Hospital (Toronto, Canada), the Norwegian Radium Hospital (Oslo, Norway), Aarhus University Hospital (Aarhus, Denmark), Skåne University Hospital (Lund, Sweden), and Medical University Graz (Graz, Austria). The outcome measure used was overall survival, which was defined as time from surgery to death from any cause or last recorded follow-up. The prediction model estimates the dynamic probability of surviving an additional five years from a prediction time point t_p called dynamic overall survival (DOS). From time of surgery predictions of 5-year DOS can be estimated based on updated patient information.

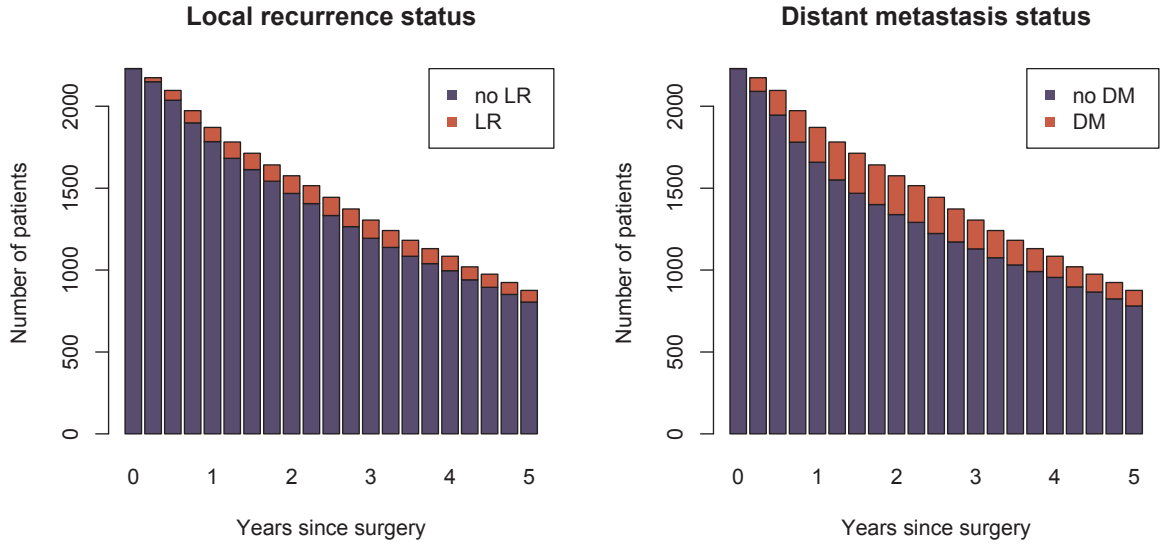

Fig. 1. Number of patients at risk at each landmark time point t_{LM}. A) Red, patients with local recurrence; blue, patients without local recurrence. B) Red, patients with distant metastases; blue, patients without distant metastases.