Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis

Dario Callegaro, Rosalba Miceli, Sylvie Bonvalot, Peter Ferguson, Dirk C Strauss, Antonin Levy, Anthony Griffin, Andrew J Hayes, Silvia Stacchiotti, Cecile Le Pechoux, Myles J Smith, Marco Fiore, Angelo P Dei Tos, Henry G Smith, Luigi Mariani, Jay S Wunder, Raphael E Pollock, Paolo G Casali, Alessandro Gronchi

Summary

Background The current American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system does not have sufficient details to encompass the variety of soft-tissue sarcomas, and available prognostic methods need refinement. We aimed to develop and externally validate two prediction nomograms for overall survival and distant metastases in patients with soft-tissue sarcoma in their extremities.

Methods Consecutive patients who had had an operation at the Istituto Nazionale Tumori (Milan, Italy), from Jan 1, 1994, to Dec 31, 2013, formed the development cohort. Three cohorts of patient data from the Institut Gustave Roussy (Villejuif, France; from Jan 1, 1996, to May 15, 2012), Mount Sinai Hospital (Toronto, ON, Canada; from Jan 1, 1994, to Dec 31, 2013), and the Royal Marsden Hospital (London, UK; from Jan 1, 2006, to Dec 31, 2013) formed the external validation cohorts. We developed the nomogram for overall survival using a Cox multivariable model, and a Fine and Gray multivariable model for the distant metastases nomogram. We applied a backward procedure for variables selection for both nomograms. We assessed nomogram model performance by examining overall accuracy (Brier score), calibration (calibration plots and Hosmer–Lemeshow calibration test), and discrimination (Harrell C index). We plotted decision curves to evaluate the clinical usefulness of the two nomograms.

Findings 1452 patients were included in the development cohort, with 420 patients included in the French validation cohort, 1436 patients in the Canadian validation cohort, and 444 patients in the UK validation cohort. In the development cohort, 10-year overall survival was 72·9% (95% CI 70·2–75·7) and 10-year crude cumulative incidence of distant metastases was 25·0% (95% CI 22·7–27·5). For the overall survival nomogram, the variables selected applying a backward procedure in the multivariable Cox model (patient's age, tumour size, Fédération Française des Centres de Lutte Contre le Cancer [FNCLCC] grade, and histological subtype) had a significant effect on overall survival. The same variables, except for patient age, were selected for the distant metastases nomogram. In the development cohort, the Harrell C index for overall survival was 0·767 (95% CI 0·743–0·789) and for distant metastases was 0·759 (0·736–0·781). In the validation cohorts, the Harrell C index for overall survival and distant metastases were 0·698 (0·638–0·754) and 0·652 (0·605–0·699; French), 0·775 (0·754–0·796) and 0·744 (0·720–0·768; Canadian), and 0·762 (0·720–0·806) and 0·749 (0·707–0·791; UK). The two nomograms both performed well in terms of discrimination (ability to distinguish between patients who have had an event from those who have not) and calibration (accuracy of nomogram prediction) when applied to the validation cohorts.

Interpretation Our nomograms are reliable prognostic methods that can be used to predict overall survival and distant metastases in patients after surgical resection of soft-tissue sarcoma of the extremities. These nomograms can be offered to clinicians to improve their abilities to assess patient prognosis, strengthen the prognosis-based decision making, enhance patient stratification, and inform patients in the clinic.

Funding None.

Lancet Oncol 2016; 17: 671–80

Published Online
April 5, 2016
http://dx.doi.org/10.1016/S1470-2045(16)00010-3

See Comment page 554

Department of Surgery (D Callegaro MD, M Fiore MD, A Gronchi MD), **Department of Clinical Epidemiology and Trial Organisation** (R Miceli PhD, L Mariani PhD), **and Department of Cancer Medicine** (S Stacchiotti MD, P G Casali MD), **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Surgery, Institut Curie, PSL Research University, Paris, France** (Prof S Bonvalot PhD); **Department of Surgery, Mount Sinai and Princess Margaret Hospitals, University of Toronto, Toronto, ON, Canada** (P Ferguson MD, A Griffin MSc); **Department of Surgery, Royal Marsden Hospital NHS Foundation Trust, London, UK** (D C Strauss FRCS, A J Hayes FRCS, M J Smith FRCSI, H G Smith MBBS); **Department of Radiation Oncology, Gustave Roussy Cancer Campus, Paris Sud University, Villejuif, France** (A Levy MD, C Le Pechoux MD); **Department of Pathology, General Hospital of Treviso, Treviso, Italy** (A P Dei Tos MD); **University Musculoskeletal Oncology Unit, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada** (Prof J S Wunder MD); **and Department of Surgery, Division of Surgical Oncology, Ohio State University Medical Center, Columbia, SC, USA** (Prof R E Pollock MD)

Introduction

Soft-tissue sarcomas are a heterogeneous group of rare tumours, consisting of several histological subtypes with an overall incidence of five cases per 100 000 people per year.[1] Patient's prognosis is highly variable.

The current American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system[2] classifies patients with soft-tissue sarcomas according to tumour size, tumour depth, nodal involvement, and distant metastases, in addition to malignancy grade. Studies have shown that this classification does not have sufficient details to encompass the diversity of soft-tissue sarcomas.[3,4]

In the past few years, nomograms that predict prognosis in patients with soft-tissue sarcomas have been developed to provide more accurate estimates of

Correspondence to:
Dr Alessandro Gronchi,
Department of Surgery,
Fondazione IRCCS Istituto
Nazionale dei Tumori,
20133 Milan, Italy
alessandro.gronchi@istitutotumori.mi.it

For the **Sarculator app (Digital Forest srl)** see https://play.google.com/store/apps/details?id=it.digitalforest.sarculator or https://geo.itunes.apple.com/us/app/sarculator/id1052119173?mt=8

Research in context

Evidence before this study

We searched PubMed for studies published before Sept 1, 2015, that investigated the use of nomograms and the role of available staging systems in prediction of the prognosis of patients with soft-tissue sarcoma. We used the search terms "sarcoma", "extremity", "surgery", "nomogram", and "staging system". At the time of our search, the use of available nomograms for soft-tissue sarcomas of the extremities was hampered by the adoption of an obsolete classification by pathology (not at time of nomogram development), whereas the current American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system for soft-tissue sarcomas was repeatedly shown to be of little prognostic value. No available nomograms for soft-tissue sarcomas of the extremities had explored the patient's outcome in terms of overall survival or crude cumulative incidence of distant metastasis.

Added value of this study

We designed and validated two nomograms for overall survival and distant metastases. The main strengths of these new nomograms are the adoption of the updated WHO histological classification, which led to the inclusion of nine well defined categories; refinement of the covariates that affect oncological outcomes; use of continuous instead of categorical variables, where appropriate; use of the three-tiered Fédération Française des Centres de Lutte Contre le Cancer (FNCLCC) grading system (grades I, II, and III); and use of two primary endpoints (overall survival and distant metastasis). Moreover, the nomogram models underwent three successful independent external validations to support their reliability. An app for smartphones and tablets (called Sarculator) has been developed to make these new prognostic tool techniques more easily available to use than a classic nomogram.

Implications of all the available evidence

Our two new nomograms are available to improve the prognostication ability of the physician, enhance patients' stratification in clinical trials or population-based analysis, guide prognosis-based decision-making processes, and possibly complement the next AJCC/UICC staging system.

patient outcome. The first nomogram to predict sarcoma-specific death was developed in 2002 by Kattan and colleagues.[5] Subsequently, this tool was externally validated on two independent cohorts from tertiary care centres[6,7] and with a national, population-based, cancer registry database.[8] Outdated histological categories and all tumour sites were included in Kattan's nomogram. Nowadays, histology-specific nomograms for liposarcoma and synovial sarcoma,[9,10] site-specific nomograms for extremity and retroperitoneal sarcomas,[7,11–14] and site-specific and histology-specific nomograms for uterine leiomyosarcoma[15] are available. The advantage of focusing on a definite subgroup is the possibility of including the model prognostic factors that might be relevant only for that histology or site. Thus a more accurate estimate of the individual patient prognosis is likely to be achieved.[5,9]

Soft-tissue sarcomas of the extremities are the most common soft-tissue sarcoma subgroup, identified by a broad histological subclassification that has been refined continuously during the past years. In view of the importance of histological changes in outcome prediction, nomograms developed a decade ago were based on outmoded histological classifications and need to be updated. Our extremity-specific nomogram developed in 2005[7] had good bootstrap-corrected concordance index (c 0·76), but also several limitations: size was managed as a discrete variable and the histological classification was the one used at the time of development. Moreover, patients included in that cohort were treated between 1980 and 2000, and one cannot rule out that outcomes have since changed.[16]

The aim of this study was to develop a new prognostic tool for patients with primary resected soft-tissue sarcomas of the extremities, backed by independent external validations, to help clinical decision making and to assist ongoing efforts, such as the forthcoming new AJCC/UICC stage classification.[2]

Methods

Study design and participants

We created two nomograms using a development cohort of patients with primary resected soft-tissue sarcomas of the extremities. To externally validate these new nomograms, we used three independent cohorts of patients with the same characteristics (validation cohorts). All consecutive adult (aged >18 years) patients with primary (non-recurrent and non-metastatic) soft-tissue sarcomas of the extremities, who had had an operation with curative intent at Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy), between Jan 1, 1994, and Dec 31, 2013, formed the development cohort of the study. We defined soft-tissue sarcomas of the extremities as all tumours arising from the shoulder girdle to the hand (upper extremity) and from the pelvic girdle (excluding endopelvic tumours) to the foot (lower extremity). We excluded patients with desmoids, soft-tissue Ewing's sarcoma, alveolar or embryonal rhabdomyosarcoma, dermatofibrosarcoma protuberans, and well differentiated liposarcoma because of the peculiar natural histories and treatment strategies for these cancers.

Three independent cohorts of patients with the same clinical characteristics, who had undergone an operation at Institut Gustave Roussy (Villejuif, France; from