Review Article

Soft Tissue Sarcoma Nomograms and Their Incorporation Into Practice

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The accurate prediction of prognosis in patients with soft tissue sarcoma (STS) is a challenging issue. Extreme variability in the clinical and pathological characteristics of this family of tumors hinders the simple stratification of patients into meaningful prognostic cohorts. Precision medicine tools for the prediction of prognosis, such as nomograms, enable personalized computation of outcome based on clinical and pathological characteristics of both patient and tumor. The eighth edition of the American Joint Committee on Cancer staging manual moved from a "population-based" to a "personalized" approach endorsing high-quality nomograms to improve clinician prediction ability in definite patient subgroups. The first nomogram for STS was published in 2002, and this was followed by several prognostic predictors offered to clinicians. Focusing on a specific STS subgroup or site, nomograms can take into consideration highly specific factors relevant only in that particular scenario, thereby maximizing prognostic ability. The objective of this review was to critically evaluate available nomograms for patients with STS to provide clinicians and researchers with a choice of the most optimal tool for each specific patient. ***Cancer* 2017;000:000-000**. © *2017 American Cancer Society*.

KEYWORDS: American Joint Committee on Cancer (AJCC), liposarcoma, nomogram, prediction tool, prognosis, retroperitoneal sarcoma, sarcoma, soft tissue sarcoma, staging, synovial sarcoma.

INTRODUCTION

The oncologist frequently is asked to predict the prognosis and chances of cure for a particular patient. In the era of precision medicine, in which medical treatments are tailored to the individual clinicopathologic and molecular characteristics of each patient's tumor, it is essential for these predictions to be as accurate as possible. Indeed, physician expectations exert a strong influence on treatment, follow-up, and patient quality of life.

Soft tissue sarcomas are a heterogeneous family of tumors comprised of >50 histological subtypes arising in nearly any site in the body and representing the full spectrum of malignant behavior.[1] Indolent tumors, such as classic dermatofibrosarcoma protuberans, are likely to be cured with fairly limited surgical resections. At the other extreme, high-grade dedifferentiated liposarcoma (LPS) or leiomyosarcoma (LMS) of the retroperitoneum harbor a significant risk of disease recurrence (albeit with distinctly different patterns of recurrence) and death. Historically, staging systems such as the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM staging system did not include specific STS histology or site of origin for most sarcomas, until the recent eighth edition.[2] Nevertheless, these are widely recognized as 2 of the most important prognostic factors in determining outcomes in patients with soft tissue sarcoma (STS).

In recent years, newer tools for prognosis prediction, such as nomograms, have been applied in many types of cancer.[3] For example, the first nomogram specific for patients with STS was developed in 2002, thereby refining the physician's prognostic capabilities.[4]

With this review, we intended to explore the nomograms available for STS and to provide the clinician with a guide for choosing the best tool for his or her patient.

STS Staging System

The various histologic and anatomic presentations of STS render the categorization and staging of these tumors particularly challenging. Until the recent eighth edition, the AJCC/UICC staging manual classified STS patients into 4 stages of disease according to malignancy grade, tumor dimension, tumor depth, lymph node involvement, and distant metastasis.[5]

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This system had intrinsic limitations: it included neither the anatomic location of the tumor nor the histological subtype and did not accurately represent all cases of STS.[6-8]

The recently released eighth edition of the AJCC staging system introduced major changes. First, STS are no longer classified as a single malignancy; instead, new site-specific staging systems for STS of the trunk and extremities, retroperitoneum, head and neck, and abdomen and thoracic visceral organs have been developed. Second, tumor dimension is no longer managed as a dichotomic covariate with a cutoff at 5 cm but rather as a 4-tier categorical variable. This new categorization of the primary tumor (T) is aimed to better reflect the direct relationship between tumor size and the metastatic risk. Moreover, the variable tumor depth has been eliminated and N1 disease has been captured as stage IV.

Despite these changes, the TNM system is still limited by being based on the anatomic stage of the tumor; in other words, it assumes that the anatomic progression of the tumor correlates with progression of tumor stage. This means that patients with the same anatomic progression are forced into the same stage of disease even if the prognosis could be substantially different based on histology.

In the latest edition, the AJCC has increasingly recognized the need for personalized prognostic tools that could take into consideration other tumor-related or patient-related factors beyond the TNM staging system to achieve a more accurate and tailored outcome prediction. To this end, the AJCC Precision Medicine Core recently published a checklist of 16 items to critically evaluate prognostic tool quality and to identify prognostic models that may be endorsed by the AJCC.[9] In the eighth edition of the AJCC manual, a validated nomogram for retroperitoneal sarcoma that met all AJCC inclusion/exclusion criteria has been included.[2,10]

Histology-Specific or Site-Specific STS Nomograms

A peculiarity of STS is that oncologic outcome is strongly influenced by both the histologic subtype and site of tumor origin. Indeed, if it is true that some histologies behave in a more indolent manner than others, regardless of site, it also is true that the same histologic subtype arising at different sites may have different outcomes. For example, a well-differentiated LPS (WDLPS) of the extremity is more likely to be cured compared with a WDLPS of the retroperitoneum.

This observation is reflected in some of the newer nomograms, with some being histology-specific (tumor site is one of the covariates) and others being site-specific (applicable to every histotype within a specific site). The first group contains nomograms specific for LPS, synovial sarcoma, rhabdomyosarcoma (RMS), desmoid-type fibromatosis, and gastrointestinal stromal tumors (not discussed here). In the second group, there are nomograms specific for extremity and retroperitoneal STS. Finally, there are tools that are both histology-specific and site-specific, such as nomograms for uterine leiomyosarcoma (ULMS) and phyllodes tumors of the breast.

Statistical Background

Nearly all of the published sarcoma nomograms are presented as graphical tools, in which known clinical and biological factors (covariates) are combined and used for risk prediction. An in-depth focus on the methodological aspects of nomogram construction is beyond the scope of this review, and many other articles already have dissected this topic.[3] A useful guide for the nonstatistician audience with a methodological approach for building, interpreting, and using nomograms to estimate cancer prognosis or other health outcomes was published by Iasonos et al.[11] Moreover, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative (www.tripod-statement.org) recently published the TRIPOD reporting guideline for clinical prediction models.[12]

In general, a nomogram is derived from a multivariable prognostic model that provides estimates of the overall probability of a specific outcome (response to treatment, overall survival [OS], or disease-free survival [DFS] at a certain time, or the median survival time). In the most common representation, each covariate is depicted on a graduated scale; a score is assigned to each covariate value; and the sum of all scores, reflecting the weighted combined contribution of the covariates, is converted into the outcome of interest. The scores reflect the strength of the relationship between a covariate and the outcome: the higher the value, the worse the prognosis. Functions such as splines[13] may allow for modeling of a complex relationship between the model outcome and continuous covariates (eg, tumor size). In addition to the nomogram picture, the corresponding model estimates and scoring system can be presented to the users by means of tables or curves, and the derived predictions may be generated by software applications. The digital interface in particular is more precise, immediate, and practical in daily clinical use.

The goal of a nomogram is to predict the outcome as accurately as possible. Thus, one important issue after

nomogram building is the evaluation of its performance as a predictive tool. Two aspects generally are evaluated: 1) how far the predictions are from the actual outcomes on average (calibration); and 2) the ability of the model to distinguish subjects with different outcomes (discrimination). Calibration typically is assessed by reviewing the plot of predicted outcome (eg, survival probability predicted at a given time in different patient groups) versus observed outcome (corresponding Kaplan-Meier survival probability). A perfectly accurate nomogram would result in a plot in which the predicted and observed probabilities fall along a 45-degree line, and agreement between the 2 can be statistically tested with the Hosmer-Lemeshow goodness-of-fit test. The discriminative ability of the nomogram usually is measured via a concordance index (Harrell C-index),[14] quantifying the agreement between predicted probabilities and the actual occurrence of the event of interest. Nomogram internal validation is performed by evaluating its calibration and discriminative ability on the same case series used to build the nomogram; in this case, the Harrell C-index is always overestimated, and a correction is needed (and not in all cases performed) for "overoptimism" adjustment. Internal validation can never be an adequate substitute for evaluation of the nomogram's generalizability,[15] which is performed by evaluating its calibration and discriminative ability on independent data (external validation). The nomogram performance in the external validation set generally is slightly worse than in the original data set; a substantially worse performance does not necessarily render the nomogram invalid if performance metrics still are within a clinically acceptable range.[3]

Good calibration and discriminative ability are not sufficient for a nomogram to be clinically useful. More recently, a proposed third relevant issue was evaluating the ability to improve the decision-making process (clinical usefulness). In the absence of the prospective randomized assignment of patients to nomogram-based or nonnomogram-based decisions, the assessment of whether nomogram-assisted decisions improve patient outcomes relies on decision analysis curves.[16] These curves demonstrate the benefit of a risk-driven treatment strategy toward "treat all" or "treat none" strategies, varying the risk threshold (above which treatment is administered) between 0 and 1.

GENERAL POSTOPERATIVE NOMOGRAMS FOR STS

The first nomogram for patients with STS was built in 2002 by Kattan et al (Table 1)[4,17-28] from Memorial Sloan Kettering Cancer Center (MSKCC) in New York.[4] We will refer to this nomogram as the "MSKCC Sarcoma Nomogram" (MSKSN). This tool combines 5 covariates to predict the 12-year sarcoma-specific death. The nomogram computes 2 separate predictions: one for patients with low-grade tumors and the other for patients with high-grade tumors. In the online version (https://www.mskcc.org/nomograms/sarcoma), sarcoma-specific death predictions also are computed at 4 years and 8 years.

This nomogram underwent various external validations, with the Harrell C-index ranging from 0.71 to 0.78 and good external calibrations.[18,21-28] Validation on a population-based cohort from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute[23] suggested that the MSKSN was applicable to the general population whereas validation on a Asian cohort[28] suggested that the MSKSN maintained good discrimination but overpredicted survival among patients with lower survival probability in this population. Validation on a cohort of patients with head and neck STS[24] suggested that it also was applicable to patients with STS rising at this site. However, the performance of this instrument is weak in patients with retroperitoneal sarcoma (RPS), with a Harrell C-index of 0.60 reported in a recent study from the same group.[29]

The MSKSN has been applied to a population of pediatric patients with nonrhabdomyosarcoma adult-type STS to explore the prognostic role of the covariates in the 2 populations and establish whether pediatric and adult patients were prognostically comparable.[30] This study revealed that MSKSN variables are indeed relevant predictors in pediatric patients with adult-type STS. However, the actual mortality observed in the pediatric population was consistently higher than the nomogram-predicted mortality. In particular, the negative prognostic effects of tumor size and depth were stronger in the pediatric population. Moreover, this study demonstrated that the age-related mortality pattern predicted by the MSKSN applied to patients aged <16 years.

Szkandera et al, from the Medical University of Graz in Austria, performed 3 different studies on institutional series of patients diagnosed with STS (all sites), and demonstrated that implementation of the MSKSN with the addition of the preoperative C-reactive protein level, fibrinogen level, and the lymphocyte/monocyte (L/M) ratio (all significant prognostic factors in multivariate analysis) improved the Harrell C-index of the model from 0.74 to 0.77, from 0.747 to 0.779, and from 0.74 to 0.78, respectively.[25-27]

TABLE 1. General and Extremity-Specific Nomograms for Patients With STS

		Development Series Characteritics			Nomogram Details			Internal Validation	External Validation	
	Study	Selection Criteria	Timeframe	No. of Centers	Predicted Outcomes	No. of Patients (Developing Set)	Nomogram's Covariates[a]	Concordance Index	Yes/No	Concordance Index
General postoperative nomograms	Kattan 2002[4]	Primary, surgically treated, any site but skin	1982-2000	1	12-y low-grade SSD, 12-y high-grade SSD	2163	Histology (7 categories), size (3 categories), age (continuous), site (6 categories), depth (superficial vs deep)	0.77	Yes[b]	0.71-0.76[b]
	Kattan 2003[17]	Local recurrent STS, any site but skin	1982-2000	1	Up to 5-y SSD	355	Histology (7 categories), size (3 categories), age (continuous), site (6 categories), grade (low vs high), depth (superficial vs deep)	NA	No	-
Nomograms specific for extremity STS	Mariani 2005[18]	Primary completely resected extremity STS	1980-2000	1	10-y SSD	642	Grade (3 tiers), histology, age (continuous), size (3 categories), depth (superficial vs deep), site (lower vs upper)	0.76	No	-
	Cahlon 2012[19]	Primary extremity STS treated with limb-sparing surgery without adjuvant therapies	1982-2006	1	3-y and 5-y LR rate	684	Histology (WDLPS vs others), surgical resection margin (negative vs close/positive), grade (low vs high), age (dichotomic, cutoff at 50 y), size (dichotomic, cutoff at 5 cm)	0.73	No	-
	Callegaro 2016[20]	Primary extremity STS treated with surgery	1994-2013	1	5-y and 10-y OS	1452	Size (continuous), histology (9 categories), age (continuous), grading (FNCLCC)	0.77	Yes[c]	0.70-0.77[c]
					5-y and 10-y DM	1452	Size (continuous), grading (FNCLCC), histology (9 categories)	0.76	Yes[c]	0.65-0.75[c]

Abbreviations: FNCLCC, Fédération Française des Centres de Lutte Contre le Cancer; DM, distant metastasis; LR, local recurrence; NA, not applicable; OS, overall survival; SSD, sarcoma-specific death; STS, soft tissue sarcoma; WDLPS, well-differentiated liposarcoma.

[a] The variables are listed according to their nomogram score range, which reflects their relative effect on the predicted outcome, on a decreasing basis (the first variable exerts the strongest influence on the predicted outcome).

[b] External validations were performed on 929 patients with primary STS from the University of California at Los Angeles (UCLA) (Harrell C-index, 0.76)[21]; 642 patients with primary extremity STS from the National Cancer Institute in Milan, Italy (Harrell C-index, 0.75)[18]; 238 high-risk patients with primary extremity STS who were treated with neoadjuvant high-dose ifosfamide-based chemoradiotherapy within the context of a phase 2 prospective trial at UCLA (Harrell C-index, 0.77)[22]; 9237 patients from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (Harrell C-index, 0.74)[23]; 187 patients with primary head and neck STS who were treated at Memorial Sloan Kettering Cancer Center (Harrell C-index, 0.78)[24]; 304 patients with STS who were undergoing surgery at the Medical University of Graz in Graz, Austria (Harrell C-index, 0.74)[25]; 294 patients with STS who were undergoing surgery at the Medical University of Graz (Harrell C-index, 0.747)[26]; 340 patients with STS who were undergoing surgery at the Medical University of Graz (Harrell C-index, 0.74)[27]; and 399 patients with STS who were undergoing surgery at the National Cancer Centre Singapore (Harrell C-index, 0.71).[28]

[c] External validations were performed on 1436 patients from Mount Sinai Hospital in Toronto, Ontario, Canada (Harrell C-index, 0.775 [95% CI, 0.754-0.796] for OS and 0.744 [0.720-0.768] for DM); 444 patients from Royal Marsden Hospital NHS Foundation Trust in London, United Kingdom (Harrell C-index, 0.762 [0.720-0.806] for OS and 0.749 [0.707-0.791] for DM); and 420 patients from Institute Gustave Roussy in Villejuif, France (Harrell C-index 0.698 [0.638-0.754] for OS and 0.652 [0.605-0.699] for DM).

The excellent results of the MSKSN external validations proved its reliability, but further critical scrutiny does reveal some limitations. First, among the model covariates, tumor size was managed as a categorical variable. Therefore, this model is not able to capture the prognostic difference within each category (ie, for equal covariates but size, a patient with an 11-cm tumor would have the same predicted prognosis as a patient with a 20-cm tumor). Second, histologic classification has been updated, and some histologies adopted in the nomogram either no longer exist (ie, the histological subtype of "malignant fibrous histiocytoma" is not included in the recent World Health Organization [WHO] classification) or may be reclassified due to advances in immunohistochemistry and molecular pathology. For example, with the use of MDM2 and CDK4 immunohistochemistry, many retroperitoneal tumors termed "malignant fibrous histiocytoma" have been reclassified as "dedifferentiated LPS."[29,31] This sort of change makes any type of prognostic model archaic with successive iterations of the WHO classifications. Furthermore, the 3-tier French Federation of Comprehensive Cancer Centers grading system has been proven to correlate better with patient prognosis compared with a 2-tier system.[18,32] Finally, prognostic tools specific for STS subgroups have been proven to have a better stratification ability. For example, the RPS-specific nomograms or the LPS-specific nomogram predicted prognosis better than the MSKSN in their respective subsets of patients.[29,33]

Nevertheless, in addition to its clinical use, the MSKSN has been used to evaluate outcomes with (neo)-adjuvant therapy. In 2007, it served as a model to evaluate the impact of neoadjuvant, high-dose, ifosfamide-based chemoradiotherapy in patients who were surgically treated for high-risk primary extremity STS within a single-arm, phase 2, prospective protocol at the University of California at Los Angeles.[22] Similarly, in 2014, Schenone et al adopted a nomogram-based cutoff (predicted 4-year sarcoma-specific death of $\geq$0.3) to distinguish between low-risk and high-risk patients in a study aimed at retrospectively assessing the benefit of adjuvant chemotherapy in patients with STS.[34]

In 2003, the MSKCC group produced a nomogram based on the same covariates to predict the 5-year sarcoma-specific death probability in patients with locally recurrent STS while adjusting for the competing effect of mortality unrelated to STS.[17]

Despite the aforementioned limitations, the MSKSN and the competing-risk nomogram remain the only personalized prognostic tools that are applicable to patients with STS regardless of histologic subtype and site of origin. In circumstances in which a subsequent subtype-specific prognostic tool revealed a better performance compared with MSKSN (such as RPS-specific or LPS-specific nomograms) or adopted an updated histological classification, the better-performing tool should be used for prediction. Nevertheless, for some STS subtype/sites, such as head and neck STS, the MSKSN remains the only available personalized prognostic tool.

NOMOGRAMS FOR EXTREMITY STS

Extremity STS accounts for approximately 50% of all cases of STS.[35] They are characterized by a broad histological diversity that reflects into very different behaviors. Patients with extremity STS usually die of metastatic spread of the disease. Local recurrence (LR) usually is manageable with limb-sparing re-resection or amputation, with the exception of very proximal locations, which can enter the pelvis or chest and lead to death due to loss of local disease control.[36]

Nomograms specific for patients with extremity STS are shown in Table 1.[4,17-28]

To the best of our knowledge, the first nomogram specific for patients with extremity STS was developed in 2005 by Mariani at al from the Istituto Nazionale Tumori (INT) in Milan during the process of external validation of the MSKSN.[18] Compared with the MSKSN, this nomogram adopted a 3-tier grading system. As in the original MSKSN, size was managed as a categorical covariate, tumor depth most likely was overemphasized, and some of the histologic subtypes are no longer used.

In 2012, Cahlon et al from MSKCC proposed a nomogram to specifically predict the LR risk after limb-sparing surgery in patients with primary extremity STS who did not undergo radiotherapy.[19] A limitation of this model is the adoption of a dichotomic histological classification (WDLPS/Atypical Lipomatous Tumor[ALT] vs others) that is not able to entirely capture the prognostic weight of the histologic subtype on local outcome. For example, within the "other" group, there are histologies such as malignant peripheral nerve sheath tumor and myxofibrosarcoma that bear a much higher risk of LR than other histologies such as leiomyosarcoma. Moreover, the clinician should keep in mind that the direct correlation between the local control of the disease and the final oncological outcome in patients with extremity STS remains controversial.[36,37]

The groups from INT, Mount Sinai Hospital (Toronto, Ontario, Canada), Royal Marsden Hospital NHS Foundation Trust (London, UK), and Institut

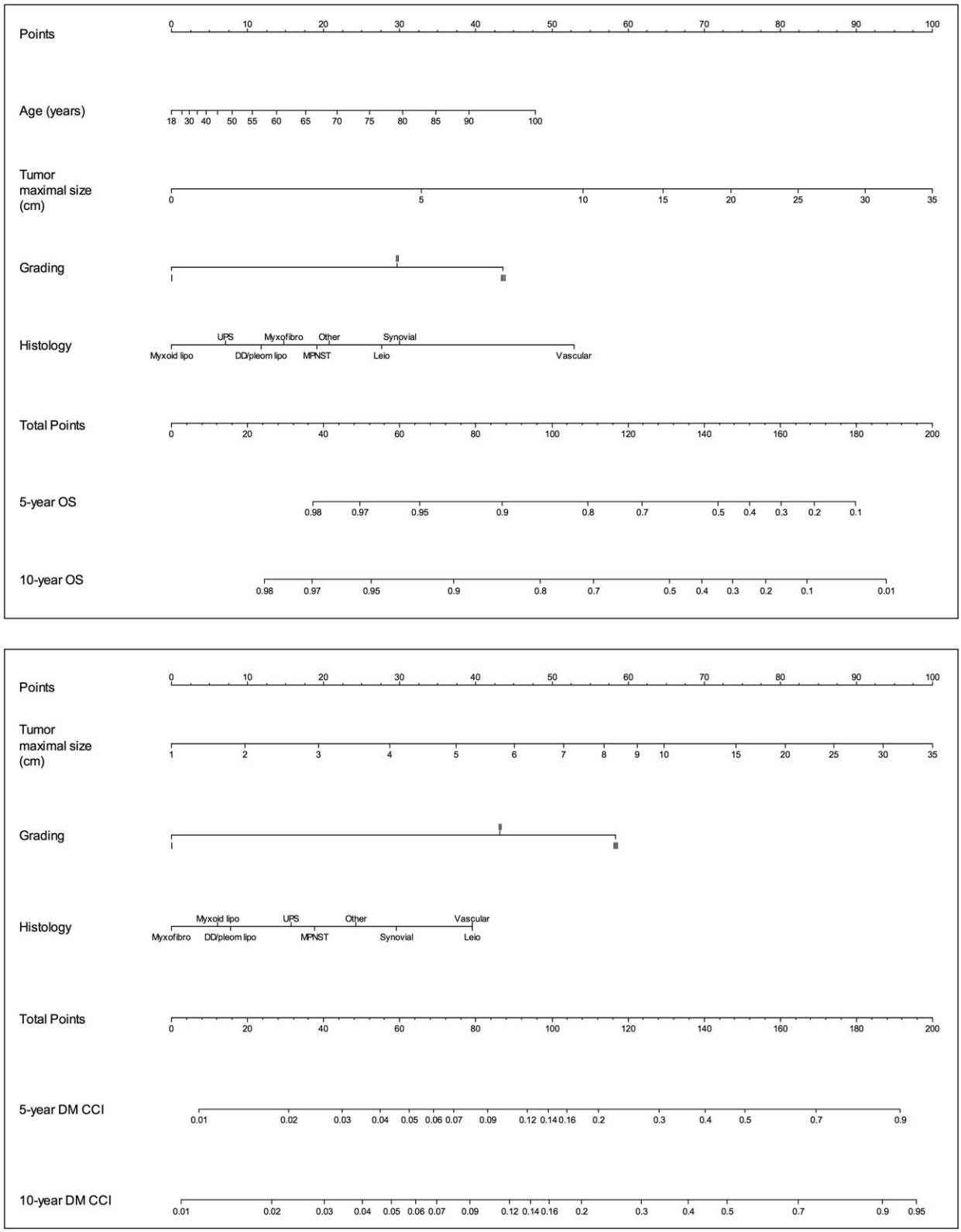
Points
0 10 20 30 40 50 60 70 80 90 100
Age (years)
18 30 40 50 55 60 65 70 75 80 85 90 100
Tumor maximal size (cm)
0 5 10 15 20 25 30 35
Grading
I II III
Histology
Myxoid lipo UPS DD/pleom lipo Myxofibro MPNST Other Leio Synovial Vascular
Total Points
0 20 40 60 80 100 120 140 160 180 200
5-year OS
0.98 0.97 0.95 0.9 0.8 0.7 0.5 0.4 0.3 0.2 0.1
10-year OS
0.98 0.97 0.95 0.9 0.8 0.7 0.5 0.4 0.3 0.2 0.1 0.01
Points
0 10 20 30 40 50 60 70 80 90 100
Tumor maximal size (cm)
1 2 3 4 5 6 7 8 9 10 15 20 25 30 35
Grading
I II III
Histology
Myxofibro Myxoid lipo DD/pleom lipo UPS MPNST Other Synovial Vascular Leio
Total Points
0 20 40 60 80 100 120 140 160 180 200
5-year DM CCI
0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.09 0.12 0.14 0.16 0.2 0.3 0.4 0.5 0.7 0.9
10-year DM CCI
0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.09 0.12 0.14 0.16 0.2 0.3 0.4 0.5 0.7 0.9 0.95

Figure 1.

Gustave Roussy (Villejuif, France) recently developed and externally validated 2 nomograms to predict OS and risk of distant metastases (DM) after surgical resection among patients with primary extremity STS (Fig. 1).[20] The Italian series served as the development cohort whereas the 3 other series served as independent external validation cohorts. The strengths of these models were that age and size were modeled as continuous covariates (both demonstrate a nonlinear prognostic effect), the French Federation of Comprehensive Cancer Centers grading system relied on 3 grades, and the histologic classification was updated with the latest WHO criteria.[1] The triple independent external validation revealed good discrimination and calibration when the nomograms were applied to foreign cohorts. The OS nomogram allows the clinician to predict survival, reflecting the effect of several factors related or unrelated to the disease, whereas the DM nomogram predictions more directly reflect cancer risk.

To the best of our knowledge, the nomogram reported by Callegaro et al[20] is the only externally validated instrument available to date with which to predict OS and DM in patients with primary resected extremity STS whereas the nomogram from Cahlon et al[19] is the only prognostic tool that is able to predict the local outcome after surgical resection.

NOMOGRAMS FOR RPS

Approximately 17% of STS cases arise in the retroperitoneum.[38] Although virtually any STS may arise in this site, only a few histotypes account for nearly 90% of the patients.[39,40] WDLPS is slow growing and virtually lacks metastatic potential; thus, the outcome after surgery is more favorable compared with other histotypes (5-year LR rate of 18%-47% in major series) but the risk of LR persists over time years after surgical resection.[39,41-44] Dedifferentiated LPS is more aggressive; the LR probability at 5 years is >40%, and a higher grade is associated with a greater chance of developing DM.[39,41,42,45,46] LMS has a strong metastatic potential, with a 5-year DM rate of >50%, but isolated LR is rare.[39,41,42] Finally, classic solitary fibrous tumor is a low-grade tumor that usually is cured after surgery, but a minority of tumors (approximately 10%) demonstrate a more aggressive behavior.[39,42,47]

In addition to histologic subtype, tumor size, grade, multifocality, intraoperative tumor rupture, and completeness of surgical resection appear to influence LR risk.[39] Complete resection is the only potentially curative option in patients with RPS. The use of extended surgical resection is a controversial topic with some latitude in interpretation that has been supported by some consensus guidelines but is not universally endorsed.[8,48]

The seventh edition of the AJCC staging system had limited value in predicting prognosis in patients with RPS[6,49-52]; indeed in a recent study, the application of the seventh edition of the TNM system to a large cohort of patients with RPS yielded a Harrell C-index as low as 0.62.[29]

In the eighth edition of the AJCC staging system for RPS, the T classification has been expanded into 4 categories, potentially improving its prognostic ability.

In this context, instruments such as nomograms are useful to physicians for prognostication; thus a prognostic nomogram for RPS was included in the last version of the AJCC staging system. Available nomograms specific for RPS are detailed in Table 2.[10,29,50-53]

Some of the variability noted in the predicted outcomes of the various RPS nomograms is likely due to a combination of a better understanding of this unique site and variation in surgical strategies over the different time intervals reflected in the individual studies.

All 4 nomograms take into consideration tumor histology as a covariate, but although the nomograms of Gronchi et al[10] and Tan et al[29] use 7 categories, the model of Anaya et al[50] adopts a more limited 3-category classification (WDLPS vs dedifferentiated LPS vs other). Tumor grade, a well-established prognostic factor in patients with RPS,[39] is considered only in the nomogram by Gronchi et al,[10] whereas the nomogram by Tan et al[29]

Figure 1. These nomograms allow for the calculation of the 5-year and 10-year probability of (*Top*) overall survival (OS) and (*Bottom*) the crude cumulative incidence (CCI) of developing distant metastases after surgical resection of a primary soft tissue sarcoma of the extremities on the basis of patient-related and tumor-related covariates. The user should locate the values of specific covariates, draw a line up to the point axis to establish the score associated with each covariate, sum the score of each covariate, and locate the total score on the total point axis. Drawing a straight line down to the OS/distant metastases axis, the user then would obtain the probability. DD/pleom lipo indicates dedifferentiated/pleomorphic liposarcoma; Leio, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; Myxofibro, myxofibrosarcoma; Myxoid lipo, myxoid liposarcoma; UPS, undifferentiated pleomorphic sarcoma. Reprinted with permission from Elsevier from Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localized soft-tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol*. 2016;17:671-680.[20]

TABLE 2. Nomograms for Patients With RPS

	Development Series Characteritics			Nomograms Details			Internal Validation	External Validation		Examples[a]	
Study	Selection Criteria	Timeframe	No. of Centers	Predicted Outcomes	No. of Patients	Nomogram's Covariates[b]	Concordance Index	Yes/No	Concordance Index	Patient 1[c]	Patient 2[d]
Anaya 2010[50]	Primary or recurrent, nonmetastatic, resected	1996-2006	1	Median OS, 3-y OS, and 5-y OS	343	Histology (3 categories), completeness of surgical resection, age (dichotomic; cutoff at 65 y), multifocality, tumor size (dichotomic; cutoff at 15 cm), presentation (primary vs recurrent)	0.73 (95% CI, 0.71-0.75)	No	-	Median survival time off the chart: 3-y OS rate, 94%; 5-y OS rate, 89%	Median survival time, 4.8 y; 3-y OS rate, 66%; 5-y OS rate, 49%
Ardoino 2010[51]	Primary, localized, resected	1985-2007	1	5-y OS and 10-y OS	192	Histology (5 categories), FNCLCC grade, size (continuous), surgical resection margins (complete vs incomplete), age (continuous)	0.73	No	-	5-y OS rate, 79%; 10-y OS rate, 65%	5-y OS rate, 28%; 10-y OS rate, 8%
Gronchi 2013[10]	Primary, localized, resected	1999-2009	3	7-y OS	523	FNCLCC grade, tumor size (continuous), histology (7 categories), patient age (continuous), multifocality (yes vs no), extent of surgical resection (complete vs incomplete)	0.74	Yes[e]	0.67-0.73	7-y OS rate, 91%	7-y OS rate, 46%
				7-y DFS	475	FNCLCC grade, tumor size (continuous), histology (7 categories), multifocality (yes vs no)	0.71	Yes[e]	0.68-0.69	7-y DFS rate, 71%	7-y DFS rate, 21%
Tan 2016[29]	Primary, localized, resected	1982-2010	1	3-y, 5-y, and 10-y DSD	632	Histology (7 categories), extent of surgical resection (R0/R1 vs R2), no. of organs resected (dichotomic, cutoff at 3 organs), size (3 categories), RT (yes vs no)	0.71 (95% CI, 0.66-0.74)	No	-	5-y DSD rate, 18%; 10-y DSD rate, 28%	5-y DSD rate, 62%; 10-y DSD rate, 81%

TABLE 2. *Continued*

Study	Development Series Characteritics			Nomograms Details			Internal Validation	External Validation		Examples[a]	
	Selection Criteria	Timeframe	No. of Centers	Predicted Outcomes	No. of Patients	Nomogram's Covariates[b]	Concordance Index	Yes/No	Concordance Index	Patient 1[c]	Patient 2[d]
				3-y, 5-y, and 10-y LR rate	574	Histology (7 categories), size (3 categories), age (dichotomic; cutoff at 65 y), surgical resection (R0 vs R1), location (pelvis vs other), vascular resection (yes vs no), no. of resected organs (dichotomic; cutoff at 3 organs)	0.71 (95% CI, 0 .67-0.75)	No	-	5-y LR rate, 42%; 10-y LR rate, 51%	5-y LR rate, 57%; 10-y LR rate, 65%
				3-y, 5-y, and 10-y DR rate	632	Histology (7 categories), no. of resected organs (0 vs 1-2 vs 3 organs), size (3 categories), RT (yes vs no), vascular resection (yes vs no)	0.74 (95% CI, 0.69-0.77)	No	-	5-y DR rate, 13%; 10-y DR rate, 16%	5-y DR rate, 54%; 10-y DR rate, 62%

Abbreviations: 95% CI, 95% confidence interval; DFS, disease-free survival; DR, distant recurrence; DSD, disease-specific death; FNCLCC, Fédération Française des Centres de Lutte Contre le Cancer; LR, local recurrence; OS, overall survival; RPS, retroperitoneal sarcoma; RT, radiotherapy.

[a] Please note that, for those nomograms without a digital interface available, the value of the predicted outcome may be biased by the analogic computation.

[b] Variables are listed according to the size of their score range, which reflects their relative effect on the predicted outcome, on a decreasing basis (the first variable exerts the strongest influence on the predicted outcome).

[c] Patient 1 was a patient aged 56 years who underwent macroscopically complete (R1) surgical resection of a 16-cm primary retroperitoneal, well-differentiated liposarcoma (grade 1) with en bloc nephrectomy, colectomy, and psoas resection. There was no intraoperative finding of multifocality. No RT was administered.

[d] Patient 2 was a patient aged 66 years who underwent macroscopically complete (R1) surgical resection of a 12-cm primary retroperitoneal, dedifferentiated grade 3 liposarcoma with en bloc nephrectomy, colectomy, distal pancreatectomy, splenectomy, and psoas resection. There was no intraoperative finding of multifocality. Preoperative RT was administered.

[e] External validations were performed on 135 patients from Institut Gustave Roussy in Villejuif, France (Harrell C-index of 0.67 for the OS nomogram and 0.68 for the DFS nomogram)[10]; 631 patients from a multicentric cohort of the Trans-Atlantic Retroperitoneal Sarcoma Working Group (Harrell C-index of 0.73 for the OS nomogram and 0.69 for the DFS nomogram)[52]; and 144 patients from Taipei Veterans General Hospital in Taipei, Taiwan (Harrell C-index, 0.72 for the OS nomogram).[53]

TABLE 3. Histology-Specific and Histology-Specific and Site-Specific Nomograms for Patients With STS

		Development Series Characteritics			Nomograms Details			Internal Validation	External Validation	
	Study	Selection Criteria	Timeframe	No. of Centers	Predicted Outcomes	No. of Patients (Developing Set)	Nomogram's Covariates[a]	Concordance Index	Yes/ No	Concordance Index
Liposarcoma	Dalal 2006[33]	Nonmetastatic liposarcoma of the extremity, trunk, or retroperitoneum	1982-2005	1	5-y and 12-y DSS	801	Histology (5 categories), tumor burden (continuous), age (continuous), surgical resection margins (R0 vs R1 vs R2), site (5 categories), presentation status (prior excision vs biopsy vs no treatment), tumor depth (superficial vs deep), sex (male vs female)	0.83	No	-
Synovial sarcoma	Canter 2008[54]	Primary, localized, surgically treated patients with synovial sarcoma who did not receive AI chemotherapy	1982-2006	1	3-y and 5-y DSS	196	Size (continuous), site (upper extremity vs lower extremity vs others), depth (superficial vs deep), variant (biphasic vs monophasic)	0.77	No	-
Rhabdomyosarcoma	Yang 2014[55]	Patients with primary RMS (both localized or metastatic) and aged birth to 19 y	1990-2010	SEER database (population-based data set)	5-y and 10-y OS, median survival time	1679	Tumor stage (localized vs regional vs distant), surgery (yes vs no), RT (yes vs no), size (continuous), histological subtype (alveolar vs embryonal vs others), age (continuous), tumor site (favorable vs unfavorable)	0.74	No	-
	Shen 2014[56]	Patients with primary RMS treated with surgery (all ages)	1990-2010	SEER database (population-based data set)	5-y and 10-y cause-specific survival and median survival time for patients treated with surgery alone or with surgery plus RT	1578	Age (continuous), size (continuous), stage (localized vs regional vs distant), histological subtype (embryonal vs alveolar vs pleomorphic vs others), positive regional lymph nodes (no lymph nodes examined vs 0 vs 1-3 vs $\geq$4)	0.78	No	-
	Chisholm 2011[57]	Children with nonmetastatic RMS and embryonal RMS who developed disease recurrence after achieving complete local control (complete remission or stable mass for >6 mo after the end of therapy) with primary therapy	1984-2003 (primary treatment)	Multicentric (international registry)	Probability of cure defined as survival $\geq$3.0 y after disease recurrence	474	Type of recurrence (local vs metastatic $\pm$ local), prior RT (yes vs no), type of chemotherapy (2-drug vs 3-drug vs 6-drug), lymph node status (N0 vs N1 vs Nx), tumor size (missing vs <5 cm vs >5 cm), tumor site (favorable vs unfavorable), histology (alveolar vs nonalveolar), time to disease recurrence (>1.5 y vs <1.5 y)		No	-

TABLE 3. *Continued*

		Development Series Characteritics			Nomograms Details			Internal Validation	External Validation	
	Study	Selection Criteria	Timeframe	No. of Centers	Predicted Outcomes	No. of Patients (Developing Set)	Nomogram's Covariates[a]	Concordance Index	Yes/ No	Concordance Index
Desmoid-type fibromatosis	Crago 2013[58]	Surgically treated desmoid-type fibromatosis	1982-2011	1	3-y, 5-y, and 7-y LRFS and median time to LR	495	Age (continuous), tumor site (extremity vs chest wall vs GI/ intrabdominal vs other vs abdominal wall), size (continuous)	0.70	Yes[b]	0.66[b]
Breast phyllodes tumors	Tan 2012[59]	Surgically treated phyllodes tumors of the breast	1992-2010	1	1-y, 3-y, 5-y, and 10-y RFS	552	Surgical resection margin (negative vs positive), mitosis per 10 high-power fields (continuous), atypia (marked vs moderate vs mild), overgrowth (present vs absent)	0.79	No	-
Uterine leiomyosarcoma	Zivanovic 2012[60]	Surgically treated uterine leiomyosarcoma	1982-2008	1	5-y OS	185	Mitotic index (continuous), tumor grade (high vs not high), locoregional metastasis (yes vs no), distant metastasis (yes vs no), tumor size (continuous), cervical involvement (yes vs no), age at diagnosis (continuous)	0.67	Yes[c]	0.67[c]

Abbreviations: AI, anthracycline-ifosfamide; DSS, disease-specific survival; GI, gastrointestinal; LR, local recurrence; LRFS, local recurrence-free survival; OS, overall survival; RFS, recurrence-free survival; RMS, rhabdomyosarcoma; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results; STS, soft tissue sarcoma.

[a] The variables are listed according to their nomogram score range, which reflects their relative effect on the predicted outcome, on a decreasing basis (the first variable exerts the strongest influence on the predicted outcome).

[b] External validation was performed on 274 patients with desmoid-type fibromatosis who underwent complete surgical resection in 24 cancer centers from the French Sarcoma Group (Harrell C-index, 0.659 [95% confidence interval, 0.598-0.712].[58]

[c] External validation was performed on 187 patients treated with hysterectomy between 1994 and 2010 at Brigham and Women's Hospital/Dana-Farber Cancer Institute in Boston, Massachusetts, and the European Institute of Oncology in Milan, Italy (Harrell C-index, 0.67 [95% confidence interval, 0.62-0.72]).[61]

distinguishes "low-grade" and "high-grade" LMS and LPS. Tumor size is considered in all studies. It is interesting to note that when this covariate is modeled as a continuous variable (as it is in the nomograms by Ardoino et al[51] and Gronchi et al[10]), increasing tumor size is associated with a worst prognosis but this trend is reversed for tumors measuring >30 cm; indeed at this point the scale wraps around, reflecting the fact that for larger tumors (typically WDLPS) to have persisted and reached that size, they tend to demonstrate a more indolent biological behavior. Furthermore, in the nomogram by Tan et al for DM,[29] greater dimensions are associated with lower risk compared with intermediate dimensions.

Across the 4 available RPS-specific nomograms, tumor grade and histologic subtype appear to be the most important predictors of prognosis. Tumor size exerts a strong influence on patient outcome with a peculiar pattern, in which patients with tumors of greater dimension fare better due to intrinsic lower biological aggressiveness.

To our knowledge to date, only the nomograms by Gronchi et al[10] have been externally validated. The process of external validation on 3 independent series (see legend in Table 2)[10,52,53] confirmed that these nomograms are well calibrated and maintain a good discrimination when applied to external cohorts (Harrell C-index range, 0.67-0.73). In particular, the validation in the Asian cohort proved the reliability of the OS model in different ethnic groups.

In the end, which nomogram(s) should be considered? For a patient with primary RPS, nomograms from Gronchi et al[10] have been externally validated, are able to predict both OS and DFS, and have been endorsed by the latest AJCC staging system for RPS. The nomogram by Anaya et al[50] is useful for patients diagnosed with recurrent RPS. The nomograms from Tan et al[29] are able to predict specifically DM and LR risk at up to 10 years after surgery.

All of these nomograms rely on some variables that are only accurately available postoperatively, and therefore they cannot be used in the preoperative setting. Furthermore, they are not designed for patients with metastatic or unresectable disease.

HISTOLOGY-SPECIFIC NOMOGRAMS

Liposarcoma

LPS accounts for approximately 20% of all cases of adult STS. There are 4 main histological subtypes of LPS: WDLPS, dedifferentiated LPS, myxoid LPS, and pleomorphic LPS. Each of these histological subtypes has its own unique molecular, pathological, and clinical pattern. Other than the histological subtype, tumor grade and site of origin are major prognostic determinants.[1]

In 2006, the MSKCC group developed an LPS-specific postoperative nomogram that combined 8 covariates (Table 3)[33,54-61] to calculate the 5-year and 12-year disease-specific survival (DSS) probability, assuming that the patient did not die first of another cause.[33] In this model, retroperitoneal LPS was further divided into 2 groups on the "site" axis according to the resection of adjacent organs (yes vs no) and myxoid liposarcoma was stratified into 3 groups on the "histology" axis according to the percentage of round cells (<5% vs 5%-25% vs >25%). This nomogram predicted the prognosis more accurately compared with the MSKSN, proving once again that focusing on a defined subgroup improved the discrimination ability of prognostic nomograms.

Synovial Sarcoma

Synovial sarcoma accounts for approximately 6% of all cases of STS. They can be divided into monophasic or biphasic variants, respectively, based on the presence of spindle cells or both spindle cells and epithelial glandular cells. In addition, 95% of synovial sarcomas are characterized by a chromosomal translocation resulting in the SS18-SSX1 or SS18-SSX2 fusion protein. The clinical behavior varies from superficial indolent tumors to highly aggressive tumors that are capable of recurring locally or at distant sites years after surgical resection of the primary tumor.

Advanced stage at presentation, positive surgical resection margins, larger tumor size (>5 cm), male sex, older age, and nonextremity tumor site are all negative prognostic factors for synovial sarcomas. However, to our knowledge, the correlation between histological subtype, fusion protein status, and survival is less clear.[62]

A nomogram to predict 3-year and 5-year DSS in patients with synovial sarcoma was developed by the MSKCC group in 2008. One of the strengths of this tool is that all covariates are available before surgical resection. Application of this nomogram to a cohort of patients who received ifosfamide-based chemotherapy demonstrated that the observed DSS of patients treated with chemotherapy was better than that predicted by the nomogram within the first 3 years after diagnosis, supporting a possible role of chemotherapy in survival in this subset of patients.[54]

Rhabdomyosarcoma

RMS is the most common STS subtype diagnosed in children.[63] Treatment consists of multimodal therapy

including chemotherapy and surgery with or without radiotherapy. A recent meta-analysis of patients with RMS of the extremity treated within 14 studies reported a 5-year OS rate of 67%.[64]

Because pediatric RMS includes different histological subtypes and sites, risk stratification is critical to guide both diagnostic and treatment algorithms. Alveolar RMS generally behaves more aggressively than embryonal RMS, and the presence of the PAX-FOXO1 fusion is associated with a worse prognosis. Moreover, large tumor size, the presence of local invasion, parameningeal site, age <3 years or >10 years, tumor stage, and lack of response to induction therapies all have emerged as negative prognostic factors. Furthermore, the use of surgery and the administration of radiotherapy were found to be associated with oncological outcome.[55,57,65]

To the best of our knowledge, the first nomogram specific for patients with RMS was reported in 2011 by Chisholm et al.[57] This model estimated the chance of cure for patients who develop disease recurrence after therapy for the primary tumor. This nomogram was created to help physicians distinguish between those patients who might have some curative potential with salvage therapy from those children with a low chance of cure who may instead benefit from protocol treatments or palliative therapies. This study had the advantage of being performed on a high-quality data set because all the patients had been enrolled in International Society of Paediatric Oncology studies.

In 2014, two studies based on the SEER database aimed to create prognostic models for patients with RMS. Yang et al[55] computed a nomogram to predict the survival of pediatric patients with RMS. Shen et al[56] built 2 nomograms to quantify the benefit of radiotherapy after surgical resection of RMS. Radiotherapy is a challenging issue in the management of this disease, considering that the median age at the time of diagnosis is 5 years. Long-term sequelae may be expected, and the benefit of radiotherapy on local control may not directly impact survival.

The development sets of both studies were derived from a population-based cancer registry (SEER database) with its well-recognized pros and cons: a good number of patients treated outside of reference centers and the standardized collection of data, but a lack of information regarding chemotherapy, comorbidities, and surgical resection margins (which have prognostic relevance) and a lack of a centralized pathological review. Moreover, the long timeframe of patient collection in both studies (approximately 20 years) may not be able to detect the improved prognosis observed in these patients over the years and thus underestimate the current prognosis. Finally, the differences in terms of OS between clinical trials and population-based analysis should be factored when interpreting the prediction of these models.[55]

It is interesting to note that Shen et al included adult patients in the model.[56] In adults, pleomorphic RMS is typically far more common, and these tumors are far less sensitive to chemotherapy and radiotherapy.

Desmoid-Type Fibromatosis

Desmoid-type fibromatosis is a locally aggressive tumor without metastatic potential but which may cause significant morbidity due to local aggressiveness. It can arise in any site and tumor location can influence the natural history of the disease: patients with intra-abdominal sites are at a higher risk of complications such as bowel perforation whereas desmoid-type fibromatosis of the extremity may cause significant functional morbidity. Historically, this disease has been treated with a frontline surgical approach but the LR rate is high and, in some anatomic locations, surgical resection with clear margins is unlikely or is associated with relevant functional impairment.[66]

In a retrospective single-institution series, the 5-year DFS rate after microscopically complete surgery was reported to be 70% to 80%.[66] The risk of disease recurrence after surgery depends on tumor site (extremity, intra-abdominal, and chest wall desmoid-type fibromatoses are more likely to recur compared with those of the abdominal wall), size (the larger the tumor, the higher the risk), and age (the younger the patient, the higher the risk). In 2013, Crago et al[58] from MSKCC developed and externally validated a nomogram based on these 3 covariates to predict postoperative 3-year, 5-year, and 7-year LR-free survival. It is interesting to note that all these covariates can be assessed preoperatively, making this instrument available from the time of the first clinical examination of the patient. In some series, microscopic surgical resection margin status was shown to be an additional prognostic factor, but this variable was not included in the MSKCC nomogram because it was not found to be significantly associated with disease recurrence on multivariable analysis in the MSKCC series, and it did not improve the nomogram's discriminative ability. Finally, β-catenin mutation status was not included, but may play some role in prognosis prediction.[67-70]

Considering the unpredictable natural history of desmoid-type fibromatosis, with long-term stabilization or spontaneous tumor regression reported in up to 20% to 28% of patients; the relatively high LR rate after surgery; and the morbidity associated with tumor resection, a

wait-and-see frontline approach has been recently endorsed in 2 consensus statements[71,72] to better distinguish progressing tumors from those that are quiescent or regressing. In the case of symptomatic or progressive tumors, several treatments could be considered: medical therapy (including nonsteroidal anti-inflammatory agents, antiestrogen agents, cytotoxic chemotherapy, targeted therapies such as imatinib or sorafenib, or new drugs such as gamma secretase inhibitors), radiotherapy, cryoablation, isolated limb perfusion, or surgery. In this context, the MSKCC nomogram is useful in identifying patients at high risk of disease recurrence after surgery who may benefit from other therapeutic options in the case of disease progression or symptomatic disease. With surgery used less often as first-line therapy, a nomogram to predict the chance of disease progression during a "wait-and-see" program would be extremely valuable.

HISTOLOGY-SPECIFIC AND SITE-SPECIFIC NOMOGRAMS

Uterine Leiomyosarcoma

ULMS accounts for <5% of all uterine malignancies. This tumor shows an aggressive behavior with a tendency to recur locally and to spread hematogenously to other organs. Before 2009, in the absence of a dedicated staging system, ULMS had been classified using the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging system or with the AJCC/UICC staging system for STS. Both these staging systems demonstrated a limited capacity to categorize patients with ULMS into prognostically significant stages. Indeed, there was significant prognostic overlap between disease stages, and the majority of patients with ULMS were clustered into the same disease stage regardless of their clinical heterogeneity.[73,74]

In 2009, a new version of the FIGO staging system specific for ULMS combined tumor size, extension with respect to the uterus and pelvic organs, and the presence/absence of DM into 4 stages.[75] Recently, the eighth edition of the AJCC staging system included a new chapter for the staging of uterine sarcomas (LMS, endometrial stromal sarcoma, and adenosarcoma) based on tumor dimension, regional lymph node involvement, and the presence of DM.[2]

To our knowledge, Zivanovic et al. from MSKCC[60] first developed a nomogram for ULMS. This nomogram incorporated 7 clinicopathologic characteristics to predict 5-year OS in resected ULMS patients. This prognostic tool demonstrated better discrimination compared with the original 1988 FIGO staging system, the 2009 FIGO staging system, and the sixth edition of the AJCC staging system for STS. It is interesting to note that only patients who underwent resection of the primary tumor were included in the development set of the model, regardless of the presence of DM. The exclusion of patients with unresectable metastatic disease from the development set may be responsible for the relatively low prognostic value of the DM covariate. This nomogram was externally validated on a combined series from the Brigham and Women's Hospital/Dana-Farber Cancer Institute and the European Institute of Oncology, demonstrating good discrimination (Harrell C-index, 0.67) and calibration.[61]

Breast Phyllodes Tumors

Phyllodes tumors are a complex group of fibroepithelial lesions of the breast. Histologically, they are characterized by an exaggerated intracanalicular pattern of the fibroepithelial architecture and stromal hypercellularity. Their histological appearance varies from "benign" lesions that resemble cellular fibroadenoma to malignant lesions that may be misdiagnosed as primary breast sarcoma or spindle cell metaplastic carcinoma.[76]

The categorization of phyllodes is based on stromal features of cytologic atypia, mitotic activity, degree of hypercellularity, overgrowth, and nature of tumor margins (circumscribed vs permeative). Moreover, the presence of heterologous stromal elements identifies a phyllodes tumor as malignant. According to these histological characteristics, phyllodes tumors are categorized as "benign" tumors that may recur locally and almost never metastasize (anecdotally, cases of DM have been reported), borderline tumors that may recur locally or rarely metastasize, and malignant tumors that demonstrate the highest metastatic risk (10%-20% in major series).[76] Metastasis is most commonly identified in lung and bone but virtually any organ may be affected.

Even though the relationship between the histological features and the clinical behavior of these tumors is clear, the application of the histologic criteria to distinguish among the 3 categories is not without problems. Furthermore, the role of each pathologic parameter in determining grade is not straightforward. In 2012, Tan et al[59] from Singapore General Hospital in Singapore developed a nomogram based exclusively on the AMOS criteria (degree of stromal atypia, stromal mitoses per 10 high-power fields, stromal overgrowth, and surgical resection margins) to predict up to 10-year recurrence-free survival in patients with phyllodes tumors. This nomogram removed the possible reproducibility issue entailed in tumor grade computation.

DISCUSSION

Added Value of Personalized Prognostic Tools

Why should we rely on nomograms to predict patient prognosis?

From an analytical view point, they allow for an individualized prognosis prediction and not a group stratification: the patient is not allocated into a prognostic group (the basic concept of the TNM staging system), but rather a point prediction is obtained based on the specific combination of tumor-related and patient-related factors. Moreover, such a prediction is based on a multivariable prognostic model that takes into account the association between all the included variables, and in which the continuous variables may possibly be modeled in a such a way as to reflect the complex association with the outcome, thus generating a continuous outcome.

From a clinical point of view, personalized prognostic tools are useful for counseling patients, assisting the therapeutic decision-making process, and planning follow-up strategy. However, when using a prognostic nomogram in the clinical scenario, the clinician should keep in mind that the predicted outcome is the result of a statistical model. Indeed, the prediction is what would be expected on average in a hypothetical cohort of patients with a specific mix of covariates. Should the model be tested on such a hypothetical group, the prediction would be accurate. However, within the group, there is individual variability. This variability is related, in part, to the single patient characteristics, such as comorbidities, that may not be factored into the model. In fact, none of the models for OS considered in this review take into consideration patient comorbidities. Moreover, adjuvant/neoadjuvant treatments administered to the patients in the development cohorts usually were not controlled or standardized; therefore, the predicted outcome was just "the best possible outcome" achievable in the development cohort center at that time. External validations thus are essential to demonstrate the generalizability of a model beyond the patients' outcome in the developing cohort. Finally, the nomograms tend to become obsolete with time and need to be updated.

Nomograms cannot replace medical knowledge. They can complement clinical judgment, scientific knowledge, patient's wishes, and quality-of-life issues in the complex process of care. Achieving a personalized prognosis does not mean improving the chance of cure. How these instruments will be incorporated into therapeutic algorithms is an open question, and to our knowledge are unexplored in patients with STS to date. In addition to the clinical setting, nomograms could serve to stratify patients for randomized trials or to determine trial eligibility criteria on the basis of suitably chosen cutoff values for the predicted outcome. Nomogram predictions also could serve as adjustment tools to assess the efficacy of a treatment or to compare the outcome of different patient populations, as previously described for the MSKSN.

The Right Nomogram for the Right Patient

It may appear that, for a single patient with STS, more than 1 nomogram is available for prognostic computation. For example, the prognosis of a 28-year-old male patient undergoing surgery for a 8 cm $\times$4 cm superficial primary myxoid LPS of the leg (>25% round cells; R0 surgical resection margins) may be computed using the general postoperative sarcoma nomogram (4-year sarcoma-specific death [SSD] after surgery, 10%; 8-year SSD rate, 15%; and 12-year SSD rate, 18%)[4]; the extremity STS nomograms by Mariani et al (10-year SSD rate, 24%),[18] Cahlon et al (3-year LR risk after surgery, 12%; and 5-year LR risk, 14%),[19] and Callegaro et al (5-year OS rate, 88%; 10-year OS rate, 82%; 5-year DM rate, 26%; and 10-year DM rate, 29%)[20]; or the histotype-specific LPS nomogram (5-year DSS rate 79%; and 12-year DSS rate 61%).[33]

The choice of the best instrument should certainly rely on the outcome of interest. Indeed, the user may want to predict the metastatic risk, the local risk, or survival.

When different nomograms generating slightly different predictions are available for a specific outcome, which has to be considered the "right" one?

It is difficult to establish which the right prediction is. We should consider that the nomogram prediction, as mentioned above, represents the average outcome in a hypothetical cohort of patients with a specific mix of covariates. The outcome of the actual population of patients with that specific mix of covariates will tend to spread around the average with a certain degree of dispersion. Therefore, due to individual variability, it is very likely that the patient for whom the prediction has to be obtained will be far from the "average patient" represented by the available nomograms.

Moreover, a nomogram conveys the results of a statistical model and, quoting a famous aphorism attributed to the statistician George Box, "All models are wrong, but some are useful." Thus, we could a priori discard those nomograms derived from "less reliable models" (Iasonos et al[11] provided a well-described set of standard criteria for model development, validation, and communication),

which are far from useful for generating precise estimates and, rather than looking for a right prediction, the more appropriate question most likely would be: which is the most useful nomogram for my patient?

To guide this choice, the physician could follow a stepwise approach. First, the nomogram generated on a population possibly "similar" to our actual population should be chosen; for example, if the nomogram was built on patients who had large STS tumors, it will not perform as well on patients with small tumors because they were underrepresented or absent in the original data.

Second, if the patient has been treated outside of a center in which the nomograms have been developed, it would be more appropriate to choose nomograms that have been externally validated on a population that is comparable to the one from which the actual patient comes from. Third, the user should evaluate whether nomograms take into account all of the relevant prognostic covariates and how these covariates are factored.

Finally, old nomograms are more likely to suffer from inherent bias compared with newer ones.

A Glimpse of the Future

The effectiveness of personalized prognostic models begs the question of whether they could substitute for available staging systems. Currently available prognostic tools for STS cannot fully replace the AJCC/UICC staging system because they do not cover all patient stages. In the future, it is not unrealistic to imagine that a comprehensive prognostic model covering all disease stages could possibly be built in a modular fashion, as recently pointed out by the AJCC Precision Medicine Core.[9] However, the TNM staging system remains a simple and straightforward way with which to categorize patients into prognostic groups and, in a balance between precision and usability, it most likely would maintain its role.

Currently, some nomograms are incorporated in the AJCC staging system to improve the prognosis prediction of subgroups of patients. In the eighth edition of the AJCC manual, the nomogram by Gronchi et al for RPS[10] was included as a model that met all AJCC quality criteria as confirmed by a systematic search of the published literature for prognostic tools for RPS by the AJCC Precision Medicine Core.[2]

How could available prognostic models for STS be improved further? First, the majority rely on postoperative variables. Thus, they cannot necessarily assist the physician at the time of diagnosis. Second, available nomograms for STS compute a static prediction at a prognostic time zero, usually the time of the surgical procedure, but they do not update the prediction according to patient follow-up status. For example, the metastatic risk of a patient with a high-grade retroperitoneal LMS drops after the first 2 to 3 years of negative follow-up but to our knowledge none of the available instruments is able to capture this. In particular, there are no instruments that are able to update the prognostic estimates considering the occurrence of new neoplastic events (event history).

Moreover, none of the available prognostic tools for STS incorporates serum markers, molecular variables, genomic data, or radiomic data as predictors. The integration of serum markers has already been proven to improve the performance of the MSKSN.[25-27] The prognostic role of gene mutations in STS is a promising field that could improve risk stratification in defined STS subtypes but to the best of our knowledge none of the available nomograms currently incorporates molecular variables. In 2010, genomic data demonstrated an association with outcome in patients with STS,[77] although to our knowledge these data have not been prospectively validated to date. It is interesting to note that gene expression changes in tumor tissue inform prognosis independently from clinical predictors. Recently, the first prognostic models built on radiomic features in patients with STS achieved promising results. In a study from McGill University, a joint [^{18}F]fludeoxyglucose-positron emission tomography and magnetic resonance imaging texture-based model to predict the risk of lung metastasis in patients with STS achieved excellent results in terms of sensitivity and specificity.[78] The preliminary report of an ongoing study from the University of Washington, presented at the 2016 annual meeting of the Connective Tissue Oncology Society, reported a better discriminative ability for a radiomic pretreatment T1-weighted, magnetic resonance imaging-based prognostic model compared with a clinical model and even better discrimination was obtained when combining clinical and radiomic features in a series of patients with STS.[79] In the era of big data, how these newer variables interact with clinical variables in prognostic models has yet to be understood.

Further development of STS nomograms may cover those histotypes that do not yet have dedicated prognostic tools. For example, a nomogram to predict 5-year survival probability and median survival time specific for patients with uterine adenosarcomas was presented by Nathenson et al at the 2016 annual meeting of the Connective Tissue Oncology Society.[80]

Finally, the user interface of these prognostic tools is of no little significance. Drawing lines on a nomogram to calculate the prediction is time-consuming and

inaccurate. Web-based calculators are available for all MSKCC nomograms at https://www.mskcc.org/nomograms, whereas INT nomograms are available on a free application for smartphones and tablets called Sarculator for multiple platforms.[81] The digital interface improves the accuracy of the prediction and makes these instruments easy to use in daily practice. Moreover, they also are available to patients though the MSKCC Web site, although the application disclaimers discourage the use of these prognostic tools outside of a medical context.

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