EUROPEAN JOURNAL OF CANCER 43 (2007) 2691–2697

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Adult-type soft tissue sarcomas in paediatric age: A nomogram-based prognostic comparison with adult sarcoma

Andrea Ferrari[a,*], *Rosalba Miceli*[b], *Michela Casanova*[a], *Alessandro Gronchi*[c], *Paola Collini*[d], *Cristina Meazza*[a], *Elena Zaffignani*[a], *Maura Massimino*[a], *Filippo Spreafico*[a], *Luigi Mariani*[b]

[a]*Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*
[b]*Division of Medical Statistics and Biometry, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*
[c]*Melanoma Sarcoma Surgery Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*
[d]*Pathology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy*

ARTICLE INFO

Article history:
Received 31 July 2007
Received in revised form
7 September 2007
Accepted 20 September 2007
Available online 30 October 2007

Keywords:
Adult-type soft tissue sarcomas
Non-rhabdomyosarcoma soft tissue sarcomas
Children
Prognostic factors
Tumour size
Nomogram

ABSTRACT

Introduction: The study compares the outcome of paediatric patients with adult-type soft tissue sarcomas with that reported for adults, taking into account the effect of established prognostic factors.

Methods: The actual mortality of our series was compared with that predicted by the nomogram developed for adults at the Memorial Sloan Kettering Cancer Center. From a previously-published series of 182 patients <18 years, 112 cases fulfilling the criteria for the nomogram application were selected.

Results: Actual 10-year mortality for the series was 29%, compared with a 16% predicted mortality. The effect of individual covariates was qualitatively consistent with that of adults, but the unfavourable prognostic effect of tumour size was stronger in paediatric cases.

Conclusion: The variables known to have a prognostic role in adults are relevant also in children. The worse outcome observed in our series might be explained by the stronger adverse effect of tumour size in young patients.

1. Introduction

Soft tissue sarcomas are rare tumours that can occur at any age. They account for less than 1% of adult tumours, but in the paediatric age they represent 8% of all malignancies.[1] In children and adolescents, more than half of them are cases of rhabdomyosarcoma. The group of the so-called 'non-rhabdomyosarcoma' soft tissue sarcomas (NRSTS) includes a variety of histotypes of diverse biology and natural history, the majority of which are tumours typical of adult age. Epidemiological data reveal a different incidence of the various soft tissue sarcoma histotypes in different age groups, i.e. synovial sarcoma and malignant peripheral nerve sheath tumour (MPNST) are more common in adolescents and young adults, while the peak incidence for liposarcoma is around the fifth decade.[1]

One of the main topics of debate concerns whether certain soft tissue sarcomas with the corresponding clinical features have the same clinical behaviour when they occur in different age groups. For the time being, there is no strong evidence to

* *Corresponding author:* Tel.: +39 02 23902588; fax: +39 02 23902648.
E-mail address: andrea.ferrari@istitutotumori.mi.it (A. Ferrari).
0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.09.012

support any biological differences between the same soft part sarcomas occurring in children or adults.

With the purpose of comparing the disease outcome between paediatric and adult patients, we estimated the actual mortality of our series along with that predicted by the postoperative nomogram developed for adult patients at the Memorial Sloan Kettering Cancer Center (MSKCC).[2] The MSKCC nomogram combines various prognostic factors to predict the probability that the patient will die of sarcoma, providing a useful tool for patient counselling, stratification and clinical trial eligibility determination. Such a use of the nomogram was not intended for checking its validity or creating a modified one that could be more accurately applied to children, but rather for obtaining major insights into the disease behaviour in paediatric patients, while taking into account the effect of established prognostic factors. In fact, overlap or discrepancy between actual and predicted mortality would indicate that the outcome of paediatric and adult patients is similar or not, once possible differences in prognostic characteristics are taken into account.

2. Materials and methods

2.1. Patient series

We already published the results from a cohort of 182 consecutive previously-untreated patients under 18-years-old diagnosed at the Pediatric Oncology Unit of the Istituto Nazionale Tumori (INT), Milan, Italy, with 'adult-type' NRSTS between 1977 and 2003.[3] The definition of 'adult-type' NRSTS (*definitely malignant, typical of adulthood and with morphological features resembling differentiated/mature tissues*) includes synovial sarcoma, MPNST, adult-type fibrosarcoma, epithelioid sarcoma, leiomyosarcoma, clear cell sarcoma, liposarcoma, alveolar soft part sarcoma, malignant fibrous histiocytoma, malignant hemangiopericytoma, angiosarcoma and dermatofibrosarcoma, and excludes borderline tumours (i.e. hemangioendothelioma), infantile histotypes (i.e. infantile fibrosarcoma) and small round cell tumours (i.e. Ewing's family tumours, desmoplastic small round cell tumours and, of course, rhabdomyosarcoma).[3]

In the present study, from the above series we captured all the cases, 112 overall, fulfilling the following criteria for MSKCC nomogram application: surgical resection of the primary tumour, lack of distant metastases, complete information on patient's age at diagnosis, and tumour size, tumour depth, disease site, tumour grade. From the original series, we excluded metastatic cases, those submitted to biopsy only, and those for whom no grading was available.

The histological diagnoses were made by pathologists at our Institution before starting any treatment, and were recently reviewed by one of the authors (P.C.). Tumour grade was assigned according to the French Federation of Cancer Centers Sarcoma Groups (FNCLCC) system, which is a three-grade classification defining a score in relation to tumour differentiation, mitotic index and tumoural necrosis.[4,5] This grading system, used at our Institution because of its high reproducibility, allows us the opportunity for a comparison with adult series.

Before starting any treatment, data were available for all patients on their physical examination, local extent of disease assessed by computerised tomography (CT) and/or magnetic resonance imaging (MRI), chest X-ray and/or chest CT scan, abdominal ultrasound, and (for the majority of cases) whole body bone scan.

Patients were treated using a multi-modality therapeutic approach including surgery, chemotherapy, and radiotherapy, based on the ongoing protocols at the time of their diagnosis. Treatment strategies did not change substantially over the years. Surgical tumour resection was initially attempted for all patients considered in the analysis. Radiotherapy was given to patients considered at risk of local failure, using external beam irradiation (megavoltage photon or electron beam energies, conventional fractionation of 1.8–2.0 Gy daily for 5 days a week). Different multi-drug regimens were used over the years, including in all cases cyclophosphamide or ifosfamide, plus anthracyclines (doxorubicin or epirubicin); actinomycin-D and vincristine were added in several cases.

2.2. Statistical methods

The study end-point was the disease-specific mortality, based on the time elapsing between surgery and the occurrence of sarcoma-related death, censoring as at the date of death not due to sarcoma or the last follow-up for survivors. The actual mortality curve was estimated using the Kaplan–Meier method, which was also used to estimate local relapse-free survival (LRFS) and metastases-free survival (MFS).[6]

The MSKCC nomogram[2] was used to obtain 10-year predictions of the probability of patients dying of sarcoma after initial surgery (assuming they do not die of another cause first) depending on a number of covariates, such as patient's age at diagnosis, tumour site (upper extremity, lower extremity, visceral sites, torax or trunk, head and neck or retro-intraabdominal location), histological subtype (fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, MPNST, synovial sarcoma or other), tumour size (< 5 cm, 5–10 cm or > 10 cm), tumour depth (superficial or deep) and histological grade (high or low). The nomogram was originally developed using data from 2136 adult patients (>16 years of age) who underwent treatment for primary soft tissue sarcoma at MSKCC from July 1982 to May 2000. These patients were prospectively entered and followed in a computerised database. The nomogram was drawn on the basis of a multiple Cox regression model including the above mentioned covariates. Histological grade was considered as a stratification factor because of non-proportional hazards, hence two separate baseline hazard functions were fitted, one for low-grade tumours and the other for high-grade tumours.

As regards histological grade, since our patients were classified according to a three-level system,[5] not the two-level classification of the nomogram, grade 2–3 tumours were grouped into a 'high grade' category, coherently with the American Joint Committee on Cancer-International Union Against Cancer (AJCC-UICC) staging system.[7]

The ratio of the 10-year Kaplan–Meier estimates over the mean of individual probabilities was computed both overall and in three distinct prognostic groups (*best*, *intermediate*,

worst), determined on the basis of the tertiles of predicted probability distribution. A ratio above (below) one indicates that the actual mortality in our series was greater (lower) than predicted by the nomogram.

To statistically compare actual and predicted mortality, we applied the model-based 'validation by calibration' approach.[8,9] In this model, the prognostic score calculated by the nomogram was entered as the covariate, and the intercept α and slope β coefficients enabled us to test whether predicted and actual mortality were consistent ($\alpha = 0$, $\beta = -1$) or not ($\alpha \neq 0$ and/or $\beta \neq -1$). Other details on the application of this approach are provided by Mariani et al. [10] In a second step, together with the prognostic score, the nomogram covariates were individually entered and tested in the model to investigate whether their effect diverged from that assumed by the nomogram. Age was modelled as a continuous variable using three-knot restricted cubic splines,[11] whereas the other covariates were modelled as categorical using dummy (0/1) variables. Negative (positive) regression coefficients for the covariates denote a prognostic worsening (improvement) beyond the trend assumed by the nomogram. For categorical covariates the reference category is implicitly assigned a coefficient of zero.

Two-sided Wald tests were considered statistically significant when the corresponding *p*-values were below the 5% threshold. All statistical analyses were performed using the R software.[12]

3. Results

3.1. Clinical findings

The patients' characteristics are shown in Table 1. Briefly, median age at the time of referral to our institution was 13 years (range 3–18 years) and the male–female ratio was 1.33. Median tumour size was 6 cm (range 1–30 cm), and was larger amongst deep-seated tumours (χ^2-test $p < 0.001$). The lower extremities were the most common primary site (46%), followed by the upper extremities (16%), trunk (15%) and head-neck region (15%). As regards histological type there was a prevalence of synovial sarcoma (one-third of the cases). The majority of tumours (80%) was graded as 2 or 3.

As for treatment, 60 patients underwent initial complete tumour resection, 26 had gross resection with microscopic residual disease, 26 had macroscopic incomplete resection. Post-operative radiotherapy was administered to 49 patients, adjuvant chemotherapy to 63 and and 38 children received both.

3.2. Survival

As at July 2006, the median follow-up was 133 months (interquartile range, 104–190). Amongst the 112 patients investigated, 13 developed local relapse as first neoplastic event, 21 developed distant metastasis and 10 developed synchronous local and distant metastasis. Five- and 10-year LRFS estimates (95% confidence interval) were 88% (79%, 93%) and 86% (78%, 92%), respectively. The corresponding MFS estimates (distant metastasis or synchronous local and distant metastasis) were 74% (64%, 81%) and 69% (58%, 77%).

Table 1 – Main patient and disease characteristics

	No.	%
Gender		
Female	48	42.9
Male	64	57.1
Age (years) – median (range)	13 (3–19)	
Tumour site		
Lower extremity	51	45.5
Upper extremity	18	16.1
Visceral	4	3.6
Thoracic/trunk	17	15.2
Retro-/intra-abdominal	5	4.5
Head/neck	17	15.2
Histological subtype		
Leiomyosarcoma	10	8.9
Liposarcoma	14	12.5
MFH	1	0.9
MPNST	14	12.5
Synovial sarcoma	35	31.3
Fibrosarcoma	8	7.1
Other	30	26.8
Tumour size (cm) – median (range)	6 (1–30)	
⩽5 cm	45	40.2
5–10 cm	43	38.4
>10 cm	24	21.4
Tumour depth		
Superficial	49	43.8
Deep	63	56.3
Histological grade (FNCLCC)		
G1	22	19.6
G2	33	29.5
G3	57	50.9
Stage (IRS group)		
I	60	53.6
II	26	23.2
III	26	23.2
Radiotherapy		
No	63	56.3
Yes	49	43.7
Chemotherapy		
No	39	34.8
Yes	63	65.2

MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; FNCLCC, French Federation of Cancer Centers Sarcoma Groups system; IRS, post-surgical Intergroup Rhabdomyosarcoma Study system (I – completely-excised tumours with negative microscopic margins; II – grossly-resected tumours with microscopic residual disease and/or regional lymph nodal spread; III – macroscopic residual disease after incomplete resection or biopsy).

Thirty-one disease-specific deaths were recorded and were thus considered in our analyses for comparing paediatric and adult patient mortality. The corresponding mortality curve is shown in Fig. 1; 5- and 10-year estimates were 21% (14%, 30%) and 29% (21%, 39%).

The actual (Kaplan–Meier) and mean nomogram-predicted 10-year mortality probabilities are given in Table 2, showing that actual mortality, both overall and in the three

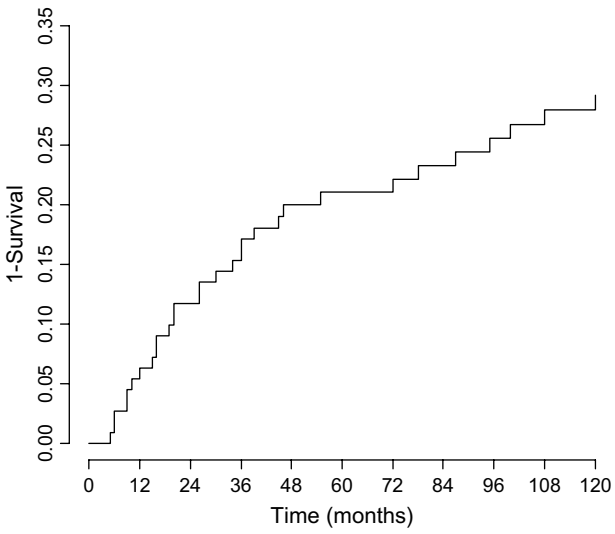

Fig. 1 – Disease-specific mortality curve for 112 paediatric 'adult-type' NRSTS patients.

above-mentioned prognostic groups, was consistently higher than the nomogram predicted. On average, observed and predicted 10-year mortality rates were 29% and 16%, respectively (ratio = 1.79). The divergence was relatively small in the *best* prognostic group (ratio = 1.11) and tended to widen with a worsening prognosis, doubling in the *worst* prognostic group (ratio = 2.05).

The model used to compare actual and predicted mortality yielded a significant result for the intercept ($\alpha = -1.12$, $p < 0.001$), indicating that our patients generally fared worse than predicted, which is consistent with the figures given in Table 2. The estimate for the slope, though not statistically significant ($\beta = -1.57$, $p = 0.125$), suggests that the covariate effect tended to be stronger in our series than was predicted by the MSKCC nomogram.

3.3. *Analysis of covariates*

The results obtained by including individual covariates into the above model are shown in Table 3. For categorical covariates, distinct categories are sorted from that with the most favorable prognosis to that with the worst according to the MSKCC nomogram. As regards age, no relevant pattern beyond the nomogram's prediction was detected within the range investigated (both linear and non-linear terms were not statistically significant, $p = 0.378$). As regards the categorical covariates, significant results were obtained for histological subtype ($p = 0.019$), tumour size ($p = 0.013$) and tumour depth ($p = 0.022$), but not for tumour site ($p = 0.120$) or histological grade in the three-level classification ($p = 0.417$). In particular, the sign and magnitude of the coefficients for tumour size and depth denotes that the unfavourable prognostic effect of these factors was even stronger in our paediatric series than in adult patients. As for histological subtype, the prognostic ordering yielded by the coefficients was the same as the one shown by the nomogram for all categories, with the sole exception of the 'other' histological subtype, which was characterised by a relatively unfavourable prognosis in the nomogram, somewhere between leiomyosarcoma and synovial sarcoma, whereas in our series it achieved the highest positive coefficient, indicating a more favorable prognosis than for any of the other categories. Concerning tumour site, in spite of the lack of significance in the overall test, a significant result was obtained for the coefficient corresponding to the 'head/neck' category; the positive coefficient means that the prognosis was more favorable than predicted.

4. Discussion

'Adult-type' NRSTS form a heterogeneous group of soft part malignancies typical of adults that arise in paediatric patients.[3] Though most of the experience gained in the past on the treatment of paediatric NRSTS was based on principles deriving from the management of rhabdomyosarcoma (which is a clearly distinct entity), there is an acknowledged need to consider experience of paediatric cases with the impressions emerging from adult studies.[13] One of the main issues is whether a given tumour type has the same biology and clinical behaviour when it develops in a child rather than an adult. For instance, adult studies have suggested that the tumour's aggressiveness and the patient's survival relate to tumour size, depth, grade of malignancy and histotype.[14–21] Prognostic factors in paediatric NRSTS have not been exhaustively defined as yet, and nobody knows whether they are the same as in adult sarcomas: in larger series, the main prognostic factors were reportedly the quality of initial surgery, initial tumour size and grade, so these variables are currently used to plan risk-adapted therapies.[3,13,22–25] The topic is important because soft tissue sarcomas are currently not always treated using the same strategy in different ages. There is still a gap between paediatric oncologists and medical adult oncologists (though they are concerned with very similar diseases), so a 15-year-old with synovial sarcoma is often treated very differently from a 22-year-old with the same tumour.[26]

Table 2 – Actual (Kaplan–Meier) and nomogram-predicted 10-year mortality probabilities

	Actual	Predicted	Actual/predicted ratio (95% confidence interval)
Overall	0.292	0.163	1.79 (1.31, 2.40)
Prognostic groups			
Best	0.073	0.066	1.11 (0.32, 3.65)
Intermediate	0.221	0.140	1.58 (0.94, 2.44)
Worst	0.554	0.270	2.05 (1.77, 2.34)

Table 3 – Possible changes in prognostic effects of nomogram covariates; results in terms of coefficient estimates, corresponding standard error (SE) and p value in the calibration model

	Coefficient	SE	*p*-Value	Overall *p*-value
Patient's age				
Linear term	−0.12	0.12	0.338	0.378
Non-linear term	0.05	0.11	0.667	
Tumour site				
Upper extremity	0	–	–	0.120
Lower extremity	−0.17	0.65	0.797	
Visceral	−0.06	1.01	0.952	
Thoracic/trunk	0.36	0.79	0.646	
Retro/intra abdominal	0.65	1.02	0.524	
Head/neck	2.28	1.05	0.030	
Histological subtype				
Fibrosarcoma	0	–	–	0.019
Liposarcoma	−0.63	1.43	0.657	
Leiomyosarcoma	−0.86	1.23	0.484	
Other[a]	0.09	1.10	0.933	
Synovial sarcoma	−1.14	1.04	0.273	
MPNST	−1.78	1.06	0.091	
Tumour size				
⩽5 cm	0	–	–	0.013
5–10 cm	−1.88	0.76	0.014	
>10 cm	−2.44	0.83	0.003	
Tumour depth				
Superficial	0	–	–	0.022
Deep	−1.27	0.58	0.022	
Histological grade				
G1	0	–	–	0.417
G2	−1.10	1.06	0.299	
G3	−0.63	1.03	0.540	

MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour.
a Including MFH.

Our study applied the MSKCC nomogram developed for adult soft tissue sarcomas[2] to a series of paediatric 'adult-type' soft tissue sarcomas with a view to establishing whether paediatric and adult patients are prognostically comparable, and whether clinical–pathological prognostic factors work in a similar way in the two populations. Despite of its limits (i.e. retrospective analysis, relatively small number of patients), the study pointed out interesting hints for discussion.

Overall, the outcome in previously-published paediatric series[3,22–25] resembled the findings in adult studies,[14–21] and were sometimes even better in particular studies focusing on single histotypes: for instance, the study conducted at our institution on a large cohort of patients with synovial sarcoma (which is the most represented tumour in the current series) reported a 5-year event-free survival of 66%, 40% and 31% in the 0–16, 17–30, and >30 age brackets, respectively.[26]

Basically, our analysis showed that the mortality observed in our patients was higher than the nomogram predicted and the discrepancy tended to increase in patients with the least favorable features: in other words, paediatric patients with 'adult-type' soft tissue sarcomas would fare worse than adults with similar tumours. But in terms of absolute mortality, no main differences in survival were observed comparing children and adults: 5- and 10-year disease-specific mortality were 21% (14%, 30%) and 29% (21%, 39%), respectively, as opposed to 25% and 35% in the original MSKCC series.[2] Moreover, though the two cohorts are hardly comparable given the great difference in size, some differences were evident in the incidence of some variables (i.e. in our series, for example, there was a higher incidence of synovial sarcoma, a lower percentage of MPNST, and a tendency for smaller-size tumours) and treatment modalities (i.e. the rate of patients receiving radiotherapy was similar, but chemotherapy was given in an higher percentage of cases in our series than in adult cohorts).[21]

The apparent discrepancy emphasises the general importance of covariate adjustment when drawing comparisons between different series.

Theoretically, several interpretations may be attempted to explain why the mortality in our series was worse than the predicted. The most obvious is that paediatric tumours intrinsically have of a more aggressive behaviour. Alternative explanations are also feasible, however. First, the MSKCC nomogram predictions, though developed on a large patient series, might suffer from poor generalisation ability to different series. This is contradicted by the results of two already published validation studies[10,27] amongst which is a study of ours[10] on a series of extremity adult sarcomas. Moreover,

though the influence of treatment should not be considered in the nomogram, it is difficult to refer the higher sarcoma-mortality of our series to differences in treatment modalities (for example, the percentage of patients receiving radiotherapy was similar to adult series, as well as the rate of local control).[21]

Second, with respect to patient's age, the mortality prediction had to be extrapolated in a range that was only partially covered by the nomogram, which assumed a minimum age of 16 years.[2] Indeed, when investigating if the effect of age diverged from that assumed by the nomogram (Table 3), the results lacked significance, meaning that the age-related mortality pattern predicted by the nomogram can be extrapolated below the age of 16 years.

Interesting findings for a causal interpretation of the divergence between adult and paediatric cases emerged when analysing the contributions of the covariates. Their effect was qualitatively consistent with that of adult patients. For histology, in particular, the same prognostic ordering of the various histotypes identified by the nomogram was preserved in our series (i.e. MPNST coincided with the worst survival), except for the 'other' histotypes category, for which the outcome was relatively favorable. This might be explained if we consider that this subgroup included epithelioid sarcoma, clear cell sarcoma and alveolar soft part sarcoma, for example: though the numbers of paediatric cases are tiny, both in our series and in the previous reports, other analyses have already suggested that their outcome may be better in children than in adults.[28–30]

From a quantitative point of view, we observed that the unfavourable prognostic effect of tumour extension – as reflected by initial tumour size – was even stronger in our series than in adult patients. Not surprisingly, similar results emerged for tumour depth – a factor strongly correlated with size that is not always easy to establish, to the point that paediatric oncologists do not use this variable for treatment stratification. In practical terms, a stronger adverse effect of tumour size would mean that a child with a given histotype and a tumour, say 5 cm in size, has a higher probability of dying of his disease than an adult with the same histotype and the same-sized tumour (all other clinical conditions being equal). On the one hand, it might be argued that the same tumours (same histotype and same volume) consist of the same number of neoplastic cells, regardless of the patients' ages, but this would go against our evidence. On the other hand, there is the concept of relative tumour size to consider, i.e. the prognostic effect of a 5 cm tumour might be more relevant in a 6-year-old weighing 20 kg with a body surface area of 0.8 m^2 than in an adult weighing 80 kg with a body surface area of 2 m^2, due to a different interaction between the tumour mass and the anatomical structures affected by or surrounding the tumour (with implications, for instance, in terms of surgical outcome). Moreover, we still do not know whether tumour size should be regarded as a chronological or a biological indicator: is a large tumour the sign of a late diagnosis or of a higher growth rate and intrinsically more aggressive tumour? All these considerations are purely speculative as yet. Indeed, in a broader series of paediatric sarcoma patients, we are conducting an investigation in which we seek to normalise tumour size to some parameters of body size.

In conclusion, our study suggests that the prognostic variables adopted in the MSKCC nomogram for predicting survival in adult soft tissue sarcomas are relevant for paediatric patients with 'adult-type' soft tissue sarcomas too, but there are some quantitative differences to consider, particularly as regards tumour extension, i.e. the prognostic effect of tumour size is stronger in children. It is difficult to make any deductions concerning potential biological differences between paediatric and adult soft tissue sarcomas, however, and biological studies might help to shed light in this topic in the future.

Conflict of interest statement

None declared.

REFERENCES

1. Okcu MF, Hicks J, Merchant TE, et al. Nonrhabdomyosarcomatous soft tissue sarcomas. In: Pizzo DC, Poplack DC, editors. *Principles and practice of pediatric oncology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 1033–73.
2. Kattan MW, Leung DHY, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. *J Clin Oncol* 2002;**20**(3):791–6.
3. Ferrari A, Casanova M, Collini P, et al. Adult-type soft tissue sarcomas in pediatric-age patients: experience at the Istituto Nazionale Tumori in Milan. *J Clin Oncol* 2005;**23**:4021–30.
4. Trojani M, Contesso G, Coindre JM, et al. Soft tissue sarcomas of adults: study of pathological prognostic variables and definition of a histopathologic grading system. *Int J Cancer* 1984;**33**:37–42.
5. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997;**15**:350–62.
6. Kaplan E, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;**53**:457–81.
7. Greene FL, Page DL, Fleming ID, et al., editors. *AJCC cancer staging manual*. 6th ed. New York: Springer-Verlag; 2002.
8. Van Houwelingen HC, Thorogood J. Construction, validation and updating of a prognostic model for kidney graft survival. *Stat Med* 1995;**14**:1999–2008.
9. Van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000;**19**:3401–15.
10. Mariani L, Miceli R, Kattan MW, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. *Cancer* 2005;**103**(2):402–8.
11. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med* 1989;**8**:551–61.
12. URL: <http://www.r-project.org/> [last access on September 7th, 2007].
13. Ferrari A, Casanova M. New concepts for the treatment of pediatric nonrhabdomyosarcoma soft tissue sarcomas. *Expert Rev Anticancer Ther* 2005;**2**:307–18.
14. Coindre JM, Terrie P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma: a study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *J Clin Oncol* 1996;**14**:869–77.

15. Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer* 2001;**91**:1914–26.
16. Eilber FC, Rosen G, Nelson SD, et al. High grade extremity soft tissue sarcomas. Factor predictive of local recurrence and its effect on morbidity and mortality. *Ann Surg* 2003;**237**:218–26.
17. Koea JB, Leung D, Lewis JJ, et al. Histopathologic type: an independent prognostic factor in primary soft tissue sarcoma of the extremity? *Ann Surg Oncol* 2003;**10**:432–40.
18. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 1996;**14**:1679–89.
19. Stojadinovic A, Leung DHY, Hoos A, et al. Analysis of the prognostic significance of microscopic margins in 2084 localized primary adult soft tissue sarcomas. *Ann Surg* 2002;**235**:424–43.
20. Zagars GK, Ballo MT, Pisters PWT, et al. Prognostic factors for patients with localized soft tissue sarcoma treated with conservation surgery and radiation therapy. An analysis of 1225 patients. *Cancer* 2003;**97**:2530–43.
21. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. *J Clin Oncol* 2003;**21**:2719–25.
22. Pappo A, Devidas M, Jenkins J, et al. Phase II trial of neoadjuvant vincristine, ifosfamide, and doxorubicin with granulocyte colony-stimulating factor support in children and adolescents with advanced-stage nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. *J Clin Oncol* 2005;**23**(18):4031–8.
23. Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group Study. *J Clin Oncol* 1999;**17**:1219–26.
24. Spunt SL, Ashley Hill D, Motosue AM, et al. Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. *J Clin Oncol* 2002;**20**:3225–35.
25. Spunt SL, Poquette CA, Hurt YS, et al. Prognostic factors for children and adoloscents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St Jude Children's Research Hospital. *J Clin Oncol* 1999;**17**:3697–705.
26. Ferrari A, Gronchi A, Casanova M, et al. Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. *Cancer* 2004;**101**:627–34.
27. Eilber FC, Brennan MF, Eilber FR, et al. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. *Cancer* 2004;**101**(10):2270–5.
28. Casanova M, Ferrari A, Bisogno G, et al. Alveolar soft part sarcoma in children and adolescents: a report from the Soft-Tissue Sarcoma Italian Cooperative Group. *Ann Oncol* 2000;**11**(11):1445–9.
29. Casanova M, Ferrari A, Collini P, et al. Epithelioid sarcoma in children and adolescents: a report from the Italian Soft Tissue Sarcoma Committee. *Cancer* 2006;**106**(3):708–17.
30. Ferrari A, Casanova M, Bisogno G, et al. Clear cell sarcoma of tendons and aponeuroses in pediatric patients: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. *Cancer* 2002;**94**(12):3269–76.