original article

Annals of Oncology 20: 425–430, 2009
doi:10.1093/annonc/mdn678
Published online 16 December 2008

Neo/adjuvant chemotherapy does not improve outcome in resected primary synovial sarcoma: a study of the French Sarcoma Group

A. Italiano[1†*], N. Penel[2,3†], Y.-M. Robin[4], B. Bui[1], A. Le Cesne[5], S. Piperno-Neumann[6], M. Tubiana-Hulin[7], E. Bompas[8], C. Chevreau[9], N. Isambert[10], S. Leyvraz[11], P. P. du Chatelard[12], A. Thyss[13], J.-M. Coindre[14] & J.-Y. Blay[15,16]

[1]Department of Medical Oncology, Institut Bergonié, Bordeaux; [2]Department of Medical Oncology, Centre Oscar Lambret, Lille; [3]Equipe d'Accueil 2694: Santé Publique, Epidémiologie et modélisation des maladies chroniques, University of Lille II, Lille; [4]Department of Pathology, Centre Oscar Lambret, Lille; [5]Department of Medicine, Institut Gustave Roussy, Villejuif; [6]Department of Medical Oncology, Institut Curie, Paris; [7]Department of Medical Oncology, Centre René Huguenin, Saint-Cloud; [8]Department of Medical Oncology, Centre René Gauducheau, Nantes; [9]Department of Medical Oncology, Institut Claudius Regaud, Toulouse; [10]Department of Medical Oncology, Centre Georges-François Leclerc, Dijon, France; [11]Department of Medical Oncology, University Hospital Centre Vaudois, Lausanne, Switzerland; [12]Department of Radiotherapy, Centre Paul Papin, Angers; [13]Department of Medical Oncology, Centre Antoine-Lacassagne, Nice; [14]Department of Pathology, Institut Bergonié, Bordeaux; [15]Departement of Medical Oncology, Hôpital Edouard Herriot, Lyon; [16]Unité INSERM 590, Centre Léon Bérard, Lyon, France

Received 29 July 2008; revised 13 September 2008; accepted 17 September 2008

Background: There are only scarce data about the benefit of adjunctive chemotherapy in patients with localized synovial sarcoma (SS).

Patients and methods: Data from 237 SS patients recorded in the database of the French Sarcoma Group were retrospectively analyzed. The respective impact of radiotherapy, neo-adjuvant chemotherapy and adjuvant chemotherapy on overall survival (OS), local recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS) were assessed after adjustment to prognostic factors.

Results: The median follow-up was 58 months (range 1–321). Adjuvant, neo-adjuvant chemotherapy and postoperative radiotherapy were administered in 112, 45 and 181 cases, respectively. In all, 59% of patients treated with chemotherapy received an ifosfamide-containing regimen. The 5-year OS, LRFS and DRFS rates were 64.0%, 70% and 57%, respectively. On multivariate analysis, age >35 years old, grade 3 and not-R0 margins were highly significant independent predictors of worse OS. After adjustment to prognostic factors, radiotherapy significantly improved LRFS but not DRFS or OS. Neither neo-adjuvant nor adjuvant chemotherapy had significant impact on OS, LRFS or DRFS.

Conclusion: As for other high-grade soft-tissue sarcomas, well-planned wide surgical excision with adjuvant radiotherapy remains the cornerstone of treatment for SS. Neo-adjuvant or adjuvant chemotherapy should not be delivered outside a clinical trial setting.

Key words: adjuvant chemotherapy, neo-adjuvant chemotherapy, radiotherapysynovial sarcoma

introduction

Synovial sarcoma (SS) accounts for 6%–9% of soft-tissue sarcomas and is most prevalent in adolescents and young adults 15–35 years of age [1–7]. This aggressive tumor is characterized by a high rate of local and metastatic recurrences which occur in 40%–50% of patients usually within 2 years after the initial diagnosis [4, 5]. Well-planned wide surgical excision complemented by radiotherapy in cases of large tumors or invaded margins is the standard for the locoregional treatment of these tumors [8]. As for other high-grade soft-tissue sarcoma subtypes, neo-adjuvant/adjuvant chemotherapy is also widely used in order to decrease the risk of developing a distant recurrence related to the existence of subclinical micrometastasis at presentation [9]. However, several randomized controlled trials [10–12] as well as a meta-analysis based on individual data [13] have shown that neo-adjuvant or adjuvant systemic chemotherapy do not improve survival significantly in patients with soft-tissue sarcomas. Despite the fact that >50 different sarcoma subtypes exist, soft-tissue sarcomas were considered as a single pathological entity in most of these trials. Therefore, it cannot be excluded that

Correspondence to: Dr A. Italiano, Department of Medical Oncology, Institut Bergonié, 229 cours de l'Argonne, 33076 Bordeaux Cedex, France. Tel: +33-05-56-33-33-33; Fax: +33-05-56-33-33-30; E-mail: italiano@bergonie.org

†These authors contributed equally to the work and must be considered as two first coauthors.

© The Author 2008. Published by Oxford University Press on behalf of the European Society for Medical Oncology.
All rights reserved. For permissions, please email: journals.permissions@oxfordjournals.org

neo-adjuvant or adjuvant chemotherapy reduces the risk of recurrence and may increase the rate of survival among patients with specific subtypes of soft-tissue sarcomas with a particular biological profile. SS is considered as a chemosensitive disease on the basis of the results of trials carried out in the advanced [14–17] or the pediatric setting [18, 19]. There are only scarce and conflicting data about the benefit of neo-adjuvant or adjuvant chemotherapy in patients with localized SS. Although two series including a small number of treated patients ($n = 68$ [20] and 61 [17], respectively) have suggested a benefit of adjuvant chemotherapy in terms of disease-specific [20] or metastasis-free survival [17], one other study ($n = 42$) has reported no improvement of metastatic failure rate and tumor-related mortality [5].

The aim of our study is to clarify the prognosis factors and the impact of neo-adjuvant/adjuvant chemotherapy for adult patients with localized SS. To this aim, we have carried out an extensive analysis of the database of the French Sarcoma Group on a series of 237 patients with centrally reviewed SS.

patients and methods

patients

From 1974 to 2006, 261 nonpediatric patients (≥15 years old) with a SS were admitted to one of the 17 tertiary cancer centers of the French Sarcoma Group for the management of a first tumoral event. Clinical and pathologic data were collected by reviewing medical records at each institution and were then entered into a comprehensive database. Twenty-four patients were excluded from the analysis because of metastatic disease at the time of diagnosis and/or no surgical treatment of the primary lesion. The histological diagnosis was reviewed for all specimens by a panel of experts of the French Sarcoma Group. In all cases, the diagnosis of SS was confirmed, according to the World Health Organization Classification of Tumors [21]. The histological grade was determined as previously described according to the Fédération Nationale des Centres de Lutte Contre le Cancer grading system [22]. A tumor could be either grade 2 or grade 3, depending on mitotic rate, the extent of necrosis or both. The margin status was classified as R0 (macroscopically and microscopically clear), R1 (macroscopically clear and microscopically involved) or uncertain (macroscopically clear and microscopically narrow margins of <1 mm). Absolute dose intensity of doxorubicine (mg/m^2/week) and ifosfamide (g/m^2/week) was determined as previously described [23, 24].

statistical analysis

The statistical analysis of baseline demographics and clinical outcome are based on all data available up to the cut-off date of 30 April 2008. Overall survival (OS) was defined as the interval between diagnosis and the time of death or last follow-up. Local recurrence-free survival (LRFS) was defined as the interval between diagnosis and the time of local recurrence or the last follow-up. Distant recurrence-free survival (DRFS) was defined as the interval between diagnosis and the time of distant recurrence or the last follow-up. Survival rates were estimated with the use of the Kaplan–Meier method and compared using the log-rank test [26]. Descriptive statistics were used to show the distribution of variables in the population. Univariate and multivariate analyses were carried out by Cox regression. Variables associated with survival with a P value <0.05 in the univariate analysis were included in the multivariate regression. Analyses were carried out using SPSS 14.0 statistical software (IPSS Inc., Chicago). All statistical tests were two sided, and $P < 0.05$ indicated statistical significance.

results

patients

The study population included 237 patients (117 men and 120 women). The median age was 35 years (range 15–76). Their characteristics are described in Table 1.

treatment delivery

All patients underwent complete surgical resection of their primary tumor. Adjuvant radiation therapy was delivered in 181 cases (76%) according to local practice guidelines (Table 1). Neo-adjuvant chemotherapy and adjuvant chemotherapy were delivered in 45 cases (19%) and 112 cases (47%), respectively. Fifteen patients (6%) received both neo-adjuvant and adjuvant chemotherapy. Several treatment regimens and dosages have been used during the study period. All the patients with available data ($n = 117$) received an

Table 1. Patients characteristics ($n = 237$)

		n	%
Sites of involvement			
Lower limb		155	65.4
Upper limb		50	21.1
Trunk		15	6.3
Abdominal wall		11	4.6
Head and neck		2	0.8
Others		4	1.7
Grade			
2		112	47.2
3		125	52.8
Tumor size, cm			
Median	7		
Range	1–35		
Margin status			
R0		90	38.0
Uncertain margin		53	22.3
R1		35	14.8
Unknown		59	24.9

Patterns of neo-adjuvant and adjuvant treatments ($n = 237$)

	n	%
Adjuvant radiotherapy		
Yes	181	76.4
No	56	23.6
Neo-adjuvant chemotherapy[a]		
Yes	45	19.0
No	192	81.0
Anthracycline-based regimen	34	14.3
Ifosfamide-based regimen	34	14.3
Unknown regimen	6	2.5
Adjuvant chemotherapy[a]		
Yes	112	47.3
No	125	52.7
Anthracycline-based regimen	86	36.3
Ifosfamide-based regimen	62	26.2
Unknown regimen	20	8.4

[a]Fifteen patients received both neo-adjuvant and adjuvant chemotherapy.

anthracycline- and/or an ifosfamide-containing regimen. Eighty-four patients (59%) received an ifosfamide-containing regimen. The median number of cycles was 4 (range 2–8) in the neo-adjuvant setting and 5 (range 1–11) in the adjuvant setting. The median dose intensity of doxorubicin was 19 and 15 mg/m^2/week in the neo-adjuvant setting and in the adjuvant setting, respectively. The median dose intensity of ifosfamide was 2.3 and 1.6 g/m^2/week in the neo-adjuvant setting and in the adjuvant setting, respectively. The median total dose of doxorubicin and of ifosfamide was 298 mg/m^2 (range 0–507) and 29 g/m^2 (range 0–56), respectively.

overall survival (Figure 1)

The median follow-up was 58 months (range 1–321). At the time of analysis (30 April 2008), 98 patients (41.5%) had died and 129 (54.5%) were still alive (Tables 2 and 3). Ten patients (4%) were lost to follow-up. Ninety-three deaths were the result of SS and five the result of other causes. One death (1%) was related to treatment (septic shock after the first cycle of adjuvant chemotherapy). The median OS was 136 months [95% confidence interval (CI) 70–204]. The 1-year, 5-year and 9-year OS rates were 85.0% (95% CI 82–88), 64% (95% CI 59–69) and 46% (95% CI 40–52), respectively. On univariate analysis, age >35 years old, extra-limb locations, tumor size >7 cm, grade 3 and not-R0 margins were adverse prognostic factors for OS. On multivariate analysis, age >35 years old, grade 3 and not-R0 margins remained highly significant independent predictors of worse OS.

local recurrence-free survival (Figure 1)

At the time of analysis (30 April 2008), 56 patients (23.5%) had local recurrence (Tables 2 and 3). The median LRFS was not reached. The 1-year, 5-year and 9-year LRFS rates were 94% (95% CI 92% to 96%), 70% (95% CI 64% to 76%) and 69% (95% CI 64% to 73%), respectively. The median time to local recurrence was 18 months. Eighteen patients had local recurrence occurring >2 years after the initial diagnosis. Median survival from the time of recurrence was longer for patients with late local recurrence (>2 years from the time of diagnosis) than for patients with earlier treatment failure (54 versus 24 months, $P = 0.022$). On univariate analysis, extra-limb locations, grade 3 and not-R0 margins were adverse prognostic factors for LRFS. On multivariate analysis, not-R0 margins remained the sole independent predictor of worse LRFS.

distant recurrence-free survival (Figure 1)

At the time of analysis (30 April 2008), 106 patients (45%) had distant recurrence (Tables 2 and 3). The median DRFS was 121 months (95% CI 101–141). The 1-year, 5-year and 9-year DRFS rates were 80% (95% CI 77% to 84%), 57% (95% CI 53% to 62%) and 46% (95% CI 41% to 51%), respectively. The median time to distant recurrence was 20 months. Forty-three patients had distant recurrence occurring >2 years after the initial diagnosis. Median survival from the time of recurrence was longer for patients with late distant recurrence (>2 years from the time of diagnosis) than for patients with earlier treatment failure (27 versus 15 months, $P = 0.0001$). On univariate analysis, age >35 years old, tumor size >7 cm, extra-limb locations and grade 3 were adverse prognostic factors for DRFS. On multivariate analysis, age >35 years old, tumor size >7 cm, and grade 3 remained independent predictors of worse DRFS.

impact of adjuvant radiotherapy on outcome =

The impact of adjuvant radiotherapy was analyzed after adjustment to the respective variables associated with OS, DFRS and LRFS on multivariate analysis (Table 4). Adjuvant radiotherapy significantly improved LRFS but not OS or DRFS.

impact of neo-adjuvant and adjuvant chemotherapy on outcome

Neither neo-adjuvant chemotherapy nor adjuvant chemotherapy had a significant impact on OS, LRFS or DRFS after adjustment to the prognostic factors identified on multivariate analysis (Table 4).

discussion

We have reported here the largest series to date describing the outcome of nonpediatric patients with localized SS.

The 5-year OS (64%) and DRFS (57%) rates as well as the proportion of patients with local recurrence (23.5%) were similar to that reported by Ferrari et al. [17] in a series of 215 patients (including 41 pediatric cases) with SS treated by

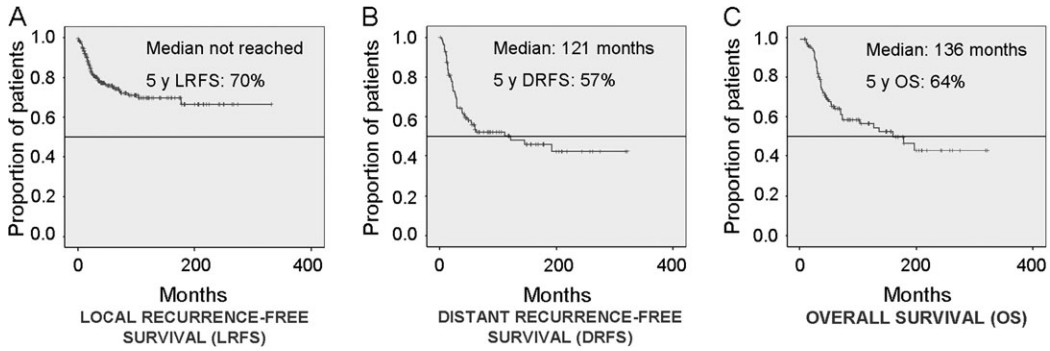

Figure 1. Kaplan–Meier curves for local recurrence-free survival (A), distant recurrence-free survival (B) and overall survival (C) of the entire cohort study ($n = 237$).

complete surgical resection (70.6%, 51.1% and 30%, respectively). Although the majority of local (68%) or distal recurrence (59.5%) occurred within 2 years after the initial diagnosis, a significant proportion of patients experienced late treatment failure up to 15 years after initial diagnosis. This underscores the need for a prolonged follow-up of patients with primary resected SS. Interestingly, patients with recurrence occurring >2 years after the initial diagnosis had a significantly better outcome than patients who relapsed earlier. Such a correlation between a longer time to recurrence and a better postrecurrence survival has been already reported for Ewing sarcomas [25], osteosarcomas [26] and in a series of 255 patients who underwent complete resection of lung metastases from soft-tissue sarcomas [27]. Nevertheless, our findings should be interpreted with caution. The time to recurrence was not significantly associated with outcome in a recent study including 104 patients with advanced SS treated at the Royal Marsden Hospital [28]. Moreover, the design of our study did not allow us to analyse the impact on postrecurrence survival of several key variables such as the type of management of local recurrence, the role of resection of metastases or the role of an additional line of chemotherapy in patients with metastatic relapse already treated with chemotherapy in the adjuvant setting.

The large cohort included in our study as well as the mature follow-up allowed us to identify robust prognostic factors for patients with localized SS. In our series, grade 3, age >35 years and not-R0 margin status were independent predictors of poor OS. These findings were consistent with the data from smaller series which have already shown a significant correlation of grade [22] and age [29] with outcome. We have also found that the margin status was the strongest predictive factor of local recurrence as previously reported in other soft-tissue sarcoma subtypes [2]. Some factors such as the histological subtype (monophasic, biphasic or undifferentiated) [20] or the fusion type (*SYT-SSX1* or *SYT-SSX2*) resulting from the characteristic translocation t(X;18) [21] were not analyzed since they were not available for the majority of the patients included in our database. However, these two factors are not independent since most biphasic cases contain the *SYT-SSX1* fusion type [22, 31, 32]. Moreover, their prognostic value is still highly

Table 2. Prognostic factors for OS, LRFS and DRFS: univariate analysis ($n = 237$)

Variables	Median OS (months)	*P*	Median LRFS (months)	*P*	Median DRFS (months)	*P*
Male	136		NR		144	
Female	126	0.931	NR	0.888	121	0.660
Age ≤ 35	NR		NR		NR	
Age> 35	79	0.0001	NR	0.102	59	0.018
Limb	160		NR		NR	
Extra-limb	46	0.0001	NR	0.0001	48	0.0001
Size ≤7 cm	232		NR		NR	
Size >7 cm	127	0.0001	NR	0.141	23	0.0001
Grade 2	NR		NR		NR	
Grade 3	69	0.0001	NR	0.020	29	0.0001
R0	NR		NR		NR	
Uncertain margin	160	0.01	NR		191	
R1	52		NR	0.043	27	0.129

OS, overall survival; LRFS, local recurrence-free survival; DRFS, distant recurrence-free survival; NR, not reached.

Table 3. Independent prognostic factors for OS, LRFS and DRFS: multivariate analysis ($n = 237$)

Variables	Adjusted hazard ratio for OS	Adjusted hazard ratio for LRFS	Adjusted hazard ratio for DMFS
Age >35	2.16 (1.28–3.64), $P = 0.004$	–	1.56 (1.05–2.34), $P = 0.028$
Grade 3	4.07 (2.22–7.40), $P = 0.0001$	–	3.01 (1.92–4.74), $P = 0.0001$
R0	1	1	
Uncertain margin	2.43 (1.34–4.54), $P = 0.005$	2.43 (1.11–5.26), $P = 0.027$	–
R1	2.56 (1.29–5.26), $P = 0.007$	2.44 (1.01–5.88), $P = 0.050$	–
Size >7 cm	–	–	2.15 (1.41–3.26), $P = 0.0001$

OS, overall survival; LRFS, local recurrence-free survival; DRFS, distant recurrence-free survival.

Table 4. Impact of neo-adjuvant and adjuvant treatments on OS, LRFS and DRFS after adjustment to prognostic factors: multivariate analysis ($n = 237$)

	Adjusted hazard ratio for OS[a]	Adjusted hazard ratio for LRFS[b]	Adjusted hazard ratio for DRFS[c]
Adjuvant radiotherapy	1.01 (0.75–2.00), $P = 0.358$	0.43 (0.22–0.90), $P = 0.026$	0.78 (0.33–4.13), $P = 0.499$
Neo-adjuvant chemotherapy	0.91 (0.56–1.49), $P = 0.725$	0.47 (0.16–1.34), $P = 0.160$	1.37 (0.89–2.18), $P = 0.175$
Adjuvant chemotherapy	1.62 (0.91–2.87), $P = 0.099$	0.81 (0.45–1.71), $P = 0.710$	0.93 (0.63–1.38), $P = 0.738$

[a]OS was adjusted to age >35, grade 3 and surgical margins (see Table 4).
[b]LRFS was adjusted to surgical margins (see Table 4).
[c]DRFS was adjusted to age >35, grade 3 and size >7 cm (see Table 4).
OS, overall survival; LRFS, local recurrence-free survival; DRFS, distant recurrence-free survival.

controversial and some authors suggest that it if exists, it is overshadowed by more relevant parameter such as grade [22, 31, 32].

The role of adjuvant and or neo-adjuvant chemotherapy in soft-tissue sarcomas is a matter of debate. A 1997 individual patient meta-analysis of all known randomized clinical data failed to show a significant benefit of adjuvant chemotherapy in terms of OS [13]. A subsequent phase III study involving 104 patients with resectable high-grade/large (>5 cm) or recurrent limb soft-tissue sarcoma showed a statistically significant benefit for OS being 13% and 19% at 2 and 4 years, respectively, in the group treated with an intensified anthracycline/ifosfamide combination [33]. However, this benefit of adjuvant chemotherapy in terms of OS rate has lost its statistical significance with further follow-up [34]. Such lack of benefit of adjuvant chemotherapy has recently been confirmed in a larger trial involving 351 patients and who were randomly allocated to receive chemotherapy with five cycles of doxorubicin 75 mg/m^2, ifosfamide 5 g/m^2 every 21 days and lenograstim or a simple surveillance after the locoregional treatment of a soft-tissue sarcoma [11]. Estimated 5-year relapse-free survival was 52% in both groups, and OS was 69% in the observational group versus 64% in the chemotherapy group (hazard ratio = 0.621 for both). Moreover, the sole randomized trial ever conducted in the neo-adjuvant setting has also shown no survival advantage in those patients treated with a doxorubicin/ifosfamide-based regimen [12]. Some authors argue that the apparent lack of benefit of chemotherapy in localized soft-tissue sarcomas is at least in part due to the fact that many trials have included heterogeneous types of sarcomas with different profiles of chemosensitivity. Several studies carried out in the metastatic [14–17] or the pediatric settings [18, 19] have suggested that SS is more chemosensitive than other soft-tissue sarcoma subtypes. A histology-specific randomized trial would be the best way to test this hypothesis in the adjuvant or neo-adjuvant setting. However, SS is a rare disease representing 80–100 new cases diagnosed yearly in a country of 60 millions inhabitants such as France. Therefore, the feasibility of such a trial is clearly compromised by the difficulties to reach a reasonable accruement goal. Despite the usual limitations of a retrospective design, this large database study provides useful insights on the specific issue of the role of neo-adjuvant and adjuvant chemotherapy in SS. We limited the potential bias by using adjustment for the significant prognostic factors. Altogether, our results indicate that neo-adjuvant or chemotherapy do not alter outcome of patients with primary SS. It is unlikely that such a lack of benefit of chemotherapy was the result of a suboptimal treatment. Although, the chemotherapy regimens used in our series were heterogeneous, a majority of patients were treated with a dose-optimal ifosfamide-containing regimen. Moreover, our data are in agreement with those of two other contemporaneous studies which also failed to show any impact of adjuvant chemotherapy on survival of patients with localized SS. A recent pooled analysis of the two largest randomized trials which assessed the role of adjuvant chemotherapy in localized high-grade soft-tissue sarcoma (EORTC 62771 and 62931) has shown that tumor size, histological grade or histological subtype had no predictive value for chemotherapy benefit [35]. In particular, no benefit of adjuvant chemotherapy was observed for the group of 108 patients with SS [35]. A large Italian single-institution study also showed that neo-adjuvant and adjuvant chemotherapy do not improve survival of patients with localized SS despite the use of an high-dose combination regimen (ifosfamide 9 g/m^2, doxorubicin 80 mg/m^2) in the majority of treated patients [29].

Despite these disappointing results, we cannot exclude that chemotherapy is of benefit in a subset of patients with tumors showing some specific biological features. For instance, the potential predictive value of the fusion types (SYT-SSX1 or SYT-SSX2) is currently under investigation. However, our present results indicate that wide surgical resection and adjuvant radiation therapy when applicable is still the gold standard of care for patients with SS and that chemotherapy should not be delivered outside a clinical trial setting.

acknowledgements

AI and NP are sincerely grateful to Dr Didier Cupissol, Dr Julien Domont, Prof. Florence Duffaud, Dr Agnès Leroux and Mrs Christine Dupouy for their helpful contribution.

references

1. Singer S, Corson JM, Gonin R et al. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. Ann Surg 1994; 219: 165–173.
2. Pisters PWT, Leung DHY, 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: 1679–1689.
3. Coindre JM, Terrier P, Guillou L et al. Predictive value of grade for metastasis development in the main histological types of adult soft tissue sarcomas. A study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91: 1914–1926.
4. Singer S, Baldini EH, Demetri GD et al. Synovial sarcoma: prognostic significance of tumor size, margin of resection and mitotic activity for survival. J Clin Oncol 1996; 14: 1201–1208.
5. Lewis JJ, Antonescu CR, Leung DHY et al. Synovial sarcoma: a multivariate analysis of prognostic factor factors in 112 patients with primary localized tumours of the extremity. J Clin Oncol 2000; 18: 2087–2094.
6. Spillane AJ, A'Hern R, Judson IR et al. Synovial sarcoma: a clinicopathologic, staging and prognostic assessment. J Clin Oncol 2000; 18: 3794–3803.
7. Trassard M, Le Doussal V, Hacene K et al. Prognostic factors in localized primary synovial sarcoma: a multicenter study of 128 patients. J Clin Oncol 2001; 19: 525–534.
8. Casali PG, Jost L, Sleijfer S et al. ESMO Guidelines Working Group. Soft tissue sarcomas: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008; 19 (Suppl 2): ii89–ii93.
9. Verweij J, Seynaeve C. The reason for confining the use of adjuvant chemotherapy in soft tissue sarcoma to investigational setting. Semin Radiat Oncol 1999; 9: 352–359.
10. McCarter MD, Jaques DP, Brennan MF. Randomized clinical trials in soft tissue sarcoma. Surg Oncol Clin N Am 2002; 11: 11–22.
11. Woll PJ, van Glabbeke M, Hohenberger P et al. EORTC Soft Tissue & Bone Sarcoma Group. Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): interim analysis of a randomised phase III trial. J Clin Oncol 2007 (Suppl 18S): 25 (Abstr 10008).
12. Gortzak E, Azzarelli A, Buesa J et al. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer 2001; 37: 1096–1103.

13. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet 1997; 350: 1647–1654.
14. Rosen G, Forscher C, Lowenbraun S et al. Synovial sarcoma: uniform response of metastases to high dose ifosfamide. Cancer 1994; 73: 2506–2511.
15. Kampe CE, Rosen G, Eilber F et al. Synovial sarcoma: a study of intensive chemotherapy in 14 patients with localized disease. Cancer 1993; 72: 2161–2169.
16. Nielsen OS, Judson I, Van Hoesel Q et al. Effect of high-dose ifosfamide in advanced soft tissue sarcoma. A multicenter phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2000; 36: 61–67.
17. 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: 627–634.
18. Landenstein R, Treuner J, Koscielniak E et al. Synovial sarcoma of childhood and adolescence: report of the German CWS-81 study. Cancer 1993; 71: 3647–3655.
19. Okcu MF, Munsell M, Treuner J et al. Synovial sarcoma of childhood and adolescence: a multicenter, multivariate analysis of outcome. J Clin Oncol 2003; 21: 1602–1611.
20. Eilber FC, Brennan MF, Eilber FR et al. Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. Ann Surg 2007; 246: 105–113.
21. Fletcher C, Unni K, Mertens F. World Health Organization Classification of Tumours Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press 2002.
22. Le Guillou L, Benhattar J, Bonichon F et al. Histologic grade, but not SYT-SSX fusion type, is an important prognostic factor in patients with synovial sarcoma: a multicenter, retrospective analysis. J Clin Oncol 2004; 22: 4040–4050.
23. Hryniuk WM. The importance of dose intensity in the outcome of chemotherapy. In De Vita VT Jr, Hellman S, Rosenberg SA (eds): Important Advances in Oncology. Philadelphia, PA: Lippincott 1988; 121–141.
24. Gurney H. How to calculate the dose of chemotherapy? Br J Cancer 2002; 86: 1297–1302.
25. Leavey P, Mascarenhas L, Marina N et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence. J Clin Oncol 2007 (Suppl 18S): 25 (Abstr 10011).
26. Gelderblom H, Sydes MR, Morgan RC et al. Survival after recurrent osteosarcoma: data from three European Osteosarcoma Intergroup (EOI) randomized controlled trials. J Clin Oncol 2008 (Suppl): 26 (Abstr 10505).
27. van Geel AN, Pastorino U, Jauch KW et al. Surgical treatment of lung metastases: the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer 1996; 77: 675–682.
28. Spurrell EL, Fischer C, Thomas M et al. Prognostic factors in advanced synovial sarcoma: an analysis of 104 patients treated at the Royal Marsden Hospital. Ann Oncol 2005; 16: 437–444.
29. Palmerini E, Staals EL, Zanella L et al. Synovial sarcoma: a retrospective analysis of 250 patients treated in a single institution. J Clin Oncol 2008 (Suppl): 26 (Abstr 10506).
30. Pisters PWT, Leung DHY, 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: 1679–1689.
31. Ladanyi M. Correlates of SYS-SSX fusion type in synovial sarcoma: getting more complex but also more interesting? J Clin Oncol 2005; 23: 3638–3639.
32. Ladanyi M, Antonescu CR, Leung DH et al. Impact of SYT-SSX fusion type on the clinical behaviour of synovial sarcoma: a multi-institutional retrospective study of 243 patients. Cancer Res 2002; 62: 135–140.
33. Frustaci S, Gherlinzoni F, De Paoli A et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 2001; 19: 1238–1247.
34. Frustaci S, De Paoli A, Bidoli E et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology 2003; 65 (Suppl 2): 80–84.
35. Le Cesne A, Van Glabbeke M, Woll PJ et al. The end of adjuvant chemotherapy (adCT) era with doxorubicin-based regimen in resected high-grade soft tissue sarcoma (STS): pooled analysis of the two STBSG-EORTC phase III clinical trials. J Clin Oncol 2008 (Suppl): 26 (Abstr 10525).