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# Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy☆

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**Abstract**

Adult patients with metastatic or locally advanced irresectable soft-tissue sarcoma (ASTS) are generally considered as incurable. Whether some of these patients achieve long-term survival after first-line treatment with chemotherapy is not known. Patients with ASTS still alive 5 years after initial treatment with a doxorubicin-containing regimen, i.e. long-term survivors, were analysed among the 2187 patients included in first-line chemotherapy protocols between 1976 and 1990 in seven trials of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) group. 1888 patients were followed for at least 5 years. The initial clinical characteristics and the outcome of the long-term survivors were investigated. 66 of the 1888 patients were alive at 5 years and the projected 5-year survival was 8% in this series. Age or histological subtypes were similar in the long-term survivors compared with the other patients. The percentages of females (69%), of grade 1 tumours (35%), of patients with an initial performance status (PS) of 0 (63%) were significantly higher in the long-term survivors while liver metastasis (6% versus 21%) were significantly less frequent. Long-term survivors were observed in all subgroups of patients. 31, 31, 31 and 6% of the long-term survivors were in complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively, after the first-line regimen. A CR to a doxorubicin-containing regimen was the major parameter correlated to 5-year survival. In multivariate analysis using a logistic model, independent parameters correlated to 5-year survival were PS, female gender, grade I tumours, and the achievement of a CR after first-line treatment, which was retained as the most powerful predictor for 5-year survival. 10 of the 66 patients died after 5 years in this series, including 8 patients in PD or SD after first-line treatment versus 2 patients in PR or CR ($P=0.01$). 8% of patients with ASTS are alive 5 years after first-line chemotherapy with a doxorubicin-containing regimen. Long-term survivors are observed in all prognostic subgroups of patients, in particular those achieving a CR to first-line chemotherapy.


*Keywords:* Soft-tissue sarcoma; Chemotherapy; Advanced disease; Clinical trials; Retrospective study; Long-term survivors

## 1. Introduction

The prognosis of patients with irresectable or advanced metastatic soft-tissue sarcoma (ASTS) remains poor with response rates to chemotherapy ranging from 20–35% in most series and a median survival of at best 12 months [1–11]. The treatment of ASTS is therefore generally considered as palliative. However, long-term survival can be achieved in patients with

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metastatic sarcoma in whom complete remission is achieved after complete resection of all metastases [12,13], as well as in patients with locally advanced disease when adequate surgery is rendered possible by preoperative chemotherapy [14]. However, whether long-term survival can be achieved in patients with irresectable metastatic or advanced sarcoma treated with chemotherapy has seldom been addressed in a large prospective series of ASTS [15]. If long-term survival can be achieved in some patients with ASTS treated with chemotherapy, the therapeutic strategy may be significantly modified for subsets of patients.

The objectives of this study were to evaluate the frequency and the clinical characteristics of long-term survivors in patients with ASTS. With this aim, we performed a retrospective study of long-term survivors in a database of 2187 patients treated with a doxorubicin-containing regimen between 1976 and 1990 in trials carried out by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) [2–8].

## 2. Patients and methods

### 2.1. Database

This study was performed retrospectively using a database involving 2187 patients ASTS, treated with a doxorubicin-containing regimen as first-line chemotherapy, within 7 prospective EORTC STBSG studies between 1976 and 1990 [1–8] (Table 1). Of these 2187 patients, 1888 (86%) had a minimum follow-up of 5 years since the initiation of chemotherapy: 66 were alive at 5 years, and 1822 had died within the first 5 years. The chemotherapy regimens used in these studies were: doxorubicin single agent [2,4,6], epirubicin single agent [2,6], doxorubicin and ifosfamide combinations [3,4,7,8], doxorubicin, vincristine, cyclophosphamide, dacarbazine (DTIC) combinations [1,4]; doses and schedules were previously reported [1–8]. Survival was not significantly different between the arms of the randomised studies. Inclusion and exclusion criteria in these seven trials were similar: patients with locally advanced irresectable ASTS and/or distant metastasis, aged between 15 and 75 years, with evidence of tumour progression within 2 months were included. The following tumour cell types were included: malignant fibrous histiocytoma (MFH), liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma, haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, miscellaneous sarcoma including mixed mesodermal tumours of the uterus. Malignant mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma were not included. Major exclusion criteria included a previous history of cardiovascular disease, renal failure, symptomatic or known Central Nervous System (CNS) metastases, abnormal serum bilirubin, and second primary malignant tumours (except adequately treated *in situ* carcinoma of cervix or basal cell carcinoma).

### 2.2. Analysis

The proportion of patients surviving at 5 years, their clinical characteristics at inclusion, their response to first-line treatment and their outcome beyond 5 years were investigated. These characteristics were compared with those of patients who died within 5 years after inclusion in the trial. Patients lost to follow-up within 5 years of inclusion were not considered in this analysis.

### 2.3. Statistics

The clinical characteristics of the patients were compared using the Chi square test or Fisher's Exact test for binary variables, the overall Chi-square test for categorical non-ordered variables and the Mantel and Haenszel Chi-square test for ordered categorical variables. Survival curves were plotted according to the method of Kaplan–Meier. Survival curves were compared using the log-rank test. Multivariate analysis of parameters correlated with 5-year survival was performed using a logistic regression model.

## 3. Results

The median overall survival of the series of 2187 patients was 354 days (11.7 months). 355 patients were still alive in October 2000. The survival estimate was 8% at 5 years, 7.6% at 6 years, 6.8% at 7 years and 5.6% at 8 years (standard error $<1\%$). No deaths were recorded beyond 8 years; 9- and 10-year survival estimates were therefore also 5.6%. Among the 66 patients alive at 5 years, 10 died beyond 5 years after inclusion. The 6-, 7- and 8-year survival estimates for 5-year survivors were 94, 85 and 70%, respectively (Fig. 1).

### 3.1. Parameters correlated to 5-year survival

The follow-up of 299 patients was shorter than 5 years: these patients were not included in any further analyses. Parameters correlated to 5-year survival were therefore analysed in 1888 patients. The characteristics of the 66 patients alive at 5 years were compared with those of the 1822 patients who died within 5 years after registration (Table 1). 69% of 5-year survivors were females and 31% males ($P=0.004$). Age was not significantly different in the two groups. The proportion of patients with PS of 0 was significantly higher in the

5-year survivors compared with the remaining patients (63% versus 41%) ($P = 0.002$). Five-year survivors more frequently had grade 1 tumours (35% versus 11%), and less frequently grade 3 tumours (38% versus 55%) ($P < 0.001$) (Table 1). There were also significantly less liver metastases (6% versus 21%) in the 5-year survivors compared with other patients ($P = 0.003$). In contrast, histological subtypes were not significantly different in the 5-year survivors compared with patients who died before 5 years (Table 1). Using a multivariate analysis with logistic regression, parameters (excluding response to chemotherapy) independently correlated to a poor 5-year survival rate were similar to those previously identified as independent prognostic variables for overall survival in the same series: male sex (Relative Risk RR: 2.1), higher tumour grade (RR: 2.3), liver metastases (RR: 4.5) and worse performance status (RR: 2.7) (data not shown). However, 5-year survivors were observed in all prognostic subgroups in this series (Table 1).

Table 1
Clinical characteristics of the 5-year survivors ($n = 1888$)

| Characteristic | 5-year survivors ($n = 66$) N (%)[a] | Others ($n = 1822$)[b] N (%)[a] | P value |
|---|---|---|---|
| Male | 22 (33) | 887 (49) | |
| Female | 44 (69) | 906 (51) | 0.004 |
| Age (years) | | | |
| <40 | 22 (34) | 458 (26) | |
| 40–50 | 13 (20) | 368 (21) | |
| 51–60 | 17 (26) | 477 (27) | |
| >60 | 13 (20) | 468 (26) | 0.13 |
| Tumour grade | | | |
| 1 | 14 (35) | 129 (11) | |
| 2 | 11 (28) | 389 (33) | |
| 3 | 15 (38) | 644 (55) | <0.001 |
| PS | | | |
| 0 | 40 (63) | 720 (41) | |
| 1 | 19 (30) | 779 (45) | |
| 2 | 5 (8) | 243 (14) | |
| 3 | 0 (0) | 3 (0.2) | 0.002 |
| Locally advanced | 27 (44) | 342 (20) | |
| Metastatic | 28 (46) | 1142 (68) | |
| Both | 6 (10) | 190 (11) | 0.005 |
| No lung metastasis | 33 (52) | 774 (45) | |
| Lung metastasis | 30 (48) | 962 (55) | 0.24 |
| Liver metastasis | 4 (6) | 328(21) | |
| No liver metastasis | 59 (94) | 1236 (79) | 0.003 |
| Histology | | | |
| MFH | 6 (14) | 185 (14) | |
| fibrosarcoma | 2 (5) | 57 (4) | |
| liposarcoma | 3 (7) | 92 (7) | |
| leiomyosarcoma | 13 (31) | 471 (36) | |
| synovialsarcoma | 2 (5) | 95 (7) | |
| neurosarcoma | 4 (10) | 96 (7) | |
| others | 12 (29) | 316 (24) | 0.946 |
| Study [reference] | | | |
| 62761 [2] | 7 (3) | 265 (97) | |
| 62801 [3] | 0 (0) | 168 (100) | |
| 62842 [4] | 0 (0) | 142 (100) | |
| 62851 [5] | 44 (7) | 596 (93) | |
| 62883 [6] | 3 (3) | 102 (97) | |
| 62901 [7] | 5 (2) | 277 (98) | |
| 62903 [8] | 7 (3) | 272 (97) | |

PS, performance status; MFH, malignant fibrous histiocytoma.

[a] Data not recorded in the database in 29 (2%) patients for gender, 52 (3%) for age, 79 (4%) for performance status, 151 (8%) for disease site (local and/or metastatic), 686 (36%) for histological grade, 534 (28%) for histological subtype, 89 (5%) for lung metastases, 261 (14%) for liver metastases.

[b] $n = 1822$ patients with a minimum follow-up of 5 years died within 5 years after the initiation of chemotherapy.

### 3.2. Response to first-line chemotherapy and 5-year survival

Among the 66 patients with ASTS alive at 5 years, 17 (31%) had experienced complete response (CR) and 17 (31%) partial response (PR) to first-line chemotherapy, respectively (Table 2). This proportion was significantly higher than in other patients ($P < 10^{-5}$). In addition, 17 (31%) of 5-year survivors had stable disease (SD) as their best response to first-line treatment and 3 (6%) had progressive disease (PD). The contribution of subsequent treatment cannot be assessed since it was not documented in the database (Table 2). When CR to first-line chemotherapy was introduced in the multivariate model, CR was found to be the most potent prognostic factor for 5-year survival (Table 3). However, here also, 5-year survival was observed in all subgroups, even in patients whose best response was PD after a first-line regimen containing doxorubicin. Of note, response to first-line chemotherapy still strongly influenced the outcome of these patients *after* 5 years: 2 of 3 patients with PD died between 5 and 7 years, compared with 6 of 17 patients in stable disease and 1 of 17 both for PR and CR patients (Fig. 1c, $P = 0.01$).

## 4. Discussion

These results show that ASTS is not an incurable disease: 8% of these patients are alive 5 years after initial diagnosis, and the majority of them experience long-term survival afterwards. Several clinical parameters, such as gender, PS, tumour grade and liver metastasis were found to be correlated to 5-year survival in univariate and multivariate analysis, and independent prognostic factors for 5-year survival were actually similar to those correlated to overall survival since the inclusion in the trial within the same series [1]. However, the histological subtype, an important prognostic factor for overall survival during the first 5 years actually lost

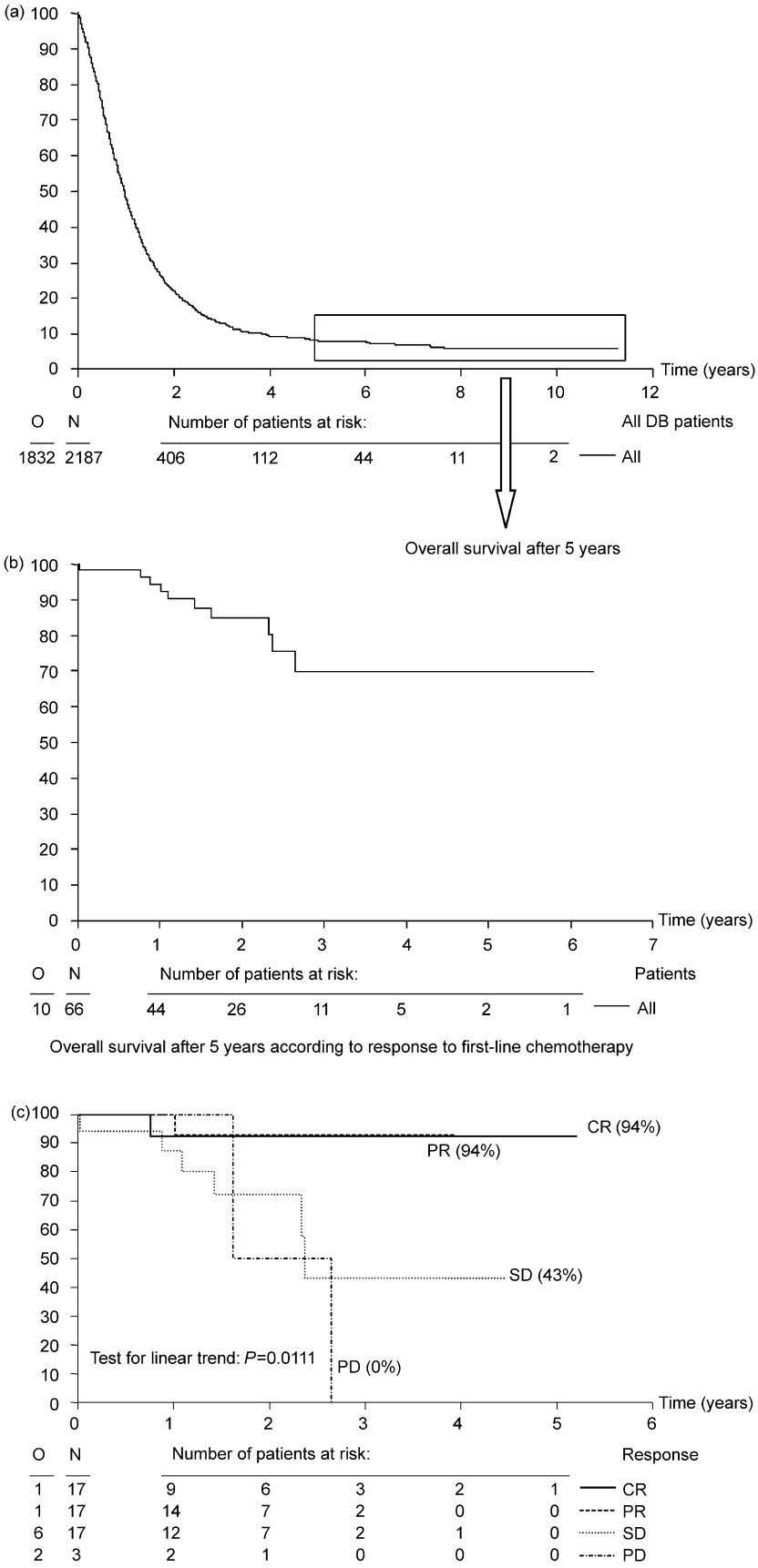


Fig. 1. (a) Overall survival in the whole series of 2187 patients; (b) overall survival after 5 years in the 66 patients alive 5 years after the inclusion in the trial; (c) overall survival after 5 years in patients in CR, PR, SD and PD after first-line chemotherapy. o, observed; N, number.

its predictive value afterwards and was found not to significantly influence 5-year survival in this study. This is likely to be related to the slower progression rate in liposarcomas compared with other sarcomas in patients with advanced disease within the first years; however, eventually a similar proportion of patient with liposarcoma relapse and die of their disease, compared with patients with other sarcoma subtypes. An important observation from this series is that 5-year survivors were observed in all subgroups of patients, even in those with high grade tumours, liver or bone metastasis, and poor performance status.

Clinical response to first-line regimen was found to be the most significant parameter correlated to 5-year survival. Actually, a major difference was observed between patients who achieved CR, and patients who achieved PR, SD, or PD, with a 21% (17/81) rate of 5-year survival for the former, compared with a $\leqslant 5\%$ rate for the latter. Interestingly, the percentage of long-term survivors among patients who achieve CR following treatment with a first-line regimen in this series is very similar to that of other published series in which CR was achieved by other means, including surgery, or surgery plus chemotherapy. This percentage ranged between 20 and 30% in the surgical series reported by Putnam and colleagues [12], in a series of a combination of chemotherapy and surgery [13], in a series of patients treated with chemotherapy only reported by Yap and colleagues [15], and with high-dose chemotherapy in a series where this unusual strategy was tested [16–21].

It should be noted that the majority of long-term survivors did not achieve CR after first-line chemotherapy. It is likely that these patients have been proposed for second-line chemotherapy or resection of metastases sites. However, the second-line treatment was not documented in the database, and the contribution of these treatments to the favourable outcome of these patients (in particular, the CR or PR rates to these treatments) is not known. Nevertheless, long-term survival was exceptional ($\leqslant 5\%$) in all subgroups of patients who did not achieve CR after first-line treatment. Overall, the patients in CR have a relative chance of achieving long-term survival which is 5.0-fold higher than patients in PR, 10-fold higher than patients in SD and 55-fold higher than patients in PD. Regarding long-term survival, three subgroups of patients may therefore be distinguished according to response to first-line chemotherapy: 1) patients in CR, 2) patients in PR or SD, who were found to have a comparable outcome in terms of 5-year survival, and 3) finally patients in PD. In view of these results, a major goal of the treatment of patients with ASTS could be to improve the *complete* response rate to chemotherapy or to combined strategies with chemotherapy and surgery. However, complete response rates are low in ASTS, ranging from 0 to 10% with single agent or combination regimens in large series [1–11]. Another relevant parameter could be the rate of "non-progressive" disease, combining stable disease, partial and complete responses: not surprisingly, these three subgroups include almost all long-term survivors in the present series. Despite a large number of phase II trials, recent agents have shown a limited efficacy on ASTS [22–25]. Therefore, strategies combining chemotherapy with surgery on multiple tumour sites to improve the rate of long-term survivors deserve to be evaluated to increase CR rate.

However, the long-term survival of patients who achieve CR remains unsatisfactory since 80% of these patients will relapse and die of their disease afterwards. Strategies to reduce the relapse rates in these potentially curable patients are therefore needed. High-dose

Table 2
Response to first line doxorubicin-containing regimens

| Response to 1st line[b] | 5-year survivor ($n=66$) | Others[a] ($n=1822$) | *P* value | % of 5-year survivors among response subgroup |
|---|---|---|---|---|
| | *N* (%) | *N* (%) | | |
| CR | 17 (31%) | 64 (4%) | | 17/81 (21%) |
| PR | 17 (31%) | 306 (19%) | | 17/323 (5%) |
| SD | 17 (31%) | 641 (39%) | | 17/658 (3%) |
| PD | 3 (6%) | 627 (38%) | 0.00001 | 3/630 (0.5%) |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

[a] Patients with a minimum follow-up of 5 years after inclusion who died within the 5 years of inclusion.

[b] Response was not documented in 196 (10%) patients.

Table 3
Multivariate analysis of prognostic factors for 5-year survival

| Variable | Parameter estimate | Standard error | Wald Chi-square | *P* value | Odds ratio | 95% CI |
|---|---|---|---|---|---|---|
| Intercept | 2.8555 | 0.8128 | 12.3408 | 0.0004 | . | |
| . | | | | | | |
| PS | 0.7052 | 0.3113 | 5.1314 | 0.0235 | 2.024 | (1.08–3.74) |
| Grade | 0.7790 | 0.2353 | 10.9625 | 0.0009 | 2.179 | (1.36–3.52) |
| Female gender | −0.8286 | 0.3798 | 4.7589 | 0.0291 | 0.437 | (0.30–0.93) |
| CR to first-line | −2.1505 | 0.4634 | 21.5363 | 0.0001 | 0.116 | (0.40–0.29) |

chemotherapy has been proposed with this aim in mind in selected patients: five year survival rates over 50% were reported in some of these small uncontrolled studies [15–21]. Whether this only reflects a selection of patients still requires to be tested in a prospective randomised trial.

In conclusion, these results indicate that a significant proportion of patients with ASTS can achieve long-term survival and probably cure after first-line chemotherapy with anthracyclines. Long-term survivors are observed in all subgroups of patients, even in those with a well established unfavourable prognosis, such as liver metastasis, and high grade tumours. The achievement of CR is the major parameter correlated to long-term survival and future clinical trials should include complete response as a major endpoint in the evaluation of therapeutic strategies.

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