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Five-year results in Ewing's sarcoma. The Scandinavian Sarcoma Group experience with the SSG IX protocol

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Abstract

The first Scandinavian protocol for Ewing's sarcoma, SSG IV, resulted in a local control rate of 74% and 5-year metastasis-free survival (MFS) of 43%. The second protocol, SSG IX, was started in order to improve upon these results. It featured four chemotherapy cycles, each consisting of two courses of VAI (vincristine, doxorubicin, ifosfamide) alternating with one course of PAI (cisplatin, doxorubicin, ifosfamide) at 3-weekly intervals. Total treatment time was 35 weeks. Local therapy was given at week 9. Inoperable or non-radically operated patients received hyperfractionated accelerated radiotherapy 1.5 Gy twice daily between chemotherapy courses to a total dose of 42–60 Gy, depending on surgical radicality and tumour localisation. 88 patients were included (58 male, 30 female, mean age 20 years; range 5–65 years). The tumour (73 M0 and 15 M1) was located centrally in 31 patients (35%), in the extremities in 34 (39%) and other sites in 23 (26%) of cases. The median size of tumour was 10 cm (range 2–23), soft tissue was invaded in 87%. Surgery was the local therapy for 60 (68%) patients: amputation in 8 and local excision in 52. The surgical margins were wide in 35 patients, marginal in 14 and intralesional in 3. Radiotherapy was given to 17 non-radically operated patients postoperatively and to 28 patients with inoperable tumours primarily. Histological responses were evaluated in 52 patients. 9 local recurrences were observed (10%). Distant metastases developed in 24 M0 patients (33%). The estimated 5-year MFS was 58% and overall survival (OS) 70% for M0 and 27% and 28% for M1 patients, respectively. Survival was favourable in patients with non-metastatic extremity tumours (90%) and tumours operated with wide margins (90%). Patients with a total necrosis after chemotherapy had a better OS than those with a partial or poor response ($P = 0.003$). The toxicity (World Health Organisation) was acceptable (gastrointestinal G1–2; haematological G3–4). The SSG IX protocol gave better local control and survival rates than the SSG IV. Whether this is due to a higher therapeutic efficacy of the present protocol cannot be ascertained in this comparison with a historical control.

Keywords: Ewing's sarcoma; Multimodal therapy; Scandinavian

1. Introduction

Prior to the era of combination chemotherapy the prognosis for patients with Ewing's sarcoma of the bone was poor, with a 5-year survival rate of 5–10% [1–2]. In recent years with the use of aggressive combination chemotherapy, the 5-year survival rates have improved up to 30–60% [1–9]. Although it is not yet proven which is the best local therapy, many authors argue that surgery alone or in combination with radiotherapy is probably better than if radiotherapy alone is used [3–9].

With Scandinavian Sarcoma Group IV (SSG IV) (according to the T-11 protocol by Rosen) the 3-year (52%) and the 5-year (43%) disease-free survival rates were comparable with results obtained by other cooperative groups [1,5–9]. However, local recurrence was high in the SSG IV study (26%) compared with either IESS I (10%) or CESS 86 (6% with combined surgery and radiotherapy and 15% by radiotherapy alone). In a previous German Cooperative Ewing's sarcoma study (CESS 81), the combination of sequential chemotherapy

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and a moderate dose of radiotherapy given relatively late, resulted in a high frequency of local recurrence: 47% after chemotherapy and radiotherapy without surgery [7–9]. The following protocol (CESS 86) was therefore modified in order to improve local control [7–9]: radiotherapy was combined with surgery whenever possible; local therapy was delivered earlier; the radiotherapy dose was increased to 46 Gy (postoperatively) or 60 Gy (for patients receiving radiotherapy alone). Accelerated and conventional radiotherapy were compared; radiotherapy and chemotherapy were given simultaneously and chemotherapy was intensified in high-risk patients. Preliminary results of CESS 86 indicated that local control was better than in the previous study. Accelerated radiotherapy was well tolerated despite simultaneous treatment with cytotoxic agents.

Many differences between SSG IV and CESS 86 might be responsible for the worse local control in the former study: (1) late timing of local therapy (24 weeks); (2) chemotherapy given every fourth, instead of every third week, and (3) the long break between each split-course radiotherapy (12 weeks).

In CESS 86, chemotherapy consisted of vincristine–doxorubicin–ifosfamide–actinomycin (VAIA) since tumour necrosis after 9 weeks in the VAIA regimen was higher than after 18 weeks in the VACA regimen (vincristine–doxorubicin–cyclophosphamide–actinomycin) and the disease-free survival rate was also higher in the VAIA group than in the VACA group [7–9] and still is [10,11]. SSG therefore replaced cyclophosphamide with ifosfamide. Moreover, cisplatin was added to the combination because, at this time, some groups using cisplatin in the treatment of local or metastatic Ewing's sarcoma had reported promising results [12–14].

Thus, the main aims of the SSG IX protocol were to improve local control and if possible also to increase the survival rate.

2. Patients and methods

2.1. Treatment protocol

In 1990, a new treatment protocol of Ewing's sarcoma, the SSG IX, was activated by the SSG. This study was closed in April 1999. The protocol features an intensive chemotherapy programme of four chemotherapy cycles, each consisting of two courses VAI (vincristine, doxorubicin, ifosfamide) alternating with one course PAI (cisplatin, doxorubicin, ifosfamide) at 3-weekly intervals. Total treatment time was 35 weeks. Local therapy was given at week 9. Inoperable or non-radically operated patients received hyperfractionated accelerated radiotherapy 1.5 Gy twice daily between chemotherapy courses to a total dose of 42–60 Gy, depending on the surgical radicality and tumour localisation (Fig. 1). Both chemotherapy courses preceding radiotherapy have been shortened from 5 to 3 days, in order to reduce toxicity. The first VAI-course in the cycle 2 was not given when the tumour was operated.

2.2. Patients

All patients with Ewing's sarcoma, also extraosseal tumours, were eligible for inclusion. 96 patients were submitted. 8 patients were excluded because of a false diagnosis upon review (2 osteosarcomas, 2 alveolar rhabdomyosarcomas, 3 malignant small round cell

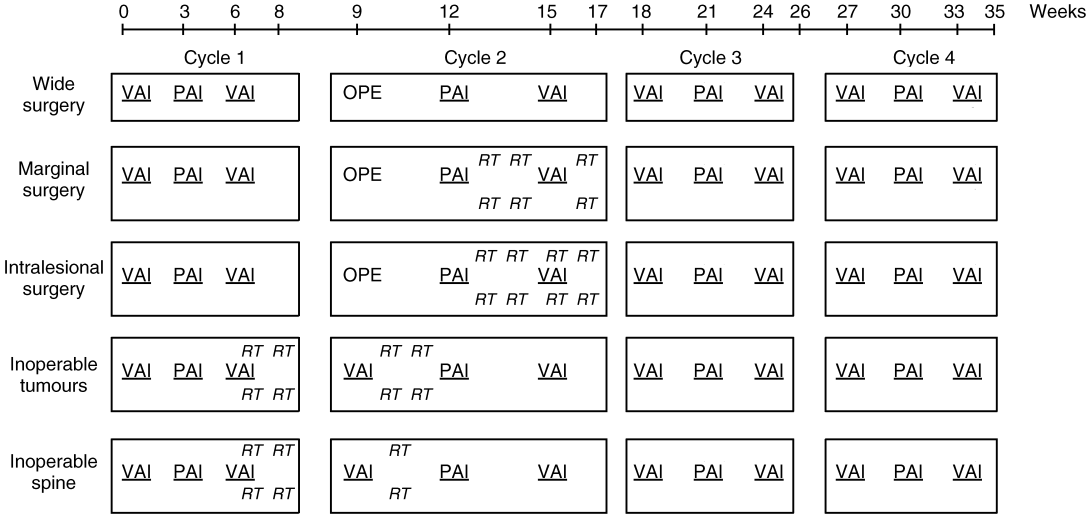

Fig. 1. Outline of the SSG IX protocol in Ewing's sarcoma. V, vincristine 1.5 mg/m^2 for 1 day; A, doxorubicin 30 mg/m^2 for 1 (PAI) or 2 (VAI) days (A was deleted after 510 mg/m^2 in adults and after 450 mg/m^2 in children); I, ifosfamide 1 g/m^2/day for 5 days; P, cisplatin 90 mg/m^2 for 1 day. OPE, surgery; RT, hyperfractionated radiotherapy (1.5 Gy twice daily) to total dose 60 Gy for inoperable or intralesionally resected non-spinal tumours, and 42 Gy to spinal tumours or following marginal surgery.

tumours and 1 breast cancer). 88 patients have been included in the analysis: 58 male, 30 female, mean age 20 years (range: 5–65 years). 73 patients had local disease (M0) and in 15 patients the disease was disseminated at the time of diagnosis (M1).

2.3. Tumours

The tumour was located at the following sites: pelvis (18), femur (13), rib (11), sacrum (9), tibia (7), scapula (6), spine (4), fibula (4), foot (4), humerus (3), mandible (2), radius (1), ulna (1), hand (1) and soft tissue (4). Thus, 31/88 (35%) of the tumours were centrally located. The median of the largest tumour diameter was 10 cm (range: 2–23 cm), with a soft tissue invasion in 87%. Pain was reported by 91%, fatigue by 25% and weight loss by 22% of patients. Median duration of symptoms was 5 months (range: 0–48 months).

2.4. Local therapy

60 patients were operated upon. The procedure was an amputation in 8 and local excision in 52 patients. The surgical margins were wide in 35 patients, marginal in 14 (sacrum 8, spine 4, pelvis 2) and intralesional in 3 (mandible 1 and rib 2 with infiltration of the thoracic wall). Radiotherapy to the inoperable tumour was given to 28 patients, 17 patients were irradiated postoperatively, if the surgery was marginal (14 patients) or intralesional (3 patients). Histological response to chemotherapy was evaluated in 52 tumours according to Huvos: 16 G1, 8 G2, 11 G3, 17 G4 and according to Picci and colleagues: 24 GI, 11 G2, 17 G3. None of the 8 patients treated by amputation were included in this analysis.

2.5. Statistical methods

Metastasis-free and overall survival were calculated according to the method of Kaplan–Meier. The prognostic factors were tested with a Cox regression analysis.

Table 1
Effects of local therapy on local recurrence-free survival (LRFS) and median survival time (MST)

	n	LRFS (%)	MST (months)
Surgery	60		
Amputation	8	100	> 57 all alive
Wide	35	89	72
Marginal[a]	14	94	77
Intralesional[a]	3		
Radiotherapy	45		
Postoperative[a]	17	94	77
Inoperable tumours	28	87	72

[a] All marginally and intralesionally operated patients were also irradiated after surgery.

3. Results

During the medium follow-up time of 57 months, 9 local recurrences (10%) have been observed (4 after operation, 3 after irradiation, 1 after surgery and postoperative radiotherapy, and 1 in a M1-patient during chemotherapy). Tumour response was favourable in 2 of the operated patients and poor in 3 of them. Local recurrence was the first site of relapse in 6 patients. Median survival time after the detection of local recurrence was 13 months. The effects of local therapy on the local control and median survival time are given in Table 1. The local recurrence-free proportion of patients was quite similar in those with inoperable tumours primarily irradiated and in those having marginally or intralesionally operated tumours postoperatively irradiated, 87 versus 94, respectively. The 5-year local recurrence-free proportion was 87% in all M0 patients (Fig. 2).

24 M0 patients (33%) developed distant metastases. First metastases appeared in the lungs (11 patients), in bone (8 patients), in lymph nodes (2 patients), in the bone marrow, liver and thoracic wall (1 patient each). The 5-year overall survival (OS) was 70% and the metastasis-free survival (MFS) was 58% for M0 patients (Fig. 2). OS was 28% and MFS was 27% for M1 patients ($P < 0.00005$, M0 versus M1). In M0 patients, 5-year OS was more favourable in patients with extremity tumours (90%) compared with other ones (57%) ($P < 0.05$) (Fig. 3). Patients with a pelvic tumour developed fewer metastases than those with a sacral tumour, MFS 58% and 50%, respectively. The type of local surgery also had an effect on survival rate: all patients treated by amputation are alive without metastases; patients having tumours operated upon with wide margins had a better survival rate (90%) than those with marginal or intralesional margins ($P < 0.001$) (Fig. 4). Furthermore, patients with a total necrosis to chemotherapy (Huvos G4/Picci G3) had a better 5-year OS (95%) than those with a partial (Huvos G3/Picci

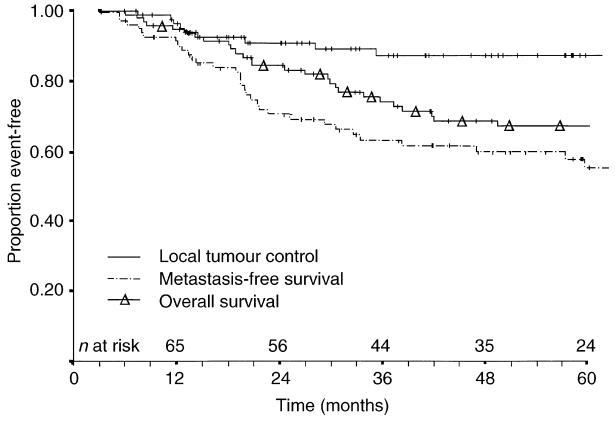

Fig. 2. Local recurrence-free, metastasis-free and overall survival in patients with M0 disease.

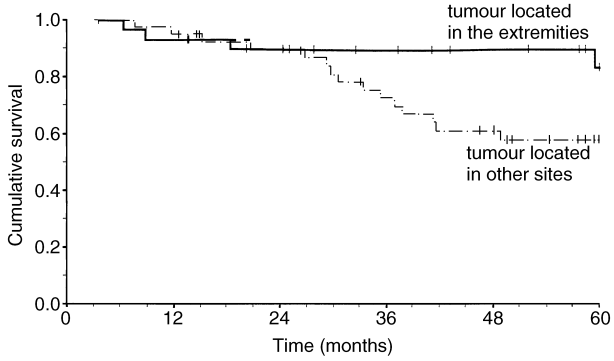

Fig. 3. Overall survival (OS) in M0 patients according to tumour localisation: extremity (—) versus other sites (–·–) ($P < 0.05$).

G2) or a poor response (Huvos G1–2/Picci G1) ($P < 0.003$) (Fig. 5). Prognostic factors influencing survival are given in Table 2.

The toxicity (WHO) was acceptable (according to WHO grading: gastrointestinal G1–2; haematological G3–4). No irreversible renal failure nor ototoxicity was observed. No iatrogenic death was reported.

4. Discussion

The aims of this trial have been fulfilled: both the local control and survival rate improved compared with the previous protocol. However, numerous differences in the present trial and the historical comparison makes it difficult to state with confidence the cause of the improvement. We therefore aim in the future to compare patients in the SSG IV and SSG IX trials according to prognostic factors, e.g. localisation, surgical margins, response to chemotherapy, M0 and M1 patients and cyto- and molecular genetic studies.

The results of non-metastatic Ewing's sarcoma have improved since 1980, the 5-year DFS now ranging from 44 to 82%, depending on the tumour size and localisation [1,4,5,10,11,15–26]. Not unexpectedly, both the

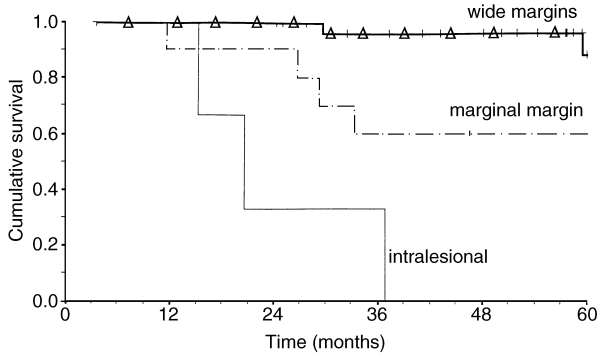

Fig. 4. Overall survival (OS) in M0 patients according to surgical margins: wide (upper curve, –△–); marginal (middle curve, –·–); intralesional (lower curve, —) ($P < 0.001$ wide versus marginal, intralesional).

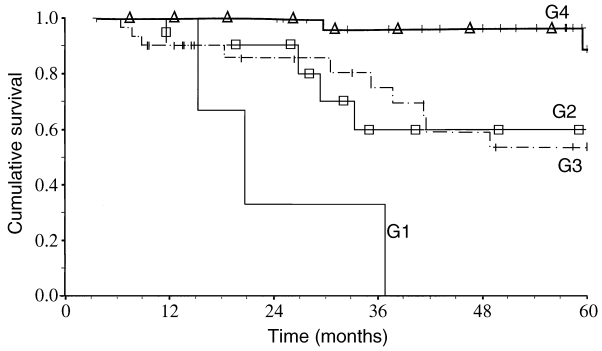

Fig. 5. OS according to tumour response (after Huvos): total necrosis (G4, –△–) gives significantly better survival ($P < 0.006$) than partial responses (G3, –·–) or poor responses (G2 –□–, G1 —) (G4 versus G3, 2, 1 $P < 0.003$).

local recurrence rate of 10% and the 5-year OS rate of 70% in SSG IX are very comparable with those of CESS 86 [11] and the Italian Cooperative Study [22], which have very similar protocols.

Surgery and hyperfractionated irradiation may play a role in the improvement of local control. However, it is impossible to evaluate which of the elements is most responsible; chemotherapy also has an impact. The role of cisplatin in this protocol is unclear, since it has been used in combination with agents of known activity in Ewing's sarcoma therapy. Cisplatin and doxorubicin might have functioned as radiosensitisers. The superimposition of chemotherapy on local treatments and intensification of chemotherapy with ifosfamide might have increased the survival rate. Nevertheless, the overall survival rate of 70% can be considered as very favourable because approximately one-third of the tumours were centrally located — a site often associated with a poor prognosis [4,20,25,26].

Despite the improved treatment results, the improvement by intensified treatments has been modest in

Table 2
Prognostic pattern for survival in 88 Ewing's patients (cut-off point median 57 months; Cox regression analysis)

Dependent variable	*n*	OS *P* value	MFS *P* value
Age	88	0.80	0.56
Sex	88	0.38	0.98
Duration of symptoms	83	0.94	0.84
Fatigue	85	0.12	0.21
Weight loss	83	0.009[a]	0.02[a]
Pain	86	0.38	0.45
Size	79	0.63	0.24
Soft tissue involvement	86	0.25	0.85
M0/M1	88	0.0006[a]	0.002[a]
Surgical margins	52	0.001[a]	0.004[a]
Response to CT	52	0.006[a]	0.003[a]
Extremity/other sites	88	0.07	0.09

[a] *P* values of significance.

OS, overall survival; MFS, metastasis-free survival; CT, chemotherapy.

recent years [27–34]. This probably implies that further intensification of treatment for all patients will lead to only a small proportion of patients without recurrence at the cost of increased toxicity for all patients. Therefore, the use of prognostic factors for stratification of the patients into standard or intensified treatment protocols will be necessary in the generation of new treatment regimens for Ewing's sarcoma.

The factors which were found to be of prognostic significance in this trial — the presence of distant metastases, non-extremity location (M0), surgical margins and the treatment-induced tumour necrosis — are all well documented prognostic factors in other series [4,10,11,19–39]. Our study confirms the recent finding of Picci and colleagues [39] that only total necrosis seems to have a significance on outcome. Picci and colleagues have used a three-grade scaling system where G3 response indicates no evidence of viable tumour [39]. We have used Huvos' four-grade scale where G4 means the same [40]. On a critical re-examination the Picci scale seems to be more suitable than Huvos' grading of assessing tumour necrosis in Ewing's sarcoma [41]. The typical Huvos method to assess necrosis in osteosarcoma utilises a tedious measurement of the entire lesion. Osteosarcoma rarely changes much from its original size, thus leaving large areas with new bone formation but without tumour cells, giving a high percentage of necrosis. Ewing's sarcoma, in contrast, frequently shows marked shrinkage of its soft tissue mass, thus leaving behind much less tissue to give large necrotic areas. This may explain why only total necrosis is correlated with outcome. Tumour necrosis, however, is not available as a prognostic factor at the onset of treatment and therefore less ideal for stratification of treatment intensity. The two other factors, however, can be used to find patients with an excellent prognosis with present treatment strategies: in our series the 5-year MFS for patients with a localised extremity tumour was 90%. Often this kind of tumour can also be operated upon with wide margins.

Since standard treatment seems to be inadequate in high-risk patients — characterised as patients with pelvic tumours [20,25,26], large non-pelvic tumours [15,24,37] and metastastic disease at the time of diagnosis [10,11,23,24,27,28,38], some groups have experimented with high-dose chemotherapy and have reported promising short-term results [27–34]. However, the role of high-dose therapy with stem cell rescue on long-term results still remains to be elucidated.

Cyto- and molecular genetic studies will possibly give early prognostic information on clinically distinct risk groups, e.g. comparative genomic hybridisation (CGH) [42,43] and expression of different EWS chimeric transcripts [44,45].

In conclusion, the SSG IX protocol gave better local control and survival rates than the SSG IV. The prognosis was excellent for patients with localised tumour in the extremities, whereas treatment results must be further improved in central tumours and tumours with metastases at presentation. Early and more specific prognostic factors should be developed in order to find the high-risk patients. The choice between treatment strategies might then be easier: for low-risk patients less toxic regimens could be given whilst high-risk patients could be given the intensive chemotherapy with the more toxic side-effects. Randomised trials are needed to answer questions about the best management when prognostic factors such as those mentioned above are well established.

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